Assessing Ventricular Function in Patients with Atrial Fibrillation

Alexander Small
BSc(Hons) MSc

Submitted in fulfilment of the requirements for the Degree of
Doctor of Philosophy,
Institute of Cardiovascular and Medical Sciences,
College of Medical, Veterinary and Life Sciences,
University of Glasgow,
March 2012.

"For My Parents, Alastair and Carola Small,
who gave me a love of learning
and
For Diana, my Wife,
who put up with it"

Abstract

The Frank-Starling law states that the stroke volume of a regular cardiac beat increases in response to an increase in the volume of blood filling the heart. If this law applies in atrial fibrillation (AF) as well as in sinus rhythm (SR) then cardiac function will depend on the duration of diastole in the preceding beat as well as the duration of the indexed beat.

Aim: The aim of this thesis was to develop a series of tools which would allow an assessment of the changes in cardiac function from one beat to the next in AF and SR. A secondary aim was to find a means of describing rhythm in a way that reflected possible functional change.

Methods: List-mode radionuclide ventriculography, RNVG, acquisitions of 373 patients in AF and a comparative group of 385 patients in SR were made. Software was written which allowed tightly defined preceding and indexed beat selection criteria to be established. Left ventricular ejection fraction (LVEF) and other functional parameters (pre-systolic volume, systolic time, the ratio of pre-systolic to end-diastolic volume, peak filling rate and first third filling fraction) were calculated for images created using different beat selection criteria based on the quartiles of beat length. Assessment used both variable and fixed time formatting and included a comparison of results achieved in the first and second half of the scan.

Traditional linear measures of heart rate variability together with descriptors of the Poincaré plot and cycle length entropy were used to describe rhythm in both AF and SR patients.

Results: Substantial variation with indexed and preceding beat length was seen in both SR and AF in all the systolic parameters measured and in particular in LVEF where the standard deviation of LVEF *for any one patient* was found to be 8.2% in SR and 14.1% in AF. A combination of descriptors of rhythm was found to have good correlation with the range of LVEF measured. Examination of the results for LVEF in several clinical sub-groups suggests that the range of LVEF may have clinical interest.

The techniques were applied in a small clinical study which considered the value of radio-frequency ablation in patients with AF and heart failure. In this study, measures of Sample entropy and the range of LVEF appeared to have prognostic value.

Conclusion: A tool which allows the investigation of beat-to-beat functional variation in RNVG has been produced. It has been shown that the functional variation depending on beat selection criteria is substantial and may have clinical significance both in patients with underlying pathology and prognostically in patients undergoing radiofrequency ablation (RFA).

Contents

List of tables

List of figures

Acknowledgements

John Donne wrote "No man is an Island, entire of itself; every man is a piece of the Continent, a part of the main..." While Donne wrote about mankind the statement is equally true of work. Every piece of work is laid on foundations built by others. It is my hope that the work presented here will lay foundations for future work and I am profoundly grateful to the many people upon whose work I have built and to those who have encouraged, supported, guided and directed me through years of study. Principal among those are my supervisors: Dr Bill Martin and Prof. Andrew Rankin. They have been interested, helpful and knowledgeable and it has a been a pleasure discussing my work with them. They have read and re-read the thesis and put up with the u-turns that I took along the way. I also owe a substantial debt to Chris Martin, Bill's wife, for proof-reading for me. Thank you.

Good friends are one of the great blessings of this life, and I am only too aware of the neglect that this thesis has caused me pay to many folk I love, thank you for bearing with me. I have been particularly humbled by the dedication which David Luke has shown in reading, and correcting, the whole of this thesis over many nights and many plane journeys. It has been a work well beyond the call of friendship. Thank you.

I am grateful to Universal U-Click, the holders of the copyright on Calvin and Hobbes cartoon strips, for granting me free permission to use the strips which appear at the beginning of each of the chapters.

All of the data which has been used in this thesis was acquired in the department of Nuclear Cardiology at Glasgow Royal Infirmary and my thanks goes to everyone in the department for their help and encouragement. Many, if not all, of the technicians were involved in acquiring the data and Adele Rice was of invaluable assistance in anonymizing and collating the data. Thank you.

Regardless of the help of all these, my deepest gratitude goes to Diana, my wife, and to Ben, Alastair, Catriona and Daniel, my children. They have accepted the time I've had to spend, they've distracted me when I've needed distraction (and when I haven't), they've lived with this for years (Catriona and Daniel: there will be life without it). They've loved me through it. Thank you.

Finally to God for giving us a world of infinite variety and unutterable beauty and the minds and the will to discover it. Thank you.

Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Alexander Small

Presentations

Parts of the work of this thesis have been presented in oral and poster form as follows:

Small A.D., Martin W. and Rankin A. *Radionuclide ventriculography: beat selection and formatting in atrial fibrillation*; 9th International Conference on Nuclear Cardiology, Barcelona, May 2009 (Poster Presentation)

Small A.D., Martin W. and Rankin A. *Can we accurately assess ventricular function in patients with atrial fibrillation?*; 8th International Conference on Nuclear Cardiology, Prague, May 2007 (Poster Presentation)

Small A.D., Motherwell D., Fletcher A., McCurrach G., Rankin A. and Martin W. *Assessing Ventricular Function in Patients with Atrial Fibrillation*; British Nuclear Medicine Society AGM, April 2007

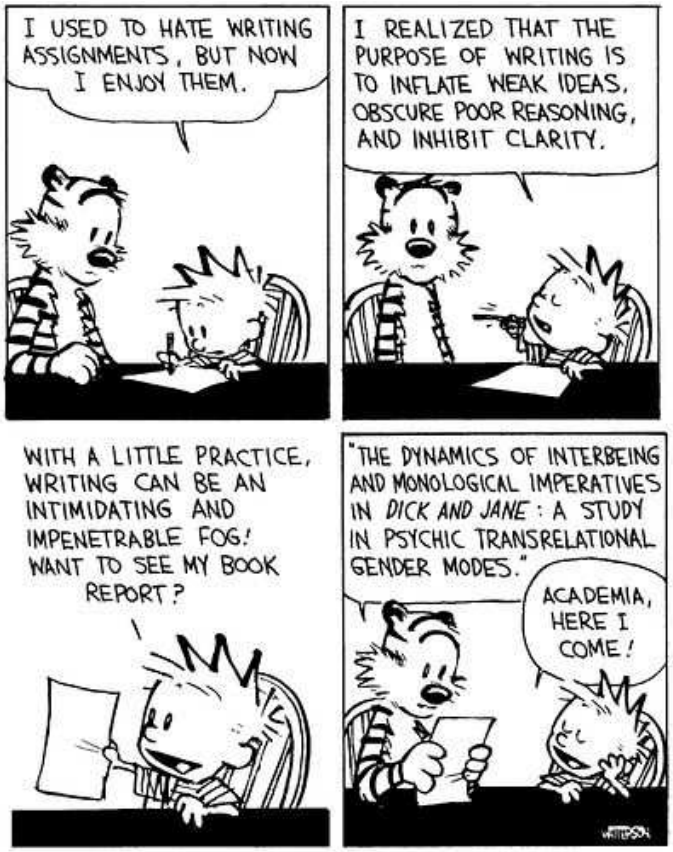
List of Abbreviations

Abbreviations	
AF	Atrial fibrillation
ApEn	Approximate entropy
ANS	Autonomic nervous system
ARP	Absolute refractory period
CABG	Coronary artery bypass graft
CMRI	Cardiac magnetic resonance imaging
ECG	Electrocardiogram
ED	End-diastolic / End-diastole
EDV	End-diastolic volume
EF	Ejection fraction
ES	End-systolic / End-systole
ETT	Exercise tollerance test
FRP	Functional refractory period
FTFF	First third filling fraction
HBP	High blood pressure
HRV	Heart rate variability
LV	Left ventricle / Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
PFR	Peak filling rate
PNS	Parasympathetic nervous system
PS	Pre-systolic
PSV	Pre-systolic volume
RFA	Radiofrequency ablation
RNVG	Radionuclide ventriculography
ROI	Region of interest
SampEn	Sample entropy
ShanEnt	Shannon entropy calculated from histogram
SR	Sinus rhythm
SymDyn	Entropy of Symbolic Dynamics

Symbols	
$\Updownarrow$	$\max(x) - \min(x)$
§	Section

Chapter 1.

Introduction



Summary

This chapter is an overview of the hypothesis and the context in which it is made. It includes a review of basic cardiac physiology and pathology together with general measures

of cardiac function. Atrial fibrillation - its nature, prevalence, principal characteristics and treatment - is described within this context.

An introduction is given to measures of heart rate variability including entropy and the Poincaré plot. This is followed by a description of radionuclide ventriculography together with the differences between fixed and variable time formatting, list mode acquisition and assessments of function - including diastolic function and ejection fraction.

1.1. Cardiac physiology

As any secondary school biology student should be able to tell you, blood is the transport system of the body, carrying the substances necessary to maintain life, e.g. oxygen, to cells and taking waste products away. Movement of the blood is powered by the heart, and in particular the left ventricle. The heart consists of four chambers, the left and right atria and left and right ventricles. The atria act as collecting reservoirs which feed the ventricles. The ventricles act as pumps: pushing blood around the lungs for oxygenation (in the case of the right ventricle) and around the rest of body (in the case of the left ventricle). Thus ventricular, and in particular left ventricular (LV) function reflects how well the "motor" for the blood transport mechanism works.

At this point, let us move away from secondary school biology and consider the heart and LV function in more detail.

1.1.1. Beating

A normal healthy heart beats regularly, with small variations, at a frequency which is governed by several different physiological factors. This normal, regular rhythm, which changes in response to varying physiological conditions, is known as *sinus rhythm* (SR).

Variations in cardiac output are regulated by a combination of processes, the main two being the Frank-Starling mechanism and the autonomic nervous system. Other processes, including humoral factors like the concentration of chatecolamines (e.g. adrenalin), also have an effect[1]. Each beat can be divided into two fundamental, separate parts: emptying (systole) and filling (diastole).

The Frank-Starling law of the heart states that the stroke volume (the volume of blood ejected) of a regular beat increases in response to an increase in the volume of blood filling the heart at the start of the beat. Put simply: the fuller the ventricle, the greater the volume of blood pumped out. Physiologically, if the heart fills with more blood than usual the force of cardiac muscular contraction increases. This happens because the extra volume causes an increased load on each muscle fibre with the result that it stretches; the force that a single cardiac muscle fibre generates is proportional to the initial length of that fibre (sarcomere)[2] (up to a maximum length). Thus stretching the fibre causes a greater force and hence a greater volume blood is ejected. Although the duration of systole does vary [3], it should be noted that in the Frank-Startling mechanism it is the force, not the duration, of contraction which increases.

In the case of *premature ventricular contraction*, premature electrical signals cause the ventricle to empty early. In most cases a premature beat will be followed by a compensatory pause as the next beat falls where it was expected to fall (the premature beat does not reset the clock). This provides a longer filling time as a result of which the ventricle will hold a greater volume of blood. As a result of the Frank-Starling mechanism the force of the following contraction will be greater, causing an increased output and approximately re-balancing the volume at end-systole.

The autonomic nervous system (ANS) acts to control many of the involuntary or semi-involuntary functions of the body including digestion, respiratory rate, perspiration and the diameter of the pupil. It also acts on heart rate and cardiac contractility, conduction and output. The ANS is usually divided into two competing systems: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). In the heart, the SNS acts to increase heart rate and output in response to immediate changes e.g. standing up. The PNS acts in the longer term to slow heart rate and reduce output. Thus the heart rate at any one time is a balance of the SNS against the PNS [4].

The ANS acts through the flow of electrical signals within the nervous system; as a result it responds quickly to the varying demands of the body. Since it is a "balancing" system the ANS operates more slowly than the Frank-Starling mechanism while the effect of changes in levels of catecholamines in the blood stream act even more slowly than the ANS. Thus the Frank-Starling mechanism is the highest frequency mechanism regulating changes in cardiac output.

In normal SR the duration of each beat does not vary substantially from one beat to the next, although modulated by the ANS it may change significantly over time as the

ANS responds to the needs of the heart. Thus the blood volume in the ventricle at the beginning of one beat will be approximately the same as the volume at the beginning of the next.

1.1.2. Electro-Mechanical Activation

Muscle contraction is caused by the unified depolarization of muscle cells. Electrical activity in muscles cells is controlled by the flow of Na^+, Ca^+ and K^+ ions across the cell membrane causing current flow (and hence voltage changes) through the muscle. The depolarization of the myocyte (cardiac muscle cell) causes it to contract. The coordinated contraction of cells results in a contraction of the atrial or ventricular cavity and the ejection of blood from the chamber.

Myocytes depolarize when their *action potential* reaches a threshold voltage, usually under the stimulus of an adjacent cell. The action potential of a typical "normal" myocyte, and the associated electrocardiogram (ECG) signal (see §1.1.3) is shown in Figure 1.1. It is characterised by rapid depolarization and slower repolarization. There are several different kinds of myocyte each with its own action potential and the variation between these controls the coordination of contraction in the myocardium. In particular the sino-atrial, SA, and atrial-ventricular, AV, node have action potentials which are much slower to depolarize and much faster to repolarize. The SA and AV nodes have an intrinsic "pacemaker" current which causes spontaneous contraction. Because the cycle is more rapid in the SA node, it is the cardiac pacemaker in the normal heart.

In the normal heart, electrical activity originates in the SA node and travels through the atrial muscle supported by *inter-nodal bands* (along which there is rapid conduction) causing coordinated contraction through the atria. *Inter-nodal bands* merge at the AV node through which there is slow conduction. The AV node bridges the atria and ventricles and, normally, all electrical activity passes through the AV node before reaching the ventricle. The slow conduction through the AV node ensures that atrial contraction finishes before ventricular contraction starts. Although the AV node has its own pacemaker current the signal from the SA node reaches the AV node and causes it to fire before the potential in the AV node builds up sufficiently by itself to reach the threshold potential.

[1]Image taken from http://ocw.tufts.edu/Content/50/lecturenotes/634463/634540 on 8.10.2011

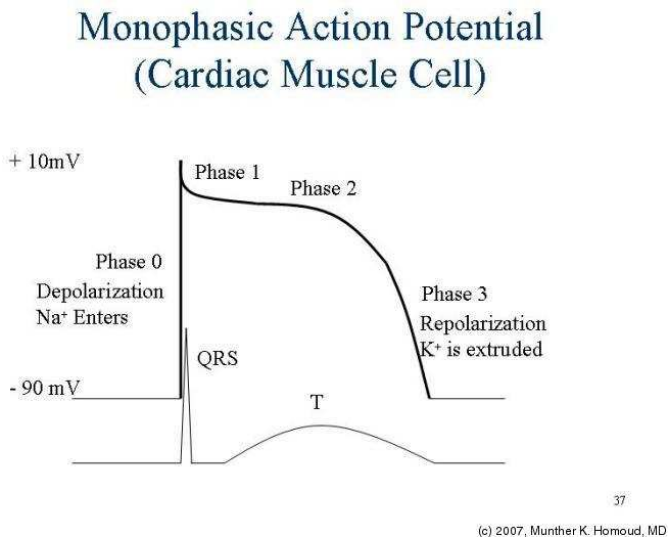


Figure 1.1.: Cardiac action potential[1].

During the absolute refractory period (ARP), immediately post depolarization, any myocyte is inexcitable. During the relative refractory period (RRP) immediately following the ARP the cell gradually recovers its excitability. An action potential during this period has a slower rate of depolarization, lower amplitude and shorter duration. The slower an impulse is conducted through the AV node and the deeper it penetrates before it is blocked, the longer the AV node will be refractory to subsequent impulses.

Electrical and mechanical events overlap considerably in time. Where a beat has an abnormal aetiology, e.g. in AF or where there are ventricular ectopics, a second depolarization may occur abnormally early. If a second action potential is generated very shortly into the RRP the second contraction is superimposed on the semi-relaxed phase of the first contraction making it relatively weak. Thus an ectopic beat will usually result in a relatively strong beat being followed by a weaker one.

1.1.3. ECG, rhythm strips and the Exercise Tolerance Test (ETT)

The changes in the individual intracellular voltage which are described above combine over all the cells of the myocardium to produce a constantly varying voltage signal which can be measured using electrodes placed on the skin. These signals are the summed voltages over all the cells on the path between the electrodes. This signal is the electro-

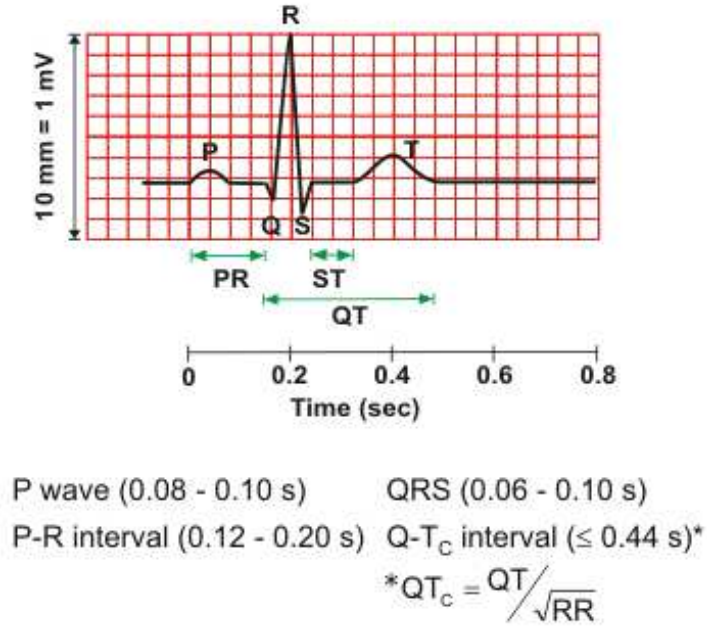


Figure 1.2.: Principal features of the ECG[2].

cardiogram (ECG). The signal will vary depending on where the electrodes are put but the principal features of the ECG for a single beat are shown in Figure 1.2.

The main features of the ECG are:

P wave: This shows the coordinated depolarization activity of the atrium. The width of the P wave approximates to the duration of contraction of the atrium.

QRS complex: This is the result of the coordinated depolarization of the ventricle, it indicates the onset of electrical and mechanical contraction.

T wave: This is the result of ventricular repolarization as the ventricular myocytes return to their base potential (see Figure 1.1).

PR interval: The time between onset of atrial depolarization and ventricular depolarization.

ST segment: The time during which the entire ventricle is depolarized.

QT interval: The total time for ventricular depolarization and repolarization. It approximates to the duration of the action potential of the ventricular myocyte.

[2]Image taken from http://www.cvphysiology.com/Arrhythmias/A009.htm on 8.10.2011

R-R interval: The total time between the onset of ventricular depolarization in one beat and the onset in the next. Although not shown on this plot the R-R interval is highly significant as it defines heart rate.

Each of these features is characteristic and variations from normal values may represent an underlying pathology. Thus the absence of a P wave is distinctive of atrial fibrillation (AF) (see §1.2); a prolonged PR interval suggests a problem with AV nodal conduction; prolonged QRS complexes are indicative of poor conduction within the ventricle; ST segment elevation or depression can result from ischaemia (see §1.1.4). As a result of these and other pathological changes in the ECG, it is a very useful tool in diagnosing cardiac problems.

Typically, a standard 12 lead ECG will involve the placement of 10 electrodes: 1 on each limb and 6 on the chest surrounding the heart. Voltages are measured between the limb electrodes (leads I-III), between each limb electrode and an average of the other two (leads aV_r, aV_l, aV_f,) and between each of the chest electrodes and an average of the limb leads. This yields a view of the electrical activity of the heart along 12 different lines (leads). A much simpler tracing can be taken simply by placing 3 electrodes on the limbs (usually at the top of both arms and the left leg). While theoretically this could be used to produce 6 different tracings, when the main information that is required is the rhythm a single lead (usually lead II) is recorded. This is known as a *rhythm strip* and it gives an indication of rhythm without the detail of a standard 12 lead ECG.

If an ECG is recorded while a patient is "stressed", usually by getting them to exercise, the changing ECG patterns can be studied to show variation with increasing stress on the myocardium. This is known as an *exercise tolerance test* (ETT) and it is particularly useful for diagnosing ischaemia.

1.1.4. Ischaemic heart disease

Ischaemic heart disease, IHD, is characterised by reduced blood supply to the myocardium, usually as a result of coronary artery disease (atherosclerosis). IHD affects about 4.6% of the population of Scotland and is the most common cause of death in the UK (1 in 5 men and 1 in 7 women die from IHD)[5].

Coronary artery disease is the narrowing of the coronary arteries due to the accumulation of plaque within the walls. As this becomes more extensive it may result in IHD with

symptoms including angina (chest pain) and breathlessness, particularly on exercise. As ischaemia develops so too do the symptoms. The progression of symptoms has been well described and is known as the ischaemic cascade. In this the ischaemic heart follows a pattern whereby there is first an imbalance of bloody supply and demand; this is followed by diastolic dysfunction, then systolic dysfunction, ECG changes and only finally anginal pain [6].

Diagnosis

Ischaemic heart disease is diagnosed using ECG, ETT, coronary angiography and myocardial perfusion imaging. ECG and ETT were discussed briefly in the previous section. Diagnosis of IHD using ETT involves looking for ST segment elevation or depression on stress when compared to rest. ST segment changes are caused by hypoxic cells which have a different action potential and consequently produce different electrical signals relative to the depolarized baseline (see §1.1.3). By stressing the myocardium a demand is made by the heart for increased blood flow to support the extra work which is done by the myocardium at increasing heart rate. Ischaemia is diagnosed if there is a change in the ST segment on exercise which reflects hypoxia in the cells.

Coronary angiography involves looking for narrowing of the arteries by tracing the flow of a radio-opaque contrast through the arteries under x-ray fluoroscopy. It is highly sensitive to the build up of plaque on the macroscopic level but performs poorly if lesions in the arteries or capillary networks are too small to be seen at the required resolution.

Myocardial perfusion imaging (MPI) involves injecting a radioactive tracer into the blood stream. The tracer is designed to be taken up by myocytes thus mimicking the effect of more naturally occurring ions (e.g. K^+). Uptake is proportional to blood supply with poorer uptake where there is poorer supply. The difference between poor and good supply can be exaggerated by stressing the patient and thus increasing myocardial demand. As a result differing uptake on stress and at rest is indicative of ischaemia. While the ECG / ETT changes occur late in the ischaemic cascade, MPI reflects early changes making it sensitive at an early stage to the presence of ischaemia.

Treatment

IHD is treated differently depending on the extent of the disease. It is most commonly treated with medical therapy which may include β-blockers, anti-platelet agents, vasodilators, calcium channel blockers and nitrates. For more serious disease the coronary arteries can be widened by inserting a device which expands to open a clear channel through the artery, a process known as percutaneous coronary intervention (PCI) or coronary angioplasty; this can be augmented by the insertion of metallic stents which may or may not be drug eluting. The more invasive treatment involves coronary artery bypass grafting (CABG) in which a replacement channel (an artery or vein from elsewhere in the body) is grafted to bypass a narrowing in the artery and thus improve blood supply. In very extreme cases the heart may be transplanted.

1.1.5. LV function

LV function can be separated into two stages: systole, during which the left ventricle empties and blood is pumped around the body, and diastole, during which the left ventricle fills from the atrium under pressure exerted by the contraction of atrial muscle augmented by the relaxation and active dilation of the LV cavity wall. Both of these are affected by cardiac pathology and it is important to be able, quantitatively, to assess both systolic and diastolic function as an indicator of cardiac health.

Assessing LV function

One would expect that in discussing "LV function" a common language is in use and yet there are a variety of techniques for assessing LV function which, although they may have similar results, are fundamentally different. The different techniques can be categorised as measuring blood flow, pressure, wall motion or volume changes; with each assessment modality involving a different technique as defined in Table 1.1.

There is a clear difference between assessments based on pressure, whether direct or derived, and those based on volume. It has been shown that even between those techniques which assess volume changes, and hence similar parameters, there is a significant variation between measurements using the different modalities [7, 8]. For example Bel-

Assessment technique	Modality
Blood flow (derived pressure)	Doppler echocardiography
Wall motion (derived volume)	MRI, MPI and advanced echocardiography
Direct pressure	Invasive catheterisation
Blood volume changes	RNVG

Table 1.1.: Techniques and modalities used in assessing ventricular function. The table shows the principal modalities associated with each assessment technique, although there is not a one to one match and, for example, blood flow measurements may be also made using MRI. Abbreviations: MRI = Magnetic resonance imaging, MPI = myocardial perfusion imaging, RNVG = radionuclide ventriculography.

lenger et al. found mean LVEF in his group of heart failure patients to vary from 24% by radionuclide ventriculography (RNVG) to 39% by M-mode echocardiography.

Invasive investigation of cardiac pressure is neither desirable nor practicable given the number of patients involved, although it probably offers the most reproducible assessment of LV function. Echocardiography is readily available and comparatively inexpensive; however, it is a difficult tool to use reproducibly, particularly if the patient is not echocardiogenic. Cardiac magnetic resonance imaging (CMRI) is expensive and not readily available. Although in SR it is the gold standard it does not work well in patients with arrhythmias (this is discussed in greater detail in Chapter 8, §8.4.2). RNVG while more expensive than echocardiography also has good availability and better reproducibility.

The focus of this thesis is on measures of LV function which can be made from changes in volume, and in particular from the LV volume-time curve. Although there are several measures of systolic function which can be made from the volume-time curve, including peak emptying rate, duration of systole and time to peak emptying, by far the most common measure is ejection fraction: the proportion of the volume of blood in the ventricle which is expelled from the ventricle during systole. LV ejection fraction (LVEF) has been shown to have powerful prognostic value in groups of patients in numerous papers [9–11]. In most studies the assessment of LV systolic function is limited to LVEF, to the extent that the two terms are commonly treated synonymously. In the normal healthy heart, systole is dominated by the single process of muscle contraction and a single measure can reasonably be used.

The assessment of diastolic function is much less well defined and no single parameter fully describes the complexity of filling which, unlike emptying, is not dominated by a single process. In those modalities for which assessment is based on volume-time curves several measures that reflect single points on the curve have been investigated and found to have diagnostic potential [12]. These include peak filling rate (PFR), time to peak filling, and first third filling fraction (FTFF) - the change in volume over the first third of filling expressed as a fraction of the overall volume change. While these have been found to be clinically significant it should be acknowledged that they attempt to describe a curve from a single point on that curve and this is inherently imprecise, even if the curve follows a known shape. Experience has shown that, particularly in the case of diastolic function, volume-time curves do not always follow a known shape.

1.2. Atrial Fibrillation (AF)

AF is the most common sustained cardiac arrhythmia. It affects $\sim 1\%$ of the population with its prevalence increasing with age from $\sim 0.5\%$ in the 50-59 year group to $\sim 9.0\%$ in the 80-89 year group [13]. Recent records for England in 2008/2009 found that 1.35% of patients registered with NHS GPs had AF [14] with a similar distribution in most other western countries [15]. In Scotland the prevalence has been found to be 9.4/1000 in men and 7.9/1000 in women increasing with age to 71/1000 in individuals aged > 85 years[16].

AF is associated with increased risk of stroke, congestive heart failure, fainting and over time can lead to more severe cardiac and circulatory problems. Typically patients in AF lose about 15% of their cardiac output and this is attributed to the absence of an atrial kick during ventricular filling (diastole).

AF describes the uncoordinated fibrillation (quivering) of cardiac muscle in the atria and it is characterised by the absence of a P wave, which represents depolarization of the atria, on the ECG and by the resultant apparently random fluctuations in ventricular beat length (R-R interval on the ECG).

1.2.1. Description, causes, risks and treatment

AF is characterised by irregularly irregular beats with R-R intervals ranging from the very short, sometimes as low as 300 ms, to the very long, up to 1500 ms. Although

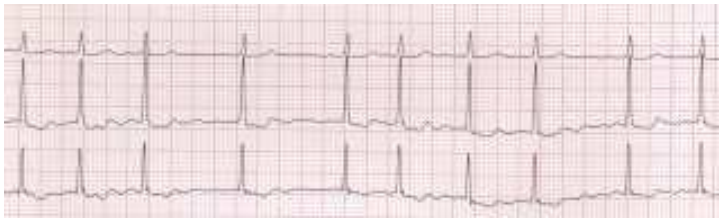


Figure 1.3.: Tracings of three leads (I, II & III) from a 12 lead ECG showing typical AF.

there are no P waves typically the QRS complex is normal. R-R intervals are short and irregular, frequently occurring before the ventricle is filled. Overall ventricular rate is typically $150 - 220$ bpm (see Figure 1.3) before rate control. R-R intervals show marked irregularity which lacks a discernible pattern (although at very rapid rates this is not easy to diagnose).

There are many causes of AF, both cardiac and non-cardiac. Cardiac causes include: ischaemic heart disease, rheumatic heart disease, hypertension and pre-excitation syndromes such as Wolff-Parkinson-White. Non-cardiac causes include: pneumonia and other acute infections, pulmonary embolism, lung carcinoma and thyrotoxicosis. AF is also a common problem post cardiac surgery. Dietary and lifestyle factors, particularly excessive alcohol or caffeine consumption, are also associated with an increased risk of the development of AF [13].

AF may occur asymptomatically, but many patients experience chest pain, dizziness, palpitations and even loss of consciousness. It can also lead to reduced exercise tolerance and impaired cognitive function. However, the main concern for patients in AF is associated with a substantially increased risk both for developing associated pathologies (e.g. stroke and thromboembolism) [17, 18] and for increased overall mortality where the odds ratio[3]for death is 1.5 for men and 1.9 for women [19].

[3]Odds ratio:the ratio between the odds of an event occurring in one group compared to the odds of it occurring in the other; in this case with and without AF at the same age. If p_1 is the probability of an event occurring in group 1 and p_2 is the probability of the same event in group 2, the odds ratio is calculated as:

$$OR = \frac{p_1/(1-p_1)}{p_2/(1-p_2)} \tag{1.1}$$

In AF this suggests an independent increase in the risk of death of between 50% and 90%.

Treatment

Although AF has a typical pattern on the ECG which makes it clearly identifiable, it is treated differently depending on the presentation of the patient. For this reason AF is normally described in terms of its onset, frequency and persistence. A variety of terms are used to describe AF [20] but the National Institute for Clinical Excellence (NICE) recognises five forms[4], each of which is treated differently [13]:

Paroxysmal AF occurs intermittently and terminates spontaneously after less than 7 days and usually after less than 48 hours. It is treated using rhythm control strategies principally aimed at preventing recurrence of AF.

Persistent AF occurs intermittently but requires some form of intervention (either drug treatment or electrical cardioversion) to terminate it. Both rate and rhythm control strategies are used to treat it.

Permanent AF is established and ongoing and does not respond to intervention. It is treated using pharmacologically based rate control strategies in conjunction with anti-thrombotic drugs.

Acute onset AF is described for patients who present with acute haemodynamic instability. If this is life threatening, or if the patient is not known to be in permanent AF, treatment is by cardioversion (rhythm control), otherwise pharmacological rate control is used.

Post-operative AF may be transient and self-limiting. NICE recommend in general that rhythm control is used.

1.2.2. AF Ablation

Treatment for AF generally takes the form of anti-thrombotic therapy and some form of either rhythm or rate control, as discussed above. Rate control is generally achieved using medical therapy while cardioversion is used in rhythm control. Cardioversion can be either electric, in which the heart is shocked back into SR, or pharmacologic, in which

[4]The NICE guidelines were in many respects superseded by the European society of cardiology "Guidelines for the management of atrial fibrillation" [21] which use a slightly different categorisation, although it is still based on the presentation of AF.

drugs are used to bring the heart back into SR. Recently a third option which may be used in conjunction with the others has become available: AF ablation.

In 1998 Haissaguerre et al. [22] investigated the origins of ectopic beats which seemed to initiate AF in patients with persistent and paroxysmal AF. They found that in 94% of cases the ectopic beat which seemed to lead to the onset of AF occurred in the pulmonary veins. They found that, by using radio-frequencies to heat the tip of a catheter and ablate the ectopic foci in the pulmonary veins, they were able to prevent the recurrence of AF in the majority (62%) of patients.

Since then AF ablation has been used in several studies (e.g. [23–25]) which have investigated the efficacy of the technique in a variety of situations with moderate success. The technique, however, is still not widely used and while many of the papers have reported reasonable results there is still doubt as to the long term benefit of a technique which is moderately invasive and expensive.

1.2.3. Ventricular response to AF

AF is principally an atrial pathology, but it profoundly influences ventricular function which has the greatest effect on cardiovascular health. Unfortunately the conduction mechanisms of the AV node are not fully understood and in particular the role of AV node physiology is still not known [26]. However, in the absence of conduction defects apart from AF, all electrical activity passes through the AV node. Thus studying the ventricular response to AF is akin to studying the effect on traffic flow out of Dover of a French lorry drivers protest; or the effect of variations in water flow above a waterfall by measuring the river flow below it. The effect will be profound but it is modulated by an intermediate process (the AV node, cross channel ferries, the waterfall), and studying variations in the ventricular function offers more insight into the behaviour of the AV node, and the intrinsic behaviour of the ventricle than it does into the pathology of AF. This study is ultimately more concerned with the physiology of ventricular function and its variation than with AF.

1.2.4. AF: the imaging challenge

In cardiac imaging, AF provides a significant challenge due to the beat-to-beat variation in beat length (R-R interval). Cardiac imaging is rarely about imaging the atria, and it is much more common for interest to be in imaging the ventricles, particularly the left ventricle which is the principal determinant of cardiac output and blood flow. The ventricular beats in AF have lower frequency than atrial beats (if atrial beats can be identified). In AF ventricular rate is typically around 100 bpm (R-R interval: 600 ms) after rate control, compared with 300 bpm (R-R interval: 200 ms) in the atria. The R-R interval, however, varies substantially suggesting, as a result of the Frank-Starling law (§1.1.1), that there will be substantial variation in beat-to-beat function. The investigation of this variation is the principal subject of this thesis and we will return to this in more detail in §1.6.

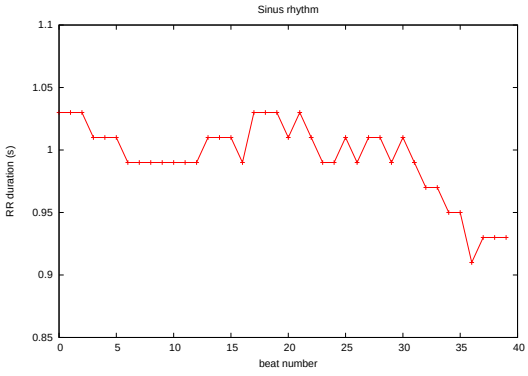
1.3. Describing Rhythm

As we have seen, AF is usually described in terms of its onset and duration (§1.2.1); however, these do not describe the characteristics of AF which would allow one to compare one occurrence of AF with another. To compare the occurrence of AF at one particular time with another at a different time or in a different patient we need to be able to describe, quantitatively, the features of rhythm in each occurrence of AF.

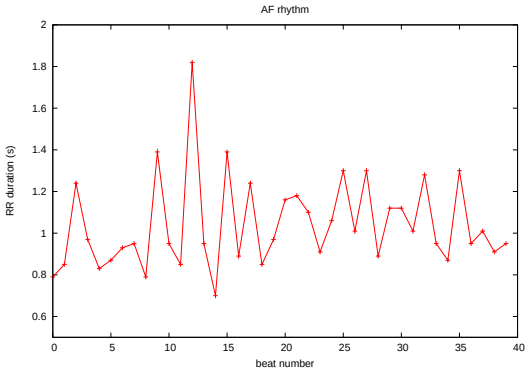
While there will be a number of variables by which this can be described, most notably the degree of variation in beat length, or regularity, there is no well defined common standard for the description of AF.

A significant amount of research has been involved with this question in relation to SR and particularly in patients with low R-R variability. There have been many fewer studies, however, which have investigated descriptions in AF, and there have been no studies which have compared descriptions in AF to those in SR.

In the following discussion let us consider two rhythms. Figure 1.4 shows a patient in SR, with a relatively constant beat length and total variation of $\sim$ 150 ms, and a patient in AF with a widely ranging beat length and a total variation of $\sim$ 1100 ms typical of AF.



(a) SR



(b) AF

Figure 1.4.: Showing forty consecutive beats from (a) a patient in SR and (b) a patient in AF. (Note the differing scales which emphasise that there is a degree of variability in both SR and AF).

1.3.1. Heart Rate Variability

Heart rate variability (HRV) is used as an indicator of cardiac autonomic nervous tone in patients in SR. In general, in patients with SR and excluding ectopic beats, it is accepted that patients with poor heart rate variability, reflecting reduced PNS activity, have a poorer prognosis than patients with a greater variability.[27, 28]

There are a number of standard linear measures used in the assessment of HRV in patients including:

Mean NN: The mean NN interval where NN is the R-R interval between adjacent QRS complexes from normal sinus node depolarizations.

NN range: The difference between the longest and shortest NN interval.

SDNN: The standard deviation (SD) of the NN interval.

SDANNx: The SD of the average on x NN intervals (e.g. SDANN5 is the SD after every 5 beats have been averaged together).

RMSSD: The square root of the mean squared difference between successive NN intervals.

NN50: The number of differences between successive intervals of greater than 50ms.

pNN50: The ratio of NN50 to the total number of NN intervals.

In SR, RMSSD and pNN50 are both moderated by the PNS although neither have been shown to have prognostic implication in terms of all cause mortality. In contrast Mean NN and SDNN appear to be reduced in conditions where there is sympathetic over-activity [29].

Linear measures of heart rate variability have been used in many studies from the investigation of premature newborns[30] to mortality in heart failure[31] and the prediction of recurrence of AF [32].

Generally, however, heart rate dynamics have not been found simply to follow linearity and measures of non-linearity are also required. It is in this area that the Poincaré plot and analysis of entropy have been found to be particularly useful.

	preceding (s)	indexed (s)
point 1	0.79	0.85
point 2	0.85	1.24
point 3	1.24	0.97
point 4	0.97	0.83
point 5	0.83	0.87

Table 1.2.: First 5 points of a Poincaré plot for a patient in AF.

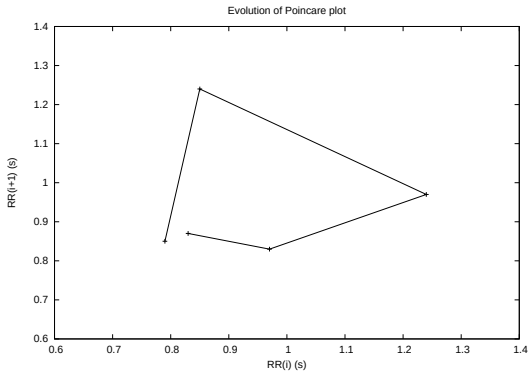


Figure 1.5.: Showing the evolution of the first 5 points of the Poincaré plot with time.

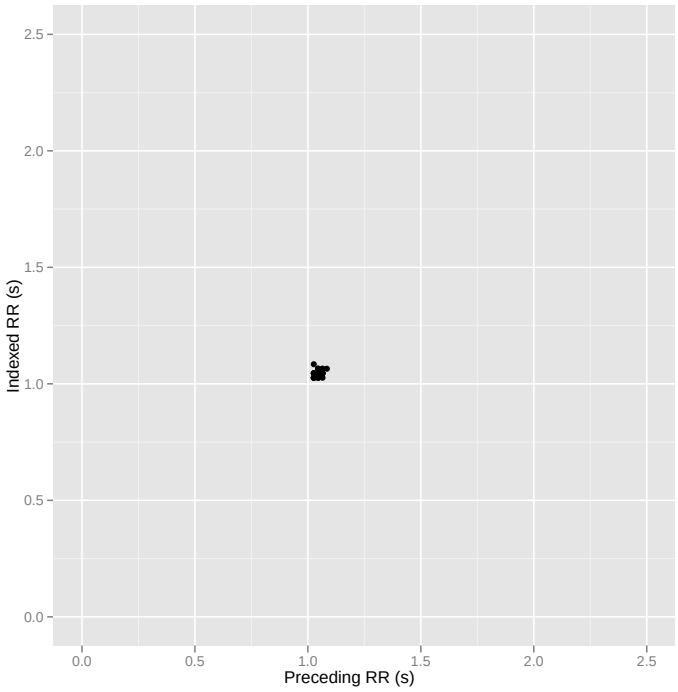
1.3.2. Poincaré plots

A Poincaré plot (also known as a Lorenz plot) plots the indexed R-R interval against the interval immediately following or, with similar effect, the preceding R-R interval against the indexed one. Similar plots (known mathematically as *return plots*) were first described by Poincaré [33] and used by Lorenz [34] in a mathematical description of the atmosphere as a long range predictor of weather. The most common use of the plot is in assessing heart rate variability and was first described by Anan et al. [35]. The plot can be considered to provide a global description in phase space of a system.

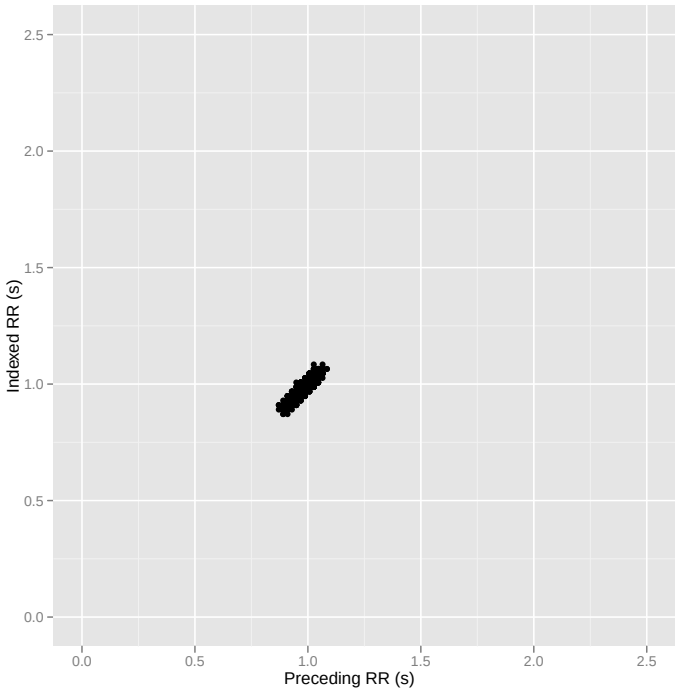
A phase space is a "space" in which all possible states of a system are represented, with each possible state corresponding to a unique point in the phase space. If we consider the states of the "cardiac beat system" as the different R-R durations then a Poincaré plot can be considered to be a phase space representation of that system. It demonstrates the degree of self-similarity of the overall process of the beating heart.

Taking as an example a patient in AF, the first five points in this process are shown in Figure 1.5 (although a standard Poincaré plot will not show the connecting lines, but simply the available states in the phase space).

Poincaré plots corresponding to the two examples of Figure 1.4 are shown in Figures 1.6 and 1.7. These demonstrate typical distributions for SR: a tight grouping of points around a central value and AF: a widely dispersed set of points with no clear structure to the plot.

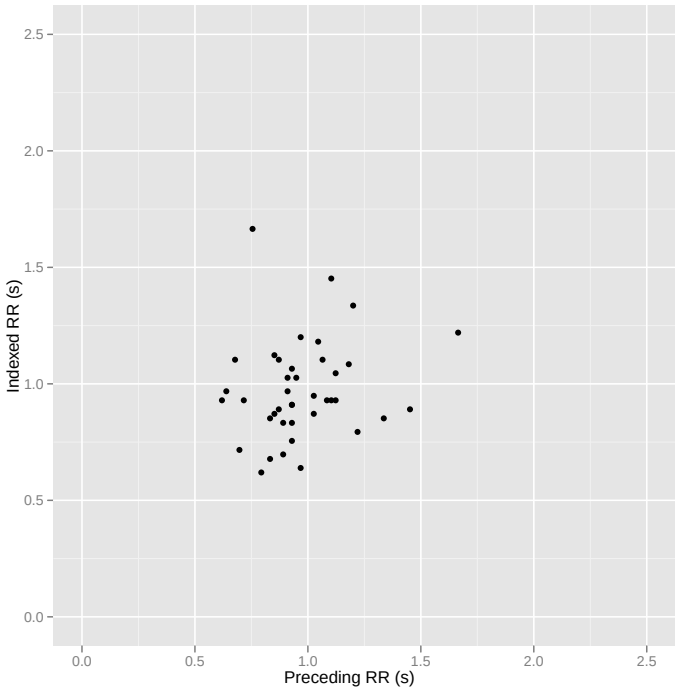


(a) First 40 points

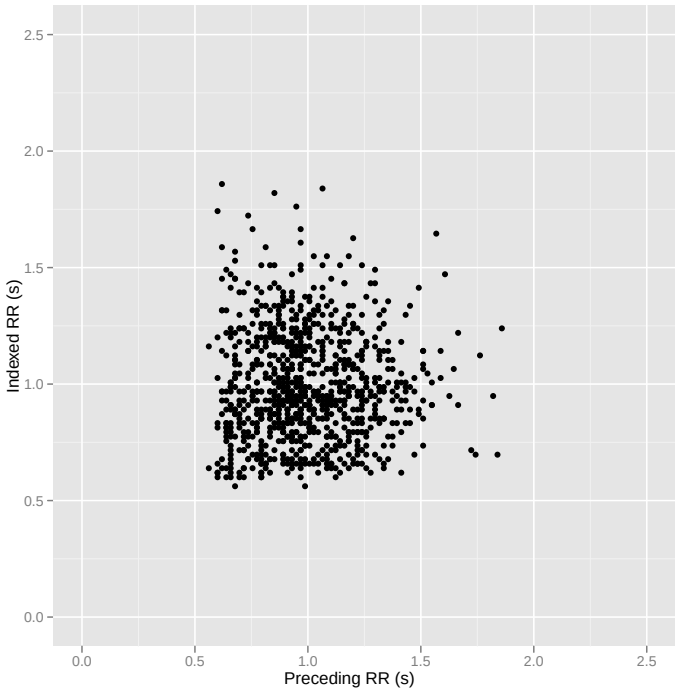


(b) Full acquisition

Figure 1.6.: SR: Poincaré plots for (a) the first 40 beats in and (b) the full acquisition (10 min, 727 beats) for a patient in SR.



(a) First 40 points



(b) Full acquisition

Figure 1.7.: AF: Poincaré plots for (a) the first 40 beats in and (b) the full acquisition (15 min, 903 beats) for a patient in AF.

Poincaré plots have been used extensively as a research tool in SR [36–39] where it has been clearly shown that there is poorer prognosis in patients with lower HRV (more tightly clustered Poincaré plots). To a lesser extent Poincaré plots and HRV measures have been used in AF [40, 41], principally to investigate the relationship between onset of AF from SR or the maintenance of SR after AF rhythm control. The plot can be further developed by adding a third dimension which represents the frequency with which a state occurs. This is known as a *Histographic Poincaré plot*.

Histographic Poincaré plot

The Poincaré plot demonstrates distribution of the available states in the phase space but it does not represent the frequency of occurrence: it is quite possible that a point in the plot may occur multiple times. This is not reflected in the standard Poincaré plot; however, by adding shading or colour to the plot, a third dimension can be added which reflects the number of occurrences of a point in the plot [42]. When information about frequency is included in the Poincaré plot the relative importance of, for example, a single ectopic beat among 1000 normal sinus beats is demonstrated and similarly structure and clustering in a widely diffuse phase space (e.g. in AF) is more obvious. The histographic Poincaré plot is shown in Figure 1.8; in these examples the plot is shown for the full 727 beats (SR) and 903 beats (AF) of a typical acquisition in the department of Nuclear Cardiology at Glasgow Royal Infirmary.

Quantifying the Poincaré plot

The Poincaré plot provides an excellent qualitative "image" of rhythm. Poincaré plot patterns are very distinctive and allow the user to establish a general impression of rhythm, and in particular any structure to the rhythm, at a glance; however by themselves they do not provide quantitative data.

Multiple indices have been developed to characterise Poincaré plots. These can be divided into several categories: correlation; ellipse fitting; pattern fitting; density and difference plots as well as some less well used measures including moments of inertia and dispersion at different R-R intervals.

Smith and Reynolds [43] investigated 28 different indices (excluding those based on density) and correlated them with SDNN, RMSSD and pNN50. Although they only

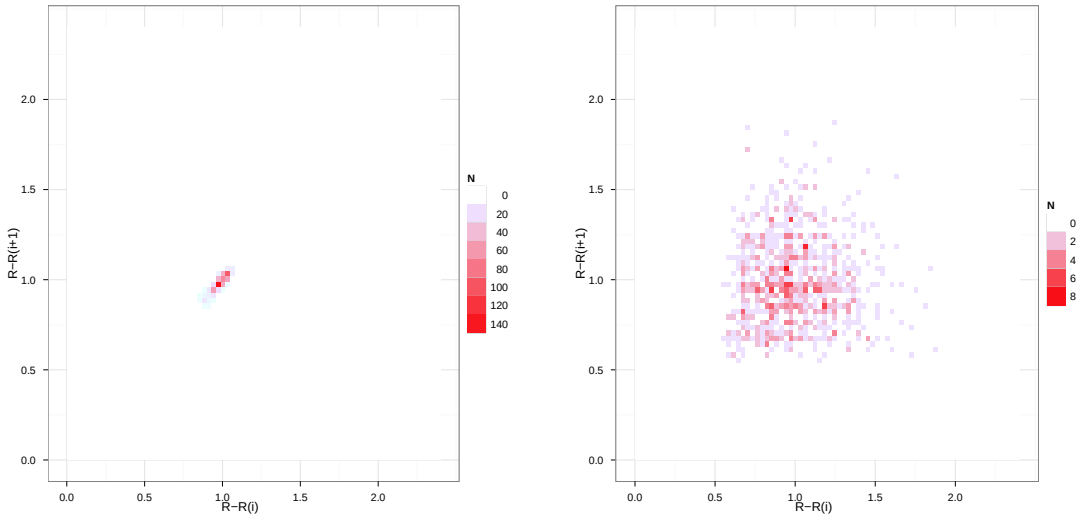


Figure 1.8.: Showing histographic Poincaré plots for the complete acquisition for the sample patients in (a) SR and (b) AF. Colour scales show number of beats at each point (points can only take integer values, even though colour scale is continuous).

looked at data from a single patient in SR in a variety of postures they found that most published Poincaré indices are correlated with SDNN and/or RMSSD. It has also been shown [37] that although ellipsoid fitting is one of the more common means of quantifying the Poincaré plot (e.g. Toichi et al. [44]) the indices derived from the short and long axes of ellipsoid plotting are mathematically related to SDNN and RMSSD respectively.

A few indices, however, have been found to give separate independent measures of variability in particular: the Pearson correlation coefficient, r_{RR}, between RR_n and RR_{n-1} [45] and a measure of the compactness of the plot [46]. While other indices have been developed (e.g. the *complex correlation measure* developed by Karmakar et al. [47]) which show some promise they have not been investigated in detail and have not been considered in this study.

Delta Poincaré plot

A variation on the Poincaré plot has been proposed by Raetz et al. [48] who suggested that plotting the changes in R-R intervals instead of the R-R intervals themselves allows the observer to view changes without the distraction of the dominant high correlation

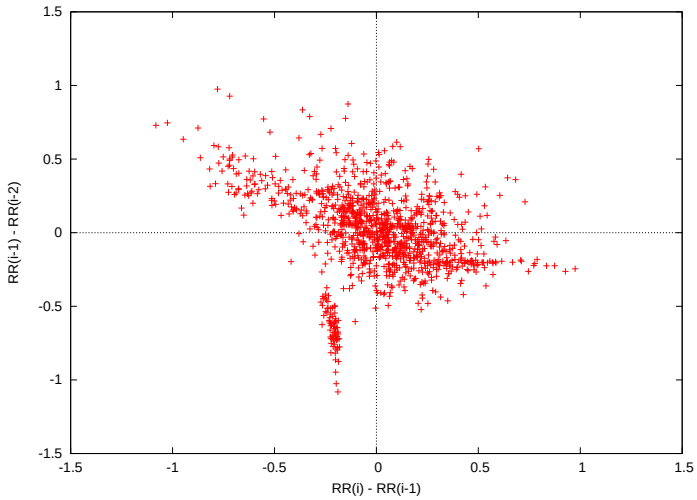


Figure 1.9.: Example of a Delta Poincaré plot from a patient in AF. The plot has the advantage of removing the inherent correlation which may exist, particularly in SR, between one beat and the next.

between one interval and the next. This allows the observer to determine whether there is a consistent pattern to beat-to-beat variations. An example is shown in Figure 1.9.

Raetz et al. used the Delta Poincaré plot to investigate R-R interval variation during sleep and found that there was a significant difference in the pattern of beat changes in SR between quiet sleep and REM sleep.

1.4. Entropy

While linear measures of heart rate variability and the Poincaré plot offer insight into beat-to-beat variations they say little about the regularity of the R-R interval sequence: a sequence might be completely regular but still show sizable variation in these measures. The concept of entropy, which was first introduced in thermodynamics, offers a means of quantifying the regularity of a system.

1.4.1. Regularity vs. Complexity

Before we proceed it is important to understand the difference between measures of regularity and measures of complexity. A measure of regularity is essentially a measure of the frequency of occurrence of a pattern of arbitrary length. Complexity is a measure of

the ease with which that pattern can be constructed. It is possible to have a system with high regularity and low complexity (a straight line), low regularity and low complexity (white noise), high regularity and high complexity (perhaps most easily envisaged as a long computing algorithm, although most music also falls into this category) and low regularity and high complexity (typical of AF).

1.4.2. Introducing entropy

Entropy is one of the fundamental concepts of thermodynamics where it defines the Second Law of Thermodynamics: *heat cannot generally flow from a material at a lower temperature to a material at a higher temperature without the input of work.* It is not immediately obvious how this translates from the world of thermodynamics to that of R-R variability but entropy can be considered to be a statistical property which defines the likelihood of a system being found in any particular state. In basic terms, in thermodynamics, the state of any given system describes the energy that each molecule has: at very low temperatures the overall energy in the system is very low so the total number of states is low and the overall entropy is low. In R-R variability the different R-R intervals can be considered to provide the number of states of the system, thus SR will have a lower entropy than AF where the number of possible R-R states is much greater than in SR. The relationship between thermodynamic entropy, information and the statistical states that other systems can take has been shown to be physically measurable and is not just conceptual [49], however an explanation of this is beyond the scope of this thesis.

A number of different measures of entropy have been described as measures of quantifying regularity / irregularity of rhythm. They include approximate entropy ($ApEn$)[50], sample entropy ($SampEn$)[51], corrected conditional entropy (CCE) [52] and measurements of Shannon Entropy involving some form of "coarse graining" of the data; notable among the last category is the use of symbolic dynamics ($SymDyn$)[53]. Most of these will be described in the following sections.

A measure of regularity has to have two principal characteristics: it must be self consistent - i.e. for a given patient it must yield the same results during one period as it does during another (provided that there are no physiological changes) and it must differentiate between rhythms. Entropy appears to offer these characteristics.

1.4.3. Shannon Entropy, *ShanEnt*

Shannon entropy is a concept of information theory which measures the uncertainty associated with a random variable. It was introduced by Shannon in his "Mathematical theory of communication" [54] but has been used extensively in other fields.

Shannon entropy is defined as:

$$H(x) = -\sum_{i=1}^{n} p(x_i) \log_b(p(x_i)) \tag{1.2}$$

where $p(x_i)$ is the probability mass function of x_i (effectively the probability of the state i occurring from among all possible states) and b defines the units of measurement: bits ($b = 2$), nats ($b = e$) or dits ($b = 10$).

By definition if $p(x_i) = 0$ then

$$0 \log_b 0 \equiv 0 \tag{1.3}$$

Which is consistent with the limit

$$\lim_{p \to 0} p \log_b p = 0$$

Shannon entropy forms the basis of all measures of entropy which have been used in assessing R-R variability [50, 51, 53, 55–57].

1.4.4. Entropy in symbolic dynamics

Symbolic dynamics is a means of coarse graining a system. In essence it involves modelling a smoothly varying dynamic system by discrete sequences of abstract symbols. Each symbol corresponds to a state of the system as defined by the discrete model. The sequence of symbols thus represents a coarse description of the original system.

Hao in his 1991 paper [55] described the use of symbolic dynamics to characterise complexity and suggested that it could be used to establish a measure of entropy in complex

systems. This work was taken into the cardiac domain by Voss et al. [56] who used symbolic dynamics as a measure of non-linear dynamics in assessing heart rate variability in 26 patients post myocardial infarction (MI). He found that the use of non-linear dynamic measures improved the discrimination of patients with high risk of developing malignant ventricular arrhythmia. The technique was further developed by Palazzolo et al. [53] who used it to assess entropy of heart rate variation in dogs, suggesting that in SR entropy reflected the parasympathetic modulation of heart rate. No further work appears to have been done using symbolic dynamics in the investigation of heart rate variability.

1.4.5. Approximate entropy (*ApEn*) and Sample entropy (*SampEn*)

Given a sequence of n real numbers (e.g. a sequence of R-R intervals) then, depending on the precision of measurement, it is possible that no single number in the sequence occurs more than once.

Pincus describes a measure of regularity, based on the *Kolmogorov entropy* (a theoretical measure of the rate of generation of new information) which he calls *Approximate entropy* (*ApEn*) [50, 57, 58]. This is based on the conditional probability that a sequence of m events which repeats B times in the complete series of N events also repeats when the length of the sequence is increased by one. A sequence is considered to repeat if each member of the sequence falls within a tolerance, r, of the corresponding member of the initial sequence.

The *ApEn* process counts each sequence as matching itself. This overcomes the problem which would occur if there were no other matching sequences because $ln(0)$ is undefined; however, part of the underlying theory of information entropy as described by Shannon [54] is that entropy is an indicator of the rate of information production. Since no new information is added by including self-matches this measure of entropy could be considered false; although a change in *ApEn* would indicate a change in the rate of information production. In the situation where there are no other matches *ApEn* is found to be 1, as it would be if every pair matched (see §2.10.3 for a mathematical treatment of *ApEn*). Thus *ApEn* is biased to give a high estimate of entropy, and the bias will be more pronounced the smaller N is (and hence the fewer matches there will be). It can also be shown [51] that *ApEn* is not consistent over all conditions; it is

possible that when comparing two samples one may have a higher entropy under one set of (m,r,N) conditions while the other may have a higher entropy under a different set of (m,r,N) conditions.

To overcome this bias Richman and Moorman [51] suggest a related measure of entropy which they call "Sample entropy" (*SampEn*). This has two substantive differences from *ApEn*: instead of being the average of logarithms of the conditional probability it is a logarithm of the average of conditional probabilities. The i^{th} conditional probability is also calculated differently.

Richman and Moorman showed that while there is still a very small bias in *SampEn*, particularly for very low values of N ($1 < N \leq 100$), there is considerably better agreement between *SampEn* and predicted theoretical values. Additionally, except at very low N, the measure shows both relative consistency (results between different patients vary as expected) and self-consistency (serial measurements on the same patient offer very similar measures of *SampEn*).

Both *ApEn* and *SampEn* are statistical estimates over N of underlying parameters which should be independent of sample length. However the approximation has been shown to be reasonable for *ApEn* for $N > 10^m$ to 30^m while for *SampEn* the estimate should be reasonable for much lower values ($N > 100$).

Both of these statistics are, in practice, a "family" of statistics with each member of the family being dependent on a different choice of r and m. With decreasing r the tolerance in determining matches will decrease which should result in lower conditional probability and hence lower *SampEn* or *ApEn*. Similarly increasing m will decrease the potential number of matches since matches have to be longer resulting in lower conditional probabilities and lower *SampEn* and *ApEn*. True entropy in either of these parameters is defined in the limits $r \to 0, m \to \infty$ and as $N \to \infty$. Thus we are clearly left with a question, namely: how do we select parameters for m and r?

Most authors seem to use values of r between 0.1 and 0.25. Lake et al. [59] proposed that the best value of r can be selected by choosing to minimise the maximum relative error of *SampEn* and conditional probability from which *SampEn* is calculated for the population.

1.5. Radionuclide ventriculography (RNVG)

Equilibrium radionuclide ventriculography (RNVG) is a nuclear medicine technique for assessing cardiac function. It was first established in the late 1970s [60] growing out of first pass radionuclide ventriculography which was developed in the early 1970s (e.g. Parker, Secker-Walker et al. 1972 [61]). Since then, RNVG has been extensively used in the assessment of cardiac function.

1.5.1. Basic Principles

Red blood cells are labelled with ^{99m}Tc- a 140 keV gamma-ray emitting radionuclide - and the position of detected gamma rays is measured using a gamma camera to produce an image of the distribution of labelled red blood cells. The highest concentration of red blood cells occurs in the heart which thus dominates the image, although in some patients red blood cells in the liver can make a significant contribution to the image.

The number of detected gamma rays is, to a very good approximation, proportional to the number of red cells in a given volume. Thus, after a few minutes during which the distribution of labelled red cells equilibrates, the number of counts in, say, the left ventricle is proportional to the volume of the ventricle [62] (ignoring factors such as attenuation and scatter).

If we consider a single heart beat, the volume of blood in the ventricle changes over the cardiac cycle from a maximum at end-diastole to a minimum at end-systole returning to a new maximum at end-diastole again. By dividing the beat into a number of smaller parts and summing the total number of detected γ photons over each of the parts (effectively integrating the counts over the duration of each part) we can get an assessment of volume change with time over the cardiac cycle. This volume-time curve is distinctive and, as discussed in §1.1.5, various characteristics of the curve have been shown to have clinical significance. Of particular interest is the Ejection Fraction (EF), which has been shown, in SR, to have good prognostic power (see §1.1.5).

Nuclear medicine images are built up over time as gamma emissions are detected by the camera. The sensitivity of the imaging system and the activity of the source is such that a comparatively long acquisition time is needed (typically > 30 s) for an image to be acquired with a sufficiently high signal to noise ratio. This is much longer than

any single R-R interval and images are built up by acquiring data over many beats. A representative image of an average beat is created by dividing each beat into several equivalent parts (typically between 16 and 32) and summing them together in a process known as gating.

1.5.2. Gating

Gating the image allows the end-diastolic and end-systolic points to be determined. This is achieved by recording the ECG signal during imaging. Each beat (determined as being from the start of one R wave to the start of the next on the ECG, the R-R interval) can then be divided into a given number of segments (usually 16, 24 or 32) using either fixed or variable time formatting. The counts from equivalent sections in each beat are added together to create frames of a dynamic image which represent different stages of an average beat. The method of dividing each beat (variable or fixed time) determines the form that averaging takes. Beats can be excluded depending on the *beat selection criteria*.

Fixed time formatting

Fixed time formatting is also known as MUGA (MUltiple Gated Acquisition). An "average" beat length is determined and this is divided into the given number of segments to give a fixed duration for each segment. Counts which fall within each time segment are added together to give an average beat. Blurring occurs throughout the cardiac cycle but particularly in the diastolic phase because small changes in the duration of a beat are amplified when beats are added together (see curve D in Figure 1.10). The distortions introduced are generally temporal.

Variable time formatting

Each beat is divided into the given number of segments. Corresponding segments from each beat are then added together to give an average beat. There is a significant blurring effect if the ratio of systolic time to diastolic time for each beat is not approximately constant (see curve E in Figure 1.10). The distortions introduced are generally volumetric.

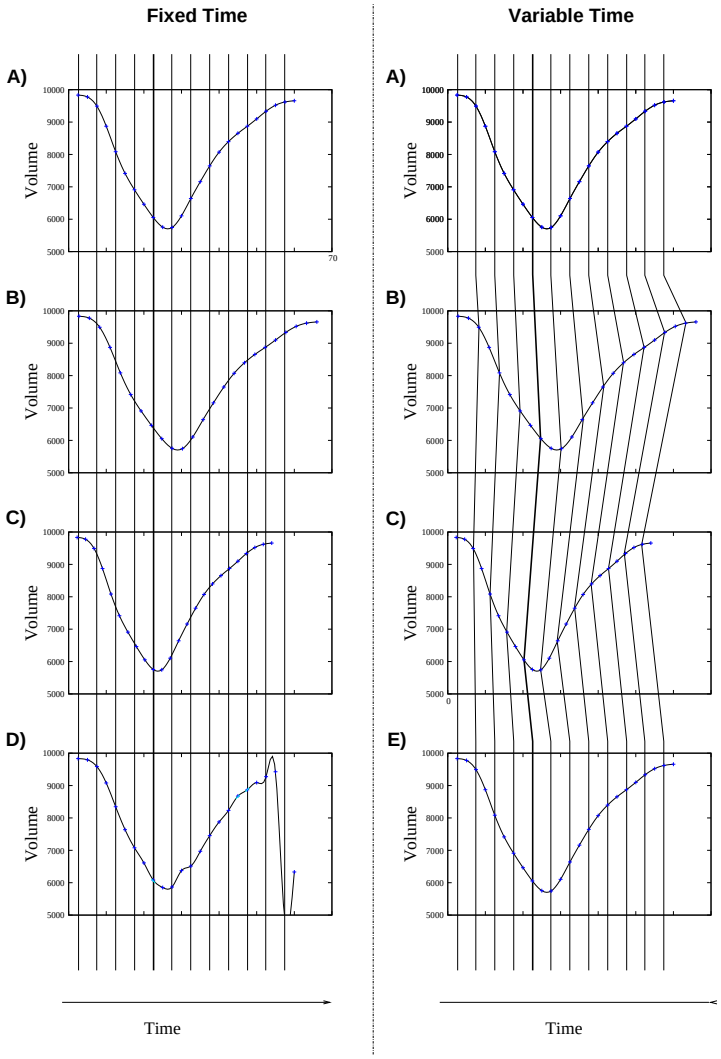


Figure 1.10.: Showing the difference between fixed and variable time processing. Vertical lines (of which one has been thickened to make it easier to follow) show contributing parts of theoretical frames. Curves A, B and C (on both sides of the diagram) show theoretical contributing curves from three single beats. Curves D and E show the representative beat created using fixed and variable time formatting respectively from curves A, B and C. Fixed time formatting introduces substantial distortion (curve D). Although in this example variable time formatting appears not to distort the curve (curve E), if there are volumetric changes these will cause distortions.

1.5.3. Distinctiveness

RNVG has a number of characteristics which uniquely distinguish it from other techniques for assessing cardiac function:

1. The image produced is an average picture of cardiac function over a large number of beats.

2. The image provides a largely geometrically independent assessment of global function.

3. Changes in activity distribution with time show changes in the fluid volume rather than in the edge of the ventricle. This makes it suitable for pixel by pixel amplitude and phase (Fourier harmonic) analysis, showing the relative time of contraction of regional segments of the left ventricle.

1.5.4. Developments

Since its initial conception a number of developments have broadened the scope of the RNVG, including phase analysis [63] and the development of SPECT [64]; more recent developments have sought to combine these [65].

1.5.5. List-mode Acquisition

List-mode is an alternative means of acquiring image data which allows data to be post-formatted in multiple ways, using differently defined criteria. While an image is built up by summing events detected in each pixel within a defined frame, a list-mode file is a one-dimensional string of data in which the position and time of every event, whether it be a scintillation detection, an ECG pulse or some other event marker, is recorded. Data are formatted into image data by combining this information in defined ways. Thus a static image can be created by summing scintillation events which occur in each pixel, without regard to timing or other event markers (top line in Figure 1.11). A dynamic image is created by summing scintillation events which occur in each pixel between given timing markers for sequential sets of timing markers (middle line in Figure 1.11). A gated image is created by summing scintillation events which occur in each pixel in corresponding

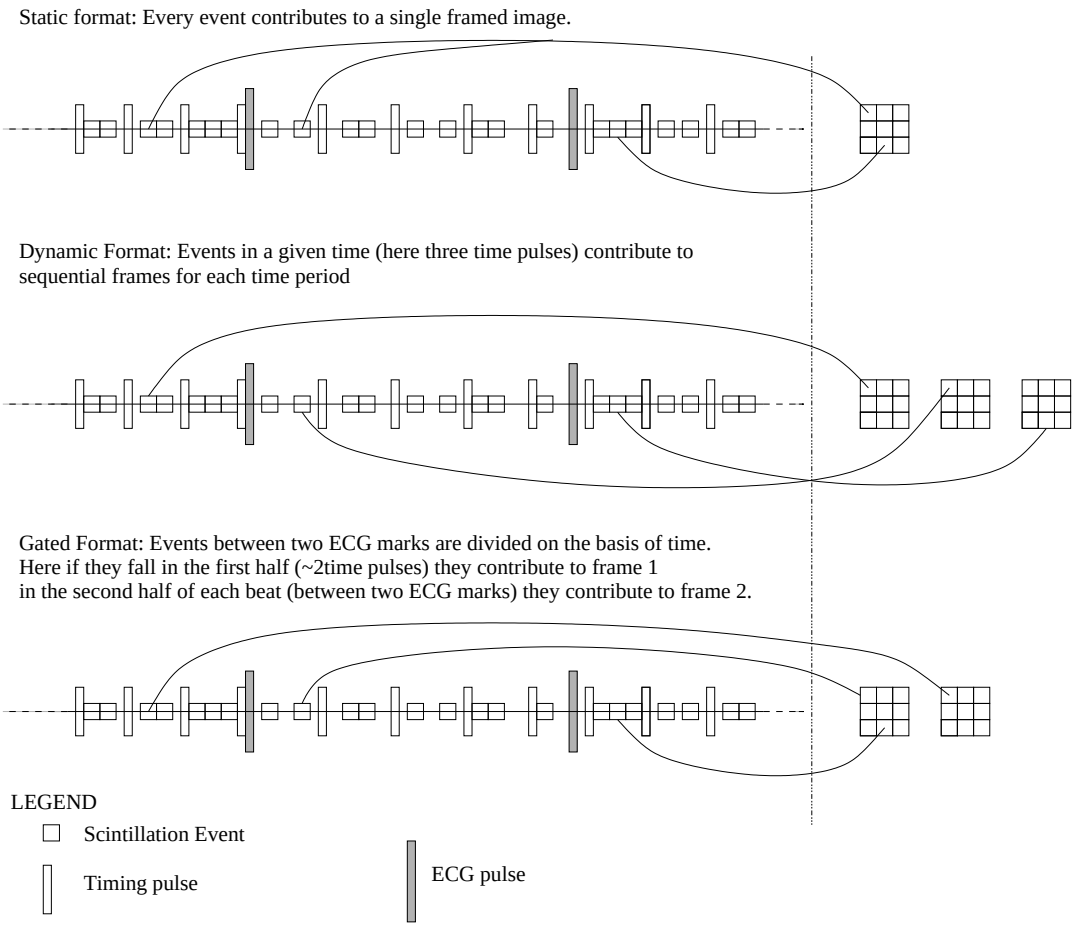


Figure 1.11.: Showing how list-mode files can be formatted into multiple different file types. A symbolic representation of the list-mode file is given on the left. On the right is a representation of frames of an image. A static image consists of a single frame. A dynamic image is a set of sequential frames created without reference to ECG pulse (gating marker). A gated image is an amalgamation of events which occur at equivalent points in time relative to a set of given gating markers, in this case the ECG pulse. The list-mode file has regular timing pulses which define the temporal resolution. Scintillation events are labelled with the position of the event but time is given by the timing pulse. ECG gating markers define the time of each R-R interval.

parts between each set of gating markers - in this case ECG pulses (bottom line in Figure 1.11).

Acquiring in list-mode allows both rhythm data (in the form of the temporal location of R waves) and image data (in the form of the temporal and spatial location of a detected scintillation event) to be acquired in the same file in a much more complete way than if the image is built up in real time.

1.5.6. Ejection Fraction (EF)

In any given heart beat the volume of the ventricle changes from a maximum at end-diastole of the preceding beat to a minimum at end-systole, returning to a maximum at end-diastole. By measuring the total count at end-diastole and the total count at end-systole the ejection fraction (change in volume as a proportion of the total volume of the ventricle) can be determined.

Ejection Fraction (EF) can be calculated, as % of end-diastolic count, from an RNVG from

$$EF = \frac{(C_{ed} - C_{bd}) - (C_{es} - C_{bs})}{(C_{ed} - C_{bd})} \times 100 \tag{1.4}$$

Where:

$\boldsymbol{C_{ed}}$**:** Counts in ventricle at end-diastole.

$\boldsymbol{C_{es}}$**:** Counts in ventricle at end-systole.

$\boldsymbol{C_{bd}}$**:** Counts in background region at end-diastole.

$\boldsymbol{C_{bs}}$**:** Counts in background region at end-systole.

There is ongoing debate about where background regions should be positioned relative to the myocardium but in most cases the same background is used at both end-systole and end-diastole in which case, the equation simplifies to:

$$EF = \frac{(C_{ed} - C_{es})}{(C_{ed} - C_{bd})} \times 100 \tag{1.5}$$

Two different techniques can be used to determine C_{ed} and C_{es}. A single region of interest technique, as used in this study, outlines the ventricle at end-diastole and the change of counts *within this region* is used to determine the minimum, end-systolic, point. In a dual region of interest technique separate regions are used to define the end-diastolic volume and the end-systolic volume. There are advantages and disadvantages to both techniques and these are explored in greater detail in the discussion (§8.3.1).

1.6. Assessing ventricular response to beat-to-beat variation in AF

The relationship between ventricular systolic function and R-R variation has been investigated by a number of authors. Schneider et al. [66] and Gosselink et al. [67] used a gamma probe to investigate beat-to-beat variation in 18 and 14 patients in AF respectively. By using a gamma probe they were able to look at changes on a beat-to-beat basis without averaging over multiple beats.

Schneider found that there was good agreement between mean LVEF, derived using the gamma probe and LVEF measured using RNVG. He demonstrated that in the probe studies LVEF was dependent on the relative end-diastolic volume (EDV) and on multiple preceding R-R intervals, concluding that a single value for LVEF does not adequately characterise LV function in AF.

Gosselink found that in patients with non-valvular chronic AF there was a positive relation between LVEF and preceding R-R interval and proposed a model which included EDV and pre-preceding beat length to approximate EF in any one beat. He suggested that the contribution of the Frank-Starling mechanism remains in some doubt, particularly given that he found a significant negative correlation between LVEF and the pre-preceding beat length. He and several other authors [68] attribute this agreement to postextrasystolic potentiation (which suggests that contractions are greater than normal following a weaker beat) or, possibly, to low afterload [69] (after a short beat only a small amount of blood will be ejected and consequently there will be lower aortic impedance during the current beat).

Tomotsugu et al. [70] used echocardiography to investigate the relationship between several, principally diastolic, left ventricular functional parameters and the preceding R-R intervals. He showed that in dogs there is a positive relationship between EDV and R-R interval in the same beat and consequently a positive relationship between EDV and peak LV systolic pressure. Tomotsugu concluded that LV diastolic function in individual beats in AF depends strongly on peak LV systolic pressure and hence that the principal advantage of a slower rhythm is that it promotes higher peak systolic pressure and greater LV relaxation.

Tanabe et al. [71], using the end-systolic pressure/volume ratio as an index of contractility, suggested that beat-to-beat changes in contractility in AF could be estimated by

the ratio of preceding to pre-preceding R-R interval, and that the pressure/volume ratio correlated positively with preceding R-R interval and negatively with pre-preceding R-R interval in both patients with depressed as well as preserved contractility.

These studies suggest that there is a definable relationship between preceding R-R interval and measured LVEF and that this may well be related to the Frank-Starling mechanism.

1.6.1. Modalities

Ventricular function is variously assessed using echocardiography, radionuclide ventriculography, gated myocardial perfusion SPECT, magnetic resonance imaging, cardiac CT and contrast angiography. While each of these modalities have different advantages and disadvantages they have in common one key fact: they are each dependent on regular SR. The assumption is made that the cycle over a representative beat, however that is constructed, is indicative of cardiac function over every other beat. This fundamental assumption is challenged in the presence of AF. This will be explored in more detail in §8.4 but in general results regarding R-R dependence for any one modality will be broadly applicable to other modalities.

This study concentrates on radionuclide ventriculography. RNVG has been chosen as the vehicle for this exploration principally because it is independent of geometry. Additionally it is readily available, applicable in almost all patients, non invasive and based on multiple beats. In list-mode RNVG yields data on both temporal and volumetric changes from beat-to-beat and as a result the well defined beat sequence it offers is particularly suitable for retrospective analysis.

1.7. The Hypotheses

The hypotheses of this thesis can be summarised in the following statements:

1. Beat-to-beat fluctuations in R-R interval are reflected in beat-to-beat changes in cardiac function, consistent with Frank-Starling's law of the heart: the greater the fluctuations, the greater the variation in function.

2. A variation in function will be seen in SR but will be much more pronounced in AF where the R-R fluctuation is much greater.

3. The duration of the preceding R-R interval has a substantive effect on measures of function, in particular LVEF, both in SR and AF.

4. AF can be reliably described using indices of rhythm which are also applicable to SR.

5. Measures of rhythm will have a predictive relationship with measures of function.

6. Measures of rhythm and function in AF can be shown to have clinical utility.

By acquiring list-mode RNVG data and formatting it to create an R-R interval stream and different images depending on the beats included in creating them, it is possible to investigate these hypotheses in a moderately large patient sample. The results of this wider study can then be investigated for their diagnostic / prognostic power in a small, but complex, clinical study.

Chapter 2.

Methods: Describing Rhythm

Summary

In which the methods which have been used to quantify rhythm are described. These include linear (time domain) measures of heart rate variability, entropy, and measures derived from the Poincaré plot. A description of the rhythm review process is also included as is a short discussion of some of the statistical techniques which will be used in the study.

2.1. Introduction

Much of the focus of this thesis is on assessing functional changes with heart rate variability, particularly in AF but also in SR.

While a considerable amount of work has been done on assessing heart rate variability in SR, little work has been done on variability in AF. Is it possible to define a quantitative

measure, or series of measures that in AF, "normally described simply as irregularly irregular", would allow comparison of one rhythm against another?

The traditional linear indices of heart rate variability used in SR offer a suitable starting place for the investigation of rhythm in AF; however, there are other measures, notably entropy and some measures linked to the Poincaré plot, which may provide useful additional descriptors.

The following describes the investigations undertaken to determine whether any of these measures provide useful information in the context of AF while corroborating some of the findings in SR.

2.2. Patient selection

Radionuclide ventriculograms were acquired in list-mode format for $\sim$ 400 patients in AF and $\sim$ 400 patients in SR. Patients were selected prospectively from those patients referred to the Department of Nuclear Cardiology at Glasgow Royal Infirmary for routine investigation either of myocardial perfusion (MPI) with radionuclide ventriculography (RNVG) or simply for RNVG.

Initially the only criteria which were applied to the selection of patients were that the patient should be clearly in either SR or AF and that the rhythm should have been maintained for the duration of the investigation. Patients in AF also had to be willing and able to have a slightly longer investigation as routine scanning times were increased if the patient was in AF (see §2.5.2).

One year into the data collection a preliminary analysis of the data found that in the SR group there was a predominance of patients with approximately normal LVEF and patient selection criteria was modified to favour those patients who, from the scan request card, seemed likely to have poorer ejection fraction (principally patients with known ischaemic heart disease including previous myocardial infarction).

2.3. Ethics

Preparatory to starting this study, ethics approval was sought in October 2006 from the *Glasgow Royal Infirmary local research ethics committee* under the title "Developments in radionuclide assessment of ventricular function" (ref. 06/S070484). The request was granted in March 2007.

The ethics application, which was described as a pilot study and was fairly broad in detail, sought permission to use any radionuclide ventriculogram and the associated patient data, acquired in the course of routine diagnostic imaging between January 2002 and December 2008, extended for this study to December 2009. Data collected would be anonymized, randomised if necessary, and used to investigate a variety of different conditions including AF, diastolic function and regional wall motion.

The application included the following statement: *"While the study must have clinical relevance, the principal area of interest is in the physics and physiology involved. Further study may be required to investigate the clinical significance of findings."* Thus the main focus of the study described in this thesis is on how the physical and physiological mechanisms involved in AF affect imaging and the quantitative results derived from it.

2.4. Summary characteristics of patients

Although patients were initially divided into two groups, AF and SR, a review of the rhythms, described in §2.6, found that some of the pre-defined rhythms required reclassification. Once this had been done the final rhythm groups consisted of:

- 375 patients in AF
- 396 patients in SR
- 5 patients with atrial flutter
- 7 patients described as having "paced AF"
- 12 patients whose rhythm was uncertain
- 3 patients for whom the data was unusable

	SR		AF	
	Total	With Perf.	Total	With Perf.
Total Studies	396	254	375	252
"No significant perfusion abnormality detected" in perfusion report	–	67	–	34
"MI" in blood pool report	75	35	72	41
"Negative ETT" in Perfusion ETT report	–	107	–	47
MI (from questionnaire)	107	61	113	73
PCI (from questionnaire)	49	37	28	22
CABG (from questionnaire)	43	20	51	29
HBP (from questionnaire)	165	122	187	131
PVD (from questionnaire)	42	23	47	36
CVA/TIA (from questionnaire)	54	35	67	56
Age range (years)	17 - 86	36 - 85	19 - 86	33 - 86
Mean age (years)	59	59	66	68
Normal perfusion, function and ETT	-	28	-	2

Table 2.1.: Patient summary characteristics after ECG review. Numbers are given for the whole data-set and for those patients who also attended for perfusion imaging.

This study investigated only those patients in definite AF or SR and although many of the parameters investigated were calculated for the other patients they have not been included in the subsequent analysis.

The patients involved in the study had a broad range of pathologies. Summary clinical characteristics for the patients whose investigations were used in the study are shown in Table 2.1. These characteristics were assessed from the standard pre-test assessment based on information supplied on the scan request and by the patient before the start of routine investigation in the department as well as from the results of MPI and ETT investigations undertaken at the time of the RNVG. Reference was not made to the patient notes.

As part of the pre-exam assessment patients are asked to supply a list of drugs which they were taking. A summary of the principal drugs and drug types is shown in Table 2.2.

The analysis which was undertaken in this study did not account for the medical therapy which patients were on because of the potential extent of such an investigation. A sub-group analysis which considered pathology and interventional treatment was performed (see §2.7.1).

Drug therapy	SR	AF
Total Patients	396	375
ACE	85 (21%)	117 (31%)
Anti-ulcer	118 (30%)	108 (29%)
ARB	33 (8%)	40 (11%)
Aspirin	241 (61%)	133 (35%)
β-blocker	175 (44%)	218 (58%)
Ca channel antagonist	80 (20%)	92 (25%)
Clopidogrel	52 (13%)	21 (6%)
Digoxin	19 (5%)	154 (41%)
Statin	232 (59%)	216 (58%)
Oral Nitrate	120 (30%)	99 (26%)
Warfarin	28 (7%)	248 (66%)

Table 2.2.: Summary of drug therapy for patients in SR and AF. Percentages give the proportion of patients with that rhythm on the given therapy.

2.4.1. Four patients

Unlike many other sciences, clinical science is curious because we tend to study populations and extrapolate results for an individual patient from the results found for the population. Yet these results will often not be represented in an individual.

Four patients were selected for use as individual examples throughout this thesis, two in AF and two in SR. The example patients were selected with the following criteria: one for each rhythm group was selected because they exhibited the most extreme variations in measured ejection fraction: patient *A1*, in AF, and patient *S1*, in SR. The other two patients (*A2* in AF, and *S2* in SR) were selected at random from the subgroup of patients for whom the minimum ejection fraction (measured in all the ways described in §4.3) was normal. Poincaré plots for patients *A2* and *S2* have already been shown in the introduction (§1.3.2).

The characteristics of these patients are summarised below:

Patient *A1*

66 year old female in AF with known previous MI, peripheral vascular disease and mitral valve regurgitation. She was referred to the department for MPI to assess the degree of ischaemia following her MI. Her drug therapy included: quinine, PPI (proton pump inhibitor), statin, Adcal, warfarin, Spironolactone, Furosemide and Digoxin.

During her positive exercise stress testing she managed 150 s of exercise on the bike at 50 W stopping with breathlessness. Heart rate changed from 57 bpm to 170 bpm; blood pressure from 138/65 to 162/82. Her ECG changed on exercise from showing infero-lateral ST depression to > 2 mm ST depression inferiorly and anteriorly.

Her thallium scan was reported as showing a small to moderate area of reversibility in the territory supplied by the left anterior descending (LAD) artery while the blood pool was reported as showing overall normal LV ($> 40\%$) and good RV ($> 30\%$) EF.

Patient *A2*

67 year old male in AF with known previous non-ST elevation MI. An ex-smoker, he was referred to the department to investigate the extent of ischaemia, particularly in his right coronary artery (RCA).

His exercise stress test was reported as inconclusive although his ECG showed minor infero-lateral ST changes on exercise. His myocardial perfusion scan was reported as showing RCA disease with a small posterior MI and a small area of significant reversibility. His blood pool was reported as showing overall normal LV ($> 40\%$) and good RV ($> 30\%$) ejection fractions.

Patient *S1*

77 year old male in SR with known previous MI. He was referred to the department for blood pool (RNVG) imaging only, as part of a study which investigated the benefits of the β-blocker Bisoprolol.

His blood pool scan was reported as showing overall moderate ($> 20\%$) LV and RV EFs which were poorer than on a previous occasion.

Time	Event	Patient state
On attendance	12-lead ECG followed by ETT	Potentially nervous
Immediately following ETT	Perfusion imaging on stress	Recovering from exercise
Three hours later	Perfusion imaging at rest	Relaxed
1/2 hour later	RNVG	At rest having lain still for 1/2 hour.

Table 2.3.: Typical timings for a patient's attendance for MPI and RNVG in the department of Nuclear Cardiology, Glasgow Royal Infirmary.

Patient *S2*

60 year old female in SR. She was referred to the department following a troponin negative, unstable admission to hospital with chest pain to investigate whether she showed any evidence of ischaemia.

Her exercise stress test was negative and her perfusion imaging was reported as overall showing no significant perfusion abnormality. Her blood pool imaging was reported as showing normal ($> 40\%$) LV and good ($> 30\%$) RV ejection fraction.

2.5. Data acquisition and processing

Most patients who come to the department receive a two-part scan consisting of MPI and RNVG. Perfusion images are taken immediately following stress and again, three hours later, after redistribution while RNVG imaging immediately follows the redistribution images. A number of patients attend the department for RNVG only. The majority of the patients in this study came for both types of scan, not simply RNVG, thus for most patients a 12-lead ECG, acquired as part of the morning exercise test, was available. This was necessarily taken at a separate time from the acquisition of RNVG data although it was acquired on the same day. The typical timings for a patient's attendance are shown in Table 2.3.

RNVG data was acquired in list-mode format (see §1.5.5). This allows each beat to be separately recorded with the result that a list of successive R-R intervals can be produced for the duration of the acquisition. This data provided the principal data used in the analysis of rhythm, although clearly the data is very coarse in that it only provides R-R interval and none of the other information which might be obtained from a typical ECG.

Most patients also had a short ($\sim$ 20 s) 3-lead rhythm strip acquired during the acquisition itself. This could be used to confirm the rhythm at the time of the acquisition.

2.5.1. Stages of data acquisition and processing

Acquiring clinically useful data using RNVG is a multistage process each stage of which has several factors that influence the final outcome: producing relevant and reproducible numbers. The stages, in order, and their principal dependencies are:

1. Data acquisition
    a) Temporal resolution
    b) Spatial resolution
    c) Position
    d) Duration
    e) Zoom / Magnification
2. Data processing: create rhythm files (both R-R listings and R-R histograms)
    a) Temporal resolution
3. Data processing: create image files
    a) Beat selection
    b) Gating
    c) Zoom / Magnification
    d) Temporal resolution
    e) Spatial resolution
    f) Uniformity correction
4. Image processing: create curves
    a) Image manipulation (e.g. smoothing)
    b) Region of interest (ROI) morphology
5. Image analysis

6. Curve analysis
    a) Curve smoothing / filtering
    b) Curve limits
    c) Calculations

Several of these but most notably 3a and 3b have been identified as having particular significance to the assessment of ventricular function.

Image, as opposed to curve, analysis plays a significant role in the reporting of RNVG but until recently has largely involved qualitative assessment of the (relative) regional wall motion. More recently other techniques have been developed which allow quantitative assessment of the image (e.g. dissynchrony [72]) but these have not been addressed in this thesis.

A process flow diagram for steps 1 to 3 is shown in figure 2.1.

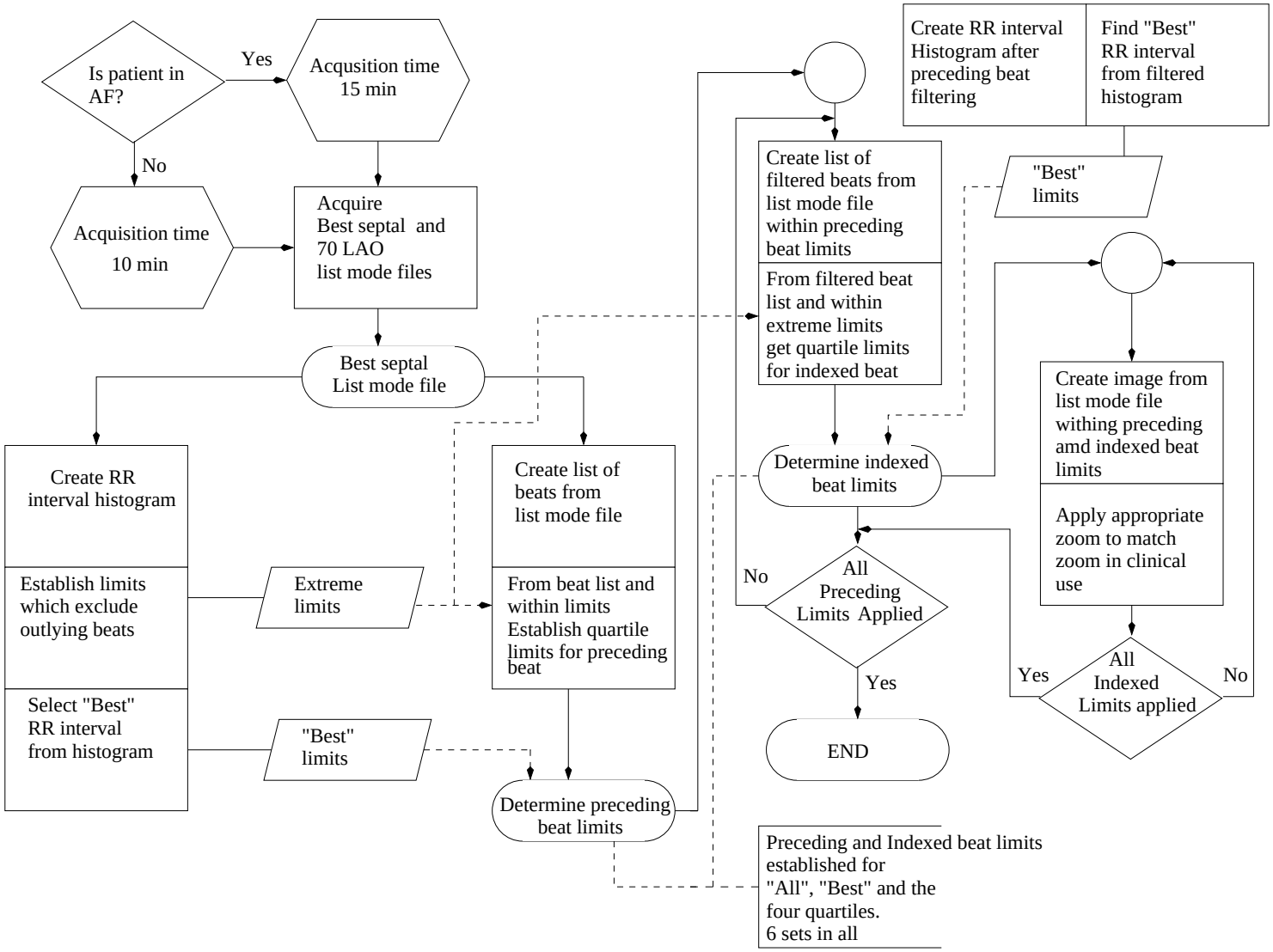


Figure 2.1.: Showing the processing algorithm by which each list-mode file was formatted into different images depending on preceding and indexed beat selection criteria.

2.5.2. Data acquisition

List-mode (see §1.5.5) files were acquired, for all patients, at best septal separation ($\sim$ 40 °) left anterior oblique (LAO) and 70 ° LAO projections. 40 ° LAO files were acquired for 15 min if the patient was in AF or for 10 min if the patient was in SR. All 70 ° LAO projections were acquired for 5 min. The longer acquisition time for patients in AF is used routinely in the department because beat selection techniques which are used can significantly reduce the amount of data composing the final, formatted, image; extending the acquisition time provides some compensation for this.

The 40 ° LAO list-mode files, with a temporal resolution of 100 µs, were formatted to create a histogram of acquired beat lengths for each file; each beat being allocated to the appropriate bin of width 25 ms.

2.5.3. Data processing: Rhythm data

In analysing rhythm in this study, both the 40 ° and 70 ° list-mode file were formatted to extract sequential lists of R-R intervals over the duration of each list-mode acquisition.

This provided two separate data-sets of varying duration for each patient at approximately the same time. These allow investigation of the reproducibility of different measures used to describe the rhythm; it should be noted that this technique only provides R-R durations, it is not a complete ECG. R-R intervals were measured to 100 µs precision, corresponding to the time resolution of the acquired list-mode files.

Text files listing each interval in the acquisition were created along with histograms of R-R intervals with 100 ms bins showing the frequency distribution of R-R intervals over the acquisition period. The histograms were used both in analysing rhythm and to define limits for beat selection which excluded outlying R-R intervals in subsequent formatting of the list-mode files to create images (see §4.3.2).

2.5.4. False triggering

The acquisition system has to discriminate the QRS complex from the rest of the three lead ECG waveform. This discrimination is built into the hardware of the acquisition system but it relies on the comparison between the ECG and a high pass filtered ECG

which removes noise and smaller wavelets within the ECG. This may be supplemented by an assessment of the gradient of the QRS complex to distinguish them from bigger T waves which are not removed by the high pass filter.

The acquisition system triggers either on the rising or falling QRS, and in our department is set to do so on the rising QRS.

In a normal ECG this should be enough to provide a clear beat length (including ectopic beats), however there will occasionally be ECGs where the T wave, particularly, can be mistaken for the QRS leading to false triggering which introduces false beat lengths into the R-R interval stream.

2.5.5. Limiting beats

Ectopic beats and "beats" due to false triggering can lead to distorted results both for function and rhythm analyses. To reduce the effect of this limits beyond which beats were excluded were determined by reviewing the beat histograms. This is discussed in greater detail in §4.3.2 and §5.2.2. In the following assessments of rhythm, where the beat sequence did not form part of the index, calculations were made on beats after the limits had been imposed, although comparison was also made with the results without limits. By excluding beats outwith the limits the assessment of rhythm more closely matches the assessments of function which will be made in Chapter 5.

2.6. ECG review

While an initial attempt was made to identify patients in SR or AF when the data was acquired, these groupings were reviewed to ensure that only patients in AF or SR were included. The review took two forms:

1. Review of the patients 12-lead ECG from their attendance in the morning. Where this was not available or there was some dubiety then the 3-lead rhythm strip taken in the afternoon was used.

2. Review of the Poincaré plot for that patient (see §2.9). This was done both to ensure that the pattern of the Poincaré plot matched the rhythm described in the ECG (there was a possibility that a patient with intermittent AF could have been

in AF during stress and SR at rest, or vice-versa) and to determine limits which would exclude any ectopic beats (regardless of aetiology) which might have been seen.

The full 12-lead ECGs and the associated Poincaré plot for patients in the AF group were reviewed in conjunction with an experienced cardiologist specialising in electrophysiology (Prof. Andrew Rankin). In addition to the rhythm and limits above or below which a beat was considered to be ectopic, for the patients in the SR group the author undertook a similar review. Where the rhythm was neither SR nor AF this was described (e.g. "ventricular pacing from a permanent pacemaker"), although the patient has been excluded from any subsequent analysis.

In AF, the ECG may show fine, high frequency, regular wavelets between R waves, known as *fibrillatory* waves. These are distinct from T or P waves (see §1.1.3) and occur multiply between R waves. The wavelets are indicative of atrial activity and suggest an element of coordinated activity within atrial muscle, with greater amplitude waves being indicative of a greater coordinated myocardial mass. Some authors [73–75] have used the amplitude of these wavelets to define AF as coarse or fine grained. As part of the review of ECG rhythm in AF a determination of graining was undertaken. If ECG tracings in leads V1 or II had fibrillatory waves with with an amplitude > 2 mm the rhythm was described as *coarse*; with amplitude < 1 mm rhythm was described as *fine* and anything in between was described as *medium* (with ECG tracing running at 10 mm/mV).

2.7. Analysis

Several different measures, ranging from standard heart rate variability measures such as mean R-R to more complex measures like entropy, were assessed. Each measure was assessed by investigating the difference between AF and SR, the reproducibility of results and the variation of results in different patient sub-groups.

The reproducibility of results was assessed by considering the variation, and correlation, between measures taken using the longer ($\sim 40\,^\circ$ LAO) and shorter ($\sim 70\,^\circ$ LAO) acquisitions. These two acquisitions were acquired separately but immediately sequentially and should thus represent the patient in the same state.

2.7.1. Patient subgroups

The variation of the measures was also assessed against several different patient subgroups:

- Ischaemic / Normally perfused. Determined from myocardial perfusion imaging (MPI) using ^{201}Tl as part of the patient's assessment in the department. The report included the phrase "No significant perfusion abnormality demonstrated", a standard phrase in the department.
- Patients with previous MI. Determined from the standard patient questionnaire given to each patient on attendance in the department.
- Patients with known HBP. Determined from the standard patient questionnaire.
- Patients with CABG or PCI. Determined from the standard patient questionnaire.
- Patients by age.
- LV function as defined by the LV ejection fraction assessed using all beats.
- Positive / Negative ETT. Patients who had had a positive or clearly negative exercise tolerance test (as part of their MPI). Inconclusive tests were excluded although borderline positive tests were considered to be positive for this analysis.
- "Pure" ECG: those patients who had no ectopic beats on ECG or Poincaré plot.
- For AF patients the "graining" of the rhythm.

2.7.2. Ectopic beats

Heart rate variability measures as described in §1.3.1 applied in SR typically exclude ectopic beats, regardless of their aetiology. Thus uncharacteristic R-R intervals which could potentially substantially affect an index (e.g. range measurements) are not included.

The aim of this part of the investigation was to determine whether there are indices which adequately describe heart rate variability in both AF and SR, with the ultimate goal of determining whether such indices can be used to explain some of the functional variation which is seen in AF.

Given a stream of R-R intervals from a patient in AF, with no record of the detailed morphology of the ECG, it is not possible to determine the aetiology of a single beat and it is possible that ectopic beats will have a similar duration to other beats in the distribution of beats in AF. This makes a generic rule by which such beats can be removed from the analysis unachievable.

Many of the indices investigated (see §2.9, §2.10) consider the variation over patterns of multiple beats and it is therefore unclear how a single beat should be removed.

For these reasons all beats were included in the analyses of rhythm which follow. In a very few cases this included beats which are clearly the result of technical faults (e.g. beats of duration 14s where the connection to the patient must have failed), but except in the determination of linear heart rate variability measures these will play only a minimal role in the overall assessment of any of the non-linear indices (entropy, Poincaré indices). Ectopic beats (and R-R intervals due to technical fault) will affect the standard, linear, time domain measures of heart rate variability (e.g. R-R range) and these were also calculated on the limited data (for details of how data was limited see §4.3.2).

2.8. Standard heart rate variability measures

As described in §1.3.1 there are several standard measures of heart rate variability in the time domain. These are typically measured after ectopic beats have been filtered out[1] [27]. By redefining the measures as being calculated with all R-R intervals, such that any beat regardless of its aetiology is included, it is theoretically possible to calculate comparable values for arrhythmia. In doing so we make the assumption that the length of the R-R sequence is sufficient to represent an arbitrarily longer sequence[2]. Calculations were also made for the standard measures after upper and lower limits had been applied to the acceptable beat criteria (see §2.7.2 for further discussion). The indices which were measured are: *Mean RR, RR range, SDRR, $RMSSD_{rr}$ and pRR50.*

An awk script (see appendix §A.1) was used to determine the following results from the R-R interval stream obtained from the list-mode files for each patient.

[1] The exclusion of ectopic beats from the R-R interval stream in SR is normally represented by referring to NN intervals (representing the normal R-R intervals selected out from the beat list).

[2] To avoid confusion the term "NN" is replaced with "RR" to indicate that all R-R intervals are included and that the measure is applied to an arrhythmia

Mean RR is simply the mean of included R-R intervals.

SDRR is the standard deviation (SD) of included R-R intervals.

RR range is the range (longest - shortest) of included R-R intervals.

RMSSD is the root mean square of the difference between one beat and the next of the included R-R intervals

pRR50 is the fraction of included R-R intervals for which the difference between one beat and the next differs by more than 50 ms.

Additionally the SD of R-R interval averaged over 5, 10 and 20 consecutive beats and the variation between SD of the average of 5 and the average of 20 beats was calculated.

The results were compared against each other and for differences between SR and AF.

2.9. Poincaré plots

Poincaré plots (see §1.3.2) were created from the R-R interval stream for each of the patients. This provided a qualitative means of assessing some of the non-linear characteristics of the rhythm of each patient.

Each Poincaré plot was reviewed both to ensure that the pattern was typical of the defined rhythm and to assess limits on the ectopic beats.

After a visual assessment of the Poincaré plots quantitative measures were sought to establish parameters which allow plots to be compared. Although a large number of potential indices have been suggested in the literature, consideration of these in the context of AF is necessary. The most commonly reported indices are based on fitting an ellipse to the data with the long axis aligned with the line of identity ($x = y$). The long (SD1) and short (SD2) axes of the ellipse providing information on the gross variability of time series data. However, Karmakar et al. [47] have shown that there is a mathematical relationship between SDRR and SD1 and SD2 which implies that there should be good correlation between them. This agrees with the findings, in one patient only, of Smith and Reynolds [76].

The results from these and other studies [38, 40, 43, 46] together with the shape of the Poincaré plot for AF suggested two promising measures to quantify the Poincaré plot: correlation and *compactness factor*. While there may be others these two were investigated in this study.

2.9.1. Correlation

The Poincaré plot displays the preceding against the indexed R-R interval (although this is normally described as being the indexed against the succeeding interval) and is suitable for regression analysis. A correlation coefficient can be determined which will give an indication of the degree to which one beat defines the next.

The correlation coefficient, r, was determined for the relationship between R_i and R_{i-1}. No assumptions were made about the line of best fit and the correlation coefficient was thus able to take any value between -1 and 1.

2.9.2. Compactness factor

The idea of compactness was introduced by Hnatkova et al. [46]. Although the detail of their calculation is unclear from their paper, the basic concept is explained.

If the maximum density of points on the Poincaré plot in increasing areas is plotted against area a *maximum density function* can be determined which shows the way that maximum density varies with area. For example a Poincaré plot which consists of a single point of high value will exhibit a *maximum density function* which decreases linearly with increasing area because the same total count is divided over an increasing area. By contrast the *maximum density function* for an absolutely uniform distribution will not change as the area is increased because the total count will increase proportionately with the area. Every Poincaré plot will have a *maximum density function* which falls somewhere between these two extremes and which is uniquely characteristic of that plot. Since there may be a substantial difference in the number of beats included from one patient to the next there is a need for normalisation. If each empirically derived function is normalised to the maximum density for that patient then the curves can be compared.

The area under the curve, the function integral, should provide a single figure measure, here called *compactness factor*, that is indicative of the spread of counts over the entire

Poincaré plot. In this measure, the more widely distributed the result the greater the *compactness factor*.

Hnatkova describes a technique which seems to look at every possible area size over every possible area position within the Poincaré plot. This is dependent on the resolution of points in the plot (Hnatkova used a resolution of 2 ms). It is also computationally extremely time consuming with the number of calculations increasing enormously with increasing resolution[3]. Hnatkova suggested there was an approximation which could be used to reduce the computation time but again the details were unclear.

A new algorithm was written to assess *compactness factor*. A substantial time saving can be achieved by requiring that the maximum count density for a smaller area must always be within the larger area in which the maximum count density was found. This is a reasonable assumption in a distribution in which each point in the x-axis is later reflected in the y-axis. Thus it is possible to start with an area equal to the largest resolution and search for the maximum density in areas of decreasing size only within the previous area (see Figure 2.2a). In practice it was found that due to rounding errors a more accurate conversion can be obtained if a small overlap is allowed. An example of this can be seen in the image. The algorithm can be made still faster by modifying the size of the step by which each area is moved in the search for an area of maximum density. This results in approximate values but should give a reasonable representation of the *maximum density function* - see Figure 2.2b. The integral of the function was then calculated by adding the product of the mean of two adjacent numbers and the difference between the two area sizes. The algorithm is shown in the script in appendix §A.2.

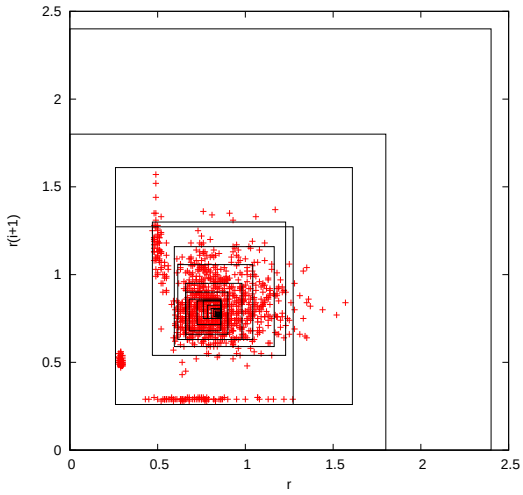
Hnatkova suggested that the integral should be against $\log(area)$ which gives a much greater prominence to smaller areas. In AF the larger areas are likely to have significant impact on the *maximum density function* and it is not clear that the integral should be against the log of the area. Both integrals were therefore calculated for comparison.

[3]To calculate every point in the function the number of calculations required increases as:

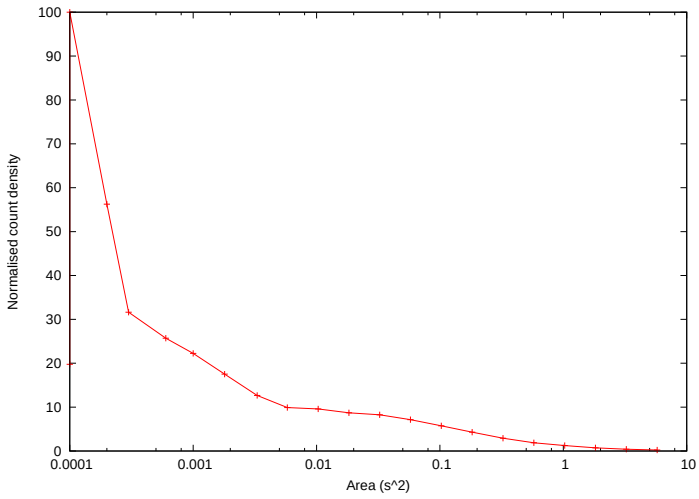
$$\sum_{n=1}^{N/2} n^2$$

where N is the resolution along one axis.

When it was investigated for this thesis changing the resolution from 50 ms to 10 ms increased the computation time from $\sim$ 10 s to $\sim$ 240 s



(a) Reducing areas



(b) Density changes

Figure 2.2.: Showing how *compactness factor* is calculated. (a) Shows the changing areas and their positions as each smaller area shows the position of maximum density within each larger area (a small overlap was permitted by the algorithm to prevent rounding errors). (b) The *maximum density function* showing the normalised maximum density as the size of area changes.

2.9.3. *Delta Poincaré plots*

The Delta Poincaré plot shows $(RR_i - RR_{i-1})$ against $(RR_{i-1} - RR_{i-2})$ (where RR_i is the i^{th} R-R interval). It offers a means of removing the correlation information from the Poincaré plot.

The *delta Poincaré plot* is divided into four quadrants about (0,0) XY axes. The four quadrants are (clockwise from top left):

A: (top left quadrant) a shorter beat (-ve X) followed by a longer beat (+ve Y).

B: (top right quadrant) a longer beat (+ve X) followed by a longer beat (+ve Y).

C: (lower right quadrant) a longer beat (+ve X) followed by a shorter beat (-ve Y).

D: (lower left quadrant) a shorter beat (-ve X) followed by a shorter beat (-ve Y).

If the variation between successive beats is truly random it is to be expected that the number of points in each quadrant will be the same since, within physiological limits, any beat should be followed with equal probability either by a longer beat or a shorter beat.

The number of points in each quadrant was calculated and a χ-squared test was used to test the distribution against an equal distribution in each quadrant. Where the distribution was found to be unequal (at a significance level of $p = 0.05$) the dominant quadrants were determined from the residuals.

Residuals, R, are calculated as:

$$R = \frac{(X - E)}{\sqrt{(X - E)}} \tag{2.1}$$

Where:

E is the expected value (in this case 1/4 of the total number of points)

X is the actual value

The residuals gives a measure of how far the actual value is from the expected value. Since we expect an equal number of counts, a positive residual (where the chi-squared test shows an unequal distribution) will show which values are dominating. Thus a single

positive residual with three negative residuals will demonstrate a quadrant is dominant. Similarly if two quadrants share the dominance then they will both be positive and if one quadrant is particularly weak it will have a sole negative value for the residual. Any form of bias shows the rhythm to have a degree of structure and to deviate from a random pattern.

Although the dominant quadrants describe rhythm in a very basic form they do not provide a quantifiable measure of rhythm change by which one rhythm can be compared against another. The *delta Poincaré plot* suggests a new quantitative measure that has been termed *swing*, which is the proportion of the beats which fall in quadrants "A" or "C" and therefore the proportion of beats in which a beat is followed by a longer beat, followed by a shorter beat or vice versa.

2.10. Entropy

As described in §1.4.2 there are several different measures of entropy which may be suitable as indices of regularity in assessing R-R rhythms. Three different measures were assessed. In increasing order of the information content of the index they are: Shannon entropy (*ShanEnt*), Shannon entropy using symbolic dynamics (*SymDyn*) and sample entropy (*SampEn*).

2.10.1. Shannon entropy (*ShanEnt*)

The Shannon entropy (see §1.4.3) is calculated from the R-R interval histogram - the frequency with which different ranges of R-R intervals occur using the equation:

$$H = -\sum_{i=1}^{n} \frac{b_i}{N} log(\frac{b_i}{N}) \tag{2.2}$$

where

b_i is the number of events in the i^{th} bin of n total bins.

N is the total number of events.

Clearly the value for entropy is dependent on the size and number of bins forming the R-R histogram: the greater the number of bins or the narrower the bin the greater the entropy.

Since entropy assessments are based on the number of possible states which a system can take, comparison between systems must consider the number of these states. It is unreasonable to compare the entropy of a system which can only take, say, two states with one which can take several million. The system with fewer states will necessarily have a lower entropy. This suggests that accurate comparison of the *ShanEnt* of the R-R variation in a patient study should require the same number of possible states, and therefore the same number of bins. Using equal numbers of bins, however, may result in bin-widths that vary dramatically from one patient to the next. This will be exaggerated where there are ectopic beats.

To investigate these factors the *ShanEnt* was calculated using both limited and unlimited data and both fixed bin widths (variable numbers of bins) and fixed bin numbers (variable bin width). Fixed bin-widths were set at 10 ms and 25 ms, while fixed bin numbers were set at 16 and 32. At 60 bpm (R-R interval: 1 s), 25 ms bins correspond to 40 bins while 10 ms bins correspond to 100 bins. Thus these selections provide a range of bin numbers while also offering measures of *ShanEnt* for the bin-widths used in assessing rhythm in the rest of this study (10 ms) and in the department generally (25 ms).

Histograms were created from the list of R-R intervals for each of these conditions and for each of these histograms *ShanEnt* was calculated using the Perl script shown in appendix §A.4.

The results were compared for AF and SR, for consistency between the two different acquisitions (at 40 ° and 70 °) and for the subgroups discussed above (see §2.7).

Combining basic R-R interval histograms with the standard equation for *ShanEnt* (equation 1.2) gives a basic assessment of entropy in terms of the frequency of occurrence of a given state (R-R interval); however, there is no information included in this calculation on sequence of intervals. Thus the sequence ABCCBCBAA will have the same entropy as the sequence AAABBBCCC, although there is considerably more regularity in the second sequence than in the first. Inclusion of sequential information in the calculation of entropy requires a more complicated model such as that provided by symbolic dynamics or in the calculation of *SampEn*.

2.10.2. Entropy of symbolic dynamics (*SymDyn*)

Symbolic dynamics in heart rate variability measures can be considered as means of quantifying the evolution of the Poincaré plot. The plot is divided into segments, typically by SD, and each segment labelled with a symbol. Each point in the plot is assigned the associated symbol in the order in which the points occur in time. This creates a string of symbols which can be analysed to determine the frequency with which patterns, "words", of varying length occur. The frequency information is then used to calculate the Shannon entropy for that frequency distribution.

The technique seems to offer two advantages over a simple assessment of *ShanEnt*: it establishes a well defined set of states for a system, in this case R-R variability, and therefore permits direct comparison of systems; it also incorporates information about the evolution of the system over time in a way in which a direct calculation of *ShanEnt* from the R-R histogram cannot. Thus *SymDyn* offers an increase in the complexity of the measure of entropy compared to *ShanEnt* of the R-R histogram

From the Poincaré plot for each patient symbolic dynamic sequences were established and "word" frequencies determined using a Perl script (see appendix §A.5).

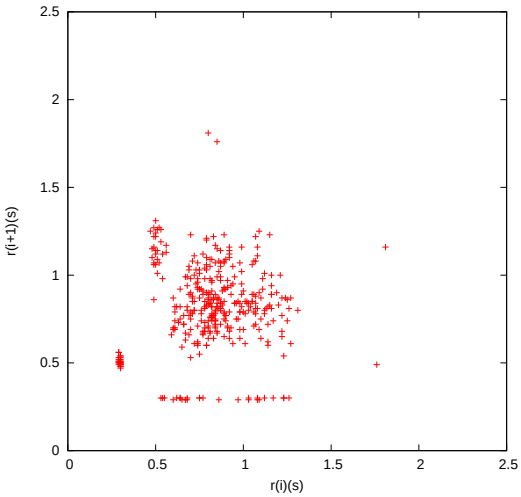
The process is most easily understood by considering an example.

Symbolic dynamic example. (Patient *A2*)

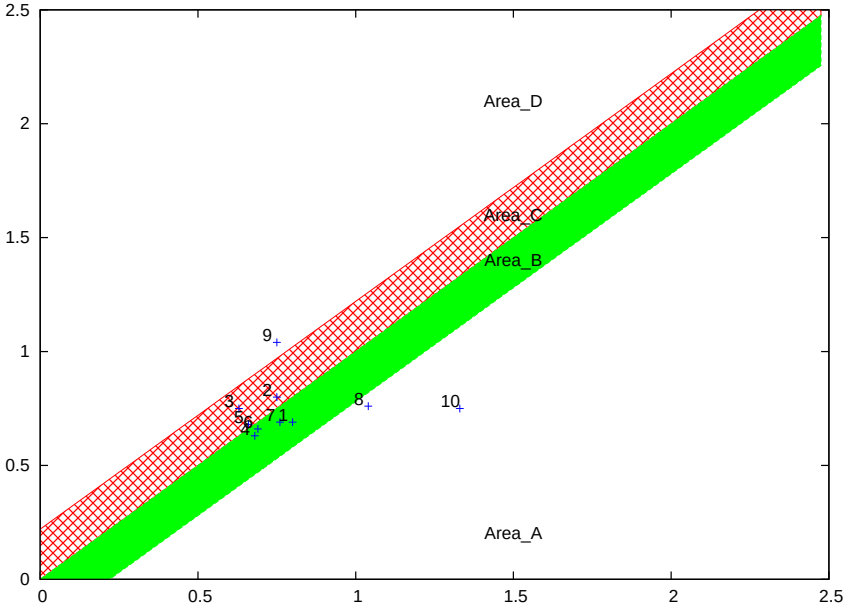
Figure 2.3 shows the Poincaré plot for a patient in AF. The patient had 1142 beats recorded over the 15 min acquisition, mean R-R interval of 0.69 s with a SD over all beats of 0.22 s.

The first 11 R-R intervals are: 0.69, 0.80, 0.75, 0.63, 0.68, 0.66, 0.69, 0.76, 1.04, 0.75 and 1.32.

Plotting these on a Poincaré plot, creates points with coordinates: (0.80, 0.69); (0.75, 0.80); (0.63, 0.75) etc. (see Figure 2.3b). Areas are then defined on the plot with area A being the area below and more than 1 SD away from the line of identity. Area B is the area between the line of identity and 1 SD less the line of identity. Area C is the area between the line of identity and the 1 SD above it and area D is the area greater than that. Each one of points with the coordinates given above correspond to areas: A,



(a) Complete plot



(b) First 10 points

Figure 2.3.: Poincaré plot of patient *A2* in AF. (a) shows the complete plot, (b) shows the first 10 points in the Poincaré plot and the four area bands created using 1 SD. These areas define the symbols attached to each point to create a symbolic dynamic sequence.

Word	Frequency	Word	Frequency	Word	Frequency	Word	Frequency
AAA	-	BAA	1	CAA	9	DAA	-
AAB	1	BAB	1	CAB	35	DAB	1
AAC	5	BAC	9	CAC	27	DAC	5
AAD	4	BAD	21	CAD	36	DAD	2
ABA	1	BBA	9	CBA	20	DBA	2
ABB	21	BBB	49	CBB	78	DBB	11
ABC	14	BBC	68	CBC	79	DBC	20
ABD	3	BBD	33	CBD	19	DBD	1
ACA	6	BCA	21	CCA	19	DCA	61
ACB	21	BCB	92	CCB	62	DCB	21
ACC	16	BCC	67	CCC	31	DCC	2
ACD	3	BCD	1	CCD	3	DCD	-
ADA	1	BDA	7	CDA	-	DDA	-
ADB	11	BDB	19	CDB	3	DDB	1
ADC	51	BDC	27	CDC	4	DDC	2
ADD	-	BDD	3	CDD	-	DDD	-

Table 2.4.: AF, symbolic dynamic 3 letter "word" frequency table.

B, C respectively. When the whole sequence is determined the first 60 points in that sequence are:

`BCCBCBBBBACCCBBBCBBDCBCBCACCBBBCBDACBBBCDBCBCBADCABCCBCBC...`

Choosing to consider 3 letter "words" finds the first four three letter "words" to be: BCC, CCB, CBC, BCB etc.

This process is applied to the complete 1141 letter sequence created from the 1142 beats acquired and the frequencies of every possible three letter word (given 4 possible letters - corresponding to areas defined by 1 SD) is calculated. This produces the frequency table shown in Table 2.4.

When the Shannon entropy is calculated for these frequencies using the equation for Shannon entropy (equation 2.2) this gives an entropy for this symbolic dynamic sequence of: 3.45 (for 1SD and 3 letter words). Other combinations, of word length and

number of letters / SDs, give:

- 3.75 (for 2SD and 3 letter words)
- 2.62 (for 2SD and 2 letter words)
- 2.40 (for 1SD and 2 letter words)

Analysis

It is clear that entropy of the symbolic dynamic sequence for any given R-R interval stream is dependent on the choice of word length, and the definition of areas on the Poincaré plot (number of letters).

In this investigation areas were defined using the SD of the R-R interval. Calculations of entropy of symbolic dynamic series, *SymDyn*, were made for "word" lengths of 2 and 3 letters and using areas defined by 1 SD (4 areas / letters) and by 1 and 2 SDs (6 areas / words). These parameters are the same as those used by Palazzolo et al. [53] in their paper investigating *SymDyn* in dogs. While other word lengths could be used, values of 2 and 3 correspond most closely to the parameters used in *SampEn* (§2.10.3) and thus allow comparison of the measures. Similarly any other division of the phase space could be used but SD offers an easily understood division and is self-normalising provided that beat distributions from one patient to another are similar.

Once entropy measurements were made for the four combinations of these parameters comparison was made of all four measures both for their ability to distinguish between SR and AF and for differences in the measures over the shorter (5 min) acquisition.

2.10.3. Sample entropy (*SampEn*)

As described in §1.4.5 *SampEn* is really a family of entropy measures with the family members defined by the two parameters r, the acceptance window for beats and m the number of additional beats for which a match within the acceptance window must be

found for a complete match to be accepted. This can be considered to be the number of beats which form a pattern which is tested for subsequent matches.

Mathematical basis

Mathematically, in *ApEn*, a sequence of events starting at point j is considered to match the initial sequence if

$$|u_{j+k} - u_{i+k}| \leq r \tag{2.3}$$

for $k = 0, 1, \ldots, m-1$ and $j = 0, 1, \ldots, N-m$.

The total number of such matches gives $B_i^m(r)$. The conditional probability used in *ApEn* (m,r,N) is defined as the proportion of these sequences ($B_i^m(r)$) for which it is also true that $|u_{j+m} - u_{i+m}| \leq r$ (call this A_i, so that the conditional probability is given by $A_i^m(r)/B_i^m(r)$ for the given (m, r, N) in this sequence).

Approximate entropy (*ApEn*) is defined as the negative of the average over $i = N-m+1$ of the natural log of this conditional probability:

$$ApEn`<(m, r, N) = -\frac{1}{(N-m+1)} \sum_{i=1}^{N-m+1} \ln\left(\frac{A_i^m(r)}{B_i^m(r)}\right) \tag{2.4}$$

The process of defining conditional probability is shown graphically in Figure 2.4.

Consider event u_i (marked on the figure as "u(i)"), which in this figure has coordinates [16,0.89], this is followed by event u_{i+1} [17,1.24] which is followed by event u_{i+2} [18,0.85]. Assuming $m = 2$ there are two other pairs of events (marked "u(j)" and "u(j`)") which fall within the acceptance bands (shown by the red and green bands) for $r = 0.1$. For the series of events starting at $u_i$, $B_i^2(0.1) = 3$. Of these three series of events only two match $u_{i+2}$: the one marked "u(i)" and the one marked "u(j`)", thus $A_i^2(0.1) = 2$.

This is done for sequences of m events for every recorded event; *ApEn* (m,r,N) is calculated from all of the resulting conditional probabilities ($A_i^m(r)/B_i^m(r)$).

As discussed in §1.4.5 *SampEn* was developed to overcome the biases introduced by *ApEn*. In *SampEn* conditional probability is calculated such that: $B_i^m(r)$ is the number

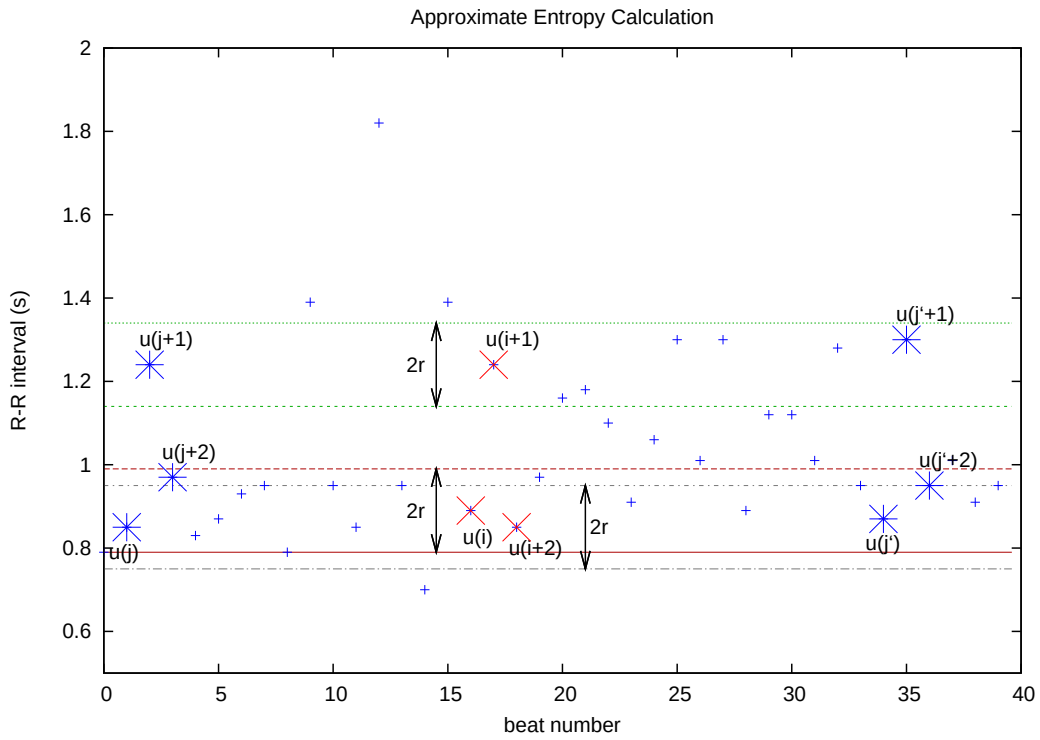


Figure 2.4.: How *ApEn* and *SampEn* are calculated. The three points in the centre of the figure (indexed i) define the sequence with the red, blue and grey lines defining the acceptance bands about each point respectively. In the first labelled sequence (indexed j) the first two points in the sequence match those of the initial sequence but the third point falls outside the band. In the second sequence (indexed j') all three points fall within the appropriate acceptance bands. The j sequence will only be considered a match if $m = 1$ while the j' sequence will match for $m = 1$ and $m = 2$.

of occurrences of the m length pattern in the complete series provided $i \neq j$ expressed as a fraction of $(N - m + 1)$, the total possible number of expressions of sequence of length m. Similarly $A_i^m(r)$ is the number of occurrences of the $m + 1$ length pattern in the complete series provided $i \neq j$ also expressed as a fraction of $(N - m + 1)$.

SampEn is then calculated as:

$$SampEn(m, r, N) = -ln\left(\frac{A^m(r)}{B^m(r)}\right) \tag{2.5}$$

where

$$A^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r) \tag{2.6}$$

And similarly with $B^m(r)$.

Normalisation:

By expressing the parameter r as a fraction of the SD of the data it is argued (e.g. by Lake et al. [59]) that *ApEn* and *SampEn* become scale-invariant; this seems to have become standard practice [77, 78].

The *sampen* [79] program (available from Physionet [80]) offers an option to normalise data by subtracting the mean from the data and then dividing the data by its SD. i.e.

$$x_i' = \frac{x_i - \bar{x}}{\sigma_x} \tag{2.7}$$

where

x_i is the i^{th} R-R interval

x' is the normalised R-R interval

$\bar{x}$ is the mean R-R interval

σ_x is the SD of the R-R interval.

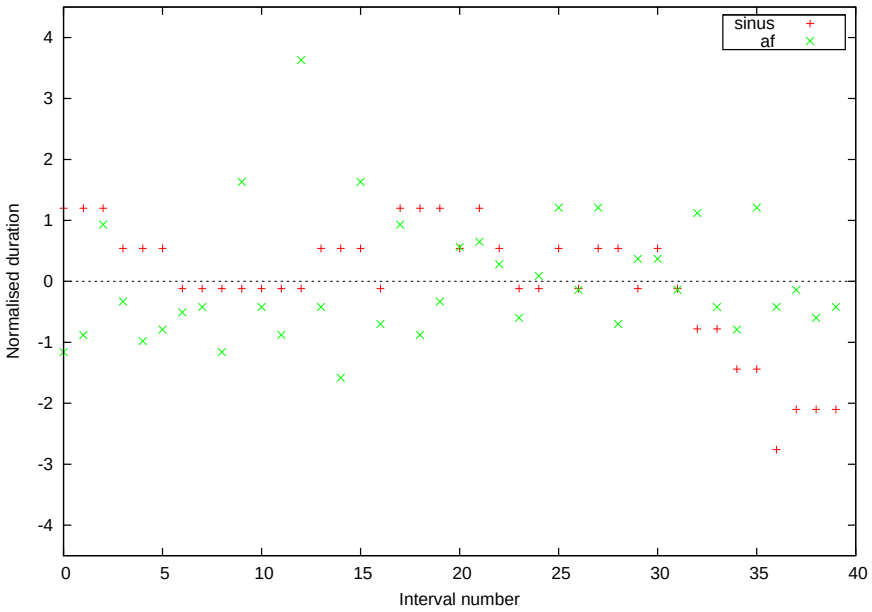


Figure 2.5.: Showing data "normalised" to the SD for AF and SR examples.

In this case each data point is modified by subtracting the mean from the data and then dividing the data by its SD. i.e.

$$u'_i = \frac{u_i - \bar{u}}{\sigma_u} \tag{2.8}$$

where

u_i is the i^{th} R-R interval

u' is the normalised R-R interval

$\bar{u}$ is the mean R-R interval

σ_u is the SD of the R-R intervals.

The effect of this is shown in Figure 2.5: each data point is now expressed in terms of the number of SDs, and the scale variations which led us to show the two samples on different scales have now been roughly eliminated.

Histogram: Given a histogram showing frequency of occurrence of each state, the probability of any particular state, i, occurring is given by:

$$p(x_i) = \frac{f(x_i)}{N} \tag{2.9}$$

Where N is the total number of events (x), and $f(x_i)$ is the frequency with which an event (x) in state i occurs.

Application

The selection of values for m and r is not clearly defined although most authors (generally working with SR) have typically used values of $m = 2$ and $r = 0.1 \ldots 0.25 \cdot SD$ [53, 58, 59, 77, 81], where the points have been normalised to the SD (see §2.10.3). Five different values of r were chosen to investigate whether normalisation provides better (more consistent / comparable) results over normalisation to the mean or whether using a fixed time interval provides the most consistent results. These were: $r = 100$ ms (which is comparable to the units into which the R-R histogram was divided in the later functional analysis), $r = 0.1\bar{RR}$ (one tenth of the mean), and $r = 0.02SD$, $r = 0.2SD$ and $r = 1SD$ which were chosen to cover the full range of possible R-R intervals. In practice a value of $r = 0.02SD$ when the mean SD of the R-R intervals (including both AF and SR) is 0.1 s suggests a typical window width of just 2 ms. This will be very close to having no allowable variation on the window width.

SampEn was measured for six values of $m = 0 \ldots 5$, with a value of 0 implying only that value was considered rather than a pattern of values. This ought to agree closely with *ShanEnt*, which does not include sequential information.

SampEn was calculated using a freely available program [79] from the Physionet service [80]. This program takes a stream of R-R intervals, normalises them to SD if required, and calculates *SampEn*.

The various measures of *SampEn* obtained from the choices of r and m described above were assessed for their agreement with each other, and with the shorter acquisitions. From these results a single combination of m and r that could be considered to adequately describe entropy in both SR and AF was determined. This measure was analysed to determine the agreement within the sub-groups.

Correlation coefficient	Descriptor
0.0-0.1	trivial, tiny, very {small, poor, weak}
0.1-0.3	low, minor, small, poor, weak
0.3-0.5	moderate, medium
0.5-0.7	major, large, high, good, strong
0.7-0.9	huge, excellent, very {large, high, good, strong}
0.9-1.0	nearly, practically, or almost: perfect, exceptionally good

Table 2.5.: Descriptors used to indicate importance of differing values of the correlation coefficients r and ρ.

2.11. Statistics

Although p values can be calculated to very high number of significant figures, a reporting limit of $p = 0.00001$ has been used in this thesis. Any smaller p value is simply reported as being less than that.

Correlation testing yields a value of r, in the case of Pearson product moment coefficients (for normal data) or ρ in the case of Spearman rank correlation coefficients (for non parametric data). The r value is the slope of the line between the two measures when the SD of those measures is the same; or in the case of Spearman rank, ρ is the slope of the line between the rank values of the measures. There is, however, no clear definition of what a meaningful r value is: the closer r (or ρ) tends to 0 the less meaningful the correlation, regardless of the associated p value (which gives a measure of the accuracy of r not its importance).

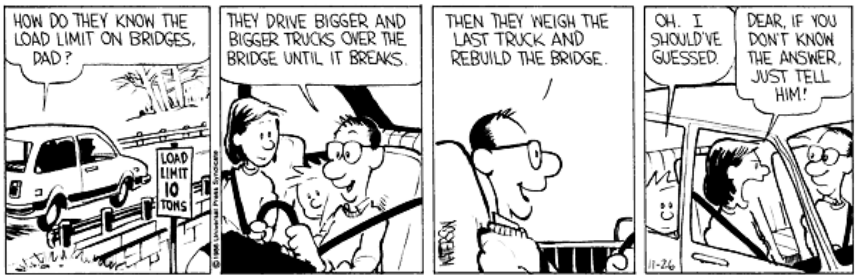
The most significant work which has been done towards establishing meaning in r values was done by Cohen [82], working in the social sciences. His scale simply defined three groupings: small ($r > 0.1$), medium ($r > 0.3$), and large ($r > 0.5$). It has been pointed out that this does not separate good correlations very well and a further development of his table has been proposed [83] which gives a wider ranging scale. The scale with some minor changes is shown in Table 2.5 and is used in this thesis. Wherever correlation is discussed in this thesis these words have been used in the restricted context defined in this table.

2.12. Going forward

The measures which have been described in this chapter have been systematically made in the groups of SR and AF patients and in the sub-groupings described in §2.7. Comparison has been made between the measures made in longer (10 min) and shorter (5 min) acquisitions. The results of these analyses are described in the following chapter and will be taken forward to investigate whether variations in functional measurement can be described by measures of rhythm.

Chapter 3.

Results: Describing Rhythm



Summary

In which the results of our investigations into methods of describing and classifying differences in rhythm are presented. Investigations considered "classical" linear measures such as mean R-R, as well as measures based on the Poincaré plot and measures of entropy.

3.1. ECG rhythm review

Review of the acquired patient ECG and Poincaré plots found a variety of rhythms as shown in Table 3.1. This table also shows the number of patients for whom there seemed to be no ectopic beats on the Poincaré plot. Rhythm determination was done firstly on a resting 12 lead ECG taken on the day of the study. If that was unavailable it was done from a resting 3 lead rhythm strip taken at the time of image acquisition. In both cases

Patient group	Number of patients	
	All patients	"Pure" ECG
AF	378	185
SR	396	184
Paced AF	7	4
Atrial flutter	5	3
Unsure	12	8

Table 3.1.: Number of patients in each rhythm and the number who, from their Poincaré plot, did not seem to have any ectopic beats.

the Poincaré plot was also considered. Very strict criteria were established that required the pattern to be indubitable before a rhythm could be assigned (it is this criteria that leads to the number of "unsure" rhythms). Only the patients in the initial AF group were assessed by the expert, patients in the initial SR group were assessed by the author, the remaining groups were excluded from any further analyses. The results are shown in Table 3.1.

For the 238 patients in AF for whom a 12 lead ECG was available a further subdivision was made based on the "graining" of the ECG where 59 were found to be fine grained, 165 medium grained and 11 coarse grained (see §2.6 for a description of graining). There were three patients, from the cohort of patients who were initially described as being in AF, for whom a 12 lead ECG did not exist and the quality of the remaining data was so poor it was impossible to determine a rhythm; these patients were removed from study.

3.2. Heart Rate Variability (HRV)

The principal time domain indices of R-R variability which were measured are: Mean R-R, SDRR, $RMSSD_{rr}$, pRR50 and the range of R-R intervals (see §2.8). Summary results are shown in Table 3.2 with histograms showing the variation in the both the SR ($N = 396$) and AF ($N = 378$) patient groups shown in Figures 3.1 to 3.5. These indices have been calculated using R-R data from each patient that has been restricted within the same set of limits as defined for the functional analysis; this excludes outlying ectopic

beats and is discussed in detail in §5.2.2. (For comparison a set of results calculated from the complete data set can be found in appendix B).

The results are broadly as expected, showing a much greater variation in R-R interval from one beat to another, and a wider overall range of R-R intervals in AF than in SR (Figures 3.1 to 3.5). All the patients in AF were under rate control which is designed to slow the mean R-R interval to a rate comparable to that in SR. It is, then, unsurprising to find that visually (Figure 3.1) there is little difference between mean R-R interval in SR and AF although statistically the difference is significant ($p < 0.00001$) with AF having slightly shorter R-R interval (see table 3.2). In comparing AF against SR, SDRR, $RMSSD_{rr}$, pRR50 and R-R range were all found to be significantly greater in AF than in SR ($p < 0.00001$ for all the measures). With the exception of mean R-R there is good separation between AF and SR for each of the indices (Figures 3.2 to 3.5), with the best single differentiator being pRR50 (Figure 3.4). Particularly in SR, pRR50 separates individual patients with the same underlying rhythm less well as can be seen from the dominance of the smallest pRR50 bin in the histogram. This is best accomplished using the R-R range which shows the widest distribution even after ectopic beats have been excluded (Figure 3.5).

Figure 3.6 shows SDRR (as seen in Figure 3.2) together with variation in the SD of the R-R interval as groups of 5, 10 and 20 beats are averaged together. There is reduced variability and the distinction between AF and SR is lost as more beats are averaged together suggesting that the variations in AF are short term (beat-to-beat). Longer term variations in AF are similar to those in SR.

3.2.1. Consistency

Comparing the longer acquisition against the shorter acquisition provides a means of determining whether results are consistent over time. In a clinical context, where a degree of variation is expected a Bland-Altman style analysis [84, 85] is the technique of choice. In this context, where measures were made immediately consecutively with no change in the state of the patient, the measures should be the same. A paired Wilcoxon and Spearman rank correlation offer two means of testing this. The results are shown in Table 3.3.

	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
Mean R-R (s)	0.51	0.79	0.87	0.97	1.35	0.89	0.15
SDRR (s)	0.000	0.020	0.030	0.040	0.090	0.029	0.015
RMSSD (s)	0.020	0.040	0.040	0.060	0.170	0.048	0.170
pRR50 (%)	0.10	0.30	1.50	7.20	80.40	6.60	11.39
R-R Range (s)	0.00	0.12	0.16	0.22	0.61	0.18	0.09
SDRR_5 (s)	0.001	0.015	0.024	0.030	0.071	0.024	0.012
SDRR_10 (s)	0.000	0.014	0.020	0.027	0.066	0.021	0.011
SDRR_20 (s)	0.000	0.012	0.017	0.023	0.064	0.018	0.010

(a) SR, N=396

	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
Mean R-R (s)	0.44	0.71	0.83	0.93	1.50	0.84	0.17
SDRR (s)	0.060	0.150	0.180	0.210	0.460	0.184	0.053
RMSSD (s)	0.090	0.210	0.250	0.300	0.700	0.263	0.078
pRR50 (%)	7.10	78.30	82.00	85.10	93.60	81.09	6.91
R-R Range (s)	0.36	0.80	0.92	1.09	1.80	0.95	0.22
SDRR_5 (s)	0.032	0.065	0.079	0.094	0.263	0.082	0.025
SDRR_10 (s)	0.022	0.045	0.055	0.065	0.248	0.057	0.0193
SDRR_20 (s)	0.009	0.030	0.038	0.046	0.239	0.041	0.0164

(b) AF, N=378

Table 3.2.: Summary results for linear HRV measures (a) SR group, (b) AF group.

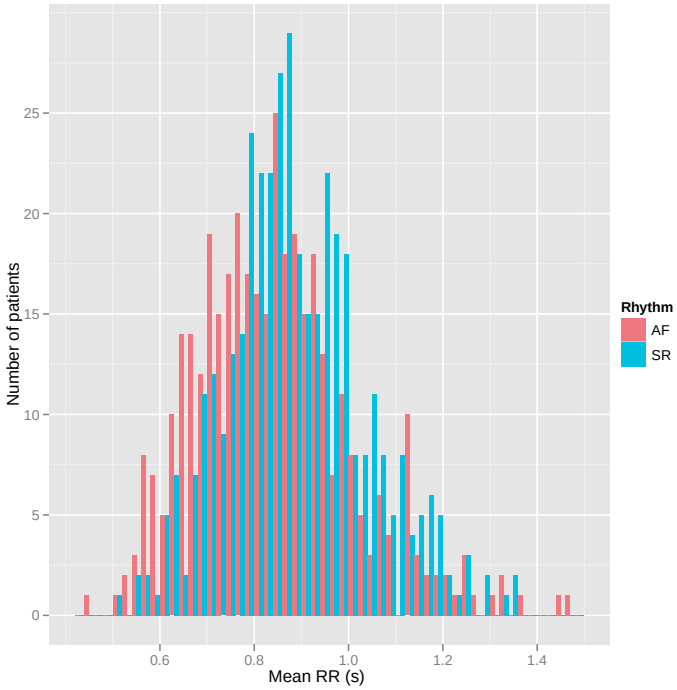


Figure 3.1.: Showing the variation in mean R-R over the whole patient sample, grouped by rhythm. Bin-width = 0.02 s, $N = 396$ (SR) and $N = 378$ (AF).

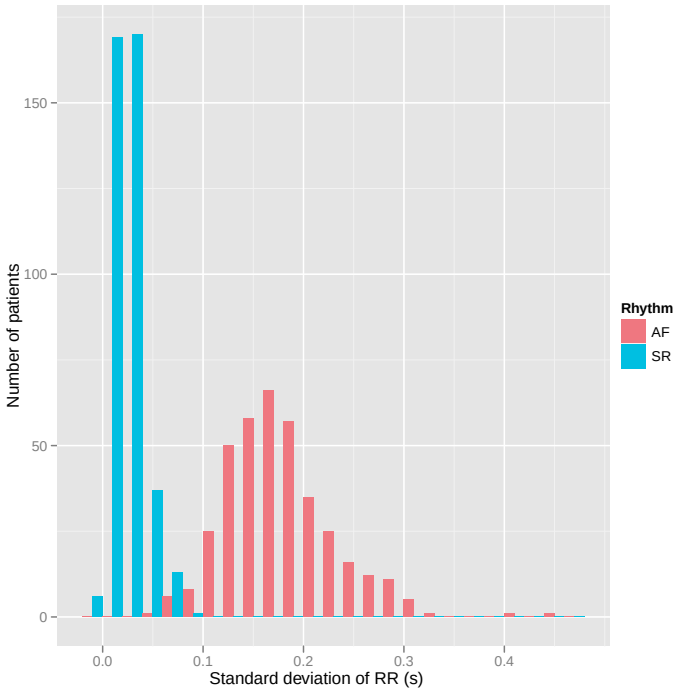


Figure 3.2.: Showing the variation in SDRR over the whole patient sample, grouped by rhythm. Bin-width = 0.02 s, $N = 396$ (SR) and $N = 378$ (AF).

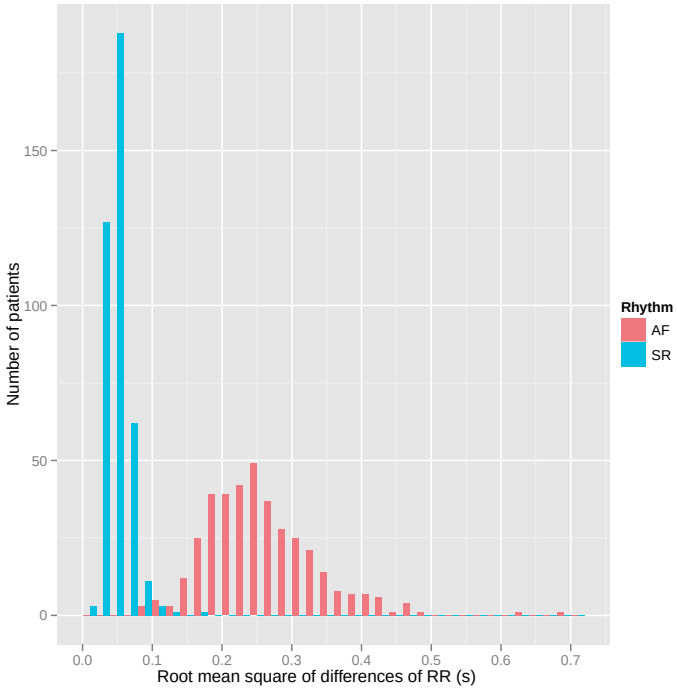


Figure 3.3.: Showing the variation in $RMSSD_{rr}$ over the whole patient sample, grouped by rhythm. Bin-width = 0.02 s, $N = 396$ (SR) and $N = 378$ (AF).

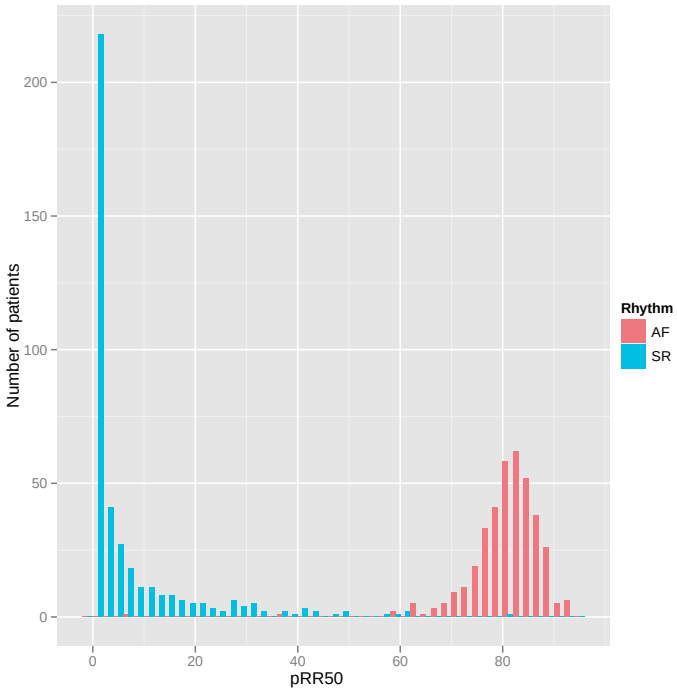
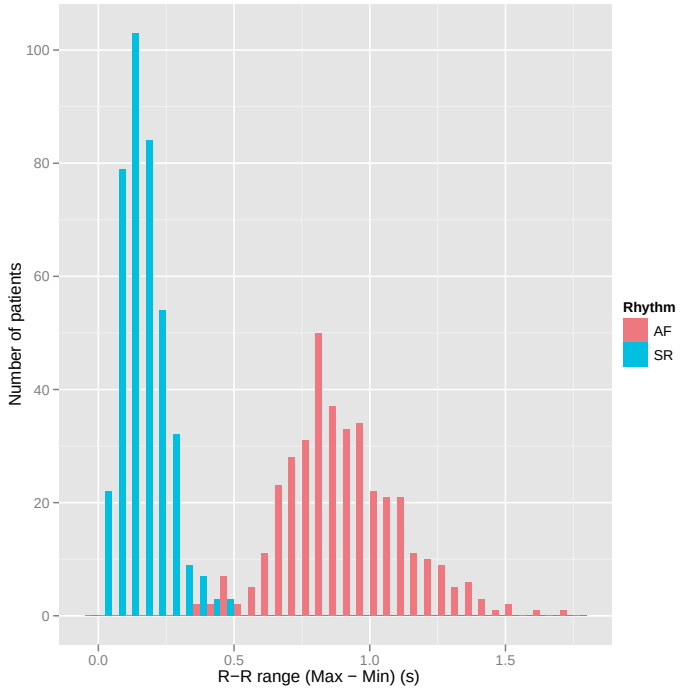


Figure 3.4.: Showing the variation in pRR50 over the whole patient sample, grouped by rhythm. Bin-width = 2%, $N = 396$ (SR) and $N = 378$ (AF).



(a) R-R Range

Figure 3.5.: Showing the variation in R-R range over the whole patient sample, grouped by rhythm. Bin-width = 0.05 s, $N = 396$ (SR) and $N = 378$ (AF).

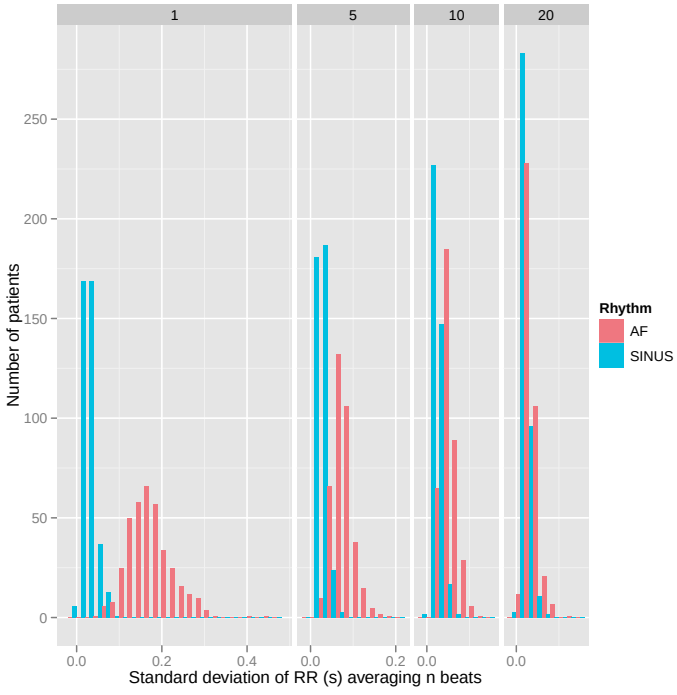


Figure 3.6.: Histograms showing SD of R-R interval averaged over every n = 1, 5, 10 and 20 beats.

In all cases the comparison between the two different acquisitions is at least good and in most cases it is very good or nearly perfect. The paired Wilcoxon signed ranks test finds there to be a significant difference in the mean R-R interval in both SR and AF, even though the correlation is almost perfect. Mean R-R interval results approximate to a normal distribution and when a (parametric) paired t-test is applied no difference is found between the two groupings in AF although there continues to be a change in SR ($p = 0.0154$).

Imposing limits on the beats included makes little difference to the consistency of results except in the case of the range where correlation between the shorter and longer acquisitions is substantially improved when the limits are imposed; this, however, is to be expected as the same limits were imposed on both acquisitions limiting the potential range equally.

3.2.2. Patient subgroups

Several different patient subgroups (see §2.7.1) were investigated to determine whether there was any change in the measure between the patient in that subgroup and the rest of the patients (for example comparing those who were known to have had MI and those who had not). In most cases the groups consist of patients who had, or did not have, a particular condition; however, in the case of function and graining (in AF) multiple, different, ordered groups existed and in this case regression testing was used. In the comparison with age, a simple Spearman rank correlation was used.

The numbers of patients, together with the mean result, for each subgroup are shown in Tables 3.4 (SR) and 3.5 (AF).

The results of comparisons between patients within and outwith the subgroups are shown in Table 3.6. As described below, several results are significant.

In both AF and SR, the "pure" group when compared with the "not pure" group had a significantly lower $RMSSD_{rr}$. In SR $pRR50$ and mean R-R were also significantly lower in the "pure" group. These differences reflect the greater variation between beats seen in rhythms in which there are ectopic beats. This difference is more pronounced in SR than AF.

	Not Limited		Without outliers	
	SR	AF	SR	AF
Mean	$p < 0.00001$	$p = 0.004$	$p < 0.00001$	$p < 0.007$
SDRR	NS	NS	NS	$p = 0.014$
RMSSD	$p < 0.00001$	NS	$p < 0.00001$	NS
pRR50	$p = 0.010$	NS	$p = 0.006$	NS
R-R Range	$p < 0.00001$	$p < 0.00001$	$p < 0.00001$	NS

(a) Paired Wilcoxon

	Not Limited		Without outliers	
	SR	AF	SR	AF
Mean	$\rho = 0.980$	$\rho = 0.980$	$\rho = 0.989$	$\rho = 0.986$
SDRR	$\rho = 0.640$	$\rho = 0.895$	$\rho = 0.838$	$\rho = 0.956$
RMSSD	$\rho = 0.717$	$\rho = 0.897$	$\rho = 0.859$	$\rho = 0.953$
pRR50	$\rho = 0.848$	$\rho = 0.849$	$\rho = 0.886$	$\rho = 0.862$
R-R range	$\rho = 0.506$	$\rho = 0.710$	$\rho = 0.916$	$\rho = 0.955$

(b) Correlation coefficients

Table 3.3.: Results comparing heart rate variability measures from the longer, 40 °, acquisition and shorter, 70 °, acquisitions using (a) paired Wilcoxon (p value given) and (b) Spearman rank correlation coefficients (ρ shown). Only significant values are shown. Colours are used here to differentiate correlations as defined in Table 2.5. $N = 395$ in SR and $N = 374$ in AF.

Subgroup	Number of patients	Mean R-R	SDRR	RMSSD	pRR50	R-R range
"Pure" ECG	185	0.88	0.027	0.052	5.68	0.155
"Not pure" ECG	213	0.90	0.030	0.055	7.12	0.173
With MI	111	0.92	0.027	0.053	5.57	0.153
Without MI	290	0.88	0.030	0.053	7.15	0.168
With HBP	231	0.87	0.027	0.051	5.17	0.152
Without HBP	170	0.90	0.031	0.055	7.84	0.174
Having had PCI &/or CABG	88	0.92	0.027	0.053	4.67	0.154
Without PCI /or CABG	313	0.88	0.030	0.053	7.28	0.167
Ischaemic on MPI	67	0.89	0.026	0.053	6.92	0.161
Not Ischaemic	329	0.87	0.032	0.052	6.00	0.181
Positive ETT	7	0.84	0.026	0.047	5.50	0.163
Negative ETT	107	0.85	0.033	0.052	7.23	0.185
$LVEF < 20$	51	0.90	0.025	0.052	7.95	0.153
$20 \leq LVEF < 40$	54	0.91	0.031	0.054	8.96	0.175
$LVEF \geq 40$	188	0.88	0.030	0.054	5.97	0.168

Table 3.4.: SR: Number of patients, and mean linear variability measures in each subgroup in SR.

The increase in mean R-R in patients with previous MI, or HBP in both SR and AF are indicative either of pathology or of drug treatment (e.g. β-blockers will slow heart rate) and these changes are corroborated by the shorter mean R-R seen with poorer function (although these were not found to be statistically significant). It is also notable that the changes in mean R-R are not significant in patients with underlying ischaemia. In AF, patients with HBP were found to have significantly lower $RMSSD_{rr}$ and SDRR while patients with previous MI were found to have significantly higher $RMSSD_{rr}$ and SDRR. (SDRR and $RMSSD_{rr}$ are closely related measures and follow similar patterns.)

There is a substantial difference in R-R range when comparing patients in SR who had positive and negative ETTs, however the number of patients with positive ETTs is so small (7) that it is not possible to show that these results are significant, and they are not duplicated in AF.

In AF the results show that there is a relationship between the "graining" of the rhythm and mean R-R, with more coarsely grained rhythms having shorter R-R duration.

Subgroup	Number of patients	Mean R-R	SDRR	RMSSD	pRR50	R-R range
"Pure" ECG	187	0.82	0.176	0.251	80.9	0.883
"Not pure" ECG	191	0.85	0.190	0.273	81.2	0.954
With MI	114	0.88	0.191	0.275	81.9	0.963
Without MI	263	0.82	0.180	0.258	80.7	0.900
With HBP	189	0.81	0.176	0.252	80.6	0.895
Without HBP	188	0.87	0.191	0.274	81.5	0.941
Having had PCI &/or CABG	67	0.91	0.176	0.276	82.0	0.946
Without PCI /or CABG	309	0.83	0.191	0.261	80.9	0.914
Ischaemic on MPI	34	0.84	0.191	0.264	81.1	0.923
Not Ischaemic	341	0.88	0.182	0.259	81.4	0.882
Positive ETT	30	0.82	0.185	0.263	81.4	0.935
Negative ETT	50	0.76	0.170	0.246	80.4	0.893
$LVEF < 20$	57	0.81	0.171	0.244	79.1	0.894
$20 \leq LVEF < 40$	99	0.83	0.190	0.272	81.7	0.954
$LVEF \geq 40$	97	0.87	0.180	0.259	81.2	0.887
Fine grained	59	**0.91**	0.188	0.270	81.5	0.893
Medium grained	165	**0.82**	0.178	0.255	80.6	0.904
Coarse grained	11	**0.75**	0.176	0.254	80.5	0.938

Table 3.5.: AF: Number of patients, and mean linear variability measures in each subgroup in AF.

	Mean R-R	SDRR	$RMSSD_{rr}$	pRR50	R-R Range
"Pure" ECG	$p = 0.029$	NS	$p = 0.016$	$p = 0.044$	NS
MI	$p = 0.025$	NS	NS	NS	NS
HBP	$p = 0.042$	NS	$p = 0.039$	NS	$p = 0.046$
Intervention	$p = 0.012$	NS	NS	NS	NS
Ischaemic	NS	$p = 0.028$	NS	NS	$p = 0.048$
Pos/Neg ETT	NS	NS	NS	NS	NS
Function	NS*	NS*	NS*	NS*	NS*
Age	$\rho = 0.166$	$\rho = -0.139$	$\rho = 0.136$	NS	$\rho = -0.121$

(a) SR

	Mean R-R	SDRR	$RMSSD_{rr}$	pRR50	R-R Range
"Pure" ECG	NS	NS	$p = 0.033$	NS	$p = 0.007$
MI	$p = 0.0007$	$p = 0.030$	$p = 0.029$	NS	$p = 0.020$
HBP	$p = 0.0014$	$p = 0.020$	$p = 0.016$	NS	NS
Intervention	$p = 0.0002$	NS	NS	NS	NS
Ischaemic	NS	NS	NS	NS	NS
Pos/Neg ETT	NS	NS	NS	NS	NS
Function	NS*	NS*	NS*	NS*	NS*
Age	$\rho = 0.173$	NS	NS	NS	NS
Graining	$p = 0.0001$*	NS*	NS*	NS*	NS*

(b) AF

Table 3.6.: Comparing HRV measures between those within and outwith the different subgroups in (a) SR and (b) AF. Comparison used Wilcoxon signed ranks test except those marked with a * where regression was used and Age in which the Spearman rank correlation coefficient, ρ is reported. The numbers in each group are shown in Tables 3.4 (SR) and 3.5 (AF).

There is also a significant but weak, positive relationship between increased age and mean R-R duration in both SR and AF. This agreement, seen using a Spearman rank correlation, is corroborated both by Anova and regression testing.

3.3. Poincaré Plot

A Poincaré plot shows the indexed R-R interval against the preceding R-R interval for every beat in an acquired sequence. The resulting plots differ for every patient but the general shape of the plot is distinctive and provides useful information about the rhythm.

Examples are shown in Figures 3.7 to 3.12 for each of the four example patients. Two additional examples, one in AF and one in SR are also shown to demonstrate some other characteristic plots. Figure 3.12 shows the plot for a patient with a demand pacemaker; when the R-R interval gets too long (in this case about 1.8 s) the pacemaker fires, thus the longest R-R interval is limited and the Poincaré plot exhibits the typical square shape shown in the figure. Figure 3.11 has characteristic features of ventricular parasystole [35] and shows a typical pattern of "normal" sinus beat followed by a coupling beat of varying length, followed by a compensatory beat, followed by another "normal" sinus beat. This rhythm, which shows substantial beat-to-beat variation, and in which the P-wave was not easily identified on ECG was initially mis-identified as AF. After reviewing the rhythms in conjunction with the Poincaré plot the true rhythm was identified and the patient was excluded from further analysis.

It should be clear from these examples that while each patient has a unique Poincaré plot, different rhythms have characteristics which are common to each plot. The basic plot for SR is generally "tight" and well ordered while AF tends to be much more diffuse, other features of the rhythm are then overlaid on these base characteristics.

3.3.1. Poincaré correlation

The correlation coefficient to a linear regression line in the Poincaré plot provides a measure of the variation in rhythm[45]. In theory in SR the points should cluster around a single point approximately on the line of identity. The lower the beat-to-beat variability the smaller the area of the cluster and the better the correlation coefficient.

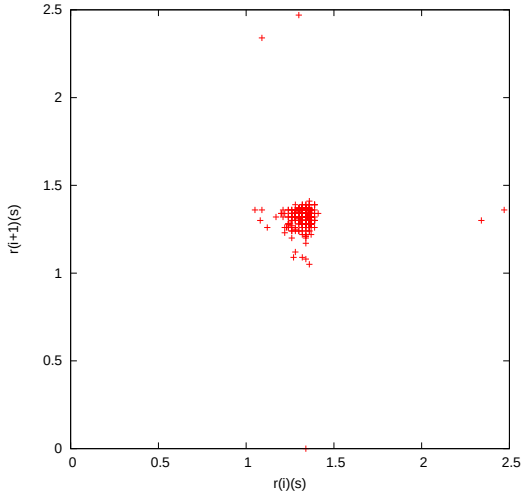


Figure 3.7.: Poincaré plot for patient S1. The plot shows a fairly moderately tight grouping of beats with R-R intervals which range from ~ 1.2 s to ~ 1.5 s with two long ectopic beats (> 2.3 s in length) and a small clustering of shorter beats of ~ 1.1 s duration which may be related to the ectopic beats.

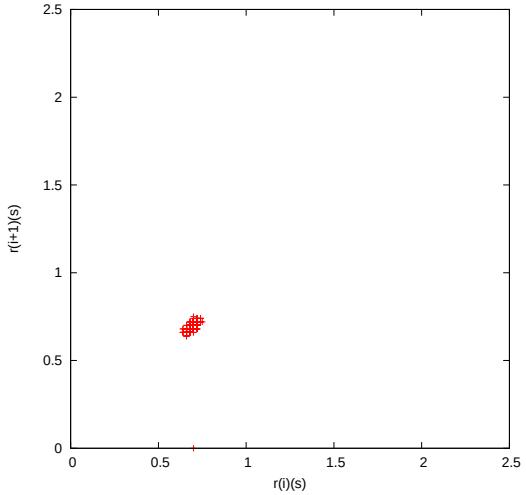


Figure 3.8.: Poincaré plot for patient S2. The plot is typical of normal SR with all beats clustered tightly together in a small range around 0.75 s. The patient has a relatively fast heart rate (~ 90 bpm), with no evidence of ectopic beats.

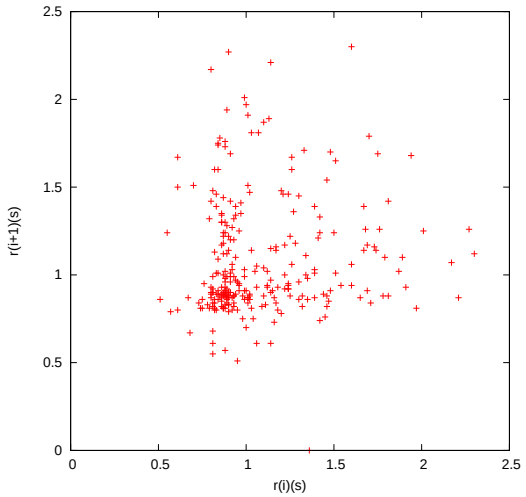


Figure 3.9.: Poincaré plot for patient A1. The plot shows a patient in AF with a wide range of R-R intervals. Although there is some clear clustering in the plot around 0.9 s the plot shows that a beat of any R-R interval may be followed by a beat of any other R-R interval. There is a hint of broad bands in the plot radiating out from the cluster suggesting that longer beats may generally be followed by a short beat. The clustering in the plot suggests a degree of coordination in R-R intervals. It is possible to identify a line in the plot about 0.75 s below which there are very few points. This line may suggest the ARP of the AV node (see §8.2.4).

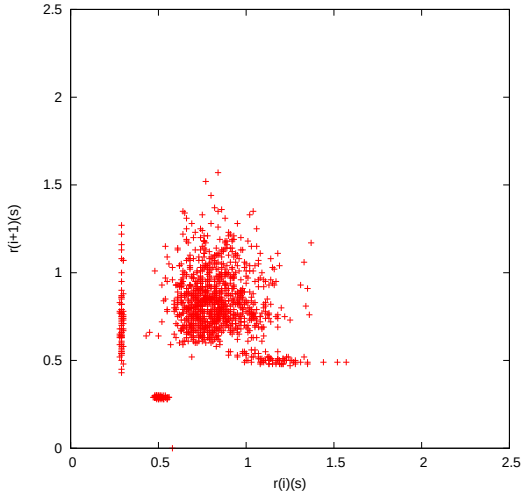


Figure 3.10.: Poincaré plot for patient A2. The plot is typical of a patient in AF with a broad range of beats and no definable features within it. The most obvious features of the plot are two lines (at 0.5 s and 0.25 s) and a small cluster at the junction of 0.25 s and 0.5 s. It has been suggested that these may define the ARP of the AV node and a second pathway within the AV node (see §8.2.4).

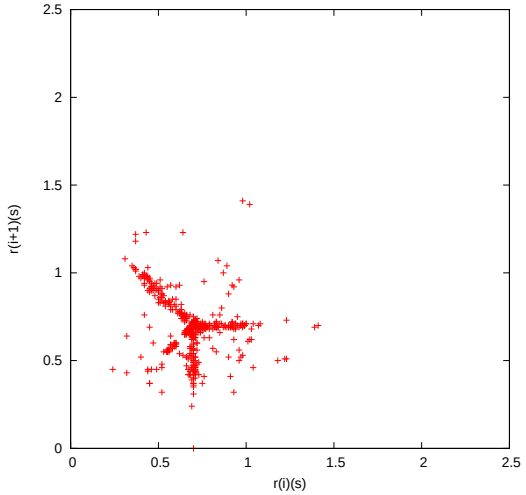


Figure 3.11.: Poincaré plot for patient with ventricular parasystole. The two pacemakers (SA node, and an ectopic) each contribute to the rhythm, resulting in a spread of beats as the two pacemakers asynchronously cause contractions. The principal sinus beat occurs at ~ 0.75 s. A "normal" beat may be followed by a shorter beat (an interruption from the second, ectopic, pacemaker) which is seen in the the near-vertical line. This line shows the range of coupling intervals with the bottom of the line, the shortest interval, being indicative of ventricular refractoriness. The short beat will be followed by a compensatory longer beat (the diagonal line) which in turn is followed by a "normal" beat. The straightness of the diagonal line shows that the sum of the coupling beat and the compensatory beat is approximately constant.

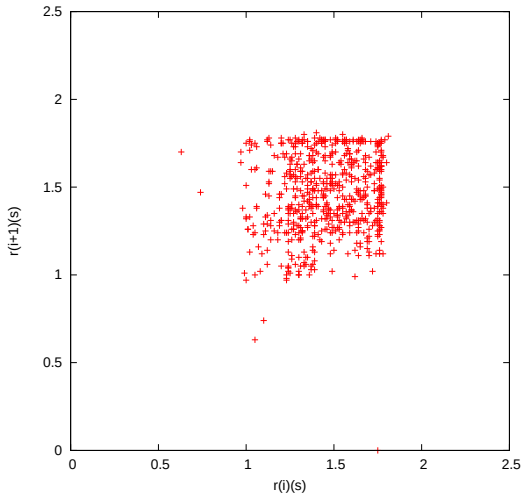


Figure 3.12.: Poincaré plot for patient in paced AF. Plot shows the broad range of beats typical of AF, but in this case a limit is imposed on the maximum R-R interval by the pacemaker leading to a well defined line on the top and right which shows the trigger level at which the pacemaker is set.

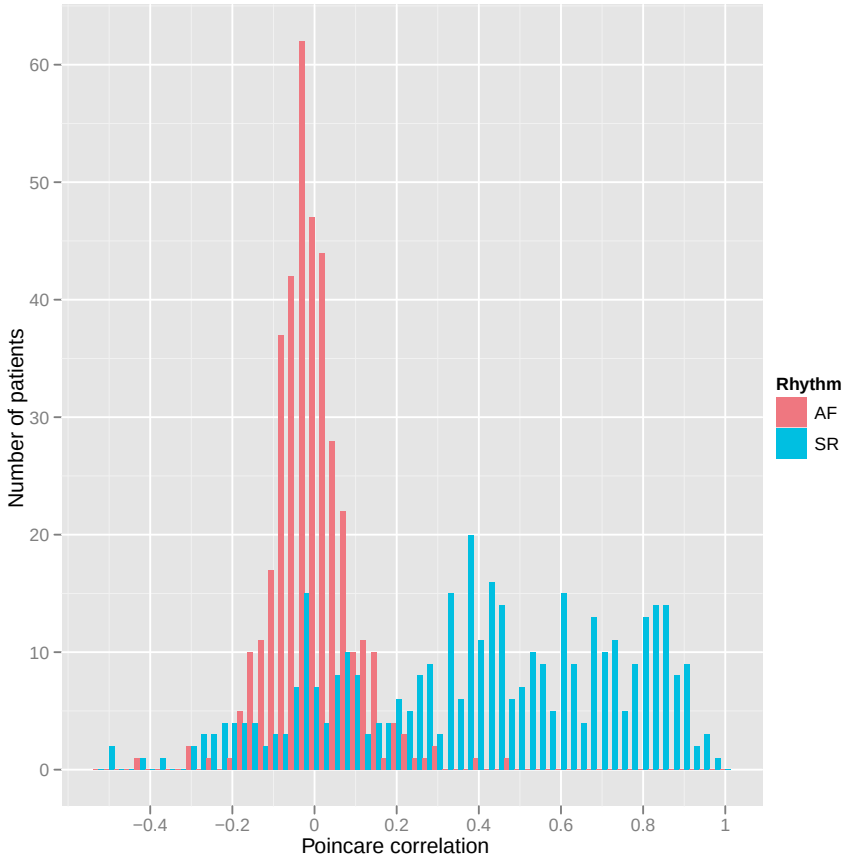


Figure 3.13.: Showing the correlation coefficients obtained for Poincaré plots in both AF (N=387) and SR (N=395). (Bin-width = 0.2).

	N	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
SR	395	-0.574	0.154	0.461	0.699	0.982	0.4209	0.339
AF	378	-0.418	-0.046	0.002	0.056	0.505	0.009	0.099

Table 3.7.: Summary results for Poincaré correlation.

The correlation coefficient was calculated for all beats in each of the longer acquisitions. The results are summarised in the histogram shown in Figure 3.13 and Table 3.7. The results are obviously different in SR and AF; confirmed by a Wilcoxon signed ranks test ($p < 0.00001$). The correlation coefficients cluster around 0 in AF; however, the wide range of coefficients in SR means that as an index the correlation coefficient fails fully to distinguish between SR and AF, although clearly a correlation coefficient nearer 1 will indicate SR and not AF.

When the results for the shorter acquisition are compared against the longer acquisition a Wilcoxon signed ranks test finds no significant difference between the two acquisitions in either AF or SR although assessing the correlation between the shorter and longer acquisitions only finds good (and not excellent) correlation between the results (in SR $\rho = 0.667$, in AF $\rho = 0.588$). This is possibly because ectopic beats, which have not been excluded, have the potential to substantially distort the correlation line; however, when the same comparison is made in the "pure" group only very similar results are found ($\rho = 0.656$ in SR, $\rho = 0.599$ in AF).

Subgroups

The results of the subgroup analyses are summarised in Table 3.8. In SR there is a very clear improvement in the correlation coefficient with improving function as well as significant differences in between in several of the sub-groups with healthier cardiology (non-MI, non-ischaemic, "pure" ECG etc.) having improved correlation when compared with the opposing group. The only group for which this was not true was the comparison of patients with positive and negative ETTs where the number of patients with positive ETTs ($N = 7$) is almost too small for statistical comparison. In AF the differences between the groups was insignificant.

3.3.2. *Compactness factor*

As discussed in §2.9.2 a measure of the variation in density over the Poincaré plot is offered by a calculation of *compactness factor*. Two methods have been employed in this thesis for the calculation of *compactness factor*: the integral can be calculated against the area, here termed *compactness factor*; or against the log of the area, here termed *compactness factor by log*. Hnatkova et al. who did the initial work on compactness calculated the integral using the log of the area [46] but doing so gives greater weight to small areas and therefore to more tightly bound distributions in the Poincaré plot. Calculating the *compactness factor* using the area gives equal weight to distributions, but may result in a poorer differentiation of SR, which is tightly bound.

While there is good correlation between the measures, a Wilcoxon signed ranks test shows a very clear difference between them (see Table 3.9). Results for the two measures are summarised in Figure 3.14 which shows that while *compactness factor* clearly

	SR			AF		
	Within	Outwith	Result	Within	Outwith	Result
"Pure" ECG	0.55	0.30	$p < 0.00001$	0.004	0.01	NS
MI	0.31	0.46	$p = 0.00006$	0.01	0.007	$p = 0.038$
HBP	0.44	0.45	NS	0.004	0.01	NS
Intervention	0.37	0.44	NS	-0.007	0.01	NS
Ischaemic	0.39	0.57	$p = 0.00008$	0.007	0.02	NS
Pos / Neg ETT	0.79	0.62	NS ($p = 0.051$)	-0.004	-0.003	NS
Function	0.20	(Poor & Very poor)	$p < 0.00001$	0.02	(Poor & Very poor)	NS
	0.33	(Moderate & Mild)		0.005	(Moderate & Mild)	
	0.51	(Normal)		0.01	(Normal)	
Age	-	-	$\rho = -0.224$	-	-	NS
Graining	-	-	-	0.005	(FINE)	NS
				0.003	(MEDIUM)	
				0.008	(COARSE)	

Table 3.8.: Subgroup analysis of Poincaré correlation results. Comparing results for patients within the group against results for patients outwith the group. The p value is given where a significant difference was found (where there was no significant difference this is marked with "NS"). The group marked "Pos / Neg ETT" compares those patients with positive ETT against those with negative ETT, patients with inconclusive ETT have been excluded from this grouping. Numbers in each group are given in Tables 3.4 (SR) and 3.5 (AF).

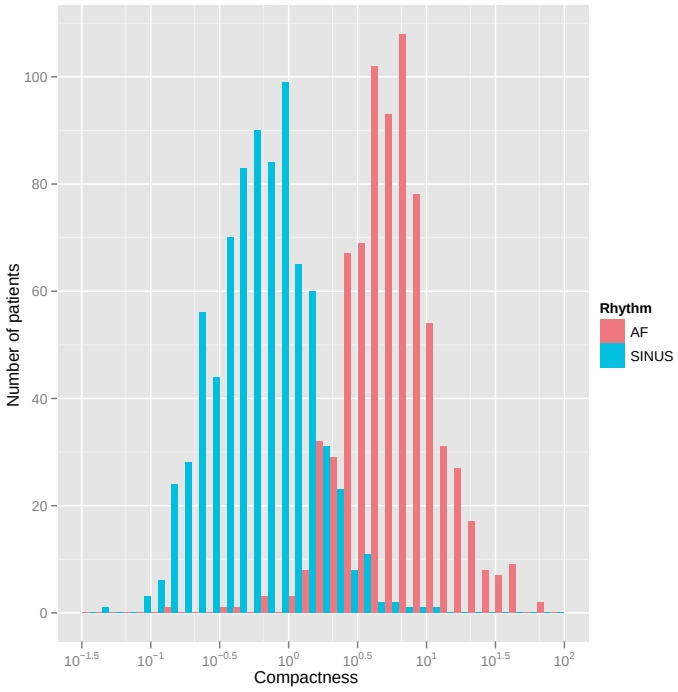
	Paired Wilcoxon	Correlation
All	$p < 0.00001$	$\rho = 0.586$
SR only	$p < 0.00001$	$\rho = 0.670$
AF only	$p < 0.00001$	$\rho = 0.690$

Table 3.9.: Agreement between *compactness factor* and *compactness factor by log*.

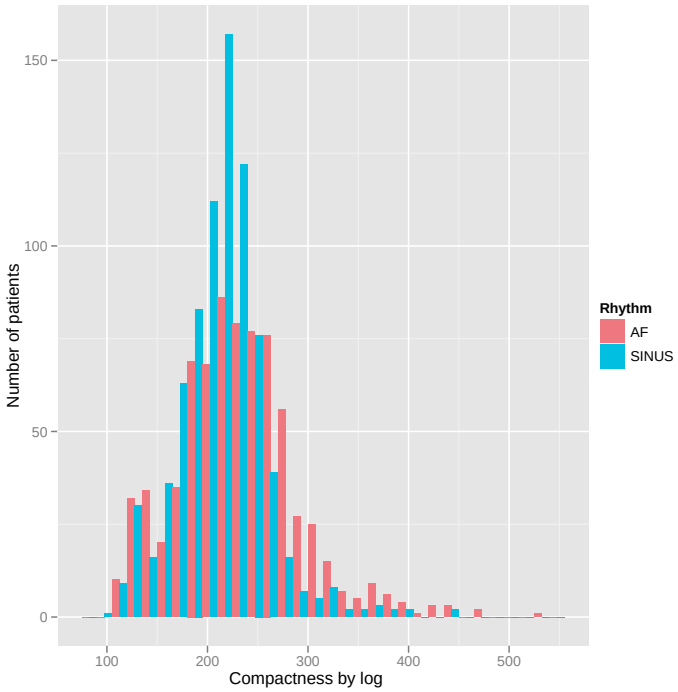
.

distinguishes between AF and SR, there is no substantive difference using *compactness factor by log*.

A statistical comparison of the indices for SR and AF finds that both *compactness factor* and *compactness factor by log* are significantly different with $p < 0.00001$. There is, however, such a degree of overlap in the *compactness factor by log* results that this index could not be used to distinguish between AF and SR. Since the Poincaré plots are visually widely different it was felt that *compactness factor* offered considerably more



(a) *Compactness factor*



(b) *Compactness factor by log*

Figure 3.14.: Histograms showing variation over the patient groups of (a) *compactness factor* (log scale, bin-width=0.1) and (b) *compactness factor by log* (bin-width=15).

	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
Compactness factor: SR	0.040	0.353	0.620	1.018	10.020	0.842	0.843
Compactness factor: AF	0.150	3.780	5.840	8.910	73.130	7.912	7.674
Compactness factor by log: SR	102.7	187.6	214.3	235.2	449.7	213.3	43.95
Compactness factor by log: AF	105.4	192.8	228.5	265.2	536.6	231.6	61.60

Table 3.10.: Summary results for *compactness factor* measures.

information than *compactness factor by log* and all further analyses concentrated on *compactness factor*.

When variations in *compactness factor* were examined in the subgroups which have been described (§2.7.1) no difference was found in *compactness factor* in either SR or AF except in the case of patients with or without high blood pressure in SR where the mean *compactness factor* in patients with high blood pressure was 0.74 while in patients without high blood pressure it was 0.88 ($p = 0.03$), suggesting that patients with high blood pressure have a more tightly bound distribution than those without. It is interesting to note that there is no significant difference when *compactness factor by log* is used. (*Compactness factor by log* is 214 in patients with high blood pressure and 215 in those without).

3.3.3. *Delta Poincaré plot*

The delta Poincaré plot is described in §2.9.3 and consists of a plot of the difference between one beat and the previous beat against the difference between the previous beat and the one before that. An example of the *delta Poincaré plot* is shown in Figure 3.15.

In SR there were 89 balanced *delta Poincaré plots* (plots in which there were a statistically equivalent number of points in each quadrant): in AF there were none. The dominant quadrants or quadrant combinations as determined from the residuals are shown in Table 3.11.

In both AF and SR the *ac* (top-left / bottom-right) combination dominates in the vast majority of patients. This corresponds to a beat being followed either by a shorter beat followed by a longer beat or by a longer beat followed by a shorter beat. There is a clear structure in this which suggests that the beat sequence is not truly random. It can to some extent be quantified by *swing* (see §2.9.3), which measures the proportion of beat

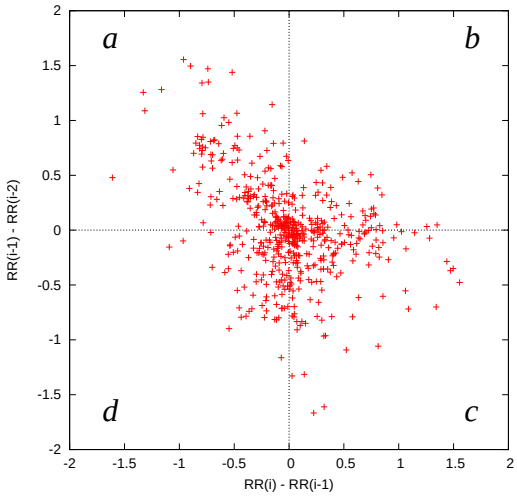


Figure 3.15.: Showing the *delta Poincaré plot* for Patient A1; quadrants are labelled a-d. *Swing* for this patient is 0.65. (The Poincaré plot for the same patient is Figure 3.9).

Quadrant	AF	SR
ab	-	1
abc	-	13
ac	374	209
acd	1	14
b	-	14
bd	-	39
cd	-	1
d	-	16

Table 3.11.: Dominant quadrant(s) for each rhythm type.

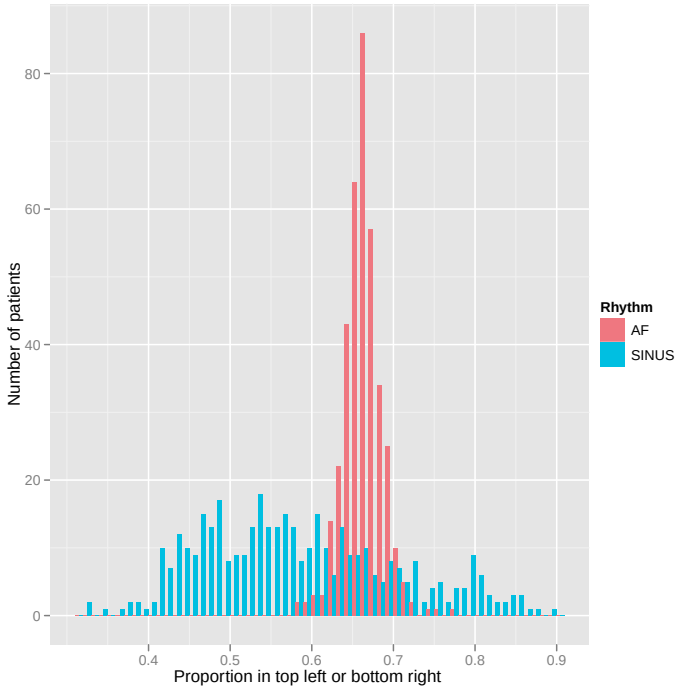


Figure 3.16.: Histogram showing *swing*, the proportion of the total number of beat changes which fall in quadrants a or c of the *delta Poincaré plot*, over all patients ($N = 395$ in SR, $N = 378$ in AF).

changes which fall in quadrants a or c. *Swing* is illustrated in the two patient groups in Figure 3.16. In AF generally between 60% and 70% of beat changes, mean 66%, for a patient are in quadrants a or c suggesting an alteration of longer and shorter beats. The range of *swing*, from 30% to 90% with a mean of 58%, is substantially greater in SR suggesting that on a beat-to-beat basis there may be less order in the variation in SR than in AF.

3.4. Entropy

As described in §2.10, the models used to describe the possible states of a system define different measures of entropy. Three different model families were used; in order of increasing complexity they were: (1) Shannon entropy, *ShanEnt* (2) Shannon entropy of symbolic dynamic descriptors, *SymDyn* and (3) sample entropy, *SampEn*.

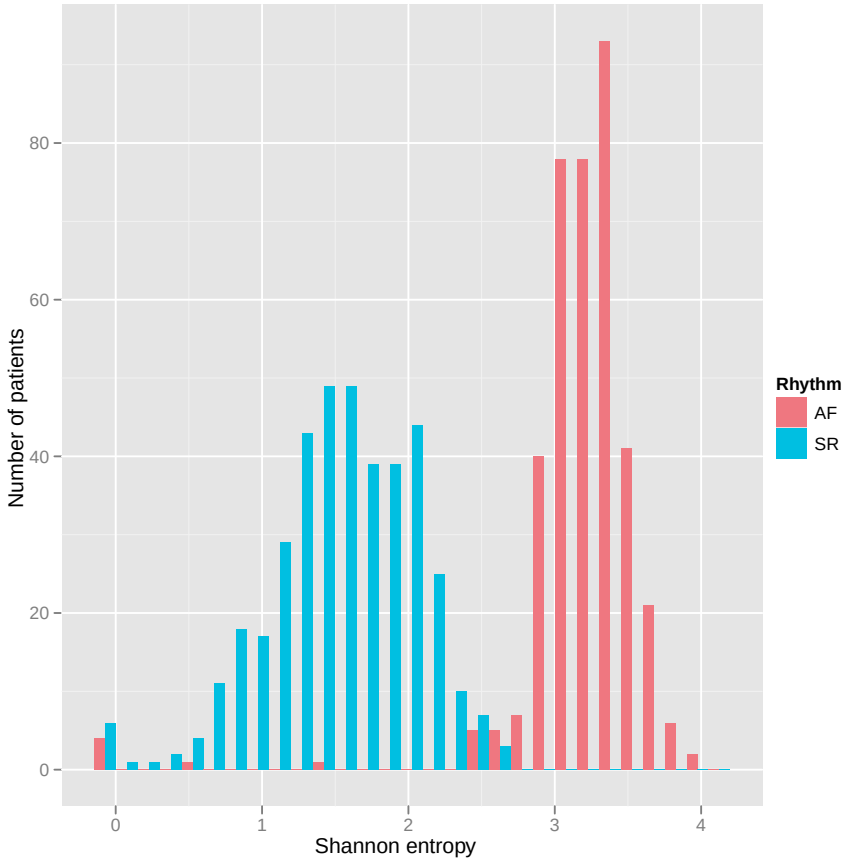


Figure 3.17.: Showing the *ShanEnt* calculated using 25 ms bins from R-R interval stream for the 40 ° view for those patients definitely identified as being in AF and SR. ($N = 395$ in SR, $N = 378$ in AF, bin-width = 0.15).

3.4.1. Shannon Entropy (*ShanEnt*)

Assessment of *ShanEnt* is described in §2.10.1.

Eight different measures of *ShanEnt* were made depending on the bin-width / number of bins and whether or not the included beats were limited (see §2.5.5).

Figure 3.17 shows a histogram of the results obtained for *ShanEnt* using the limited R-R stream. There is good separation of AF and SR values when the bin width is fixed, although having fixed numbers of bins reduces this separation but this is likely to reflect the greater bin-width associated with the chosen number of bins, particularly in AF. It is also interesting to note that the SR results are broader than the AF ones. When calculations were made on the unlimited R-R interval stream a similar set of results was obtained.

	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
t=10 ms	0.000	3.662	4.020	4.230	4.760	3.893	0.583
t=25 ms	0.000	3.080	3.250	3.408	3.940	3.202	0.445
n=16	0.000	2.390	2.450	2.520	2.740	2.419	0.292
n=32	0.000	3.060	3.130	3.190	3.420	3.081	0.364

(a) AF

	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
t=10 ms	0.000	1.880	2.300	2.710	3.600	2.259	0.0612
t=25 ms	0.000	1.270	1.560	1.900	2.700	1.538	0.495
n=16	0.000	2.210	2.370	2.460	2.710	2.275	0.317
n=32	0.000	2.730	3.010	3.120	3.360	2.835	0.483

(b) SR

Table 3.12.: Summary results for differing *ShanEnt* measures using limited R-R intervals.

A summary of the results using the limited data is shown in Table 3.12. Analysing the results to test whether there is a significant difference between SR and AF for *ShanEnt* finds the entropy to be significantly different (using a Wilcoxon signed ranks test) for all limited and unlimited measures with $p < 0.00001$ in all cases. However examination of the plots shows that there is significant overlap with increasing bin size (decreasing bin number).

Figure 3.18 shows the different measures of *ShanEnt*, depending on the definition of the R-R interval bins, plotted against each other. This clearly shows that while there is generally higher entropy in patients with AF the widest range of entropy measures is found for the smaller bin-widths (10 ms and 25 ms). It can also be seen that there is a plateau in the *ShanEnt* values determined for the fixed number of bins and a resultant reduction in discrimination between different patients. As discussed previously there is uncertainty whether the number of bins or the bin size should be held constant to allow the best comparison. Since the best separation of the groups is achieved with the smallest bin size (largest number of bins) this measure (bin-width of 10 ms) was carried forward into the remainder of the analysis. The use of fixed bin-width over fixed bin number is reasonable since a bin with no counts in it will not contribute to the overall entropy value (consider equation 2.2 where $b_i = 0$). Thus bins using a fixed bin-width can

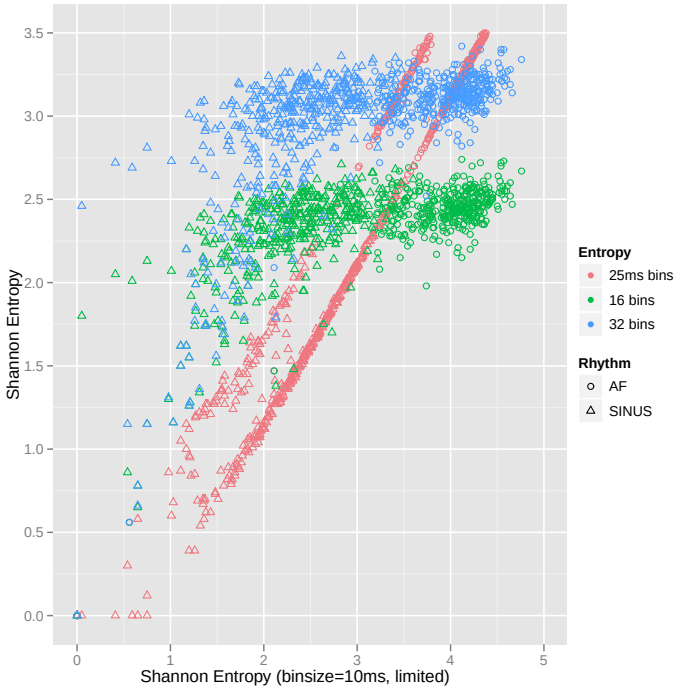
be considered to include all possible R-R interval times with most of them contributing nothing to the overall measure of entropy.

Looking at the results for *ShanEnt* measured using a bin size of $t = 10$ ms a paired Wilcoxon test finds a significant difference between the results for the long (10 min or 15 min) and the short (5 min) acquisitions in both SR and AF ($p < 0.00001$). However a Spearman rank correlation finds almost perfect correlation with $\rho = 0.904$ in SR and $\rho = 0.969$ in AF. This suggests that there is a systematic difference between results for *ShanEnt* in longer and shorter acquisitions. This is confirmed by a Bland-Altman style analysis[84, 85] which shows longer acquisitions to have a greater entropy than shorter ones (see Figure 3.19). The difference (longer acquisition - shorter acquisition) is however very small (0.08 ± 0.26 in SR, and 0.09 ± 0.17 in AF) and is not seen in all cases. The most likely explanation for this difference is that the longer acquisition was always performed first and there is potential that heart rate slowed as the patients relaxed on the imaging table, this slowing may be accompanied by a reduction in entropy.

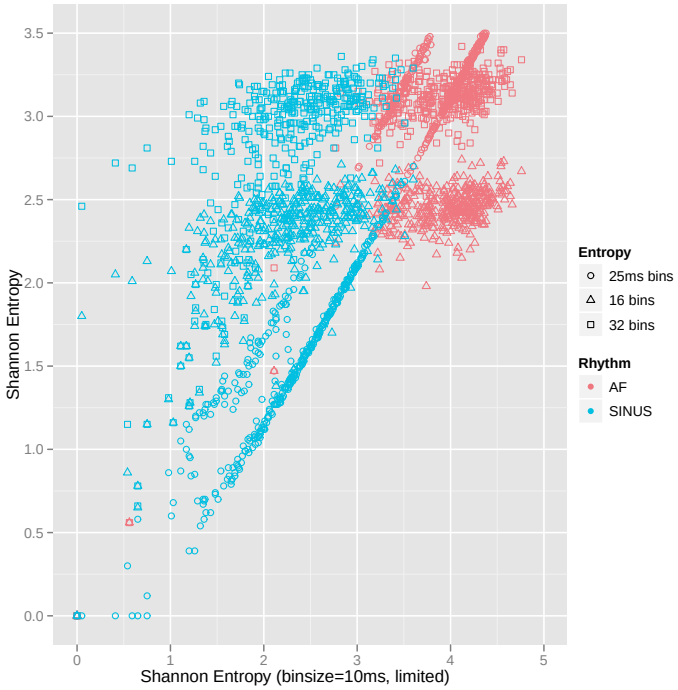
The subgroup analyses found significance as shown in Table 3.13. In general no significant difference was found between the matched groups, although in AF there was a general tendency that the healthier group had a lower entropy than the counterpart group. For example patients in AF with previous MI had significantly higher entropy than those without known MI. In SR this pattern is reversed: patients with known pathology appear to have a lower entropy than those without; thus patients in SR with known ischaemia generally had a lower entropy than did those with normal coronary arteries.

3.4.2. Entropy of symbolic dynamics (*SymDyn*)

The use of symbolic dynamics has been discussed in §2.10.2. Two and three letter word lengths, which define changes over three or four beats respectively, and plot areas defined by 1 and 2 SDs, corresponding to 4 or 6 different areas, were used to define the symbolic dynamic series. The results are summarised in Figure 3.20 and Table 3.14. Although a Wilcoxon signed ranks test (Mann-Whitney) finds there to be a significant difference ($p < 0.00001$) between SR and AF for measures of *SymDyn* using all four combinations of word length and plot area, there is essentially nothing to distinguish between SR and AF when only one boundary (at 1 SD) is defined. When two boundaries are defined a difference between AF and SR becomes apparent.

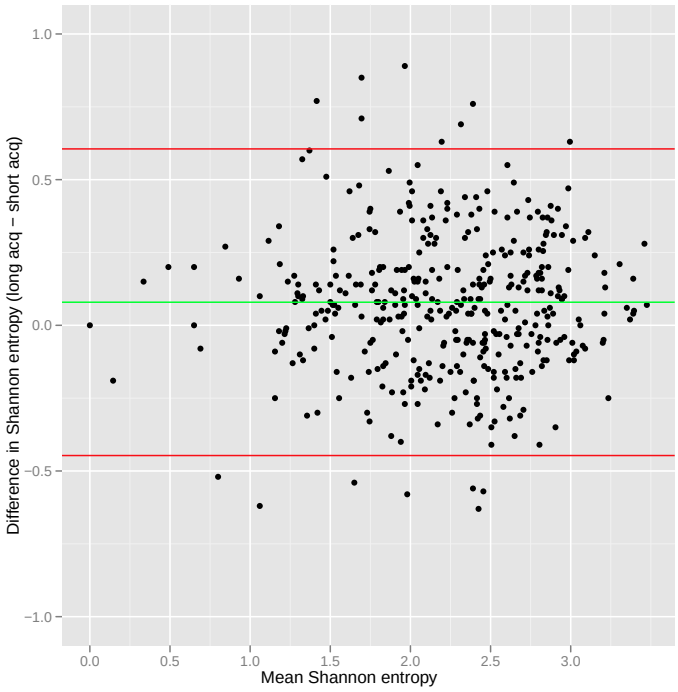


(a) Emphasising entropy

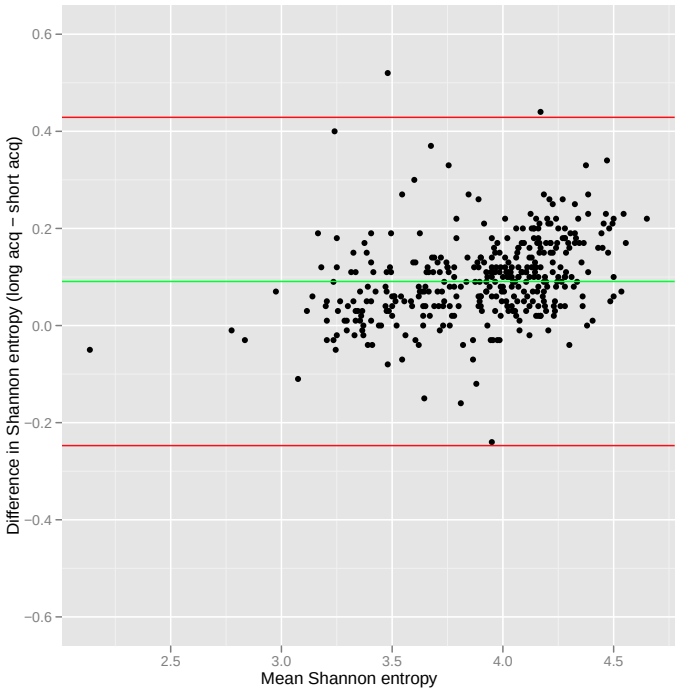


(b) Emphasising rhythm

Figure 3.18.: *ShanEnt* using different bin sizes / numbers. Each of the measures is plotted against entropy determined with R-R interval bins of 10 ms. Plotting in this way explores whether there is a possible plateau in the results. The plots present the same data with colour used in plot (a) to show the R-R interval bin-widths and in plot (b) to show rhythm.



(a) SR



(b) AF

Figure 3.19.: Bland-Altman style plot comparing *ShanEnt* measured on the longer and shorted acquisition. In both AF and SR there is a systematic bias towards higher entropy values in the longer acquisitions. Mean difference: 0.08 in SR (N=395), 0.09 in AF (N=378).

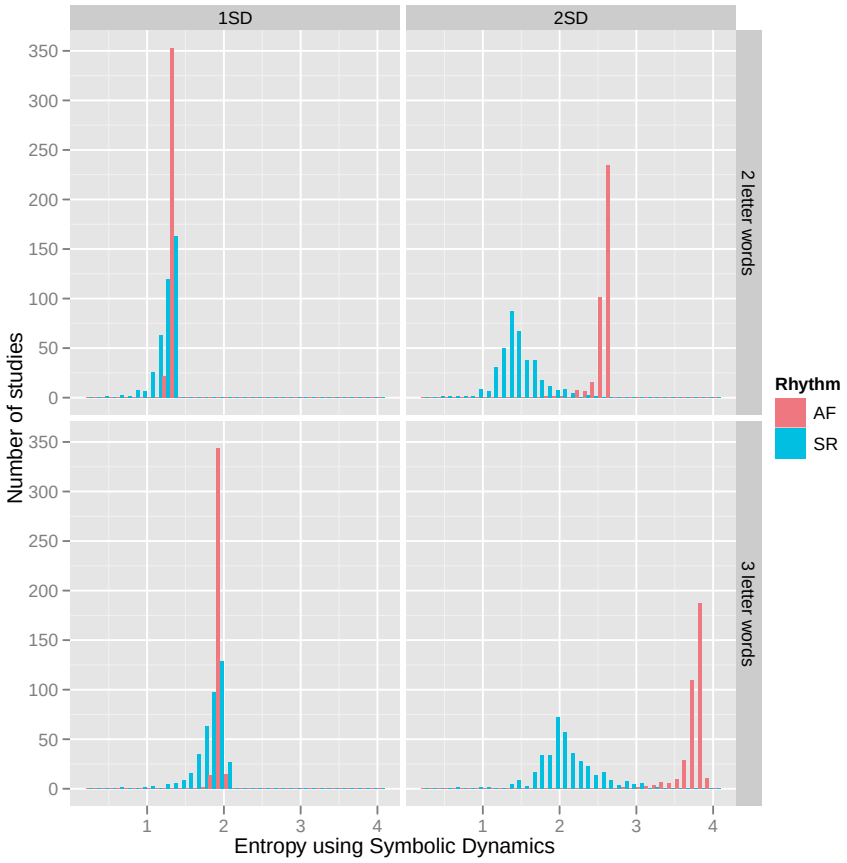


Figure 3.20.: Showing the change in *SymDyn* with increasing multiples of the SD horizontally and increasing word length vertically from the $\sim 40\,^{\circ}$ acquisition for those patients definitely identified as being in AF and SR. It should be noted that superpositions are shown as summed, not overlayed, data.

	SR			AF		
	Within	Outwith	Result	Within	Outwith	Result
"Pure" ECG	2.22	2.30	$p = 0.035$	3.92	3.97	NS
MI	2.17	2.30	NS	4.01	3.84	$p = 0.003$
HBP	2.19	2.31	NS	3.91	3.87	NS
Intervention	2.21	2.28	NS	3.97	3.88	NS
Ischaemic	2.23	2.42	$p = 0.029$	3.88	4.06	NS
Pos / Neg ETT	2.38 (+ve)	2.50 (-ve)	NS	4.05 (+ve)	3.98 (-ve)	NS
Function	2.05	(Poor & Very poor)	NS	3.81	(Poor & Very poor)	NS
	2.20	(Moderate & Mild)		3.91	(Moderate & Mild)	
	2.35	(Normal)		4.00	(Normal)	
Age	-	-	$\rho = -0.157$	-	-	NS
Graining	-	-	-	3.71	(FINE)	NS
				4.00	(MEDIUM)	
				4.09	(COARSE)	

Table 3.13.: Subgroup analysis of *ShanEnt* using 10 ms bins and limited data. Mean values are given together with the Wilcoxon signed ranks p values where a significant difference was found (where there was no significant difference this is marked with "NS"). Comparison against function used analysis of variance while comparison against age used linear regression. Number of patients in each group can be found in Tables 3.4 (SR) and 3.5 (AF).

Rhythm	Length	Boundaries	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
AF	2	1	1.23	1.32	1.33	1.34	1.30	1.33	0.017
AF	2	2	1.57	2.59	2.62	2.64	2.69	2.58	0.216
AF	3	1	1.77	1.94	1.96	1.98	2.04	1.96	0.032
AF	3	2	2.30	3.75	3.81	3.86	3.94	3.76	0.197
SR	2	1	0.36	1.18	1.28	1.33	1.38	1.24	0.151
SR	2	2	0.42	1.29	1.41	1.60	2.58	1.45	0.299
SR	3	1	0.53	1.73	1.87	1.94	2.07	1.81	0.220
SR	3	2	0.63	1.86	2.04	2.28	3.76	2.08	0.413

Table 3.14.: Summary values for *SymDyn*.

On first glance this result seems to suggest that the difference between the distribution of sequential beats in AF and SR is found at the margins. Although the scale of the changes may be much greater in AF than in SR, the differences appear to be lost because the symbolic dynamic technique collapses scale changes into variations with respect to the SD. It is clear, however, from Figure 3.21 that, where only one SD defines the areas used to determine appropriate symbols (in both AF and SR), the results plateau. This demonstrates a limit to the upper value of entropy and suggests that collapsing the data

	l=2, s=1	l=2, s=2	l=3, s=1
l=2, s=2	$\rho = 0.733$		
l=3, s=1	$\rho = 0.904$	$\rho = 0.666$	
l=3, s=2	$\rho = 0.743$	$\rho = 0.984$	$\rho = 0.730$

(a) SR

	l=2, s=1	l=2, s=2	l=3, s=1
l=2, s=2	$\rho = 0.243$		
l=3, s=1	$\rho = 0.922$	$\rho = 0.217$	
l=3, s=2	$\rho = 0.256$	$\rho = 0.974$	$\rho = 0.260$

(b) AF

Table 3.15.: Comparison of *SymDyn* in (a) SR and (b) AF. All results had significance of $p < 0.00001$.

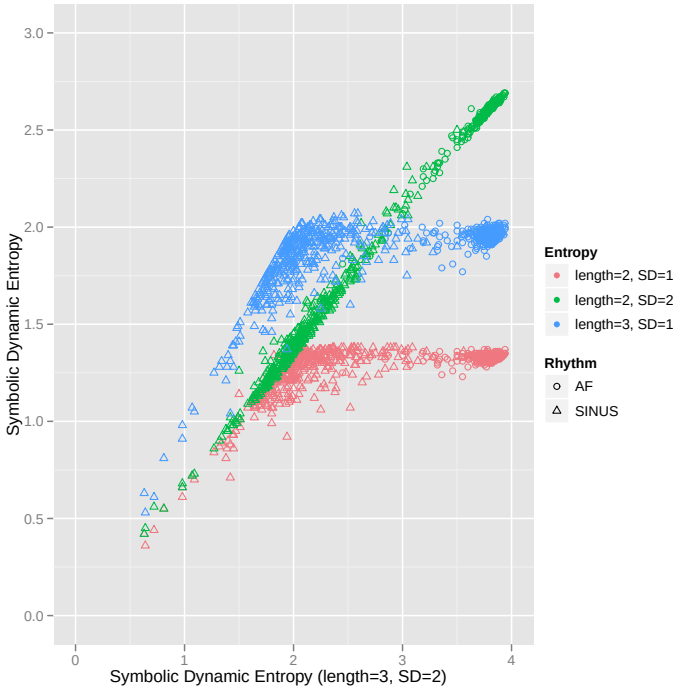
into only four areas does not give sufficient range to measure entropy in either SR or AF.

The correlations between different measures are shown in Table 3.15. There is almost perfect correlation, both in SR and AF, between the results in which the number of SDs used to define the areas is the same regardless of whether this is one or two; there is much poorer correlation otherwise, particularly in AF.

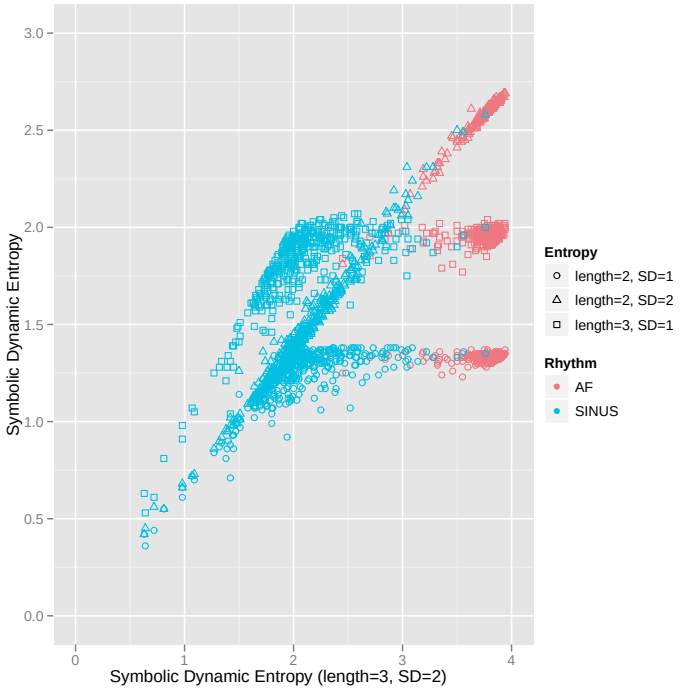
The best separation of AF and SR comes from using a "word" length of 3 letters and 6 areas defined by 2 SDs. This combination also avoids the plateau in the values described above and it was this measure that was taken forward in the analyses. When this measure was used to compare AF against SR they were found, perhaps not surprisingly, to be significantly different ($p < 0.00001$).

In comparing the longer acquisition against the shorter one a paired Wilcoxon test found the measures to be significantly different in both AF and SR ($p < 0.00001$ in both cases) although there was good correlation with $\rho = 0.761$ in AF and $\rho = 0.637$ in SR. As in the case of *ShanEnt* this suggests a systematic bias in the results and a Bland-Altman analysis finds this to be slight with longer acquisitions having on average an entropy 0.07 ± 0.28 higher in SR and 0.06 ± 0.14 in AF than in the shorter acquisitions.

In the subgroup analysis no significant difference was found in any of the subgroups other than the "pure" group in which there are no ectopic beats. Mean *SymDyn* in the "pure" group was 2.03 in SR and 3.80 in AF; in the "not pure" group mean *SymDyn* was 2.12 in SR and 3.71 in AF. These variations match the variations already seen in *ShanEnt* (see table3.13).



(a) Emphasising entropy



(b) Emphasising rhythm

Figure 3.21.: *SymDyn* using the techniques with the lower ranges plotted against the entropy found using the parameter with the highest range (word length = 3 letters, using areas defined by both 1 and 2 SD). The two plots present the same data with colour used in plot (a) to show the different symbolic dynamic definitions and in plot (b) to show differing rhythm.

3.4.3. Sample entropy (*SampEn*)

The third measure of entropy which was investigated, *SampEn*, is the most complex in that it incorporates the most information. *SampEn* is based on the conditional probability of finding repeating sequences of length $m + 1$ within a window of width r in the R-R interval stream (see §2.10.3).

The window width, r, may be expressed either in absolute terms or as a normalised fraction of the SD, here described as r_n (§2.10.3). *SampEn* was measured for five different values of r: $r_n = \{0.02, 0.20, 1.00\}$ and for and $r = 0.1$ s and $r = 0.1\bar{RR}$ (10% of mean R-R duration). These values of r were chosen to offer a very tight window, $r_n = 0.02$, a window comparable to that used in other studies in SR, $r_n = 0.2$, a window which is comparable to the division of the Poincaré plot in *SymDyn*, $r_n = 1$, a fixed window $r = 0.1$ s and an alternative form of normalisation, $r = 0.1\bar{RR}$. The number of additional beats, after the first one, in the sequence required for the sequence to be considered to match is defined by the parameter m. In this study assessments were made of *SampEn* for $m = \{0 \ldots 5\}$. These values were chosen to offer values which would allow comparison against *ShanEnt* ($m = 0$) and a standard sequence by which changes could be assessed.

The results for each combination of these measures are shown for r_n in figure 3.22 and for the alternative values of r in Figure 3.23.

The total number of patients for whom measures of *SampEn* could be calculated for each combination of m and r in both SR and AF are shown in Table 3.16.

The value for *SampEn* using normalised r exhibit a noticeable decrease in *SampEn* with increasing m for patients in AF. *SampEn* is incalculable in AF at larger m ($m > 3$) with smaller r_n ($r_n = 0.02$); there is a corresponding increase in *SampEn* with increasing r. These results seem intuitively correct so it is surprising that in SR there is little variation in the distribution of *SampEn* with increasing m although increasing r_n does reduce the spread and there was a small reduction in the number of patients for whom a value of *SampEn* could be obtained at very small r ($r_n = 0.02$) and high m ($m = 5$).

Considering *SampEn* calculated with the alternative values of r, there is little difference shown with increasing m. The fixed interval of $r = 0.1$ s gives a wider spread of entropy values for AF than using an interval of $r = 0.1\bar{RR}$. The two measures of r are likely to

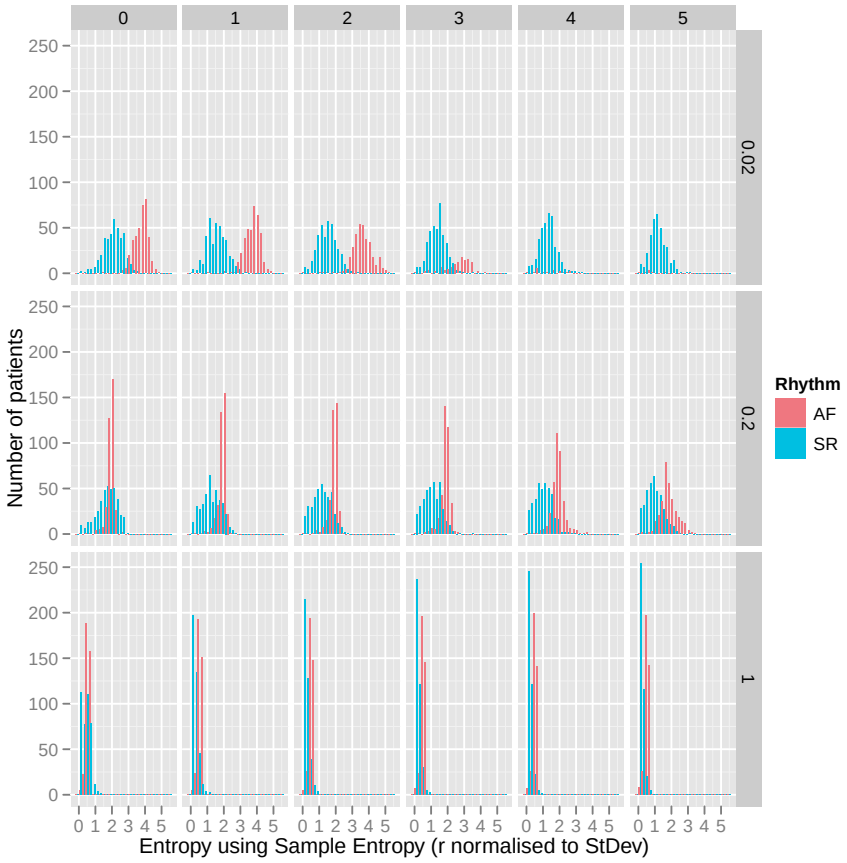


Figure 3.22.: Showing the change in *SampEn* with increasing values of m horizontally and different values of r_n vertically.(Bin-width = 0.2, Number of patients is shown in Figure 3.16).

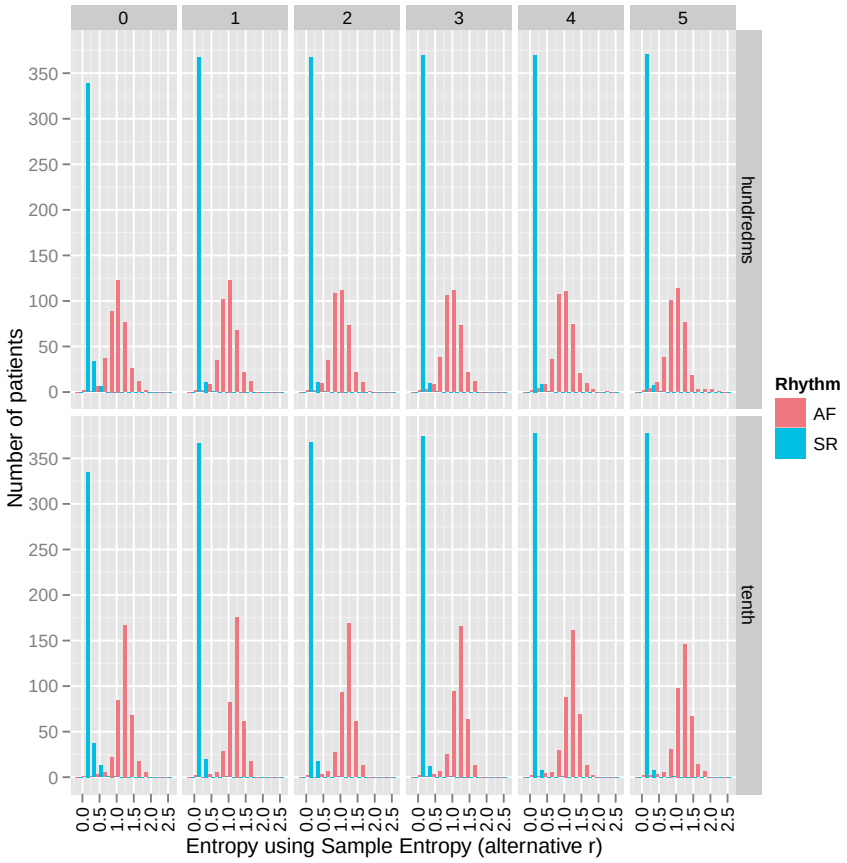


Figure 3.23.: Showing the change in *SampEn* with increasing values of m horizontally and different values of r, using $r = 0.1$ s (hundredms) and $r = 0.1\bar{R}R$ (tenth). (Bin-width = 0.2, Number of patients is shown in Figure 3.16).

	$m=0$		$m=1$		$m=2$		$m=3$		$m=4$		$m=5$	
	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N
$r = 0.1\bar{R}R$	0.102	388	0.057	388	0.053	388	0.049	388	0.046	388	0.045	388
$r = 0.1$ s	0.079	380	0.046	380	0.043	380	0.040	380	0.038	380	0.037	380
$r_n = 0.02$	2.041	397	1.530	397	1.436	397	1.329	396	1.250	381	1.151	**347**
$r_n = 0.20$	1.661	397	1.197	397	1.118	397	1.037	397	0.978	393	0.933	381
$r_n = 1.00$	0.407	397	0.233	397	0.214	397	0.192	397	0.179	397	0.171	397

(a) SR

	$m=0$		$m=1$		$m=2$		$m=3$		$m=4$		$m=5$	
	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N
$r = 0.1\bar{R}R$	1.281	376	1.256	376	1.249	376	1.246	376	1.247	376	1.249	376
$r = 0.1$ s	1.089	376	1.069	376	1.065	376	1.063	376	1.064	376	1.062	375
$r_n = 0.02$	3.808	376	3.756	376	3.669	**338**	2.693	**116**	1.420	**19**	0.737	**7**
$r_n = 0.20$	1.970	376	1.935	376	1.925	376	1.920	376	1.955	375	1.894	330
$r_n = 1.00$	0.563	376	0.557	375	0.555	375	0.555	375	0.554	375	0.554	375

(b) AF

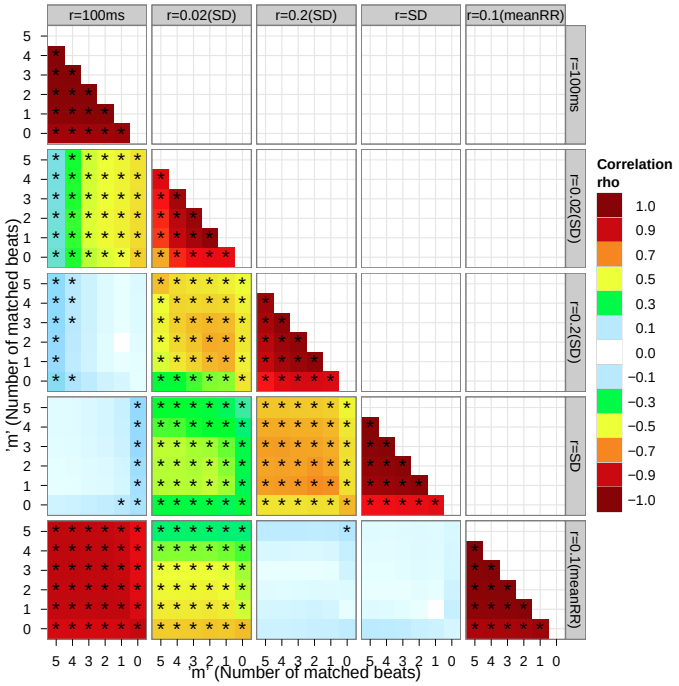
Table 3.16.: Mean and number of successful *SampEn* calculations with varying r and m for (a) SR and (b) AF.

be of the same order of magnitude as $RR \sim 1.3$ s (80 bpm). Surprisingly there are few differences in *SampEn* in SR with changes in either parameter.

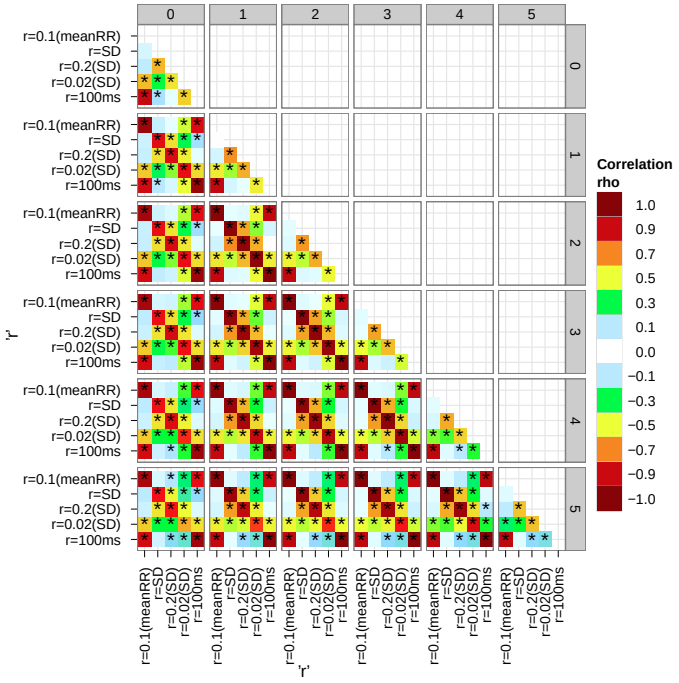
SampEn correlation

The correlation between the different measures of *SampEn* is shown in correlation Figures 3.24 (SR) and 3.25 (AF).

There are several observations which can be made from these plots. Firstly, the correlation between one member of a group defined by r and a member of another group, defined by a different r, is largely matched by the correlation between other members of the two groups; this can be seen in the clustering of colours in the plots which are grouped by r. Secondly, the deep red clustering on the central diagonal in SR, and to a lesser extent in AF, shows there is near perfect correlation between members of one group and the other members of the same group when the groups are defined by r (this is not true when the groups are defined by m). Thirdly, the clustering of colours when grouping is done by r, which is not seen when the grouping is by m, suggests that r has

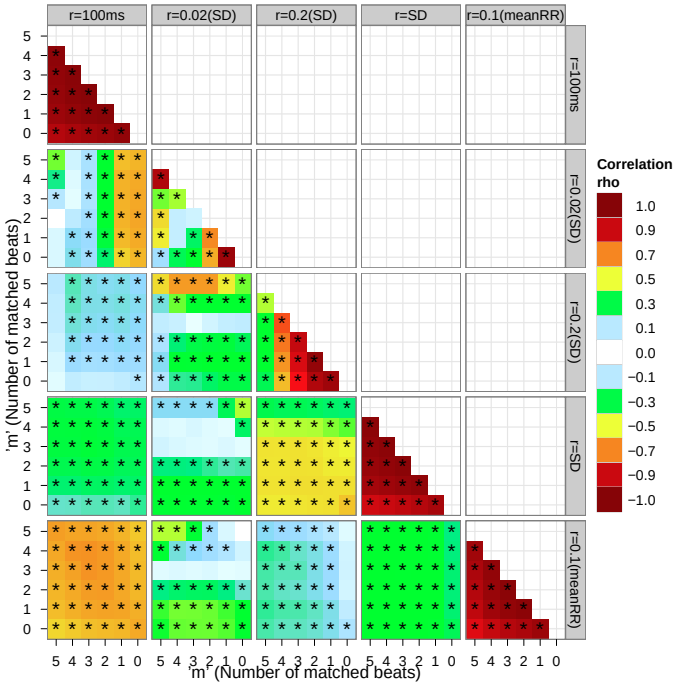


(a) Grouped by "r" (window width)

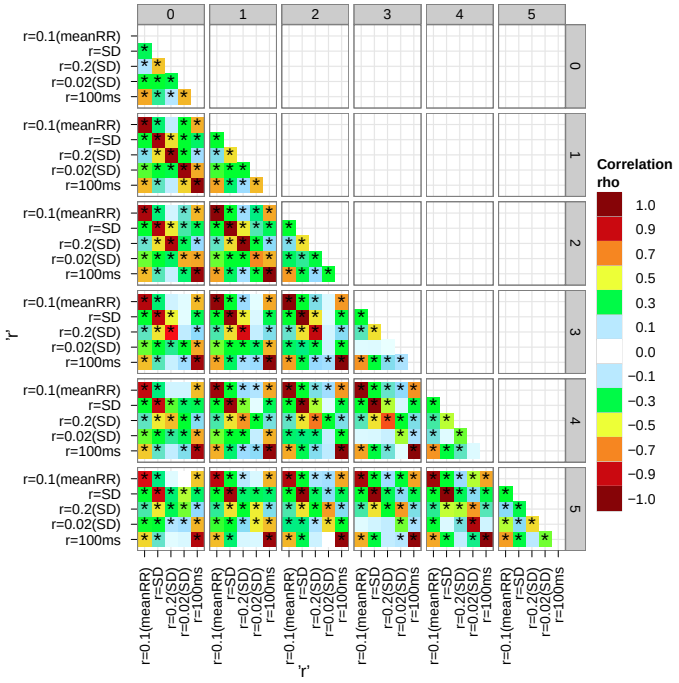


(b) Grouped by "m" (number of matched beats)

Figure 3.24.: SR: Showing the correlation between different measures of *SampEn* in SR. The colour shows the degree of correlation (with red being excellent correlation and blue being a weak correlation etc.). Results which are significant at the $p < 0.05$ level are flagged with a "*". The top half of the plot is blank to avoid reproducing results. The two plots show the same results grouped (a) by the value of r (the window width) and (b) by the number of matched beats. (Colour scale corresponds to the scale shown in Table 2.5).



(a) Grouped by "r" (window width)



(b) Grouped by "m" (number of matched beats)

Figure 3.25.: AF: Showing the correlation between different measures of *SampEn* in AF. The colour shows the degree of correlation (with red being excellent correlation and blue being a weak correlation etc.). Results which are significant at the $p < 0.05$ level are flagged with a "*". The top half of the plot is blank to avoid reproducing results. The two plots show the same results grouped (a) by the value of r (the window width) and (b) by the number of matched beats. (Colour scale corresponds to the scale shown in Table 2.5).

a greater effect on the assessment of *SampEn* than does m. Fourthly when the plots are considered as a whole, the dominance of blue and green in the plots, particularly in AF, suggests that there is generally better correlation between the different family members, defined by both r and m, in SR than there is in AF.

Which family member?

It is impractical to take all these measures of *SampEn* into any further analysis. Is there a single combination of m and r which is likely to provide the most information about about heart rate entropy?

Since SR is approximately regular while AF is irregular, it is to be expected that entropy, which is essentially a measure of regularity rather than complexity (lower entropy being indicative of greater regularity), should be greater in AF than in SR. The selection of a single combination of m and r should give good separation of AF and SR (SR being intrinsically better organised and therefore having lower entropy than AF) and a good spread of values for entropy (it being unlikely that results will all be the same over the 350+ patients in each group). The combination must also be measurable in all situations and should offer the same results regardless of duration.

Figure 3.26 shows the range of *SampEn* measurements for patients in SR and AF with each of the combinations of r and m. It is clear from this that the combination of $r = 0.02SD$ and $m = 0 \ldots 3$ gives the widest range and clearest division between SR and AF.

The number of cases for which *SampEn* could be calculated are shown in Table 3.16, and it can be seen from this table that, unsurprisingly, increasing the number of beats considered reduces the number of calculable results. The highest m value for which *SampEn* can be calculated in every case with $r = 0.02SD$ is $m = 1$ which still gives good separation of AF and SR although it offers only a small increase in information content.

Figure 3.28 presents the correlation between the longer and shorter acquisitions in SR and AF. The best overall correlation is with $r = 0.02(SD)$ and $m = 0 \ldots 1$.

There is a possibility that *SampEn* measures show a similar plateau as is found for certain measures of *SymDyn*. The plot in Figure 3.27 shows this not to be the case. It

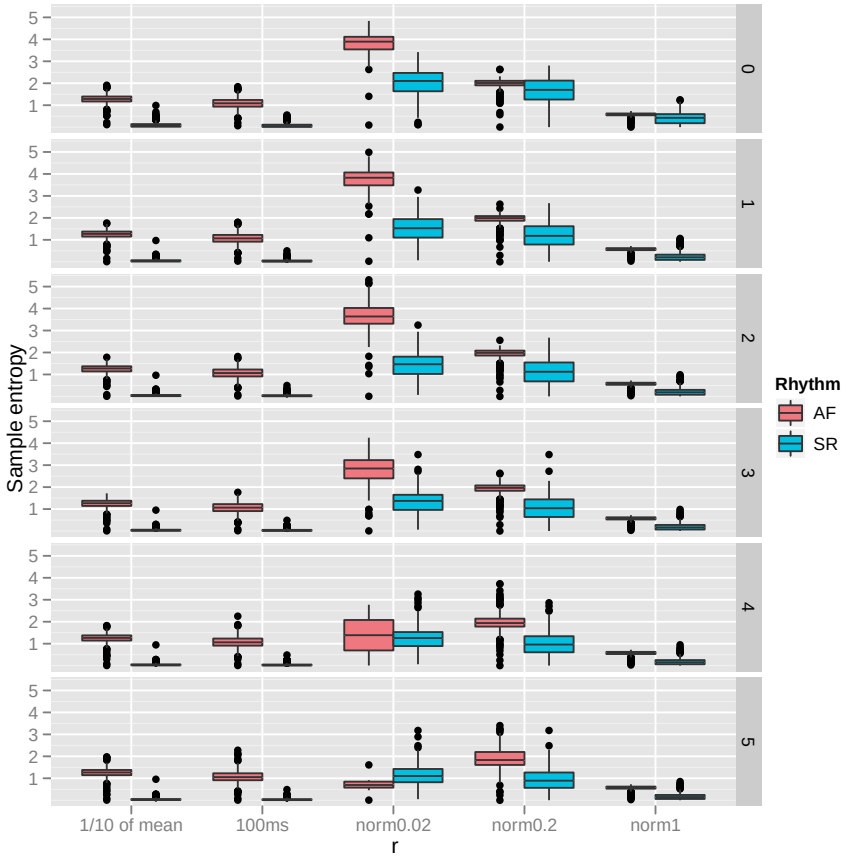


Figure 3.26.: Showing the range of *SampEn* for different different metrics with Y-axis showing different values of r and with separate plots grouped by m. Y-axis in each plot shows the value for *SampEn* calculated from the long acquisition.

is therefore reasonable to take this measure (*SampEn* with $r = 0.02SD$ and $m = 1$) into the rest of the analysis.

SampEn with $m = 1$ and $r = 0.02SD$

Having selected a single combination of $m = 1$ and $r = 0.02SD$ for calculation of *SampEn* these results were carried forward in a similar analysis to that of previous measures of entropy and variability.

When the results were compared, for this combination of m and r, between the long and short acquisitions a paired Wilcoxon test found there to be a significant difference between the acquisitions in SR ($p = 0.030$) but not in AF. The Spearman rank correlation between the acquisitions showed $\rho = 0.951$ in SR and $\rho = 0.856$ in AF (both with

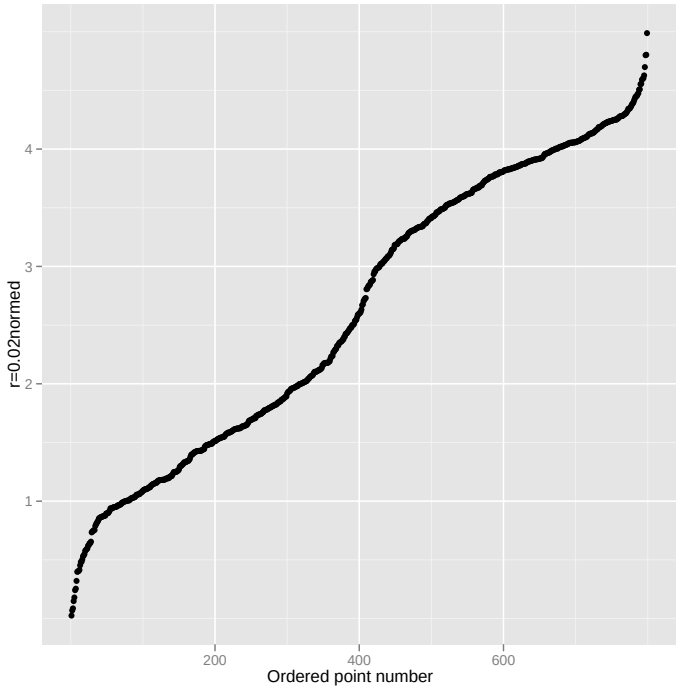
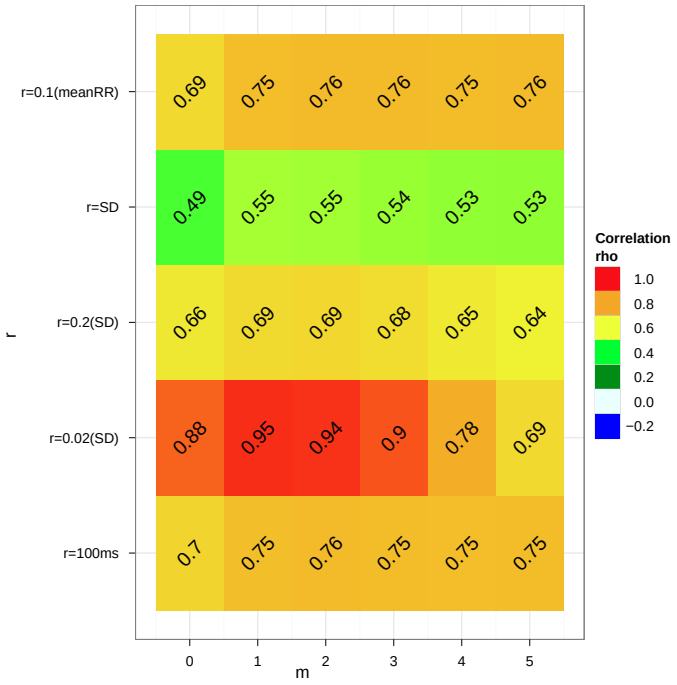


Figure 3.27.: Showing the values of *SampEn* with $r = 0.02SD$ and $m = 1$ for all patients in both SR and AF combined. Sorted by value to determine whether there is a plateau in the results.

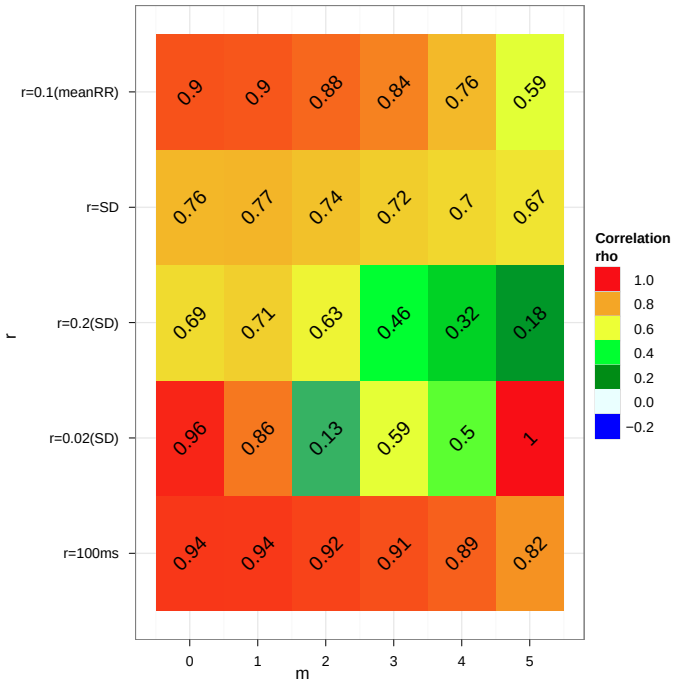
$p < 0.00001$). This suggests that in SR there is a slight change in entropy as the acquisition time increases. This is confirmed by the Bland-Altman analysis which finds the longer acquisition to have a slightly lower entropy with a mean difference (long - short) in SR of -0.021 and in AF of -0.046. Although *SampEn* is intended to be consistent over short time intervals, there is inevitably a duration of acquisition which is too short for the calculation to be accurate. It is possible that a 5 min acquisition is in this region.

Since the choice of m and r was visually made to ensure that there was good separation between AF and SR it is unsurprising that a Wilcoxon signed ranks test finds that the measured values of *SampEn*, summarised in Table 3.17a are significantly different with $p < 0.00001$ for the comparison between AF and SR.

Looking at the subgroups, the comparison is shown in Table 3.18, a significant variation was found in patients with ischaemia and with function in both SR and AF (summary statistics shown for these results in Table 3.17b). There was also found to be a very weak negative correlation with age in SR. There was no significant difference in any of the other subgroups.



(a) SR



(b) AF

Figure 3.28.: Showing the correlation in *SampEn* between the longer and shorter acquisitions for each combination of r and m for which measurements were made in (a) SR and (b) AF.

Rhythm	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
AF	1.092	3.483	3.827	4.067	4.988	3.761	0.469
SR	0.069	1.102	1.527	1.955	3.268	1.531	0.575

(a) All Patients

Rhythm	Subgroup	Min	1^{st} Quartile	Median	3^{rd} Quartile	Max	Mean	SD
AF	Ischaemic	3.081	3.841	4.003	4.093	4.388	3.928	0.318
AF	Non-Ischaemic	1.092	3.459	3.804	4.058	4.988	3.744	0.479
AF	Very poor function	2.973	3.250	3.459	3.543	3.751	3.395	0.296
AF	Poor function	1.092	3.412	3.660	3.933	4.429	3.616	0.561
AF	Moderate function	2.178	3.440	3.801	4.065	4.803	3.730	0.474
AF	Mildly impaired function	1.531	3.487	3.847	4.072	4.600	3.792	0.437
AF	Normal function	2.873	3.599	3.905	4.133	4.800	3.868	0.402
SR	Ischaemic	0.180	1.324	1.706	2.001	3.268	1.670	0.571
SR	Non-Ischaemic	0.069	1.073	1.488	1.892	2.956	1.503	0.573
SR	Very poor function	0.531	0.906	1.095	1.464	1.958	1.191	0.405
SR	Poor function	0.087	1.018	1.379	1.666	2.956	1.371	0.671
SR	Moderate function	0.398	1.130	1.543	2.087	2.934	1.562	0.585
SR	Mildly impaired function	0.06903	1.098	1.486	1.811	2.808	1.498	0.561
SR	Normal function	0.406	1.181	1.623	2.009	3.268	1.612	0.559

(b) Subgroup

Table 3.17.: Summary values for *SymDyn*. Table (a) shows the results for the whole group, table (b) for the subgroups.

3.4.4. Comparing entropy

The three different measures of entropy which have been measured in this study all purport to offer a measure of regularity and hence it is to be expected that there should some agreement between them. Each measure, however, uses a different set of variables and, in the case of *SampEn*, a different equation by which the entropy is calculated. Thus each of the three measures form a different approximation to the regularity of the system.

It should be possible to determine a set of variables for each measure which allow them to be compared. Since *ShanEnt* relies only on the bin-width / number of bins and there is no sequencing information incorporated, measures of *ShanEnt* should be comparable to measures of *SampEn* with $m = 0$ where there is also no sequencing information included. It is unlikely that there will be a clear agreement with *SymDyn* since the

	SR			AF		
	Within	Outwith	Result	Within	Outwith	Result
"Pure" ECG	1.481	1.572	NS	3.765	3.768	NS
MI	1.445	1.563	NS	3.843	3.718	NS
HBP	1.479	1.569	NS	3.742	3.769	NS
Intervention	1.454	1.552	NS	3.819	3.743	NS
Ischaemic	1.501	1.670	$p = 0.026$	3.739	3.928	$p = 0.012$
Pos / Neg ETT	1.580 $(+ve)$	1.694 $(-ve)$	NS	3.921 $(+ve)$	3.796 $(-ve)$	NS
Function	1.315	(Poor & Very poor)	$p = 0.014$	3.596	(Poor & Very poor)	$p = 0.006$
	1.562	(Moderate & Mild)		3.730	(Moderate & Mild)	
	1.612	(Normal)		3.868	(Normal)	
Age	-	-	$\rho = -0.119$	-	-	NS
Graining	-	-	-	3.810	(FINE)	NS
				3.819	(MEDIUM)	
				3.916	(COARSE)	

Table 3.18.: Subgroup analysis of *SampEn* using $m = 1$ and $r = 0.02SD$. The p value is given where a significant difference was found (where there was no significant difference this is marked with "NS"). Number of patients in each group are given in Tables 3.4 (SR) and 3.5 (AF).

principal determinant of the number of states in the symbolic dynamic representation is sequencing information and not bin-width [1]. Similarly it might be expected that there would be agreement between *SymDyn* and *SampEn* where $r \sim SD$ $(r_n = 1)$ since measures of *SymDyn* have been made based on areas determined by the SD, SD. However the calculation of *SampEn*, while based on Shannon theory, is not the same as the calculation of Shannon entropy used in *SymDyn* and there is unlikely to be direct agreement.

Figures 3.29 and 3.30 show correlation plots for selected measures of entropy using the three different techniques in SR and AF respectively. The plots show the predicted agreement ($p = 0.98$ in SR, $p = 0.95$ in AF) between *ShanEnt* and *SampEn* with $m = 0$ when $r = 0.02SD$. The agreement is still excellent, although slightly poorer, when $m = 1$ ($p = 0.82$ in SR, $p = 0.91$ in AF). The expected agreement is not seen when *SymDyn* is compared with *SampEn* where $r = 1SD$ (or any other value of r). This is true in both AF and SR although the difference is more pronounced in AF. The most likely reason for the non-agreement is that in assessing *SampEn* the window position changes to be centred on each beat. In *SymDyn* the areas are fixed, based on summary measures of all beats and do not shift.

[1] In *SymDyn* the number of combinations of letters, N_s, increases according to the formula $N_s = b^l$ where b is the number of areas and l is the length of "word" (sequencing information)

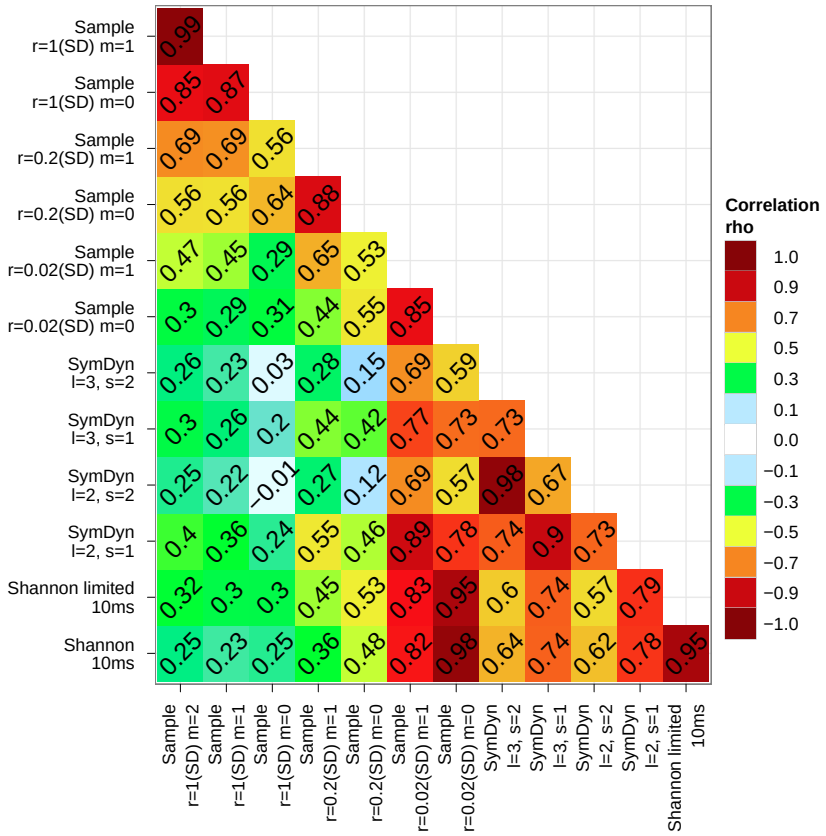


Figure 3.29.: SR: Showing the correlation between selected measures of entropy in SR. (Colour scale corresponds to the scale shown in Table 2.5.)

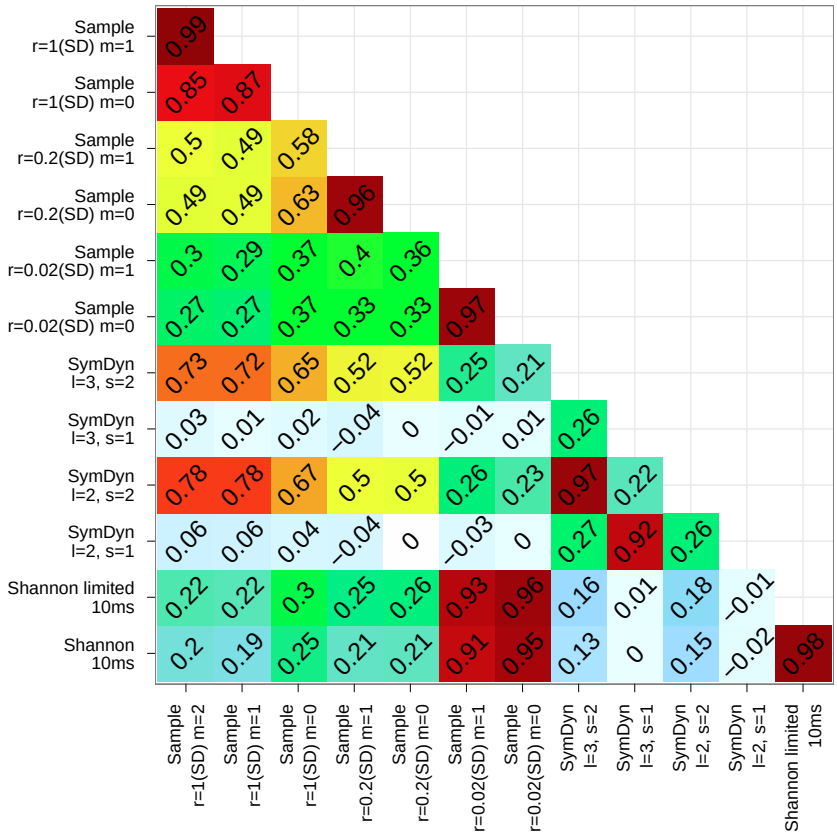


Figure 3.30.: AF: Showing the correlation between selected measures of entropy in AF. (Colour scale corresponds to the scale shown in Table 2.5.)

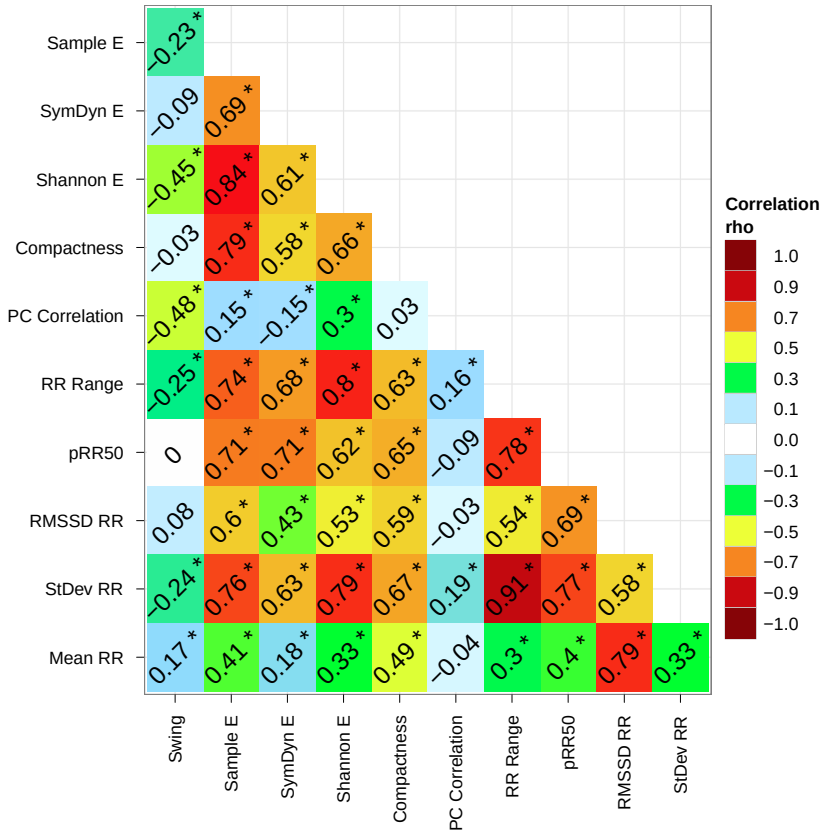


Figure 3.31.: SR: Showing the correlation between the different measures which have been made to describe R-R variability in SR. (Colour scale corresponds to the scale shown in Table 2.5.)

3.5. Comparing all measures of rhythm

The analysis of rhythm has considered six typical linear measures of variability (in the time domain), two measures of the Poincaré plot and three different measures of entropy. How do these compare?

Figures 3.31 (SR) and 3.32 (AF) show the correlations between the various measures which have been used to describe R-R variability in this thesis.

The good or excellent correlation between R-R range, SD and RMSSD is to be expected, as "tighter" distributions are likely to have less variability. It is also reasonable to expect that rhythms in which there is a lower pRR50 value will have lower $RMSSD_{rr}$ and SDRR a low pRR50 suggests that beats are largely within 50 ms of each other.

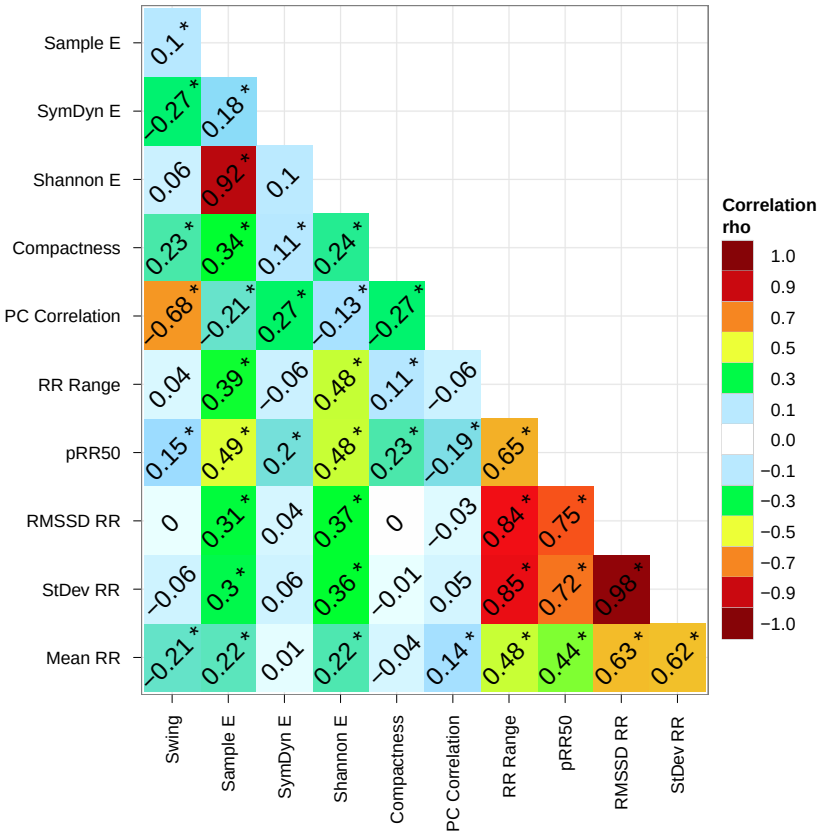


Figure 3.32.: AF: Showing the correlation between the different measures which have been made to describe R-R variability in AF. (Colour scale corresponds to the scale shown in Table 2.5.)

There is a clear negative correlation between *swing*, the proportion of R-R changes on the *delta Poincaré plot* which fall in the top left or bottom right quadrants, and the Poincaré correlation - this suggests that "long - short - long - short" alternating beats tend to alternate across the mean. "Long - short - long - short" appears to be a better description in AF than in SR where the correlation is weaker.

There is a, perhaps surprisingly, good correlation between mean R-R interval and RMSSD in both AF and SR. It is also unclear that there should be a moderate negative correlation between *swing* and mean R-R interval in AF which is not seen in SR. This suggests that in AF the faster the rhythm the fewer beats follow the "long-short-long" pattern. The number of patients involved makes this likely to be a genuine result as the sample group is relatively large.

In SR, SDRR, and RMSSD, correlate well with the chosen measures of entropy; this is not true in AF. Similarly they correlate well with *compactness factor* in SR but not in AF. The converse is also true: in SR there is a good or excellent correlation between *compactness factor* and all three measures of entropy while there is only poor or moderate correlation in AF. This shows that in SR the spread of beats (as measured using the *compactness factor*) is closely associated with the regularity of the rhythm. In AF the association is much less well defined.

In AF there is a good negative correlation between *swing* and the Poincaré correlation which suggests that the better the agreement between one beat and the next the lower the proportion of "long-short-long" beats. This is intuitively unsurprising although the Poincaré correlation in AF is so poor that the result may have little import.

These measures allow a picture of the rhythm of an individual patient to be built up in terms of the beat-to-beat relationships, and the pattern and spread of change seen within them. These indices may be indicative of the functional variations seen within patients, particularly those in AF, and will be taken forward (in Chapter 6) for comparison with the functional measures which are discussed in Chapters 4 and 5.

Chapter 4.

Methods: Describing Function

Summary

In which the initial postulate is described, together with modifications to the Link Medical list-mode formatting program to permit beat selection on preceding R-R interval criteria. An experiment to prove the effectiveness of these modifications is detailed together with its results.

Later sections explain the process of data acquisition and formatting, the steps involved in analysis, a summary of the parameters measured, and a description of the comparisons made.

4.1. Beat to beat dependence

It seems intuitively likely that there is a relationship between one heart beat and the next both in AF and SR; in particular we can hypothesise that the longer the ventricle

has to fill, the greater the volume of blood within it. Since there is no clear mechanism by which the duration of systole could be predicted by the pre-systolic volume, a longer beat must cause either a greater change in the volume of blood in the heart during subsequent systole or an increase in the total volume of blood in the ventricle.

Various studies [67–71, 86] have found evidence to support the hypothesis that behaviour of the beat under investigation (the indexed beat) is dependent on characteristics of the previous beat.

The first aim in describing function in both SR and AF was to determine whether there was evidence to support the hypothesis that measured LVEF was dependent on the preceding beat and, if so, to try to determine the parameters which most accurately reflect cardiac function in patients in SR or AF. In particular, to what extent does assessment of LVEF in patients with AF depend on the range of R-R intervals selected for gating studies? To investigate this a number of questions can be asked:

- What is the range of EFs that can be measured by applying different R-R selection parameters to the same patient / acquisition?
- Does the EF change if the same R-R selection parameters are applied at different times in the acquisition?
- How does measured EF change with increasing R-R?
- How does measured EF for all beats relate to that determined using the selected R-R interval?
- How does average measured EF using a variety of beat selection criteria compare with measured EF for all beats?
- Are the results from the above true for fixed as well as variable time processing?
- Does processing based on the length of the previous beat reduce the range of EF measured, if you process only on the previous beat?
- Does previous beat processing reduce the range of EFs measured if you process on both the previous and the indexed beat?

A similar set of questions can also be asked about other measurements of ventricular function such as pre-systolic volume, the duration of systole or peak filling rate. These questions can be addressed by making use of list-mode acquisition which allows post-processing on pre-defined criteria (see §1.5.5).

4.2. Modifying and proving the program

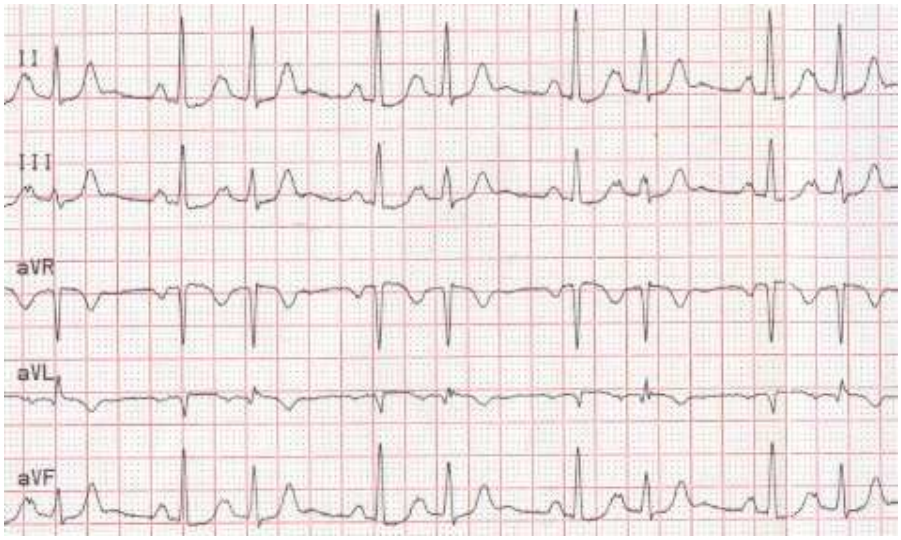
4.2.1. Method

It is conceptually possible to format a list-mode file in any way you choose (see §1.5.5); however, standard formatting programs produced by manufacturers, including Link Medical Ltd., do not allow preceding beat selection criteria. A modification was made to the original source code for list-mode formatting in the MAPS 10000 software (made available by Link Medical Ltd.) in the "C" programming language. Tests were performed to prove that the modification is correct. These involved moving a pair of sources synchronously with a bigeminy rhythm.

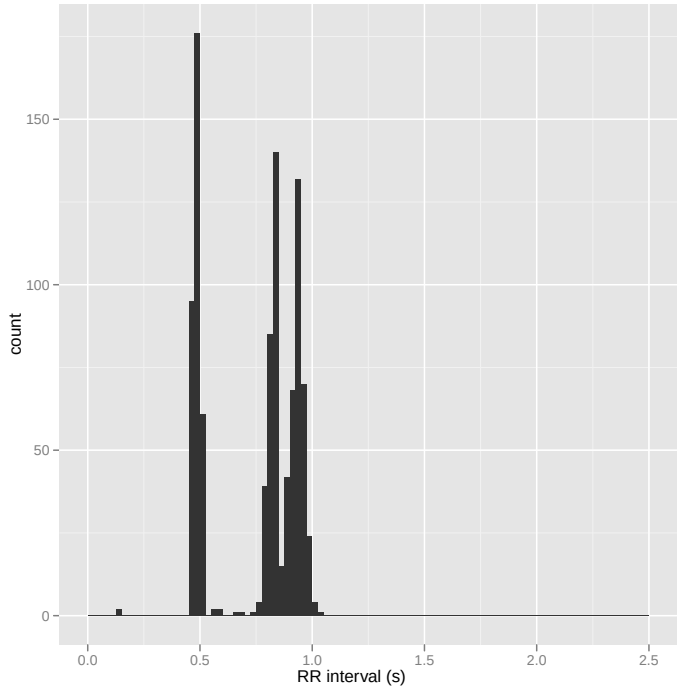
A bigeminy rhythm consists of regular beats with regular ventricular ectopic beats superimposed in such a way that every normal beat is succeeded by an ectopic beat. Every ectopic beat is followed by short pause and then a normal beat. The effect is to produce a regular "long - short - long - short" beat pattern which has an ECG trace and histogram as shown in Figure 4.1

An ECG simulator was used to generate an absolutely regular bigeminy pattern. By moving two sources of different activity along perpendicular lines such that one source moves horizontally during, say, the long beats and the second source moves vertically during the short beats, it should be possible to isolate movement in one or other direction by selecting only the short or the long beats. This can be done in one of two ways: either by selecting on the indexed beat, or by selecting on the preceding beat. Thus the image which is generated (from the same list-mode file) when selecting on the short indexed beat, should be the be same as that generated when selecting on the long preceding beat, and vice versa.

Two $\sim$ 12MBq ^{99m}Tc sources of $\sim$ 0.5 ml in 10 ml vials were manually slid in perpendicular directions across the surface of the collimator on the gamma camera. Each source was moved $\sim$ 20 cm and back to the starting point. Movement of the sources was alternated so that one source was moved vertically during the long beats and the second source was moved horizontally during the short beats. Only one source was moved at a time. Using this process a list-mode file was acquired over $\sim$ 82 s. Considerable rhythmic skill is required to move one source in one direction with duration A and delay B while moving a second source in a perpendicular direction with duration B and delay A but with practice it was achieved.



(a) Bigeminy ECG



(b) Bigeminy histogram

Figure 4.1.: Showing (a) part of a typical atrial bigeminy rhythm and (b) the resulting histogram for the same patient.

	Counts	Accepted Beats	Rejected Beats
Long Indexed	286232	55	56
Short Indexed	167235	55	56
Long Preceding	167235	55	56
Short Preceding	286232	55	56
Short - Short	0	0	111
Short - Long	286232	55	56

Table 4.1.: Counts in images for different beat selection criteria in absolutely regular bigeminy rhythm used to test program modifications.

The effectiveness of the modifications can be assessed by comparing the images generated by selecting beats on the following criteria.

1. Long indexed beat
2. Short indexed beat
3. Long preceding beat
4. Short preceding beat
5. Short preceding beat and short indexed beat
6. Short preceding beat and long indexed beat.

In the case of number 5 all beats should effectively be excluded (since a "short - short" pattern should never occur), while the image produced for number 6 should be the same as that produced for number 4. Otherwise the image and the total counts in the image should be very similar for numbers 1 and 4 and for numbers 2 and 3.

4.2.2. Results

The resulting images are shown in Figure 4.2; the associated total counts in each image are listed in Table 4.1. It is clear from these results that the modification to the program is correct and subsequently the modification has been incorporated by Link Medical into its standard list-formatting program.

It is notable that the ratio of counts in the short indexed beats, R-R interval: 0.54 s (111 bpm), to those in the long indexed beats, R-R interval: 0.93 s (64 bpm), is the same as the ratio of the R-R intervals (0.584 compared to 0.581). While this is to be expected

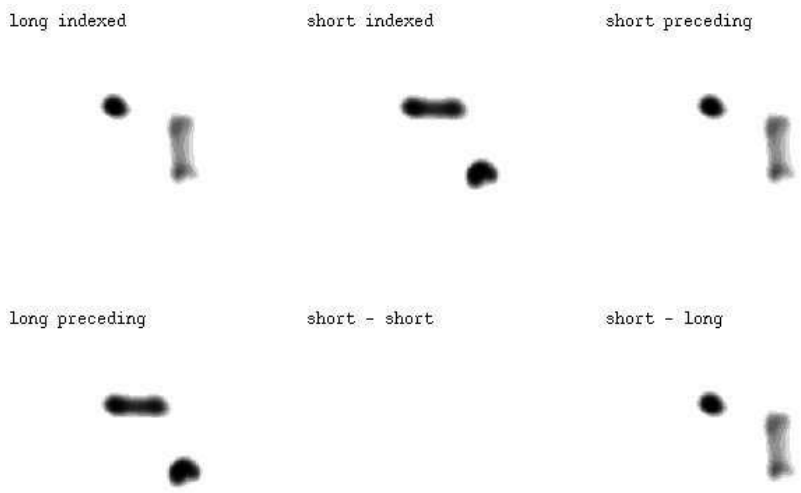


Figure 4.2.: Images produced using different beat selection criteria in bigeminy rhythm to prove the modifications to the list-mode formatting program. Short indexed beats produce the same image as long preceding beats and vice versa thus proving the program modifications.

it demonstrates the statistical problem in comparing images made up of shorter beats to those consisting predominantly of longer beats.

A minor difference in counts between those images with preceding beat selection criteria and those selected only on the indexed beat would be expected because the initial beat cannot be counted when processing on the preceding beat. However no difference is seen because the formatting program is written such that when processing on the indexed beat the initial beat is also ignored. Data acquired before the first ECG pulse, after the last ECG pulse and between the first and second ECG pulses is ignored in all cases where a gated image is acquired. This means that summing the total counts in the short and long beat images ($286232 + 167235 = 453467$) gives fewer total counts than formatting the whole list-mode file into a single image (461452 counts).

Overall the results showed the modifications that were made to the list-mode formatting program to correctly select beats depending on criteria set for indexed and preceding beats.

4.3. Data acquisition and processing

The selection of patients and the initial acquisition of list-mode files has been described in §2.2 and §2.5.2 respectively. While Chapters 2 and 3 investigated the sequence of R-R intervals in the R-R interval stream obtained from the list-mode files, the analysis of function described in this chapter investigated images that were produced from the list-mode files.

4.3.1. Data acquisition

As described in §2.5.2 list-mode files were acquired at best septal separation ($\sim 40\,^\circ$) left anterior oblique (LAO) and 70 ° LAO projections. In this part of the study, only the best septal separation acquisitions are of interest as all functional measurements were made from these. Quantitative functional measurements cannot be made from 70 ° LAO projections because results are distorted by the overlap of the left and right ventricles.

The 40 ° LAO list-mode files were acquired for 15 min if the patient was in AF or for 10 min if the patient was in SR. List-mode files were acquired with a temporal resolution of 100 μs and a spatial acquisition matrix of 1024×1024, corresponding to a spatial resolution of ~ 0.4 mm (this is considerably smaller than the system resolution of the gamma camera with a low energy high sensitivity collimator, ~ 4 mm).

Two different models of gamma camera were used: the IS2 Pulse and a GE Optima. The IS2 cameras allow native list-mode acquisition with list-mode files being transferred in a private DICOM format to the Link Medical MAPS 10000 system for processing. List-mode acquisitions on the GE Optima camera are made through a third party (Link Medical Ltd) hardware interface. Thus list-mode files are acquired directly on to the Link Medical MAPS 10000 system from the GE Optima heads. Low energy, high sensitivity collimators were used on both cameras (sensitivities at 140 keV: 330 ± 30 cts/MBq (GE Optima), 308 ± 34 cts/MBq (IS2 Pulse)).

4.3.2. Data processing: Image files

Processing list mode files to create images for cardiac studies involves:

1. Selecting which heart beats (R-R intervals) should be included and
2. Constructing a gated image from scintillation events occurring in the selected R-R intervals within the list-mode study.

Dealing with each of these in turn:

Beat selection

Beat selection was done on the basis of:

1. Inclusion or exclusion of outlying beats
2. Indexed beat length (R-R interval) as each beat (from beat 2 to N) in the list mode file is considered in turn
3. Preceding beat length (R-R interval) as each beat (from beat 1 to $N-1$) in the list mode file is considered in turn.

Outlying beats: The beat histogram (see §2.5.3) for the complete list-mode file was examined and limits which excluded beats considered to be outliers were determined for each patient, regardless of rhythm. Thus a patient in SR with a modal beat length of 0.9 s ranging from 0.85 s to 0.95 s but with a single ectopic beat of 1.5 s would have a limit defined (say, at 1.3 s) between 0.95 s and 1.5 s which would exclude the single long beat.

The subsequent formatting programme automatically determined limits from the longest and shortest beats *within the manually imposed limits*. Thus in the above example the final maximum limit would be defined as 0.95 s although the manual limit was placed as 1.3 s.

Images were also created without limiting the R-R interval range and comparison was made between the two sets of images to determine whether outliers had a substantial effect on functional measures.

Beat length and formatting criteria: A text file was created from the list-mode file listing individual beat lengths.[1] By sorting the individual beat lengths and dividing the total number of beats by 4, the beat length quartiles, Q1 to Q4, could be determined.

[1] Temporal resolution is limited by the frequency of time markers which in a list-mode file from the IS2 pulse gamma cameras occurs every 100 µs.

Q1 was defined as being the first $N/4$ beats with the shortest R-R interval, while Q4 was the $N/4$ beats with the longest R-R interval for each patient (where N, here, is the total number of beats within overall acceptance limits). Each of these quartiles was then used to define a series of limits of inclusion for both the indexed and preceding beat. In most patients in SR the inter-quartile limit would occur between beats of the same length, in which case beats of the same length were included in both "quartiles".

Two further sets of limits were defined:

"All": In which all beats are taken.

"Best": Beat acceptance limits of 300ms centred on the most frequent group of beats (100ms bins) in the beat histogram.

These two sets of limits were chosen because "All" offers the most comprehensive average of the beats and therefore is likely best to represent average cardiac function. The "Best" limits are most similar to the limits used in many Nuclear Medicine departments, including the department of Nuclear Cardiology in Glasgow. They offer a fairly narrow band of frequent beats which will cause little distortion of the curve from one beat to the next.

The limits were applied both to preceding and indexed beats with preceding beat criteria taking precedence over indexed beat criteria, so that where both preceding and indexed beat criteria were applied, the indexed beat criteria were used only after selection of beats had already been made on the preceding beat. The effect of this, in a perfectly uniform, random distribution (which AF is not, as shown in Chapter 3), would be to reduce the total number of counts in the image by a factor of 16. Taking a quartile of the preceding beat would reduce the number of accepted beats by a factor of 4 with the full range of indexed beats represented, taking quartiles of these reduces the remaining beats by further factor of 4 thus reducing the total number of beats (and therefore counts) by a factor of ~ 16.

It should be remembered that selecting "All" preceding beats is the same as not applying any preceding beat selection criteria; similarly using "All" indexed beats is equivalent to not applying any indexed beat selection criteria.

Image creation

Two distinct techniques exist for creating gated images: variable time and fixed time formatting (see §1.5.2). Standard practice in the department is to use 24 frame gating. This has been shown to be sufficient for an accurate determination of end-systole [87] and functional parameters including EF and first third filling.

List files were formatted into 24 frame gated images using both fixed and variable time formatting.

Each list-mode file was formatted using every combination of the three parameters: gating (fixed or variable), preceding beat selection (Q1-Q4, "All" and "Best"), and indexed beat selection (Q1-Q4, "All" and "Best"), within the pre-determined R-R interval acceptance limits. In addition list-mode files were also divided into three time ($t_i = t_{all}/2$) segments (start to middle, first quarter to third quarter, and middle to end) each of which was formatted in both fixed and variable time for "All" and "Best" indexed and preceding beat selection criteria (and not Q1 to Q4). This was done to determine whether results were consistent over time for a single patient. In total each list-mode file was formatted into 84 different image files:

- 36 (6×6) preceding (Q1-Q4, "All" and "Best") and indexed (Q1-Q4, "All" and "Best") criteria in fixed time mode.
- 36 (6×6) preceding (Q1-Q4, "All" and "Best") and indexed (Q1-Q4, "All" and "Best") criteria in variable time mode.
- 12 ($2 \times 2 \times 3$) "All" and "Best" preceding and "All" and "Best" indexed criteria for each of the three $t_i = t/2$ segments in variable time.

4.3.3. Image processing

Each of the images resulting from the process described above (§4.3.2) was further analysed to produce a final set of images from which curves showing functional changes for both left and right ventricles could be assessed.

All patients in this study came to the department for diagnostic imaging and all images were routinely reported. The routine process involves formatting list-mode data using beat selection limits which are manually defined around the principal peak in the R-R

histogram. The resultant images are zoomed to create an image in which the pixel size is constant over all three gamma cameras in the department and in which the heart occupies most of the centre of the image (although clearly this will vary depending on the size of the heart). The zoomed images are subsequently processed by drawing regions of interest (ROIs) around the left and right ventricles and corresponding background regions. A second set of regions is drawn to estimate the error in measurement.

A similar process was applied to each of the 84 images for each patient in this study.

1. The same zoom (both in terms of location and magnification factor) was applied to each image as was applied to the images in the original report.

2. The zoomed and gated images were then smoothed twice using a 9 point [4,2,1] Gaussian smooth [2], and twice more, cyclically, using a linear [1,2,1] temporal kernel.

3. The ROIs used in the routine clinical report, consisting of LV, LV background, RV and RV background, each drawn twice to assess consistency, were applied to the smoothed gated image to create two sets of curves for each region. *The same regions were used for every image.* Each set of regions was separately checked by a second observer against both the original, clinical image and the image produced using all beats to ensure that the ROI was appropriately positioned.

4. Background curves were smoothed 100 times using a 3 point [1,2,1] Gaussian smooth. This is a slightly curious way of averaging all the counts in the background curve. A similar result could be achieved simply by calculating an average of the complete curve.

5. After accounting for the difference in area between the background and ventricular regions, each of the massively smoothed background curves were subtracted from each of the ventricular curves to give four curves ($LV_1 - Bg_1$, $LV_1 - Bg_2$, $LV_2 - Bg_1$, $LV_2 - Bg_2$) of counts vs. frame for each ventricle.

[2]Smoothing works by convolving a 2D image by a 2D kernel such that each point in the image is weighted by the kernel. A 9 point [4,2,1] Gaussian smooth has a kernel:

$$\begin{pmatrix} 1 & 2 & 1 \\ 2 & 4 & 2 \\ 1 & 2 & 1 \end{pmatrix}$$

The kernel is centred on each pixel; the pixel is assigned a new value based on the weighted average of the 9 pixels covered by the kernel with the weighting given by the value in the kernel. This is

To ensure that the ROIs were positioned correctly and the the correct zoom had been applied each of the formatted and zoomed images, with all beats included, and their regions were manually compared against the original, clinically reported, images. Where an apparent difference was found (3 cases) the difference was investigated and corrected; in each case it was because a different imaging head (on the same camera) had been used.

An example of the regions of interest is shown in Figure 4.3.

4.3.4. Curve analysis

Analysis of the curves formed the principal assessment of function. Several different analyses were carried out and are described in later sections; however, the principal measures determined were:

- Left ventricular ejection fraction (LVEF)
- Pre-systolic volume (PSV)
- Pre-systolic vs. end-diastolic volume (EDV/PSV)
- Systolic time interval
- First third filling fraction (FTFF)
- Peak filling rate (PFR).

Although measurements were taken for both the left and the right ventricle the analysis in this thesis has been limited to LV values.

---

done for every pixel in the image. At the edges, that part of the kernel which does not overlap a pixel is simply ignored (although other options, such as wrapping, could be used).

Mathematically the new image O is expressed as:

$$O(i,j) = \sum_{k=1}^{m}\sum_{l=1}^{n} I(i+k-1, j+l-1)K(k,l)$$

Where $1 \leq i \leq M-m+1; 1 \leq j \leq M-m+1$ and image I has dimensions (M,N) and kernel, K, has dimensions (m,n).

A cyclical smooth applies the same thing but, instead of using X vs Y coordinates, the, orthogonal, X vs Time coordinate system is used and the last frame is wrapped to be beside the first frame[88].

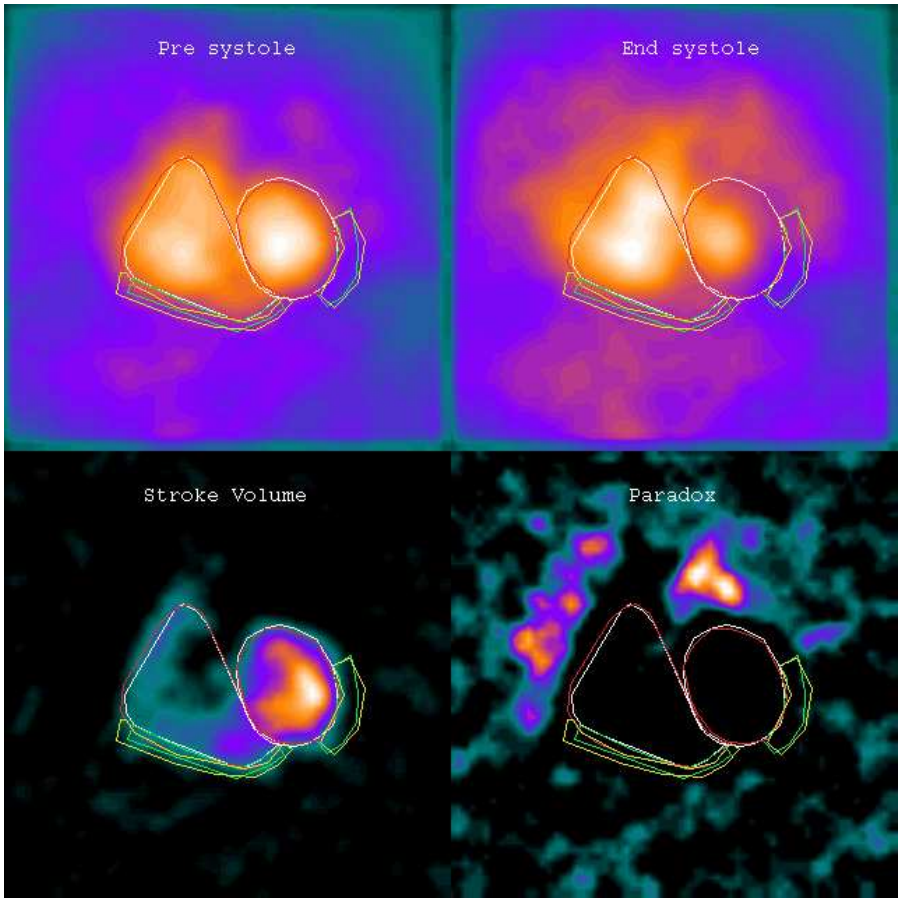


Figure 4.3.: Showing how regions of interest were drawn: two regions for each of left ventricle, right ventricle, left background, right background. Images show pre-systolic image, end-systolic image, the stroke volume (pre-systole - end-systole) and paradox (end-systole - pre-systole) images. Regions were drawn to be just inside the stroke-volume envelope at pre-systole.

To analyse these parameters, each curve was passed through the ef_analysis.awk script (see appendix A.3) to identify the pre-systolic and end-diastolic points on the curve. The curve was cropped to include only those points between pre-systole and end-diastole (inclusive). The effect of this was to cut out potential up-sloping points before the pre-systolic point, and to remove that portion of the curve after end-diastole which results from averaging many beats of potentially widely varying lengths.

The cropped curve was passed through a Link Medical program (cardiac_slope) to analyse the characteristic properties of the curve including peak emptying and filling rates and FTFF.

Finally, the cropped curve was again passed through ef_analysis.awk to determine EF and the error on EF.

4.3.5. Problems

Several problems were found which were not anticipated and which resulted in the entire data-set needing to be reformatted and / or reprocessed before robust data was obtained.

1. List mode acquisitions were generally made using a specific imaging head that depended on which camera was being used; however several of the acquisitions were performed using an alternative imaging head (at 90 degree to the normal acquisition). With automatic formatting, this could only be detected by examining at least one image from every acquisition. Once detected the problem was resolved by manually specifiying the alternative head in reconstructing the image from the list-mode file.

2. Image files were zoomed before being analysed. When the zoom was omitted the regions did not match the image.

3. Selecting beats automatically from the limits of the histogram gave excessive weight to outliers and resulted in distorted beat acceptance windows. To overcome this the beat histogram for each patient was viewed and manual acceptance limits imposed as described in §4.3.2.

4. Beat by beat listings were made with two decimal place precision while beat acceptance testing against the defined window used five decimal place precision; by

rounding beats lengths to the nearest value at that precision, it was possible that beats that should have been included were, in practice, excluded.

5. The cardiac_slope program was modified by Link Medical for an unrelated purpose. The modification caused some real numbers to be seen as integers, with the result that the measure of FTFF was incorrectly calculated.

4.4. Analysis of function

This study involved two groups of patients: AF and SR. Each of these groups was divided into several subgroups of potential clinical interest as described in §2.7.1.

The principal investigation considered the effect of beat selection parameters involving both the indexed beat and preceding beat on the functional indices listed in §4.3.4 (explained in more detail in §4.5). While variable time formatting was used as the base technique, fixed time formatting was performed throughout the study and comparison has been made between fixed and variable time formatting for each parameter measured.

While the changes in a measured parameter with beat selection criteria were considered, so too was the overall range of values obtained for each patient. This was done simply by subtracting the maximum and minimum measure giving the largest possible measure of range. There are several other possibilities that could also have been considered as an assessment of variation, e.g. some multiple of standard deviation or inter-quartile range, but it was felt that showing the maximum measured range would be more indicative of the clinical significance of changes.

An in-depth, sub-group analysis of patients according to the groups described in §2.7.1 was undertaken only for LVEF which is the functional parameter of greatest clinical interest. As with the analysis of the groups as a whole, this analysis considered both the variation with beat selection criteria, and the overall range.

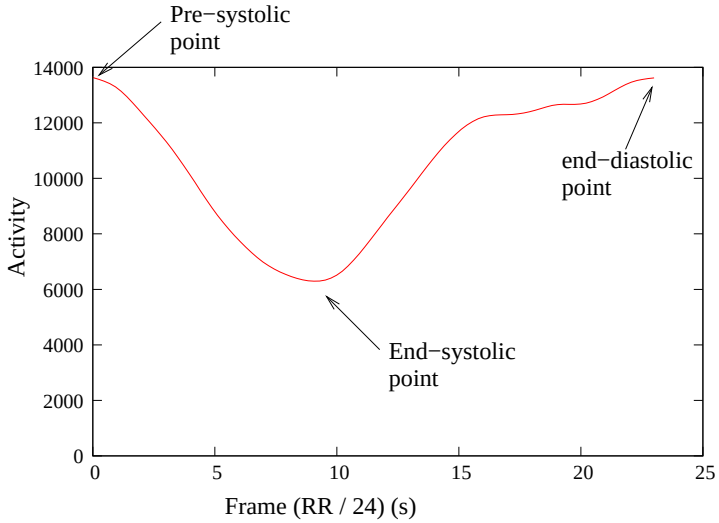


Figure 4.4.: Sample activity-time curve.

4.5. Measured functional parameters

A detailed description of the functional parameters that were measured follows. In each case the parameters were taken from the curve produced by applying the appropriate ROIs to each of the images created using the different beat selection criteria.

4.5.1. Sample curve

In the following discussion several points on the activity-time curve are described. An example curve is shown in Figure 4.4.

The principal points are:

Pre-systole: The initial peak point in the curve.

Systole: That initial falling segment of the curve during which activity decreases reflecting the reducing volume of the ventricle.

End-systole: The bottom of the curve after systole. After this point the activity (reflecting the volume) increases.

Diastole: The part of the curve following end-systole during which the curve rises, reflecting the increasing volume of the ventricle, to a peak at end-diastole.

End-diastole: The peak point which marks the end of diastolic filling. This may be followed by another down-sloping segment, but this reflects methodological "error" rather than physiological change.

The measured parameters divide into two groups depending on whether they are associated with diastole or systole.

4.5.2. Left ventricular ejection fraction (LVEF)

Ventricular EF is the proportion of blood pushed from the ventricle during systole. Expressed as a percentage, it is the change in ventricular volume divided by the pre-systolic volume. (Although most investigators would not differentiate between pre-systolic and end-diastolic volume, considering the curve to be cyclical. As a result they would be more likely to express EF as the change in volume divided by the end-diastolic volume). In radionuclide ventriculography detected count is, approximately, proportional to volume; thus the pre-systolic count, C_{ps} is proportional to the pre-systolic volume and the end-systolic count, C_{es} is proportional to the end-systolic volume. EF can either be calculated incorporating a background correction as described in equation 1.4 or, as in this case, it can be determined after background subtracting the complete curve (see §4.3.3) in which case:

$$EF = \frac{(C'_{ps} - C'_{es})}{C'_{ps}} \tag{4.1}$$

where the "′" (prime) mark here indicates the value after subtraction of the background curve.

Pre-systolic and end-systolic counts were taken from the background subtracted cropped curves as described in §4.3.3. EF calculations were done for the LV using both fixed and variable time formatting with all beat selection criteria.

4.5.3. Pre-systolic volume (*PSV*)

Since detected count is proportional to volume[3], a measure of pre-systolic volume is given by the count in a frame, normalised to the duration of the frame and the number of beats which contribute to the overall count in the image.

$$V_{ps} = \frac{C_{ps}}{N \cdot T} \tag{4.2}$$

which has actually been calculated as:

$$V_{ps} = \frac{F \cdot C_{ps}}{N \cdot R} \tag{4.3}$$

Where:

C_{ps} is the pre systolic count

F is the number of frames

R is the mean RR interval for variable time formatting or the mid-range RR interval for fixed time formatting

N is the number of beats which contributed

T is the mean time per frame for variable time formatting or mid-range time per frame for fixed time formatting

V_{ps} is a measure approximately proportional to the pre-systolic volume.

Pre-systolic volume may vary substantially for different patients depending on the attenuation of each patient.

Pre-systolic counts were taken from the background subtracted, cropped curves as described in §4.3.3. Pre-systolic volume calculations were done for LV only using both fixed and variable time formatting with all beat selection criteria.

[3]The concentration of radio-labelled blood cells is assumed to be constant throughout the blood (it has a constant specific activity) with the result that changes in the volume of red blood cells are reflected in a change in the count rate. This also assumes that attenuation is uniform, and although it is not, the approximation is acceptable [89].

4.5.4. Pre-systolic vs. end-diastolic volume (*EDV/PSV*)

In normal SR, the pre-systolic and end-diastolic points on the volume-time are approximately equal. In AF, however, normal ventricular beats may be interrupted by irregular firing of the AV node or may be prolonged causing the ventricle to fill for longer than expected. As a result the end-diastolic volume, for a beat which has been prematurely interrupted, may be considerably smaller than the pre-systolic volume in the same beat. Similarly it is possible that in a beat which has filled for longer than expected the end-diastolic volume may be substantially greater than the pre-systolic volume.

To explore this, the ratio of counts at end-diastole to those at pre-systole (corresponding to the volume ratios) was calculated: the counts being taken from the background subtracted, cropped curves. This was done for the LV only using both fixed and variable time formatting with all beat selection criteria.

4.5.5. Systolic time interval

As discussed in Chapter 1 (see §1.1.1) the Frank-Starling mechanism, on which some of the basic hypotheses of this thesis are predicated, expects that beat-to-beat changes in systole are reflected more in volume change than in variations in the duration of systole. Thus a change in beat length is primarily exhibited as a variation in the duration of diastole which, in turn, determines the pre-systolic volume of the subsequent beat.

Although systolic time is defined as the time between end-diastole and end-systole, there is a question as to whether this is the time between the electrical activation (onset of the R wave) or mechanical activation (pre-systole on our sample curve, see Figure 4.4). Since changes in volume in radionuclide ventriculography reflect changes in the morphology of the ventricle and not electrical activation (despite the R wave being used as a trigger), it was decided to use the pre-systolic point as the marker for the onset of systole and hence the cropped curves, which accepted only that part of the curve between pre-systole and end-diastole, were used to determine the systolic time.

Assessment of systolic time is limited by the number of frames as it can only be measured to an accuracy equal to the frame time. Sampling theory defining the accuracy to be:

$$\sigma = \frac{t_{frame}}{2} \tag{4.4}$$

Systolic time was measured by determining the frame time from the mid-range (for fixed time formatting) or the mean (for variable time formatting) beat and dividing by the number of frames (24), and then simply multiplying by the frame number of the end-systolic point on the cropped curve.

Systolic time calculations were performed only for the LV using both fixed and variable time formatting with all beat selection criteria.

4.5.6. Peak filling rate (PFR)

Rumberger and Reed [90] found that both peak emptying and PFR in SR were dependent on end-diastolic volume. Examining the PFR allowed this finding to be tested in the context of AF. Together with peak emptying rate, it offers a measure of ventricular compliance.

The Link Medical cardiac_slope program was used to assess PFR in the background corrected, cropped curve. This program assesses the PFR by calculating the gradient over both 3 and 4 points in the curve giving two slightly different measures. It was decided to use the 4 point value as this should be slightly less susceptible to random count fluctuations which may be significant in potentially low count data.

4.5.7. First third filling fraction (FTFF)

FTFF is the most commonly quoted measure of diastolic filling. It is the proportion of end-diastolic volume at 1/3 of the diastolic time; as such it is dependent on an accurate assessment of diastolic time. Since it is expected that patients in AF will have widely differing diastolic times from one beat to the next this may not be measurable in a consistent manner.

FTFF was assessed from the background corrected, cropped curve using Link Medical cardiac_slope program which calculates FTFF from a linear extrapolation of the activity in the frames either side of the first third of diastole, determined as the time between end-systole and the end of the cropped curve.

4.6. Statistics

In all of the following statistical analyses the interest is in the *changes* in a measured value, e.g. LVEF, introduced by three different variables: formatting mode (fixed or variable time), preceding beat selection and indexed beat selection.

It is appropriate to consider the differences between variable and fixed time formatting separately, as they are of secondary interest in this investigation. While they may show a statistically significant difference, centres for Nuclear Cardiology will generally use one or the other without "mixing" results.

The beat selection options used divide into two types: quartiles which provide a pseudo-normalised numerical measure and hence lend themselves to numerical analyses, and the categorical groupings of "All" and "Best" beats, to which can be added a grouping that combines all the results based on quartiles into a single group. The statistical analyses for these types are different, even though they have been treated as the same in formatting and processing the data. Changes with increasing quartile are best assessed using multi-variate regression (with two explanatory variables: preceding and indexed beat selection criteria). Changes within the categorical grouping must be assessed with a two way analysis of variance, Anova.

4.6.1. Regression

Regression allows two interval variables to be compared - in this case changes in functional measure with preceding or indexed beat length as represented by the quartile (expressed as a number) or the mid point of the quartile range (expressed in seconds). Neither all the beats nor the "Best" beats can be expressed as interval (numeric) values and so they cannot be included in a regression except as fixed terms in *either* the preceding or indexed beat.

By taking a linear regression against the quartile values, linear changes with preceding or indexed beat length can be determined. This is preferable to analysing differences between every possible combination of beat selection criteria which is liable to produce "false" significances both on a patient-by-patient basis and if the group is considered as a whole.

While there is a theoretical possibility that some other form of regression may model the changes more accurately (e.g. a quadratic) there are two reasons to use the linear model: (1) the data appear to be approximately normally distributed (see appendix §C.1) suggesting that a linear regression will suffice; and (2) the four points defined by taking quartiles are insufficient to determine higher order models.

There are two very different means of regressing the results. They can be considered on a patient-by-patient basis or they can be considered in the group as a whole, possibly included in a mixed effects model where patients are included as a random effect. By considering the results in the group as a whole, gross changes can be determined with a high degree of significance but the form of the change is obscured by the variation within the group - because there is no means of normalising individual R-R ranges. The form of the change can only be seen on a patient-by-patient basis by regressing against individual quartiles. Including patient variation as a random effect in a mixed effects model adds considerably to the complexity of the statistical analysis without substantially changing the results. The results become less easily understandable. The decision was taken not to pursue the mixed effects model after it was tested for changes in LVEF with beat selection criteria and for variation of LVEF with pre-systolic volume; in neither situation was any substantial difference found when compared with linear regression in the group as a whole.

Considering the results on a patient-by-patient basis allows the patient specific form of the change to be determined; however the significance of the result will be weakened by the poor number of points (4) which can be included. Regression in this form can be taken against both quartile and time (represented by the mid-point of each quartile range). All three of these analyses (whole group, patient-by-patient on quartile and patient-by-patient on time) have been investigated (results for regression on a patient-by-patient basis with time are reported in appendix C.3).

In each situation a linear regression model was used. This can be described as:

$$LVEF = a + \beta_p Q_p + \beta_i Q_i + \beta_{pi} Q_p Q_i \tag{4.5}$$

where

a & β_x are constants

Q_p is the preceding quartile (or midpoint of quartile R-R range in seconds).

Q_i is the indexed quartile (or midpoint of quartile R-R range in seconds).

Similarly linear regression (with only one variable) was used to investigate whether there were trends when either the preceding or indexed beat criteria were fixed (either "All" or "Best").

Where regression was done on a patient-by-patient basis an index (e.g. LVEF, systolic time) was weighted by the inverse of the standard deviation of the index ($1/SD$) using the *lm* function in the *R statistical package*. The SD was obtained by determining the index from the four combinations of two myocardial and two background regions of interest. It reflects the accuracy with which regions were drawn but will also reflect the total count in each image and hence the noise in the image. Taking the inverse gives more weight to the points with smaller error [91].

Individual results obtained on a patient-by-patient basis which were found not to be significant were discarded. The mean r^2 of the remaining results has been reported.

4.6.2. Analysis of Variance

Analysis of variance compares measures made using the different variables with a base measure. It is used here to investigate whether there is a significant difference between functional measures obtained with the nominal beat selection criteria: "All", "Best" and "Quartiles" (in which all quartile results are clumped together in a single group). In this model there are two different variables: preceding and indexed beat selection criteria each of which can take one of three values: "All", "Best" or "Quartiles". Analysis of variance was only used for the group as a whole and not on a patient-by-patient basis.

The base measure against which all other measures are compared is the result obtained with all preceding and indexed beat selection criteria.

4.6.3. Comparing tables

In several places in this thesis it is necessary to compare tables of count data, e.g. the number of patients for whom each combination of beat selection criteria gave valid results in fixed vs. variable time formatting (this example is worked out in §5.4.4).

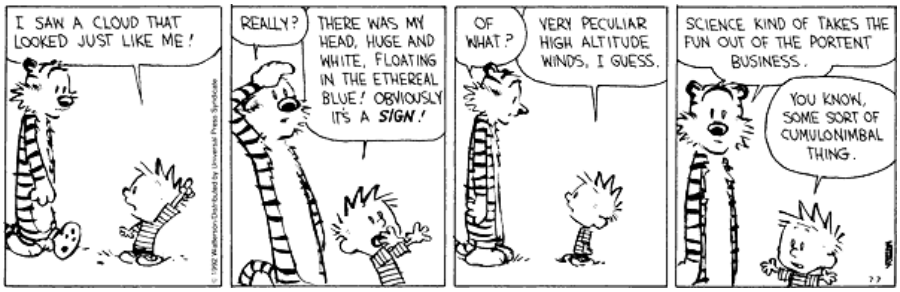
The comparison involves a successive reduction technique using a log-linear model with a Poisson predictor as described in *The R book* by Michael Crawley [92]. This technique treats the data as a single multi-dimensional table with initially every possible term included in the model. The table is compared against a Poisson distribution. If a term is removed and a comparison of the models, using a chi-squared test, proves to be insignificant that term can be considered to have no impact as a descriptor. Where two tables, with the same descriptors (e.g. beat selection criteria) are compared the term which links the tables is the complete interaction term, in the above case it would be $preceding : indexed : framemode$. If this term is removed without affecting the model the statistical inference is that there is no interaction between the tables indicating similar relationships, in this case similar results with beat selection criteria, in the two tables.

4.7. Going forward

The measures and techniques which have been described in this chapter have been systematically applied to each of the images produced using the different criteria defined by the beat selection and formatting technique in the group of patients in AF and SR. The results of these analyses are presented in the following chapter. In Chapter 6 the results are compared with the analyses of rhythm described in Chapters 2 and 3.

Chapter 5.

Results: Describing Function



Summary

In which we look at the results from measures of function of the LV, both systolic and diastolic, which have been derived from the RNVG. The results are considered both for the group of patients in AF and the group in SR. In the case of left ventricular ejection fraction, LVEF, analysis has also been performed on several clinical subgroups.

Comparison is made between fixed and variable time formatting, and between the different measures: LVEF, pre-systolic volume, systolic time interval, the ratio of pre-systolic to end-diastolic volume, first third filling fraction and peak filling rate.

5.1. Introduction

As discussed in §4.3.2 each acquired list was formatted into 84 different images, each of 24 frames. These included different time spans (the whole acquisition, the first half, the

second half or the middle two quarters of the acquisition); different formatting techniques (variable time or fixed time); and different beat selection methods based on the duration of the preceding beat, the indexed beat or both.

The resulting images were each processed by applying the same ROIs to create curves as discussed in §4.3.3. The results allow us to investigate several different questions, notably:

- Do functional parameters change depending on beat selection criteria?
- If functional measures do change is there a trend in the relationship?
- Does variable time framing produce similar results as fixed time framing for the defined functional parameters ?
- Given the beat selection criteria is there self consistency for functional measures acquired at approximately the same time?

5.2. "Cleaning" the data

Before any meaningful conclusions could be drawn from the data it was necessary to ensure that the data were reasonable in that they were not skewed by artifacts. Although the process was evolutionary it can be summarised in three parts: removal of unanalysable curves, exclusion of outlying beats and filtering of results.

5.2.1. Unanalysable curves

The process of determining beat selection criteria, formatting the list-mode file on the acceptable beats only, and producing a curve from the resulting image was followed in an identical manner for every image created. The resulting curve, however, was not always found to be analysable, in that it might not not have yielded a clearly defined pre-systolic, end-systolic and end-diastolic point (see Figure 4.4). In this case the curve would be considered to be unanalysable. Several aspects of the curve might make it unanalysable: the curve must start at, or rise to, a maximum (pre-systolic) point before falling to a minimum (end-systolic) point. It was a requirement of the analysis program (see appendix §A.3) that the curve should rise (without further falling) by a minimum

of 1/3 of the difference between the count at pre-systole and end-systole before the end-systolic point could be considered to have been found. The end-diastolic point would then be considered to be the first maximum after this point. Where these points could not be determined the curve was defined as being unanalysable. There are several possible reasons for this to occur but the most likely are (in no particular order):

1. The limits on acceptable beats have been incorrectly set.
2. The total count in the image is too low to give accurate results (see §5.2.3).
3. The limitations of the formatting technique lead to inappropriate smoothing or truncation of the curve.

We will return to these in the discussion in Chapter 8 (§8.3.2, §8.3.3).

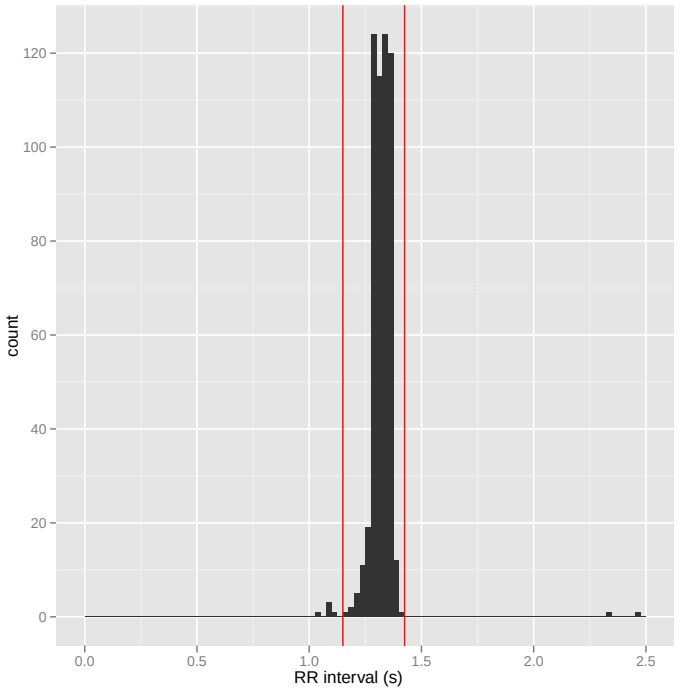
5.2.2. Limiting the beat selection criteria

Initially beat selection quartiles were based on the full range, including outliers, of R-R intervals. This caused problems, particularly with fixed time formatting, because only one or two beats might significantly distort the duration of the mid-range beat about which all beats in that quartile were grouped.

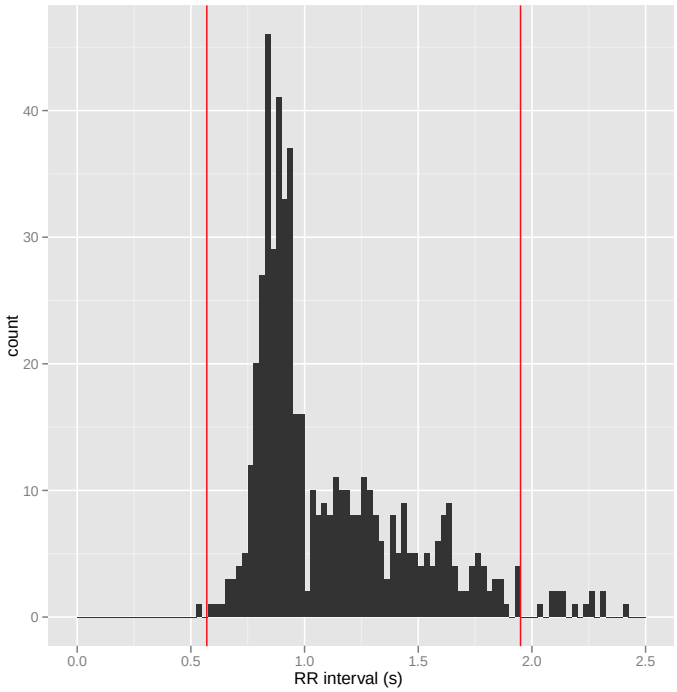
This problem is demonstrated in the histograms in Figure 5.1. Considering the SR example, it can be seen that the mid-range beat when the outlying beats are included is around 1.8 s, substantially greater than almost all the beats in the histogram. The effect of this, particularly where fixed time formatting is used, is to compress all the data into the first half of the curve, causing a serious distortion of the "real" curve.

To avoid this methodological error each histogram was reviewed and limits were determined outside of which beats were excluded from the analysis. Two separate observers were involved in this review and where there was disagreement a consensus view was agreed. The data was then reformatted using beat acceptance limits with quartiles calculated based on these manually defined limits.

The effect of this was to substantially reduce the number of curves defined as unanalysable (see Table 5.1). An example of the effect that limiting the acceptable beats has on the curve is shown in Figure 5.2. It can be seen that in the curve that is not limited the first and final few frames show very reduced activity (volume) which is clearly



(a) SR



(b) AF

Figure 5.1.: Sample histograms for (a) SR (patient S1) and (b) AF (patient A1) showing outlying beats and (in red) manually determined beat acceptance limits.

	AF	SR
Not limited	2123	1866
Limited	2036	78
Total possible curves	36000	38016

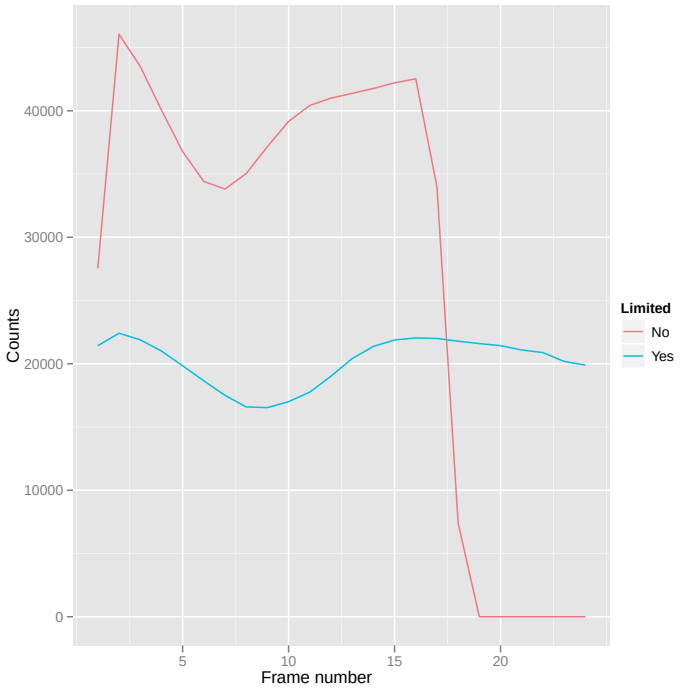
Table 5.1.: Effect of limiting the acceptable range of R-R intervals on the number of unanalysable (null) LVEF values.

not physiological. Additionally the end-systolic point does not occur in the same frame, or at the same time, in both curves because the unlimited curves have longer frames with the result that the true end-systolic point is captured in an earlier frame than in the limited curves. Thus the temporal resolution of the unlimited curves is poorer than in the limited curves.

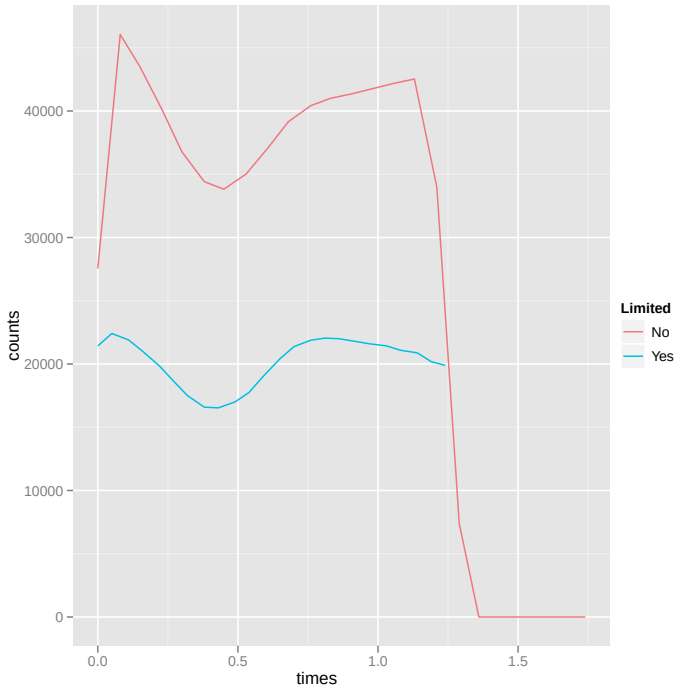
It is noticeable that the curve produced from limiting the acceptable beats appears to have fewer counts than the unlimited curve, and further examination of curves of other patients showed this to be true in all cases in both SR and AF. This apparent discrepancy is due to two factors: the unlimited curve is condensed into the first 16 or 17 frames while the limited curve occupies all 24 frames. Since there are approximately similar counts in each image the counts in each frame must be at least 1/3 greater in the unlimited curve. This is compounded by the background which in both cases is smoothed over the full 24 frames with the result that a lower background is removed in the unlimited case. Overall the reduction is in line with the number of beats removed. In this case 21 of 541 beats were discarded ($\sim 4\%$). In the unlimited curve there are 11,189,296 counts while the limited curve has 10,675,076 counts, a difference of $\sim 4.6\%$. The slight increase is to be expected since a greater number of longer beats (which have more counts in them) were discarded.

5.2.3. Filtering data

The same ROIs and the same initial data acquisition were used to produce each of our images. In theory this should mean that all of the images produce acceptable curves for analysis; however, it has already been noted that a proportion of the curves could not be analysed to give an adequate LVEF. While the remaining curves do provide an assessment of LVEF, some images included so few beats that random noise and the



(a) By frame



(b) By time

Figure 5.2.: Sample change in curve as a result of limiting acceptable R-R intervals in SR (patient S1). The same curve is shown in (a) by frame number and (b) by time. (Formatting parameters: Fixed time: p:All,c:All).

statistical fluctuations of the decay process are such as to invalidate the measurement of LVEF.

There are two principal sources of error: error due to the random nature of radioactive emissions which is modelled by the Poisson distribution; and error due to positioning of the ROI, which is modelled by the SD of calculated EF.

EF Poisson error

Detected count is a statistical process which follows a Poisson distribution such that the statistical error on measured count is the square root of the detected count. It can therefore be shown that for ejection fraction, EF:

$$EF = \frac{(C_d - C_s)}{C_d} \tag{5.1}$$

Where:

C_d is the pre-systolic (end-diastolic) count after background subtraction.

C_s is the end-systolic count after background subtraction.

The error due to the Poisson noise, ΔEF, in this calculation is:

$$\Delta EF = EF \times \sqrt{\left(\frac{\sqrt{C_d}}{C_d}\right)^2 + \left(\frac{\sqrt{C_d + C_s}}{C_d - C_s}\right)^2} \tag{5.2}$$

A limitation was placed on the Poisson error of $\pm 10\%$, such that curves / images with an error in LVEF greater this were discarded from any further analysis.

Error due to ROI positioning

Every image resulting from the different beat selection criteria would produce, for each ventricle, four separate curves obtained from the combinations of two ventricular and

two background ROIs. The mean and SD, σ_{EF}, for each parameter was measured from these curves (after filtering as applied above) to give an estimate of the error due to positioning of the ROI. A further filter was applied to the summary data which required that any curve for which $\sigma_{EF} > 10\%$ was excluded, thus an image which produced a mean LVEF of 40% would be excluded if the SD of the LVEF was greater than 4% (EF units).

Pre-systolic point

Several curves were found to have pre-systolic points that were several frames into the 24 frame gate. A delay of one or two frames could be expected due to delayed onset of mechanical contraction after electrical "firing". It was decided that a delay in onset could be considered to be "real" provided that it was less than or equal to three frames (this corresponds to a delay of ~ 0.19 s in a slow heart beat of 40 bpm). Any curve in which the pre-systolic frame was > 3 was excluded.

Filtering summary data

The effect of these filters on the overall number of acceptable curve values, after each value had been averaged over the four possible curves as described above (§5.2.3) is shown in Table 5.2. In many cases the same curve may have been excluded by more than one criterion so the total after filtering is not simply the cumulative difference from the number available before filtering. There is a small possibility that excluding almost one third of the curves will skew some of the statistical analyses, however, the exclusions are justified and there are sufficient remaining data that statistical conclusions are well validated. Table 5.3 shows the number of scans remaining by beat selection criteria. It is clear that the shorter the beat the more likely it is that the curve will be excluded. It is also noticeable that the curve is more likely to have been included if all the beats (either preceding or indexed) were accepted. Both of these results suggest that the principal exclusion criterion was having insufficient counts since shorter beats will have fewer counts than do longer, ones and including all the beats will cause the least limitation on the number of counts in the image.

	AF	SR
Total	36000	38016
No LVEF	2123	1866
ES count < 100	22	450
$\Delta LVEF > 10\%$	9311	7680
$\sigma LVEF > 10\%$	355	290
PS frame > 3	824	713
Total after filtering	24236	27755

Table 5.2.: Effect of filtering on numbers of acceptable curves for LV in SR and AF.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	385	385	357	361	366	367
	Best	385	385	357	361	364	367
	Q1	355	355	159	192	196	210
	Q2	361	362	189	219	229	231
	Q3	367	367	196	229	242	230
	Q4	365	364	198	221	231	245

(a) SR, Variable time

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	387	384	354	361	365	373
	Best	386	382	355	363	365	371
	Q1	362	354	160	189	195	222
	Q2	362	361	185	217	225	245
	Q3	365	364	188	224	235	247
	Q4	366	364	193	216	225	246

(b) SR, Fixed time

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	372	360	312	346	349	349
	Best	341	301	221	255	278	284
	Q1	274	194	89	128	133	156
	Q2	327	252	134	174	199	211
	Q3	347	284	153	205	226	249
	Q4	360	306	182	241	265	273

(c) AF, Variable time

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	275	340	223	346	358	371
	Best	281	298	165	267	285	335
	Q1	291	208	87	127	139	216
	Q2	279	253	105	196	211	280
	Q3	276	290	124	211	240	310
	Q4	277	301	147	252	274	321

(d) AF, Fixed time

Table 5.3.: Number of acceptable scans, after limiting and filtering, by beat selection criteria in SR and AF.

	SR				AF			
	Variable		Fixed		Variable		Fixed	
	No. patients	No. curves	No. patients	No. curves	No. patients	No. curves	No. patients	No. curves
Not limited, Not filtered	396	13412	375	13415	396	13273	375	12211
Not limited, filtered	386	9405	373	8833	392	9418	375	8581
Limited, not filtered	396	14239	375	13422	395	14171	375	12290
Limited, filtered	387	10753	373	9130	391	10756	375	8959

Table 5.4.: Number of patients and curves included in the analysis after beat limiting and filtering.

5.2.4. Effect of limitations and filtering on overall data

The effect of the limitations and filters on the range (max - min) of LVEF on a per-patient basis is shown in Figure 5.3. This shows, for each *patient* the number of different measures of LVEF which could potentially contribute to the maximum range, $EF_{max} - EF_{min}$, of LVEF measurements *for that patient* plotted against the range. The separate effects of limiting the beat selection window and filtering the data can be seen: the limitation reduces the range but has little effect on the spread of selection techniques. Filtering reduces the range further but also reduces the available pool of measures from which the range can be determined.

As an example, using fixed time formatting on the whole list-mode file, 36 images would be created, of these 35 give non-null values of LVEF producing a range of 19% (EF units) between the maximum and minimum LVEF for that patient with those image parameters. Filtering the curves, as described above, reduces the number of acceptable measures to 26 and the range to 17%. Limiting the acceptable beats makes it possible to measure LVEF in all 36 curves but increases the range of measures LVEF to 26% for that patient. When a filter is applied again there are found to be 28 acceptable measures with a range of 18%.

The number of patients and curves contributing to each plot can be seen in Table 5.4 from which it is clear that limiting the beat selection criteria actually increases the total number of curves which were available for analysis. From this point on only the limited and filtered data will be used.

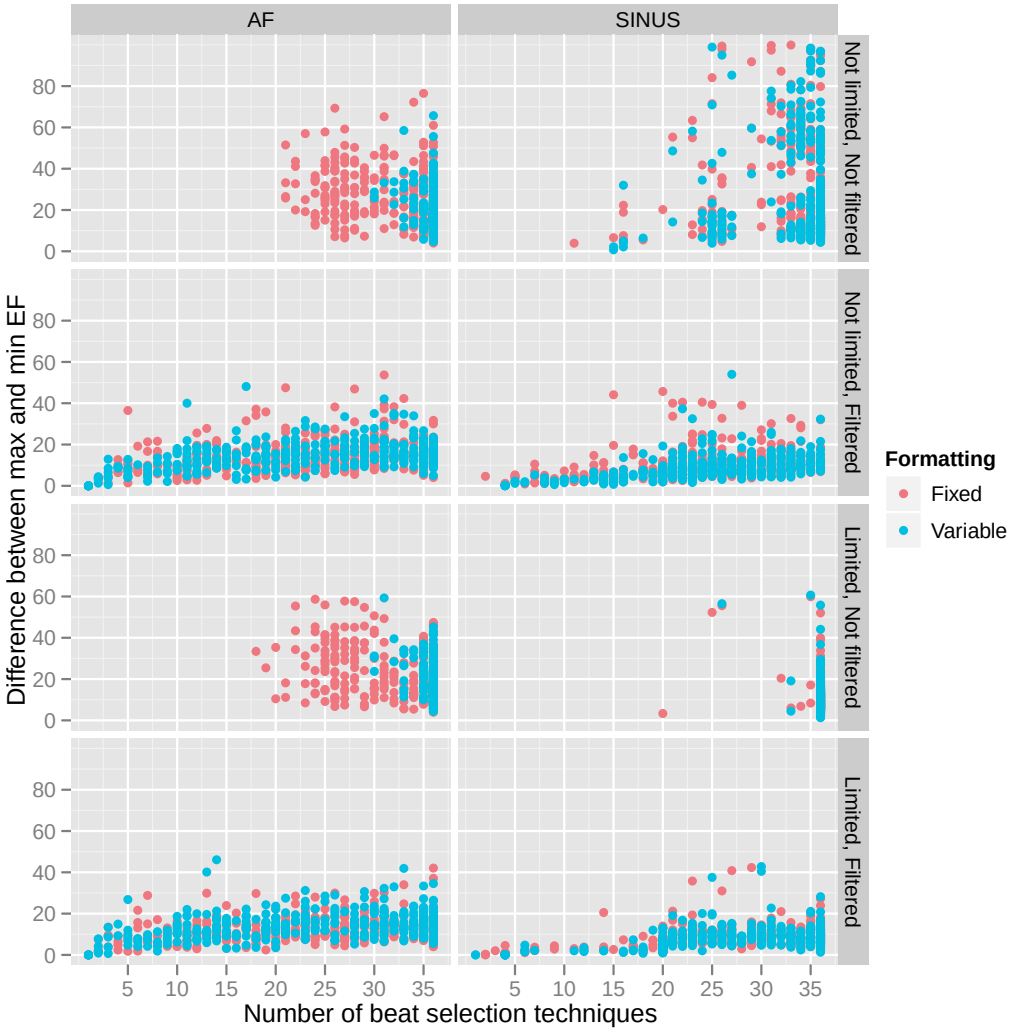


Figure 5.3.: Showing the range (max - min for each patient) of LVEFs calculated for each patient, using variable time formatting on the whole list-mode file, plotted against the number of different beat selection techniques which produce unfiltered results. The effect of both limiting the acceptable range of R-R intervals (limited) and filtering the curves (filtered) is shown. The number of patients and curves in each situation are shown in Table 5.4.

5.3. Presentation of results

Before we can progress to considering the functional measures, a short digression is required to explain the presentation of results.

5.3.1. Terminology

Applying different beat selection criteria produces a variety of different values for the indices being measured. The *difference* between the maximum and the minimum value $(max(x) - min(x))$ has, in this thesis, been termed *range* and is referred to with the symbol: $\Updownarrow$.

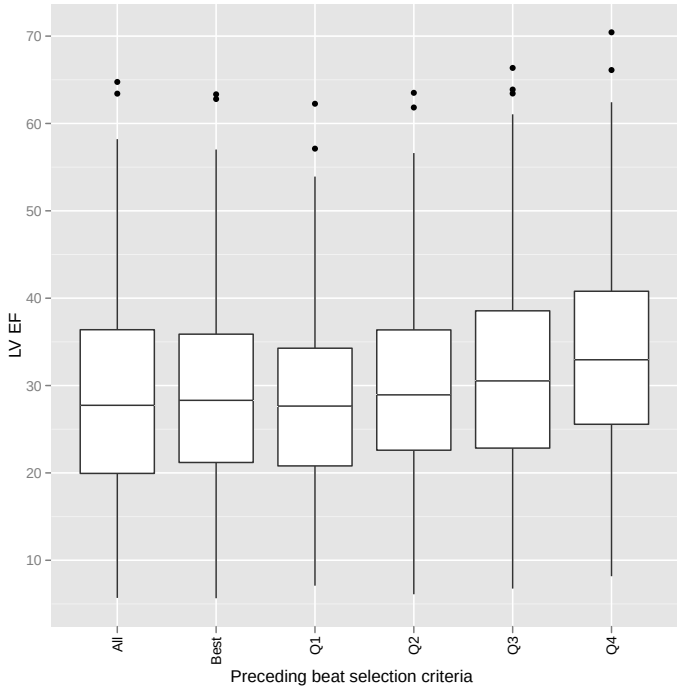
5.3.2. Notation

In much of the discussion that follows, it is necessary to describe the beat selection criteria used to achieve a specific result. This is done using the notation "p:*preceding*_c:*indexed*" where *preceding* gives the preceding beat selection criteria and *indexed* gives the indexed (current) beat selection criteria. So p:Q1_c:Best would mean that the preceding beat selection criteria required beats to be in the first quartile (Q1) and the indexed beat criteria took only the "Best" beats (the beats in a 300 ms window centred on the modal beat length) (see§4.3.2).

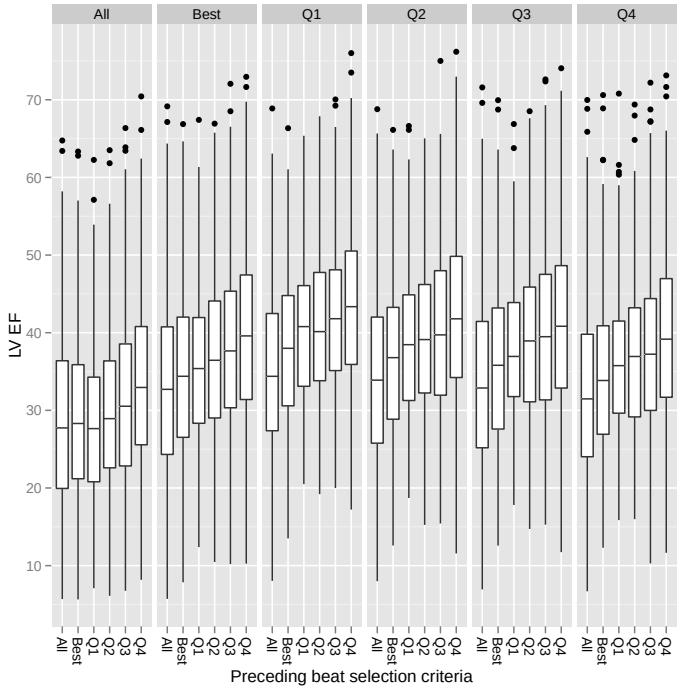
5.3.3. Box-plots

Results are presented in tables detailing the mean and SD of a measure for different preceding and indexed beat criteria; however trends are more clearly seen graphically and the data has also been presented in the form of two sets of grouped box-plots. Each set of box-plots presents the same data grouped either by preceding or indexed beat. An example set is shown in Figure 5.4b.

Each set of box-plots comprises six separate plots, each one of which shows the median, quartile, range and outliers for each indexed or preceding criterion (see Figure 5.4a). Thus in our example (Figure 5.4b, which shows data for LVEF in AF grouped by indexed



(a) A single box-plot



(b) Grouped by indexed beat

Figure 5.4.: Example of two parts of the box-plot display, showing (a) a single box-plot corresponding to indexed beat criteria in which all beats were selected, and (b) set of box-plots each one showing one of the possible indexed beat selection criteria. Plot (a) is the same as the first group in plot (b). Box plots show median, inter-quartile range and outliers.

beat) the single plot (Figure 5.4a), which shows the data for each preceding beat selection criterion with all indexed beats being accepted, corresponds to the first plot in the set.

In presenting the results two sets of plots are shown, the first groups the results by preceding beat criteria, the second groups them by the indexed beat selection criteria. By plotting two sets, trends in either grouping can be seen.

Statistical analysis used regression and analysis of variance as, described in §4.6, together with Wilcoxon signed ranks test (for comparing non-normal unpaired data), paired Wilcoxon (for comparing non-normal, paired data) and Spearman rank correlation (for determining relationship between non-normal, paired indices). Significant results are highlighted.

5.3.4. Regression

Regression results are presented in different tables for the two types of regression undertaken. In both tables (Table 5.9 can be taken as an example) where a beat selection criterion has been marked as "(Constant)" it has been held constant and only the other beat selection criterion has been used in the regression calculation (from Q1 to Q4). Thus in a row in which the preceding beat is shown to be "Best (Constant)" with the indexed beat shown to be "Q1 - Q4", the regression calculation has been made on the results from images created using the "Best" preceding beat with indexed beats ranging from Q1 to Q4.

Whole group regression

A single table is presented showing SR and AF results side-by-side. The r^2 and p values are given with significant results highlighted.

Patient-by-patient regression

A table is presented for each of SR and AF. Each table shows the results (mean $\pm$ SD of the R^2 value, and the number) of patients who showed a significant ($p > 0.05$) regression separated into those for whom the regression showed a positive correlation and those for whom the regression was negative. A final column (labelled "NC") shows the number of

patients for whom no calculation could be performed (because there were fewer than 3 points in the regression equation). The total number of patients in each of SR and AF is given in the caption.

As an example the first line in Table 5.9a shows the regression, in SR, with varying indexed beat (Q1-Q4) for "All" preceding beats. 371 patients in SR were included, 140 patients had a positive regression (with mean $R^2 = 0.78 \pm 0.14$) and 40 patients had a negative regression (with mean $R^2 = 0.76 \pm 0.13$). There were 4 patients for whom a calculation was not possible, leaving $371 - 140 - 40 - 4 = 87$ patients for whom the regression was not significant.

In the case of multiple regression, where both indexed and preceding beat were varied, the table shows the mean ± SD R^2 value for those patients who showed a significant regression the number of patients who showed a correlation are indicated in the appropriate "N (+ve)" or "N (-ve)" column with preceding beat correlations indicated with "(p)" and indexed beat correlations marked with "(i)".

5.3.5. Anova

Anova results are shown in a single table which presents the p values for SR and AF side by side. The comparison for each combination of beat selection criteria against a base value (here the result when all beats are included) is shown. All results achieved using any quartile for that particular beat selection criterion are grouped together. Significant results are highlighted.

5.4. LVEF

Once an acceptable subset of the acquired data had been determined, attention turned to the functional measures of interest; in particular LVEF.

Rhythm	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
SR	387	4.2	33.1	42.1	49.7	86.8	41.4	13.6
AF	373	5.7	27.1	35.4	43.1	76.2	35.4	11.6

Table 5.5.: LVEF: Summary statistics for measured LVEFs (variable time formatting) showing the distribution of LVEF in SR and AF.

5.4.1. LVEF in SR and AF

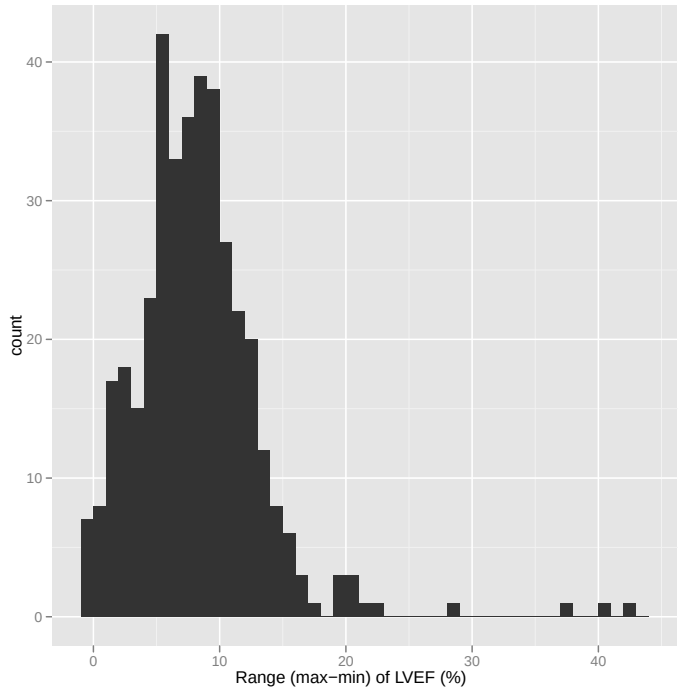
A range of different beat selection criteria were applied to produce images from which LVEF can be calculated as discussed in §4.5.2. This produces a *range*[1] of LVEFs, denoted hereafter by ⇳LVEF, as shown in Figures 5.5 (SR) and 5.6 (AF). These figures show (a) a histogram of the ranges of LVEF measured per patient which demonstrates that most patients show ejection fractions which differ by between 5% and 12% in SR and between 10% and 20% in AF. It can be seen from (b) the plots of range against the number of images which contribute to determining that range that in AF the range is substantial even when there are few contributing images. In SR a larger number of images may be required to see full range. Since the number of contributing images is determined by the number of images which have been filtered out, as discussed in § 5.2, this may suggest that there is a wider range where the underlying data is more robust.

Examining these figures, there are some clear outliers in both SR and AF but review of these found no reason to exclude them from the analysis, and they were deemed to be genuine. There did not appear to be any definable trend in the beat selection criteria which caused the outliers: the maximum ranges occurred, for example, between p:Q1_c:Q1 and p:All_c:Q3 in one instance and p:Q2_c:All and p:Q4_c:Q2 in another.

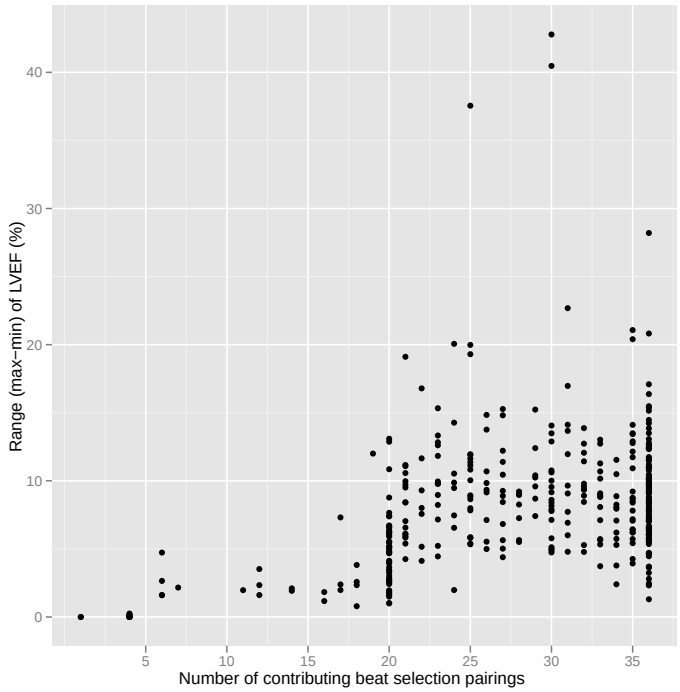
Table 5.5 summarises the LVEF results for all patients and all beat selection criteria while the variation in ⇳LVEF ($LVEF_{max} - LVEF_{min}$) is summarised in Table 5.6. From these it can be seen that a substantially greater range of LVEFs is normally measurable on a per-patient basis in AF, although there is little difference in the maximum range and the median LVEFs are comparable in the two patient groups.

Given the substantial range of measurements of LVEF that can occur for each patient, is there a relationship between the beat selection criteria and LVEF?

[1] See note on terminology §5.3.1

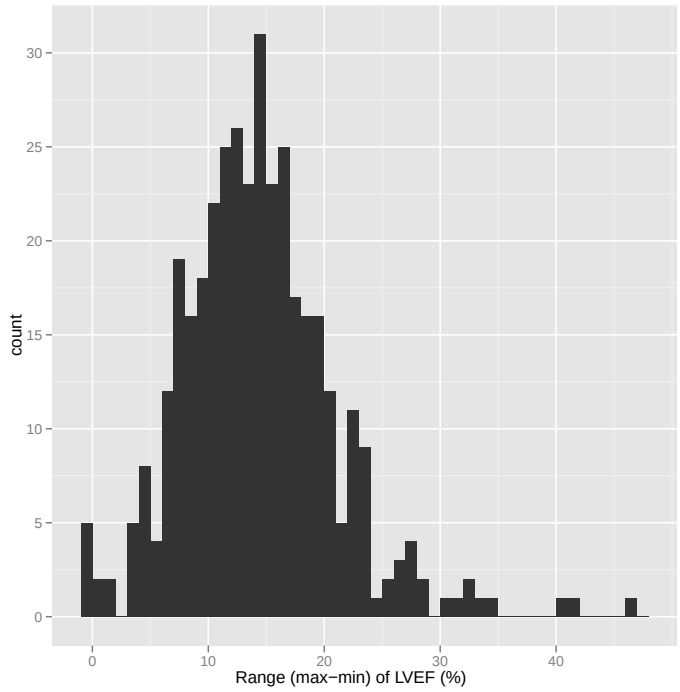


(a) ⇳LVEF histogram

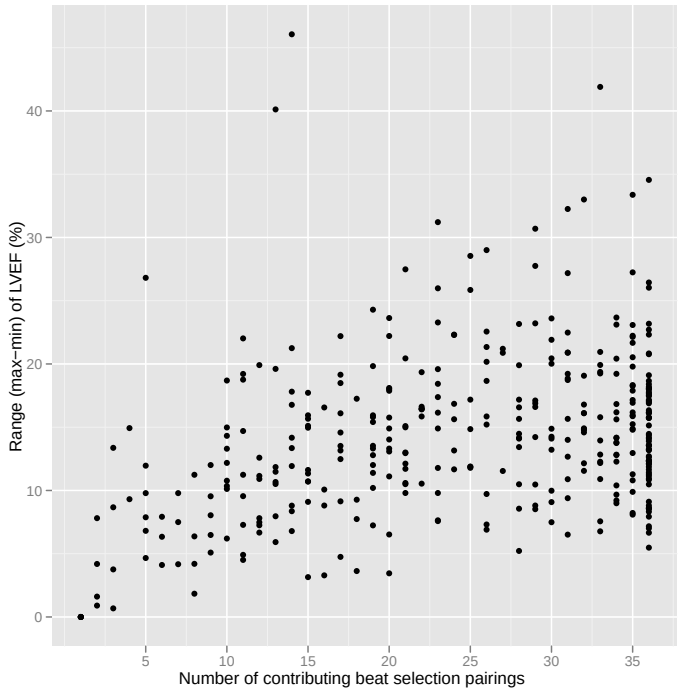


(b) ⇳LVEF with count

Figure 5.5.: SR, ⇳LVEF: Showing (a) the histogram of ⇳LVEF obtained for all patients in SR and (b) a plot of the ⇳LVEF against the number of contributing beat selection preceding:indexed pairings for patients in SR using variable time mode (N=387).



(a) LVEF range histogram



(b) LVEF range with count

Figure 5.6.: AF, ⇳LVEF: Showing (a) the histogram of ⇳LVEF obtained for all patients in AF and (b) a plot of ⇳LVEF against the number of contributing beat selection preceding:indexed pairings for patients in AF using variable time mode (N=373).

Rhythm	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
SR	387	0.00	5.3	7.8	10.5	42.8	8.2	5.1
AF	373	0.00	10.2	14.0	17.8	46.1	14.3	6.6

Table 5.6.: ⇳LVEF: Summary statistics for ⇳LVEFs (in EF units) showing the distribution of ⇳LVEF (the difference between maximum and minimum LVEF for each patient) in SR and AF (variable time formatting).

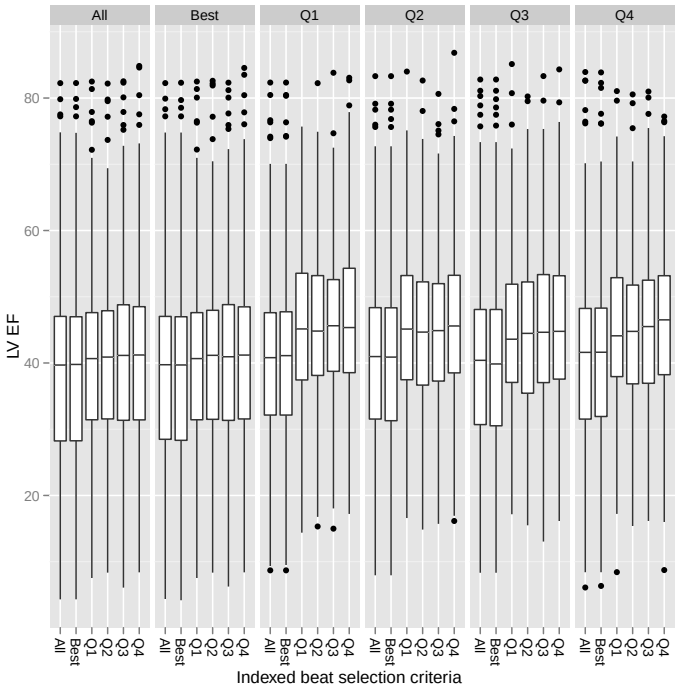
		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	38.2 ± 14.6	38.2 ± 14.7	40.0 ± 13.1	40.2 ± 13.3	40.1 ± 13.7	40.4 ± 13.9
	Best	38.2 ± 14.6	38.2 ± 14.7	40.0 ± 13.2	40.3 ± 13.3	40.2 ± 13.6	40.4 ± 13.8
	Q1	40.3 ± 13.0	40.3 ± 13.1	45.3 ± 12.4	45.2 ± 12.4	45.6 ± 11.6	46.0 ± 12.1
	Q2	40.2 ± 13.4	40.1 ± 13.5	45.6 ± 12.5	44.4 ± 12.8	44.7 ± 12.1	45.6 ± 12.4
	Q3	39.9 ± 13.7	39.8 ± 13.7	44.5 ± 12.5	44.4 ± 12.8	44.4 ± 12.6	45.1 ± 12.4
	Q4	40.3 ± 13.7	40.4 ± 13.6	45.0 ± 12.5	44.4 ± 12.3	45.1 ± 12.3	45.6 ± 12.6

Table 5.7.: SR, LVEF: $Mean \pm SD$ LVEF in SR with variable time formatting for different beat selection criteria. (Note: The box-plots show the median not the mean). The number of patients contributing to each measure is given in table 5.3

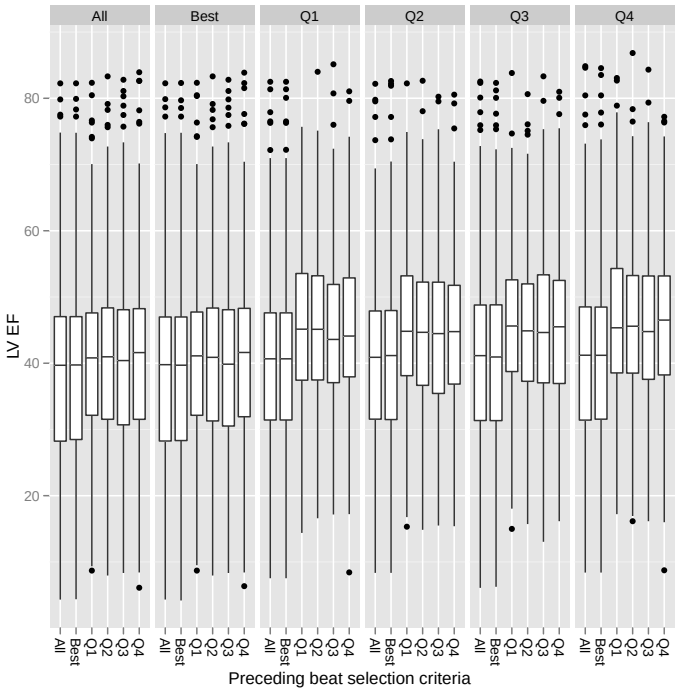
LVEF results are summarised, for SR, in Figure 5.7 and Table 5.7 and for AF in Figure 5.8 and Table 5.8 (it should be noted that the table reports mean and SD while the box-plots show the median value). A detailed explanation of the form of the figures can be found in §5.3.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	28.2 ± 11.2	32.7 ± 11.9	34.8 ± 11.0	33.9 ± 11.6	33.7 ± 11.6	32.1 ± 11.5
	Best	28.7 ± 10.5	34.3 ± 11.0	37.6 ± 10.1	36.5 ± 10.5	35.5 ± 10.9	34.0 ± 10.5
	Q1	28.2 ± 9.7	35.3 ± 10.0	40.1 ± 10.3	38.1 ± 9.9	37.8 ± 9.3	36.2 ± 9.7
	Q2	29.6 ± 10.3	36.3 ± 10.8	40.9 ± 10.2	39.4 ± 10.5	38.7 ± 10.5	36.9 ± 10.5
	Q3	31.1 ± 10.6	37.5 ± 11.3	42.0 ± 10.3	40.1 ± 10.9	39.5 ± 11.4	37.5 ± 10.9
	Q4	33.4 ± 11.1	39.5 ± 12.0	43.7 ± 11.5	42.0 ± 11.5	41.1 ± 11.5	39.3 ± 11.4

Table 5.8.: AF, LVEF: $Mean \pm SD$ LVEF in AF with variable time formatting for different beat selection criteria. The number of patients contributing to each measure is given in table 5.3

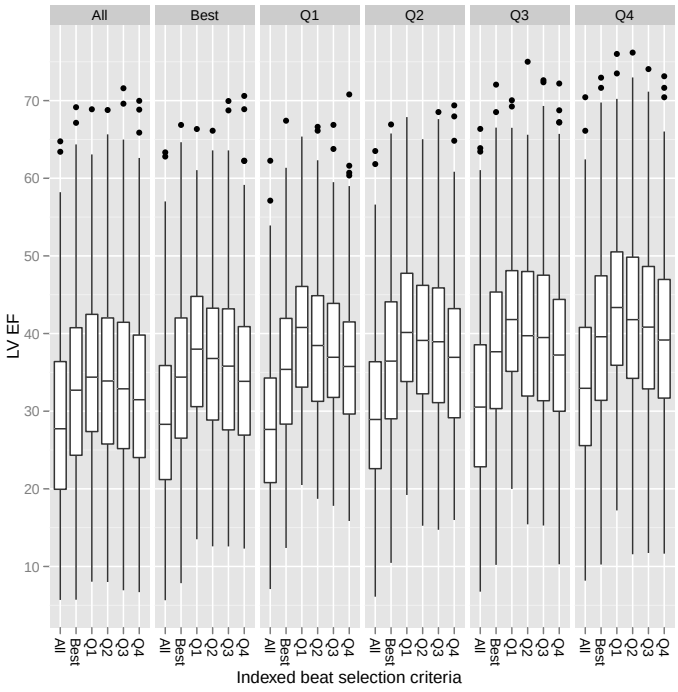


(a) Grouped by preceding beat

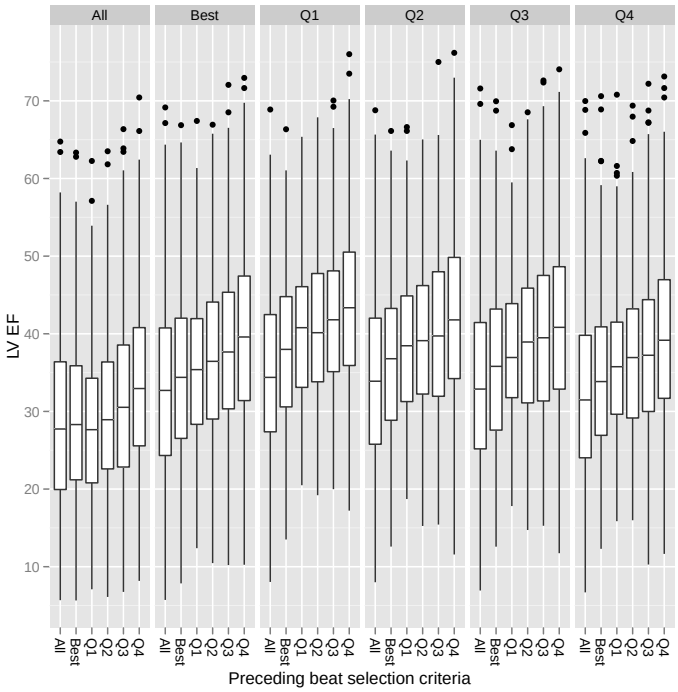


(b) Grouped by indexed beat

Figure 5.7.: SR, LVEF: Box-plots showing median and inter-quartile ranges for LVEF measured in variable time mode for patients in SR using variable time formatting. The two plots show the same data grouped either by (a) preceding beat selection criteria or (b) indexed beat selection criteria (N=387).



(a) Grouped by preceding beat



(b) Grouped by indexed beat

Figure 5.8.: AF, LVEF: Box-plots showing median and inter-quartile ranges for LVEF measured in variable time mode for patients in AF rhythm using variable time formatting. The two plots show the same data grouped either by (a) preceding beat selection criteria or (b) indexed beat selection criteria (N=373).

In both SR and AF, the LVEF is higher where beat selection has involved quartiles in either the preceding or the indexed beat. While there does not appear to be any significant systematic variation with R-R interval in SR, it is clear from the two presentations of the data that in AF there is a positive correlation with increasing preceding beat length (quartile) and a negative one with increasing indexed beat length.

Regression analysis was performed as discussed in §4.6.1. Results for the regression performed on a patient-by-patient basis are shown in Table 5.9 and summarised by quartile in Figure 5.9 for the multiple regression comparing both preceding and indexed beat.

The high number of positive correlations on a patient-by-patient basis with preceding beat variation (299 when all indexed beats are taken) in AF suggest a very strong relationship with preceding beat criteria. There are substantially fewer negative correlations with indexed beat (98 when all preceding beats are taken) suggesting that the correlation with indexed beat in AF is much weaker.

The relationship is much weaker in SR: fewer than half of the patients exhibited a significant dependence on beat selection criteria. In those that did, there was a balance between the effects of preceding and indexed beat leading to both positive and negative correlation coefficients. Where there was a relationship it was generally good, but weaker than the similar relationship in AF.

To try to quantify this further regression analysis was performed on a global basis; the results of this are shown in Table 5.10. In SR there is no significant linear variation of LVEF with R-R interval duration (either preceding or indexed), while in AF there is a highly significant relationship with both indexed and preceding beat criteria. These results support the patient-by-patient findings presented in Table 5.9.

Considering all patients together, analysis of variance found that the use of quartiles, particularly the interaction term between indexed and preceding beat length, contributed significantly to measured LVEF in both SR and AF with all the quartile results grouped together. However, particularly in SR, there was little difference between the results obtained with “Best” beats and those obtained with all beats, either preceding or indexed (see Table 5.11).

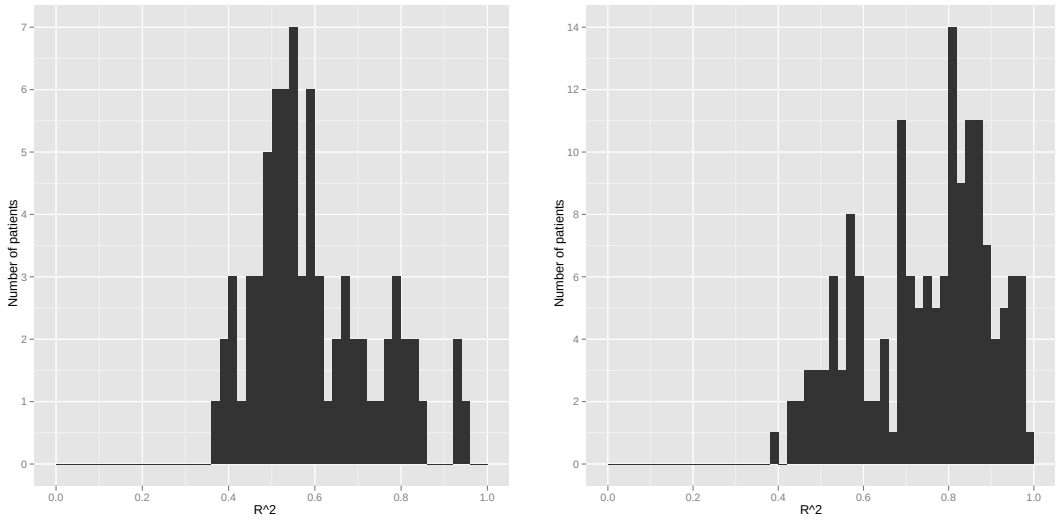
Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.78 ± 0.14	130	0.76 ± 0.13	40	4
Best (Constant)	Q1 - Q4	0.79 ± 0.15	129	0.76 ± 0.13	41	4
Q1 - Q4	All (Constant)	0.77 ± 0.15	107	0.78 ± 0.16	55	7
Q1 - Q4	Best (Constant)	0.75 ± 0.15	107	0.76 ± 0.16	63	6
Q1 - Q4	Q1 - Q4	0.60 ± 0.14	45 (p), 49(i)		29 (p), 25(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.77 ± 0.16	20	0.77 ± 0.13	98	7
Best (Constant)	Q1 - Q4	0.75 ± 0.17	15	0.78 ± 0.16	88	26
Q1 - Q4	All (Constant)	0.89 ± 0.12	299	0.66 ± 0.22	2	13
Q1 - Q4	Best (Constant)	0.86 ± 0.12	192	–	0	34
Q1 - Q4	Q1 - Q4	0.74 ± 0.15	158 (p), 26(i)		0 (p), 133(i)	55

(b) AF

Table 5.9.: LVEF: showing the regression results by quartile on a patient-by-patient basis for LVEF in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).



(a) SR (N=74) **(b)** AF (N=159)

Figure 5.9.: LVEF regression: histogram showing the number of patients in each band (0.02 wide) of r^2 coefficients for the multiple regression comparing both indexed and preceding beat criteria. Only results which have significance at $p < 0.05$ level have been shown.

		SR		AF	
Preceding	Indexed	r^2	p	r^2	p
All (Constant)	Q1 - Q4	7.7×10^{-5}	0.73	6.6×10^{-3}	0.003
Best (Constant)	Q1 - Q4	6.3×10^{-5}	0.76	1.5×10^{-2}	$< 1 \times 10^{-5}$
Q1 - Q4	All (Constant)	9.6×10^{-6}	0.91	3.2×10^{-2}	$< 1 \times 10^{-5}$
Q1 - Q4	Best (Constant)	1.7×10^{-6}	0.96	1.8×10^{-2}	1×10^{-5}
Q1 - Q4	Q1 - Q4	5.6×10^{-4}	0.59	3.1×10^{-2}	$< 1 \times 10^{-5}$

Table 5.10.: Regression results showing significance of preceding and indexed beat selection on LVEF (variable time formatting).

	SR, p	AF, p
p:All_c:All vs. p:Best_c:All	9.6×10^{-1}	5.8×10^{-1}
p:All_c:All vs. p:Quartiles_c:All	9.0×10^{-3}	1.0×10^{-4}
p:All_c:All vs. p:All_c:Best	9.8×10^{-1}	$< 1 \times 10^{-5}$
p:All_c:All vs. p:All_c:Quartiles	9.0×10^{-3}	$< 1 \times 10^{-5}$
p:All_c:All vs. p:Best_c:Best	9.6×10^{-1}	3.6×10^{-1}
p:All_c:All vs. p:Quartiles_c:Best	9.8×10^{-1}	1.9×10^{-2}
p:All_c:All vs. p:Best_c:Quartiles	9.7×10^{-1}	6.0×10^{-2}
p:All_c:All vs. p:Quartiles_c:Quartiles	9.9×10^{-4}	$< 1 \times 10^{-5}$

Table 5.11.: LVEF: p values from analysis of variance comparing LVEF with preceding and indexed beat selection criteria grouping all quartile results together for all patients using variable time formatting.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	6	5	32	15	15	8
	Best	7	7	36	12	15	7
	Q1	20	15	20	12	8	10
	Q2	16	16	11	6	4	9
	Q3	14	16	7	11	8	5
	Q4	6	6	11	6	10	9

(a) Minima

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	3	4	8	4	6	9
	Best	4	4	11	5	4	7
	Q1	0	1	17	18	11	29
	Q2	4	5	15	8	15	28
	Q3	6	8	11	12	25	13
	Q4	12	12	15	14	30	38

(b) Maxima

Table 5.12.: SR, LVEF: Showing the number of patients for whom the given combinations of preceding and indexed beat selection gave rise to the minimum (a) and maximum (b) measured LVEF in SR.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	20	0	0	1	0	3
	Best	30	1	0	0	1	0
	Q1	186	3	3	0	2	6
	Q2	15	0	1	0	0	0
	Q3	1	1	0	0	0	0
	Q4	0	0	0	1	0	0

(a) Minima

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	4	2	3	1	3	0
	Best	0	2	2	2	2	2
	Q1	0	0	2	0	2	0
	Q2	0	3	1	2	1	3
	Q3	0	4	10	7	9	3
	Q4	11	36	52	73	77	30

(b) Maxima

Table 5.13.: AF, LVEF: Showing the number of patients for whom the given combinations of preceding and indexed beat selection gave rise to the minimum (a) and maximum (b) measured LVEF in AF.

In considering the source of the difference in measured LVEF the beat selection combinations that contribute to the minima and maxima are shown in Tables 5.12 (SR) and 5.13 (AF).

Although it is not obvious in SR, when the tables are compared (see §4.6.3) they are found to be significantly different ($p = 0.039$). In AF the tables are self evidently different and there are too many singularities for a statistical comparison.

Subgroup	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
"Pure"	176	4.4	30.5	40.8	48.4	82.3	39.5	15.0
"Not pure"	211	4.3	27.6	39.0	46.0	74.6	37.1	14.3
MI	105	4.4	18.9	28.8	42.6	77.5	31.2	16.0
Not MI	278	4.4	35.1	41.5	48.4	82.2	40.9	13.18
HBP	164	7.0	34.8	40.8	49.2	82.3	41.3	13.7
Not HBP	219	4.3	25.0	38.5	46.0	77.5	36.0	14.9
PCI &/ CABG	83	8.6	23.1	38.0	46.4	77.2	36.5	16.1
Neither PCI nor CABG	300	4.3	30.0	40.1	47.6	82.3	38.8	14.2
Normal coronary perfusion	67	29.9	40.1	45.4	53.3	82.2	47.7	10.5
Ischaemic	320	4.3	25.2	38.4	45.9	77.5	36.2	14.6
Negative ETT	107	27.8	39.2	44.2	50.5	79.8	45.4	9.6
Positive ETT	7	24.9	36.4	42.4	49.2	53.8	41.7	10.1
Normal	188	38.4	43.8	47.2	53.9	82.3	49.8	8.3
Moderate & Mildly impaired	146	20.6	26.9	33.1	37.2	40.1	32.1	5.9
Very poor & poor	51	4.3	9.1	13.0	16.8	19.7	12.9	4.5

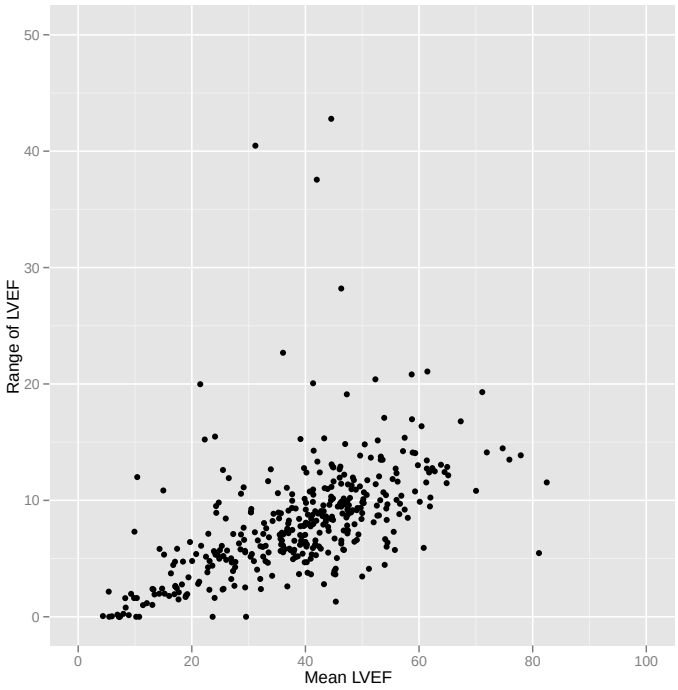
Table 5.14.: SR subgroups, LVEF: Summary statistics for LVEFs for subgroups for patients in SR using variable time formatting.

5.4.2. Comparing LVEF with ⇳LVEF

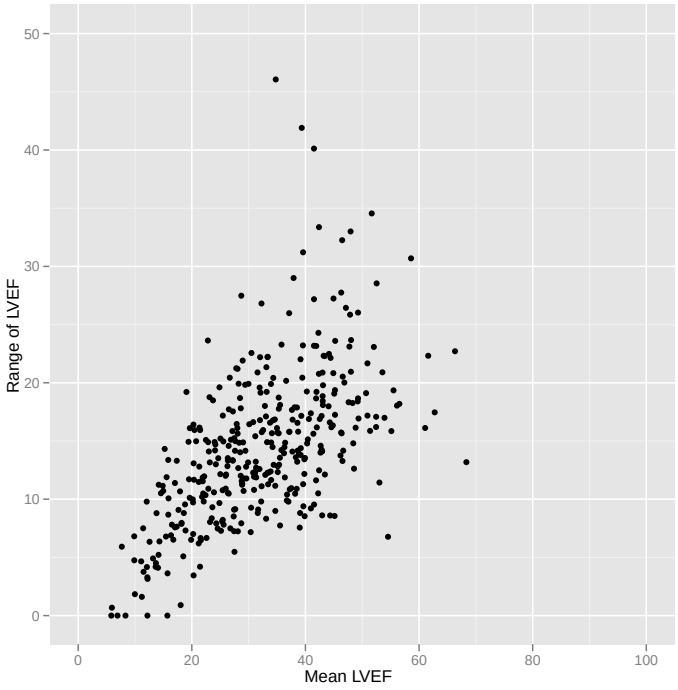
Since a poorly functioning ventricle should not be able to produce beats with good EFs while a well functioning ventricle may produce beats with poor EFs, it is to be expected that ⇳LVEF for each patient will be closely associated with LVEF. The comparison is shown in Figure 5.10 where it can be seen that patients with poorer LVEF also generally show a lower ⇳LVEF in both SR and AF. A Spearman rank correlation finds there to be good correlation between LVEF and ⇳LVEF with $r = 0.66$ in SR and $r = 0.62$ in AF.

5.4.3. Subgroups

Several different subgroups were investigated in both SR and AF as detailed in §4.4 and, while a full analysis was performed for each of the subgroups, the majority of the results followed similar patterns as for AF and SR as a whole. The LVEF summary statistics for each of the subgroups are given in Tables 5.14 (SR) and 5.16 (AF) while summary statistics for ⇳LVEF are given in Tables 5.15 (SR) and 5.17. A summary of the results for each subgroup in both SR and AF aggregated by beat selection criteria can be found in appendix C (§C.2).



(a) SR (N=387)



(b) AF (N=373)

Figure 5.10.: Comparing mean LVEF with ⇳LVEF using variable time formatting. Mean LVEF is calculated as the mean of all measured LVEFs after filtering using the whole list-mode file.

Subgroup	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
"Pure"	176	0.0	5.2	8.3	10.5	40.5	8.4	5.2
"Not pure"	211	0.0	5.0	7.4	10.5	42.8	8.0	5.1
MI	105	0.0	3.2	6.4	9.7	40.5	7.2	5.6
Not MI	278	0.0	5.8	8.4	10.8	42.8	8.6	4.9
HBP	164	0.0	6.10	8.57	10.88	42.78	9.01	5.3
Not HBP	219	0.0	4.78	7.07	10.18	40.47	7.67	4.93
PCI &/or CABG	83	0.0	5.5	7.7	9.8	22.7	7.8	4.3
Neither PCI nor CABG	300	0.0	5.2	8.0	10.7	42.8	8.4	5.3
Normal coronary perfusion	67	3.7	8.00	10.0	12.6	32.8	11.0	6.0
Ischaemic	320	0.0	4.8	7.2	9.8	40.5	7.6	4.7
Negative ETT	107	3.7	7.4	9.3	12.0	42.8	10.3	5.0
Positive ETT	7	6.1	8.5	9.6	9.6	10.6	8.9	1.5
Normal	188	1.3	7.9	9.7	12.2	28.2	10.1	3.8
Moderate & mildly impaired	146	1.6	5.2	6.5	8.7	42.8	7.7	5.6
Poor & very poor	51	0.0	1.0	1.9	3.6	20.0	2.9	3.5

Table 5.15.: SR subgroups, ⇳LVEF: Summary statistics for ⇳LVEF for each of the separate subgroups for patients in SR.

o

Subgroup	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
"Pure"	185	5.7	20.6	29.0	37.8	63.4	29.5	11.4
"Not pure"	187	5.8	19.1	26.0	34.8	64.8	27.0	10.8
MI	113	5.7	17.4	26.0	34.2	64.8	26.4	10.8
No MI	259	5.8	20.3	28.9	36.8	63.4	29.1	11.3
HBP	187	5.9	21.4	29.5	37.0	64.8	29.8	11.7
No HBP	185	5.7	18.2	26.6	35.3	49.5	26.8	10.4
PCI &/or CABG	67	9.4	19.2	27.2	34.7	63.4	28.1	11.4
Neither PCI nor CABG	306	5.7	20.1	27.9	36.6	64.8	28.3	11.1
NCP	34	17.1	31.2	36.6	41.9	55.8	37.0	9.1
No NCP	339	5.7	19.2	26.6	35.3	64.8	27.4	11.0
Negative ETT	50	8.6	20.7	27.9	37.1	64.8	29.0	11.6
Positive ETT	30	10.7	20.6	27.5	35.5	58.2	28.8	11.4
Very poor & poor	57	5.7	10.9	13.0	16.0	20.0	13.4	3.5
Moderate & Mildly impaired	206	12.6	22.2	26.5	30.9	38.1	26.7	5.7
Normal	97	27.4	38.1	40.1	45.4	64.8	42.1	6.5

Table 5.16.: AF subgroups, LVEF: Summary statistics for measured LVEFs in AF, assessed by subgroup with variable time formatting.

Opposing groups (e.g. patients with and without previous known MI), each one of which will be discussed separately in the following sections, were compared using a Wilcoxon signed ranks test to determine whether there was any significant difference in LVEF,

Subgroup	No. Pats	Minimum	1^{st} Quartile	Median	3^{rd} Quartile	Maximum	Mean	SD
"Pure"	185	0.0	10.6	14.2	18.4	41.9	15.0	6.7
"Not pure"	187	0.0	9.7	13.5	17.2	46.1	13.7	6.4
MI	113	0.00	9.1	12.5	18.8	41.9	13.6	6.7
Without MI	259	0.0	10.7	14.4	17.7	46.1	14.7	6.5
HBP	187	0.0	10.9	14.9	18.2	40.1	14.8	6.7
Without HBP	185	0.0	9.9	13.3	17.1	46.1	13.9	6.5
CABG &/or PCI	67	1.8	10.1	12.7	16.6	33.0	13.5	5.5
Without CABG & PCI	306	0.0	10.3	14.2	18.0	46.1	14.5	6.8
Normal Perfusion	34	8.5	14.1	16.6	18.8	30.7	16.8	4.5
Ischaemic	339	0.0	9.8	13.4	17.4	46.1	14.1	6.7
Negative ETT	50	1.6	10.4	14.6	16.9	32.3	14.1	5.5
Positive ETT	30	3.8	12.3	15.9	19.3	41.9	16.6	7.4
Very poor & poor	57	0.7	4.8	7.6	11.2	23.6	8.2	4.5
Moderate & Mildly impaired	206	4.2	10.7	13.3	16.4	46.1	14.2	5.7
Normal	97	6.8	15.6	18.0	22.1	34.6	18.7	5.6

Table 5.17.: AF subgroups, ⇳LVEF: Summary statistics for ⇳LVEF in AF, subgroups with variable time formatting.

	SR	AF
"Pure" vs. "Not pure"	$p = 8.2 \times 10^{-2}$	$p = 3.4 \times 10^{-2}$
MI vs. No MI	$p < 1 \times 10^{-5}$	$p = 4.5 \times 10^{-2}$
HBP vs No HBP	$p = 0.0012$	$p = 2.7 \times 10^{-2}$
PCI or CABG vs. No intervention	$p = 1.2 \times 10^{-1}$	$p = 6.9 \times 10^{-1}$
Normal coronary perfusion vs. Ischaemic	$p < 1 \times 10^{-5}$	$p < 1 \times 10^{-5}$
Positive ETT vs Negative ETT	$p = 5.4 \times 10^{-1}$	$p = 9.1 \times 10^{-1}$

Table 5.18.: LVEF, subgroups: Wilcoxon signed ranks tests comparing LVEF measured using all beats in opposing groups except in the case of the functional groups where a Wilcoxon is not appropriate because there are more than two functional groups and an Anova is used instead.

when all beats were taken, and in ⇳LVEF. The results of this analysis are shown for both AF and SR in Tables 5.18 and 5.19. Regression results on a patient-by-patient basis in each group were also compared yielding the results shown in Tables 5.20 (SR) and 5.21 (AF).

	SR	AF
"Pure" vs. "Not pure"	$p = 3.1 \times 10^{-1}$	$p = 1.1 \times 10^{-1}$
MI vs No MI	$p = 7.9 \times 10^{-4}$	$p = 9.2 \times 10^{-2}$
HBP vs No HBP	$p = 4.0 \times 10^{-3}$	$p = 1.0 \times 10^{-1}$
PCI or CABG vs. No intervention	$p = 5.4 \times 10^{-1}$	$p = 2.4 \times 10^{-1}$
Normal coronary perfusion vs. Ischaemic	$p < 1 \times 10^{-5}$	$p = 2.0 \times 10^{-3}$
Positive ETT vs Negative ETT	$p = 5.4 \times 10^{-1}$	$p = 1.6 \times 10^{-1}$
Anova comparing functional groups	$p < 1 \times 10^{-5}$	$p < 1 \times 10^{-5}$

Table 5.19.: ⇳LVEF, subgroups: Wilcoxon signed ranks tests comparing LVEF ranges in opposing groups except in the case of the functional groups where a Wilcoxon is not appropriate because there are more than two functional groups and an Anova is used instead.

Wilcoxon comparisons used the LVEF obtained when all beats were taken (without the inclusion of beat selection criteria) to provide a common comparison value. It should be noted that when the Wilcoxon test was performed with every possible measured LVEF using each pair of beat selection criteria in all cases there was a highly significant difference with $p < 1 \times 10^{-5}$. This reflects the substantial variation obtained in LVEF for any one patient and the very large number of values being compared, and as a result offers little insight into the variation between opposing subgroups.

"Pure" ECG

Patients with an ECG with no ectopic beats and a Poincaré plot that could not be considered to have any obvious outliers were considered to have a "pure" ECG.

When a Wilcoxon rank-sum (Mann-Whitney) test was used to compare LVEF (determined using all beats) in the "pure" and "not pure" groups no difference was found between the groups in SR. In AF, however, the two groups were found to be significantly different with "pure" rhythms showing a higher LVEF than "not pure" rhythms (Table 5.18). When a similar test was used to compare ⇳LVEF, no difference was found between those patients with and without a "pure" ECG in either SR or AF.

Regression and Anova results are shown for the "pure" and not "pure" groups in SR and AF in Tables 5.22 (regression) and 5.23 (Anova). Although regression analysis in the "pure" and "not pure" subgroups found a similar pattern to that of the whole

	p:All_c:Q	p:Best_c:Q	p:Q_c:All	p:Q_c:Best	p:Q_c:Q
"Pure" ECG	0.80	0.80	0.75	0.74	0.57
	$N = 78$ (2)	$N = 79$ (2)	$N = 77$ (3)	$N = 79$ (2)	$N = 34$ (17)
"Not pure" ECG	0.78	0.79	0.80	0.78	0.62
	$N = 95$ (2)	$N = 95$ (2)	$N = 88$ (4)	$N = 96$ (4)	$N = 40$ (21)
Wilcox comparison	$p = 0.42$	$p = 0.76$	$p = 0.09$	$p = 0.08$	$p = 0.13$
MI	0.76	0.77	0.77	0.78	0.57
	$N = 49$ (0)	$N = 52$ (0)	$N = 43$ (1)	$N = 43$ (1)	$N = 18$ (10)
No MI	0.80	0.80	0.77	0.75	0.60
	$N = 124$ (3)	$N = 122$ (3)	$N = 119$ (6)	$N = 129$ (5)	$N = 52$ (28)
Wilcox comparison	$p = 0.12$	$p = 0.14$	$p = 0.92$	$p = 0.28$	$p = 0.48$
HBP	0.78	0.77	0.76	0.74	0.61
	$N = 74$ (0)	$N = 76$ (0)	$N = 62$ (2)	$N = 68$ (1)	$N = 23$ (22)
No HBP	0.79	0.80	0.78	0.77	0.58
	$N = 99$ (3)	$N = 98$ (3)	$N = 100$ (5)	$N = 104$ (5)	$N = 47$ (16)
Wilcox comparison	$p = 0.55$	$p = 0.17$	$p = 0.35$	$p = 0.20$	$p = 0.40$
PCI or CABG	0.79	0.78	0.75	0.77	0.58
	$N = 37$ (0)	$N = 37$ (0)	$N = 37$ (2)	$N = 39$ (1)	$N = 17$ (11)
No intervention	0.78	0.80	0.78	0.75	0.60
	$N = 136$ (3)	$N = 137$ (3)	$N = 125$ (5)	$N = 133$ (5)	$N = 53$ (27)
Wilcox comparison	$p = 0.66$	$p = 0.66$	$p = 0.44$	$p = 0.48$	$p = 0.61$
Normal MPI	0.77	0.75	0.76	0.72	0.63
	$N = 27$ (0)	$N = 26$ (0)	$N = 29$ (0)	$N = 33$ (0)	$N = 11$ (5)
Ischaemic	0.79	0.80	0.78	0.77	0.59
	$N = 146$ (4)	$N = 148$ (4)	$N = 136$ (7)	$N = 142$ (6)	$N = 63$ (33)
Wilcox comparison	$p = 0.59$	$p = 0.11$	$p = 0.42$	$p = 0.10$	$p = 0.48$
Positive ETT	0.87	0.84	0.91	0.91	0.59
	$N = 3$ (0)	$N = 3$ (0)	$N = 3$ (0)	$N = 3$ (0)	$N = 1$ (2)
Negative ETT	0.78	0.78	0.77	0.74	0.64
	$N = 43$ (0)	$N = 43$ (0)	$N = 41$ (0)	$N = 45$ (0)	$N = 14$ (10)
Wilcox comparison	$p = 0.42$	$p = 0.52$	$p = 0.08$	$p = 0.02$	$p = 0.67$

Table 5.20.: SR subgroups, LVEF: Showing the mean R^2 value for patient-by-patient regression in each subgroup in SR and the results of a Wilcoxon rank sum test comparing the matched groups. The number in brackets gives the number of incalculable results (any others were not significant). In this table "Q" indicates the beat selection criteria (preceding or indexed) against which regression was performed. Total numbers for each group can be found in Table 5.14.

	p:All_c:Q	p:Best_c:Q	p:Q_c:All	p:Q_c:Best	p:Q_c:Q
"Pure" ECG	0.78	0.86	0.90	0.89	0.76
	$N = 64$ (2)	$N = 65$ (10)	$N = 159$(6)	$N = 116$ (21)	N=81 (26)
"Not pure" ECG	0.79	0.79	0.89	0.87	0.72
	$N = 64$ (2)	$N = 64$ (16)	$N = 165$ (7)	$N = 116$ (13)	N=78 (29)
Wilcox comparison	$p = 0.44$	$p = 0.02$	$p = 0.74$	$p = 0.33$	$p = 0.10$
MI	0.77	0.85	0.89	0.89	0.72
	$N = 39$ (4)	$N = 43$ (8)	$N = 100$ (4)	$N = 70$ (11)	$N = 54$ (19)
No MI	0.79	0.80	0.90	0.88	0.76
	$N = 90$ (3)	$N = 86$ (18)	$N = 224$ (9)	$N = 162$ (23)	$N = 106$ (36)
Wilcox comparison	$p = 0.54$	$p = 0.22$	$p = 0.55$	$p = 0.86$	$p = 0.13$
HBP	0.76	0.83	0.89	0.89	0.76
	$N = 66$ (3)	$N = 62$ (15)	$N = 160$ (6)	$N = 118$ (15)	$N = 79$ (27)
No HBP	0.81	0.81	0.90	0.88	0.72
	$n = 63$ (4)	$N = 67$ (11)	$N = 164$ (7)	$N = 114$ (19)	$N = 81$ (28)
Wilcox comparison	$p = 0.06$	$p = 0.70$	$p = 0.64$	$p = 0.69$	$p = 0.12$
PCI or CABG	0.78	0.80	0.90	0.88	0.72
	$N = 21$ (1)	$N = 28$ (4)	$n = 64$ (2)	$N = 49$ (7)	$N = 36$ (8)
No intervention	0.79	0.83	0.89	0.88	0.75
	$N = 108$ (6)	$N = 102$ (22)	$N = 261$ (11)	$N = 184$ (27)	$N = 123$ (47)
Wilcox comparison	$p = 0.92$	$p = 0.42$	$p = 0.71$	$p = 0.40$	$p = 0.13$
Normal MPI	0.69	0.84	0.87	0.86	0.73
	$N = 13$ (0)	$N = 7$ (3)	$N = 31$ (0)	$N = 21$ (2)	$N = 15$ (6)
Ischaemic	0.80	0.82	0.90	0.89	0.75
	$N = 116$ (7)	$N = 123$ (23)	$N = 294$ (13)	$N = 212$ (32)	$N = 144$ (49)
Wilcox comparison	$p = 0.01$	$p = 0.80$	$p = 0.47$	$p = 0.38$	$p = 0.65$
Positive ETT	0.77	0.86	0.92	0.89	0.74
	$N = 11$ (1)	$N = 15$ (2)	$N = 24$ (1)	$N = 20$ (3)	$N = 15$ (5)
Negative ETT	0.81	0.87	0.90	0.89	0.76
	$N = 23$ (3)	$N = 14$ (6)	$N = 43$ (4)	$N = 28$ (5)	$N = 17$ (7)
Wilcox comparison	$p = 0.36$	$p = 0.98$	$p = 0.61$	$p = 0.69$	$p = 0.82$

Table 5.21.: AF subgroups, LVEF: Showing the mean R^2 value for patient-by-patient regression in each subgroup in AF and the results of a Wilcoxon rank sum test comparing the matched groups. The number in brackets gives the number of incalculable results (any others were not significant). In this table "Q" indicates the beat selection criteria (preceding or indexed) against which regression was performed. Total numbers for each group can be found in Table 5.16.

		SR				AF			
Preceding	Indexed	"Pure" r^2	"Pure" p	"Not pure" r^2	"Not pure" p	"Pure" r^2	"Pure" p	"Not pure" r^2	"Not pure" p
All (Constant)	Q1 - Q4	3.9×10^{-5}	0.87	1.2×10^{-4}	0.76	5.3×10^{-3}	5.5×10^{-2}	8.4×10^{-3}	1.8×10^{-1}
Best (Constant)	Q1 - Q4	2.6×10^{-5}	0.90	1.0×10^{-4}	0.77	1.5×10^{-2}	4.0×10^{-3}	1.5×10^{-2}	5.0×10^{-3}
Q1 - Q4	All (Constant)	1.8×10^{-5}	0.92	9.2×10^{-5}	0.79	3.4×10^{-2}	$< 1 \times 10^{-5}$	3.2×10^{-2}	$< 1 \times 10^{-5}$
Q1 - Q4	Best (Constant)	8.1×10^{-5}	0.82	3.9×10^{-5}	0.77	2.0×10^{-4}	1.0×10^{-3}	1.6×10^{-2}	2.0×10^{-3}
Q1 - Q4	Q1 - Q4	1.7×10^{-4}	0.96	1.0×10^{-4}	0.54	3.2×10^{-2}	$< 1 \times 10^{-5}$	3.1×10^{-2}	$< 1 \times 10^{-5}$

Table 5.22.: p values from regression tests for patients in SR and AF with "pure" and "not pure" ECGs using variable time formatting.

	SR		AF	
	"Pure" p	"Not pure" p	"Pure" p	"Not pure" p
p:All_c:All vs. p:Best_c:All	0.943	0.996	0.900	0.372
p:All_c:All vs. p:Quartiles_c:All	0.088	0.045	0.009	0.004
p:All_c:All vs. p:All_c:Best	0.985	0.990	0.0003	$< 1 \times 10^{-5}$
p:All_c:All vs. p:All_c:Quartiles	0.077	0.049	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$
p:All_c:All vs. p:Best_c:Best	0.946	0.993	0.324	0.720
p:All_c:All vs. p:Quartiles_c:Best	0.939	0.972	0.043	0.184
p:All_c:All vs. p:Best_c:Quartiles	0.947	0.986	0.073	0.371
p:All_c:All vs. p:Quartiles_c:Quartiles	0.069	0.005	0.0002	0.002

Table 5.23.: LVEF, pure subgroup: Analysis of variance results comparing LVEF with preceding and indexed beat selection criteria, grouping all quartile results together, for patients in SR and AF with a "pure" ECG using variable time formatting. (Significant values are highlighted).

groups, there are two notable differences: the "pure" group in SR exhibited no significant difference with beat selection criteria in either the regression analysis or the Anova; and in the "not pure" group in AF there was found to be no significant difference between the base measure (with all beats included) and that taken with p:Quartiles_c:Best.

Myocardial infarction (MI)

Patients in the MI group had reported a known previous MI as part of the routine pre-exam assessment based on the referral letter and information supplied by the patient.

Aggregated LVEF results are summarised for the groups with and without known previous MI using all beats in Tables 5.14 for SR and 5.16 for AF. A Wilcoxon rank-sum test (see Table 5.18) shows there to be a highly significant difference between LVEFs

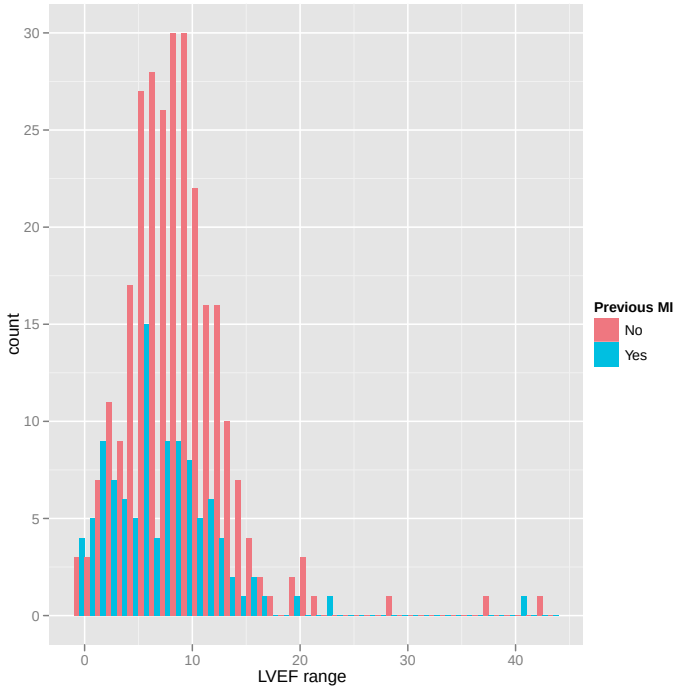


Figure 5.11.: SR, MI subgroup, ⇳LVEF: Histogram showing variation of ⇳LVEF with beat selection techniques for patients with and without known previous MI in SR (variable time formatting). (N=387).

measured using all beats between the MI (mean: 31.2) and non-MI (mean: 40.4) groups in SR which is matched by a less significant difference in AF (mean 26.4 in MI group, 29.1 in the non-MI group).

Despite the apparently similarity of the ranges shown in Table 5.15 a Wilcoxon rank-sum (Mann-Whitney) test against the ranges of LVEF comparing patients with and without known previous MI finds the two groups to be significantly different in SR but not in AF (see Table 5.19). This is demonstrated graphically in Figure 5.11.

Regression analysis found no significant linear relationships between LVEF and beat selection techniques for patients in SR with or without known previous MI. In AF there was a significant relationship in all comparisons in the group without known MI, although in the group with MI there was no significant linear relationship with indexed beat, although there was with preceding beat where LVEF increases with preceding beat duration.

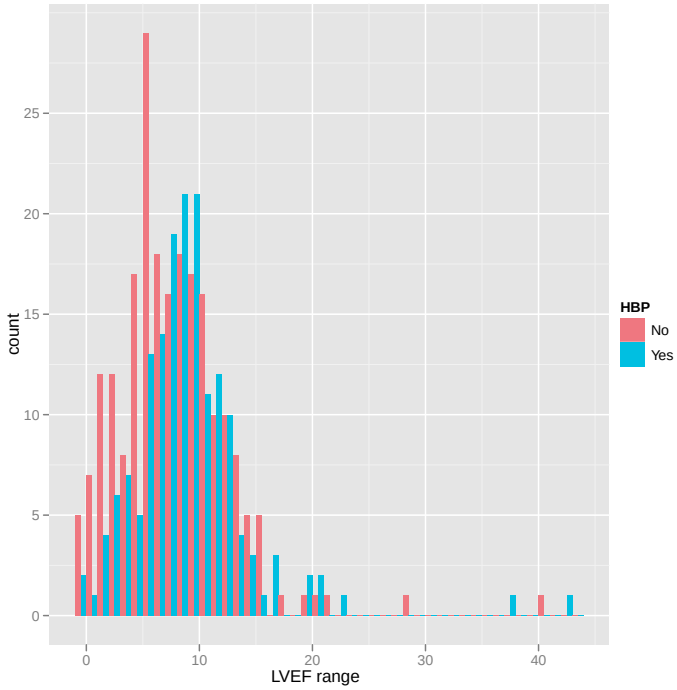


Figure 5.12.: SR, HBP subgroup, ⇳LVEF: Histogram showing variation of measured range of LVEF with beat selection techniques for patients with and without known hypertension in SR (N=387).

The Anova comparison found a similar pattern of dependence in both groups in AF and in the SR group without MI. The SR group with MI showed a significant difference only when both quartiles in both indexed and preceding beats were selected.

Hypertensive

Patients with hypertension, HBP, declared that they had high blood pressure as part of the routine pre-exam assessment. Patients would have been on therapy to treat high blood pressure. Thus, in some cases, the patient currently did not exhibit hypertension.

As in the case of the patients with MI there is a significant difference in LVEF in both SR and AF between those patients who had HBP and those who did not (Tables 5.14, 5.16 and 5.18); patients with HBP having generally higher LVEF than those without.

In SR, patients with HBP had a significantly greater ⇳LVEF than did those without HBP (demonstrated graphically for SR in Figure 5.12). This difference was not seen in AF (Tables 5.15, 5.17 and 5.19).

Regression analysis found no significant dependence on beat selection criteria in SR with a highly significant but extremely weak significance in AF except where all preceding beats were taken ($p = 0.065$). The analysis of variance found significance in the HBP group in SR only where beat selection involved quartiles in both indexed and preceding beats. In the group without HBP as well as both groups in AF the Anova showed no difference from that of the AF and SR group as a whole.

CABG and / or PCI

Patients were included in this group if they declared on the routine pre-exam questionnaire that they had a previous PCI or CABG, or if the request form specified this.

In neither the SR nor AF groups was a significant difference seen in either LVEF or range of LVEFs (see Tables 5.14, 5.16, 5.18, 5.15, 5.17 and 5.19). Regression testing revealed no substantive difference in the group who had had neither PCI nor CABG from the AF and SR groups as a whole (no relationship in SR, in AF a highly significant, very weak, dependence). Similarly the Anova showed a relationship following the same form as for the whole group. A significant difference was revealed in SR if both indexed and preceding beat selection criteria involved quartiles, otherwise there was no dependence in SR with AF following the same pattern as the group as a whole.

Ischaemic

Patients were considered not to be ischaemic if they had an associated myocardial perfusion scan in which the report used the phrase "No significant perfusion abnormality detected", a standard reporting phrase used in the department for patients who did not exhibit signs of ischaemia.

A Wilcoxon rank sum test found both LVEF and ⇳LVEF to be significantly different when comparing those patients in the ischaemic and non-ischaemic groups both in SR and AF (Tables 5.14, 5.16, 5.18, 5.15, 5.17 and 5.19); patients without ischaemia having a generally higher LVEF and greater ⇳LVEF. Regression and analysis of variance results followed the same pattern as the group as a whole in both AF and SR.

Positive vs. Negative ETT

Patients who had a clearly positive or negative ETT as part of their attendance for MPI and RNVG in the department were compared. Thus, for example, a patient who failed to reach target heart rate during exercise would not be included as their ETT would have been inconclusive. Unfortunately this left only seven patients in SR with a positive ETT compared with 107 in the group of patients in SR with a negative ETT. The small numbers in the positive ETT group (N=7) mean that statistical comparison is likely to be flawed and results are unlikely to be significant.

The number of patients in the two groups in AF are more statistically valid with 50 patients having negative ETTs and 30 having positive ETTs.

No difference was found in either SR or AF between LVEF (Tables 5.14, 5.16, 5.18) or ⇳LVEF (Tables 5.15, 5.17 and 5.19).

In SR, regression testing showed that there was no significant dependence of LVEF on preceding or indexed beat selection criteria in either the positive ETT or negative ETT group. This follows the same pattern as for the SR group as a whole. However in AF, unlike in the whole AF group, there was also no significant dependence found except very weakly in patients with positive ETT with indexed beat (see Table 5.24). This may simply be due to the smaller numbers involved as a plot of the results shows similar trends (see figure 5.13). The analysis of variance also showed little significant variation, particularly with preceding quartile.

Analysis of variance, in SR, found significant differences only between p:All_c:All and p:Quartiles_c:All in the positive ETT group and between p:All_c:All and p:Quartiles_c:Quartiles in the negative ETT group. In AF Anova results for patients with both positive and negative ETT were broadly similar to those of the whole AF group.

LV Systolic Function

It is standard practise in the department to label LVEF according to the criteria shown in Table 5.25. These labels provide a quick clinical summary of cardiac function.

Preceding	Indexed	Negative ETT p	Positive ETT p
All (Constant)	Q1 - Q4	0.157	0.044
Best (Constant)	Q1 - Q4	0.153	0.072
Q1 - Q4	All (Constant)	0.057	0.072
Q1 - Q4	Best (Constant)	0.199	0.461
Q1 - Q4	Q1 - Q4	0.062	0.424

(a) Regression

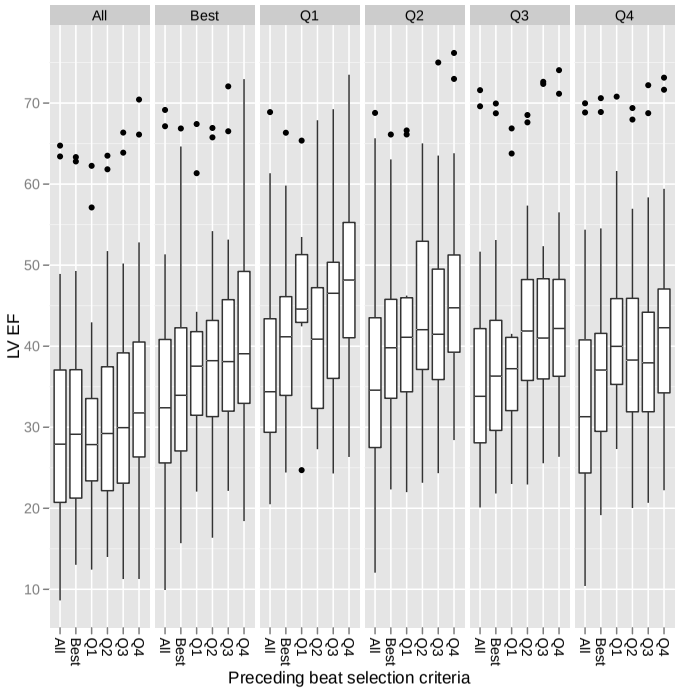
	Negative ETT p	Positive ETT p
p:All_c:All vs. p:Best_c:All	0.630	0.841
p:All_c:All vs. p:Quartiles_c:All	0.113	0.164
p:All_c:All vs. p:All_c:Best	0.062	0.047
p:All_c:All vs. p:All_c:Quartiles	0.001	0.005
p:All_c:All vs. p:Best_c:Best	0.741	0.683
p:All_c:All vs. p:Quartiles_c:Best	0.253	0.473
p:All_c:All vs. p:Best_c:Quartiles	0.287	0.337
p:All_c:All vs. p:Quartiles_c:Quartiles	0.019	0.056

(b) Analysis of variance

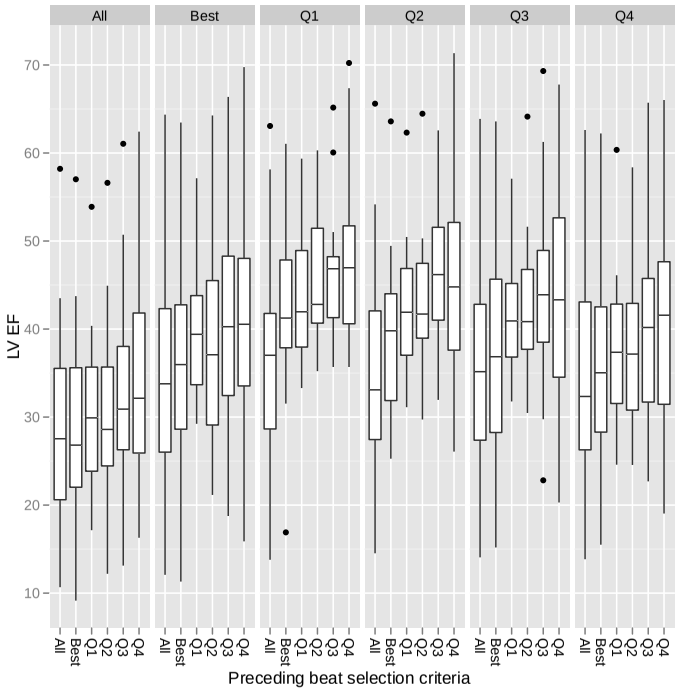
Table 5.24.: AF, ETT subgroup, LVEF: (a) Regression and (b) Anova results showing significance of preceding and indexed beat selection on LVEF in patients in AF with normal coronary perfusion or ischaemia using variable time formatting.

EF	Label
$LVEF < 10\%$	Very Poor
$10\% \leq LVEF < 20\%$	Poor
$20\% \leq LVEF < 30\%$	Moderate
$30\% \leq LVEF < 40\%$	Mildly impaired
$40\% \leq LVEF$	Normal

Table 5.25.: LVEF functional categories.



(a) Negative ETT



(b) Positive ETT

Figure 5.13.: AF, ETT subgroup, LVEF: Showing changes in LVEF with beat selection criteria in patients in AF by ETT result.

Function	SR Number	AF Number
Very poor	16	6
Poor	35	53
Moderate	54	100
Mildly impaired	92	108
Normal	188	98

Table 5.26.: Number of SR patients in functional groups.

The patients in this study were found, during routine reporting, to fall into these functional categories as shown in Table 5.26. In order to ensure adequate numbers for statistical analysis the reduced function groups were grouped in pairs: Very poor & poor, moderate & mildly impaired.

By definition the groups will have significantly different LVEF and no testing was carried out to determine whether there were significant differences between LVEFs. However when analysis of variance was used to compare ⇳LVEF these were found to be significantly different in both AF and SR (see Tables 5.15, 5.17 and 5.19). This is in keeping with the results of the direct comparison between LVEF and ⇳LVEF (§5.4.2).

Regression analysis on each of the functional groups found no significant correlation with either preceding or indexed beat criteria in SR. The analysis of variance found a difference only in the *mild & moderate* group when quartiles were used in both indexed and preceding beats and in the *poor & very poor* group only when quartiles were used in either indexed or preceding beat criteria (but not both).

The results for the regression and Anova analyses in AF are shown in Table 5.27 and show results which are also broadly in line with those for the whole group, although the small numbers in the *poor & very poor* group affect the significance of results.

5.4.4. Comparing variable time with fixed time formatting

In comparing LVEF in variable and fixed time formatting in SR there are four questions to be investigated:

Preceding	Indexed	Normal p	Mildly impaired & Moderate p	Poor & Very poor
All (Constant)	Q1 - Q4	0.112	0.005	0.099
Best (Constant)	Q1 - Q4	0.039	0.00002	0.227
Q1 - Q4	All (Constant)	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$
Q1 - Q4	Best (Constant)	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$	0.001
Q1 - Q4	Q1 - Q4	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$	0.114

(a) Regression

	Normal p	Mild & Moderate p	Poor & Very poor p
p:All_c:All vs. p:Best_c:All	0.202	0.403	0.971
p:All_c:All vs. p:Quartiles_c:All	0.632	0.009	0.0002
p:All_c:All vs. p:All_c:Best	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$	0.009
p:All_c:All vs. p:All_c:Quartiles	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$
p:All_c:All vs. p:Best_c:Best	0.8653	0.383	0.468
p:All_c:All vs. p:Quartiles_c:Best	0.5637	0.080	0.305
p:All_c:All vs. p:Best_c:Quartiles	0.6112	0.080	0.093
p:All_c:All vs. p:Quartiles_c:Quartiles	0.043	0.0001	0.0002

(b) Analysis of variance

Table 5.27.: AF, function subgroups, LVEF: Regression and analysis of variance results showing significance (p only) of preceding and indexed beat selection on LVEF in patients in AF grouped by systolic function using variable time formatting. r^2 values are uniformly very weak.

1. Can LVEF be obtained equally well using both formatting techniques?
2. Are measures of LVEF comparable?
3. Is the range of LVEF similar with both formatting techniques?
4. Are the factors which contribute to variation in LVEF the same in both fixed and variable time formatting?

Considering first the number of acceptable LVEFs measured using each technique (after beat limiting and data filtering - see §5.2). The cross tabulation of the number of valid LVEF measurements is shown in Tables 5.28 for SR and 5.29 for AF.

In SR these look very similar while in AF there is a reduction in the total number of acceptable LVEF measurements when fixed time mode is used. It is also interesting to note that in AF there were more acceptable LVEFs measured when either preceding or indexed beat were "All" or "Best" in variable time than in fixed time mode, and that regardless of formatting mode there is poor acceptability in the Q1:Q1 group.

To compare the tables a log-linear successive reduction technique as described in §4.6.3 was used. The initial model used in both SR and AF analyses was:

$$count \sim p + i + f + p:i + p:f + i:f + p:i:f \tag{5.3}$$

where:

p: is the preceding beat selection criteria

i: is the indexed beat selection criteria

f: is the frame mode.

In both AF and SR the successive reduction technique found that the inclusion of the $p:i:f$ term which defines differences between the two tables made no difference to the model; from which it can be concluded that there is no significant three way interaction and therefore that there is no significant difference between the behaviour with beat selection criteria when using fixed time compared with variable time. In SR further reduction found that the frame-mode term could be removed from the model completely, suggesting that frame-mode has no significant effect on the number of acceptable mea-

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	385	385	357	361	366	367	2221
	Best	385	385	357	361	364	367	2219
	Q1	355	355	159	192	196	210	1467
	Q2	361	362	189	219	229	231	1591
	Q3	367	367	196	229	242	230	1631
	Q4	365	364	198	221	231	245	1624
	TOTAL	2218	2218	1456	1583	1628	1650	10753

(a) Variable time

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	387	384	354	361	365	373	2224
	Best	386	382	355	363	365	371	2222
	Q1	362	354	160	189	195	222	1482
	Q2	362	361	185	217	225	245	1595
	Q3	365	364	188	224	235	247	1623
	Q4	366	364	193	216	225	246	1610
	TOTAL	2228	2209	1435	1570	1610	1704	10756

(b) Fixed time

Table 5.28.: SR: Number of acceptable LVEF by beat selection technique in (a) variable and (b) fixed time mode in SR.

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	372	360	312	346	349	349	2088
	Best	341	301	221	255	278	284	1680
	Q1	274	194	89	128	133	156	974
	Q2	327	252	134	174	199	211	1297
	Q3	347	284	153	205	226	249	1464
	Q4	360	306	182	241	265	273	1627
	TOTAL	2021	1697	1091	1349	1450	1522	9130

(a) Variable time

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	275	340	223	346	358	371	1913
	Best	281	298	165	267	285	335	1631
	Q1	291	208	87	127	139	216	1068
	Q2	279	253	105	196	211	280	1324
	Q3	276	290	124	211	240	310	1451
	Q4	277	301	147	252	274	321	1572
	TOTAL	1679	1690	851	1399	1507	1833	8959

(b) Fixed time

Table 5.29.: AF: Number of acceptable LVEFs by beat selection technique in (a) variable and (b) fixed time mode in AF.

surements of LVEF at all (this is consistent with the finding that there is only a very weak dependence of LVEF on beat selection criteria in SR - see §5.4.1).

The relationship between LVEF in variable and fixed time is shown in Figures 5.14 (SR) and 5.15 (AF). In both AF and SR a Spearman rank (non-parametric) correlation test finds there to be a nearly perfect, highly significant correlation in both SR ($\rho = 0.997$, $p < 1 \times 10^{-5}$) and AF ($\rho = 0.979$, $p < 1 \times 10^{-5}$) from which we conclude that there is little difference in LVEF measured using fixed and variable time.

The Bland-Altman [85] type analysis finds that in SR there is a mean difference of 0.19 ± 2.07 (mean $\pm$ 2SD) which is not clinically significant and well within the expected error of any measurement of LVEF. (This compares with SD over all LVEFs as assessed from the combination of two LV ROIs and two background ROIs of 0.686 and from count rate variation of 2.096 in variable time mode, 0.676 and 2.079 respectively in fixed time mode). In AF the Bland-Altman analysis finds that there is a mean difference of -0.54 ± 4.84 (mean $\pm$ 2SD) which, again, is unlikely to be clinically significant and is

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	37.8 ± 14.5	38.0 ± 14.4	40.0 ± 13.0	39.9 ± 13.2	39.9 ± 13.6	39.7 ± 13.8
	Best	37.9 ± 14.4	38.1 ± 14.4	40.0 ± 13.1	39.8 ± 13.4	39.9 ± 13.6	39.7 ± 13.5
	Q1	39.7 ± 12.9	40.3 ± 12.9	45.4 ± 12.1	44.7 ± 12.3	44.9 ± 12.3	44.6 ± 12.0
	Q2	40.0 ± 13.0	40.2 ± 13.3	45.5 ± 12.7	44.2 ± 12.9	44.6 ± 12.3	44.5 ± 12.0
	Q3	39.8 ± 13.1	39.9 ± 13.5	44.7 ± 12.6	44.4 ± 12.8	44.1 ± 12.5	44.2 ± 12.2
	Q4	39.7 ± 13.2	40.1 ± 13.5	44.8 ± 12.7	44.0 ± 12.3	44.3 ± 12.5	44.6 ± 12.5

Table 5.30.: SR, LVEF (fixed time): $Mean \pm SD$ LVEF in SR with fixed time formatting for different beat selection criteria.

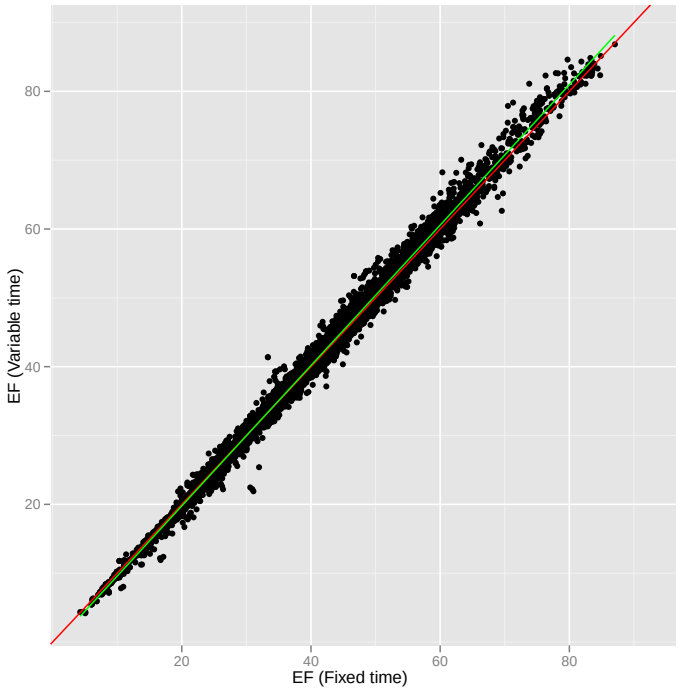
		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	33.4 ± 9.7	33.8 ± 11.5	36.7 ± 11.4	34.2 ± 11.4	33.4 ± 11.3	31.2 ± 9.8
	Best	32.1 ± 9.7	34.3 ± 11.0	38.4 ± 10.4	36.0 ± 10.5	35.1 ± 10.5	31.8 ± 9.4
	Q1	30.3 ± 9.1	34.5 ± 10.3	40.3 ± 10.2	37.2 ± 9.6	36.8 ± 9.2	32.0 ± 9.1
	Q2	33.0 ± 9.5	36.2 ± 10.7	41.4 ± 10.5	38.4 ± 10.7	37.8 ± 10.6	33.3 ± 9.5
	Q3	34.6 ± 9.7	37.1 ± 11.2	42.9 ± 10.5	39.7 ± 10.9	38.6 ± 10.9	34.6 ± 9.4
	Q4	36.7 ± 10.0	39.9 ± 11.5	44.3 ± 11.4	41.5 ± 11.4	40.4 ± 11.2	36.7 ± 9.8

Table 5.31.: AF, LVEF (fixed time): *Mean* LVEF in AF with fixed time formatting for different beat selection criteria.

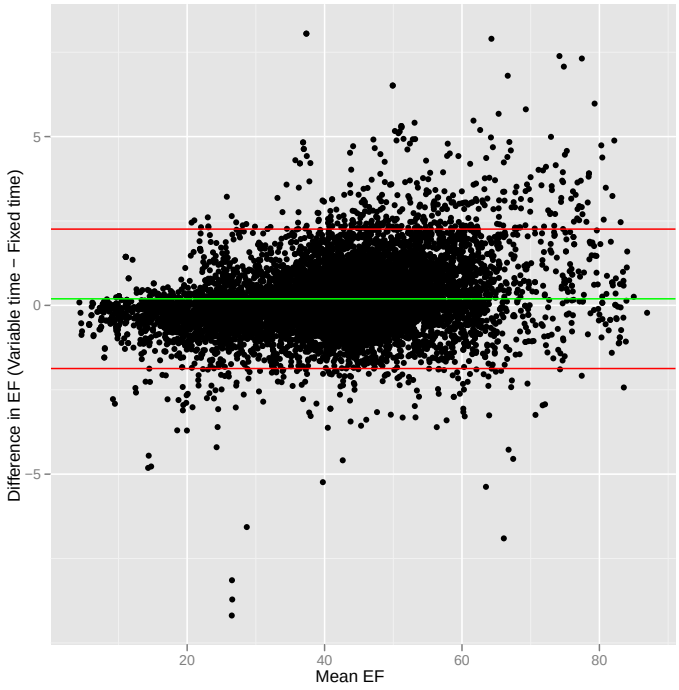
within the expected error of any measurement of LVEF. It is clear from the plots that in AF at lower LVEFs, variable time formatting slightly underestimates LVEF compared with fixed time formatting and that at higher LVEFs this is reversed, however the overall changes are not large.

The variation in measured LVEF with different beat selection techniques using fixed time formatting is shown for SR in Figure 5.16 and Table 5.30 (this can be compared with the plot for variable time formatting, Figure 5.7). In AF the variation in measured LVEF with different beat selection techniques is shown in Figure 5.17 and Table 5.31 (this can be compared with the plot for variable time formatting, Figure 5.8). These changes are broadly in line with the changes seen using variable time formatting.

The range of LVEF ($\Updownarrow$LVEF) obtained for each patient is shown in Figure 5.18 (SR) and Figure 5.19 (AF). This is clearly broadly the same distribution of ranges as that for variable time shown in Figures 5.5 and 5.6 respectively.

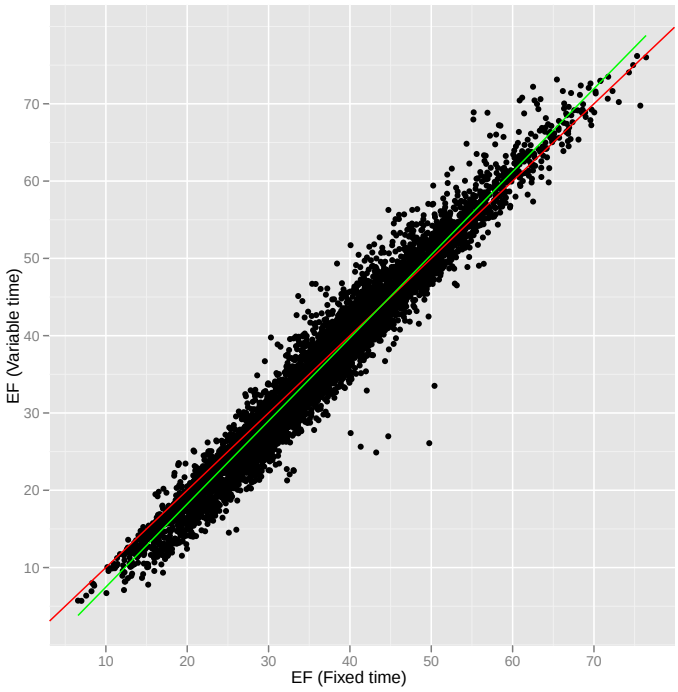


(a) Variable vs. Fixed

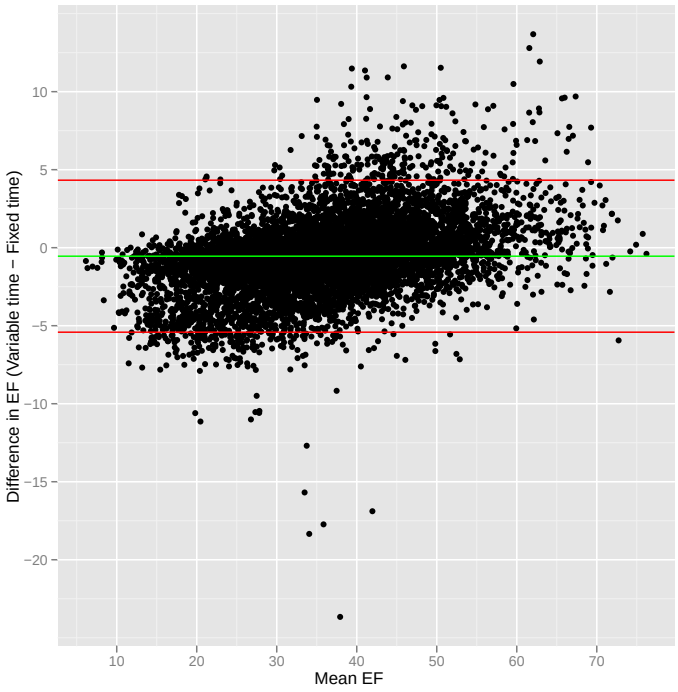


(b) Bland - Altman style

Figure 5.14.: SR, LVEF:Showing relationship between fixed and variable time mode for LVEF in SR. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.) (N=10528).

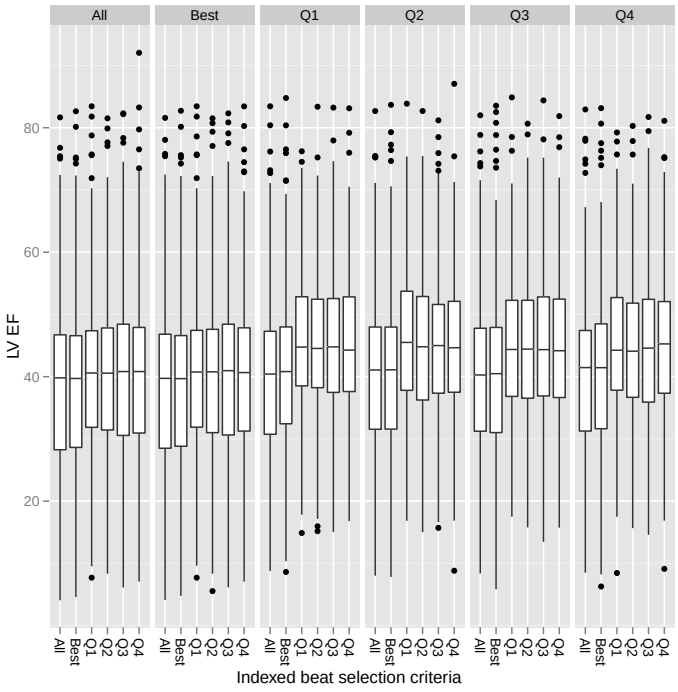


(a) Variable vs. Fixed

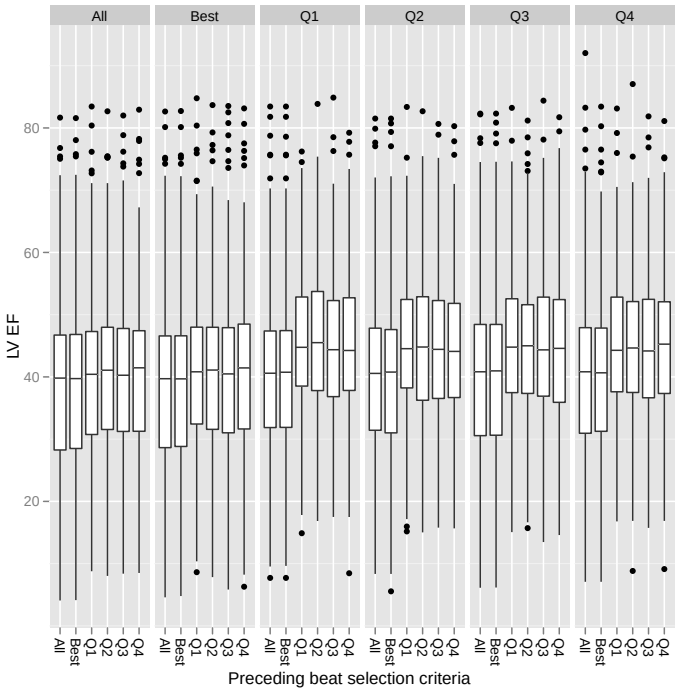


(b) Bland - Altman style

Figure 5.15.: AF, LVEF: Showing relationship between fixed and variable time mode for LVEF in AF. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.) (N=8230).

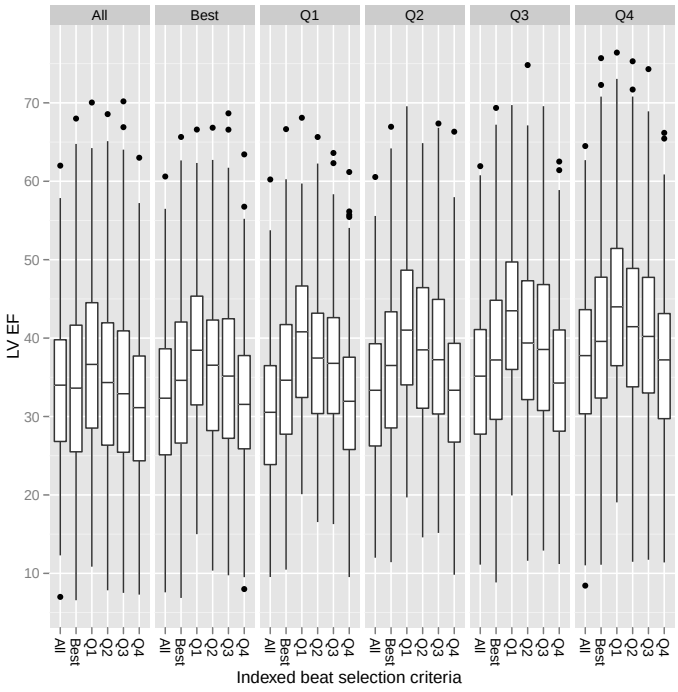


(a) Grouped by preceding beat

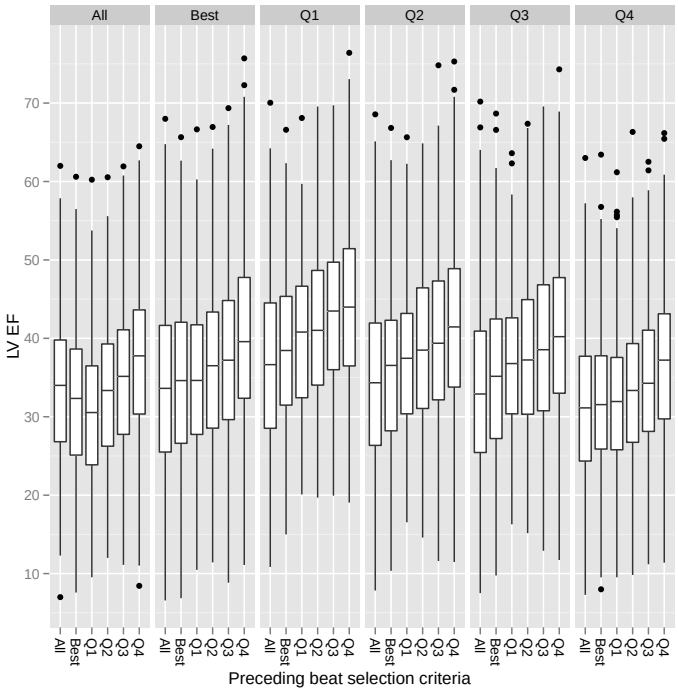


(b) Grouped by indexed beat

Figure 5.16.: SR, LVEF (fixed time): Box-plots showing median and inter-quartile ranges for LVEF measured for patients in SR using fixed time formatting. The two plots show the same data grouped either by (a) preceding beat selection criteria or (b) indexed beat selection criteria.

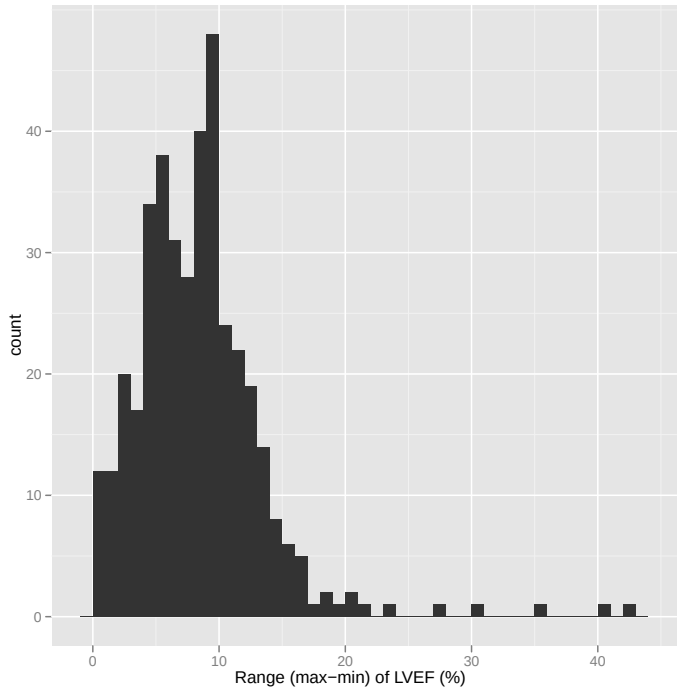


(a) Grouped by preceding beat

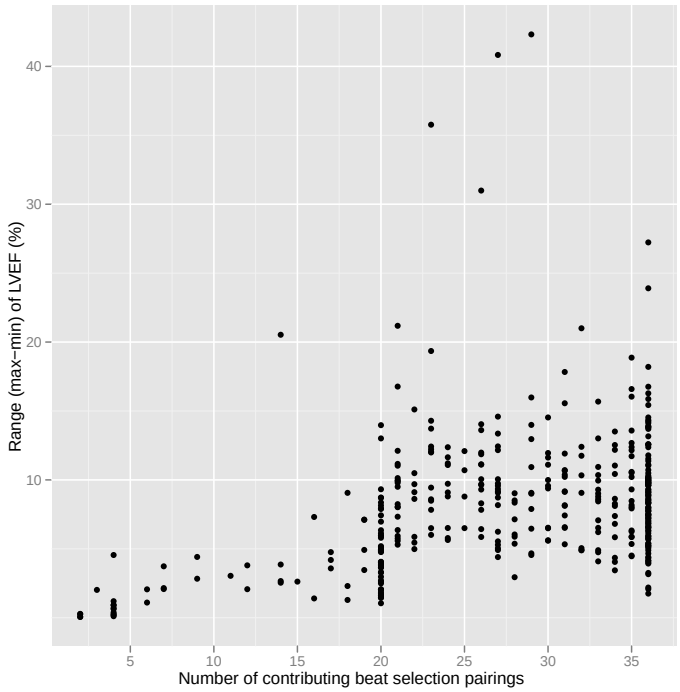


(b) Grouped by indexed beat

Figure 5.17.: AF, LVEF (fixed time): Box-plots showing median and inter-quartile ranges for LVEF measured for patients in AF using fixed time formatting. The two plots show the same data grouped either by (a) preceding beat selection criteria or (b) indexed beat selection criteria.

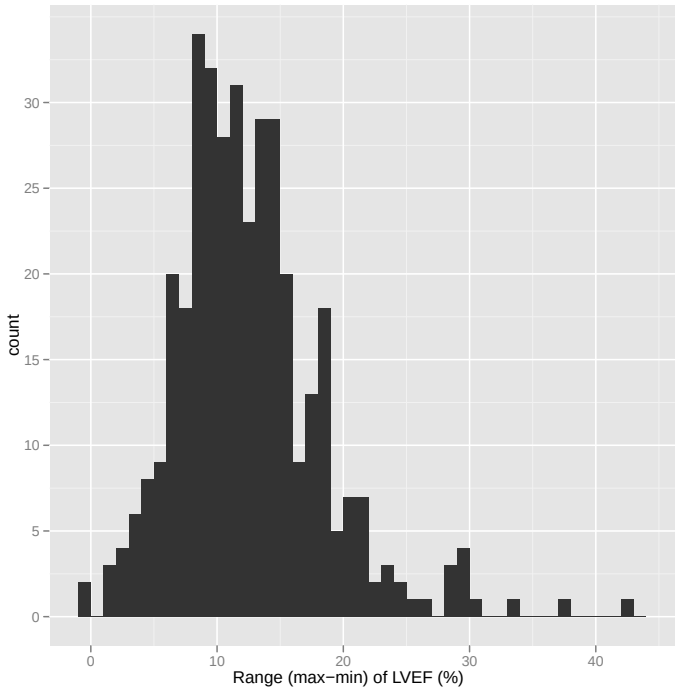


(a) LVEF range histogram

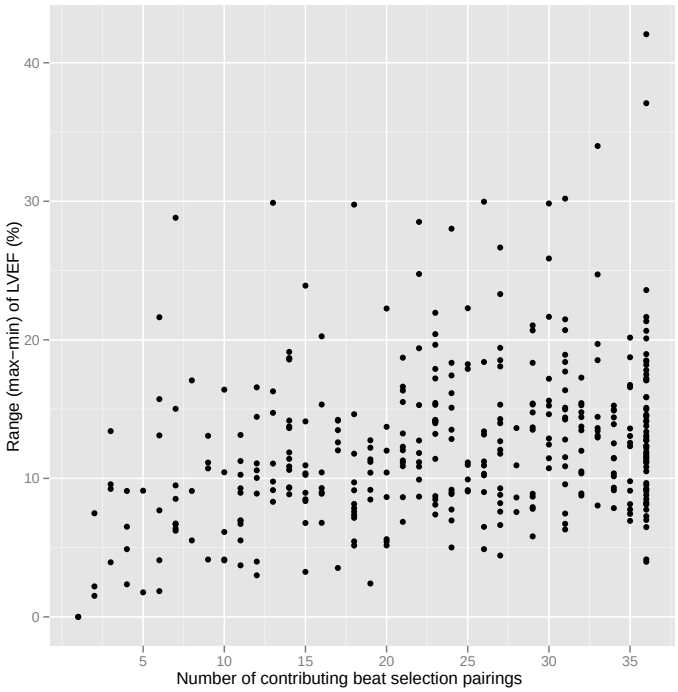


(b) LVEF range with count

Figure 5.18.: Showing (a) the histogram ranges (independent of mean LVEF) obtained for all patients and (b) a plot of the range (independent of mean LVEF) against the number of contributing beat selection preceding:indexed pairings for patients in SR using fixed time mode.



(a) LVEF range histogram



(b) LVEF range with count

Figure 5.19.: Showing (a) the histogram ranges (independent of mean LVEF) obtained for all patients and (b) a plot of the range (independent of mean LVEF) against the number of contributing beat selection preceding:indexed pairings for patients in AF using fixed time mode.

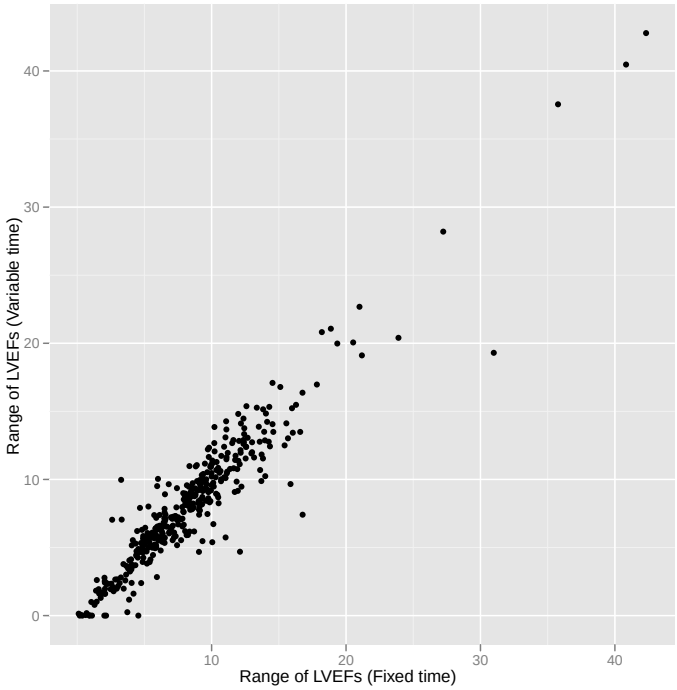


Figure 5.20.: Showing the relationship between LVEF ranges obtained using fixed and variable time formatting in SR.

A comparison of the ranges for variable vs. fixed time is shown in Figures 5.20 (SR) and 5.21 (AF). The data are not normally distributed and, in SR, a Spearman rank correlation finds an almost perfect, highly significant correlation ($\rho = 0.92$, $p < 1 \times 10^{-5}$). In AF, a Spearman rank correlation finds an excellent, highly significant correlation ($\rho = 0.807, p < 1 \times 10^{-5}$).

The ranges are a result of the differences between maxima and minima. The beat selection preceding:indexed pairings which give rise to the maximum and minimum LVEFs for each patient are shown cumulatively in Tables 5.32 (SR) and 5.33 (AF).

A visual comparison of the maxima and minima tables with the same tables in variable time (Tables 5.12 for SR and 5.13 for AF) suggests that there is a difference between the two modes, however a log-linear analysis similar to that carried out to compare the number of LVEFs assessed (see also §4.6.3) finds that removing the interaction term between all three variables makes no significant difference to the model and therefore that the difference between the tables is not significant. This is true in both SR and AF, both for the maxima ($p = 0.824$ in SR, $p = 0.827$ in AF) and minima ($p = 0.977$ in SR, $p = 0.612$ in AF) tables.

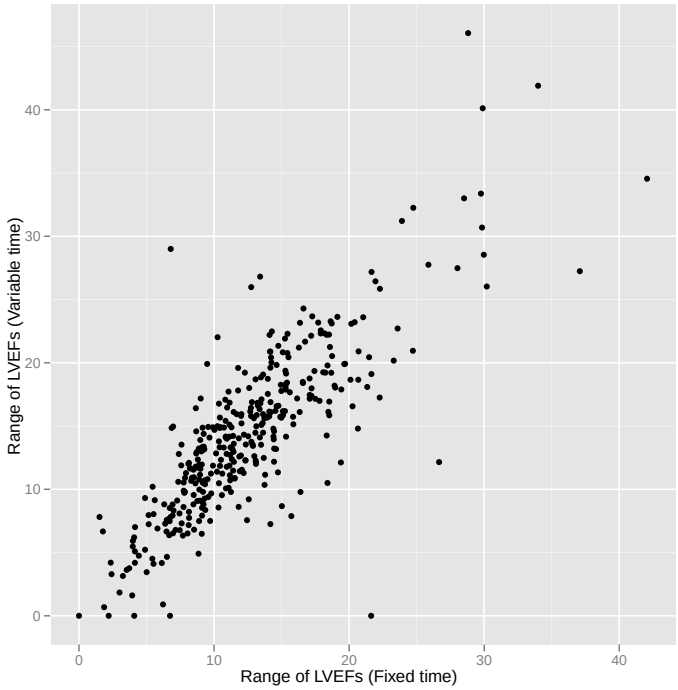


Figure 5.21.: Showing the relationship between LVEF ranges obtained using fixed and variable time formatting in AF.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	6	3	27	15	8	11
	Best	7	4	29	14	9	7
	Q1	20	9	16	9	10	9
	Q2	14	13	10	11	4	8
	Q3	8	11	6	8	5	13
	Q4	13	4	8	7	7	8

(a) Minima

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	3	1	6	2	3	11
	Best	0	1	8	3	2	12
	Q1	2	5	15	11	10	25
	Q2	2	6	13	12	11	32
	Q3	3	5	13	14	20	25
	Q4	9	7	22	12	23	40

(b) Maxima

Table 5.32.: LVEF, SR (fixed time): Showing the number of patients for whom the given combinations of preceding and indexed beat selection gave rise to the (a) minimum and (b) maximum measured LVEF in patients in SR using fixed time formatting.

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	0	5	3	6	19	20
	Best	3	5	1	5	4	26
	Q1	78	21	0	6	12	88
	Q2	3	4	1	2	0	15
	Q3	0	0	0	0	1	1
	Q4	0	0	0	0	0	2

(a) Minima

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	0	1	1	2	3	2
	Best	0	1	5	2	0	3
	Q1	0	0	3	1	2	0
	Q2	0	0	2	1	5	3
	Q3	2	5	15	8	5	4
	Q4	17	49	50	66	56	41

(b) Maxima

Table 5.33.: AF, LVEF (fixed time): Showing the number of patients for whom the given combinations of preceding and indexed beat selection gave rise to the (a) minimum and (b) maximum measured LVEF in patients with AF using fixed time formatting.

At no point in answering the four questions by which the comparison of different formatting modes was approached (see page 183) has a significant difference between fixed and variable time formatting in SR been found. In AF too, although there were fewer LVEFs rejected from the analysis in variable time formatting and there is a small difference between the measures, overall there seems to be no significant difference between fixed and variable time formatting. Additionally, the broad agreement in ⇳LVEF using the two formatting modes, suggests that the range of LVEFs measured for each patient is likely to be real and not simply methodological.

5.4.5. Assessing the consistency of results

Any measure of function that is to be clinically useful must have good reproducibility. In SR, LVEF has been shown to have good reproducibility. To test the methodological reproducibility of LVEF assessment in AF compared with SR, list-mode files were formatted in two separate halves and the differences between the first and second half compared using a Bland-Altman style analysis [84, 85].

Comparisons were only made between LVEF using either All or "Best" preceding beats and All or "Best" indexed beats. These criteria most closely mimic those used in clinical practice and it was felt that there would be insufficient counts in other images after the acquisition duration was halved and subsequently formatted using beat selection criteria based on quartiles. This conclusion is to some extent corroborated by the results shown in Table 5.3 (§5.2.3) which demonstrate that reduced count substantially affects the

Rhythm	Half	Preceding	Indexed	Number of studies
SR	First	All	All	375
SR	First	All	Best	375
SR	First	Best	All	374
SR	Second	All	All	371
SR	Second	All	Best	371
SR	Second	Best	All	371
AF	First	All	All	362
AF	First	All	Best	343
AF	First	Best	All	324
AF	Second	All	All	356
AF	Second	All	Best	317
AF	Second	Best	All	284

Table 5.34.: Number of contributing studies comparing consistency of LVEF in two halves of each study.

number of acceptable curves and that in both AF and SR there are substantially more acceptable results with the "Best" beats (either preceding or indexed) than when quartiles were used. Despite these results, the lack of quartiles in assessing the consistency of results *is* a limitation of the study and offers an area for further investigation.

The number of studies that contributed to each measurement is shown in Table 5.34 while the $mean \pm 2SD$ of the differences between the first and second half of the study are shown in Table 5.35. There is little difference between the results in SR; however in AF, although not clinically significant, there is a substantially smaller difference between LVEFs where all beats are taken (p:All_c:All) and where the "Best" beats are taken (either preceding or indexed). This suggests that taking all beats may give the most consistent results. The Bland-Altman plot (not shown, to conserve space) showed a very slight tendency towards larger differences between the two halves at higher LVEF in both SR and AF.

Investigation of the average beat for the different halves found that there was a only a very small deviation in beat length as shown in Table 5.35b. In both AF and SR these differences can be considered to be minimal and have been shown to be substantially

	SR			AF		
	First	Second	Difference	First	Second	Difference
p:All_c:All	38.4	39.3	-0.75 ± 2.38	28.6	29.4	-0.68 ± 2.24
p:Best_c:All	38.6	39.3	-0.72 ± 2.45	29.4	31.5	-0.91 ± 2.87
p:All_c:Best	38.4	39.3	-0.75 ± 2.48	33.4	35.3	-1.00 ± 3.43
p:Best_c:Best	38.4	39.3	-0.75 ± 2.49	35.9	38.0	-1.43 ± 3.68

(a) LVEF changes

	SR			AF		
	First	Second	Difference	First	Second	Difference
p:All_c:All	0.885	0.888	-0.0023 ± 0.0180	0.836	0.841	-0.0021 ± 0.0268
p:Best_c:All	0.885	0.888	-0.0027 ± 0.0186	0.849	0.861	-0.0031 ± 0.0261
p:All_c:Best	0.884	0.888	$-0.0.0026 \pm 0.0189$	0.762	0.771	-0.0071 ± 0.0802
p:Best_c:Best	0.883	0.888	-0.0030 ± 0.0197	0.770	0.776	-0.0008 ± 0.0732

(b) Average beat changes (s)

Table 5.35.: Showing the mean value and $Mean \pm SD$ of the difference between (a) LVEF and (b) average beat length in first and second half of study with different beat selection criteria.

smaller than the variations in LVEF ($\sim 2\%$ for LVEF compared with $\sim 0.2\%$ for average beat length).

5.5. Pre-systolic LV volume (PSV)

It is to be expected that pre-systolic volume, PSV, will change with preceding beat criteria. Short preceding beats in which the time for diastolic filling is, presumably, reduced should result in reduced end-diastolic volumes from the preceding beat (corresponding to the pre-systolic volume of the indexed beat).

PSV is, to an excellent approximation, proportional to the count and therefore a measure of pre-systolic volume (with units of cts/s), can be calculated as:

$$PSV = \frac{C_{ps}}{N_a(\bar{T_{RR}}/F)} \tag{5.4}$$

Where

C_{ps} is the pre-systolic count

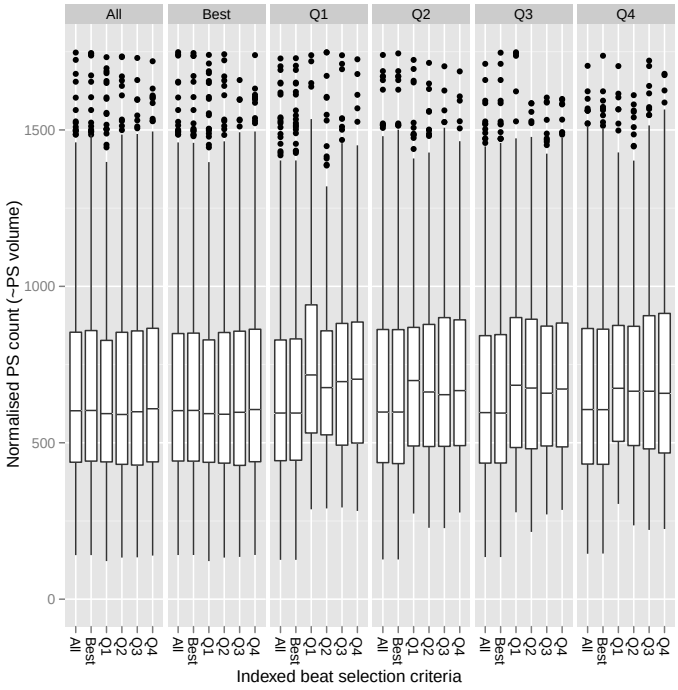
N_a is the number of accepted beats

$\bar{T_{RR}}$ is the mean (in variable time) or mid-point (in fixed time) RR interval

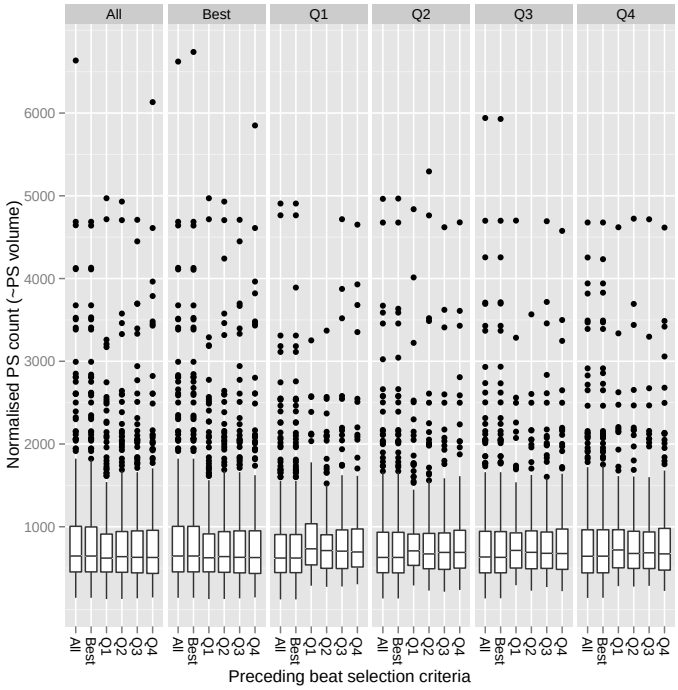
F is the number of frames.

The variation of PSV, with beat selection criteria in SR is shown in Figure 5.22 and for AF in Figure 5.23.

PSV is not normally distributed (see Figure C.5 in appendix C, §C.1) and a more normal distribution can be achieved by taking the logarithm of PSV. After taking the logarithm of PSV, regression testing confirmed the visual conclusion that there is no significant linear variation in PSV with either indexed or preceding beat length in SR or AF. However when regression is done on a patient-by-patient basis (against $\log(PSV)$) the results shown in Table 5.36 are found. It is clear from these results that in some patients there is an exceptionally good R^2 suggesting that in these patients there is a high dependency of PSV on beat selection criteria. The variation between these results is due to a lack of normalisation. While individually there is a very strong dependency

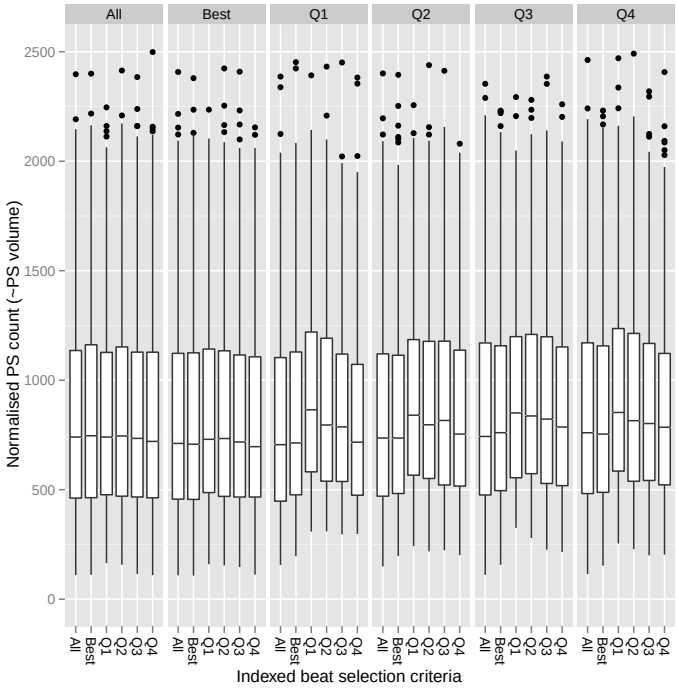


(a) *PSV* in SR preceding beat grouping

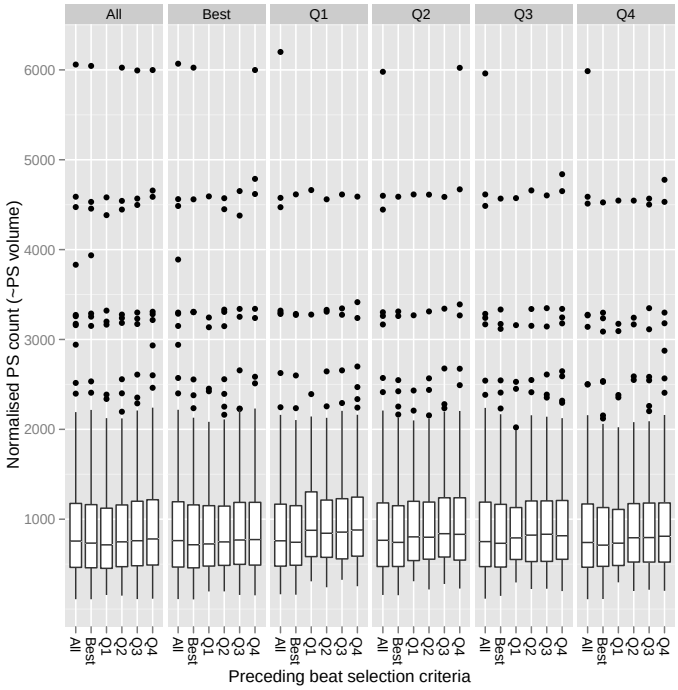


(b) *PSV* in SR indexed beat grouping

Figure 5.22.: SR, *PSV*: Showing the variation in *PSV* with varying indexed and preceding beat selection criteria in SR using variable time formatting. (a) shows the variation grouped by preceding beat selection criteria and limiting the extent of the y-axis so that some outliers are excluded. (b) shows *PSV* grouped by indexed beat - this plot includes all outliers to show their extent.



(a) *PSV* in AF preceding beat grouping



(b) *PSV* in AF indexed beat grouping

Figure 5.23.: AF, *PSV*: Showing the variation in *PSV* with varying indexed and preceding beat selection criteria in AF using variable time formatting. (a) shows the variation grouped by preceding beat selection criteria and limiting the extent of the y-axis so that some outliers are excluded. (b) shows *PSV* grouped by indexed beat - this plot includes all outliers to show their extent.

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.86 ± 0.13	196	0.79 ± 0.16	37	4
Best (Constant)	Q1 - Q4	0.87 ± 0.12	199	0.79 ± 0.15	35	4
Q1 - Q4	All (Constant)	0.85 ± 0.12	155	0.79 ± 0.16	48	7
Q1 - Q4	Best (Constant)	0.84 ± 0.12	149	0.79 ± 0.16	45	6
Q1 - Q4	Q1 - Q4	0.71 ± 0.15	96 (p), 111(i)		22 (p), 7(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.96 ± 0.05	335	$0.94 \pm NA$	1	7
Best (Constant)	Q1 - Q4	0.94 ± 0.07	243	NA	0	26
Q1 - Q4	All (Constant)	0.83 ± 0.14	137	0.80 ± 0.15	33	13
Q1 - Q4	Best (Constant)	0.79 ± 0.14	75	0.77 ± 0.14	29	34
Q1 - Q4	Q1 - Q4	0.90 ± 0.09	140 (p), 225(i)		83 (p), 0(i)	55

(b) AF

Table 5.36.: *PSV*: showing the regression results by quartile on a patient-by-patient basis for *PSV* in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

on beat selection criteria, globally the spread of *PSV* is such as to mask the individual dependency.

The analysis of variance of the data found that there is a significant difference between beat selection criteria which included quartiles (in either the preceding or indexed beat) in SR but not in AF (see Table 5.37).

Analysis of variance on the log transformed data found no significance in the beat selection criteria in SR and only weak significance in AF.

Comparing the ranges can be done either by comparing the difference between the maximum and minimum *PSV* or by comparing the ratio of minimum to maximum. The problem with comparing the differences is that there may be substantial variation in the underlying volumes of the LV (hearts are not a uniform size) and therefore there is no standard of comparison. By comparing the ratios, a natural normalisation is introduced and the results can be considered on the same scale.

Figures 5.24 (SR) and 5.25 (AF) show in plot (a) a histogram showing the number of patients with absolute volume ranges falling in 20 ms bins and in plot (b) the fractional

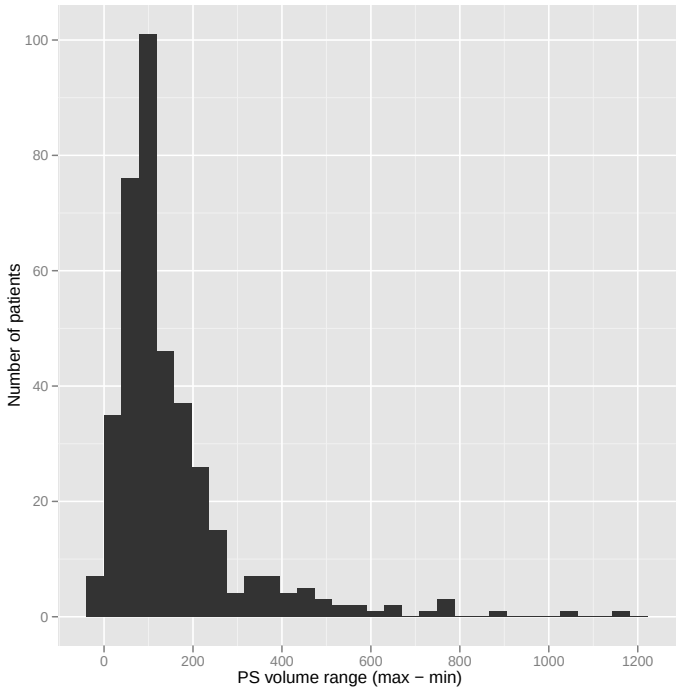
	SR p	AF p
p:All_c:All vs. p:Best_c:All	0.724	0.076
p:All_c:All vs. p:Quartiles_c:All	0.026	0.604
p:All_c:All vs. p:All_c:Best	0.989	0.0002
p:All_c:All vs. p:All_c:Quartiles	0.030	0.253
p:All_c:All vs. p:Best_c:Best	0.798	0.946
p:All_c:All vs. p:Quartiles_c:Best	0.953	0.861
p:All_c:All vs. p:Best_c:Quartiles	0.729	0.601
p:All_c:All vs. p:Quartiles_c:Quartiles	0.017	0.189

Table 5.37.: *PSV*: Analysis of variance results considering contribution of preceding and indexed beat selection criteria to measurement of *PSV* with variable time formatting.

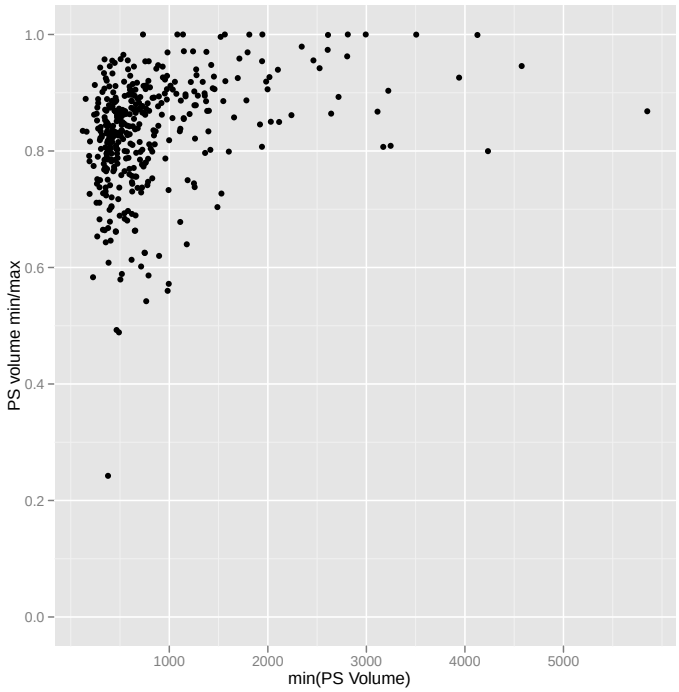
change as a function of the minimum volume. It is interesting to note that there is a greater absolute change in volume in SR than there is in AF when all the results are considered, although if the outliers in SR are excluded the results are similar with the bulk of patients having *PSV* between 500 and 1000 cts/s. The mean ratio of minimum to maximum *PSV* is 0.831 ± 0.097 in SR and 0.875 ± 0.056 in AF. A Mann-Whitney test shows these to be significantly different, although clinically the difference is unlikely to prove significant.

5.5.1. Comparing Pre-systolic volume (*PSV*) with ⇳*PSV*

It can be seen from Figure 5.25b that there is a tendency towards smaller *PSV* variations in patients who have a high minimum *PSV*. A similar result is achieved if the plot is made against mean *PSV*. The result is however affected by the number of patients in each volume range. Since there are many more patients with lower volumes it is unsurprising that there is a greater change. A Spearman rank correlation finds a moderate, but highly significant ($p < 0.00001$ in both AF and SR), correlation in both SR ($\rho = 0.29$) and AF ($\rho = 0.31$) between the fractional range and the mean *PSV*.

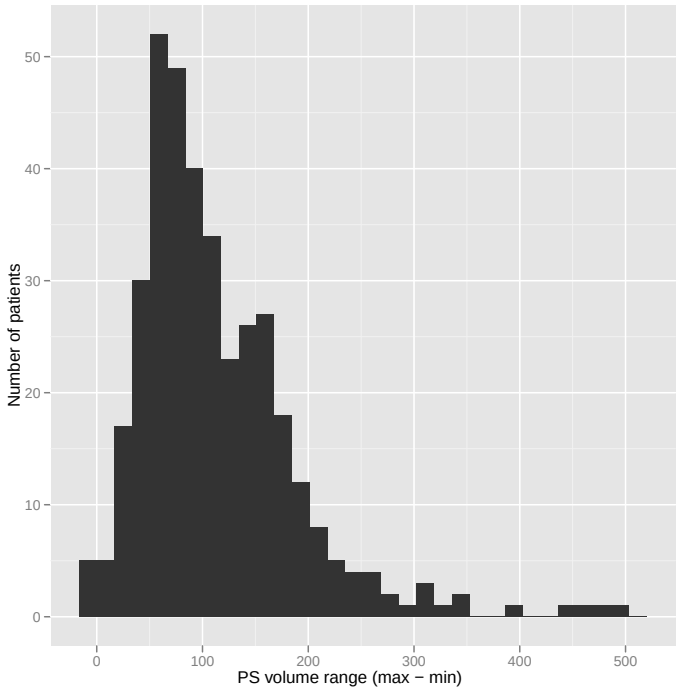


(a) Histogram

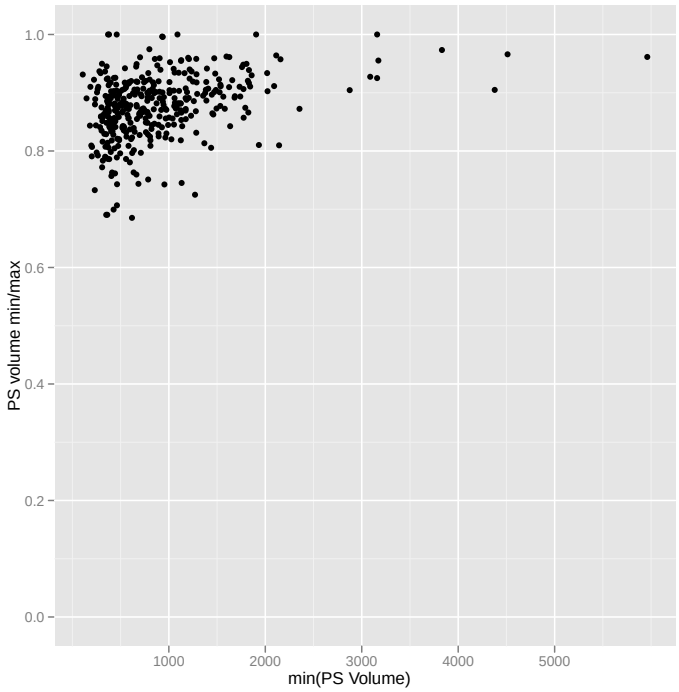


(b) Fractional change

Figure 5.24.: SR, *PSV* ranges: Showing the range of *PSV* for each patient in SR. (a) Shows a histogram of the range (max - min) (bin-width = 20), (b) shows the fractional change (min / max) as a function of the minimum. (N=387.)



(a) Histogram



(b) Fractional change

Figure 5.25.: AF, *PSV* ranges:Showing the range of *PSV* for each patient in AF. (a) Shows a histogram of the range (max - min) (bin-width = 20), (b) shows the fractional change (min / max) as a function of the minimum. (N=373).

5.5.2. Comparing variable time with fixed time formatting

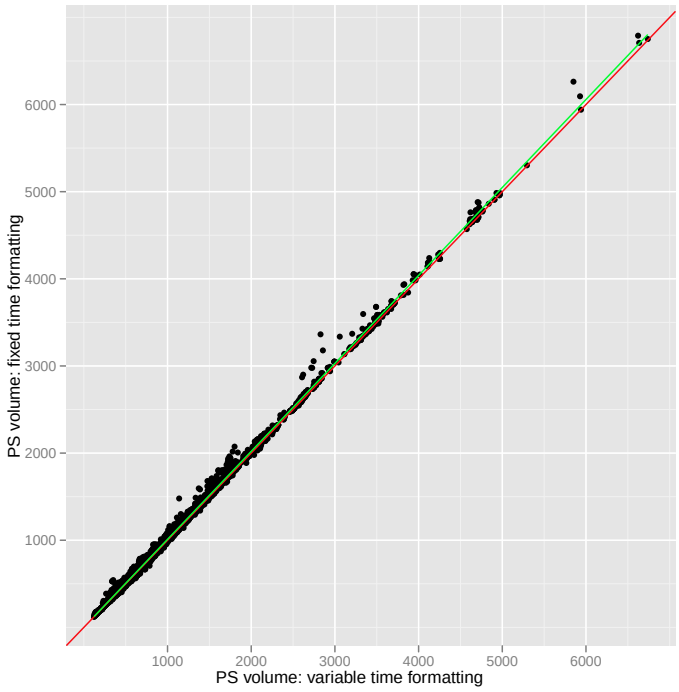
The comparison between fixed and variable time formatting is shown for SR in Figure 5.26 and for AF in Figure 5.27. There is exceptionally good correlation between the two techniques in both SR ($\rho = 0.998$, $p < 1 \times 10^{-5}$), and AF ($\rho = 0.986$, $p < 1 \times 10^{-5}$). Bland-Altman analysis [85] yields a mean difference of -8.737 and a SD of 23.12 with a mean "volume" of 831.9 counts in SR. In AF the analysis yields a mean difference of -81.2 and a SD of 101.0 with a mean "volume" of 928.2 counts. Although the Spearman rank correlation is exceptionally good in both cases it is noticeable that in AF the mean difference is an order of magnitude larger although the mean "volume" is of the same order of magnitude.

In both SR and AF variable time formatting underestimates volume compared to fixed time formatting. This is because variable time formatting leads to a greater blurring in volume than in time, while this is reversed in fixed time formatting (see Figure 1.10 in §1.5.2). Any blurring in volume will have the effect of reducing the assessment of volume when averaged over all selected beats.

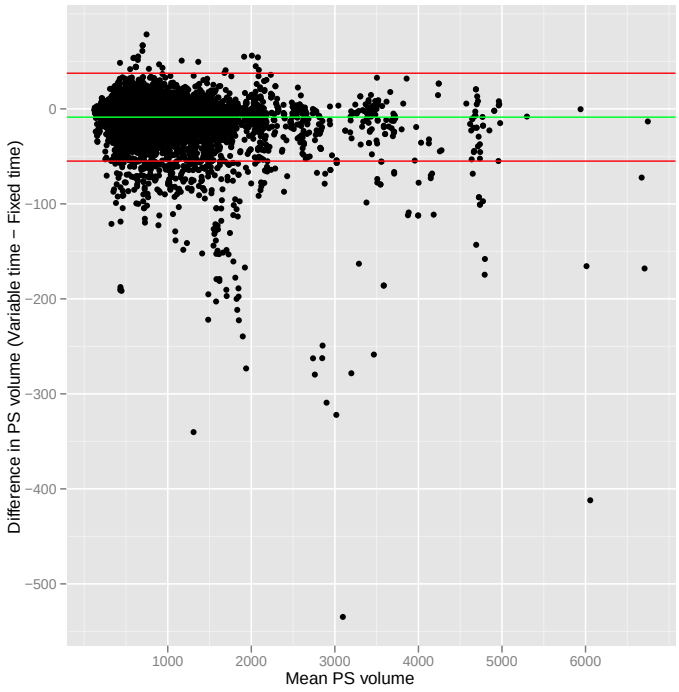
5.6. Pre-systolic volume vs. end-diastolic volume (EDV/PSV)

In SR, the ratio of end-diastolic to pre-systolic volume, EDV/PSV, should, in a normal beat, be approximately equal to 1. The volume time curve is expected to start and end at roughly the same volume on a beat-to-beat basis and averaging over all the selected beats ought to increase the probability of achieving equal pre-systolic and end-diastolic volumes. In AF, however, beat length is random and normal filling may be interrupted or prolonged. Thus it might be expected that a short preceding beat, followed by a long indexed beat (short followed by long filling time) would have a high EDV/PSV while similarly a long preceding beat followed by a short indexed beat would have a low (EDV/PSV).

The variation in EDV/PSV with beat selection criteria is shown in Figures 5.28 (SR) and 5.29 (AF) with values tabulated in Tables 5.38 and 5.39. In SR there seems to a be a weak correlation between indexed beat length and EDV/PSV with longer beats giving lower EDV/PSV. There is no obvious correlation with preceding beat length.

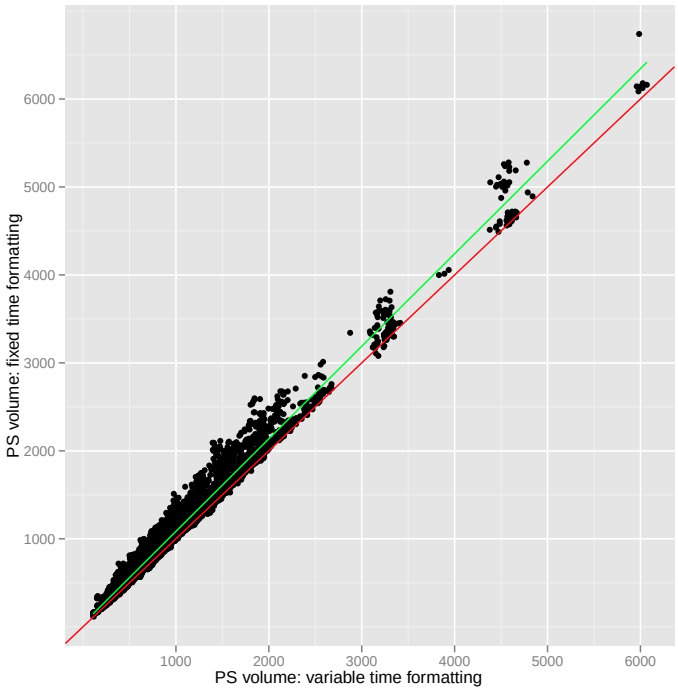


(a) Variable vs. Fixed

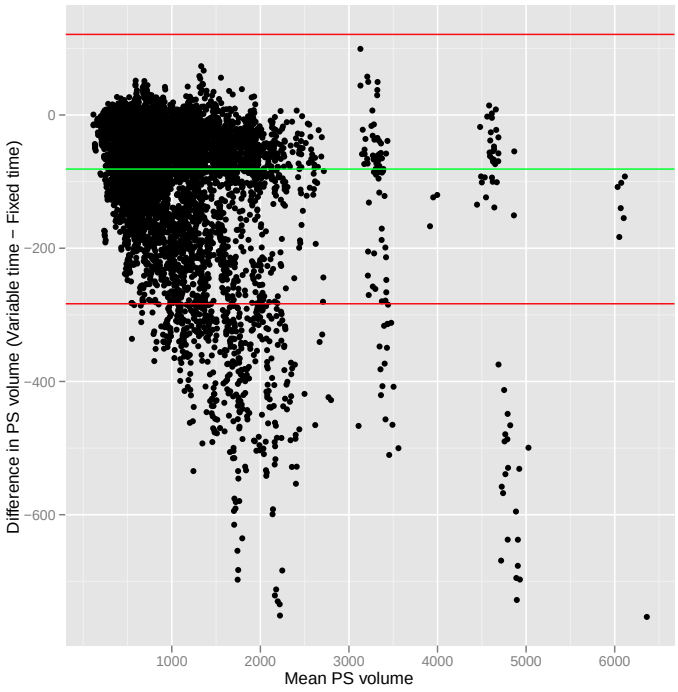


(b) Bland - Altman style

Figure 5.26.: SR, *PSV*: Showing relationship between fixed and variable time mode for *PSV* in SR. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.) (N=10528).



(a) Variable vs. Fixed



(b) Bland - Altman style

Figure 5.27.: AF, *PSV*: Showing relationship between fixed and variable time mode for *PSV* in AF. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.) (N=8230).

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	0.996 ± 0.032	0.996 ± 0.032	1.001 ± 0.040	0.997 ± 0.039	0.997 ± 0.039	0.994 ± 0.037
	Best	0.996 ± 0.032	0.996 ± 0.032	1.000 ± 0.040	0.998 ± 0.039	0.997 ± 0.039	0.994 ± 0.038
	Q1	0.996 ± 0.039	0.996 ± 0.039	0.999 ± 0.042	0.995 ± 0.048	0.990 ± 0.045	0.986 ± 0.043
	Q2	0.995 ± 0.040	0.995 ± 0.040	1.000 ± 0.048	0.995 ± 0.038	0.989 ± 0.042	0.988 ± 0.045
	Q3	0.998 ± 0.039	0.998 ± 0.040	1.006 ± 0.046	0.995 ± 0.043	0.992 ± 0.045	0.992 ± 0.046
	Q4	0.998 ± 0.037	0.998 ± 0.037	1.003 ± 0.047	1.000 ± 0.043	0.996 ± 0.038	0.988 ± 0.044

Table 5.38.: SR, EDV/PSV: *Mean* $\pm$ *SD* EDV/PSV ratio for patients in SR using variable time formatting.

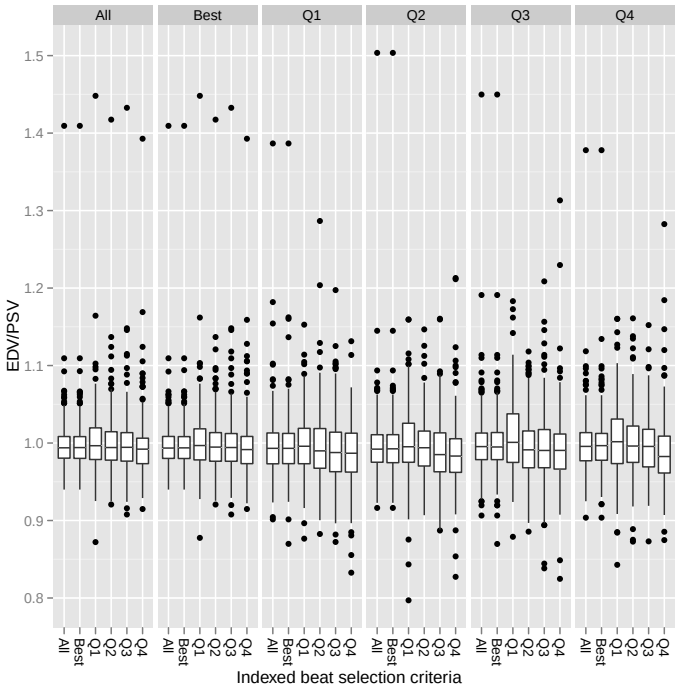
		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	1.016 ± 0.023	1.000 ± 0.044	0.948 ± 0.060	1.006 ± 0.033	1.034 ± 0.029	1.055 ± 0.031
	Best	1.024 ± 0.038	1.008 ± 0.051	0.957 ± 0.074	1.014 ± 0.038	1.043 ± 0.039	1.062 ± 0.041
	Q1	1.062 ± 0.039	1.045 ± 0.054	0.992 ± 0.049	1.050 ± 0.043	1.081 ± 0.059	1.101 ± 0.057
	Q2	1.019 ± 0.031	1.007 ± 0.048	0.960 ± 0.066	1.011 ± 0.041	1.040 ± 0.035	1.061 ± 0.044
	Q3	1.002 ± 0.035	0.989 ± 0.053	0.938 ± 0.079	0.995 ± 0.044	1.022 ± 0.034	1.047 ± 0.034
	Q4	0.987 ± 0.041	0.974 ± 0.057	0.925 ± 0.087	0.978 ± 0.049	1.008 ± 0.038	1.032 ± 0.038

Table 5.39.: AF, EDV/PSV: *Mean* $\pm$ *SD* EDV/PSV ratio for patients in AF using variable time formatting.

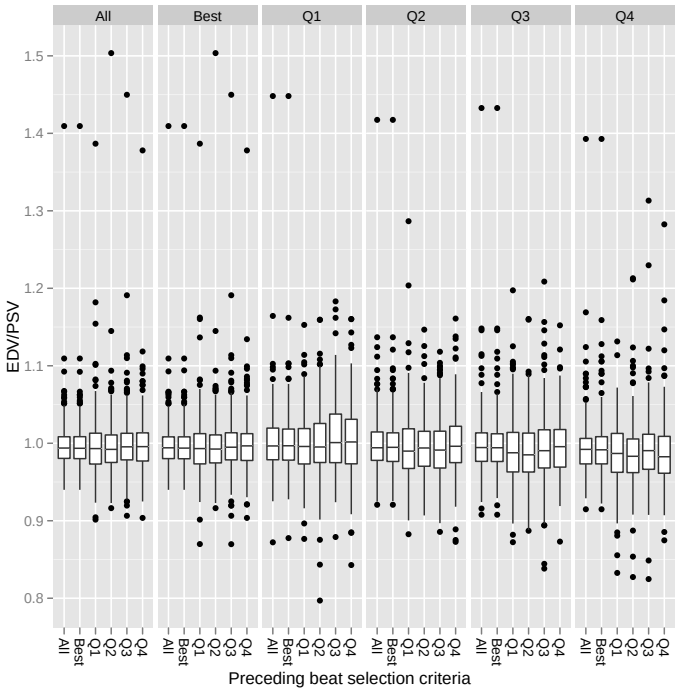
These conclusions are confirmed by regression analysis, the results of which are shown in Table 5.41. Although there is a highly significant correlation when both sets of quartiles are considered, neither the preceding beat nor the interaction term between preceding beat and indexed beat were significant in the analysis of variance which found no significance with any of the beat selection criteria. Overall this suggests that preceding beat had no significant effect on EDV/PSV in SR.

In AF it is clear, from Figure 5.29 and Table 5.39, that beat selection criteria have a substantial impact on EDV/PSV in AF and this is shown to be highly significant in the regression analysis where both preceding and indexed beat (and the interaction term) have a high significance ($p < 1 \times 10^{-5}$), see Table 5.41. Interestingly the analysis of variance which compares the categorical beat selection criteria finds that only the "Best" indexed beat gives a significant result ($p = 0.0002$).

Results for patient-by-patient regression against beat selection criteria are shown in table 5.40. There is a very strong positive relationship with indexed beat length and a negative relationship with preceding beat length in AF. The same effect is not seen in

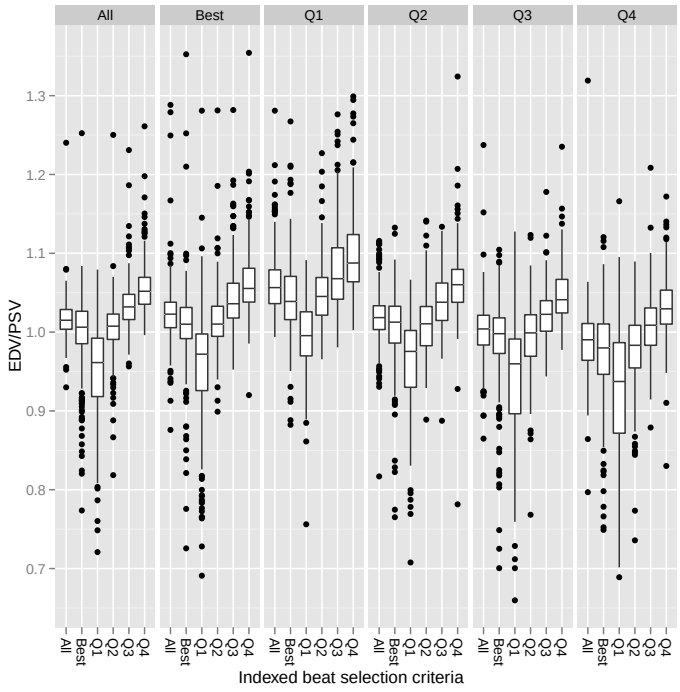


(a) EDV/PSV in SR preceding beat grouping

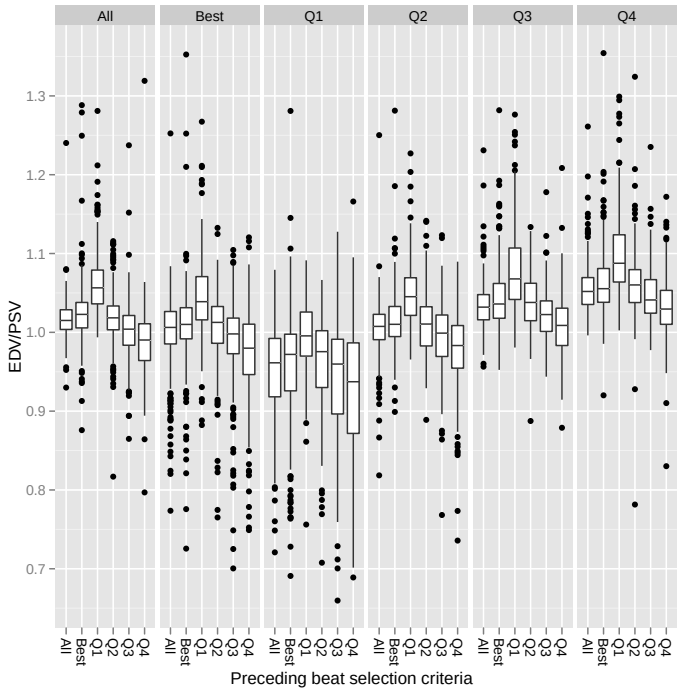


(b) EDV/PSV in SR indexed beat grouping

Figure 5.28.: SR, EDV/PSV: Showing the variation in EDV/PSV ratio with varying indexed and preceding beat selection criteria in SR using variable time formatting.



(a) EDV/PSV in AF preceding beat grouping



(b) EDV/PSV in AF indexed beat grouping

Figure 5.29.: AF, EDV/PSV: Showing the variation in EDV/PSV ratio with varying indexed and preceding beat selection criteria in AF using variable time formatting.

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.78 ± 0.14	51	0.75 ± 0.15	93	4
Best (Constant)	Q1 - Q4	0.78 ± 0.14	55	0.76 ± 0.15	102	4
Q1 - Q4	All (Constant)	0.78 ± 0.13	75	0.76 ± 0.15	65	7
Q1 - Q4	Best (Constant)	0.79 ± 0.14	74	0.76 ± 0.15	64	6
Q1 - Q4	Q1 - Q4	0.72 ± 0.16	34 (p), 17(i)		23 (p), 40(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.84 ± 0.12	297	NA	NA	7
Best (Constant)	Q1 - Q4	0.84 ± 0.13	201	0.80 ± 0.15	4	26
Q1 - Q4	All (Constant)	0.79 ± 0.16	4	0.83 ± 0.13	227	13
Q1 - Q4	Best (Constant)	0.79 ± 0.14	16	0.81 ± 0.14	132	34
Q1 - Q4	Q1 - Q4	0.75 ± 0.15	13 (p), 172(i)		158 (p), 0(i)	55

(b) AF

Table 5.40.: EDV/PSV: showing the regression results by quartile on a patient-by-patient basis for EDV/PSV in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

		SR		AF	
Preceding	Indexed	r^2	p	r^2	p
All (Constant)	Q1 - Q4	0.004	0.02	0.467	$< 1 \times 10^{-5}$
Best (Constant)	Q1 - Q4	0.003	0.03	0.358	$< 1 \times 10^{-5}$
Q1 - Q4	All (Constant)	0.0004	0.444	0.326	$< 1 \times 10^{-5}$
Q1 - Q4	Best (Constant)	0.0007	0.312	0.171	$< 1 \times 10^{-5}$
Q1 - Q4	Q1 - Q4	0.014	$< 1 \times 10^{-5}$	0.424	$< 1 \times 10^{-5}$

Table 5.41.: EDV/PSV: Regression results showing the effect of differing beat selection criteria on EDV/PSV ratio using variable time formatting.

.

SR where, in those patients for whom a relationship was actually exhibited, there was a balance between the positive and negative influences of both the indexed and preceding beat. These results support the findings of the regression in the group as a whole.

Having ascertained that in AF the beat selection criteria have a significant impact on EDV/PSV it is worth investigating this further. A histogram showing the range of EDV/PSV for each patient in AF using variable time formatting is shown in Figure 5.30.

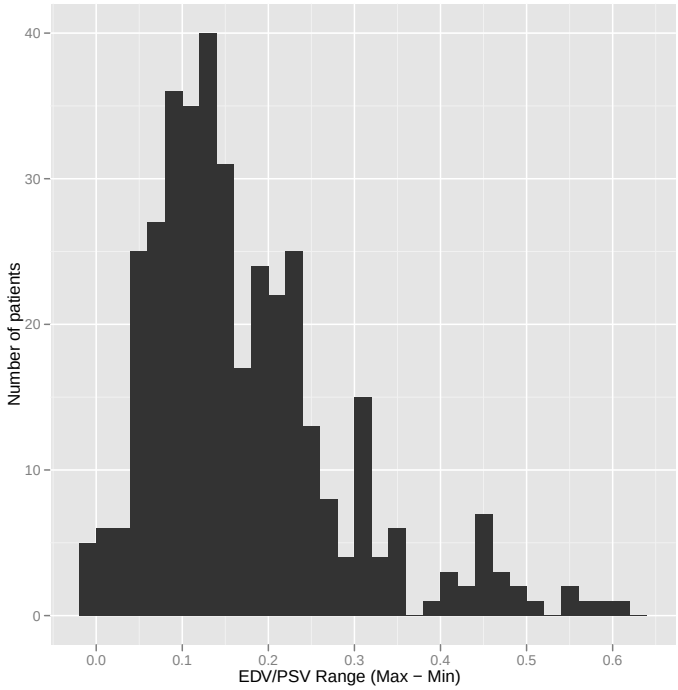
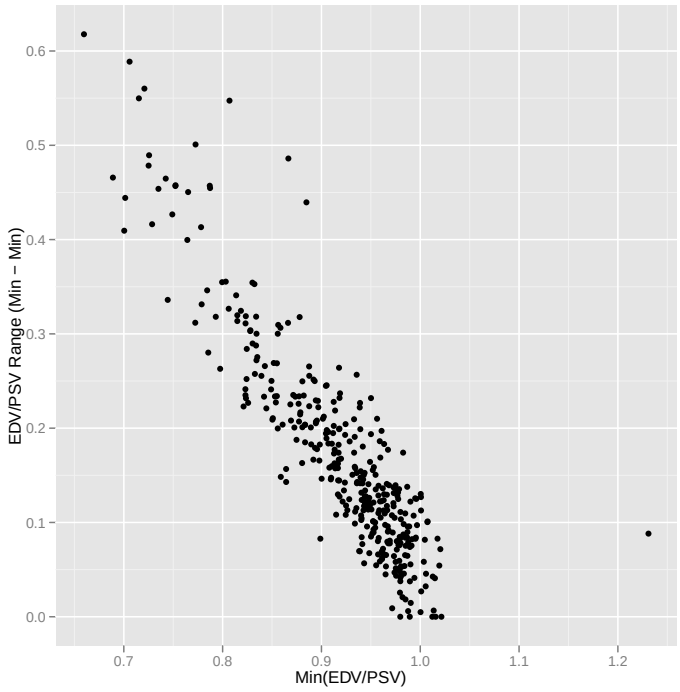


Figure 5.30.: AF, $\updownarrow EDV/PSV$: Showing the range (max - min) of measured EDV/PSV for patients in AF using variable time formatting.

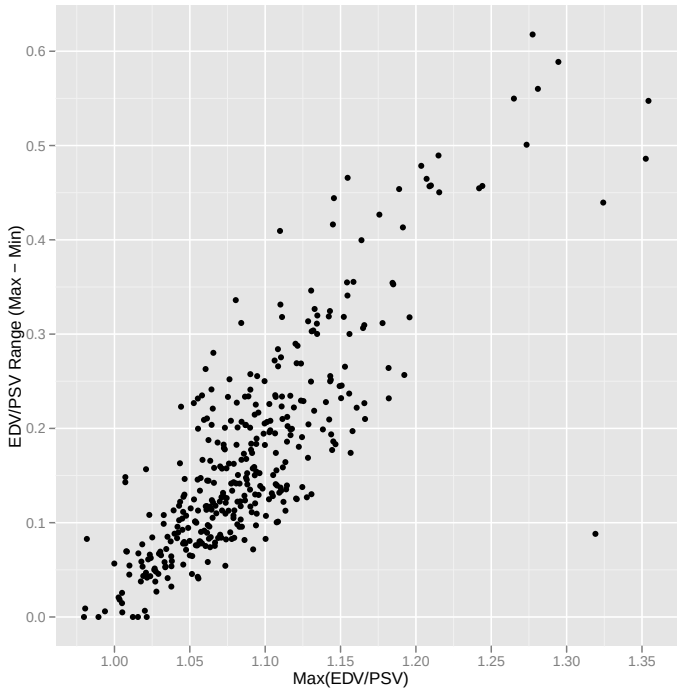
The relationship between min and max EDV/PSV and the range is shown in Figure 5.31. It is noticeable that in only a very few instances is the minimum greater than 1.0 or the maximum less than 1.0, and that there is very good (Spearman rank) correlation between range and both minimum ($\rho = -0.880$, $p < 1 \times 10^{-5}$) and maximum ($\rho = 0.799$, $p < 1 \times 10^{-5}$). This suggests that the variation is systematic and the patterns displayed here and in Table 5.39 confirm the "interrupted beat" hypothesis. Images for which the preceding and indexed beat fall in the same quartile (e.g. p:Q2_c:Q2) showed a mean $EDV/PSV \approx 1$ while those in which the preceding beat was shorter than the indexed beat (e.g. p:Q1_c:Q4) showed a mean $EDV/PSV > 1$. Those images formed where the preceding beat was longer than the indexed beat (e.g. p:Q4_c:Q1) had $EDV/PSV < 1$. The results beg the question: is the extent of variation in EDV/PSV reflected in the range of beat lengths? This question will be addressed in Chapter 6.

5.6.1. Comparing EDV/PSV with $\updownarrow EDV/PSV$

A visual comparison of EDV/PSV with $\updownarrow EDV/PSV$ (see Figure 5.32) does not show any clear association, although statistically a Spearman rank correlation finds a weak



(a) EDV/PSV range vs min in AF



(b) EDV/PSV range vs max in AF

Figure 5.31.: AF, EDV/PSV: Showing the variation in EDV/PSV ratio with varying indexed and preceding beat selection criteria in AF using variable time formatting.

positive correlation in SR and weak negative correlation in AF and the spread of $\updownarrow EDV/PSV$ appears to be greater for AF. It is difficult to understand physiologically why there should be a relationship between the two since the range of EDV/PSV should reflect the difference in duration of short-short and long-long beat combinations.

5.6.2. Comparing variable time with fixed time formatting

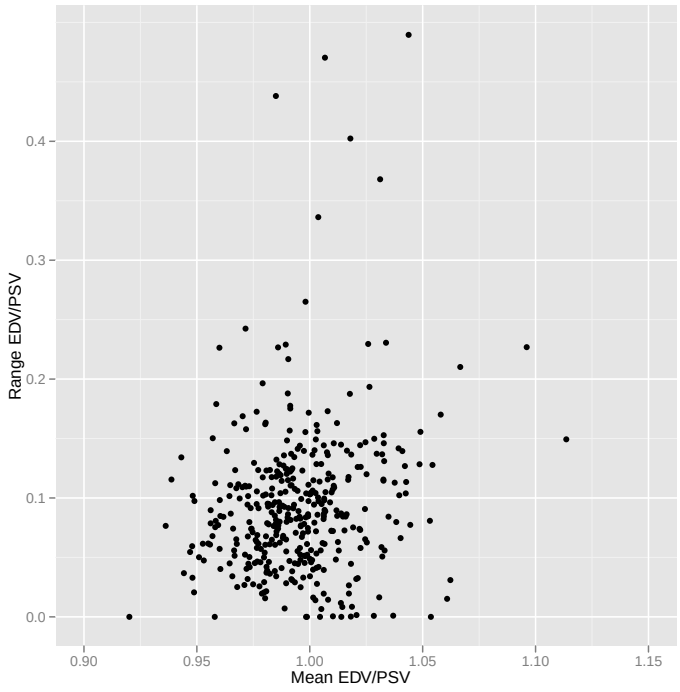
A very similar pattern is seen using fixed time formatting as using variable time formatting.

In SR the Spearman rank correlation between fixed and variable time formatting finds very strong correlation with $\rho = 0.818$, $p < 1 \times 10^{-5}$. The Bland-Altman analysis [85] finds mean difference in EDV/PSV to be 0.014 and the SD of the difference to be 0.024. These results have to be understood beside the very small variation in EDV/PSV which is seen in SR.

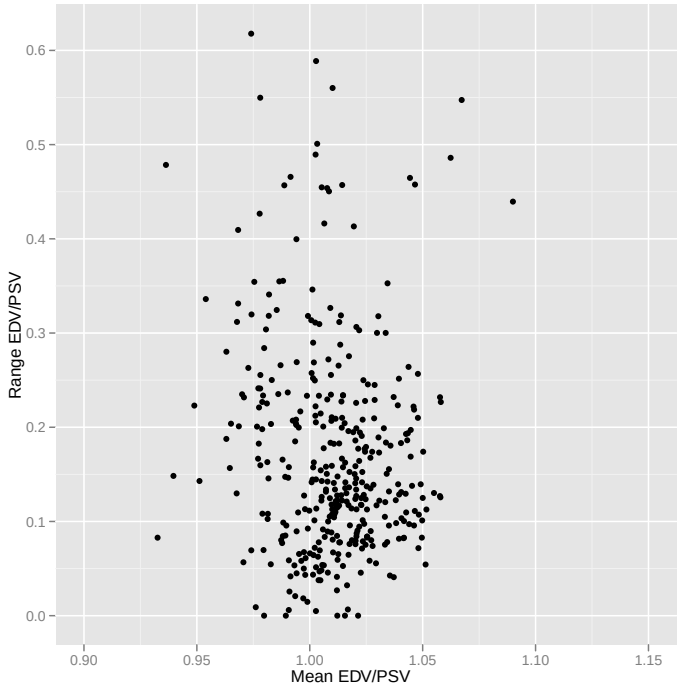
In AF there is still is good correlation between fixed and variable time results ($\rho = 0.688$, $p < 1 \times 10^{-5}$), although it is weaker than in SR. The Bland-Altman analysis, see Figure 5.34, finds the mean difference to be greater than in SR to be 0.039 with a SD of difference to be 0.059. It is clear that, compared to fixed time formatting, variable time formatting increases the difference at lower EDV/PSV, and therefore increases the overall measurable difference in EDV/PSV in AF.

5.7. Systolic time

One of the principal predicates of this thesis is that variation in R-R interval is primarily reflected in the duration of diastole. For this to be true the systolic time interval should not vary substantially from one beat to the next for any patient. Although the systolic time interval has been shown to vary [3], for the Frank-Starling mechanism to work the principal variation in systole from one beat to the next should be in the force and not the duration of contraction. The corollary of this is that longer filling times will be reflected in a fuller ventricle, which therefore has a greater volume of blood which can be ejected, resulting in a higher LVEF. This assumes a healthy heart which is not affected by other pathologies which might affect systole.

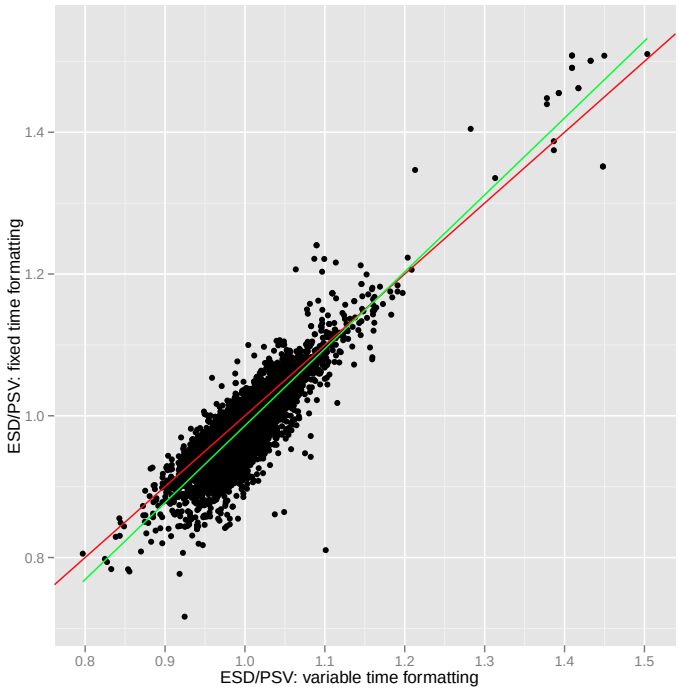


(a) SR

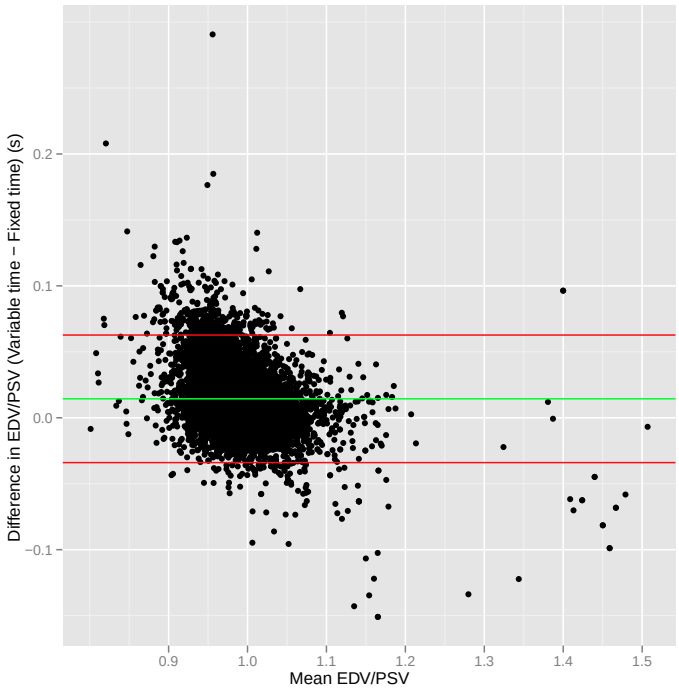


(b) AF

Figure 5.32.: EDV/PSV: Showing the variation of $\updownarrow EDV/PSV$ with mean EDV/PSV in (a) SR and (b) AF using variable time formatting.

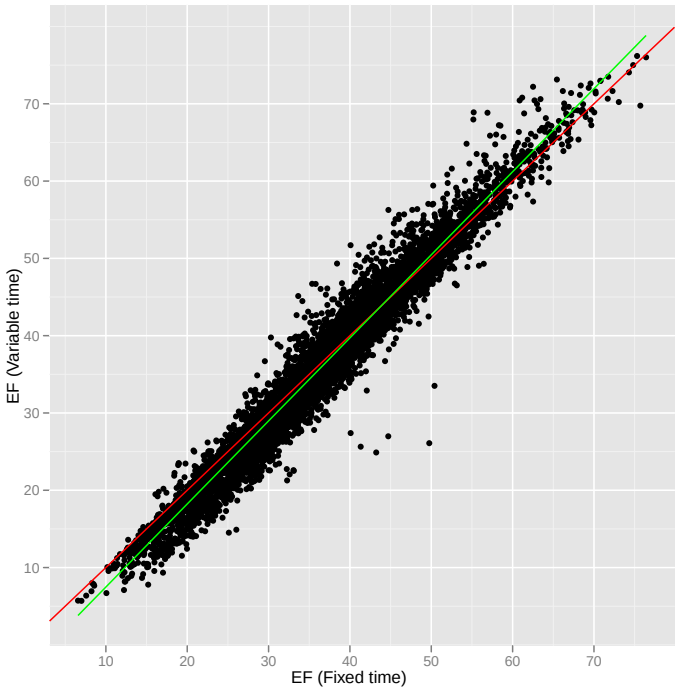


(a) Variable vs. Fixed

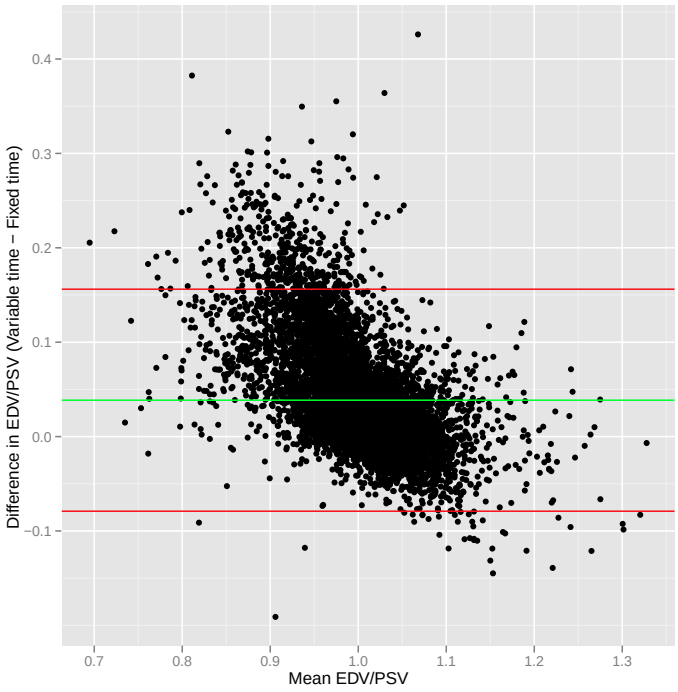


(b) Bland - Altman style

Figure 5.33.: Showing relationship between fixed and variable time mode for EDV/PSV in SR. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.)



(a) Variable vs. Fixed



(b) Bland - Altman style

Figure 5.34.: Showing relationship between fixed and variable time mode for EDV/PSV in AF. (In direct plot, red line shows best fit linear correlation, green line shows line of equality; in Bland-Altman plot red line shows 2 SDs and green line shows mean.)

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	0.307 ± 0.045	0.307 ± 0.046	0.304 ± 0.046	0.309 ± 0.047	0.310 ± 0.046	0.316 ± 0.046
	Best	0.306 ± 0.046	0.307 ± 0.046	0.303 ± 0.046	0.309 ± 0.046	0.309 ± 0.046	0.316 ± 0.048
	Q1	0.306 ± 0.045	0.306 ± 0.046	0.309 ± 0.048	0.313 ± 0.050	0.310 ± 0.047	0.313 ± 0.044
	Q2	0.306 ± 0.046	0.306 ± 0.046	0.307 ± 0.050	0.313 ± 0.044	0.312 ± 0.049	0.315 ± 0.053
	Q3	0.309 ± 0.047	0.310 ± 0.047	0.310 ± 0.049	0.313 ± 0.047	0.316 ± 0.047	0.317 ± 0.049
	Q4	0.313 ± 0.046	0.313 ± 0.045	0.310 ± 0.050	0.312 ± 0.049	0.320 ± 0.071	0.315 ± 0.045

Table 5.42.: *Mean* $\pm$ *SD* Systolic time intervals for patients in SR using variable time formatting.

To test this principle, the variation in systolic time was investigated in both the AF and SR groups.

Systolic time, T_s was calculated as

$$T_s = (P_{ps} - P_{es}) \times \frac{\overline{T_{RR}}}{N_f} \tag{5.5}$$

Where

P_{ps}: Pre-systolic frame number

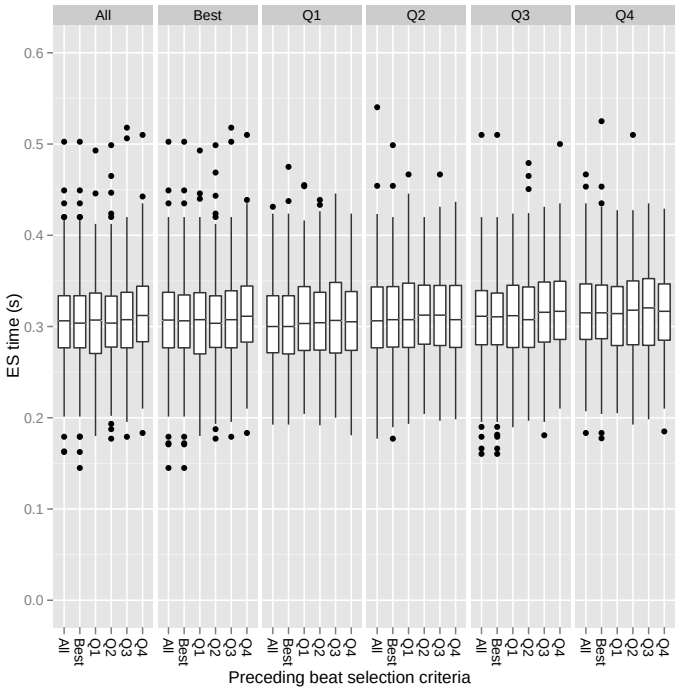
P_{es}: End-systolic frame number

$\overline{T_{RR}}$: Mean (in variable time) or mid-range (in fixed time) R-R interval for the group of beats in use

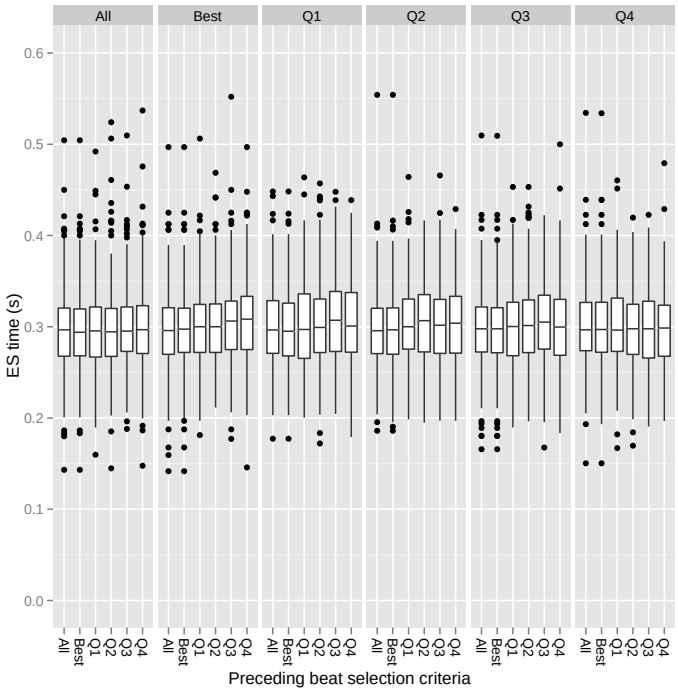
N_f: Number of frames in the image (in this study $N_f = 24$).

The variation in systolic time with variable time formatting is shown for SR in Figure 5.35 and in tabular form in Table 5.42. The results for AF, which are very similar, are shown in Figure 5.36 and Table 5.43. In SR there appears to be only a very small variation in systolic time which is even smaller in AF.

When regression testing, for which the results are shown in Table 5.44, was used to consider the effect of varying the beat acceptance criteria, both preceding and indexed, it was found that in SR there is a highly significant, but extremely weak, correlation between indexed beat length and systolic time (seen when preceding beat criteria are "All" or "Best"). The correlation with preceding beat criteria, in SR, has much weaker

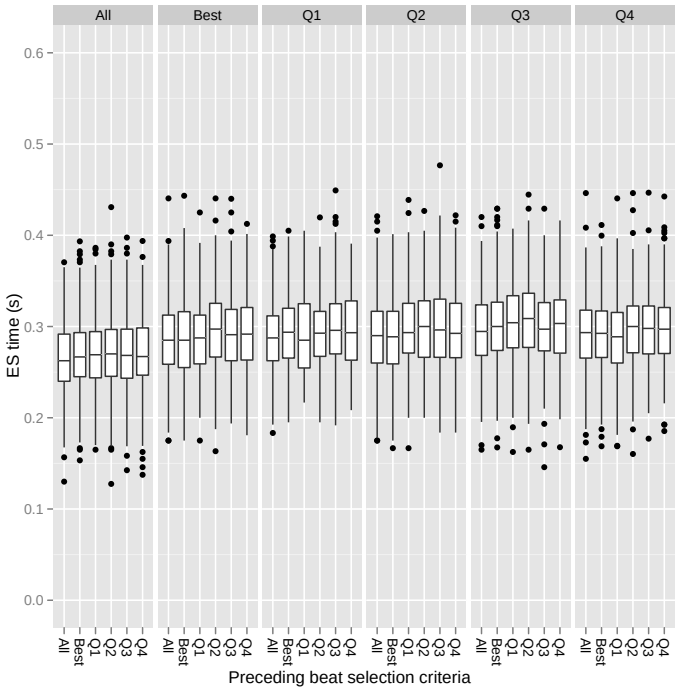


(a) Variable time

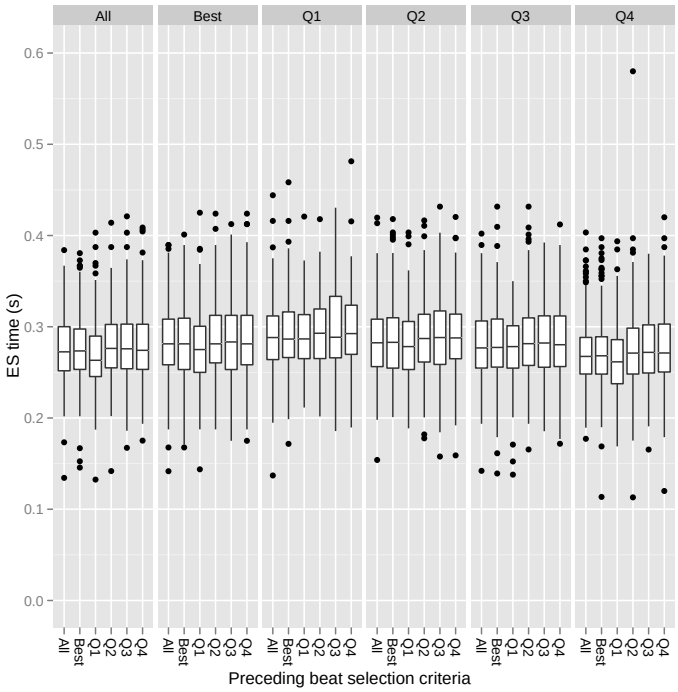


(b) Fixed time

Figure 5.35.: SR, systolic time: Box-plot showing systolic time interval for all patients in SR for each combination of preceding and indexed beat selection techniques with indexed beat changes shown in blocks. (a) variable time, (b) fixed time formatting. (Note: These plots remove a single outlier in each at 1.1s.) (N=387).



(a) Variable time



(b) Fixed time

Figure 5.36.: AF, systolic time: Box-plot showing systolic time interval for all patients in AF for each combination of preceding and indexed beat selection techniques with indexed beat changes shown in blocks. (a) variable time, (b) fixed time formatting. (N=373).

		Indexed beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	0.266 ± 0.040	0.286 ± 0.039	0.288 ± 0.037	0.290 ± 0.042	0.295 ± 0.044	0.294 ± 0.039
	Best	0.269 ± 0.040	0.289 ± 0.044	0.292 ± 0.041	0.291 ± 0.044	0.301 ± 0.044	0.292 ± 0.040
	Q1	0.270 ± 0.041	0.288 ± 0.043	0.292 ± 0.044	0.298 ± 0.045	0.303 ± 0.045	0.289 ± 0.043
	Q2	0.272 ± 0.043	0.296 ± 0.043	0.293 ± 0.040	0.297 ± 0.044	0.305 ± 0.046	0.299 ± 0.052
	Q3	0.270 ± 0.042	0.293 ± 0.044	0.297 ± 0.044	0.299 ± 0.047	0.299 ± 0.042	0.297 ± 0.041
	Q4	0.272 ± 0.041	0.294 ± 0.044	0.296 ± 0.041	0.298 ± 0.045	0.302 ± 0.043	0.299 ± 0.044

Table 5.43.: *Mean* $\pm$ *SD* Systolic time intervals for patients in AF using variable time formatting.

		SR		AF	
Preceding	Indexed	r^2	p	r^2	p
All	Q1 - Q4	0.007	0.0008	0.004	0.027
Best	Q1 - Q4	0.008	0.0006	0.001	0.315
Q1 - Q4	All	0.004	0.017	1×10^{-5}	0.904
Q1 - Q4	Best	0.003	0.033	0.0009	0.341
Q1 - Q4	Q1 - Q4	0.0025	0.035	0.0007	0.553

Table 5.44.: Regression results showing the effect of differing beat selection criteria on systolic time interval using variable time formatting.

.

significance. In AF the only significant, extremely weak, correlation was seen when all preceding beats were taken.

The corresponding analysis of variance found no significant contribution for either preceding or indexed beat selection criteria in SR when quartiles are considered together. In AF, the analysis found that systolic time with beat selection based on indexed beat differed significantly for "Best" and quartile beat selection although there was no significance to the interaction term. The preceding beat had a much weaker significance for quartile beat selection and found no difference for "Best" beats (see Table 5.45). This suggests that taking tighter limits on indexed beat affects the systolic time interval. In AF, since there was no significance in the regression results, this suggests the effect is a result of averaging fewer beats in a tighter band and, while the systolic time interval is not constant, it is largely independent of preceding beat length (and therefore also of systolic volume which has been shown to be dependent on the duration of the preceding beat - see §5.5).

	SR p	AF p
p:All_c:All vs. p:Best_c:All	0.88	0.298
p:All_c:All vs. p:Quartiles_c:All	0.52	0.043
p:All_c:All vs. p:All_c:Best	0.94	$< 1 \times 10^{-5}$
p:All_c:All vs. p:All_c:Quartiles	0.32	$< 1 \times 10^{-5}$
p:All_c:All vs. p:Best_c:Best	0.93	0.828
p:All_c:All vs. p:Quartiles_c:Best	0.94	0.592
p:All_c:All vs. p:Best_c:Quartiles	0.94	0.783
p:All_c:All vs. p:Quartiles_c:Quartiles	0.62	0.642

Table 5.45.: Analysis of variance results considering contribution of preceding and indexed beat selection criteria to measurement of systolic time.

This analysis is corroborated by the regression results for individual patients which are shown in Table 5.46. These do not demonstrate any clear dominance with beat selection criteria in AF. In SR there is a suggestion that there is a positive relationship between systolic time interval and indexed beat length with longer beats having longer systole. In these situations the Frank-Starling mechanism cannot be the principal cause of beat-to-beat variation as it affects the systolic time.

Each measurement of systolic time is made with a sampling error which is given by:

$$E_s = \frac{1}{2} \cdot \frac{\overline{T_{RR}}}{N_f} \tag{5.6}$$

Although there is a very small but significant increase in systolic time with increasing beat length (both preceding and indexed), it is possible that this is a reflection of the decreasing precision of the measurement ($\overline{T_{RR}}$ increases). If this is the case it is to be expected that the difference between mean and measured values should fall within the sampling error E_s. Counting the number of values which fall outwith this should provide a measure of consistency of measured systolic time. The results, by beat selection criteria, are shown in Tables 5.47 (SR) and 5.48 (AF) and for patients in SR on a patient-by-patient basis in the histogram shown in Figure 5.37

There is no appreciable difference in deviation of systolic time interval for beat selection techniques based on preceding or indexed quartiles, however there are markedly fewer

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.83 ± 0.15	114	0.67 ± 0.13	33	4
Best (Constant)	Q1 - Q4	0.87 ± 0.14	118	0.70 ± 0.13	25	4
Q1 - Q4	All (Constant)	0.80 ± 0.14	97	0.69 ± 0.12	55	7
Q1 - Q4	Best (Constant)	0.80 ± 0.15	103	0.71 ± 0.12	52	6
Q1 - Q4	Q1 - Q4	0.62 ± 0.18	14 (p), 20(i)		13 (p), 7(i)	39

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.77 ± 0.14	79	0.72 ± 0.16	44	7
Best (Constant)	Q1 - Q4	0.75 ± 0.15	43	0.74 ± 0.16	31	26
Q1 - Q4	All (Constant)	0.75 ± 0.14	103	0.72 ± 0.15	42	14
Q1 - Q4	Best (Constant)	0.80 ± 0.14	71	0.80 ± 0.15	35	34
Q1 - Q4	Q1 - Q4	0.56 ± 0.16	17 (p), 13(i)		3 (p), 7(i)	55

(b) AF

Table 5.46.: Systolic time: showing the regression results by quartile on a patient-by-patient basis for systolic time in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	4	4	38	27	44	52	169
	Best	5	3	46	27	44	52	177
	Q1	49	46	40	44	39	41	259
	Q2	44	45	40	39	47	61	276
	Q3	33	30	37	49	49	46	244
	Q4	36	33	45	44	48	45	251
	TOTAL	171	161	246	230	271	297	1376

Table 5.47.: SR, Systolic time: Systolic time interval outwith sampling error by beat selection in SR using variable time. (Total numbers in each category are given in Table 5.3b)

deviations when all beats or the "Best" group of beats (both indexed and preceding) are taken, particularly in SR. Overall the deviations account for 12.8% of the measured values in SR compared with 9.5% in AF.

		Indexed beat						
		All	Best	Q1	Q2	Q3	Q4	TOTAL
Preceding beat	All	43	12	17	14	26	24	136
	Best	37	16	11	16	28	24	132
	Q1	50	16	15	12	11	14	118
	Q2	40	24	10	16	21	20	131
	Q3	37	27	15	26	24	32	161
	Q4	42	33	19	31	35	33	193
	TOTAL	249	128	87	115	145	147	871

Table 5.48.: AF, Systolic time: Systolic time interval outwith sampling error by beat selection in AF using variable time. (Total numbers in each category are given in Table 5.3d)

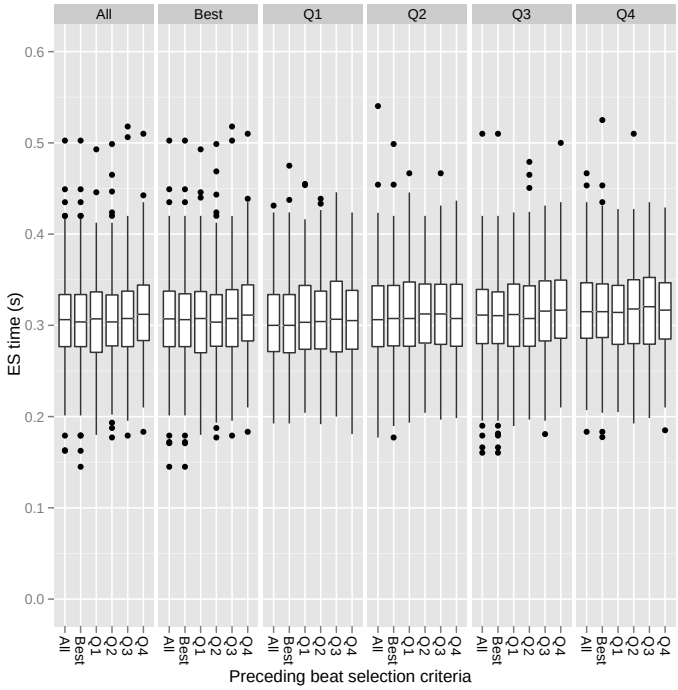


Figure 5.37.: Showing the number of measurements of systolic time resulting from different beat selection criteria (from a total of 36) which deviate from the mean by more than the sampling error for patients in SR using variable time formatting.

		$> E_s$	$> 2E_s$	No. measured
SR	Variable	1376	112	10753
SR	Fixed	1226	109	10756
AF	Variable	871	35	9130
AF	Fixed	351	13	8959

Table 5.49.: Number of systolic time intervals outwith sampling error.

Although it has been shown that systolic time intervals are not constant and that the differences cannot simply be explained by changes in the sampling error it is interesting to know the degree of change. This can be shown by considering the ratios of the minimum and maximum systolic times and is shown in Figure 5.38a from which it can clearly be seen that in both AF and SR there is typically a ratio of $\sim 70\% - 75\%$ between the minimum and maximum systolic time intervals.

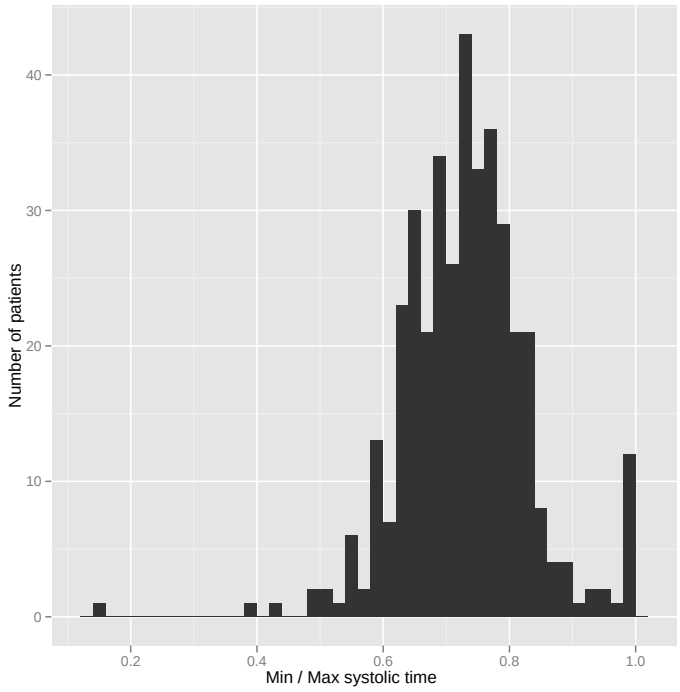
5.7.1. Comparing Systolic time with ⇳Systolic time

Comparing systolic time with the range of systolic time intervals shows a tendency for there to be a greater range of intervals when the mean is greater in both AF and SR. This is to be expected as small fractional changes in longer intervals will have a greater impact than in shorter ones.

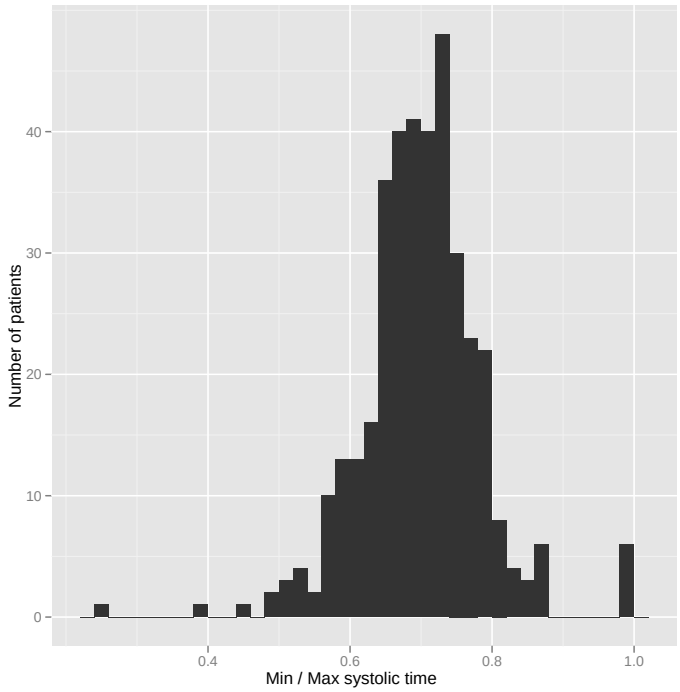
5.7.2. Comparing variable time with fixed time formatting

As can be seen from Figure 5.35 there is very similar behaviour in fixed time and variable time formatting and, as Table 5.49 shows, there were a similar number of measurements in SR outwith the sampling error. In AF however there were substantially more measurements outwith the sampling error in variable time formatting than in fixed time. This also corroborates the suggestion that in AF the duration of systole does not vary substantially, particularly in relation to the duration of the whole beat.

A plot of systolic time interval for fixed vs. variable time formatting in SR is shown in Figure 5.39 from which it is clear that there is good general agreement (within the same



(a) SR



(b) AF

Figure 5.38.: Showing the ratio of minimum to maximum systolic time intervals for each patient.

range as the agreement between minimum and maximum systolic times for variable time formatting) between fixed and variable time formatting.

In SR, a Pearson product moment correlation (the results are approximately normally distributed) test finds a highly significant, very good correlation ($r = 0.82$, $p < 1 \times 10^{-5}$). The angle on the best fit line suggests that there is a slightly wider distribution of systolic time intervals when variable time formatting is used than when fixed time formatting is used, although there is generally reasonable agreement between them. This is in agreement with the results shown in Table 5.49. The Bland-Altman analysis shows that variable time formatting slightly overestimates systolic time (by 0.010 s with a SD of 0.027 s).

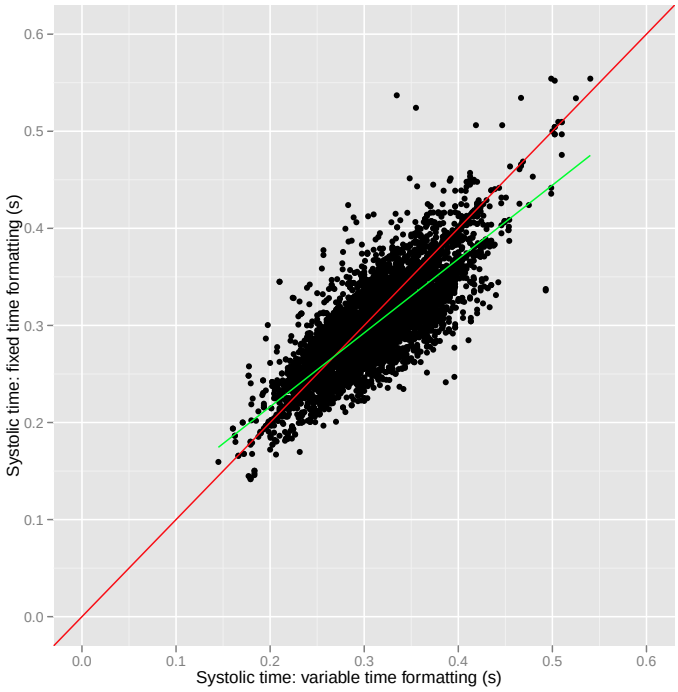
In AF, the correlation is not as good as it is for SR ($r^2 = 0.706$, $p < 1 \times 10^{-5}$). Bland-Altman analysis (see Figure 5.40) gives mean difference of 0.010 s and SD of 0.322 s.

5.8. First third filling fraction (FTFF)

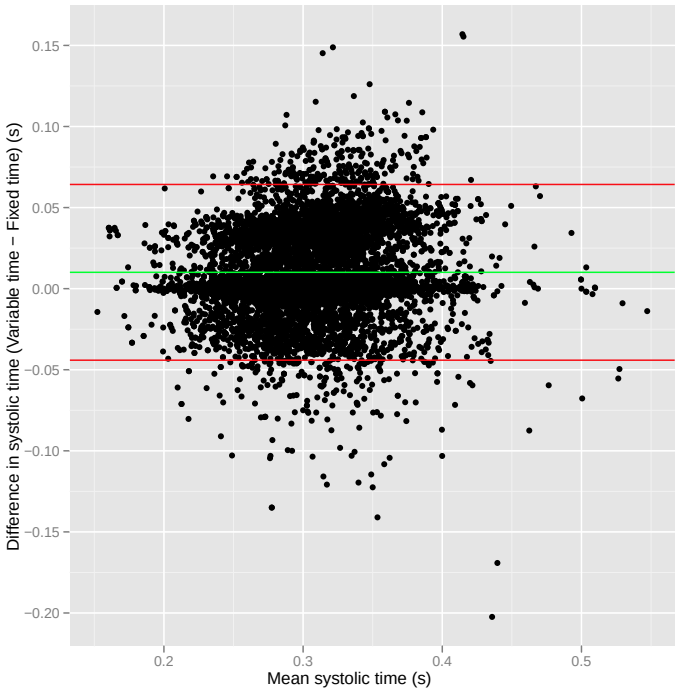
First third filling fraction (FTFF), the proportion of pre-systolic volume by which the volume of the ventricle has increased from end-systole 1/3 of the way into diastole, is the most common measure of diastolic function. It can be assessed from the activity time curve in radionuclide ventriculography. In this investigation it has been used to assess whether, in AF, there is a beat-to-beat variation in diastolic function. In this analysis diastolic time has been determined from the cropped activity time curves.

The variation in FTFF in SR and AF is shown in Figures 5.41 and 5.42 respectively. In SR there appears to be a mild positive relationship between both preceding and indexed beat quartile and FTFF. In AF there appears to be a strong negative relationship with preceding beat and a very strong positive relationship with indexed beat.

Regression results, shown in Table 5.50, found that both preceding and indexed beat had a significant effect on measured FTFF in SR but that there was no significance in the interaction term. In AF there was a significant contribution from both preceding and indexed beat. It is noticeable that there is a much better correlation when all preceding beats are taken and that there is no significance to the correlation with preceding quartile when the "Best" indexed beats are taken.

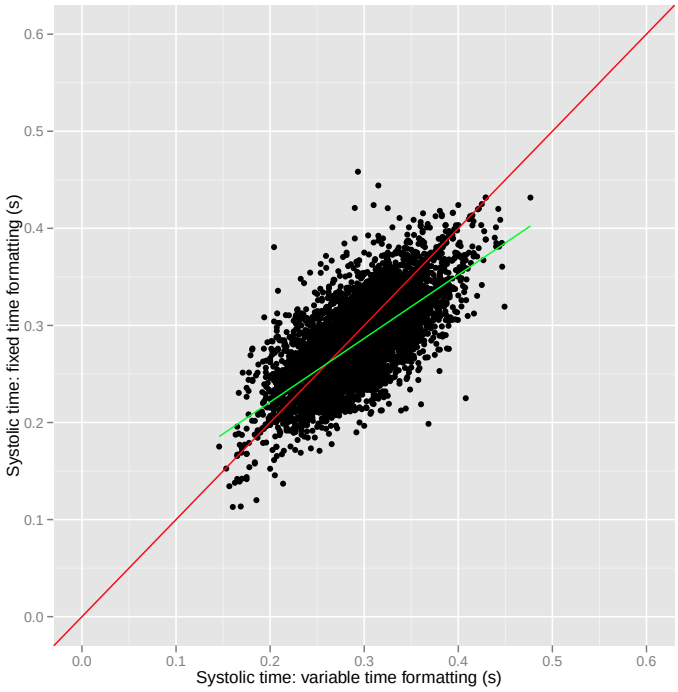


(a) Direct plot

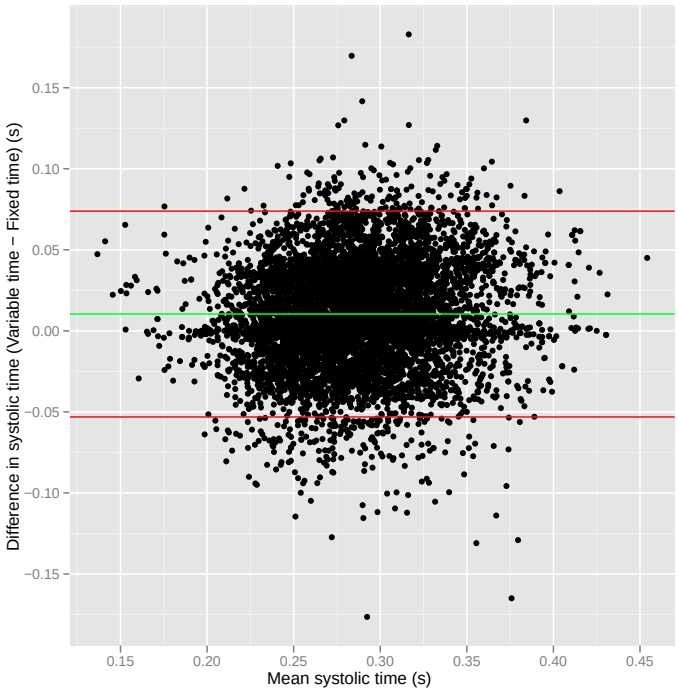


(b) Bland Altman

Figure 5.39.: Systolic time, SR: Showing the relationship between systolic time using fixed and variable time formatting in SR. (a) Direct plot, The green line shows the best fit correlation, the red line shows the line of equality. (b) green line shows mean difference, red lines show 2SD limits.

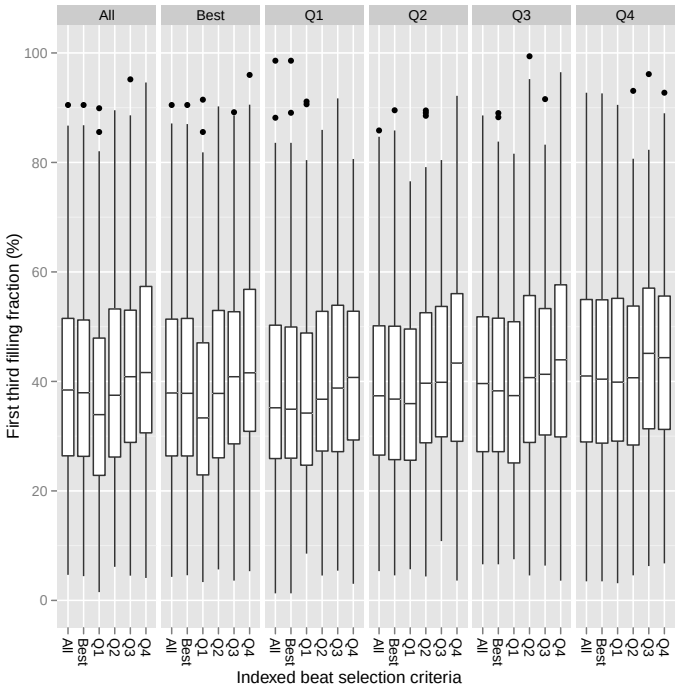


(a) Direct plot

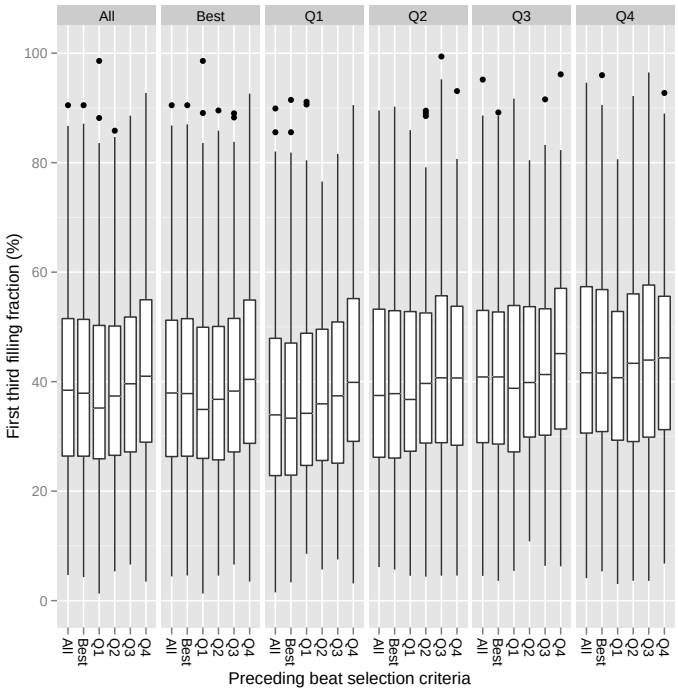


(b) Bland Altman

Figure 5.40.: Systolic time, AF: Showing the relationship between systolic time using fixed and variable time formatting in AF. (a) Direct plot, The green line shows the best fit correlation, the red line shows the line of equality. (b) green line shows mean difference, red lines show 2SD limits.

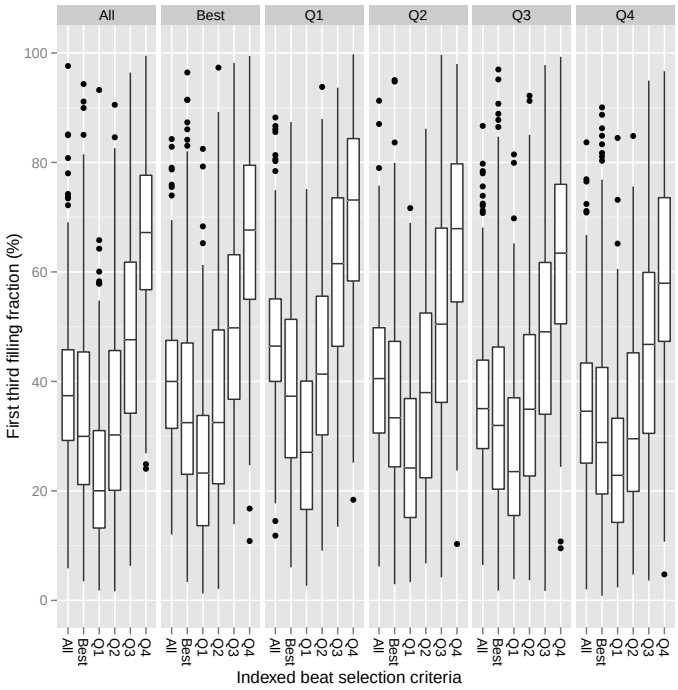


(a) Grouped by preceding beat

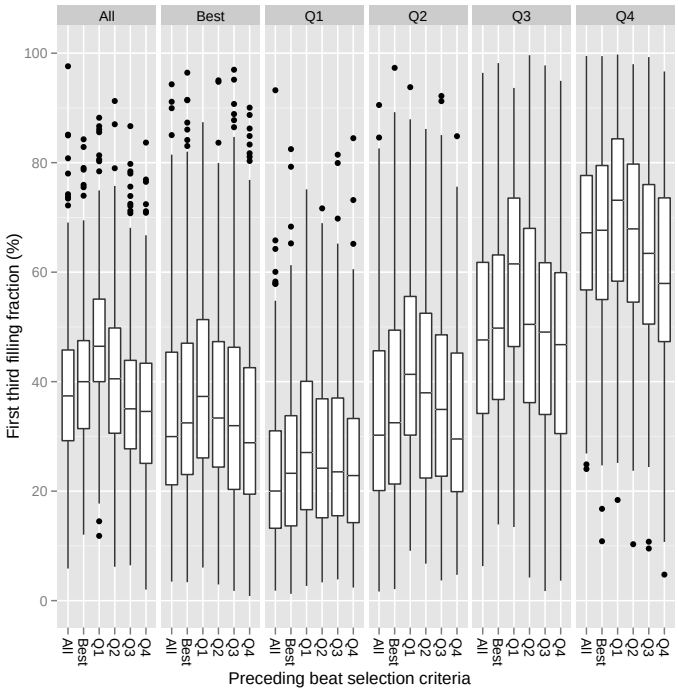


(b) Grouped by indexed beat

Figure 5.41.: SR, FTFF: Showing the variation in FTFF with varying indexed and preceding beat selection criteria in SR using variable time formatting.



(a) Grouped by preceding beat



(b) Grouped by indexed beat

Figure 5.42.: AF, FTFF: Showing the variation in FTFF with varying indexed and preceding beat selection criteria in AF using variable time formatting.

		SR		AF	
Preceding	Indexed	r^2	p	r^2	p
All (Constant)	Q1 - Q4	0.011	0.00006	0.414	$< 1 \times 10^{-5}$
Best (Constant)	Q1 - Q4	0.021	$< 1 \times 10^{-5}$	0.091	$< 1 \times 10^{-5}$
Q1 - Q4	All (Constant)	0.006	0.002	0.086	$< 1 \times 10^{-5}$
Q1 - Q4	Best (Constant)	0.006	0.003	0.00017	0.67
Q1 - Q4	Q1 - Q4	0.002	0.079	0.002	1×10^{-5}

Table 5.50.: FTFF: Regression results showing the effect of differing beat selection criteria on FTFF using variable time formatting.

.

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.79 ± 0.14	129	0.76 ± 0.13	40	4
Best (Constant)	Q1 - Q4	0.79 ± 0.15	128	0.78 ± 0.13	41	4
Q1 - Q4	All (Constant)	0.76 ± 0.15	106	0.78 ± 0.16	55	8
Q1 - Q4	Best (Constant)	0.75 ± 0.15	106	0.76 ± 0.16	63	6
Q1 - Q4	Q1 - Q4	0.50 ± 0.20	95 (p), 103(i)		72 (p), 64(i)	21

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.76 ± 0.16	20	0.77 ± 0.13	100	7
Best (Constant)	Q1 - Q4	0.75 ± 0.17	15	0.79 ± 0.16	90	27
Q1 - Q4	All (Constant)	0.89 ± 0.12	299	0.66 ± 0.22	2	14
Q1 - Q4	Best (Constant)	0.86 ± 0.12	191	NA	0	34
Q1 - Q4	Q1 - Q4	0.69 ± 0.19	219 (p), 36(i)		3 (p), 189(i)	28

(b) AF

Table 5.51.: FTFF: showing the regression results by quartile on a patient-by-patient basis for FTFF in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

In SR, analysis of variance, grouping all quartiles together, found no significant difference. In AF, as with SR, there was no difference found between quartile, "All" and "Best" groups in either preceding or indexed beat selection criteria. Considering mean regression on a patient-by-patient basis yields the results shown in Table 5.51 which corroborate the results for regression in the group as a whole and using analysis of variance.

The very strong relationship seen between indexed beat length and FTFF in AF is likely to be methodological and probably has little relevance in the assessment of diastolic function. There is no clear definition of diastolic time since any beat may be "interrupted" by another with the result that measures are made at a different time after end-diastole in each of the different quartiles and are not therefore comparable. It is probable, since there is no clear physiological reason, that the negative relationship which is seen with preceding beat simply reflects the approximate alternation between long and short beats which has been shown to occur in AF (see Chapter 3, particularly §3.3.3). This alternation would mean that a short beat (e.g. Q1) is typically followed by a longer beat (and thus longer diastole and greater FTFF) and vice-versa with the result that there appears to be a negative relationship between long and short beats.

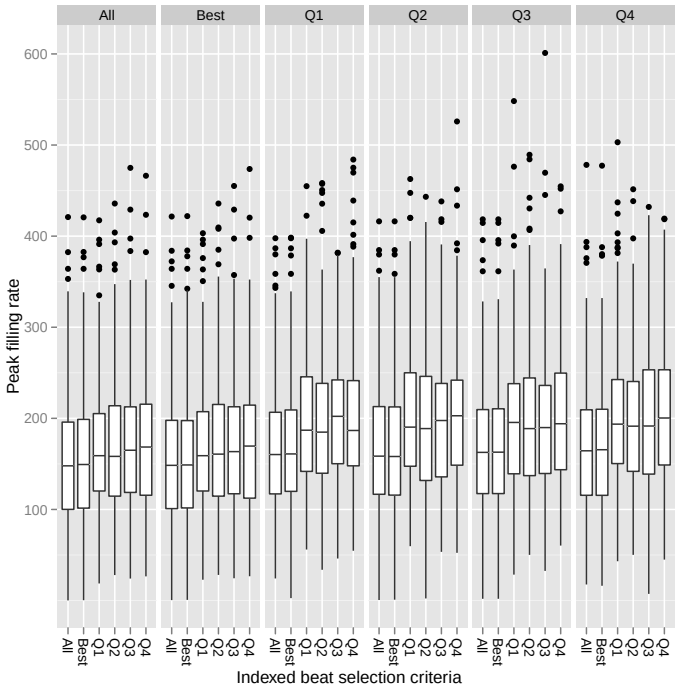
5.9. Peak filling rate (PFR)

One of the underlying assumptions of RNVG is that the dynamics of the emptying and filling processes are the same from one beat to the next. This is the assumption that is made in the process of gating from multiple images. It has been shown in the previous sections that for systole, even in SR, this assumption is false since different beat selection criteria lead to different measurements of a variety of systolic indices. In AF this variation becomes more pronounced. There is a good physiological explanation for this, as the pre-systolic volume has been shown to vary substantially and to be dependent on the duration of the preceding beat.

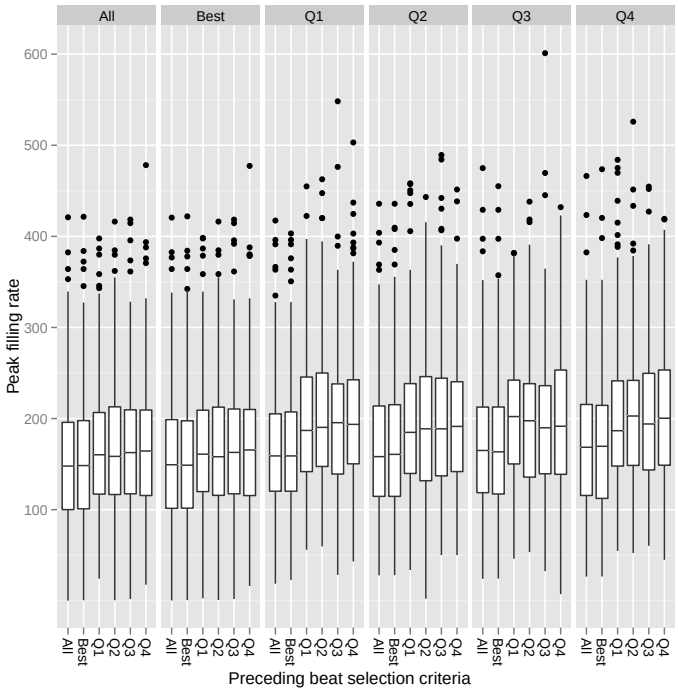
Investigating the variation in PFR provides a means of determining whether the assumption is true for diastole or not. If filling progresses in approximately the same way in each beat until the beat is interrupted then, provided that an interruption occurs after peak filling, PFR should be constant.

The variation in PFR with preceding and indexed beat is shown in Figure 5.43 for SR and in Figure 5.44 for AF. It can be seen from these that there is little variation in SR but there does appear to be a systematic change in PFR with both indexed (positive) and preceding (negative) beat length in AF.

These impressions are corroborated by regression testing which found that in SR there is no significant change in PFR with increasing quartile, preceding or indexed. In AF however there is a highly significant, if weak, dependence of PFR on quartile, both

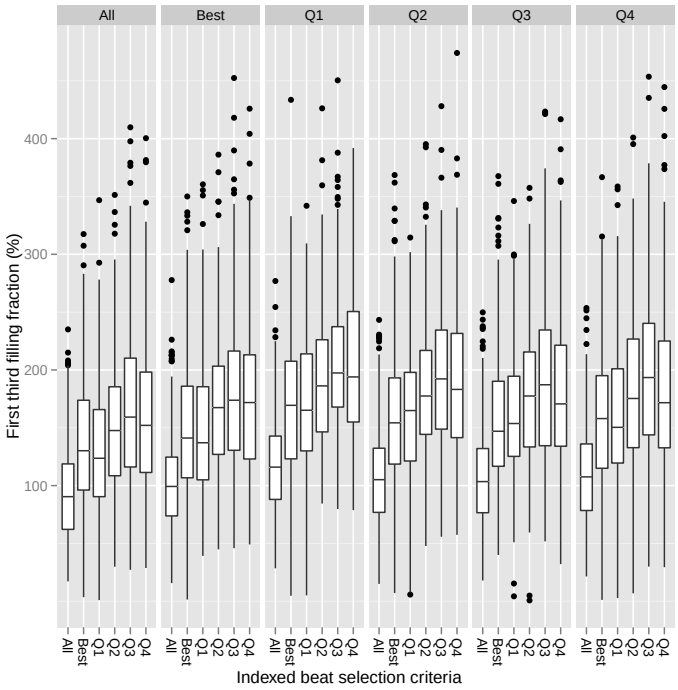


(a) Grouped by preceding beat

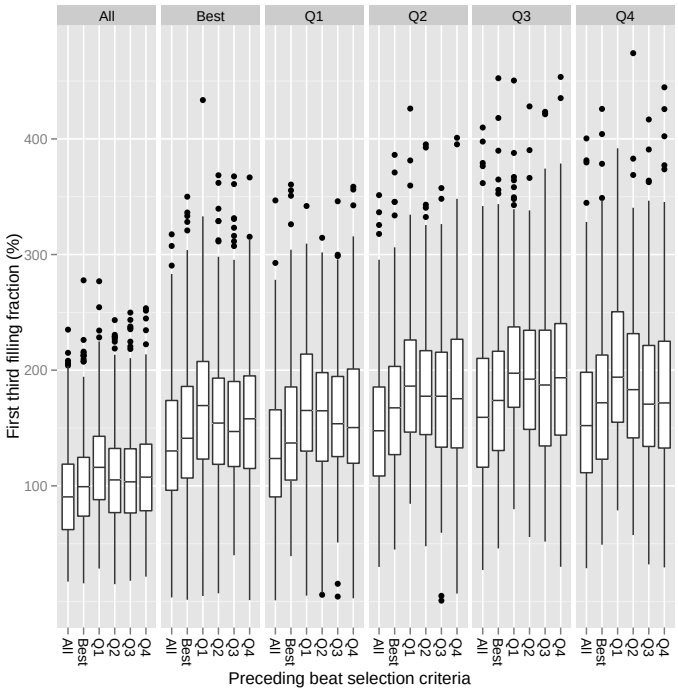


(b) Grouped by indexed beat

Figure 5.43.: SR, PFR: Showing the variation in PFR with varying indexed and preceding beat selection criteria in SR using variable time formatting.



(a) Grouped by preceding beat



(b) Grouped by indexed beat

Figure 5.44.: AF, PFR: Showing the variation in PFR with varying indexed and preceding beat selection criteria in AF using variable time formatting.

Preceding	Indexed	Gradient	r^2	P
All	Q1 - Q4	10.19	0.032	$< 1 \times 10^{-5}$
Best	Q1 - Q4	8.07	0.019	$< 1 \times 10^{-5}$
Q1 - Q4	All	-1.59	0.002	0.136
Q1 - Q4	Best	-3.41	0.004	0.048
Q1 - Q4	Q1 - Q4	-1.13*	0.019	$< 1 \times 10^{-5}$

Table 5.52.: AF, PFR regression: Regression results showing the effect of differing beat selection criteria on PFR in AF using variable time formatting. *This shows the gradient of the interaction term.

.

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.69 ± 0.11	53	0.71 ± 0.13	20	4
Best (Constant)	Q1 - Q4	0.67 ± 0.10	59	0.69 ± 0.12	22	4
Q1 - Q4	All (Constant)	0.68 ± 0.11	52	0.65 ± 0.10	20	8
Q1 - Q4	Best (Constant)	0.66 ± 0.12	52	0.64 ± 0.10	26	6
Q1 - Q4	Q1 - Q4	0.41 ± 0.18	72 (p), 56(i)		29(p), 43(i)	21

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Constant)	Q1 - Q4	0.72 ± 0.13	133	0.80 ± 0.15	12	7
Best (Constant)	Q1 - Q4	0.72 ± 0.13	76	0.79 ± 0.16	12	27
Q1 - Q4	All (Constant)	0.71 ± 0.13	61	0.67 ± 0.12	16	14
Q1 - Q4	Best (Constant)	0.78 ± 0.14	43	0.72 ± 0.12	14	34
Q1 - Q4	Q1 - Q4	0.50 ± 0.21	81 (p), 101(i)		34 (p), 17(i)	28

(b) AF

Table 5.53.: PFR: showing the regression results by quartile on a patient-by-patient basis for PFR in (a) SR, and (b) AF. The form of these tables is described in §5.3.4. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

preceding and indexed, with indexed quartile having a more dominant effect (gradient is substantially greater) than does the preceding quartile (see Table 5.52). These results also agree with mean patient-by-patient regression results (shown in Table 5.53).

In SR, analysis of variance found that there was a significant difference between results when quartiles were taken in either preceding or indexed beat (see Table 5.54). Similarly

Preceding	Indexed	SR p	AF p
Best	-	0.886	0.056
Quartiles	-	0.003	$< 1 \times 10^{-5}$
-	Best	0.831	$< 1 \times 10^{-5}$
-	Quartiles	< 0.00006	$< 1 \times 10^{-5}$
Best	Best	0.913	0.351
Quartiles	Best	0.897	0.053
Best	Quartiles	0.912	0.050
Quartiles	Quartiles	0.0007	0.00004

Table 5.54.: Analysis of variance results considering contribution of preceding and indexed beat selection criteria to measurement of PFR.

in AF the analysis of variance shows that there is a significant difference in PFR between groups depending on the beat selection criteria.

This measure should be less dependent on diastolic filling time, and therefore on R-R interval, than FTFF; however, there will still be a dependence particularly when the R-R interval is short and peak filling may not have been reached before the beat is interrupted. It is also particularly noticeable that PFR is substantially lower when all indexed beats are included.

Overall the results suggest that the assumption that filling progresses the same way from beat-to-beat until "interrupted" by the next beat is false. There is a physiological variation from one beat to the next. The mechanism for this is unclear, but, although it has not been possible to investigate in this thesis, it may reflect a varying base line: end-systolic volume is not constant.

5.10. Comparing the measures

To investigate the relationship between the measures previously considered (LVEF, PSV, EDV/PSV, Systolic time, FTFF, and PFR) Spearman rank correlation testing was used. Comparisons were made both against individual values measured from a single image and against the range of measures made on a patient-by-patient basis.

Spearman rank correlation was used because many of the ranges investigated are not normally distributed (see appendix C, §C.1). This ensured uniformity of analysis whereby non-parametric statistics have been used throughout. Where data are actually normally distributed a Spearman rank correlation will underestimate the strength of a correlation, where one is seen.

The results summarising the comparison between functional measures can be found in figures 5.45 (for SR) and 5.46 (for AF). These show a comparison both in the groups as a whole and on a patient-by-patient basis.

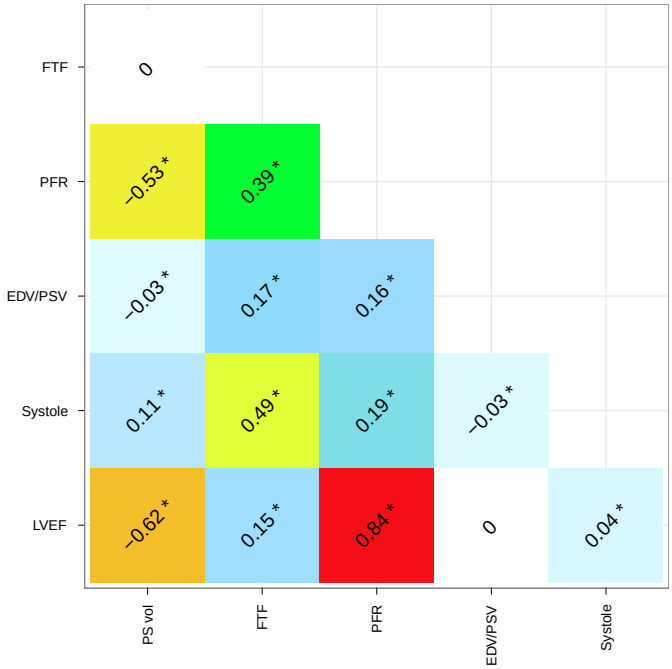
Correlating the paired ranges (⇳) on a per patient basis leads to the results shown in Figures 5.47 (SR) and 5.48 (AF).

It is noticeable that when the comparison between functional measures is considered on a patient-by-patient basis using a Spearman rank correlation a different pattern of agreement is found than when all the measures are correlated as a group. In particular there are disagreements between the two statistics when comparing LVEF with both PFR and PSV; and comparing PFR with PSV in both SR and AF. In the case of PSV these differences reflect the lack of normalisation which leads to different results when all patients are included than when variation is considered against a single patient. In the case of PFR the difference is likely to be in part statistical, since correlation on a patient-by-patient basis can only include up to four points. It may also reflect the fact that patients may have diastolic dysfunction without having systolic dysfunction while the reverse is not true. Thus an individual patient may not show substantial agreement between changes in LVEF and changes in PFR although the group as a whole may do so.

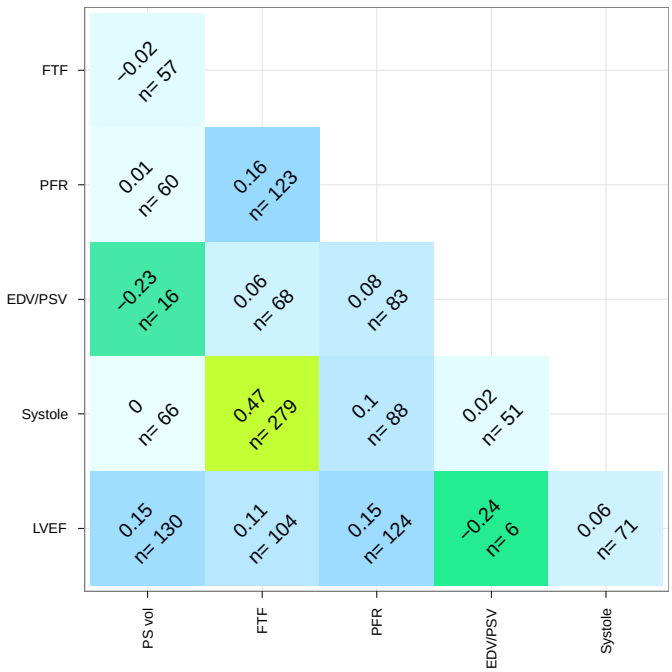
A summary of the most significant relationships between the functional indices which have been measured follows:

5.10.1. LVEF vs. systolic time

In both AF and SR there seems to be little agreement between the LVEF and systolic time interval, although a Spearman rank (non-parametric) correlation test yields a highly significant (but very weak) correlation with $\rho = 0.041$, $p = 0.00002$ in SR and $\rho = 0.085$ and $p < 1 \times 10^{-5}$ in AF. This is corroborated by the patient-by-patient analysis.

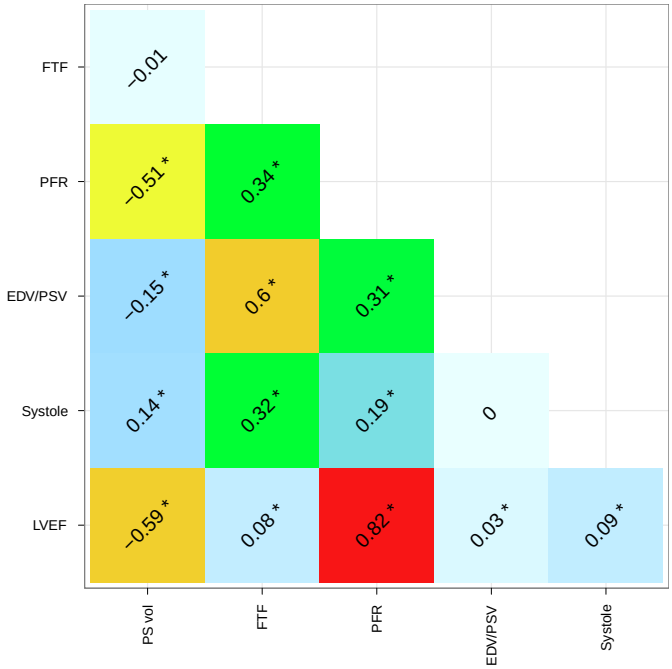


(a) Group basis

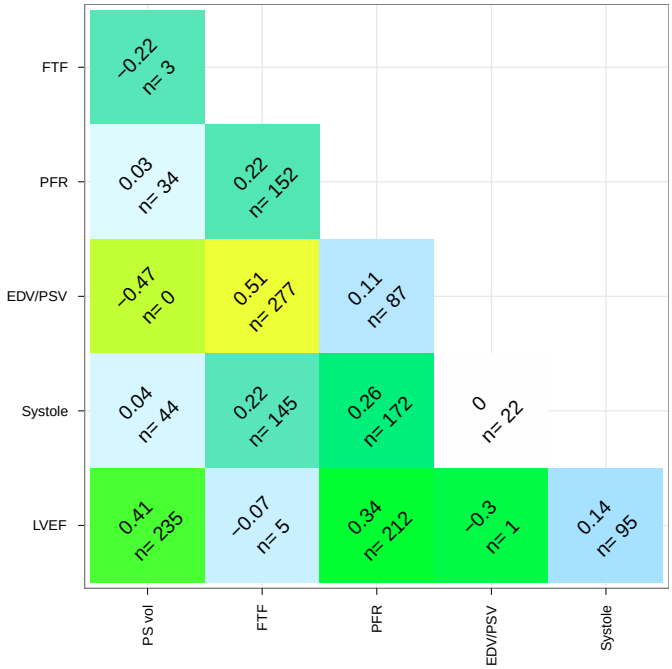


(b) Patient-by-patient basis

Figure 5.45.: SR, comparing measures: Showing (a) the correlation between the six functional measures investigated in SR. A * indicates significance at the $p < 0.05$ level. (b) the mean correlation coefficient on a patient-by-patient basis excluding patients where $p < 0.05$. In plot (b) the number of patients, n, included in the mean is also shown. (In both plots the colour scale corresponds to the scale shown in Table 2.5, N=387).



(a) Group basis



(b) Patient-by-patient basis

Figure 5.46.: AF, comparing measures: Showing (a) the correlation between the six functional measures investigated in AF. A * indicates significance at the $p < 0.05$ level. (b) the mean correlation coefficient on a patient-by-patient basis excluding patients where $p < 0.05$. In plot (b) the number of patients, n, included in the mean is also shown. (In both plots the colour scale corresponds to the scale shown in Table 2.5, N=373).

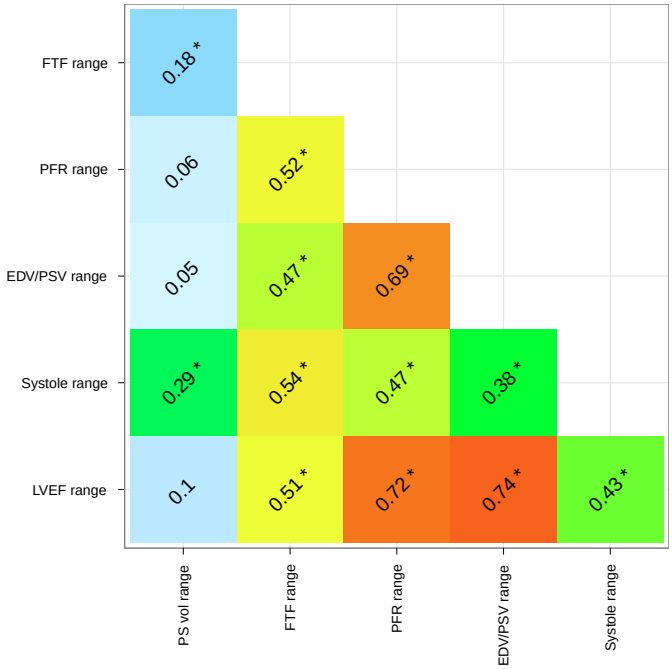


Figure 5.47.: SR, ⇳comparison: Showing the correlation between the ranges of the six functional measures investigated in SR. A * indicates significance at the $p < 0.05$ level. (Colour scale corresponds to the scale shown in Table 2.5).

Comparing the ranges there is a better correlation in SR than in AF, with SR yielding a highly significant moderate positive correlation between the changes ($\rho = 0.425$, $p < 1 \times 10^{-5}$) while in AF the correlation was weak ($\rho = 0.179$, $p = 0.0005$).

Taken together these results show that while there is no direct relationship between systolic time and LVEF in SR, a patient who has a more widely varying systolic time interval will also have a more widely varying LVEF. This may reflect cardiac health as poor variation in beat length in SR is a marker of poor cardiac health.

5.10.2. LVEF vs. EDV/PSV

In both AF and SR there is effectively no (very weak in AF) correlation between EDV/PSV and LVEF when the measures are compared on an individual basis, but when ⇳EDV/PSV is compared with ⇳LVEF there is a good correlation ($\rho = 0.736$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.685$, $p < 0.0001$ in AF). This is demonstrated in AF in the plots of Figure 5.49.

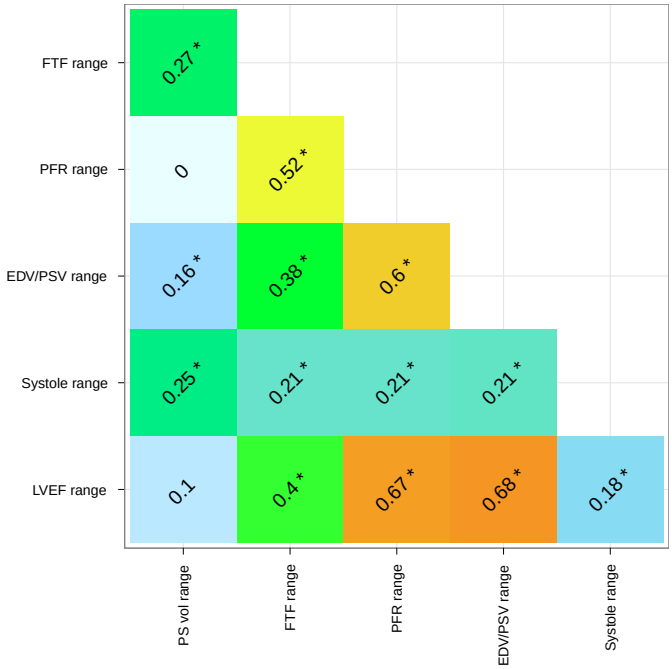
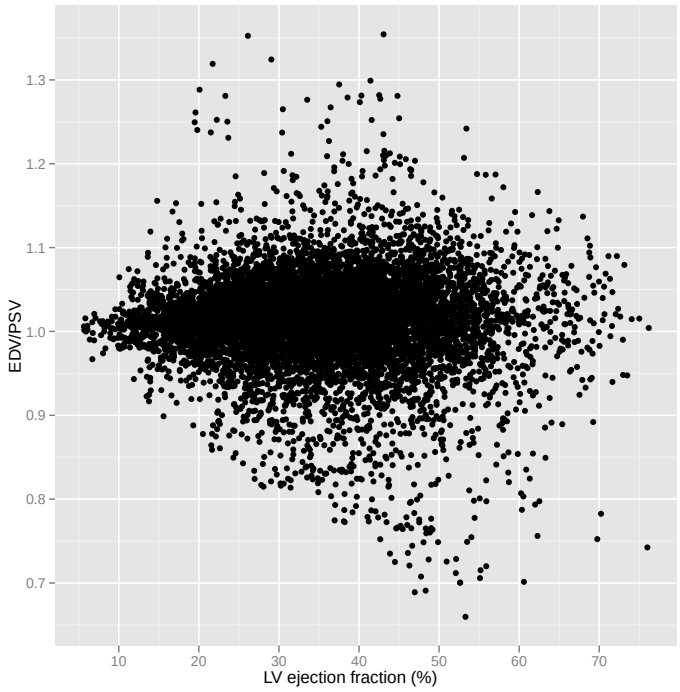


Figure 5.48.: AF, ⇳comparison: Showing the correlation between the ranges of six functional measures investigated in AF. A * indicates significance at the $p < 0.05$ level. (Colour scale corresponds to the scale shown in Table 2.5).

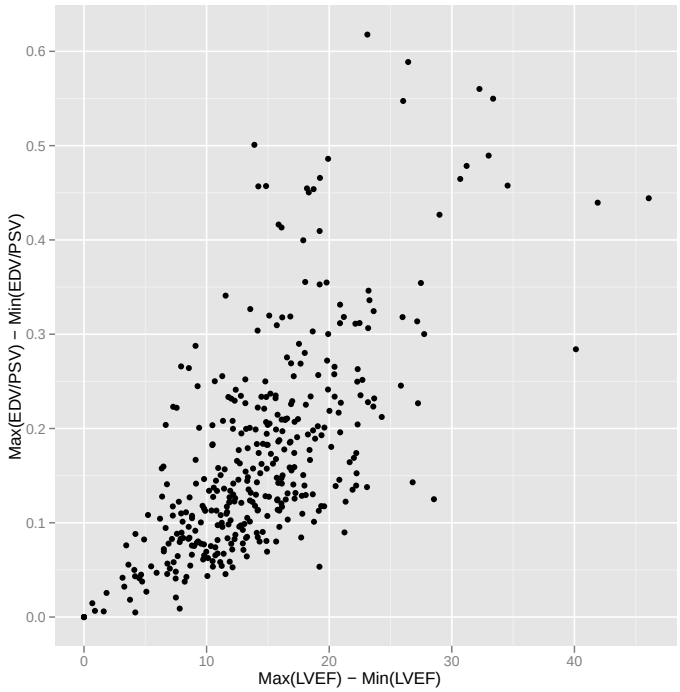
Measured LVEF has been shown, particularly in AF, to be affected by both preceding and indexed beat length, as has EDV/PSV. Both preceding and indexed beat length are determinants of EDV/PSV since preceding beat length will directly affect PSV and indexed beat length will affect EDV. In contrast, on a beat-to-beat basis, LVEF is only affected by the preceding beat length which determines PSV- the inclusion of the indexed beat in determining *measured* LVEF is likely to be methodological and not physiological. The comparison of LVEF and EDV/PSV reflects this as there is only poor agreement in absolute values but the ranges, which in both cases are principally affected by beat-to-beat variation, do show an agreement.

5.10.3. LVEF vs. *PSV*

There is a strong negative correlation between LVEF and PSV in both SR and AF ($\rho = -0.622$, $p < 1 \times 10^{-5}$ in SR and $\rho = -0.594$ and $p < 1 \times 10^{-5}$ in AF); however, there is no significant correlation between range of LVEF and PSV. Plots showing this effect in AF are shown in Figure 5.50.

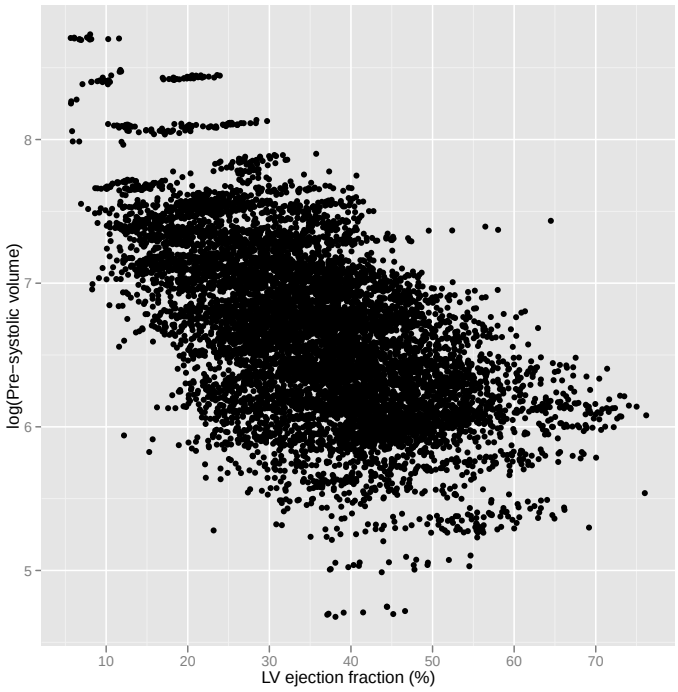


(a) LVEF vs. EDV/PSV

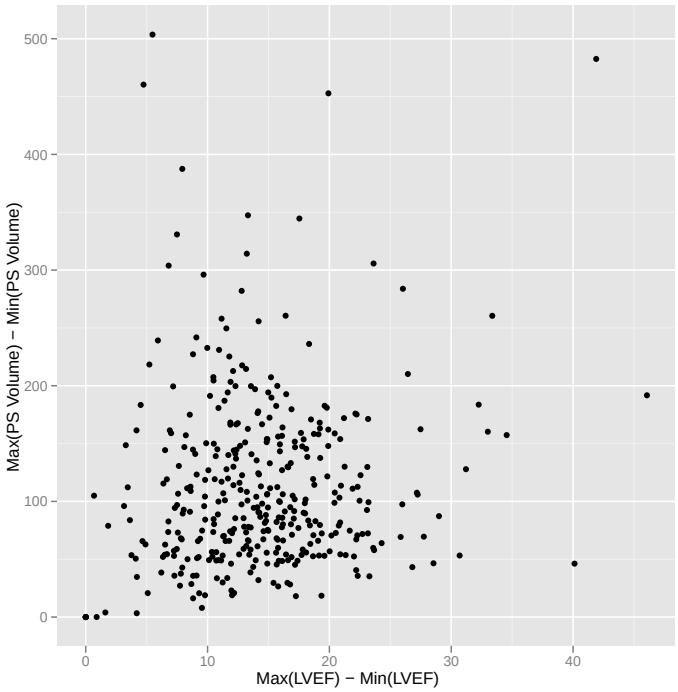


(b) ⇳LVEF vs. ⇳EDV/PSV

Figure 5.49.: AF: Showing (a) a plot of LVEF against EDV/PSV and (b) a plot of ⇳LVEF vs. ⇳EDV/PSV in AF using variable time formatting.



(a) LVEF vs. log(PSV)



(b) Ranges: LVEF vs. $log(PSV)$

Figure 5.50.: Showing a plot of LVEF against log(PSV) in AF using variable time formatting.

Although the negative correlation suggests that a better LVEF is achieved with a lower PSV, when correlation is done on a per patient basis (Figure 5.51), it is clear that the majority of patients have a positive correlation (greater LVEF with greater PSV) with AF generally showing better correlation (mean $\rho = 0.46$) compared with SR (mean $\rho = 0.18$).

This suggests that the pathological phenomenon whereby an enlarged LV has poorer ejection fraction is more dominant than the variation of ventricular volume with ejection fraction for any one patient. That there should be no correlation between the ranges is surprising and reflects the complexity of a mechanism in which the Frank-Starling effect is not the only influence on cardiac output.

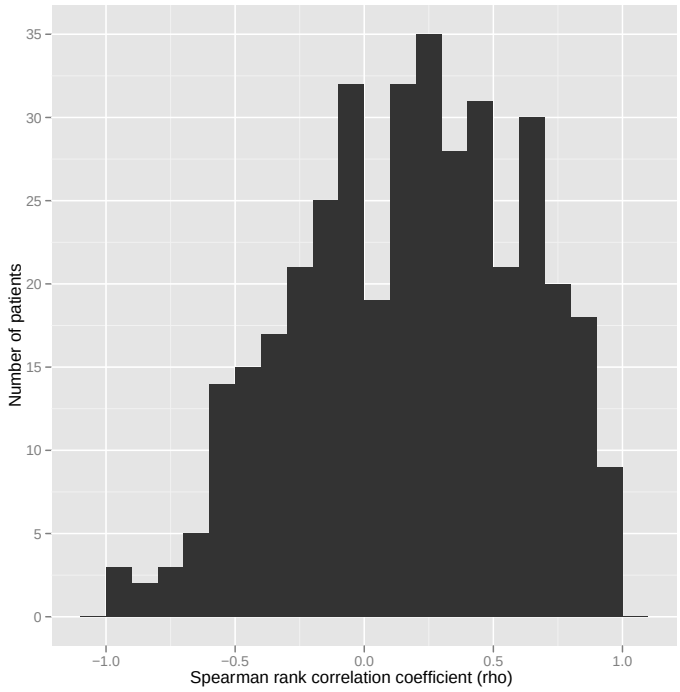
5.10.4. LVEF vs. FTFF

There is a significant, but weak, correlation between LVEF and FTFF in SR and a very weak correlation in AF, corroborated by correlation on a patient-by-patient basis. There is also a strong correlation between range of LVEF and range of FTFF in SR with a moderate correlation in AF. This is demonstrated in AF in Figure 5.52.

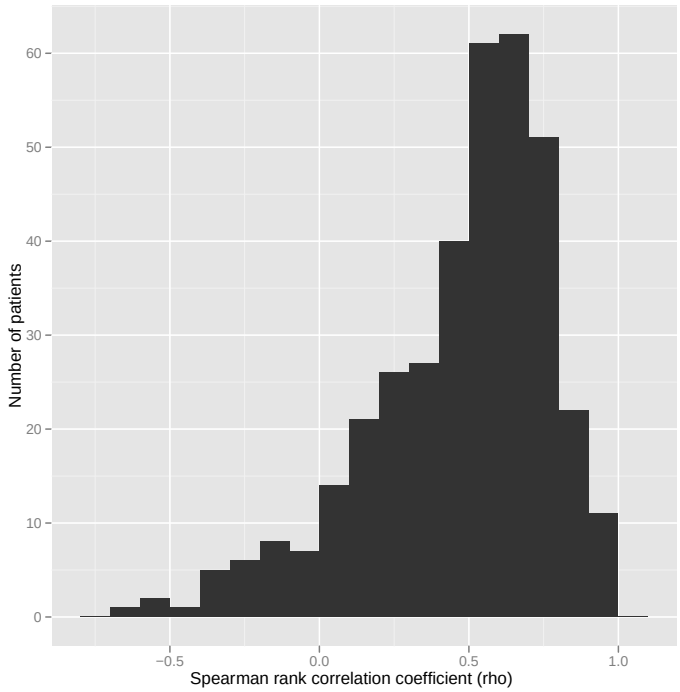
Although these results can be explained physiologically, they may also be the result of methodological error. It has been shown that shorter indexed beats have lower LVEF. Since the measure of FTFF is dependent on a determination of the duration of diastole this is also dependent on the length of the indexed beat (as has been shown in §5.8). If there is significant variation in the duration of diastole, as there may be in AF, there may be substantial variation in FTFF with longer beats giving greater FTFF. Thus it is to be expected that there should be a moderate agreement between range of LVEF and range of FTFF without any substantial agreement between the measures.

5.10.5. LVEF vs. PFR

A very good correlation is seen between PFR and LVEF in both SR and AF ($\rho = 0.836$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.823$, $p < 1 \times 10^{-5}$ in AF); however on a patient-by-patient basis the correlation is much weaker. There is also a strong correlation between the ranges ($\rho = 0.716$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.675$, $p < 1 \times 10^{-5}$ in AF).

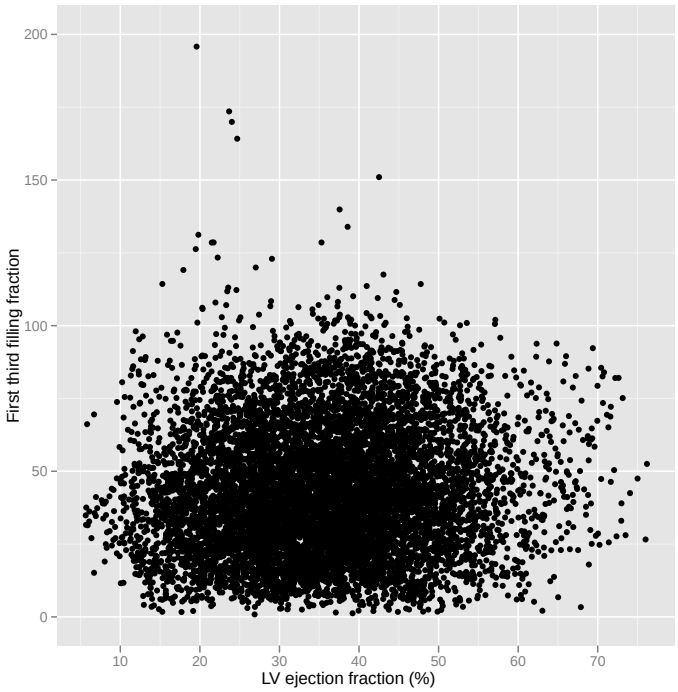


(a) SR

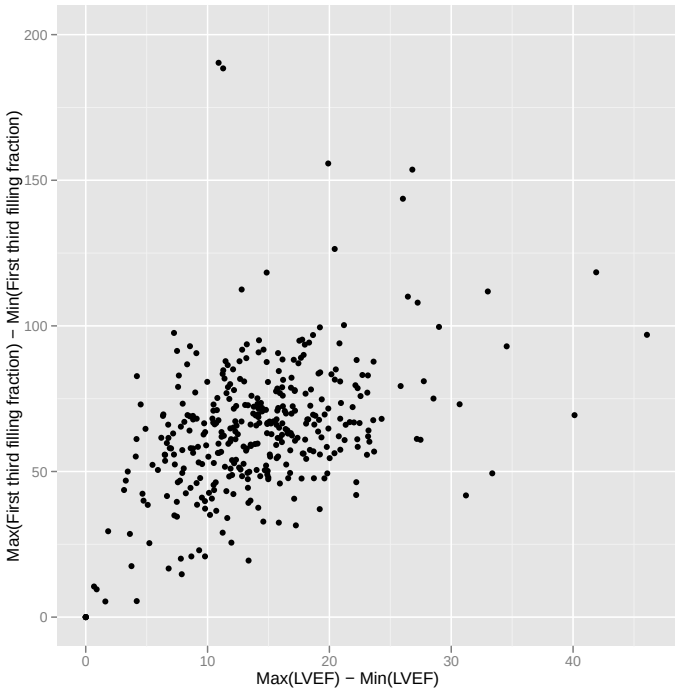


(b) AF

Figure 5.51.: LVEF vs. $\log(PSV)$: Showing the Spearman rank correlation coefficients on a patient-by-patient basis for LVEF against $\log(PSV)$ in (a) SR and (b) AF using variable time formatting.



(a) LVEF vs. FTFF



(b) Ranges: LVEF vs. FTFF

Figure 5.52.: Showing a plot of LVEF against FTFF in AF using variable time formatting.

As discussed in the introduction to this section (page 239) the discrepancy between the whole group comparison and that done on a patient-by-patient basis may in part be a result of the poor statistics involved in regressing with only four points for each patient. It may also reflect the possibility that a patient may have diastolic dysfunction without systolic dysfunction while the converse is unlikely.

5.10.6. *PSV* vs. PFR

There is a highly significant, strong, correlation between PSV and PFR ($\rho = -0.535$, $p < 1 \times 10^{-5}$ in SR, $\rho = -0.513$, $p < 1 \times 10^{-5}$ in AF) when the group is considered as a whole. However this is not seen on a patient-by-patient basis nor when the ranges are compared. See figure 5.53 for the changes seen in AF.

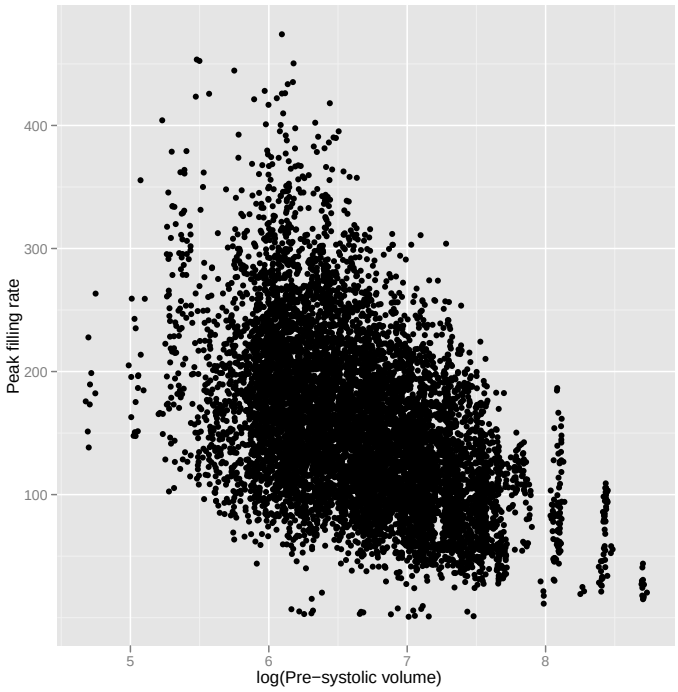
This also reflects the pathological effect of a dilated ventricle and suggests that the assessment of PFR is likely to reflect physiology rather than a methodological variation since it is to be expected that the dilated ventricle will have poorer diastolic function. If the variation in PFR were purely methodological it is unlikely that there would be such a good correlation when the whole group is considered and it would be reasonable to expect a better correlation on a patient-by-patient basis.

5.10.7. Systolic time vs. FTFF

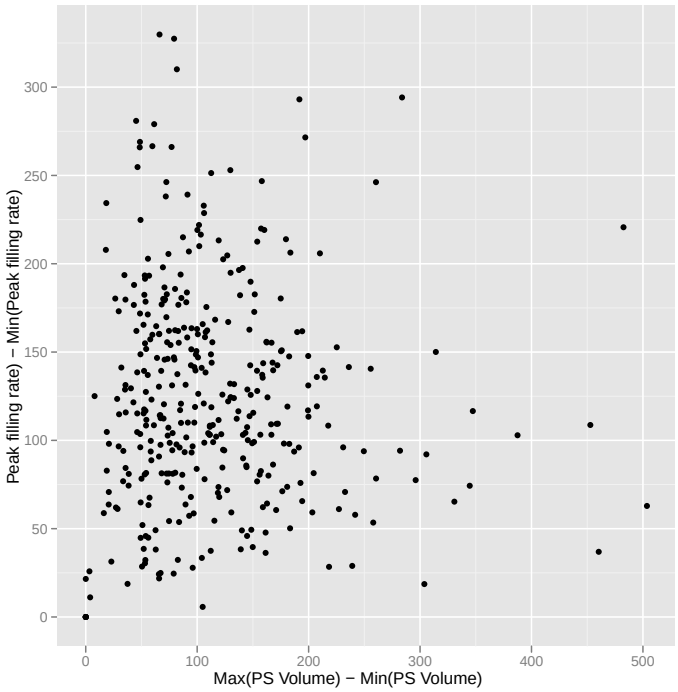
There is a highly significant, moderate, correlation between systolic time and FTFF in both AF and SR ($\rho = 0.493$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.323$, $p < 1 \times 10^{-5}$ in AF). This is corroborated by the patient-by-patient analysis and is matched by a good correlation ($\rho = 0.549$, $p < 1 \times 10^{-5}$) in SR and a weak correlation in AF ($\rho = 0.206$, $p = 0.00006$) between the ranges.

5.10.8. Systolic time vs. PFR

There is a highly significant, but weak, correlation between systolic time and PFR ($\rho = 0.187$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.190$, $p < 1 \times 10^{-5}$ in AF). On a patient-by-patient basis the agreement is shown to be better in AF than it is in SR. When the ranges are



(a) *PSV* vs. PFR



(b) ⇳*PSV* vs. PFR

Figure 5.53.: Showing a plot of the log of *PSV* against PFR in AF using variable time formatting. Plot (a) shows a comparison on an image by image basis; (b) shows the comparison of range on a patient-by-patient basis.

compared there is found to be good correlation in SR ($\rho = 0.470$, $p < 1 \times 10^{-5}$) and weak correlation in AF ($\rho = 0.205$, $p = 0.00006$).

5.10.9. *EDV/PSV* vs. FTFF

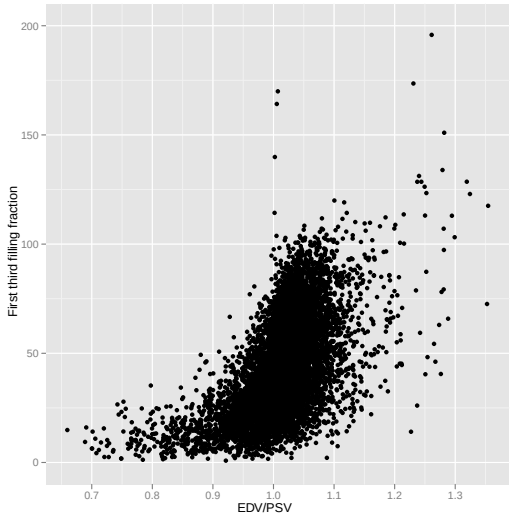
A highly significant poor correlation is seen when comparing EDV/PSV and FTFF ($\rho = 0.173$, $p < 1 \times 10^{-5}$) in SR. In AF the correlation is good ($\rho = 0.599$, $p < 1 \times 10^{-5}$) as illustrated in Figure 5.54. The agreement here actually looks like it is exponential and a more natural regression line is achievable if the log of FTFF is taken, Figure 5.54c (although because the Spearman rank correlation is non-parametric this doesn't change the correlation coefficient). These results agree with those achieved when the correlation is considered on a patient-by-patient basis.

Comparing the ranges shows a moderate correlation in SR($\rho = 0.384$, $p < 1 \times 10^{-5}$) and AF ($\rho = 0.468$, $p < 1 \times 10^{-5}$).

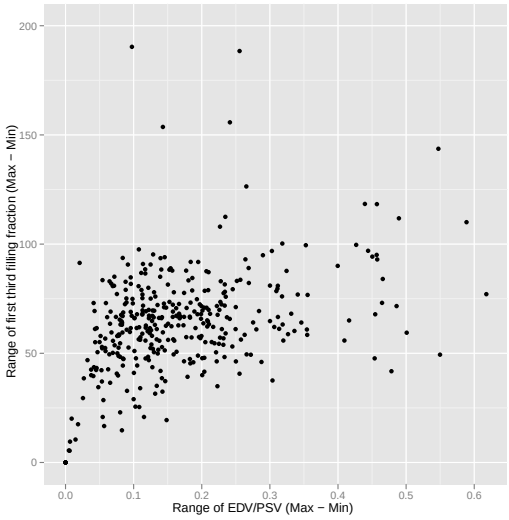
EDV/PSV is a measure of the variation in filled volume from one beat to the next, as such it offers a means of determining how consistently a fixed volume is achieved during filling. Thus EDV/PSV is a surrogate marker for variation in diastole and since FTFF is determined by the duration of diastole there is likely to be good correlation in AF where the duration of diastole changes significantly but not in SR where there is little change in the duration of diastole.

5.10.10. *EDV/PSV* vs. PFR

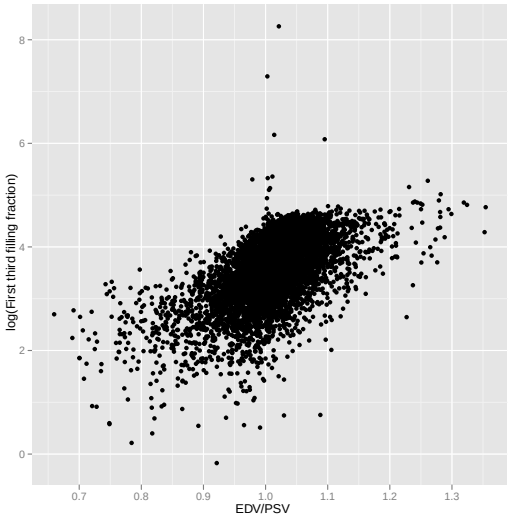
There is a highly significant weak correlation between EDV/PSV and PFR ($\rho = 0.162$, $p < 1 \times 10^{-5}$ in SR, $\rho = 0.312$, $p < 1 \times 10^{-5}$ in AF) with good correlation between the ranges in both SR and AF ($\rho = 0.691$, $p < 1 \times 10^{-5}$, $\rho = 0.597$, $p < 1 \times 10^{-5}$) respectively. More rapid filling is likely to result in a greater end-diastolic volume and the plateau phase of diastole will be reached more quickly. It is, then, to be expected that there will be a relationship between PFR and EDV/PSV.



(a) EDV/PSV vs FTFF



(b) Ranges: EDV/PSV vs FTFF



(c) EDV/PSV vs. log(FTFF)

Figure 5.54.: Showing (a) a plot of EDV/PSV against FTFF in AF using variable time formatting. (b) A plot of the range of EDV/PSV against range of FTFF. (c) A plot of EDV/PSV against log(FTFF) where a more linear relationship is found.

5.10.11. FTFF vs. PFR

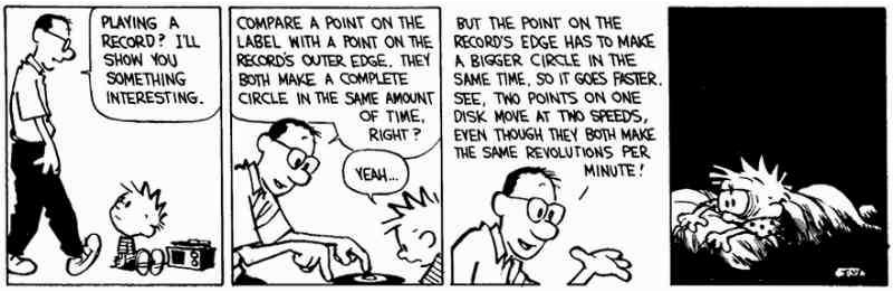
It is to be expected that there will be good correlation when comparing between both the individual values and the ranges of FTFF and PFR. Physiologically both FTFF and PFR are indices of diastolic filling, methodologically they are both affected by the duration of diastole. The good correlation is confirmed in both SR and AF although it unclear whether the correlation has a physiological or methodological aetiology.

5.11. Going forward

Having determined these results and, for most variables, demonstrated substantial variation in the functional measures being investigated with differing beat selection criteria, it is now possible to consider whether there is any relationship between the functional measures and the indicators of rhythm described in Chapter 3. This will be the subject of the following chapter.

Chapter 6.

Results: Comparing Rhythm and Function



Summary

In which we look at the relationship between rhythm and function as described in this thesis. The comparison is made using Spearman Rank correlation for uni-variate comparison and regression testing to allow multivariate models to be used.

6.1. Introduction

The principal measure of left ventricular function in the clinical context is left ventricular ejection fraction (LVEF). As a result, while several measures of both diastolic and systolic function have been investigated, this thesis has concentrated on LVEF. It has been shown in Chapter 5 that in both SR and AF there is a substantial, and significant, variation

in LVEF depending on the beat selection criteria. In AF the variation (mean ⇳LVEF of 14.3 EF units) has been shown to have a clear dependence on the beat selection criteria: in particular there is a very strong positive correlation with the duration of the preceding beat and a weaker negative correlation with the length of the indexed beat. In SR, although there is a substantial variation (mean ⇳LVEF of 8.2 EF units), it does not correlate with either preceding or indexed beat length.

In Chapter 3 several measures were investigated to describe the rhythm. These measures were selected in an attempt to provide a complete description of rhythm covering not simply the mean and range of R-R intervals but also measures which describe the pattern, regularity and complexity of the rhythm.

Since the variation in LVEF for any patient is achieved by varying the indexed and preceding beat selection criteria, it is reasonable to expect that there will be some level of agreement between measures of rhythm and functional variation.

6.2. Correlation

A correlation matrix comparing individual measures of rhythm with the SD of each measure of function are shown in Figures 6.1 (SR) and 6.2 (AF). The SD has been chosen as the measure of choice rather than the maximum range because it is less influenced by single outliers. A comparison against the *maximum* range in functional measurement can be found in appendix D.

In addition to the comparison against SD, a comparison of the mean functional result (over all measured combinations of preceding and indexed beat using variable time formatting) has been performed. The results of this are shown in Figures 6.3 and 6.4.

The correlations with SD of the functional measures are, at best, moderate in both SR and AF and many of them are not significant. This is surprising as there are several measures e.g. EDV/PSV which could be expected to be well described by some measure of rhythm variability.

When the agreement between *mean* functional measure and the indices of rhythm are considered, the majority of the results are either not significant or show only a weak correlation although there are several which show a strong agreement.

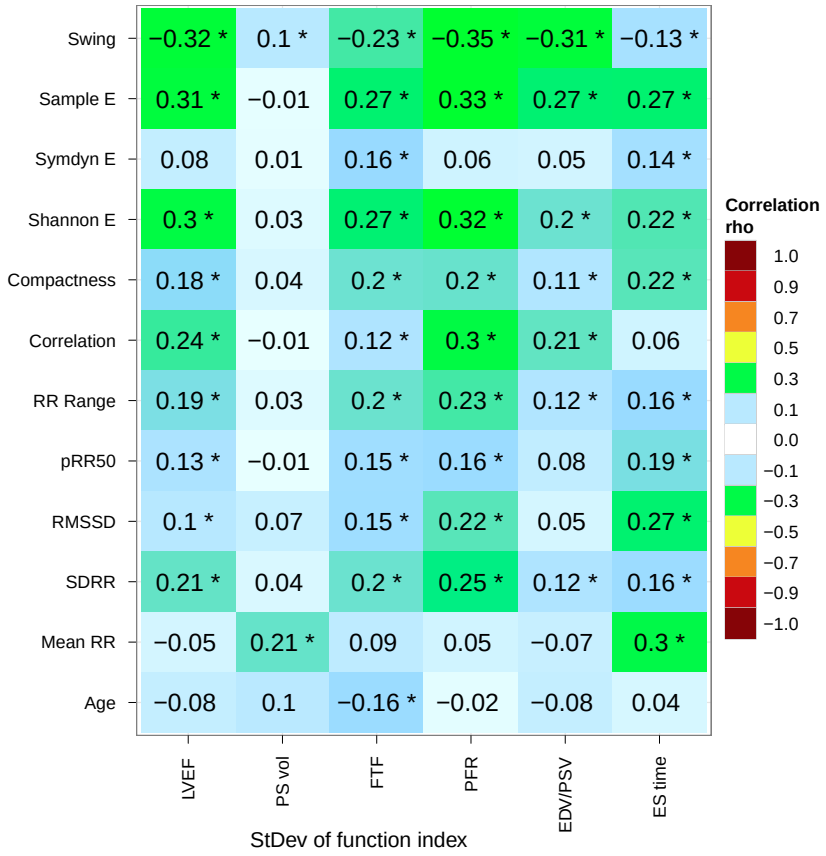


Figure 6.1.: SR: Showing the correlation between measures of R-R variability and the SD of measures of function (per patient) in SR. (N=387).

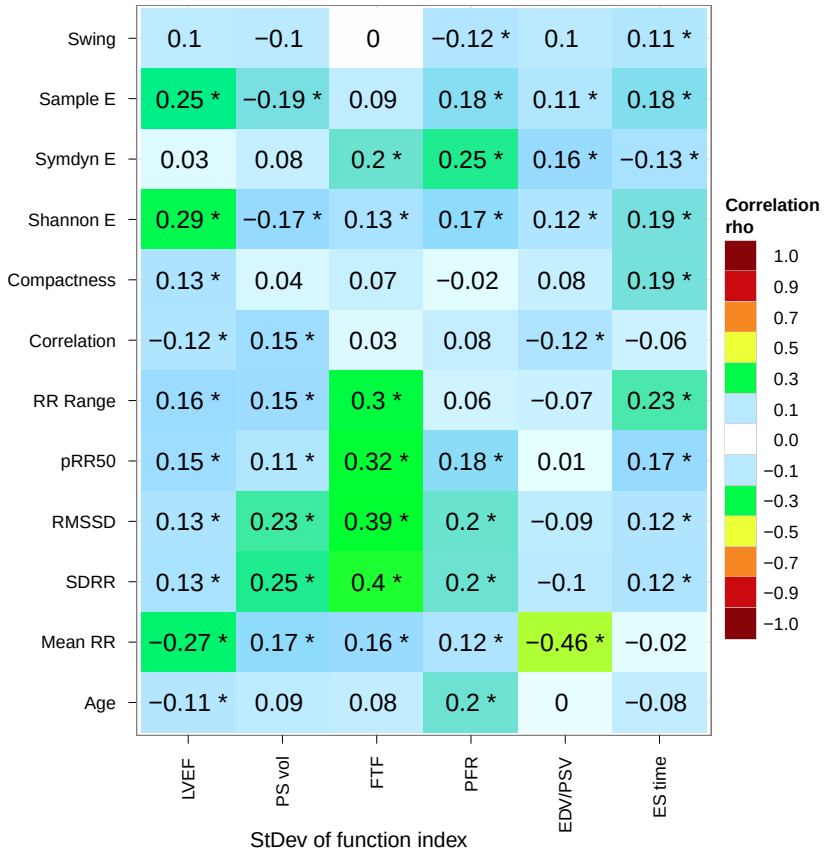


Figure 6.2.: AF: Showing the correlation between measures of R-R variability and the SD of measures of function (per patient) in AF. (N=373).

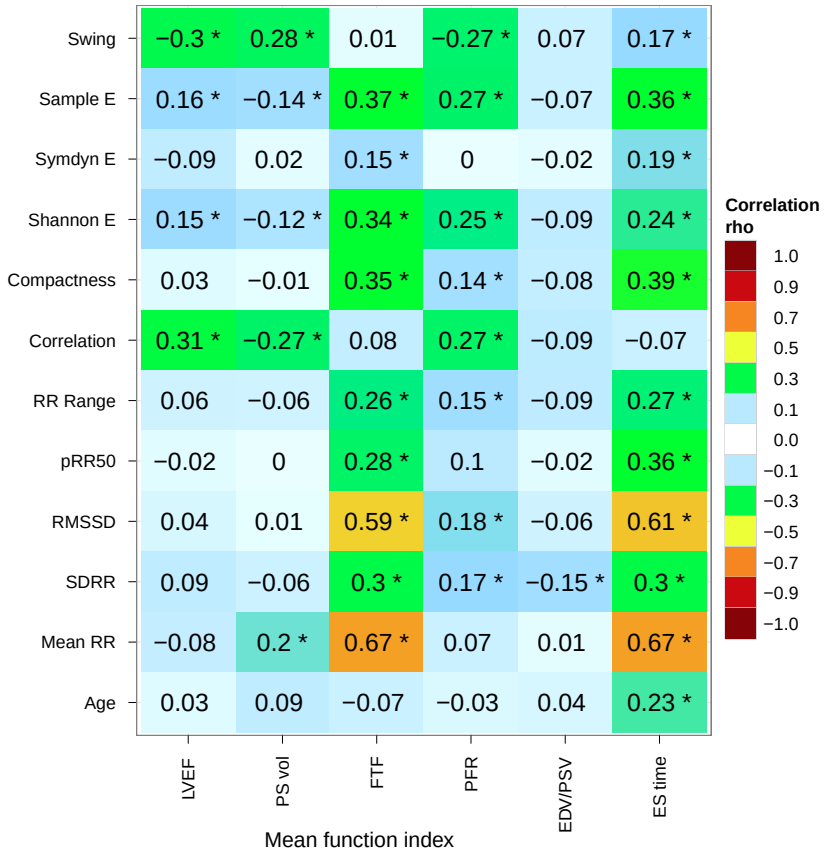


Figure 6.3.: SR: Showing the correlation between measures of R-R variability and the mean measures of function (per patient) in SR. (N=387).

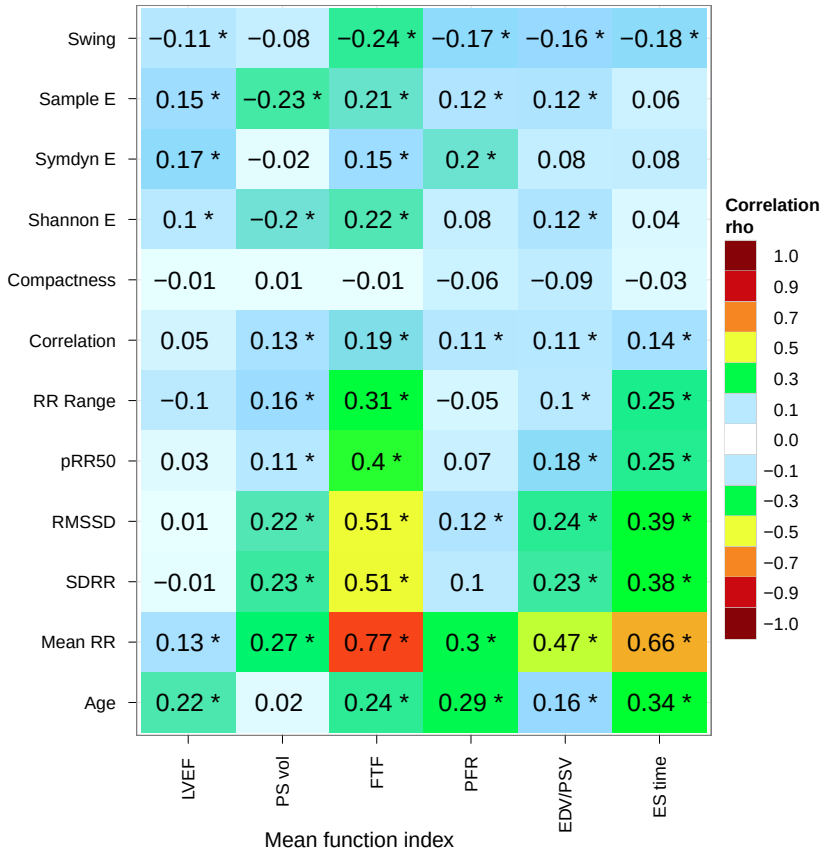


Figure 6.4.: AF: Showing the correlation between measures of R-R variability and the mean measures of function (per patient) in AF. (N=373).

The individual results are discussed in §6.4 to §6.9; however, while correlation between individual variables offers an initial insight into the potential for indices of rhythm to act as descriptors for functional change it is more likely that multiple indices of rhythm will be required. This can be investigated through regression modelling.

6.3. Regression modelling

The absence of a strong correlation between the range of LVEF and any individual measure of R-R variability is not surprising as it has been shown that on a patient-by-patient basis there is a strong correlation with both preceding and indexed beat. No single measure reflects this; however, since beat selection criteria appear to be the principal determinants of ⇳LVEF in AF, it should be possible to determine a combination of measures which are predictive of the range of LVEF.

If the range of R-R intervals is very small it is unlikely that there will be a substantial variation in LVEF while a large range of R-R intervals offers scope for a greater variation in LVEF. Thus it is to be expected that the range of R-R interval will be a significant factor in determining LVEF range, to some extent this is corroborated by the weak correlation between LVEF and R-R range which is seen in both AF ($\rho = 0.19$ in SR, $\rho = 0.16$ in AF).

The range of R-R interval does not, by itself, offer a model of range of LVEF, since it does not include any information about the sequential beat patterns (e.g. a beat in Q1, followed by a beat in Q3, followed by a beat in Q4 followed by a beat in Q1 etc.) which is included in selecting beats based on both the preceding and indexed beat. There are several different measures which reflect this variation and which, when included with a measure of R-R range, may contribute to an accurate model of the extent of LVEF variability.

Entropy measures provide an assessment of the regularity of the R-R interval stream: effectively a measure of the repeating patterns of R-R variability. While *ShanEnt* offers a very basic measure, both *SampEn* and *SymDyn* attempt to incorporate information about patterns of different lengths and therefore offer an assessment of *pattern* as opposed to *beat* regularity.

Swing is a measure of the frequency with which the R-R intervals alternate in a "short-long" or "long-short" pattern. It is a crude measure in that it does not include any information about the size of the swing, just that *swing* occurs. Thus an R-R interval stream which followed the pattern (4,3,4,2,4,3) would have the same *swing* as a stream in which the beats followed the pattern: (4,1,4,1,4,1) although in the second case there is a bigger swing and higher regularity (and lower entropy).

Compactness factor gives a measure of clustering within the Poincaré plot: the more clustered the data, the lower the *compactness factor*. This could be considered to be a measure of complexity (as opposed to regularity). Because the measure is taken from the Poincaré plot it incorporates information about the association between one beat and the next as well as about the range of R-R intervals.

Poincaré correlation gives a measure of how well one beat agrees with the next, but does not address long term variation at all.

6.3.1. Modelling

Any model should adhere to several fundamental rules: the model should not involve an excessive number of terms (in an extreme situation a model which has as many terms as there are elements to be modelled will give a perfect, and perfectly meaningless, model). The model should include enough terms to have predictive value[1] (effectively a significant and high value for R^2) and it should not include terms which do not significantly change or improve the model (either explicitly or implicitly - e.g. R-R range is reflected both in the range and in the SD). Ideally, in this study, it should also work in both AF and SR.

The uni-variate correlation tables, shown in Figure 6.1 and Figure 6.2, offer a starting point for determining a suitable model as it is unlikely that a term will be significant in a multivariate model if it is not significant in a uni-variate analysis, although this clearly can not be true for interaction terms.

The format of Table 6.1 presents an easy means of determining potentially significant contributors to the multivariate model. The table allocates a tick (✓) for every 0.1 in the uni-variate (Spearman rank) correlation coefficient: the greater the number of ticks the higher the uni-variate correlation.

[1] R is used here to indicate that parametric statistics have been used, by contrast ρ is used to indicate non-parametric correlation.

	AF	SR
Age	✓	
Mean R-R	✓✓	
SDRR	✓	✓
RMSSD	✓	✓
pRR50	✓	✓
R-R Range	✓	✓
Correlation	✓	✓✓
Compactness factor	✓	✓
ShanEnt	✓✓	✓✓✓
SymDyn		
SampEn	✓✓	✓✓✓
Swing	✓	✓✓✓

Table 6.1.: Showing the potential terms for inclusion in the model of LVEF. Each "✓" marks a change of 0.1 in the uni-variate regression coefficient.

Initial models in the regression analysis were chosen to include the most significant terms in both AF and SR combined. A successive reduction technique was then used to find the smallest possible predictive model: the least significant terms in the model were successively removed and the new model compared (using an Anova technique) against the old one. If no significant difference was found, that element was removed from the model otherwise it was kept in. This technique is fully described in "The R book" [93].

While the successive reduction technique was applied in all cases, it results in different final models for SR and AF and the elements removed from the model are typically interaction terms (e.g. mean_RR:*SampEn*) that describe an element which only has effect in combination. This thesis has been considering potential rhythm descriptors for the function measures but it is beyond the scope of the thesis to investigate the detail of all the interaction terms. Thus, to allow the reader an easier understanding, the initial model and the R^2 value for that model have been reported; the final minimum adequate model, which might typically consist of eight or ten interaction terms, has not been reported. Since successive removal of multiple elements does affect the value of R^2 the R^2 value for the minimum adequate model has also been given.

6.4. LVEF

It can be seen from Figures 6.1 to 6.4 that in terms of mean LVEF there is a moderate correlation with *Poincaré correlation* and *swing* in SR and with age in AF. Otherwise the correlation is either weak or not significant. When ⇳LVEF, expressed in terms of the SD, is considered there is a moderate negative correlation with mean R-R interval in AF, with only a poor negative correlation in SR. In SR there is moderate correlation between ⇳LVEF and *swing*, the proportion of beat-to-beat changes which follow a pattern of being either "short-long" or "long-short", and with both *SampEn* and *ShanEnt*. In AF a correlation between ⇳LVEF and *SampEn* and *ShanEnt* is found but there is only poor correlation with *swing*. Curiously there is a moderate positive correlation with *Poincaré correlation* in SR, but a weak negative correlation in AF.

A consideration of Figure 6.1 and the summary table, 6.1 suggests that the most promising measures of R-R variability which might be used in predictive model are: *ShanEnt*, *SampEn*, *swing*, SDRR, and Poincaré correlation; in AF, mean R-R is also significant. *ShanEnt* and *SampEn* have been shown to be closely related and are likely simply to duplicate information. This suggests the following possible model[2]:

$$\Updownarrow \boldsymbol{LVEF \sim SampEn * mean\_RR * swing * correlation * SDRR}$$

This model gives a good correlation with $R^2 = 0.307, R = 0.554$ ($R^2 = 0.252, R = 0.502$ after successive reduction) in AF and $R^2 = 0.300, R = 547$ ($R^2 = 0.287, R = 0.536$ after successive reduction) in SR.

Although the correlation is not perfect LVEF variation is well described by a combination of the traditional measures of mean R-R and SDRR, the correlation of the Poincaré plot, which describes how well related one beat is to the next, the *swing*, which describes the regularity of the short-long-short beat pattern and *SampEn* which describes the repetitiveness of beat patterns. Each of these indices clearly define a different aspect of rhythm variation. Although each aspect does not in itself have a substantial impact on LVEF, in combination they have a large determining effect. There will be other effects, most notably pathology, which will also affect LVEF and which have not been included in this investigation.

[2]Notation in defining models: "∼" can be interpreted as "is modelled by"; "+" separates the elements of the model; ":" implies the interaction between elements which it separates and "*" is a shorthand for "+" including the interaction term. Thus $A \sim B * C * D$ is shorthand for $A \sim B + C + D + B : C + B : D + C : D + B : C : D$

6.5. *EDV/PSV*

Both EDV/PSV and $\updownarrow EDV/PSV$ (expressed by SD) show a moderate correlation with mean R-R interval in AF (Figures 6.2 and 6.4) but not in SR (Figures 6.1 and 6.3) for which there are no indices of rhythm that show more than a weak correlation with mean EDV/PSV. In SR there is a moderate correlation between $\updownarrow EDV/PSV$ and swing, and a correlation in the upper range of "poor" between $\updownarrow EDV/PSV$ and *SampEn*.

Examination of Figures 6.2 and 6.1 suggests that the most promising R-R variability indices for correlation against EDV/PSV are: swing, *SampEn*, correlation and mean R-R, suggesting an initial model in which:
$\updownarrow \boldsymbol{EDV/PSV \sim swing * SampEn * correlation * mean\_RR}$

This model gives a correlation of $R^2 = 0.291, R = 0.540$ ($R^2 = 0.278, R = 0.527$ after model simplification) in AF and $R^2 = 0.192, R = 0.438$ ($R^2 = 0.127, R = 0.356$ after model simplification) in SR.

This appears to a be a good model in AF but only a moderate model in SR. It is surprising that the R-R range does not appear to substantially affect $\updownarrow EDV/PSV$ in either AF or SR as it would be expected that a very short beat followed by a very long beat would give a high value for EDV/PSV, similarly a very long beat followed by a very short beat would be expected to give a low value for EDV/PSV. Two conclusions can be determined from these results and those of §5.6: the variation in volume in SR is insufficient to cause marked variation in EDV/PSV and the pattern of beat change as described by *swing* and *SampEn*, is more significant than the extent of beat change. This can be understood by considering that if the longest beats are never preceded or followed by the shortest beats the variation in PSV or EDV will never be maximised resulting in a reduced $\updownarrow EDV/PSV$.

6.6. *PSV*

Investigation of Figures 6.1 to 6.4 finds that in both AF and SR there are no indices of rhythm which show even a moderate correlation with either PSV or $\updownarrow PSV$ (as described by the SD) although there are several for which $\rho > 0.2$.

When considering mean PSV the most significant correlations are with mean R-R, SDRR, RMSSD and *SampEn* (negative) in AF while in SR the most significant descriptors are mean R-R, Poincaré correlation (negative) and *swing*. These results are generally in line with theory which would suggest that longer R-R intervals allow greater filling and that the more chaotic the rhythm (increased *SampEn*) the more blurred (and therefore reduced) the result. In SR a higher Poincaré correlation generally suggests a poorer R-R variability, which is associated with reduced function.

In terms of $\updownarrow PSV$, the most significant correlation in SR is with mean R-R intervals while in AF it is with RMSSD and SDRR. None of these offer a clear set of indices against which multivariate regression can be performed. A model which includes mean R-R, SDRR, swing and *SampEn* was investigated against $log(PSV)$ which has been shown to be more closely normally distributed.

$$\mathbf{log(}\boldsymbol{PSV}\mathbf{)} \sim \boldsymbol{mean\_RR} * \boldsymbol{swing} * \boldsymbol{SampEn} * \boldsymbol{SDRR}$$

This model gives only moderate correlation $R^2 = 0.144. R = 0.379$ ($R^2 = 0.133, R = 0.365$ after successive reduction) in AF and $R^2 = 0.109, R = 0.33$ ($R^2 = 0.079, R = 0.281$ after successive reduction) in SR. In the reduction in SR the *swing* term falls out of the model in all but the complete interaction term.

These results suggest that while PSV has been shown to vary significantly with beat selection criteria (§5.5) the variation is poorly explained by indices of rhythm.

6.7. Systolic time

In both SR and AF there is a strong correlation between systolic time interval and mean R-R. While there is also a strong correlation with RMSSD in SR, the correlation is only moderate in AF. The correlation between mean R-R and systolic time is to be expected as systolic time is a component of the R-R interval. The relationship between systolic time and RMSSD is less clear, suggesting that the greater the variability between beats the longer the systolic time interval. This may reflect pathology (shorter beats producing less output) or it may be a statistical error resulting from the inclusion of longer beats.

The range of systolic time (⇳systole) correlates poorly with all measures of R-R variability in both AF and SR with the best agreement being with R-R range in AF and with mean R-R, *SampEn*, *compactness factor* and RMSSD in SR.

This suggests a multivariate regression model in which $\Updownarrow \boldsymbol{systole} \sim \boldsymbol{mean\_RR} * \boldsymbol{SampEn} * \boldsymbol{compactness} * \boldsymbol{RR\_range}$

In AF this gives $R^2 = 0.158, R = 0.397$ ($R^2 = 0.147, R = 0.383$ after successive reduction). In SR, $R^2 = 0.144, R = 0.379$ ($R^2 = 0.119, R = 0.344$ after successive reduction).

These results suggest that the rhythm indices chosen describe systolic time variation only moderately well.

6.8. FTFF

Mean FTFF shows strong correlation in both AF and SR with mean R-R interval and RMSSD. In AF there is also a strong correlation with SDRR although the correlation is only moderate in SR.

⇳FTFF in SR shows a weak correlation with *ShanEnt* and *SampEn* and with swing, but otherwise does not correlate with any of the other functional measures. In AF, however, there is moderate correlation between the variation in ⇳FTFF and RMSSD, SDRR, R-R range and pRR50.

It is difficult to see how these can be combined in a multivariate model which describes both AF and SR and although several models were tried they did not substantially add to the description of variation of FTFF in either SR (where $R^2 = 0.05, R = 0.22$) or AF where the model: $\Updownarrow \boldsymbol{FTFF} \sim \boldsymbol{RR\_range} * \boldsymbol{SDRR} * \boldsymbol{pRR50} * \boldsymbol{RMSSD}$
gave $R^2 = 0.157, R = 0.396$ ($p < 0.00001$). Successive reduction could not improve these results.

The inconsistency of these results in AF and SR suggests, as has been discussed previously, that FTFF in the context of AF (or SR if there are ectopic beats) is methodologically flawed.

6.9. PFR

PFR correlates moderately well with age and mean R-R interval in AF, but not in SR where there is better correlation with entropy, *swing* (negative) and Poincaré correlation. ⇳PFR correlates only poorly with any of the indices of rhythm in AF, although there is moderate correlation between ⇳PFR and *SampEn*, *swing* (negative) and Poincaré correlation in SR.

As with FTFF, no consistent multivariate regression model could be found that described ⇳PFR in both SR and AF. In AF, no model could be found that added to the description of the variation. In SR the model:

$$\Updownarrow PFR \sim swing * SampEn * correlation * RMSSD$$

found $R^2 = 0.235, R = 0.484$ ($R^2 = 0.226, R = 0.475$).

This suggests that the measurement of PFR in AF may be flawed as there is no clear descriptor for it, although the moderate correlation with age is unexpected and suggests there may be a valid physiological explanation for the measurements which are seen.

In SR the principal descriptors of ⇳PFR have been shown to be associated with beat-to-beat change, with generally more variable rhythms leading to higher PFR. This suggests that variability in PFR may be a marker of cardiac health, because in SR HRV has also been shown to be indicative of cardiac health.

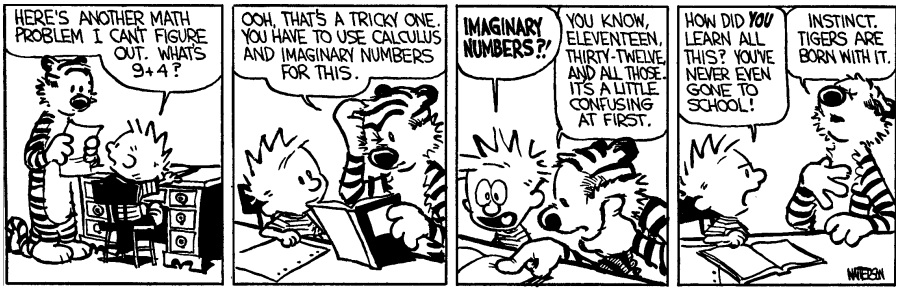
6.10. Going forward

A clear relationship between the functional parameters and patterns of beats (in this case sequences of just two beats) has been demonstrated in Chapter 5. In this chapter we have seen that overall indices of rhythm do not individually describe variations in the functional parameters that have been measured in this study. However in assessing variation in systolic parameters, combinations of rhythm descriptors - in particular *SampEn*, *swing*, mean R-R and the Poincaré correlation - have been shown to have much better predictive value than any single index alone.

These results will be brought together in the general discussion (Chapter 8). In order to put the measures in a clinical context, they have been investigated in a small clinical study. This will form the subject of the next chapter.

Chapter 7.

Clinical Application: AF Ablation



Summary

In which the AF ablation study is described together with the general results that were found. The study is used to assess any predictive potential of rhythm and functional measures investigated in this thesis, and to compare rhythm measures on a serial basis.

7.1. Introduction

It has been shown that there is a substantial variation in functional measures for patients in AF and that different methodological techniques can produce results which represent significant physiological change. These differences result from physical beat-to-beat variations in cardiac function which, although they are seen to a limited extent in SR, are particularly prevalent in AF. Patients in AF experience a variety of symptoms which

are, at least in part, a direct result of the beat-to-beat changes, but there a remains a question as to whether beat-to-beat changes are clinically significant. A second, related, question is: how is function best measured in patients with AF where functional measures appear to change so much?

The department of Nuclear Cardiology at Glasgow Royal Infirmary was involved in a study investigating the effect of radio-frequency ablation (RFA) in patients with persistent AF and advanced heart failure. This study offered the opportunity to apply the techniques which have been described in the rest of this thesis in a clinical context: a small series of patients in AF who were assessed pre and post randomised intervention.

7.2. AF ablation study

The AF ablation study, which has since been published by McDonald et al. [94], considered the response of patients to RFA. 41 patients were recruited to the study if despite optimal medical therapy they had New York Heart Association functional class II - IV, ongoing symptoms despite, $LVEF < 35\%$ (as measured using RNVG), and persistent AF. Patients were randomised to either RFA (22 patients) or medical therapy (19 patients). All patients had received optimal medical therapy for at least 3 months.

Patients randomised to medical therapy remained on optimal medical therapy; patients randomised and treated with RFA to isolate the pulmonary veins had isolation of all 4 veins, with additional ablation at sites of complex fractionated electrocardiograms. If after RFA the patient remained in AF, SR was restored by cardioversion. On follow-up (six months after the initial randomisation) if the patient had returned to AF a second RFA procedure was carried out and the patient had a final follow-up 3 months later (approximately 9 months after the initial baseline assessment).

The following assessments were made, in both groups of patients, at baseline and in the final visit: physical examination, 12 lead ECG, 24 hour ambulatory ECG, six minute walk test, and LVEF measured using both cardiovascular magnetic resonance imaging, CMRI, and RNVG. A change in LVEF by CMRI was defined as the primary end-point. The study was funded by the Office of the Chief Scientist, Scotland (grant number: CZB4475) and was given ethical approval by the West Glasgow Research Ethics Committee.

Intervention	No in group	Mean R-R pre (s)	Mean R-R post (s)	Mean LVEF pre (%)	Mean LVEF post (%)	No in SR post
Ablation	20	0.863	0.857	16.1	23.3	10
Medical therapy	17	0.848	0.886	19.6	21.04	0

Table 7.1.: AF ablation summary results for LVEF and rhythm calculated from RNVG.

7.2.1. Summary results

Table 7.1 shows the principal results (in terms of RNVG) for the two groups of patients. After six months (three months if a second RFA was required) 10 patients remained in SR. Post hoc analysis showed a significant increase in LVEF assessed by both CMRI and RNVG for those in SR. This improvement could be seen (using CMRI) as early as one week after RFA. In the remaining patients however, no significant change was found in LVEF by CMRI ($p = 0.6$) or in other factors (BNP, 6 minute walk and quality of life score) although an increase in LVEF [1] by RNVG was found to be significant ($p = 0.032$).

Unfortunately there was found to be a significant risk of complication, with one patient having a stroke, two patients developing cardiac tamponade and three patients developing worsening heart failure. With no change in the defined primary end-point of improved LVEF by CMRI (when *all* patients randomised to RFA were considered) and with a significant rate of complication it was concluded that RFA did not produce sufficient benefit for it to be considered in the future treatment of patients falling into this group.

7.3. Application to current study

The AF ablation study presents two groups of patients: those randomised to medical therapy for whom there was little further intervention and those randomised to RFA. These two groups offer the potential to investigate the serial reproducibility (in the group randomised to medical therapy) of measures both of rhythm and of function as well as the potential predictive value of these measures (in the group randomised to RFA).

The R-R interval stream and images formatted using all beats were available for further investigation but unfortunately a backup failure meant that 19 of the list-mode acquisitions for the patients in this study were lost, precluding some of the analysis.

[1] Measured using all beats

7.4. Rhythm measures

The indices of rhythm which have been considered in this thesis can be applied to the images acquired as part of the AF ablation study. In doing so they offer some insight into the way that rhythm changes, principally as a result of successful RFA, but also due to therapy and failed RFA. The serial nature of the study also offers some insight into the reproducibility of the indices.

7.4.1. Standard linear HRV measures

Comparing the main HRV measures: mean R-R, SDRR, $RMSSD_{rr}$, pRR50 and R-R range finds a substantial difference in those patients who went into and maintained SR as a result of RFA, but in the remainder of patients there was little change (see Table 7.2). Several of the patients who maintained SR, demonstrated a substantial increase in mean resting R-R to the extent that the SR group showed an average increase in resting R-R of 17%, although those patients on medical therapy, or who returned to AF after RFA, all showed a minimal, non-significant, change in mean resting R-R interval (0.7% and 3.5% respectively). The slowing of heart rate is an expected, and desirable, outcome of successful RFA.

A positive change was seen in SDRR for every patient who responded suggesting that a significant ($p = 0.004$) decrease in SDRR was seen. This is to be expected as there should be much less variation in SR. The change in the other groups was not significant. The same pattern was followed for RMSSD and pRR50. Slightly curiously, the same is not true for R-R range for which no change was seen in the patients who underwent RFA, although a slightly significant ($p = 0.041$) increase was seen in the R-R range of the patients who had medical therapy; however, this can be attributed to the inclusion of ectopic beats in the calculation of R-R range. When these were excluded (from both early and late acquisitions) no significant change was seen.

7.4.2. Poincaré measures

The R-R range for patients who maintained SR after RFA has been shown not to change significantly (§7.4.1). Review of the Poincaré plots for these patients demonstrates that

	All mean pre	Group mean pre	Group mean post	post - pre	p-value
Mean R-R	0.85	0.86	0.86	0.01	0.81
SDRR	0.24	0.21	0.25	0.04	0.09
RMSSD	0.34	0.40	0.35	0.05	0.17
pRR50	82.59	83.62	83.14	-0.47	0.66
R-R range	2.07	1.87	2.64	0.77	0.04
Swing	0.66	0.66	0.67	0.00	0.46
Compactness factor	9.54	10.62	11.87	1.25	0.54
Poincaré correlation	0.01	0.01	0.03	0.02	0.95
ShanEnt	3.33	3.33	3.38	0.05	0.73
SymDyn	3.71	3.79	3.70	-0.09	0.33
SampEn	3.54	3.76	3.50	-0.34	0.001

(a) Medical therapy (N=16)

	All mean pre	Group mean pre	Group mean post	post - pre	p-value
Mean R-R	0.85	0.90	0.86	-0.03	0.40
SDRR	0.24	0.26	0.24	-0.02	0.53
RMSSD	0.34	0.37	0.34	-0.03	0.48
pRR50	82.59	84.60	81.96	-2.64	0.16
R-R range	2.07	2.52	2.46	-0.06	0.95
Swing	0.66	0.67	0.66	-0.01	0.55
Compactness factor	9.54	11.67	11.55	-0.12	0.84
Poincaré correlation	0.01	-0.03	0.00	0.03	0.54
ShanEnt	3.33	3.43	3.27	-0.16	0.12
SymDyn	3.71	3.73	3.64	-0.08	0.80
SampEn	3.54	3.81	3.49	-0.31	0.30

(b) RFA (AF) (N=11)

	All mean pre	Group mean pre	Group mean post	post - pre	p-value
Mean R-R (%)	0.85	0.82	0.98	0.16 (17%)	0.16
SDRR (%)	0.24	0.29	0.12	-0.17	0.004
RMSSD (%)	0.34	0.40	0.17	-0.23	0.008
pRR50 (%)	82.59	79.53	26.04	-53.49	0.004
R-R range (s)	2.07	2.19	1.49	-0.69	0.50
Swing	0.66	0.67	0.72	0.05	0.16
Compactness factor (s^{-2})	9.54	6.07	1.53	-4.55	0.02
Poincaré correlation	0.01	0.06	0.15	0.09	0.65
ShanEnt	3.33	3.29	2.01	-1.28	0.004
SymDyn	3.71	3.56	2.45	-1.12	0.01
SampEn	3.54	3.16	1.51	-1.65	0.004

(c) RFA (SR) (N=8)

Table 7.2.: Mean rhythm indices pre and post intervention in the AF ablation study. Change (post - pre) in rhythm measures is given together with the p-value from a paired Wilcoxon test to compare the results pre and post. (The minor discrepancies are due to rounding errors in reporting values.)

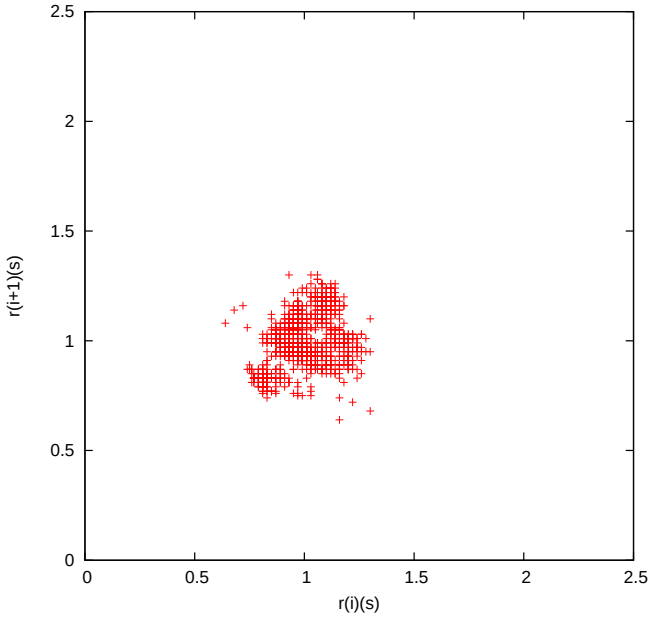
although patients are in SR their Poincaré plots are, except in one case, not typical of SR, having ectopic beats and other abnormalities of rhythm.

Three distinct patterns emerged: a single patient showed normal SR with a plot similar to that shown in Figure 3.7. Three patients showed plots with wide distributions (type I) such as that shown in Figure 7.1a, these plots show SR (it should be possible to define an ellipse which tightly encompasses the majority of beats) but the R-R range is substantial. Four patients showed plots similar to that shown in Figure 7.1b (type II) in which there appear to be many points of focus. The dominant R-R interval lies on the line of identity (in this example between about 0.8 s and 1.0 s) but the range of focus points suggest regular ectopic beats which are likely to have the same aetiology, although what that is cannot be defined from the Poincaré plot.

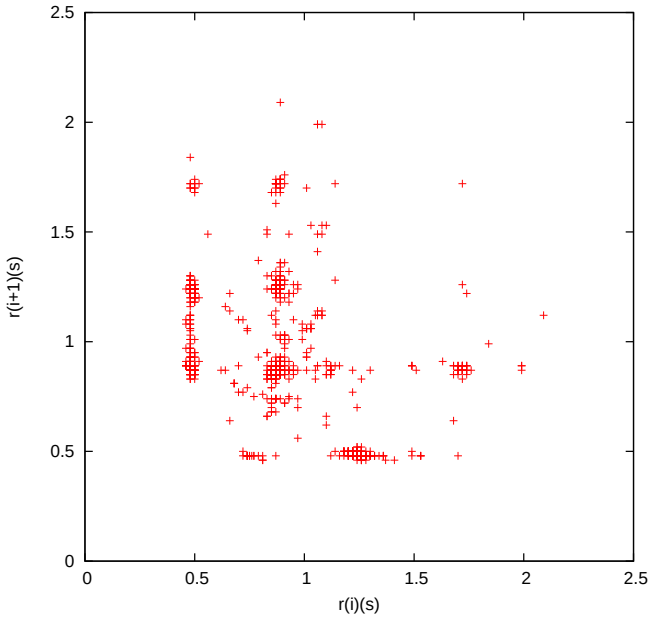
Several measures related to the Poincaré plot have been investigated in this thesis: *swing*, correlation and *compactness factor*. *Swing*, which measures the proportion of beat-to-beat changes which follow the "long-short-long" pattern, is found not to change significantly in any of the groups. Generally, although there is a difference between SR and AF in the population as a whole (see §3.3.3), there is no reason to expect that *swing* should change when a patient changes from AF to SR as a result of RFA; although the extent of the difference between a long beat and a short beat might be expected to be reduced. The small variation between successive measurements for each of the patients suggests that the measure is consistent.

Patients who maintained SR following RFA exhibited a significant decrease in *compactness factor*, although there was no significant difference in *compactness factor* in patients who were in AF at the end of the study. This change is to be expected as *compactness factor* measures are significantly different for patients in AF compared with SR (§3.3.2). Although there was significant decrease in *compactness factor* (suggesting that the Poincaré plot becomes more compact) the *compactness factor* for patients in SR after RFA was substantially greater than in the general SR population (6.4 /s^2 compared with 0.8 /s^2 in the SR population - see §3.3.2).

No significant change was seen in the Poincaré correlation coefficient for any of the groups, although variation in correlation coefficient was substantial and of the same order of magnitude as the correlation coefficient. This suggests that there is little consistency in this measure. See Figure 7.2.



(a) Type I



(b) Type II

Figure 7.1.: Typical examples of the two main types of Poincaré plot for patients in SR following RFA in AF ablation study.

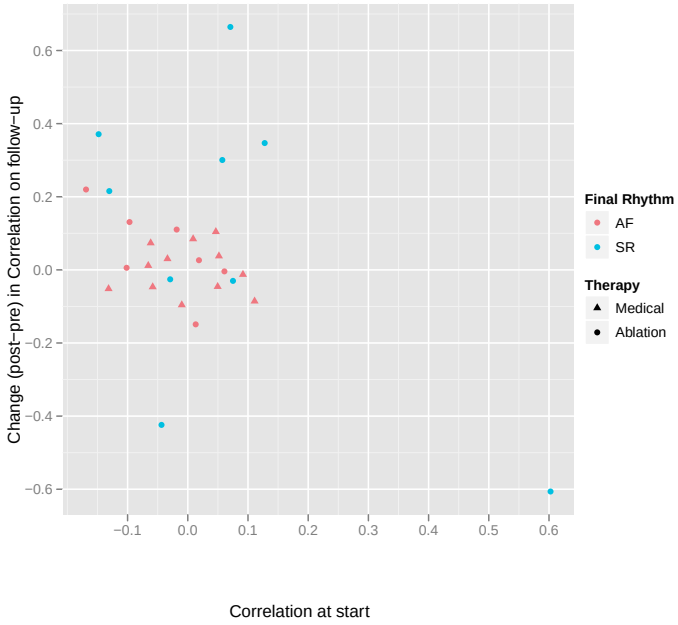


Figure 7.2.: Change in Poincaré correlation coefficient between a patient being accepted on the study and at follow-up (6 to 9 months later).

7.4.3. Entropy measures

Three different measures of entropy were investigated: Sample entropy, *SampEn*; Shannon entropy, *ShanEnt*; and entropy of symbolic dynamics, *SymDyn*. Of these the most important result was found in *SampEn*, this result can be seen in Figure 7.3. There is a clear separation, when considering the *SampEn before* intervention, between the majority of the responders (those patients who maintained SR after ablation) and the remainder of the patients. When the responders to RFA are compared with those who did not respond, a significant difference is found in the *SampEn* ($p = 0.042$). Mean *SampEn* at the start of the study in those patients who responded was 3.16 while in those patients who did not respond, but who did have RFA, the mean *SampEn* was 3.81. The minimum *SampEn* in the non-responders was 3.35 while in the responders it was 2.03. Although the full range of *SampEn* is present in the responders this is not true for the non-responders suggesting that if a patient has a *SampEn* of less than 3.3 they will maintain SR after RFA. This is a very small sample of patients and, while it is statistically significant, a result of this nature needs considerably more investigation. It is possible that in a larger patient sample there will not be such clear cut-off and

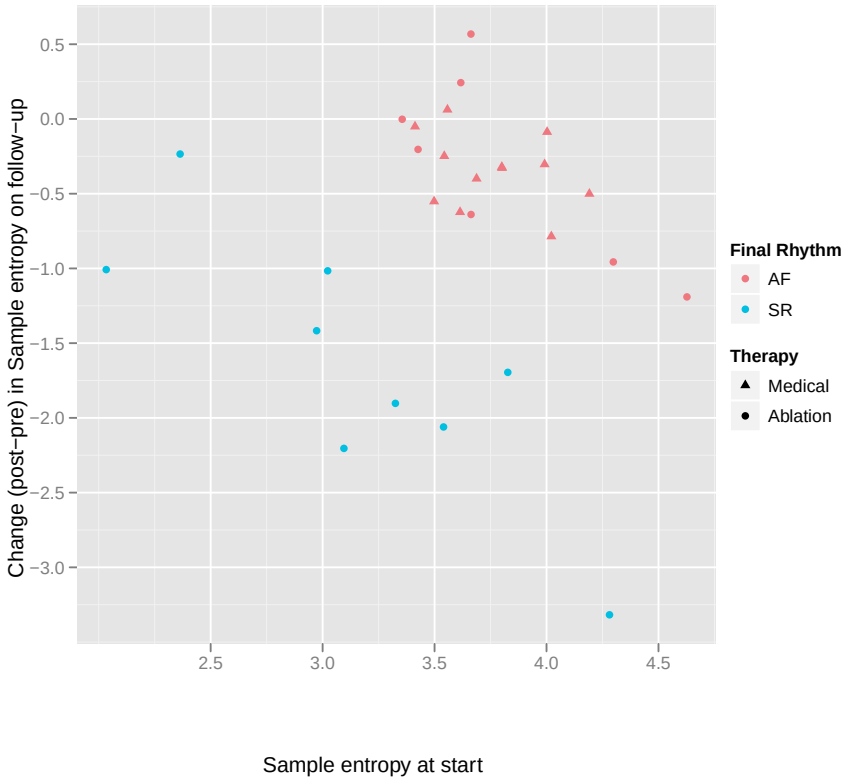


Figure 7.3.: Showing the effect of intervention (either medical therapy or ablation) on *SampEn* in the patients recruited to the AF ablation study.

that two overlapping ranges would be established which suggest a likelihood of a patient maintaining SR after RFA.

Apart from the clear separation of responders, Figure 7.3 also demonstrates that while there is a substantial change in most of the patients who maintained SR the change is much smaller in all the other patients although in each case the change is generally negative suggesting that *SampEn* improved even with medical therapy only.

The other measures of entropy (*ShanEnt* and *SymDyn*) showed a similar pattern of change to the more standard measures of rhythm (see Figure 7.4). *ShanEnt* demonstrated a significant decrease ($p = 0.004$) in those patients who responded to RFA but showed no significant change in the other patients (although there was a general trend towards decreasing entropy). This is in keeping with the lower entropy values which are associated with SR when compared with AF.

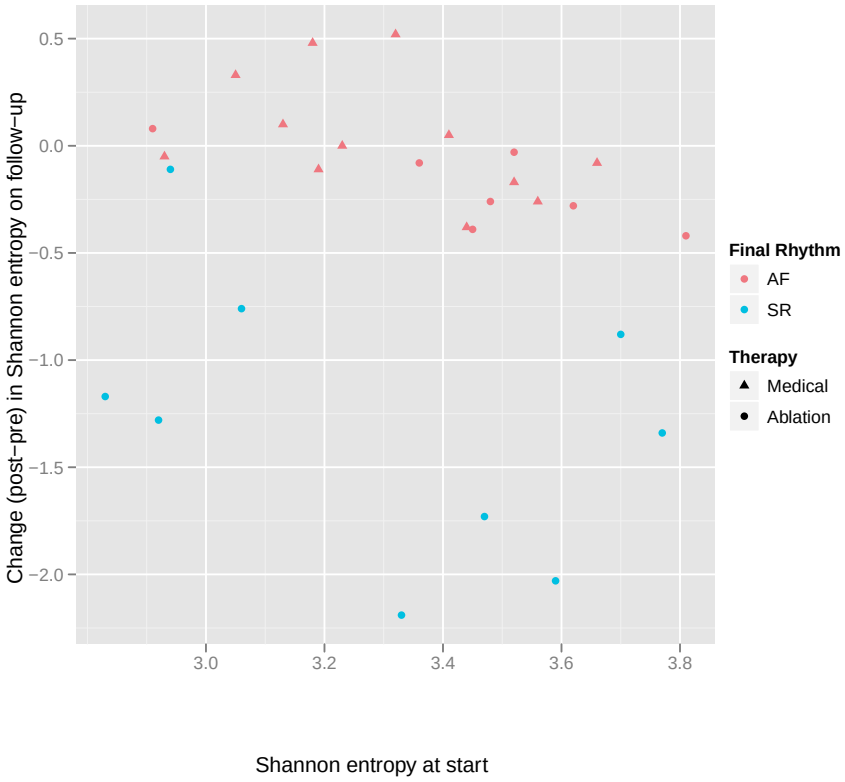


Figure 7.4.: Showing the effect of intervention (either medical therapy or ablation) on *ShanEnt* in the patients recruited to the AF ablation study.

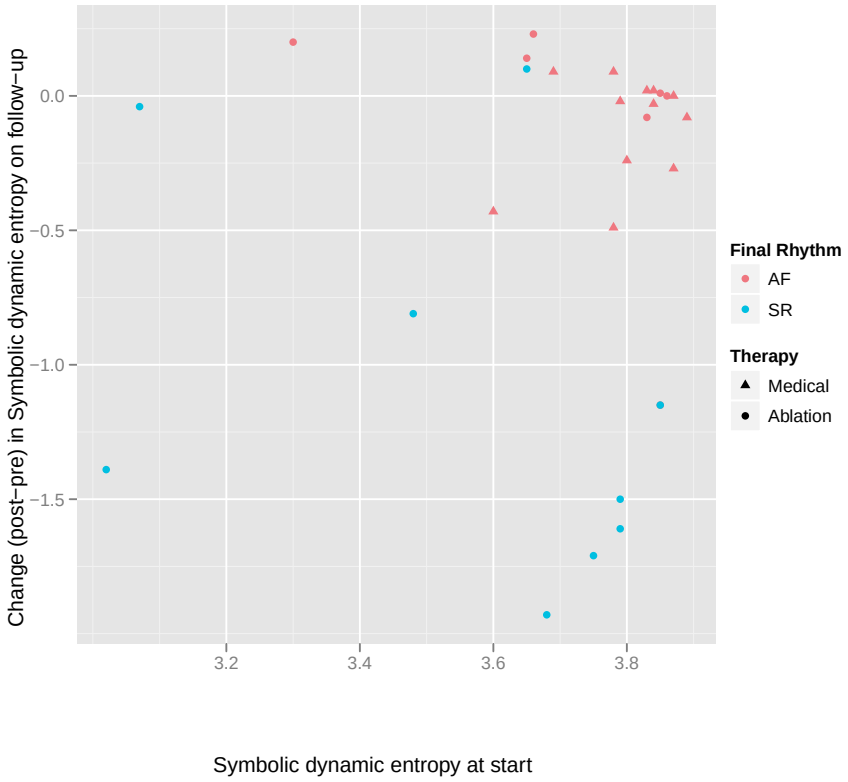


Figure 7.5.: Showing the effect of intervention (either medical therapy or ablation) on entropy of *SymDyn* in the patients recruited to the AF ablation study.

SymDyn, which like *SampEn* includes some information about beat sequence, suggests the potential for discriminating between patients who will respond to RFA. Mean *SymDyn* at the start of the study in the group who went on to have RFA was 3.56 in those patients who remained in SR and 3.73 in those patients who did not. However, this difference was not found to be statistically significant (see Figure 7.5).

A change in *SymDyn* that was considered statistically significant ($p = 0.01$) was found in those patients who changed from AF to SR as a result of RFA, but there was no difference for the other patients. A Bland-Altman style analysis [85] found no difference in the measures.

Table 7.3 shows, for each patient who responded to RFA, the change in *ShanEnt*, *SymDyn* and *SampEn* between the initial and final assessments. It can be seen that with one exception (*SymDyn* for patient 9) there was a decrease in all measures of entropy. While the different measures of entropy give substantially different values there is a general

Patient	Δ *ShanEnt*	Δ *SymDyn*	Δ *SampEn*
1	-1.28	-0.81	-1.01
2	-2.03	-1.93	-3.32
3	-1.17	-1.71	-1.42
4	-2.19	-1.39	-2.20
5	-1.34	-0.04	-1.90
6	-0.88	-1.50	-1.70
7	-1.73	-1.61	-2.06
8	-0.76	-1.15	-1.02
9	-0.11	0.10	-0.23

Table 7.3.: Change (post - pre) in *ShanEnt*, *SymDyn* and *SampEn* between initial and final assessments in those patients who responded to RFA and maintained SR.

tendency which suggests that they do measure a fundamental intrinsic characteristic of the rhythm.

7.5. Relationship to varying beat selection techniques

One of the principal aims of the AF ablation study is to restore, or at least improve, left ventricular function. It has been shown that there is a substantial variation in the assessment of ventricular function both in AF and SR. By applying the techniques which have been developed in the rest of this thesis it is hoped that further insight can be gained into the functional response of the ventricle to RFA.

There is a highly significant but very weak correlation between LVEF and beat selection criteria in AF (§5.4); although this relationship is very weak the variation in LVEF that can be measured on a per-patient basis is substantial. The analysis for the AF ablation study was performed before that of the current study had been completed, but with the knowledge that substantial variation existed in measured ejection fraction. It was assumed that the most reproducible assessment would be that which included all beats. This assumption has subsequently been shown to be true (§5.4.5).

The primary end-point of the AF ablation study was LVEF measured using CMRI. Unlike LVEF measured using RNVG this was not found to change significantly as a result of RFA. There are good methodological reasons for the lack of change seen using CMRI when compared with RNVG (see discussion §8.4.2) but are the variations which are seen using RNVG likely to be real? Any changes that are seen in patients who were in AF on follow-up should be minimal while changes seen patients who were in SR on follow-up should reflect the physiological change involved in correcting AF to SR.

In those patients who maintained SR it seems reasonable to expect that there should be a relationship between LVEF in SR and that in AF. The form of that relationship may offer some insight into myocardial health in AF. Several possibilities for this relationship exist.

1. The most likely relationship is that the LVEF for the patients in SR corresponds to the LVEF for the equivalent beats in AF. This would seem reasonable if it is considered that the SR beats define the "natural" beats in AF (i.e. the beats which would occur in the absence of AF).

2. A second possibility is that the maximum measurable LVEF in AF is related to the LVEF in SR. This would be reasonable if the maximum LVEF in AF defines "capability" of the myocardium: the functionally impaired myocardium, whatever the cause of impairment, will not be capable of achieving the same LVEF as a non-impaired heart. The effect of beat variation in AF may obscure function causing the two to appear functionally equivalent in AF.

3. A final possibility is that the variation in measured LVEF in AF is related to the change in LVEF when the patient changes to SR. This would be a reasonable explanation if the range of LVEF is indicative of myocardial tone: those patients with a greater range having better tone and as a result having better LVEF when SR is achieved.

Although only a few patients maintained SR, the AF ablation study offers the ability to compare functional measures in those patients who remained in AF (either post RFA or because they were treated with medical therapy). In those patients a comparison of the mean and range of measured LVEFs offers an insight into the consistency of measures.

Six different functional measures have been investigated in this thesis; of these only two, LVEF and EDV/PSV, have been investigated in this study. Four measures have not been included in the analysis. The two diastolic measures: peak filling rate (PFR) and first third filling fraction (FTFF), while they show substantial, significant variation with beat selection criteria in AF (see §5.9 and §5.8) are subject to such methodological error (discussed in more detail in §8.5.7) that it is unclear to what extent they can be used. Although there was substantial variation in systolic time, the variation was not shown to be significant with beat selection criteria and it has therefore not been included in this analysis as the source of variation is unclear. Pre-systolic volume has not been included simply because it would appear to offer little additional information over LVEF and EDV/PSV.

7.5.1. LVEF

Figure 7.6 compares LVEF at the start and on follow-up in the AF ablation study (medical therapy and RFA patients included). In the patients for whom data were not lost, mean LVEF in the group who remained in SR changed from 14% to 31% while in the rest of the group LVEF changed from 18% to 20%.

For those patients who remained in SR a comparison was made of the LVEF obtained in SR against that obtained in AF using beat selection criteria that would mimic the beat selection criteria required to include all the beats in the SR image. This offers only very limited insight. Unfortunately several list-mode files both at the start and on follow-up were lost before they could be re-analysed with the defined limits. This meant that four of the 10 patients could not be re-analysed. It was also found that in one patient changing from AF to SR slowed the heart rate to such an extent that there were no beats in AF which corresponded to those in SR and an image could not be formed. In several other cases the number of beats from AF which could be included was so low as to make the error due to the Poisson statistics of the image substantial. The results for the patients for whom an analysis was possible are shown in Table 7.4. The number of patients is too small for a statistical comparison but there is surprisingly good agreement between the LVEF in three out of five of the results; however, all of them are very limited by the number of beats which were included in AF. The conclusion is that the first suggestion as to the relationship between LVEF and rhythm (see list on page 281) cannot be valid because the mean R-R interval changes too greatly.

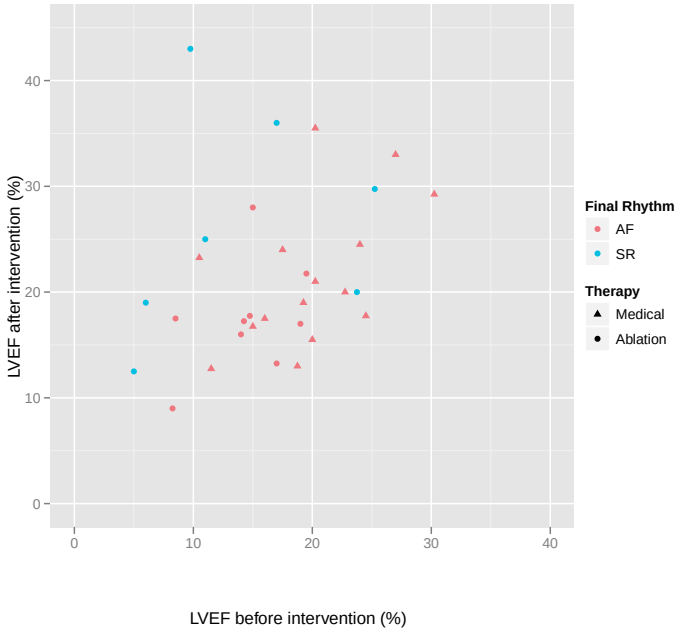


Figure 7.6.: Showing the relationship between LVEF at start and follow-up in AF ablation study (both medical therapy and ablation).

	AF Included beats	AF ED Counts	AF LVEF	SR LVEF
Patient 1	121	3066	29.7 ± 2.4	29.8
Patient 2	118	6801	15.1 ± 1.7	25.0
Patient 3	0	-	-	19.0
Patient 4	72	4980	10.3 ± 2.0	12.5
Patient 5	4	94	63.9 ± 13.7	59.5
Patient 6	634	34270	17.8 ± 0.7	36.0

Table 7.4.: Comparing LVEF obtained in SR with that obtained in AF when the same beat selection limits are applied in AF as would be required in SR to include all the SR beats.

Figure 7.7 shows the relationship between LVEF on follow-up, measured using all beats, and the maximum measured LVEF at the start of the trial. Since the majority of those patients who remained in SR lie above the line of equality it appears that the maximum LVEF (assessed using preceding and indexed quartiles in the beat selection criteria) underestimates the resulting LVEF. By comparison for those patients in AF the maximum preceding LVEF appears to overestimate the measured LVEF on follow-up. This, however, is to be expected if the overall functional capacity has not changed since LVEF, measured using all beats, is unlikely to supply the maximum LVEF (see Figure 5.13 in §5.4). A paired Wilcoxon which compares the rank of measures rather than the measures themselves suggests that there is no significant difference between the rank of the maximum LVEF in AF and that of the LVEF measured in SR. By contrast the patients who remain in AF are found to have significantly different maximum LVEF ranks ($p = 0.0002$) at the start compared to the LVEF measured using all beats on follow-up[2]. This suggests that the maximum does have a predictive value in those patients who maintained SR; however, here too the numbers are too small to offer conclusive proof and, while there appears to be a strong correlation in SR, it is not statistically significant.

The relationship between the range of LVEFs measured on any patient at the start of the study and the change in LVEF between the start and follow-up is shown in Figure 7.8. Here again there appears to be a positive relationship for patients who maintain SR: patients with a smaller range of measured LVEFs at the start of the study (in AF) generally appear to have a smaller change. This is confirmed by the Wilcoxon analysis which finds no difference between the ranks of LVEF range before the study and LVEF change for patients in SR. By contrast the group of patients still in AF at the end of the study is found to have a range of LVEF the ranks of which are significantly different from the ranks of the change in LVEF ($p = 0.00006$).

The general agreement between the results of Figure 7.8 and those of the previous Figure (7.7) is not unexpected. If the range of LVEF is indicative of tone then it is not surprising that the maximum LVEF is also indicative of tone and therefore of the resulting LVEF when the patient returns to SR.

A comparison of measured LVEF range and mean LVEF has been made for those patients who remained in AF. No significant difference was found in either the ranges or the means, $p = 0.98$ and $p = 0.74$ respectively (see Figures 7.9 and 7.10). This is particularly

[2]The use of the statistical test here has changed. Instead of looking for differences we are looking for similarities. Similarities, or high correlation, suggest that an index has predictive value.

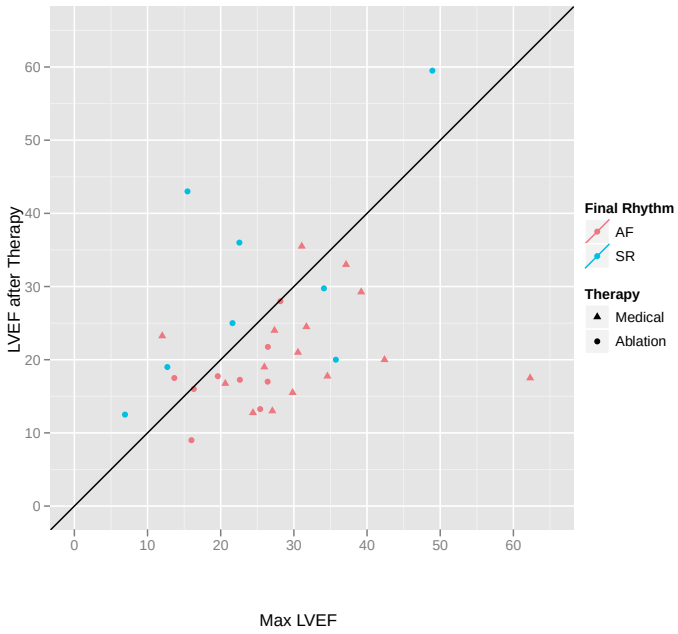


Figure 7.7.: Shows the relationship between the maximum measured LVEF before the start of the AF ablation trial and the resulting LVEF on follow-up. The diagonal line shows the line of equality.

interesting because the ranges do not vary significantly which suggests that the variation in range is not simply methodological but has its roots in a well defined physiology.

7.5.2. *EDV/PSV*

EDV/PSV, the fractional change between pre-systolic and end-diastolic volume has been shown to be well correlated with beat selection criteria in AF. The variation of this is indicative of the degree to which diastole is "interrupted": a shorter beat will produce a lower filling volume and vice versa. When all beats are averaged together it is to be expected that the pre-systolic and end-diastolic volumes should be equal. This suggests that deviations from a value of 1.00 may be indicative of the degree to which filling is foreshortened and hence of the degree of beat-to-beat variation. Consequently it is possible that there is a relationship between function in SR (assessed by LVEF) and EDV/PSV in AF.

Figure 7.11 shows the relationship between mean EDV/PSV at the start of the study and LVEF on follow up. There does not appear to be any relationship between the

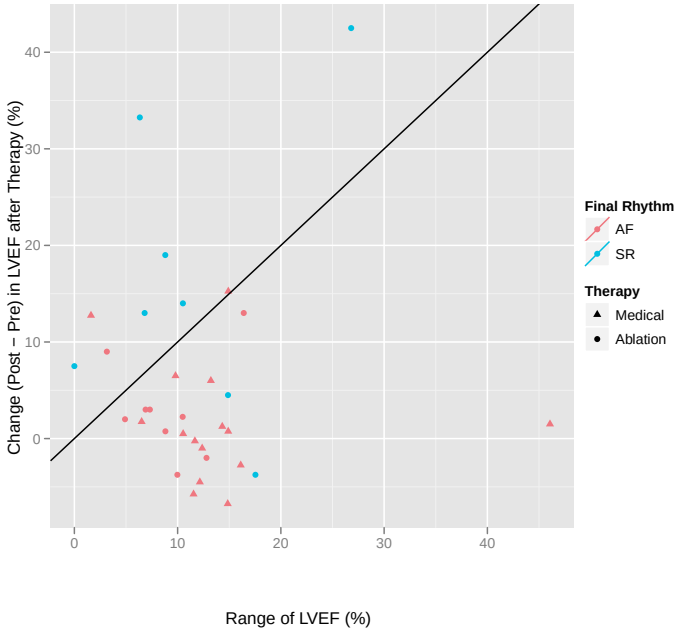


Figure 7.8.: Showing the change (post - pre) of LVEF between initial investigation and follow-up as a function of the measured range of LVEFs for patients in the AF ablation study.

.

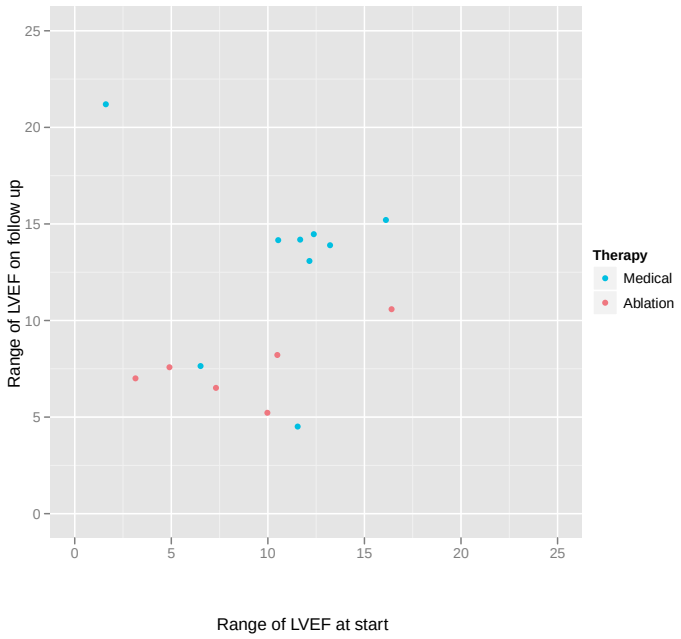


Figure 7.9.: Showing the range of LVEF at the start and on follow-up for patients who remained in AF on follow-up in the AF ablation study.

.

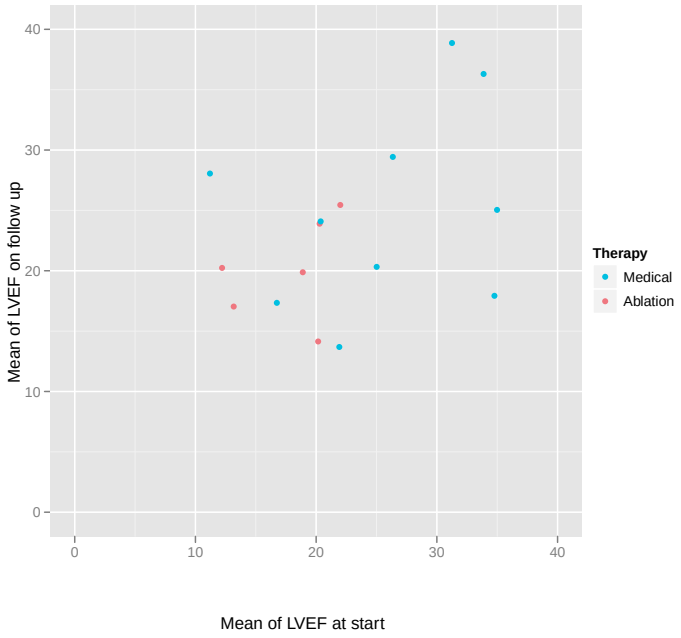


Figure 7.10.: Showing the mean of LVEF at the start and on follow-up for patients who remained in AF on follow-up in the AF ablation study.

.

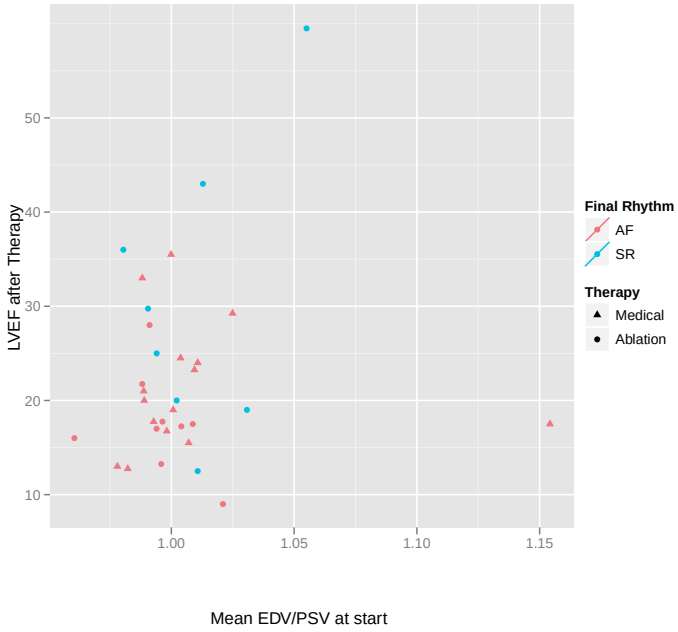


Figure 7.11.: Showing the relationship between EDV/PSV at start and LVEF on follow-up in the AF ablation study.

.

indices. This is confirmed by the paired Wilcoxon which finds the ranks of the indices to be significantly different in both those patients in AF and those in SR at follow-up.

When the range of measured EDV/PSV is compared with the change in LVEF (see Figure 7.12) there is no relationship found in those patients in SR at follow-up (paired Wilcoxon finds the two groups to be different), but there does appear to be a weak relationship in the group who remained in AF, substantiated by the paired Wilcoxon ($p = 0.17$). This is likely to be a reflection of the weak relationship that exists between EDV/PSV and LVEF in general (see §5.10).

When the means and ranges of EDV/PSV are compared for those patients who remained in AF only, a paired Wilcoxon finds no significant difference between the groups although visually they appear quite different (see Figures 7.13 and 7.14).

These results for EDV/PSV again corroborate the theory that this is a genuine index with repeatable measures, but it is not at all clear that the index has any clinical significance.

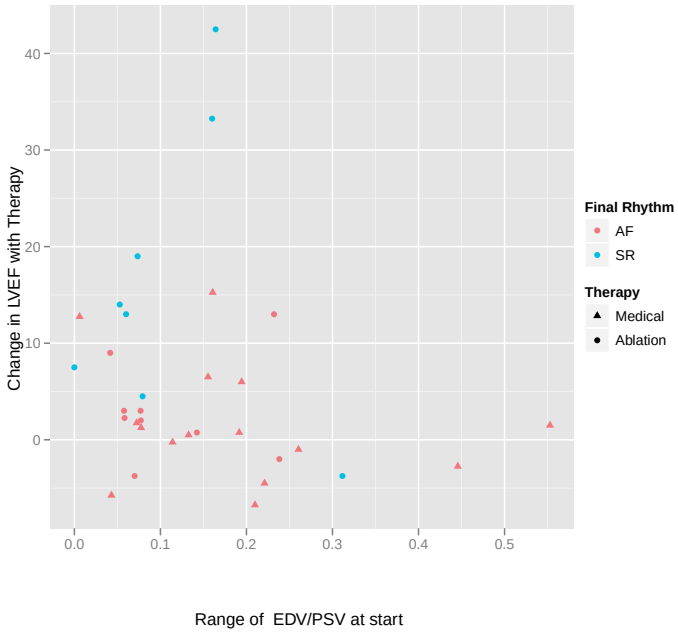


Figure 7.12.: Showing the initial range of EDV/PSV compared with change in LVEF on follow up in patients in the AF ablation study.

.

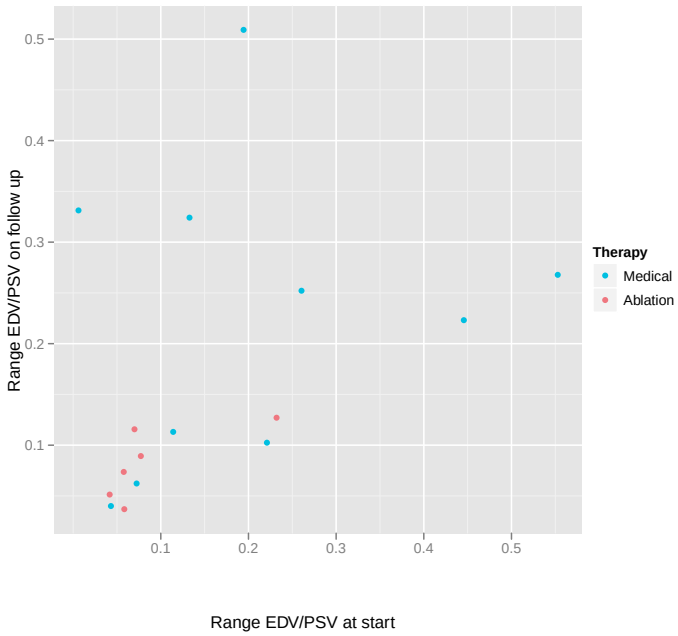


Figure 7.13.: Showing the range of EDV/PSV at the start compared with follow-up for patients who remained in AF on follow-up in the AF ablation study.

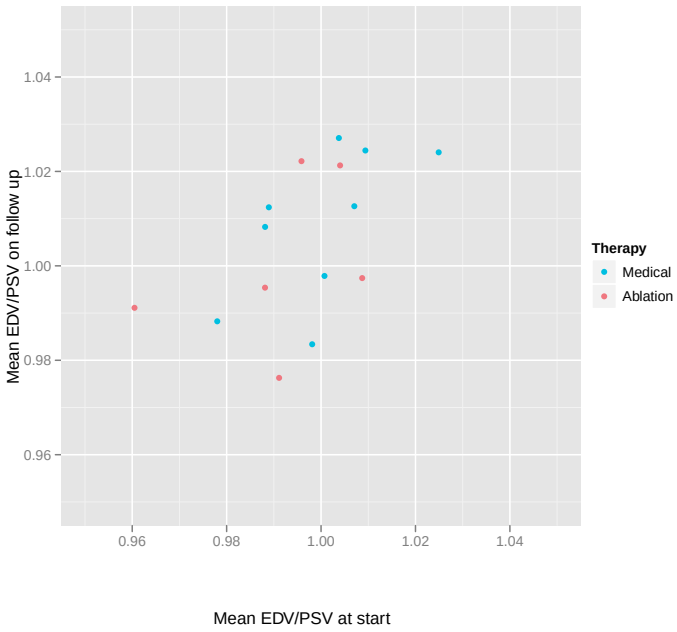


Figure 7.14.: Showing the mean of EDV/PSV at the start and on follow-up for patients who remained in AF on follow-up in the AF ablation study. To aid visualisation this plot excludes one point, at (1.151, 1.023), which has been included in the analysis.

.

7.6. Discussion

The investigation of the behaviour of the indices of rhythm and function, which have been employed in the rest of this thesis, in the context of the AF ablation study has had two purposes: (1) to investigate whether there is consistency in the measures on a serial basis, and (2) to determine whether there is any predictive value in the measures in terms of the response of a patient to RFA. This might be expected if indices of rhythm or function (particularly LVEF) are indicative of an underlying pathology beyond AF.

The AF ablation study offered a convenient means of testing these, but there are two substantial problems associated with the data: the time lapse between RFA and follow-up, and the poor response which this particular group of patients (heart failure: NYHA class II and above) had to RFA. The study when it was originally devised expected a 10% drop out and an 80% success rate after two ablations. The number of patients included in the AF ablation study was designed to have an 80% power to detect a change in ejection fraction of 6.8% between the two groups. This was based on several studies [25, 95–98] which exhibited a success rate, in maintaining SR, of $> 78\%$. Unfortunately the success rate in this group of patients was considerably lower than that (50%) and this has resulted in the statistical value being considerably reduced.

The serial comparison of indices in those patients who did not respond to RFA, or who were treated with medical therapy showed in almost all cases (with the possible exception of *compactness factor*) that there is good reproducibility of results, despite the substantial difference (up to 9 months) in time between the initial investigation and follow-up during which patients underwent medical therapy and in some cases two ablation procedures.

There has been little reported work on factors which may be prognostic of the success of RFA. A study by Richter et al. [99] suggested that patients were unlikely to return to AF in the long term if, in the short term, AF could not be induced immediately after RFA using decremental atrial stimulation from the proximal coronary sinus. No other prognostic studies have been found, and Richter's study still requires that the patient undergo RFA. If an index indicative of the success of RFA could be found, the associated risks might be substantially alleviated.

These investigations suggest that patients with a lower $SampEn$ (< 3.3, calculated using parameters of $m = 1$ and $r = 0.02SD$), are likely to remain in SR after RFA. It is also

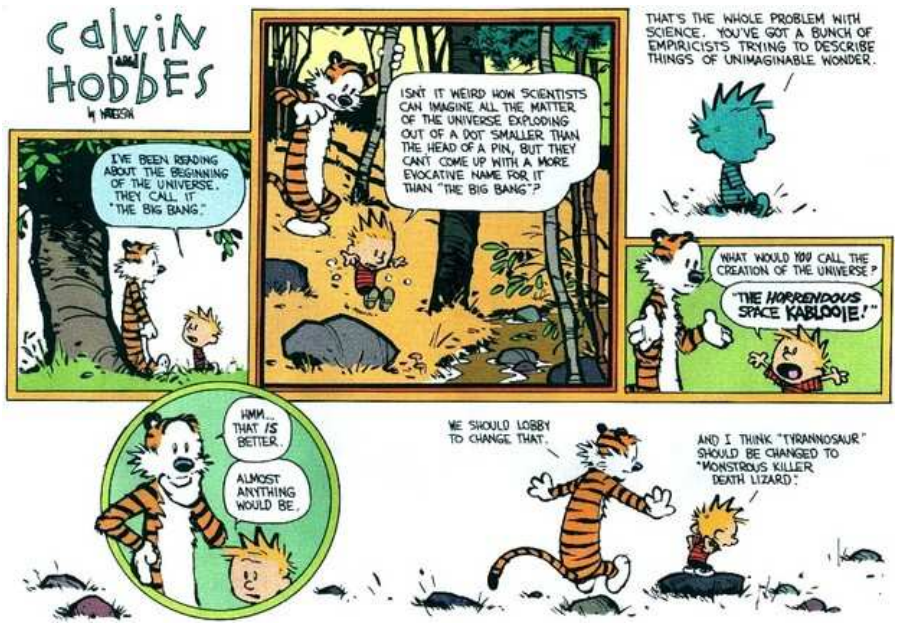
possible that the range of LVEF measured using different beat selection criteria may be indicative of the change in LVEF that may be induced in patients who maintain SR following RFA. However, although these results have been found to be statistically significant, the very small numbers of patients involved requires that considerably more investigation is undertaken.

7.7. Conclusion

While much of the discussion in this thesis has been essentially esoteric in nature, the potential for some of these results (most notably those for *SampEn* and the range of LVEF) to have prognostic value in RFA demonstrates the potential clinical value of such indices and suggests areas for future investigation. These will be discussed further in the next and final chapters.

Chapter 8.

Discussion



Summary

In which we discuss the general results of the thesis. Initially the results of the investigation into the analysis of rhythm are discussed. A brief section addressing some of the more controversial aspects of the RNVG technique follows. It is shown how the functional results can be generalised to other modalities before the functional results are discussed. The chapter finishes with a discussion of some of the limitations of the study.

8.1. Introduction

In Chapter 1 (§1.7) six hypotheses were presented. Hypotheses 1 to 3 (Page 36) are associated with the effect that variation in beat-to-beat interval duration has on beat-to-beat functional assessment. Hypotheses 4 to 6 are involved with describing rhythm and the associations between the description and the beat-to-variation in function. These hypotheses can be summarised as:

1. Irregular fluctuations in cardiac rhythm are reflected in associated variations in beat-to-beat function.
2. These fluctuations and changes are measurable and to some extent predictable.
3. These changes will be seen in both AF and SR.

In the subsequent chapters, three areas were investigated: the form of beat-to-beat variation in both SR and AF; the variation that can be seen in functional parameters with differing beat selection criteria using list-mode acquired RNVG; and the relationship between these parameters of rhythm and function. This chapter will consider some of the implications of the results.

8.2. Describing AF

AF is poorly described. Most clinicians when presented with a patient in SR would report the heart rate in beats per minute, equivalent to the mean R-R interval. When presented with a patient in AF a mean heart rate might be reported with the caveat that the rhythm is irregular. Beyond mean heart rate however, while heart rate variability has been extensively investigated in SR [27, 100, 101] there has been little work done in AF; it is generally simply described as “irregularly irregular”.

While some work has been done on understanding atrial electrical activity in AF from ECG [102] and using invasive measurements [103], most characterisation of ventricular response in AF has actually focused on assessment of ECG during SR in patients either with paroxysmal AF or after cardioversion. In such studies rhythm measures have been shown to be predictive of a return to AF after cardioversion (using spectral analysis of

HRV [32]) and of entropy if the patient returns to AF (using standard temporal HRV measures [78]).

In this thesis, three major branches of investigation have been pursued in an attempt to provide an insight into the assessment of rhythm in AF. They are: conventional linear measures of heart rate variability, descriptors of the Poincaré plot, and assessment of entropy. While the standard linear measures of HRV describe point to point changes, the indices based on the Poincaré plot offer global insight and the entropy measures detail the regularity of the rhythm.

The different levels of description are perhaps better explained with an example. Consider two rhythms: the first consists of a pattern of beats in which a beat of length a is followed by a beat of length b followed by a and so on in the sequence: $a, b, a, b, a, b \ldots$. The second rhythm consists of a steadily decreasing sequence e.g. $1.50, 1.49, 1.48, 1.47 \ldots$. Depending on the values of a and b, the two sequences may be indistinguishable in mean and SD. RMSSD values are likely to be substantially different: in the first sequence RMSSD will be the same as the SD, in the second sequence RMSSD will be 0.01. There need not be any difference between the sequences in terms of pRR50 unless a and b differ by more than 50 ms. The RR ranges will differ. These conventional linear indices of rhythm give an insight into the immediate, point to point, variability but provide no information about the global changes. The Poincaré plot for the first sequence will show two single points while the plot for the second sequence will show a straight line: clearly demonstrating the global change. Entropy in the the first instance will be small as there is good regularity, in the second instance, although the changes are not complex, entropy will be very high as the state is continuously changing without ever repeating.

Although each of these will form part of a complete description of rhythm we will consider each of them in turn.

8.2.1. Linear indices of HRV

With the exception of mean R-R interval, the traditional linear measures of HRV showed a clear distinction between SR and AF (§3.2). This is to be expected as the beat-to-beat variation in AF is substantially greater than that in SR, although the form (complexity and regularity) of the changes is not made clear by these results.

Although overlap in the histograms of mean RR for SR and AF is almost total (Figure 3.1 on Page 75), the mean RR interval was found to be significantly different in AF (0.84 ± 0.34 s) from SR (0.89 ± 0.30 s). There were very few criteria applied in selecting patients, and while in some cases this could be detrimental to the study it meant that a large patient sample could be studied (see §8.7). None of the patients in AF were new onset and therefore all of them were on some form of rate control. One of the aims of rate control is to reduce the ventricular rate to something which is more comparable to SR and, although significant differences were found, the rates are comparable.

The literature on heart rate variability is extensive and HRV has been shown to be a strong marker of autonomic nervous activity in SR [27, 28, 31, 45] but very little work has been done on AF. In this thesis linear HRV measures have been considered not for their use as a potential marker of underlying pathology but as descriptors of rhythm which could be used to explain functional variation. In this respect, mean RR and SDRR, in particular, have been shown to be significant contributors to models of functional variation (see §6.4 and the following sections in Chapter 6).

8.2.2. Poincaré assessment

The Poincaré plot offers a useful visual means of assessing rhythm and, since using it in this study, it has been adopted in the department of Nuclear Cardiology at Glasgow Royal Infirmary for use with patients with unusual rhythms. Where a larger number of beats is available (typically collected over several hours) the histographic (or 3D) Poincaré plot may be of more use in assessing rhythmic variation and it has been used in qualitative and quantitative assessments in several studies [104–106].

Van den Berg et al. [42] found that where there was clustering in the Poincaré plot from a 24 hour Holter recording, the patient was considerably more likely to be restored to SR using electrical cardioversion. They calculated a clustering index based on determining the number of peaks in a 3D (histographic) Poincaré plot using a 25 ms grid. A similar technique could be used in this study although there is a question as to whether a 15 min acquisition would be sufficient to show clustering in the Poincaré plot of a patient in AF.

It would be of interest to investigate how the clustering, which was seen in some of those patients who maintained SR after RFA (§7.4.2), compares with possible clustering in the Poincaré plot in AF. However, to do so with accuracy would require a longer acquisition

period than was used in this study where patients typically had $\sim$ 1500 points in a plot, spread out over the entire area.

Poincaré descriptors

As discussed in the introduction (§1.3.2), many different indices have been used to describe the Poincaré plot. In this study two indices were considered: correlation and *compactness factor*. In theory correlation would appear to be a good measure since it is to be expected that in SR there should be a better match between successive beats than in AF; however, while the correlation coefficient demonstrates the poor relationship between successive beats in AF (values for r clustering around 0) many of the patients in SR had a similar poor agreement. Considering only those patients with no ectopic beats made no difference. This suggests that in SR the variation between beats may be just as, if not more, random than it is in AF; RR intervals are simply more tightly constrained.

The newly proposed measure of *compactness factor* clearly distinguishes between AF and SR although reproducibility when compared sequentially in the AF ablation study is only of the order of ($\sim$ 10%) (see §7.4.2), suggesting that it may only offer an insight into rhythm on a fairly coarse scale.

8.2.3. Entropy

The three calculations of entropy which have been considered involve increasing detail of sequencing information. Although each calculation forms a family of indices, this study has shown that there are substantial differences between measures of entropy and, particularly in AF, only a poor correlation between most of them (see Figure 3.30 on Page 116), although there are measures that correlate well (e.g. *ShanEnt* with 10 ms bins and *SampEn* with $r = 0.02SD$ and $m = 0$ or 1).

It is not surprising that there is such a substantial variation in the correlation of measured entropies. At the extremes of measurement it would be possible to make selections for the different parameters that result in wildly different results. For example if *ShanEnt* were calculated from a histogram in which the bin-width incorporated all the beats the entropy would be 0, while it would be high if the bin-width matched the temporal resolution of the acquisition. Similarly with *SampEn* it should be possible to make

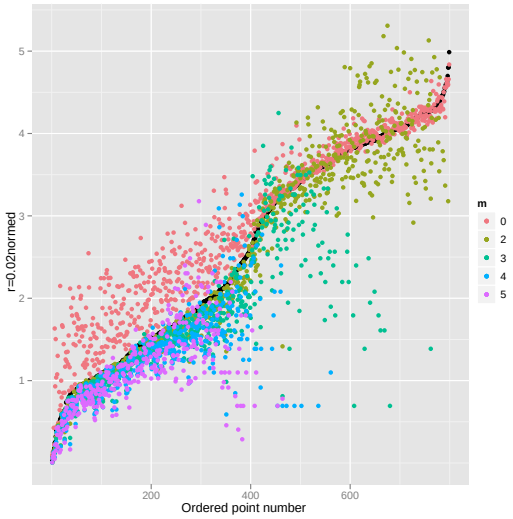


Figure 8.1.: Showing the values of *SampEn* with $r = 0.02SD$ and changing m. The points are plotted against the sorted position of the values for $m = 1$ with the black dots showing the changes for $m = 1$. Patients in both SR and AF included as a single group.

selections of m and r which gave minimal entropy ($E_s = 0$) or near maximal entropies for all studies. Inevitably many of the members of the different families will not correlate with each other or with members of other families. This is illustrated in Figure 8.1 where changes in *SampEn* can be seen as m changes. If there was good agreement between the results they would roughly parallel each other because rankings would be approximately the same. Instead, they can be seen to cluster in different areas of the plot.

Although no guidelines exist for establishing the metrics, m and r for *SampEn*, the choice of $r = 0.02(SD)$ and $m = 1$ contradicts that used in most studies. Chua et al. [107] compared both *SampEn* and *ApEn* to compare various rhythms including AF and different forms of SR. They used values of $m = 2$ and $r = 0.15SD$ for calculation of both forms of entropy and found that in comparison to normal SR, patients in AF had a *lower* entropy by both *ApEn* and *SampEn*. Although these exact parameters were not calculated in SR and AF, values of $r = 0.2SD$ and $m = 1$ were considered and found that AF had a higher entropy than SR. Chua et al. argued that their result indicated an inherent periodicity in AF. Although no measures of entropy in the study presented here were found to present a higher value for SR than AF, other measures (particularly *swing*) suggest that on some scale there may be a periodicity which is seen in AF but not in SR. Lake et al. [59] suggested a semi-quantitative method for determining r and m which led them in their study of neonates in SR to use values of $m = 3$ and $r = 0.2SD$. The

problem with their solution is that it is dependent on the population being measured and in the case of the current study the inclusion of two rhythms (AF and SR) in the population would result in a choice of metrics which could not distinguish between the rhythms. Pincus [50, 57] used values of $1 \leq m \leq 3$ and $0.1SD \leq r \leq 0.25SD$ in his initial introduction of *ApEn*, and also in an investigation of neonates in SR. In AF, Alcaraz et al. [108] found that a choice of $m = 2$ and $r = 0.25SD$ gave optimal results although how they defined what the optimal results should be is not clear. Segerson et al. [78] chose to use $m = 2$ and an unnormalised value of $r = 0.043$ s.

In none of the above studies was a selection of $r < 0.1SD$ chosen. While the choice of $r = 0.02SD$ in this study was originally a misunderstanding on the part of the investigators it leads to an index which distinguishes well between AF and SR, with a comparatively wide range of measures within each rhythm type (which is to be expected given that all patients, regardless of their state of cardiac health were included). It has good reproducibility, clinical value (§7.4.3), and correlates well with *ShanEnt* suggesting that these metrics do not produce random results. The choice of $r = 0.02SD$ means that the window on each R-R interval is so small as to be negligible and therefore that *SampEn*, with $m = 1$, reflects repeating patterns of two beats *of the same length* throughout the R-R interval stream.

There appears to be poor agreement between *SymDyn* and *SampEn* particularly in AF. In SR there is generally moderate or good agreement between the measures (Figure 3.29 on Page 115) but in most cases in AF this agreement is lost (Figure 3.30). This is simply a reflection of the metrics and the fact that *SymDyn* is a coarse graining tool which reflects gross changes without subtlety. Even in AF, however, the agreement is good where the measures compare similar metrics with $r = 1SD$ and $m = 1$ or $m = 2$ for *SampEn* and for *SymDyn* where word length is 2. This is to be expected since a word length of 2 corresponds to $m = 1$ and *SymDyn* divisions are fixed on a number of SDs. The measures are not exactly the same because in *SampEn* the window position shifts with the beat being investigated while in *SymDyn* the window has a fixed position.

Interpretation of entropy

To determine the physiological meaning of entropy it is necessary to look beyond this study. Palazzolo et al. [53] suggested that in dogs in SR, entropy (*ApEn* and *SymDyn*) reflects parasympathetic modulation of heart rate. Segerson et al. [78] found that

in patients with paroxysmal AF the inter-beat correlation coefficient (ICC), which is equivalent to the *Poincaré correlation* index in this study, correlated closely with *ApEn* when the patients were in AF. ICC is known to reflect parasympathetic function in SR and Segerson et al. suggest therefore that entropy during AF may be an indicator of autonomic function.

This study found only a weak negative correlation ($\rho = -0.21$) between *SampEn* and *Poincaré correlation* in this group of patients and while there is a moderate positive correlation of Poincaré correlation with LVEF in SR there is only a poor, negative correlation in AF (§6.4 on Page 263). Despite this it is likely that entropy does provide an assessment of autonomic function: entropy assesses the complexity of the variation in R-R interval and it must therefore be an indicator of the ability of the AV node to bring coordination to the apparently random electrical signals in the atria before they are conducted to the ventricles. Since autonomic function to some extent regulates AV nodal conduction, entropy must provide a measure of the influence of autonomic function.

8.2.4. AV node

As discussed in the introduction (§1.2.3), investigation of LV function in AF is also an investigation of the function of the AV node, which brings sufficient order to the action potentials of the atria to allow coordinated contraction of the ventricle. It has been suggested [109] that the lower envelope of the Poincaré plot, which shows the minimum R-R interval, indicates the AV nodal functional refractory period (FRP). Several authors [110–112] have postulated the existence of dual atrio-ventricular nodal pathways and Oka et al. [113] suggest that, although these cannot apparently be detected using electrophysiological studies, the presence of two sectors in the Poincaré plot is indicative of the two pathways with the vertexes of each sector giving the FRP of the two pathways. This would explain the presence of two clear edges in the Poincaré plots of many of the patients (e.g. Figure 3.10) and offers an area in which further investigation would be desirable.

8.2.5. Is AF chaotic?

Stein et al. [114] found that it was possible to produce a computational model of ventricular response to AF which had statistically significant predictability in patients with AF. This in itself suggests that AF is not wholly random and several other studies [108, 115, 116] have also suggested that AF may not in fact be as chaotic and irregular as is commonly suggested. Results in this study support this theory.

The dominance of points in the top-left / bottom-right of the delta-Poincaré plot, represented by *swing*, in AF suggests that there is a regular pattern of longer and shorter beats. If a change from one beat to the next has resulted in an increase in R-R interval it is generally true that the next change will result in a shorter R-R interval and vice-versa (§3.3.3 on Page 91). The changes are not equal in size but because heart rate has been shown not to vary substantially over the course of the acquisition (see Table 5.35b) there must be a general tendency towards variation about the mean R-R interval. When this variation is quantified (without regard to the magnitude of changes) by the index which has been termed *swing* in this thesis, it is clear this pattern is more dominant in AF than in it is in SR (see §3.3.3 on Page 91).

These results suggest that AF is not in fact chaotic and, although the rhythms appear irregular, there is a degree of patterning in them. This can also be observed in Poincaré plots many of which show clustering, suggesting that some beat intervals are more frequent than others.

8.2.6. New measures

Two new indices of rhythm have been introduced in this thesis: *compactness factor* and *swing*. *Compactness factor* gives an assessment of the density distribution of the Poincaré plot. *Swing* gives a very general (without regard to the degree of change) assessment of the frequency with which a beat is followed by a shorter beat, then a longer beat, and then a shorter beat, and so on.

Although neither of them have been shown to be significant by themselves, in conjunction with other measures, notably mean RR and entropy, *swing* has been shown to be indicative of the degree of variation that might be seen in LVEF, PSV, EDV/PSV and peak filling rate. By contrast *compactness factor* has only been used in correlation with systolic time where the resulting correlation was poor (see Chapter 6).

Overall *swing* may prove to enhance a description of rhythm while it is unlikely that *compactness factor* offers much additional information.

8.3. RNVG Technique

There are several criticisms that could be levelled at the technique which has been used in the acquisition and analysis of RNVG in this study. The three principal issues are:

1. the use of a single region of interest for each patient
2. the treatment of ectopic beats
3. the use of variable rather than fixed time formatting.

8.3.1. Why use a single region?

There are effectively two techniques for analysing RNVGs: a dual region technique and a single region technique. National guidelines recommend a dual region technique although they acknowledge that a single region may be used where a pre-established normal range has been determined[117]. A dual region technique involves separately determining regions for end-diastolic and end-systolic LV volumes. This may be done automatically or manually and may also involve determining regions for the LV at each intermediate stage. Background regions may be a single, end-diastolic region, or regions on each frame or regions at end-diastole and end-systole. Each type of background is likely to slightly change final quantitative results.

Using a dual region technique has two advantages: it results in LVEFs which equate much more closely to those obtained using other modalities (largely because other modalities use techniques which more closely match the dual region technique - see above §8.4.1 & §8.4.2). The dual region technique is also more able to allow for lateral motion of the heart which may move the LV in and out of a single region. It has two major disadvantages: it has much poorer reproducibility because it is not only harder to draw two regions in the same place than a single one, but it also much harder to determine the edge of the ventricle at end-systole which adds to the poorer reproducibility. The second disadvantage is that it is difficult (unless regions are drawn on every frame of the

image which, practically, requires some form of automation) to determine volumetric changes over the whole beat because there are different changes within each region and some assumptions must be made in order to convolve them.

The single region technique that was used in this study has been described in the methods (§4.3.3). Essentially a single LV region and background are used and the change in count within that region is used to model the change in volume. It has two major advantages and two disadvantages. The disadvantages are that there is no way, using a single region technique, to account for lateral movement of the myocardium, and LVEF is substantially underestimated in comparison with other techniques / modalities. The advantages are that a single curve can be determined that shows volumetric changes over the whole beat and the results have a much better reproducibility.

The department of Nuclear Cardiology in Glasgow Royal Infirmary routinely uses a single region of interest technique in analysing RNVGs. This offered some particular benefits for this study. The extremely large number of images that were analysed for this study ($\sim$ 64000) made separate regional analysis of each image impractical. By using a single region technique the same region, which defined the *greatest* extent of the ventricle, could be used on each image. (This assumes the lateral motion is either consistent on all images for a particular patient, or negligible). This substantially reduced the amount of work involved in analysing the images and made it possible to analyse the large data set. While a study could be done which investigated changes in which regions of interest were drawn on every image, it is unlikely that the results would be substantially different from those presented in this study and would necessitate a much smaller study population.

8.3.2. Ectopic beats

Ectopic beats in this study have been treated by removing extreme outliers (§5.2) and by considering a sub-group of patients in whom ectopic beats could not be identified from the Poincaré plot.

Limiting the acceptable beat length, thus removing the extreme outliers, changes the shape of the curve, particularly in frame mode (see Figure 5.2 on Page 149). Even if the fall off at the end of the unlimited curve is ignored, the shape of diastole appears to change. This is purely a result of averaging beats in different bin sizes. The effect is much less pronounced where variable time formatting is used (see Figure 1.10, Page 31).

In SR the comparison of the group which excluded ectopic beats ("pure") with the remainder of the patients found that there was a significant variation of LVEF with beat selection criteria in the "not pure" group which was not seen in the "pure" group (provided there was a division on quartiles in either the preceding or indexed beat). This suggests that the presence of ectopic beats introduces a greater beat-to-beat dependence. Since it seems unlikely that a few beats will substantially affect the curve, particularly using variable time formatting, this must reflect underlying pathology and suggests that there may be a greater beat-to-beat dependence in those patients for whom an underlying pathology may be a cause for ectopic beats. This is an area in which further investigation may be worthwhile.

In AF there is a statistically significant ($p = 0.034$) difference between LVEF in the "pure" and "not pure" groups; however, there is not any substantive difference between their behaviour with beat selection (§5.4.3). Although this difference is statistically significant it cannot be considered to be clinically so, and this is to some extent confirmed as there is no difference between the ranges in the two groups.

8.3.3. Fixed vs. Variable time formatting

Most centres that perform RNVG will use fixed time formatting simply because manufacturers do not offer variable time formatting; although *MiE* recently (2010) started to offer, and *Siemens* are developing, software to allow "on the fly" variable time gating. A literature search does not reveal any studies which prefer one method over the other, each having their own advantages and disadvantages (see §1.5.2).

In this study, with the exception of systolic volume, little difference was found between fixed and variable time formatting in those images for which results could be obtained using both techniques; no significant difference was found between the values of LVEF. However, fixed time formatting substantially reduced the number of curves that could be analysed when all the beats were used: 275 using fixed time formatting against 372 with variable time formatting (see Table 5.29); this amounts to $\sim 26\%$ fewer patients in fixed time.

In the case of systolic volume, significantly fewer measures (as determined by the differing beat selection criteria) were found to be outwith the sampling error using fixed time formatting. This was particularly pronounced in patients with AF, where there were half

as many measures outwith the sampling error than in SR. This reflects the volumetric blurring that is the result of using variable time formatting.

Throughout this study both techniques were investigated but results have concentrated on those determined using variable time formatting, principally because the loss of data which may occur with fixed time formatting makes it an inferior technique, and the volumetric blurring is not sufficient to make a significant difference to the functional measures (see §5.4.4, §5.5.2, §5.6.2 and §5.7.2).

The temporal distortions introduced by fixed time formatting (see §1.5.2) make it unsuitable for assessment of diastolic function and comparison was not made between fixed and variable time formatting for the diastolic measures.

8.4. Alternative modalities

LVEF is usually assessed from changes in volume rather than from pressure measurements (see §1.1.5) and, although other modalities exist, the three most common in assessing LVEF are echocardiography, CMRI and RNVG. Many of the results of this thesis have an impact on the assessment of LVEF, particularly in AF, regardless of modality. To understand this requires a brief understanding of echocardiography and CMRI.

8.4.1. Echocardiography

In echocardiography the most common method for assessing LVEF is Simpson's biplane [118]. This technique involves outlining the endocardial wall of the LV on two orthogonal views. The ventricle can then be divided into elliptical slices and the volume calculated from each of these. If this is done at end-diastole (ED) and end-systole (ES), the fractional difference in volumes should represent LVEF. The regions are drawn on freeze-frame images that capture the physical position of the myocardium at a specific point (ED or ES) in a single beat.

The technique has four problems associated with it. It assumes that a slice through the ventricle is adequately modelled by an ellipse. This can be avoided if a three dimensional technique is used but 3D echocardiography is still not common and delineation of the

myocardium on multiple slices [119] is considerably more labour intensive and has a much greater associated error. Like other techniques Simpson's biplane requires good delineation of the ventricle. This can be difficult given the relatively poor contrast between the ventricular cavity and the myocardium, particularly in subjects who are poorly echogenic. The differentiation can be improved with the use of micro-bubbles, which increase the contrast ratio and substantially enhance the ability of the analyser to delineate the endocardial wall. Most investigators recommend the use of a contrast agent in determining LVEF using echocardiography in studies where serial assessment is expected [120–123]. Because LVEF in echocardiography is determined from a single beat, the technique assumes that any one beat is representative of all beats; this stands against the Frank-Starling rule but it is, nevertheless, common practice to accept measurement on a single beat as being indicative of the overall LVEF. It is generally recognised that to compensate for beat-to-beat variations in AF, measurements of LVEF should be made on several (typically three or four) beats and the mean of the results taken [118, 124]; however this study shows that the variation in both SR and AF can be substantial and there is little assurance that measuring on a single, or even several, beats gives an accurate representation of overall LVEF. The fourth substantive problem with assessing LVEF using Simpson's biplane technique is that it is highly dependent on the views taken. If the view does not slice through the apex the chamber will be foreshortened in the image. In patients who are not echogenic it may mean that it is not possible to perform echocardiography satisfactorily with the result that assessment of LVEF is impossible. While there is no solution for the latter, 3D imaging offers the potential to avoid the former [124, 125].

8.4.2. CMRI

In SR, CMRI is generally considered to provide the gold standard for assessment of LVEF. Similar techniques to those used in echocardiography are used in that the endocardium is delineated on multiple slices. From these the volume of the resulting shape can be determined with good precision and high reproducibility. In SR, it has the disadvantages that it is both expensive and not readily available - with MRI machines generally being used extensively in hospitals for investigations for which other alternatives do not exist. Unlike echocardiography, CMRI does not rely on a single beat but is built up over multiple beats and thus offers an image of an average beat. To minimise

movement distortion the image is acquired over several breath holds [126]. This may have a significant physiological effect on cardiac function and on R-R intervals.

In AF assessment of LVEF using CMRI frequently fails. In very basic terms, CMRI uses gating in a similar fashion to RNVG: the R-R interval is divided into frames (typically between 12 and 18) such that the final image consists of multiple frames per slice. Each frame corresponds to a separate k-space (frequency space into which echoes from the entire volume are recorded). Slices of each frame are reconstructed at the appropriate angle from their respective k-space. K-spaces are filled with data with a spatial resolution which depends on the number of phase-encoding steps used (typically 128). Conventionally a single phase encoding step is acquired for each beat, although more recent developments have allowed multiple phase encoding steps to be acquired simultaneously. Herein lies the problem. Consider 2 sequential beats, one short, one long. In the first beat point A on the myocardium at point, a, in the reference frame of the scanner is involved in a signal in k-space 3 (say); in the second beat the same point, A, on the myocardium may be at a substantially different point, b, in the reference frame of the scanner in k-space 3, while it is at point a in the reference frame of the scanner in k-space 5 (say). In real space this would result in a blurring of the boundaries, in a reconstruction from k-space it results not only in a blurring of the boundaries but in a general loss of contrast. In SR the problems that might be caused by ectopic beats can be avoided simply by discarding the data from that beat but in AF the variation is too great. A tight beat window in which most of the beats are discarded requires too long an acquisition time, a wide window degrades the image - in some cases completely. The result is that measurements using CMRI in AF may be subject to significant artifact [127].

8.5. Assessing LV function with RNVG

It has been shown that there is substantial variation in functional measures, of which the most important is LVEF, for any one patient in both SR and AF depending on the beat selection criteria. This suggests that there is substantial functional change that is dependent on the duration of both the previous and the indexed beat. This needs to be explored further.

8.5.1. Reproducibility

A search of any bibliographic database for *LV ejection fraction* and *atrial fibrillation* will yield thousands of results, many of which consider the implications of a change in LVEF or a variation from a "normal" value. In SR assessment of change in LVEF is commonly used in monitoring the progression of disease or treatment, the use of Trastuzumab (Herceptin) being a particularly relevant example. Trastuzumab is a chemotherapy agent used in the treatment of breast cancer. It has been shown to be cardio-toxic and guidelines for its use recommend regular serial assessment of LVEF to monitor the effect it may have on cardiac health [128–130]. While few, if any, patients in AF will be given Trastuzumab therapy, the variation that has been demonstrated in this study gives cause for concern in the serial assessment of LVEF.

In general RNVG has been shown to have good (inter- and intra-observer) reproducibility with values typically being quoted as being between ±7% and ±9% [8, 131, 132], although the department of Nuclear Cardiology in Glasgow Royal Infirmary has shown that using a single region technique it is possible to get reproducibility as good as ±3% [133]. The reproducibility of LVEF by echocardiography is poorer than this, typically between ±10% and ±12% [8], although this can be improved with the use of contrast [121]. CMRI has a reproducibility of ±2.5% to ±7.0% in SR [134–136] and has been shown to correlate well with invasive techniques of LVEF assessment in AF[137].

This study has shown that in both SR and AF a substantial variation in LVEF can be measured depending simply on beat selection criteria (§5.4). This corroborates several studies which, using echocardiography, have also found substantial variation (see §1.6). Since all assessment of LVEF will require some form of gating, this variability will apply to all modalities and the variation will be at least comparable to, if not greater than, the reproducibility of LVEF measure. Measures of reproducibility will involve the same image and are therefore independent of beat selection criteria, making beat choice an additional source of error.

It has been clearly demonstrated in this study that in AF there is a systematic variation of LVEF with both preceding and indexed beat criteria, and in most cases the correlation is strong. This is not true in SR, although there are still substantial changes measurable within an acquisition for each patient. The poor correlation in SR between preceding beat length and LVEF suggests that while the Frank-Starling mechanism (increased filling leads to greater force of contraction and increased LVEF) is dominant in AF it

plays a smaller role in SR. This may be because the fluctuations in pre-systolic volume are insufficient to trigger the mechanism; although this study has also shown that the fluctuations in pre-systolic volume may be substantial (see Figure 5.24 on Page 204) and, in the majority of patients, are significantly related to preceding and indexed beat criteria.

Concentrating only on the variation with preceding and indexed beat may put too much emphasis on the Frank-Starling effect. As was discussed in §1.1.1 there are several different mechanisms which affect cardiac output. Patients were all imaged at roughly the same time of day (early to mid afternoon) at rest, which ought to minimise the effects of other influences, and the Frank-Starling law should be the most high frequency effect; however, other influences cannot be completely ignored. The results of this study suggest that in SR other effects play a more significant role, in comparison with the Frank-Starling mechanism, than they do in AF.

8.5.2. LVEF Portability: SR to AF

At this point it is necessary to consider a question the answer to which has been assumed in the rest of this thesis; namely: is it reasonable to take a measure of function (LVEF) used in SR and apply it to patients in AF?

Few studies have investigated the prognostic value of LVEF in AF, and it is generally assumed that LVEF has similar prognostic value in AF as it does in SR. In a study by Pai et al. [138] LVEF and AF were found to be separate, independent predictors of five year mortality. AF is a pathology of the atria and not of the LV and in broad terms the results of the study described in this thesis corroborate this conclusion: mean LVEF is reduced in patients with known MI (see Page 176) in both SR and AF and similar results are found for patients with high blood pressure (see Page 178). Additionally this study has shown that there is substantially greater variation in measured LVEF in AF than in SR, highlighting the importance of establishing the criteria by which serial changes in LVEF are measured, as the error on a measurement in AF is likely to be considerably greater than that in SR.

Serial variation in LVEF can be minimised by accepting a very broad range of beats which excludes only substantial outliers. There is a better consistency of results in AF where all beats are taken than where a portion of them are taken. There is a notable increase in the difference between immediately sequential measures of LVEF (comparing

the first half of the acquisition against the second half) when only the *"Best"* beats were taken compared to the LVEF when *All* beats were taken (§5.4.5). This suggests that there is improved reproducibility when LVEF is averaged over all acquired beats, in this case typically several hundred. It is probable, given the significant difference between LVEF when *All* or *"Best"* beats were used compared to beat selection based on quartiles (either preceding or indexed) (§5.4), that this difference would be further exaggerated had the comparison been made with any of the images created using quartile ranges.

8.5.3. LVEF

At the start of Chapter 5 four questions, which have been addressed in this thesis, were asked:

- Do functional parameters change depending on beat selection criteria?
- If functional measures do change, is there a trend in the relationship?
- Does variable time framing produce similar results for the defined functional parameters as fixed time framing?
- Given the beat selection criteria, is there self consistency for functional measures acquired at approximately the same time?

In SR, although there was substantial variation in measured LVEF on an individual patient basis (up to 43%, SD: 8.2%), there seemed to be no clear correlation between either preceding or indexed beat length (quartile) and the measured LVEF.

In AF the variation in measured LVEF on a per patient basis was even more substantial (up to 46% with a SD of 14.3%); however, there was a clear correlation with both preceding and indexed beat with the preceding beat having a greater influence on measured LVEF than the indexed beat.

When the source of the variation of LVEF with beat selection criteria was investigated, the maxima were found to occur when only the longest preceding beats were included in both SR and AF, by contrast the minima occurred where only the shortest preceding beats were included (see Tables 5.12 and 5.13 on Page 168) although this was a considerably more dominant effect in AF than in SR.

Functional dependence on preceding beat

As discussed in the introduction (§1.6) several authors have investigated the functional dependence of one beat on the previous one and these results confirm a positive dependence although the degree of variation is not predicted.

Wallis et at.[139] investigated changes in LVEF in AF with different indexed beat selections and found that there was no predictable relationship between LVEF and windowing. He attributed this to lack of a predictable amount of ventricular filling for a given cycle length. This study has attempted to address this by considering the changes with preceding beat as a predictor of filling.

Wallis also found that there was variation with different indexed beat selection criteria, with results varying over up to $\sim$ 20% (EF points) for each of his 20 patients. When the results obtained from the set of (10%) windows that covered the complete set of R-R intervals was averaged, the resulting LVEF was found to be approximately the same as that achieved simply by taking all the beats. This does not agree with similar results in this study, which found that LVEF obtained with beat selection based on each of the indexed quartiles, without regard to the preceding beat, were significantly and consistently greater than the results when all the beats were taken. Although Wallis use fixed time formatting no significant difference was found, in this study, when comparing fixed and variable time formatting and it is therefore unlikely that this is the cause of the discrepancy between the results of the study reported here and that undertaken by Wallis.

This study has shown preceding beat criteria to have a more dominant effect on LVEF than indexed beat criteria. It has also shown there to be a systematic, negative relationship between indexed beat criteria and LVEF - a relationship which Wallis did not see. It is likely that the blurring effect of taking all beats both reduces the mean pre-systolic and increases the mean end-systolic volume with the overall effect of reducing ejection fraction as is shown in this study. While the cause of the difference in results is not clear, the most likely reason is simply that the number of patients in Wallis' study was insufficient to give statistically significant results.

Effect of pathology?

With the exception of the "pure" group, the subgroups that were investigated were defined by very broad pathologies: whether or not a patient had had an MI; whether the patient was being treated for high blood pressure; if they had known ischaemia; or if they had undergone interventional treatment for ischaemia; etc.

By and large the results for the subgroups followed the results for the AF and SR groups as a whole, although the comparison between opposing groups offers some further insight. Since function is a marker of underlying pathology, it is to be expected that patients with known previous MI, HBP, or ischaemia will have lower LVEFs (so too do those who have had PCI and/or CABG although the difference is not statistically significant, see Tables 5.14, 5.17 and 5.19). It is more surprising that the range of LVEF also decreases significantly in SR, although not in AF (except in the ischaemic and functional groupings). This probably reflects overall reduced ability of the heart to vary its output as the overall elasticity of the ventricle is reduced. LVEF typically varies by $\sim 30\%$, the absolute range of LVEF will be smaller if the average LVEF is smaller.

That there should be no difference in AF between LVEF in the group with positive ETTs and those with negative ETTs is also surprising, particularly since electrical changes normally follow functional changes in the ischaemic cascade [6].

Functional variation

Returning to the questions considered at the start of this section, assessment of LVEF with different preceding and indexed beat criteria has shown that LVEF changes, sometimes quite substantially, with indexed and preceding beat length. In AF there is a clear trend to these results with longer preceding beats giving higher ejection fractions. As has previously been discussed (§8.3.3) there is little substantive difference in either LVEF or ⇳LVEF using fixed or variable time formatting and this study has shown that the results for LVEF are self consistent (see §5.4.5).

These results have been shown for LVEF and for the other functional parameters as discussed in the following sections.

8.5.4. *PSV*

One of the more surprising results of this study is that there is no significant variation on a whole group basis in pre-systolic volume, PSV, in either SR or AF despite the changes which are seen in LVEF (§5.5). Although the changes in the whole group are not significant, on a per patient basis the variation in PSV may be substantial (see Figures 5.24 on Page 204 and 5.25 on Page 205). It has been shown (see Figure 5.51 on Page 247) that on a patient-by-patient basis there is good correlation between LVEF and PSV in AF (poor correlation in SR). The better correlation in AF is likely to be a result of the lack of an atrial component to filling which means that, unlike in SR, ventricular emptying and filling is controlled by a single matched process. There is poor correlation between the range of LVEF and range of PSV which reflects patient-by-patient differences and may reflect pathology, although this has not been explored in this thesis (e.g. do patients with high blood pressure have a different comparative response of LVEF to PSV?).

It is also notable that when the results for all patients are considered together, in both SR and AF there is good negative correlation between LVEF and PSV. Better ejection fractions appear to occur at lower PSV. This also is likely to reflect pathology in that larger volumes may be more compliant but exert less pressure (e.g. patients with dilated cardiomyopathy).

Statistically there was no difference between LV volume measured using variable time formatting and that using fixed time formatting but it is notable (Figure 5.27) that variable time formatting underestimates LV PSV when compared with fixed time formatting. This is clearly methodological, and is the result of the mid-range beat (fixed time formatting) generally being longer than the mean beat. In fixed time formatting the mid-range beat is divided into N frames while in variable time it is the mean beat which is effectively divided into N frames thus frames in the early part of the beat have fewer counts in variable time formatting than they do in fixed time formatting. (An alternative way of looking at this is to consider that the same number of events occurs in each beat but that in fixed time formatting there are typically reduced counts in the bins towards the end of the beat).

8.5.5. *EDV/PSV*

The ratio of the end-diastolic volume to the pre-systolic volume is not an index which has been discussed in the literature. Ideally it is to be expected that a single beat will have the same end-diastolic volume as the pre-systolic volume. However it has been clearly shown in this study that there is substantial variation between the two in both SR and AF. The preceding beat has no significant effect on EDV/PSV in SR but there is a significant, if weak, correlation with indexed beat length. In AF there is a moderate correlation with both preceding and indexed beat. The correlation with beat selection criteria is much stronger for EDV/PSV than it is for LVEF.

Increasing EDV/PSV can occur either with decreasing PSV or with increasing EDV. It has been argued in this thesis that end-diastolic volume is determined by the duration of diastole. Thus PSV, the end-diastolic volume of the previous beat, is determined by the duration of diastole in the previous beat and EDV by diastolic time in the indexed beat.

The moderate positive correlation with preceding beat length and negative correlation with indexed beat length confirms the hypothesis that premature contraction reduces end-diastolic volume: a short preceding beat or a long indexed beat leads to higher EDV/PSV, likewise a long preceding beat or a short indexed beat leads to a lower EDV/PSV. This would suggest that there should be a fairly strong correlation between EDV/PSV and SDRR or R-R range but this is not seen (§6.5) and indeed *swing* and *SampEn* appear to be better descriptors of EDV/PSV.

Because EDV/PSV appears to be a marker of beat variation there is a possibility that it will be indicative of variation in LVEF. There is good correlation between the range of LVEF and the range of EDV/PSV but there is no clear correlation between EDV/PSV and $\updownarrow EDV/PSV$ (see Figure 5.32 on Page 216) and a comparison of EDV/PSV obtained using all beats found no clear relationship with range of $LVEF$ so it cannot be used as a marker for LVEF variation.

8.5.6. Systolic time

It is probably that the correlation between EDV/PSV and beat selection criteria is not better because systolic time is not constant and therefore changes in beat length are not completely reflected by changes in diastolic time interval. Many studies have shown that

systolic time varies and is in itself a useful prognostic tool [140–142]. This investigation has also shown that there is a small variation in systolic time interval with beat selection criteria, and that in SR the variation is significant, if very weak. Typically the minimum systolic time is $\sim 70\% - 75\%$ of the maximum with slightly lower values in AF compared to SR.

It is not absolutely clear why there should be a significance in SR and not in AF except that the variation in overall time is so much greater in AF than in SR (shortest beat is typically $\sim 35\%$ of the longest beat compared with $\sim 80\%$ in SR) that the small changes in systolic time interval may be insignificant in comparison to the overall changes in beat length.

8.5.7. Diastolic function

The investigation of diastolic function in this study has been very limited because it became clear that the methodological problems associated with it are substantial. Two measures of diastolic function were chosen: first third filling fraction (FTFF) and peak filling rate (PFR).

There was a good correlation between FTFF and indexed beat selection criteria (§6.8). This may be artificially introduced since the comparison is made against a changing variable: longer beats will have longer diastolic time and hence the time to FTFF will be longer. If filling follows a similar pattern, independent of duration, this method will select different points on the filling curve. Since curves gradually increase during filling the correlation between indexed beat selection and FTFF is expected but does not necessarily have any physiological basis. To some extent this is confirmed by the much better correlation between the range of systolic time and range of FTFF in SR when compared to AF. In SR, while systolic time and FTFF may change on a beat-to-beat basis the change is likely to be consistent. In AF it will not be because the point of measurement for FTFF will fluctuate. A similar argument can be used to explain why EDV/PSV correlates better with FTFF in AF.

It was not clear how to analyse FTFF in such a way that the methodological dependence could be removed. A future area of study could use similar techniques to determine a theoretical filling curve which may be followed in each beat, however such an analysis is beyond the scope of this study.

There was also a good correlation between LVEF and PFR (§5.10.5). While this may be methodological, Bacharach [143] showed that filling was shorter than the time to peak filling in fewer than 2% of cardiac cycles and Rumberger and Reed [90] found that both peak emptying and peak filling rates in SR were dependent on end-diastolic volume. In general a ventricle which contracts well is also likely to have good active dilation characteristics. If the ventricle is functioning poorly on systole it is likely also to be functioning poorly during diastole. The results here seem to support this theory and suggest that the variations in the index may be physiological and not methodological. It would have been useful to assess the time to peak filling as well as the PFR to determine whether it was constant, or whether the variation was largely limited to the shorter beats. This is a potential area for further investigation.

8.6. Clinical implications

While this study has generally shown that there are substantial variations two questions in particular are raised:

1. In light of the variations, how should beat windows be set in the acquisition of clinical images, both in RNVG and other modalities?
2. Is there any clinical value in assessing the variations and rhythm descriptors which have been found here?

8.6.1. Beat windows

In order to minimise variation in sequential assessment of LVEF in AF, all beats must be taken. This is likely to provide a low assessment of LVEF (see Figure 5.8 on Page 164) but by removing the beat selection dependence it is likely to provide a more consistent measure (see §5.4.5).

8.6.2. Clinical value

Results, both in the small clinical study and when considering LVEF in the patient subgroups (see above - §8.5.3), suggest that there may be clinical value in assessing the ⇳LVEF and in investigating entropy.

In the AF ablation study (Chapter 7) there was a suggestion that the range of LVEF measurements may be indicative of the change in LVEF that will be seen if the patient maintains SR, although the data in the study was only sufficient to suggest that a greater range will produce a greater change in LVEF. There was also a suggestion that *SampEn* may be indicative of the probability of a patient maintaining SR after RFA. (*SampEn* has also been shown to have prognostic value in other areas of cardiology in both SR and AF [77]).

8.7. Limitations of the study

There were several limitations to the study as it was carried out. The selection of patients both in AF and SR was very broad: provided patients were identifiably in SR or AF they were accepted into the study. This was done to maximise the data set and to provide sub-groups of sufficient size to be statistically relevant; however there is potential for other pathologies to be obscuring results, in particular valvular disease will affect volume change. Unfortunately other data on pathology, etc. is not kept by the department and it would have fallen outwith the ethics approval to gather it).

In assessing the variation of function with beat selection criteria, only predefined inter-quartile ranges were used. This was done for two reasons: it allowed list-mode files to be processed automatically and provided a means of normalising beat selection criteria from one patient to the next. Perhaps a more conclusive result could have been obtained if different criteria had been used, or if some other means of normalising data had been achieved. Careful examination of the beat histogram for each acquisition might have allowed beat selection which could account for groupings that could be seen in the histogram, the use of quartiles does not discriminate between these.

There was an issue in comparing rhythm measures against functional measures. For the reasons discussed in §2.7.2, all beats were included in the analyses of rhythm while the functional analyses used limited data. Limiting the data would have changed the beat

interval stream and thus changed the results obtained for the different rhythm indices. There was no way around this problem, and it was felt that including the whole interval stream would give a more accurate representation of the rhythm.

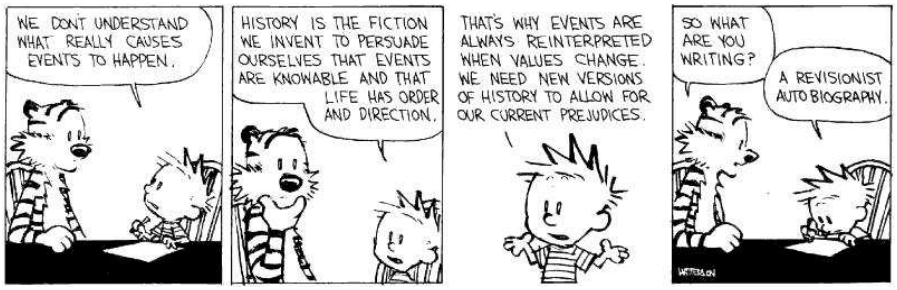
RNVG, as it has been used in this study, is a planar (2D) technique that is used to model a 3D anatomy. One of the advantages of RNVG is that it is relatively geometrically independent, since the volume of blood is directly proportional to the count rate. This means, however, that changes in the anatomy caused by cardiac motion, other than simple changes in volume, are poorly accounted for. While SPECT (3D) RNVG is available it would not be possible to acquire sufficient beats at each imaging position to sub-select beats.

Medical therapy (and in particular β-blockers) will have a significant impact both on rhythm and function in both SR and AF. In many cases it may have a greater impact than pathology. This thesis has not looked at the effect of therapy on either rhythm or function. Most of the patients who have been investigated will be on a combination of therapies and although it would be interesting to investigate the separate effects of these it would be hard to distinguish them. Never-the-less this could be a fruitful area for future study.

A final concern with this study is that its scope has been too great. The study considered a very wide range of patients and functional measures. As a result it has only been possible to develop an overview of the techniques that could be used to investigate beat-to-beat variation between patients in detail. The small clinical study (Chapter 7) provided some evidence that there may be value in these measurements, but further clinical investigation is required to determine whether they have genuine value.

Chapter 9.

Conclusion



9.1. Addressing the hypotheses

This clinical physics study has predominantly been an investigation of the physics of measurement of cardiac function. In medical imaging the heart poses a particularly difficult challenge because, more than any other organ, it moves. In SR reasonable assumptions can be made with regard to the regularity of the heart rate which allow us to make accurate approximations of cardiac function. The irregularly irregular beats of AF challenge these assumptions and require that the methods used to assess cardiac function in SR are re-evaluated in the presence of AF. The results presented in this thesis go a substantial way to providing that re-evaluation.

In addressing the six hypotheses detailed in §1.7 the aim of the thesis has not been to provide a detailed clinical investigation of AF but to create a set of tools by which the rhythmic and functional variations of the heart, and in particular the left ventricle, could be described. In this respect the study could be considered as a pilot study (as it was labelled in the application for ethics approval).

Addressing each one of those hypotheses:

1. **Beat-to-beat fluctuations in R-R interval are reflected in beat-to-beat changes in cardiac function, consistent with Frank-Starling's law of the heart: the greater the fluctuations, the greater the variation in function.**

2. **A variation in function will be seen in SR but will be much more pronounced in AF where the R-R fluctuation is much greater.**

3. **The duration of the preceding R-R interval has a substantive effect on measures of function, in particular LVEF, both in SR and AF.**

These hypotheses have been shown to be true. In AF where there are substantial beat-to-beat fluctuations in R-R interval there is a substantial and significant variation in measured LVEF with longer preceding beats having greater ejection fraction than shorter ones (SD of the range of LVEF in each patient is 14.3%), variation in preceding beat interval had a more dominant effect on LVEF than variation in the indexed beat interval. In SR where the fluctuations in R-R interval are less extreme, there are still variations in measured LVEF but the range of these is, generally, smaller with SD of measured LVEF being 8.2%. In SR, the variation was not found to be significantly dependent on either the preceding or indexed beat length.

4. **AF can be reliably described using indices of rhythm which are also applicable to SR.**

A variety of different indices of rhythm have been investigated and it has been shown that not only do the linear measures of heart rate variability such as SDRR and pRR50 clearly, and significantly, differentiate between SR and AF but so too do indices which describe the Poincaré plot and indices of entropy. Each of these indices has been shown not only to separate patients in AF from those in SR, but also to differentiate between patients in AF as well as between patients in SR.

Of the measures of entropy which have been considered, Sample entropy, $SampEn$, (using metrics of $r = 0.02SD$ and $m = 1$) has been shown to have the best descriptive value. Entropy of symbolic dynamics, $SymDyn$, has been shown to be largely uninformative in describing AF.

5. **Measures of rhythm will have a predictive relationship with measures of function.**

It was found that no individual measure of rhythm had substantial predictive power but that when several measures were combined (notably *SampEn*, mean RR, SDRR, *swing* and the correlation of the Poincaré plot) it was possible to achieve a correlation between rhythm and the potential variation in LVEF with a coefficient of $R = 0.55$ in AF and $R = 0.536$ ($p < 0.00001$ in both cases). While good, this is insufficient to fully determine the range of LVEF that might be obtained and suggests that there may be other factors (particularly underlying pathology) which will also have an influence.

6. **Measures of rhythm and function in AF can be shown to have clinical utility.**

Reduced variation in LVEF has been shown to be associated with myocardial infarction, hypertension and ischaemia in AF and SR suggesting that there may be some prognostic value in the range of measurable LVEF.

In the AF ablation study the range of measurable LVEF appeared to have the potential to predict the degree of change in LVEF that might be seen in patients who maintained SR. However the small numbers involved in the study made any statistical analysis impractical and a larger study would be required to confirm this.

9.2. Impact

Although this study has used radionuclide ventriculography, RNVG, many of the results are equally applicable to other modalities: any kind of assessment that considers cardiac function will be affected by beat-to-beat variation. In imaging patients in AF the significant beat-to-beat variability and concomitant variation in function suggests that assessing function on a small selection of beats is likely to have poor reproducibility. A more reproducible result could be achieved by selecting all beats (with the exclusion of some extreme outliers).

After using the Poincaré plot in this study, it has been adopted for regular use in the department of Nuclear Cardiology in Glasgow Royal Infirmary, particularly in patients with curious rhythms where it has proved to be very useful in determining the most likely limits for "true" beats.

9.3. Further areas of investigation

RNVG offers a rich seam of information about the heart in general and the LV in particular. Many different measures which offer further insight into cardiac function have been considered to a greater or lesser degree in SR. These include measures of regional function, phase imaging and measures of dissynchrony. Each one of these may be affected by beat-to-beat variation which is seen not only in AF but also in SR. From the physics point of view there would be value in investigating whether the variation affects the measures and whether the blurring that results from accepting all beats in AF affects these measures.

An investigation into the effects of medical therapy on indices particularly of rhythm would be of interest, particularly if it was performed pre and post the introduction of the therapy. While there is a considerable amount in the literature in reference to medical treatment and standard measures of HRV in SR, very little work has been done investigating measures of entropy in SR or, in AF, any of the measures discussed in this thesis.

There is a suggestion of structure in the Poincaré plots of patients prior to RF ablation who maintained SR, which may not be seen in patients who did not maintain AF. This should be investigated further, using 24 Holter recordings, as should the potential for *SampEn* to predict whether or not a patient will maintain SR.

This investigation has presented tools that permit the investigation of beat-to-beat variation, albeit averaged over many similar beats, of any functional measure which can be made in RNVG or, with appropriate modification, other modalities. These tools offer the potential for clinical study and a better understanding of atrial fibrillation.

Appendix A.

Scripts

The following are basic scripts written to extract information from files produced within the MAPS 10000 NM system. The fundamental modifications which were made to the list-mode formatting program cannot be included here as they are the property of Link Medical.

A.1. Heart rate variability

An awk script to calculate basic heart rate variability results from a list of RR intervals. Values calculated are: N, Mean RR, SDRR, $RMSSD_{rr}$, RR50, RR60 , pRR50, pRR60, shortest RR interval, longest RR interval, RR interval range, standard deviation of RR interval averaged over 5, 10 and 20 consecutive beats.

```
#!/usr/bin/awk -f
##############################################################################
#
# file: variability.awk
# author: Sandy Small
# description:
#   Given a list of RR intervals (on STDIN) calculate some standard
#   heart rate variability parameters
#
##############################################################################

BEGIN {
#
# Set up some initial variables the values of which will be
#  established in the script
#
  RR50 = RR60 = 0
  short = 60
  long = 0
  n5 = n10 = n20 = 1
  num5 = suman5 = av5 = 0
```

```
  num10 = suman10 = av10 = 0
  num20 = suman20 = av20 = 0

#
# Get study and label by piping input from a command to a variable
#
  "study" | getline stdy;
  "label_file -g label" | getline label;
}
{
#
# $i gives RR interval
#
  for(i=1; i <= NF; i++) {
    # get longest and shortest RR intervals
    if ($i < short) short = $i
    if ($i > long) long = $i

    # Total duration will be sum of RR intervals
    # Get duration + sum of squares of RR interval
    # and difference
    sum += $i
    sumsq += $i ** 2
    diff = $i - $(i+1)

    # We're only interested in the absolute value of the difference
    if (diff < 0) diff *= -1
    if (diff > 0.05) RR50++
    if (diff > 0.06) RR60++

    # Sum of difference squared
    sumdiffsq += diff * diff

    #
    # Over 5 average
    if (n5 == 5) {
      av5 += $i
      suman5 += (av5 / 5)
      sumsqan5 += (av5 / 5)**2
      num5++
      av5 = 0
      n5 = 1
    }
    else {
      av5 += $i
      n5++
    }
    #
    # Over 10 average
    if (n10 == 10) {
      av10 += $i
      suman10 += (av10 / 10)
      sumsqan10 += (av10 / 10)**2
      num10++
```

```
      av10 = 0
      n10 = 1
    }
    else {
      av10 += $i
      n10++
    }
    #
    # Over 20 average
    if (n20 == 20) {
      av20 += $i
      suman20 += (av20 / 20)
      sumsqan20 += (av20 / 20)**2
      num20++
      av20 = 0
      n20 = 1
    }
    else {
      av20 += $i
      n20++
    }
  }
}
END {

#
# And output results

# Uncomment the next lines for header

#  printf("%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s,%s\n",
#  "Study","Label","N","MeanRR","SDRR","RMSSD","RR50","RR60",
#        "pRR50","pRR60",
#  "RRshort","RRlong","RRrange","SDAN5","SDAN10","SDAN20")
  printf("%s,%s,%d,%3.3f,%3.2f,%3.2f,%d,%d,%3.1f,%3.1f,%3.2f,
         %3.2f,%3.2f,%3.3f,%3.3f,%3.3f\n",
 stdy,label,NF, sum/NF, sqrt(sumsq/NF - (sum/NF)**2),
         sqrt(sumdiffsq/NF),
 RR50, RR60, RR50*100/NF, RR60*100/NF,
         short, long, long - short,
 sqrt(sumsqan5/num5 - (suman5/num5)**2),
 sqrt(sumsqan10/num10 - (suman10/num10)**2),
 sqrt(sumsqan20/num20 - (suman20/num20)**2))
}
```

A.2. Compactness

This script calculates the *compactness factor* of a Poincaré plot by determining the maximum density in decreasing areas. Each area is moved around the previous area taking every possible position at that step size. From this the maximum count and hence the maximum density is determined. A new area size is established based on a scaling factor and the position of the new area is moved around within the previous box, etc. etc.

The *compactness factor* is the integral under the resulting curve. Three different integrals are calculated: the direct integral, the integral under a curve normalised to the maximum measured count density and the integral of the normalised curve plotted against the log of the area.

```
#!/usr/bin/perl
#
###############################################################################
#
# File: poincare_density.pl.perl
# Author: Sandy Small
# Date:
#
###############################################################################
#
# Description:
#
# Parameters:
#
# History:
#
# NC CVS ID: $Date: $ $Revision:  $
###############################################################################

#------------------------------------------------------------------------------
# Add library
#------------------------------------------------------------------------------

#------------------------------------------------------------------------------
# Call Modules
#------------------------------------------------------------------------------
#use Pg;          # Postgres communication functions
use Getopt::Std; # Command line parsing

#------------------------------------------------------------------------------
# Pragmas
#------------------------------------------------------------------------------

use warnings;                 # Give warnings about variable use etc.
no warnings "uninitialized";  # Don't warn about unitialized variables
                              # I use this "feature"
```

```
use strict 'vars';    # Force all variables to have defined scope

#-----------------------------------------------------------------------
# Global variables
#-----------------------------------------------------------------------
our ($opt_l, $opt_m);

#-----------------------------------------------------------------------
# Local Sub Functions
#-----------------------------------------------------------------------

#-----------------------------------------------------------------------
# Main program
#-----------------------------------------------------------------------

#
# Major controllables
#
my $total_size = 2.4; # Defines the maximum RR interval which will be considered
                      # And therefore the size of the first box.
my $minsize = 0.005;  # Effectively defines the pixel size (resolution) at
                      # which points are recorded (plotted).
my $boxscale = 0.75;  # The factor by which successive boxes should be reduced
my $accuracy = 0.05;  # Fraction of box size by which
                      # box should be moved around area looking
                      # for max this has a huge influence on time to run
                      # Ultimate limit is $minsize (since there's no point
                      # in looking at fractions of pixels
#
# Some files to record stuff
# I am going to assume we are working with a MAPS study and will record
# plot information in the study, but send integrals to a complete
# recording file
#
chomp(my $disk = `disc`);
chomp(my $fs = `filestore`);
chomp(my $stdy = `study`);
chomp(my $label = `label_file -g 'label' c0`);

my $studydir = join("/",$ENV{STUDY_DIR},$disk,$fs,$stdy);
my $gnufile = join("",$studydir,"/","denssquares_",$label,".gpl");
my $densplot = join("",$studydir,"/","densplot_",$label,".txt");
my $resfile = join("/",$ENV{HOME},"research/af/data/pcdensity.txt");

# Is this new or not so we can put header in
my $newres = (-r $resfile ? 0 : 1);

my @base;
my @results;

#
# Calculate a basic matrix at the minimum size
# Need to add 1 because indexes go from 1 not 0
#
```

```
my $tcount = 0;
while (<>){

    my @tmp = split(/\s+/);
    my $x = int($tmp[0]/$minsize);
    my $y = int($tmp[1]/$minsize);
    $base[$x][$y]++;
    $tcount++
}

#
# Find the area of maximum density within a shrinking box
# Start with the box size at total_size
#

my $maxsum = 0;
my $maxxpos = 0;
my $maxypos = 0;
my $maxdensity = 0;
my $prevdens = 0;

my $xoffsetstart = 0;
my $yoffsetstart = 0;

my $areaintegral = 0;
my $normintegral = 0;
my $normlogintegral = 0;

my $areasize = $total_size;
my $boxsize = $areasize;

#
# And off we go
#
while ($boxsize > $minsize){
    my $result = {};

    #
    # How much should it move
    # Make sure it is an integer mulitplier of $minsize since there is no
    # point in smaller units
    # The step size is the same in both dimensions
    #
    my $offsetstep = int(($boxsize * $accuracy)/$minsize) * $minsize;

    #
    # However it has to have a step so if it has come out as zero make
    # it step by at least minsize
    #
    $offsetstep = $minsize if ($offsetstep == 0);

    my $xoffset = 0;

    #
```

```
    # Loop around x
    while (1){
my $yoffset = 0;

#
# Loop around y
while (1){

    my $xoff = $xoffsetstart + $xoffset;
    my $yoff = $yoffsetstart + $yoffset;

    my $xstart = int($xoff / $minsize);
    my $ystart = int($yoff / $minsize);

    my $xend = $xstart + int($boxsize / $minsize);
    my $yend = $ystart + int($boxsize / $minsize);

    #
    # Calculate total sum in box
    #
    my $sum = 0;
    for my $x ($xstart .. $xend){
for my $y ($ystart .. $yend){
    $sum += $base[$x][$y];
}
    }
    if($sum > $maxsum){
$maxsum = $sum;
$maxxpos = $xoff;
$maxypos = $yoff;
    }

    $yoffset = $yoffset + $offsetstep;

    # Break out if we're bigger than the area
    # But because of rounding errors and the fact that the box
    # may not fit exactly in the area give it a little leaway
    #
    last if ($yoffset + $boxsize - ($boxsize * $accuracy) >= $areasize);
}

$xoffset = $xoffset + $offsetstep;
# Break out if we're bigger than the area
last if ($xoffset + $boxsize - ($boxsize * $accuracy) >= $areasize);
    }

    #
    # Print results
    #

    $result->{'areasize'} = $areasize;
    $result->{'boxsize'} = $boxsize;
    $result->{'count'} = $maxsum;
    $result->{'density'} = $maxsum/($boxsize**2);
```

```
    $result->{'xposition'} = $maxxpos;
    $result->{'yposition'} = $maxypos;

    push(@results, $result);

    #
    # Get overall max density so that we can calculate a normalised integral
    #
    $maxdensity = $result->{'density'}
        if ($result->{'density'} > $maxdensity);

    #
    # Calculate integral assuming we're plotting against area (not side)
    # Do this by approximating the area to be
    # the difference between the points on the x axis * the mean of the
    # densities at those two points.
    # boxsize becomes areasize so these give the x points
    #
    $areaintegral += (($result->{'density'} + $prevdens) / 2) *
        ($areasize**2 - $boxsize**2) if ($prevdens != 0);

    $result->{'areaintegral'} = $areaintegral;

    #
    # Set parameters for next round
    #
    $prevdens = $result->{'density'};
    $areasize= $boxsize;
    $xoffsetstart = $maxxpos;
    $yoffsetstart = $maxypos;
    $boxsize = $areasize * $boxscale;

    #
    # Reset holding variables
    #
    $maxsum = 0;
    $maxxpos = 0;
    $maxypos = 0;
#    printf("********************%.4f, %d, %.4f, %.4f, %.4f\n",
#        $result->{'boxsize'}, $result->{'count'},
#        $result->{'density'}, $result->{'xposition'}, $result->{'yposition'});
}

open(RES,">> $resfile") or die "could not open $resfile for writing\n";
open(DEN,"> $densplot") or die "could not open $densplot for writing\n";
open(GNU,"> $gnufile") or die "could not open $gnufile for writing\n";

#
# Print headers
#
print(RES "basestudy, label, integral, normalised,
      norm_v_log\n") if ($newres);
print(DEN "Boxsize, log_Size, Area, log_Area, Count, Density,
```

```
      Normalised density, X, Y\n");

my $prevnormdens = 0;
my $c = 1;
for my $r (@results) {

    $r->{'normdensity'} = ($r->{'density'}/$maxdensity) * 100;

    #
    # Calculate integrals for densities normalised to max
    # Do it the same way as before
    #
    $normintegral += ($r->{'normdensity'} + $prevnormdens)/2 *
        ($r->{'areasize'}**2 - $r->{'boxsize'}**2)
        if ($prevnormdens != 0);

    #
    # Also against a log x scale - this give more prominence to smaller
    # boxsize. Mulitple by 1000 so we're working with positive numbers
    # milliseconds not seconds
    #
    $normlogintegral += ($r->{'normdensity'} + $prevnormdens)/2 *
        (log((1000 * $r->{'areasize'})**2) - log((1000 * $r->{'boxsize'})**2))
        if ($prevnormdens != 0);

    #
    # Set the previous density to carry over
    #
    $prevnormdens = $r->{'normdensity'};

    #
    # And output results to file
    #
    printf(DEN "%.4f, %.4f, %.4f, %.4f, %d, %.4f, %.4f, %.4f,
                %.4f, %.4f, %.4f\n",
                $r->{'boxsize'}, log(1000 * $r->{'boxsize'}),
                ($r->{'boxsize'})**2, log((1000 *$r->{'boxsize'})**2),
                 $r->{'count'}, $r->{'density'}, $r->{'normdensity'},
                 $r->{'xposition'}, $r->{'yposition'});

    printf(GNU "set object %d rect from %.4f,%.4f to
                 %.4f,%.4f fc ls 2 fs empty\n", $c,
                 $r->{'xposition'}, $r->{'yposition'},
                 $r->{'xposition'} + $r->{'boxsize'},
                 $r->{'yposition'} + $r->{'boxsize'});

    #
    # Increment counter
    #
    $c++
}

printf(RES "%s,%s,%.2f,%.2f,%.2f\n", $stdy, $label, $areaintegral,
       $normintegral, $normlogintegral);
```

```
printf("%s: %s\n", $stdy, $label);
printf("\tIntegral = %.2f\n", $areaintegral);
printf("\tNormalised Integral = %.2f\n", $normintegral);
printf("\tNormalised log Integral = %.2f\n", $normlogintegral);

exit 0
```

A.3. Curve analysis

The following script calculates the end-diastolic and end-systolic points in curve data supplied to it in the form of a string of numbers; from this the ejection fraction is calculated.

```
#!/bin/awk -f

BEGIN{
    ed_pt = max2_pt = 0
    max = ed = max2 = 0
    min_pt = es_pt = 0
    es = 0;
    ef = 0
}

#
# First max point (ED)
#
{
if (min_pt == 0 && $1 > ed){
    ed_pt = NR
    ed = min = $1
}
#
# Min point after first max found
#
if (NR > ed_pt && $1 < min){
    min_pt = NR
    min = $1
}
#
# True min must be followed by a change of at least 1/3 ED to ES
#
if((min_pt != 0) && (NR > min_pt) && ($1 > (ed - min)/3 + min)){
    es = min
    es_pt = min_pt
}

#
# If we've found a true minimum, what is the final max
#
if((es_pt != 0) && (NR > es_pt) && ($1 > max2)){
    max2_pt = NR
    max2 = $1
}
if($1 > max){
    max_pt = NR
    max = $1
}
}
END {
```

```
#
# Ejection fraction is from first max point to true minimum
#
  if(es_pt != 0){
    ef = ((ed - es) / ed)* 100
  }

  if (inline == 1){
    printf("%d,%d,%d,%d,%d,%d,%d,%d,%d,%d,%.2f\n", ed_pt, ed,
        max2_pt, max2, es_pt, es, min_pt, min, max_pt, max, ef);
  }
  else {
    printf("Ed_Pt:=%d\nEd:=%d\nMax2_Pt:=%d\nMax2:=%d\nEs_Pt:=%d\nEs:=%d\n
            Min_Pt:=%d\nMin:=%d\nMax_Pt:=%d\nMax:=%d\nEF:=%.2f\n",
            ed_pt, ed, max2_pt, max2, es_pt, es, min_pt, min, max_pt, max, ef);
  }
}
```

A.4. Shannon Entropy

This Perl script takes a file with line by line values representing the frequency of R-R intervals in each bin and calculates the Shannon Entropy for that file.

```
#!/usr/bin/perl
#
###############################################################################
#
# File: shannon_entropy.perl
# Author: Sandy Small
# Date:
#
###############################################################################
#
# Description:
#    Given a file corresponding to a histogram, work out the Shannon Entropy.
#
# Parameters:
#   None
#
# History:
#
# CVS $Revision$ $Date$
###############################################################################

#------------------------------------------------------------------------------
# Add library
#------------------------------------------------------------------------------
#use lib "$ENV{HOME}/perllib";

#------------------------------------------------------------------------------
# Call Modules
#------------------------------------------------------------------------------
use Getopt::Std;      # Command line parsing

#------------------------------------------------------------------------------
# Pragmas
#------------------------------------------------------------------------------

use warnings;                 # Give warnings about variable use etc.
no warnings "uninitialized";  # Don't warn about unitialized variables
                              # I use this "feature"
use strict 'vars';    # Force all variables to have defined scope

#------------------------------------------------------------------------------
# Global variables
#------------------------------------------------------------------------------
our ($opt_T, $opt_t, $opt_b, $opt_c,);

#------------------------------------------------------------------------------
# Some functions
```

```
#-----------------------------------------------------------------------


# log Returns the natural logarithm (base e) of EXPR. If EXPR is
# omitted, returns log of $_ . To get the log of another base, use
# basic algebra: The base-N log of a number is equal to the natural log
# of that number divided by the natural log of N. For example:
# The following holds:  log2(x) = ln(x) / ln(2)
#                     :  log10(x) = ln(x) / ln(10)

sub log10 {
    my $n = shift;
    return log($n)/log(10);
}
sub log2 {
    my $n = shift;
    return log($n)/log(2);
}


#-----------------------------------------------------------------------
# Main program
#-----------------------------------------------------------------------


#
# Shannon Entropy is given by
# H = - sum_from_1_to_n probability of x_i * log (probability of x_i)
#

#
# We will call the states (i) the bins of the histogram.
#

# So read the values in the file into a perl array

my (@fields, @data);

while (<>) {

    #
    # get each field in turn
    #
    @fields = split /\s/, $_;
    push(@data, $fields[1]);
}

my $sum;
for my $i (0 .. $#data) {
    $sum += $data[$i];
}

my $entropy;
for my $i (0 .. $#data) {
```

```
    my $p = $data[$i] / $sum;

    #
    # If p is 0 it won't change the entropy (defined),
    # but the program will complain
    # because it will try to take a log(0) so check.
    #
    $entropy += -1 * $p * log($p) if ($p != 0)
}

printf("%3.2f\n", $entropy);

exit 0;
```

A.5. Symbolic Dynamics

This script takes a stream of R-R intervals (separated by spaces) and calculates the position of each point in the Poincaré plot. The list of positions are then converted into a stream of symbols (letters) depending on where they lie in the Poincaré plot and the number of standard deviations (-l parameter) of all R-R intervals being used to define areas of the plot. Frequencies of "words" of length n (defined by -m parameter) are calculated and output to standard out. The Shannon entropy of the symbolic dynamic sequence for those values of -l and -m can be calculated by piping the output of this script to the Shannon entropy script defined in section A.4.

```
#!/usr/bin/perl
#
###############################################################################
#
# File: symbolic_dynamics.perl
# Author: Sandy Small
# Date:
#
###############################################################################
#
# Description:
#
# Parameters:
#
# History:
#
# NC CVS ID: $Date: $ $Revision:  $
###############################################################################

#------------------------------------------------------------------------------
# Add library
#------------------------------------------------------------------------------

#------------------------------------------------------------------------------
# Call Modules
#------------------------------------------------------------------------------
#use Pg;          # Postgres communication functions
use Getopt::Std; # Command line parsing

#------------------------------------------------------------------------------
# Pragmas
#------------------------------------------------------------------------------

use warnings;                 # Give warnings about variable use etc.
no warnings "uninitialized";  # Don't warn about unitialized variables
                              # I use this "feature"
use strict 'vars';    # Force all variables to have defined scope

#------------------------------------------------------------------------------
```

```
# Global variables
#-----------------------------------------------------------------------------
our ($opt_l, $opt_m);

#-----------------------------------------------------------------------------
# Local Sub Functions
#-----------------------------------------------------------------------------

#-----------------------------------------------------------------------------
# Main program
#-----------------------------------------------------------------------------

#
# Sort out command line
#

my $maxsds = 3;
my $letters = 3;

getopts('l:m:');

$letters = $opt_l if ($opt_l ne "") ;
$maxsds = $opt_m if ($opt_m ne "") ;

my $alphabet = "ABCDEFGHIJKLMNOPQRSTUVWXYZ";
my @vals;

#
# Put all values into an array - include all lines
#
while (<>){
    my @tmp = split(/\s+/);
    push(@vals, @tmp);
}

#
# Loop through once - calculating standard deviation etc
#
my ($sum, $sumsq, $diff, $sumdiffsq) = 0;
for (my $i = 1; $i<=$#vals - 1; $i++){
    $sum += $vals[$i];
    $sumsq += $vals[$i] ** 2;
    $diff = $vals[$i] - $vals[$i+1];
    $sumdiffsq += $diff ** 2;
}

my $sd = sqrt(($sumsq/($#vals + 1)) - ($sum/($#vals +1))**2);
my $rmsd = sqrt($sumdiffsq/($#vals + 1));

#
# Loop through again to get words
#

my $countshort;
```

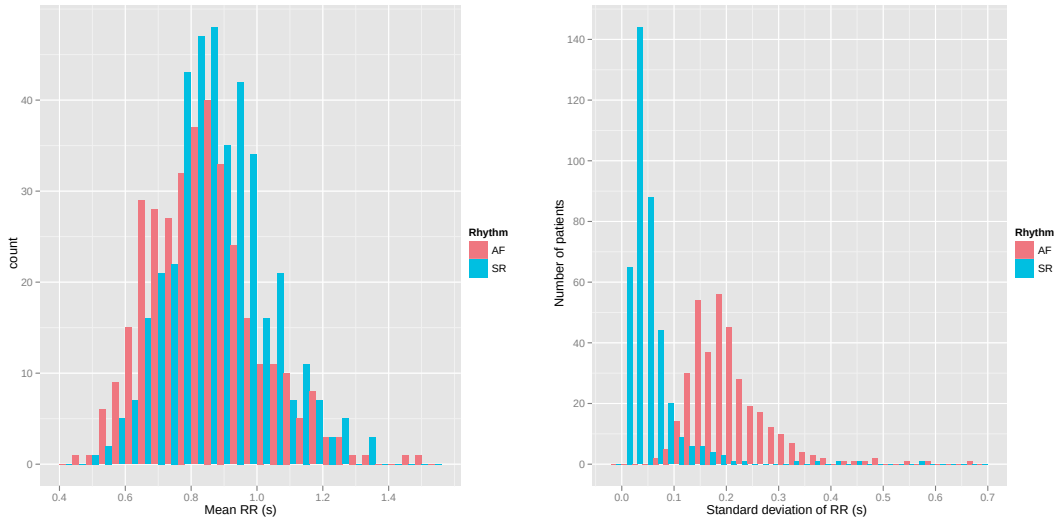
```
my $word;

for(my $i=1; $i<=$#vals - 1; $i++){
    my $x = $vals[$i];
    my $y = $vals[$i+1];
    my $tmp = (($x == $y) ? 1 : ($y - $x) / $sd + (($y-$x) / abs($y-$x)));
    my $posnum = int($tmp);

    #
    # Only go to the number of sds specified
    $posnum = $maxsds if ($posnum > $maxsds);
    $posnum = $maxsds * -1 if (abs($posnum) > $maxsds);

    my $letnum = 13 + $posnum;

    # Find the appropriate letter in the alphabet
    # Actually this is semantic but its a nice thing to do
    my $sym = substr($alphabet,$letnum,1);

    if ($i > $letters){
        $word=sprintf("%s%s", substr($word,1,$letters-1), $sym);
$countshort->{$word}++;
    }
    else{
        $word=sprintf("%s%s", $word, $sym);
$countshort->{$word}++ if ($i == $letters);
    }
}

foreach my $word (sort(keys(%$countshort))){
    printf("%s\t%d\n", $word, $countshort->{$word});
}
```

Appendix B.

Rhythm results: supporting data

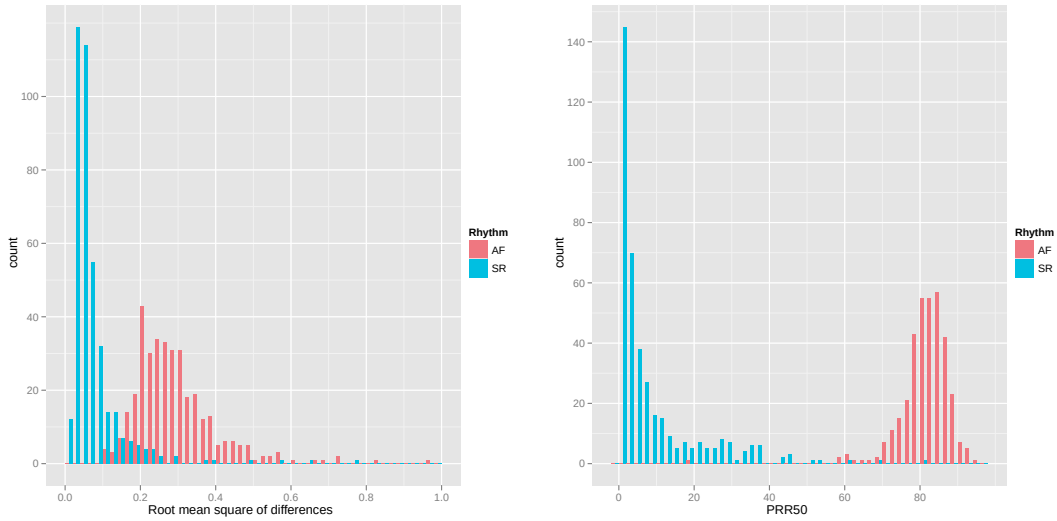
B.1. Unlimited variability results

While variability results were calculcated using the limits which were imposed on the R-R intervals for the functional processing, other assessments of rhythm were calculated using all the data. For comparison the results calculated from the whole data without excluding ectopics etc. are shown here.



(a) Mean R-R **(b)** SDRR

Figure B.1.: Histograms showing distribution of Mean R-R and SDRR calculated using all beats without excluding ectopics etc..



(a) $RMSSD_{rr}$ **(b)** pRR50

Figure B.2.: Histograms showing distribution of $RMSSD_{rr}$ and pRR50 calculated using all beats without excluding ectopics etc..

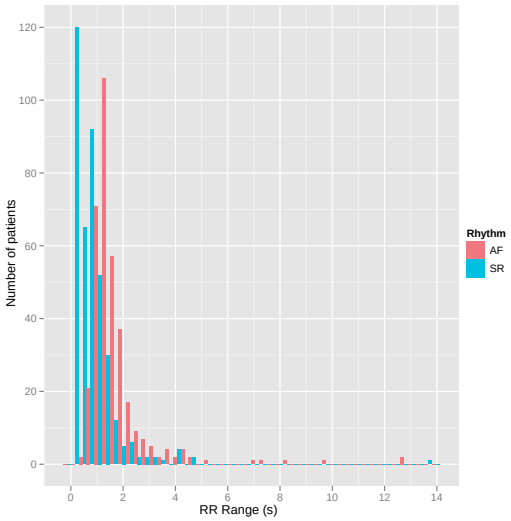


Figure B.3.: Histogram showing distribution of R-R range calculated using all beats.

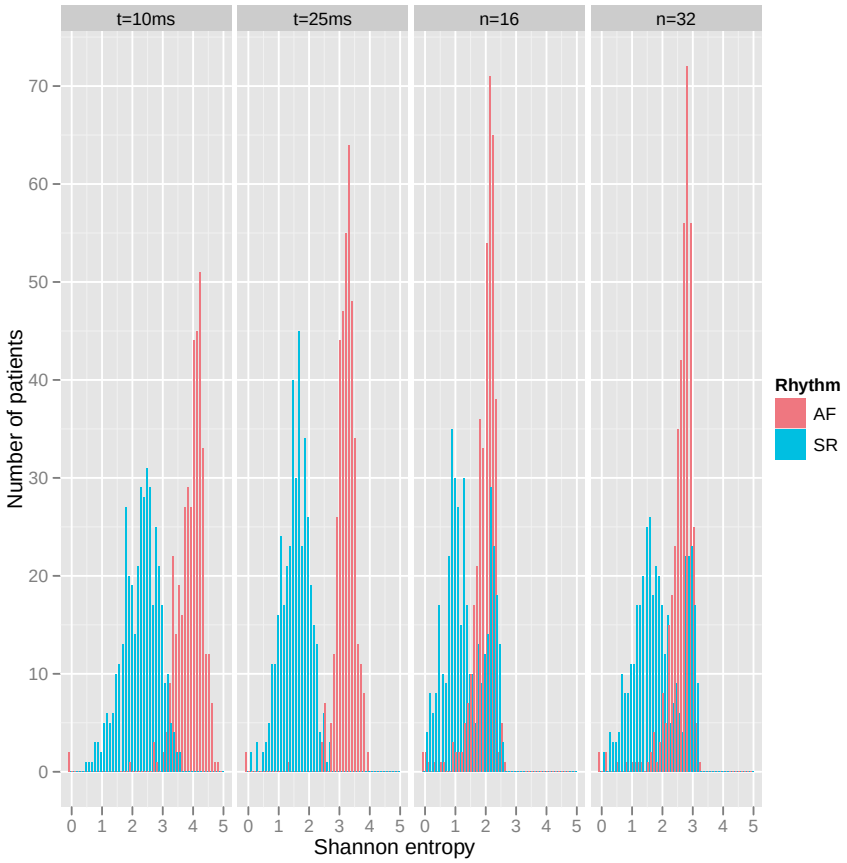


Figure B.4.: Histogram showing the Shannon entropy calculated from the "A" view for those patients definitely identified as being in AF and Sinus rhythm using unlimited R-R data (without excluding ectopics etc.).

Appendix C.

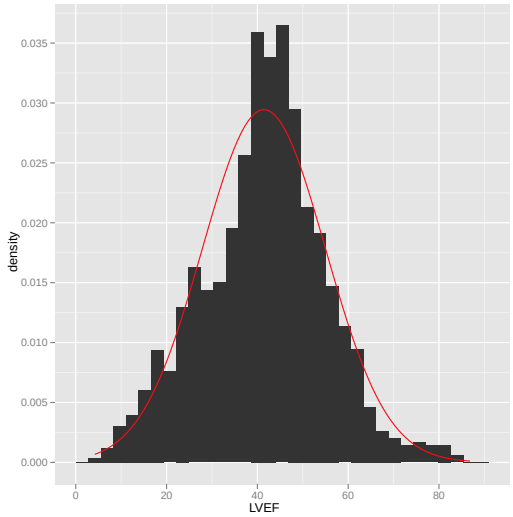
Function results: supporting data

C.1. Normality

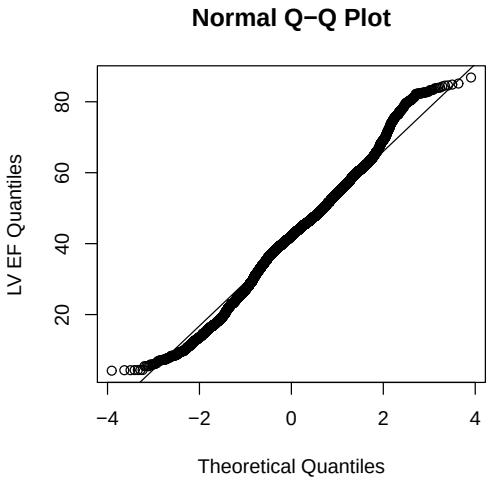
To assess whether data is normally distributed or not two plots were produced for each data set: a histogram with superimposed normal distribution and a QQ normality plot which plots the actual quantiles against the theoretical quantiles from a normal distribution. The closer the plot is to being linear the more closely the distribution is to being normal. None of the measures can really be described as normally distributed in either SR or AF, although most of them approximate to it. Only one variable required a major transformation: pre-systolic volume, where a logarithmic transformation brings approximate normality.

Plots are as follows:

- *LVEF* in Figure C.1 (SR) and Figure C.2 (AF)
- *Systolic time* in Figure C.3 (SR) and Figure C.4 (AF)
- *PSV* in Figure C.5 (SR) and Figure C.6 (AF)
- *log(PSV)* in Figure C.7 (SR) and Figure C.8 (AF)
- *EDV/PSV* in Figure C.9 (SR) and Figure C.10 (AF)
- *FTFF* in Figure C.11 (SR) and Figure C.12 (AF)
- *PFR* in Figure C.13 (SR) and Figure C.14 (AF)

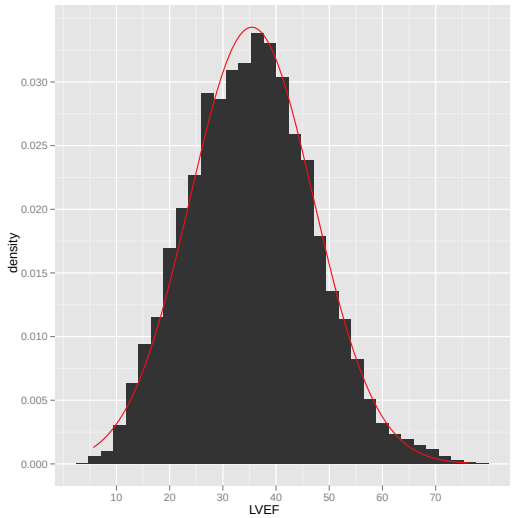


(a) LVEF histogram

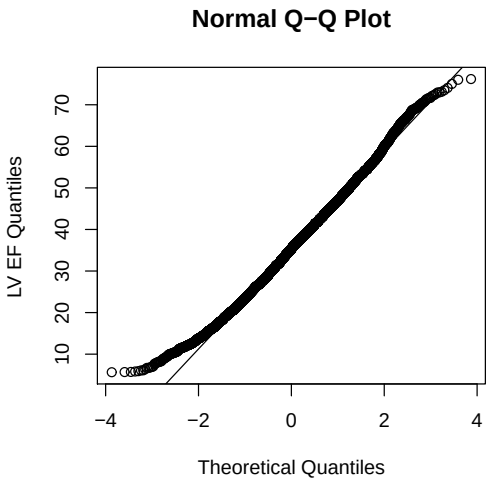


(b) LVEF

Figure C.1.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for LVEF in SR.

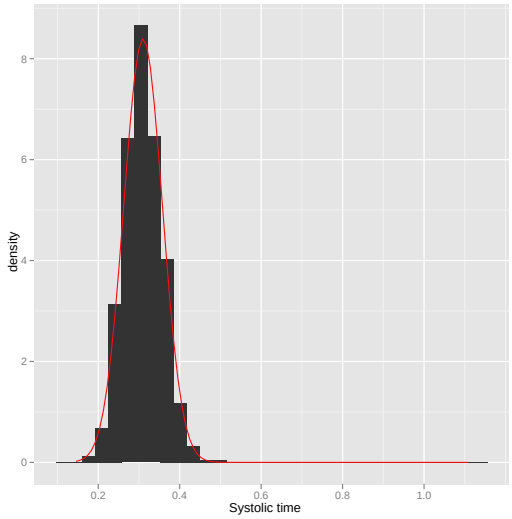


(a) LVEF histogram

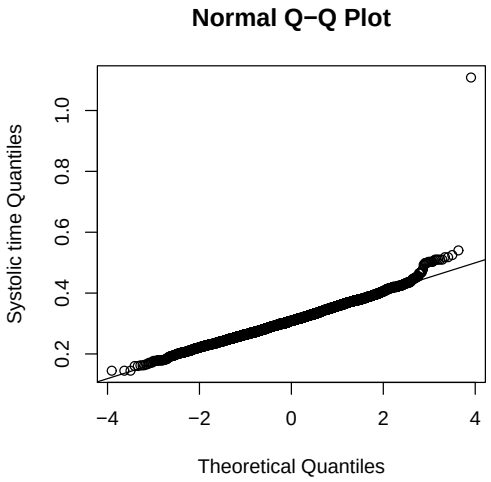


(b) LVEF

Figure C.2.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for LVEF in AF.

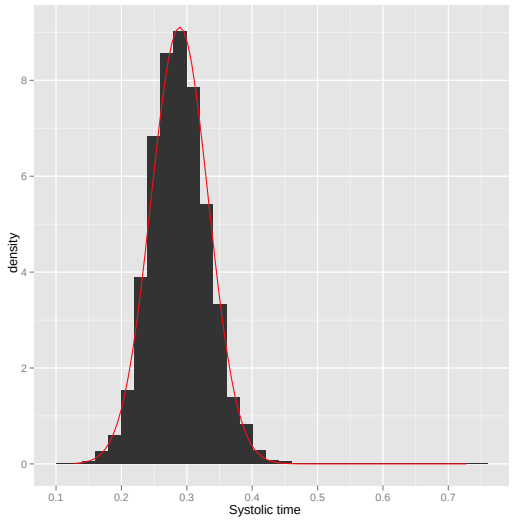


(a) Systolic time histogram

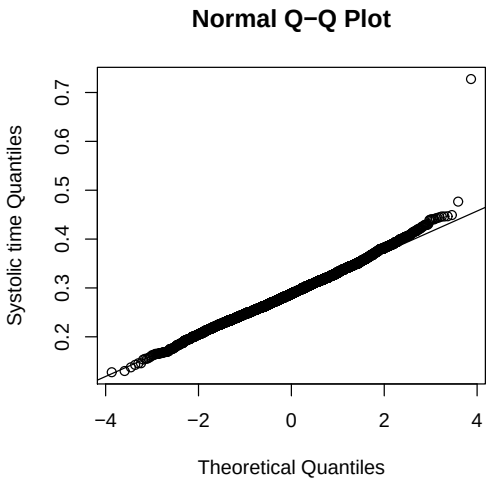


(b) Systolic time

Figure C.3.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for systolic time interval in SR.

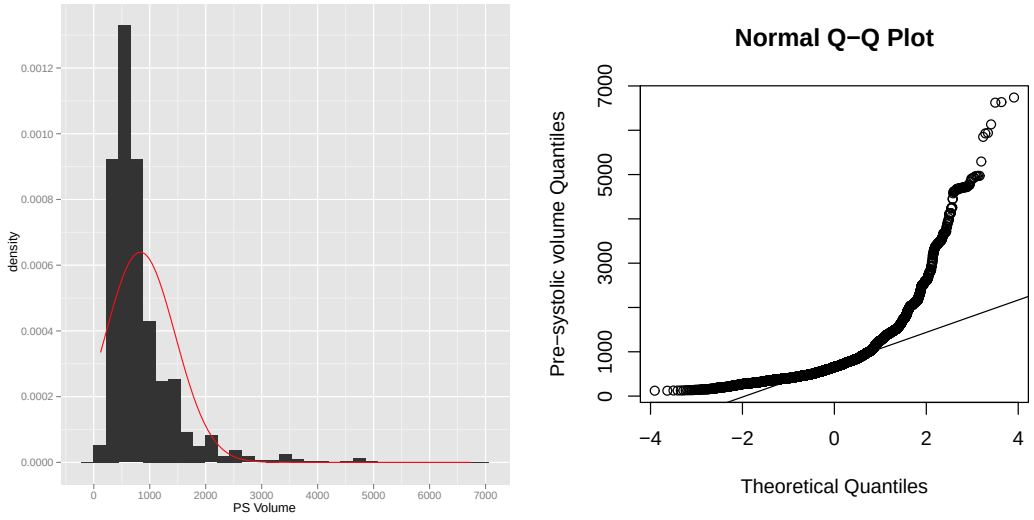


(a) Systolic time histogram



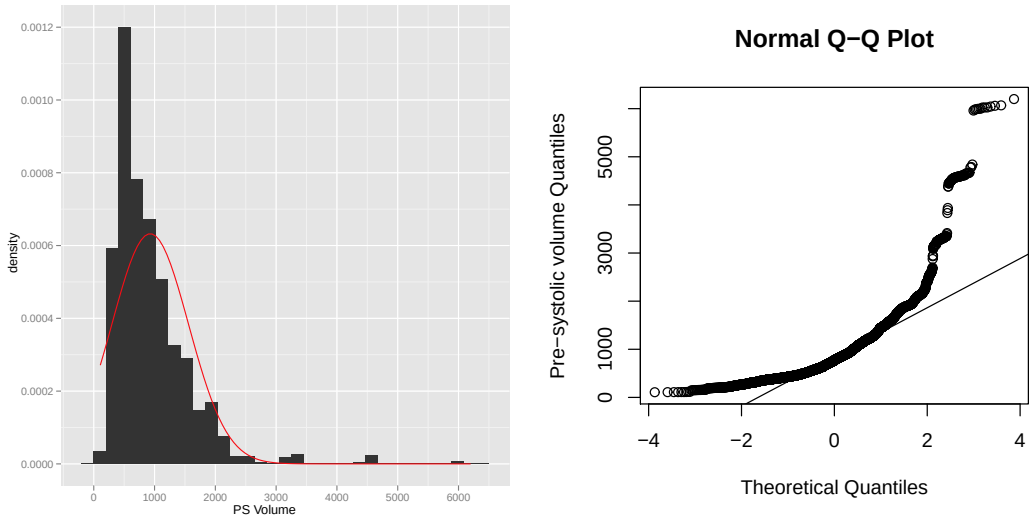
(b) Systolic time

Figure C.4.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for systolic time interval in AF.



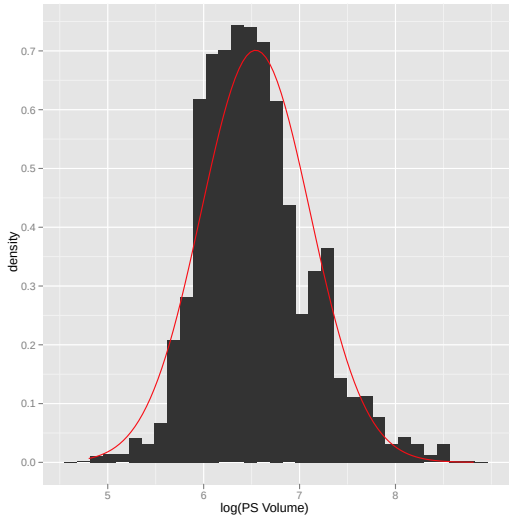
(a) PSV histogram **(b)** PSV

Figure C.5.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for PSV interval in SR.

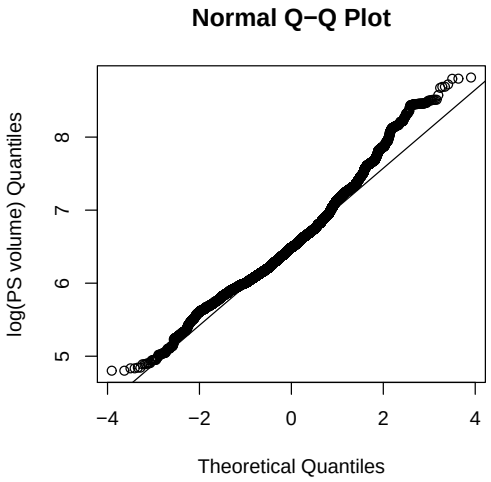


(a) PSV histogram **(b)** PSV volume

Figure C.6.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for PSV interval in AF.

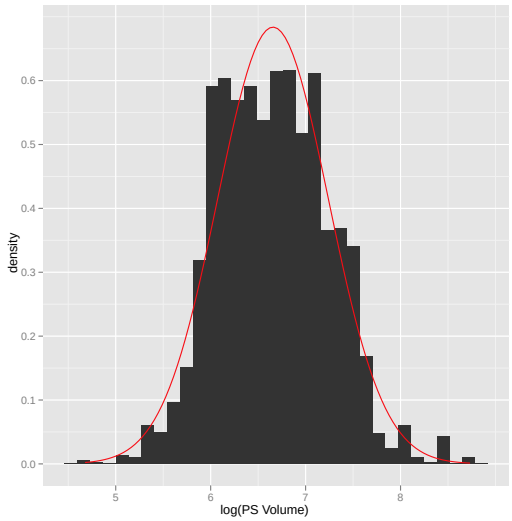


(a) log(PSV) histogram

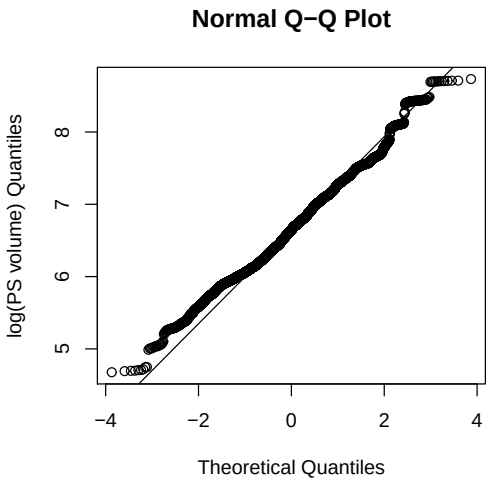


(b) log(PSV)

Figure C.7.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for logarithm of PSV interval in SR.

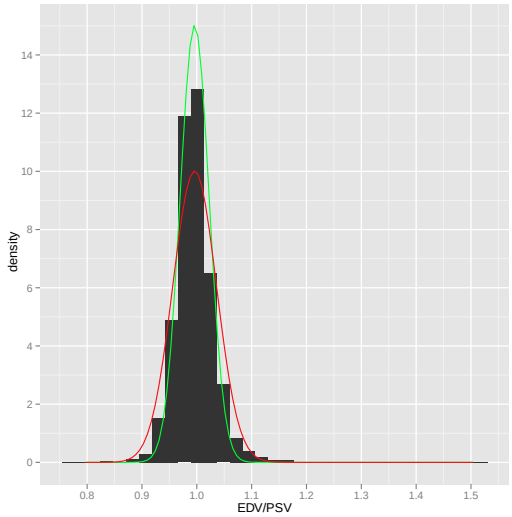


(a) log(PSV) histogram

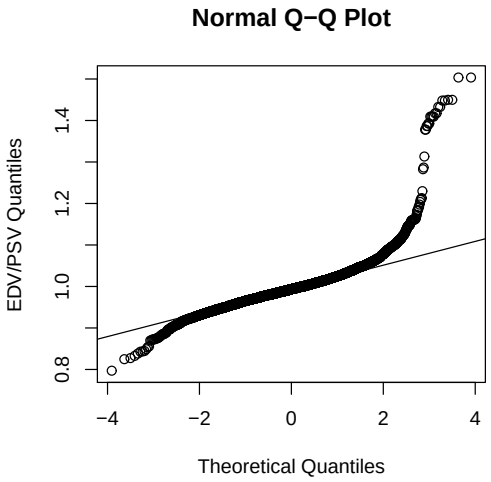


(b) log(PSV)

Figure C.8.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for logarithm of PSV interval in AF.

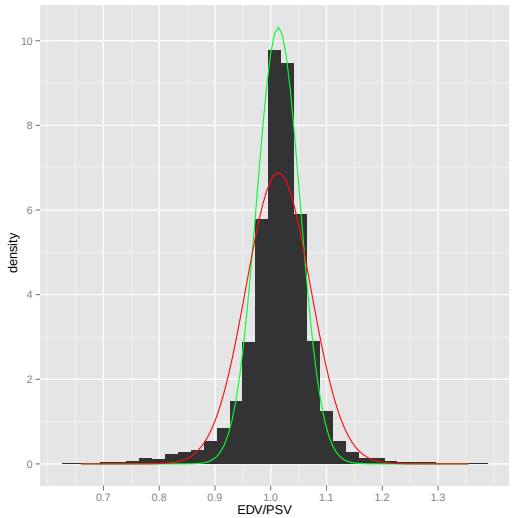


(a) EDV/PSV histogram

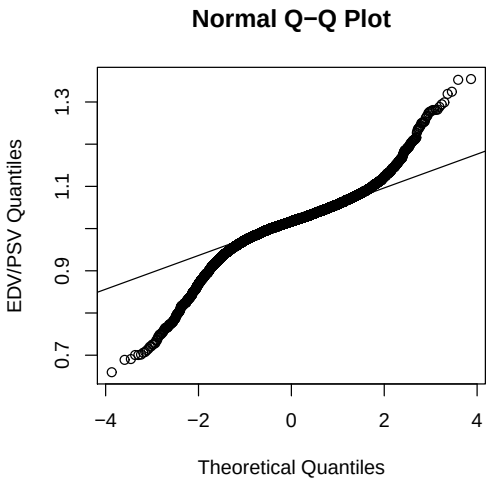


(b) EDV/PSV ratio

Figure C.9.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for EDV/PSV in SR.

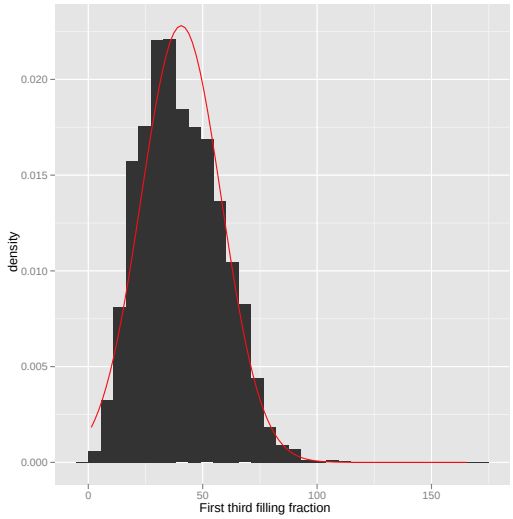


(a) EDV/PSV histogram

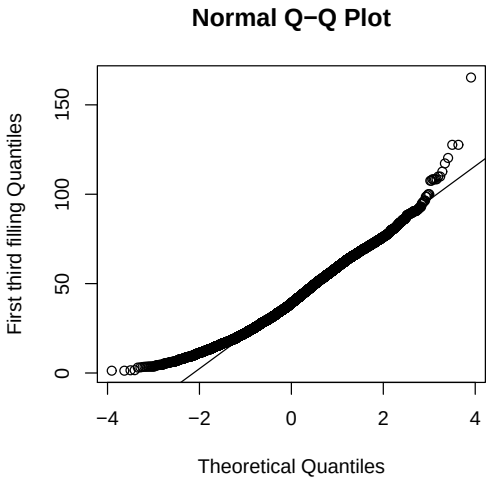


(b) EDV/PSV ratio

Figure C.10.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for EDV/PSV in AF.

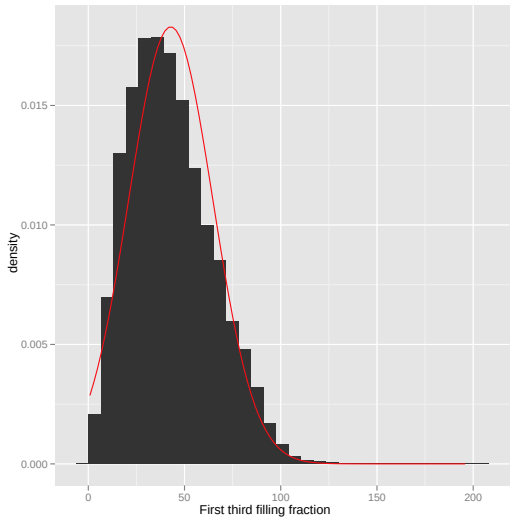


(a) FTFF histogram

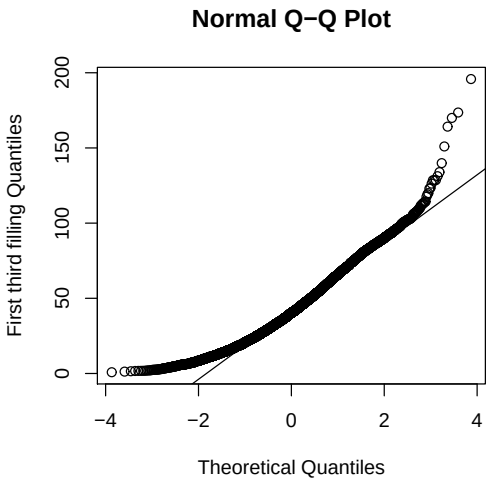


(b) FTFF

Figure C.11.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for FTFF in SR.

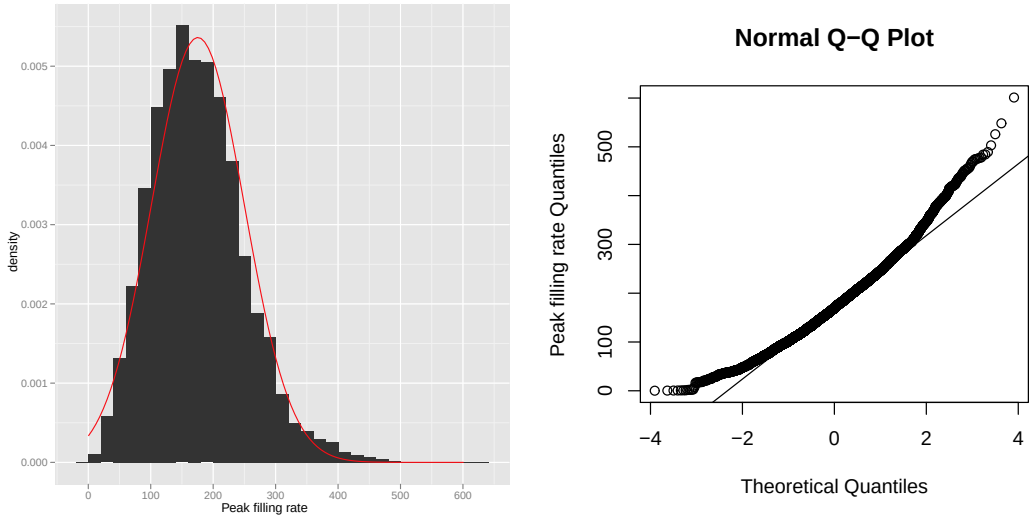


(a) FTFF histogram



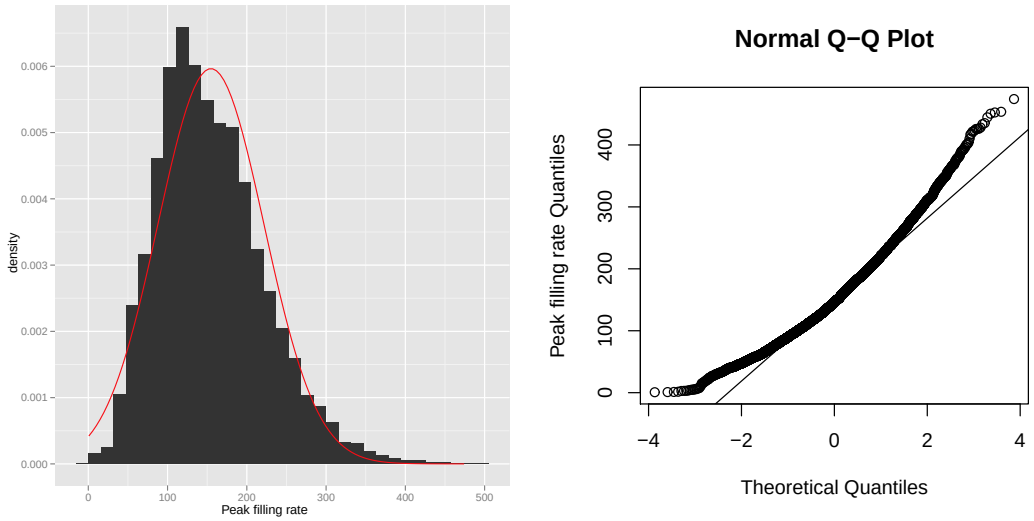
(b) FTFF

Figure C.12.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for FTFF in AF.



(a) PFR histogram **(b)** PFR

Figure C.13.: SR: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for PFR in SR.



(a) PFR histogram **(b)** PFR

Figure C.14.: AF: Showing (a) the histogram with a normal distribution overlaid and (b) the QQ normality plot for PFR in AF.

C.2. LVEF subgroup aggregated results tables

The variation in LVEF with beat selection criteria in different clinical subgroups has been tested and the results reported in §5.4.3. The results for the each group with different beat selection criteria are summarised in the following tables:

- "Pure": Table C.1 and Table C.2 (AF)
- Not "Pure": Table C.3 (SR) and Table C.4 (AF)
- MI: Table C.5 (SR) and Table C.6 (AF)
- No MI: Table C.7 (SR) and Table C.8 (AF)
- HBP: Table C.9 (SR) and Table C.10 (AF)
- Without HBP: Table C.11 (SR) and Table C.12 (AF)
- CABG &/or PCI: Table C.13 (SR) and Table C.14 (AF)
- Without CABG &/or PCI: Table C.15 (SR) and Table C.16 (AF)
- Non-ischaemic: Table C.17 (SR) and Table C.18 (AF)
- Ischaemic: Table C.19 (SR) and Table C.20 (AF)
- Negative ETT: Table C.21 (SR) and Table C.22 (AF)
- Positive ETT: Table C.23 (SR) and Table C.24 (AF)
- Very poor and Poor function: Table C.25 (SR) and Table C.26 (AF)
- Moderate and mildly impaired function: Table C.27 (SR) and Table C.28 (AF)
- Normal function: Table C.29 (SR) and Table C.30 (AF)

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	39.5 ± 15.0	39.5 ± 15.0	41.4 ± 13.4	41.7 ± 13.4	41.2 ± 14.1	41.8 ± 14.4
	Best	39.6 ± 14.8	39.5 ± 15.0	41.4 ± 13.4	41.8 ± 13.5	41.1 ± 14.2	41.8 ± 14.4
	Q1	41.5 ± 13.3	41.4 ± 13.5	45.9 ± 11.8	46.1 ± 11.7	45.7 ± 11.8	46.4 ± 12.3
	Q2	41.3 ± 13.7	41.1 ± 13.9	46.6 ± 12.1	45.1 ± 12.0	45.9 ± 11.4	46.2 ± 12.2
	Q3	41.3 ± 13.9	41.2 ± 13.9	45.7 ± 12.4	45.1 ± 12.5	46.0 ± 11.9	45.8 ± 12.2
	Q4	41.7 ± 14.4	41.7 ± 14.3	45.8 ± 12.9	45.2 ± 12.1	46.4 ± 12.1	45.9 ± 12.6

Table C.1.: SR, "pure", LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR "pure" group with variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	29.4 ± 11.4	33.6 ± 12.4	36.0 ± 11.6	35.1 ± 11.8	34.6 ± 12.1	33.5 ± 12.0
	Best	29.3 ± 10.9	35.2 ± 11.1	39.2 ± 10.1	37.5 ± 10.6	36.5 ± 10.8	35.4 ± 10.7
	Q1	29.3 ± 10.2	36.7 ± 10.3	41.6 ± 10.0	39.5 ± 9.7	39.2 ± 9.2	38.2 ± 9.4
	Q2	30.4 ± 10.4	37.4 ± 11.1	43.0 ± 9.4	40.8 ± 9.7	40.2 ± 10.1	38.0 ± 10.7
	Q3	32.2 ± 10.9	39.1 ± 11.5	44.7 ± 9.9	41.6 ± 10.9	41.0 ± 11.1	39.0 ± 11.0
	Q4	34.7 ± 11.4	41.0 ± 12.2	44.8 ± 11.0	43.5 ± 11.9	42.1 ± 12.0	40.9 ± 11.6

Table C.2.: AF, "pure", LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF "pure" group with variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	37.0 ± 14.3	37.1 ± 14.3	38.9 ± 12.7	38.9 ± 13.1	39.2 ± 13.3	39.2 ± 13.3
	Best	37.1 ± 14.3	37.1 ± 14.3	38.9 ± 12.8	39.0 ± 13.1	39.4 ± 13.2	39.1 ± 13.2
	Q1	39.3 ± 12.8	39.4 ± 12.8	44.7 ± 12.9	44.3 ± 13.1	45.5 ± 11.5	45.7 ± 11.8
	Q2	39.3 ± 13.1	39.3 ± 13.2	44.5 ± 12.8	43.9 ± 13.5	43.6 ± 12.6	45.0 ± 12.6
	Q3	38.7 ± 13.4	38.7 ± 13.4	43.5 ± 12.5	43.8 ± 13.0	42.9 ± 13.1	44.6 ± 12.6
	Q4	39.1 ± 13.0	39.2 ± 12.8	44.3 ± 12.0	43.7 ± 12.5	44.0 ± 12.5	45.4 ± 12.6

Table C.3.: SR, "not pure", LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR "not pure" group with variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	27.0 ± 10.8	31.7 ± 11.3	33.6 ± 10.4	32.7 ± 11.2	32.7 ± 11.1	30.6 ± 10.9
	Best	28.1 ± 10.0	33.3 ± 10.8	36.0 ± 10.0	35.6 ± 10.4	34.4 ± 10.9	32.6 ± 10.2
	Q1	27.0 ± 9.1	33.8 ± 9.6	38.4 ± 10.7	37.0 ± 9.9	36.3 ± 9.2	34.0 ± 9.7
	Q2	28.7 ± 10.1	35.1 ± 10.5	38.9 ± 10.7	38.0 ± 11.2	37.2 ± 10.7	35.8 ± 10.4
	Q3	29.9 ± 10.3	36.0 ± 10.9	39.6 ± 10.2	38.6 ± 10.7	38.1 ± 11.6	35.9 ± 10.7
	Q4	32.1 ± 10.6	38.0 ± 11.6	42.5 ± 11.9	40.5 ± 10.9	40.1 ± 10.8	37.6 ± 10.9

Table C.4.: AF, "not pure", LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF "not pure" group with variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	31.2 ± 16.0	31.2 ± 16.0	33.7 ± 14.5	33.6 ± 15.2	33.7 ± 15.3	33.7 ± 15.6
	Best	31.2 ± 16.0	31.2 ± 16.0	33.5 ± 14.6	33.6 ± 15.3	33.8 ± 15.2	33.7 ± 15.6
	Q1	34.1 ± 14.6	33.9 ± 14.9	41.2 ± 14.6	40.4 ± 14.3	40.6 ± 13.5	42.4 ± 13.7
	Q2	33.4 ± 15.2	33.4 ± 15.2	41.6 ± 13.5	39.2 ± 13.7	41.3 ± 13.7	41.0 ± 14.3
	Q3	33.2 ± 15.3	33.2 ± 15.4	40.8 ± 15.2	40.9 ± 14.3	39.6 ± 14.0	40.1 ± 14.0
	Q4	33.6 ± 15.5	33.9 ± 15.4	40.6 ± 15.0	40.0 ± 14.2	41.8 ± 14.6	40.4 ± 14.8

Table C.5.: SR, MI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with previous known MI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	26.4 ± 10.8	30.4 ± 11.9	32.0 ± 10.8	32.0 ± 11.4	31.5 ± 11.3	30.0 ± 11.3
	Best	26.6 ± 10.0	32.0 ± 10.6	34.4 ± 9.9	34.1 ± 10.1	32.3 ± 11.0	31.7 ± 10.3
	Q1	25.8 ± 9.3	33.0 ± 10.0	39.0 ± 7.8	37.2 ± 9.9	36.3 ± 8.4	34.3 ± 9.0
	Q2	27.3 ± 9.9	33.6 ± 11.1	38.9 ± 9.4	38.0 ± 9.8	37.5 ± 10.3	34.6 ± 10.0
	Q3	29.0 ± 10.6	35.4 ± 11.4	41.6 ± 10.1	38.5 ± 10.8	37.5 ± 11.1	35.3 ± 11.3
	Q4	31.3 ± 11.2	37.4 ± 12.3	41.9 ± 10.7	40.3 ± 11.4	39.2 ± 11.4	37.7 ± 11.7

Table C.6.: AF, MI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with previous known MI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	40.9 ± 13.2	41.0 ± 13.2	42.4 ± 11.7	42.7 ± 11.6	42.6 ± 12.3	42.9 ± 12.3
	Best	41.0 ± 13.1	40.9 ± 13.2	42.5 ± 11.7	42.8 ± 11.7	42.5 ± 12.3	42.9 ± 12.3
	Q1	42.7 ± 11.6	42.8 ± 11.6	46.8 ± 11.2	46.9 ± 11.4	47.2 ± 10.6	47.4 ± 11.2
	Q2	42.9 ± 11.7	42.8 ± 11.8	47.1 ± 11.8	46.6 ± 11.7	46.1 ± 11.1	47.3 ± 11.2
	Q3	42.5 ± 12.1	42.4 ± 12.1	46.0 ± 11.1	46.0 ± 11.7	46.3 ± 11.5	47.0 ± 11.2
	Q4	42.9 ± 12.1	42.9 ± 12.0	46.7 ± 11.1	46.3 ± 11.0	46.7 ± 11.0	47.8 ± 10.9

Table C.7.: SR, non-MI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients excluding those with previous known MI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	29.1 ± 11.3	33.7 ± 11.8	36.1 ± 10.9	34.7 ± 11.6	34.6 ± 11.6	33.0 ± 11.5
	Best	29.7 ± 10.6	35.3 ± 11.0	39.0 ± 10.0	37.7 ± 10.5	37.1 ± 10.5	35.1 ± 10.4
	Q1	29.3 ± 9.7	36.2 ± 9.9	40.5 ± 11.2	38.5 ± 9.9	38.5 ± 9.6	37.1 ± 9.9
	Q2	30.7 ± 10.2	37.6 ± 10.5	41.7 ± 10.5	40.1 ± 10.7	39.4 ± 10.5	38.0 ± 10.6
	Q3	32.0 ± 10.6	38.4 ± 11.2	42.2 ± 10.5	40.9 ± 10.8	40.5 ± 11.4	38.5 ± 10.6
	Q4	34.4 ± 10.9	40.4 ± 11.8	44.6 ± 11.7	42.8 ± 11.4	42.0 ± 11.4	40.1 ± 11.2

Table C.8.: AF, non-MI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients excluding those with previous known MI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	41.3 ± 13.7	41.4 ± 13.7	41.9 ± 13.0	42.5 ± 12.9	42.6 ± 13.4	42.6 ± 13.6
	Best	41.3 ± 13.8	41.3 ± 13.8	42.0 ± 13.0	42.6 ± 12.9	42.5 ± 13.4	42.6 ± 13.5
	Q1	42.6 ± 12.6	42.6 ± 12.6	48.4 ± 12.0	47.3 ± 11.8	47.9 ± 11.1	48.0 ± 11.7
	Q2	42.6 ± 13.1	42.4 ± 13.3	47.7 ± 12.8	47.0 ± 12.3	47.1 ± 11.4	49.1 ± 11.7
	Q3	42.4 ± 13.5	42.3 ± 13.5	47.4 ± 12.3	46.6 ± 11.7	46.3 ± 12.4	47.7 ± 11.9
	Q4	42.5 ± 13.0	42.5 ± 13.0	47.4 ± 12.0	46.8 ± 11.4	47.0 ± 10.9	48.1 ± 11.4

Table C.9.: SR, HBP, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with known hypertension using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	29.8 ± 11.7	34.2 ± 12.3	36.3 ± 11.5	35.7 ± 12.0	35.4 ± 12.2	33.8 ± 11.9
	Best	30.2 ± 11.0	35.9 ± 11.2	39.1 ± 10.5	38.4 ± 10.7	37.8 ± 11.3	35.5 ± 11.2
	Q1	29.3 ± 10.4	37.3 ± 10.6	42.4 ± 10.8	40.7 ± 10.6	40.1 ± 10.2	38.5 ± 10.6
	Q2	31.2 ± 10.8	38.0 ± 11.3	43.3 ± 10.6	41.6 ± 11.0	40.8 ± 11.4	39.3 ± 11.3
	Q3	32.8 ± 11.1	39.4 ± 11.9	44.3 ± 10.7	42.5 ± 11.5	42.4 ± 12.0	39.5 ± 12.0
	Q4	35.3 ± 11.4	41.4 ± 12.2	45.7 ± 12.2	44.4 ± 11.9	43.1 ± 12.2	40.9 ± 12.1

Table C.10.: AF, HBP, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with known hypertension using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	36.0 ± 14.9	36.0 ± 14.9	38.7 ± 13.0	38.5 ± 13.4	38.4 ± 13.7	38.8 ± 13.9
	Best	36.1 ± 14.8	36.0 ± 14.9	38.7 ± 13.1	38.6 ± 13.5	38.4 ± 13.6	38.7 ± 13.8
	Q1	38.8 ± 13.0	38.8 ± 13.2	43.6 ± 12.0	43.9 ± 12.6	44.0 ± 11.8	44.7 ± 12.1
	Q2	38.6 ± 13.4	38.6 ± 13.4	44.1 ± 12.0	43.2 ± 12.7	43.6 ± 12.1	43.6 ± 12.1
	Q3	38.1 ± 13.5	38.1 ± 13.5	42.7 ± 12.2	43.5 ± 13.1	43.4 ± 12.4	43.6 ± 12.3
	Q4	38.8 ± 13.9	39.0 ± 13.8	43.6 ± 12.6	43.3 ± 12.4	44.4 ± 12.9	44.3 ± 13.0

Table C.11.: SR, non-HBP, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients excluding those with known hypertension using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	26.7 ± 10.4	31.2 ± 11.3	33.4 ± 10.3	32.1 ± 10.9	32.0 ± 10.8	30.3 ± 10.8
	Best	27.3 ± 9.7	32.6 ± 10.5	36.0 ± 9.6	34.6 ± 9.9	33.3 ± 9.9	32.6 ± 9.5
	Q1	27.1 ± 8.7	33.3 ± 8.9	38.2 ± 9.6	36.0 ± 8.8	36.0 ± 8.1	34.3 ± 8.5
	Q2	28.1 ± 9.4	34.6 ± 9.9	38.8 ± 9.4	37.5 ± 9.5	37.0 ± 9.1	35.0 ± 9.4
	Q3	29.4 ± 9.9	35.6 ± 10.4	39.9 ± 9.5	38.0 ± 9.7	37.2 ± 10.2	35.6 ± 9.4
	Q4	31.6 ± 10.4	37.6 ± 11.5	42.0 ± 10.5	39.7 ± 10.5	39.3 ± 10.3	37.8 ± 10.3

Table C.12.: AF, non-HBP, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients excluding those with known hypertension using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	36.5 ± 16.1	36.5 ± 16.0	37.5 ± 14.9	37.7 ± 15.3	37.9 ± 16.1	37.0 ± 15.9
	Best	36.5 ± 16.1	36.5 ± 16.1	37.3 ± 15.0	37.7 ± 15.2	38.1 ± 15.9	37.0 ± 15.8
	Q1	38.0 ± 14.9	37.7 ± 15.1	43.7 ± 12.8	44.6 ± 13.4	44.9 ± 12.5	45.9 ± 13.0
	Q2	37.3 ± 15.5	37.0 ± 15.7	45.4 ± 12.9	42.9 ± 14.1	45.0 ± 12.8	44.5 ± 13.3
	Q3	37.5 ± 16.2	37.5 ± 16.2	44.5 ± 13.6	43.0 ± 12.8	43.3 ± 12.1	43.0 ± 12.3
	Q4	37.3 ± 15.4	37.6 ± 15.2	42.8 ± 13.0	43.0 ± 13.0	44.7 ± 13.7	44.9 ± 13.6

Table C.13.: SR, CABG &/or PCI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with previous CABG &/or PCI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	28.1 ± 11.4	32.0 ± 12.7	33.4 ± 12.2	32.4 ± 12.5	32.2 ± 12.4	30.6 ± 12.5
	Best	27.3 ± 11.4	32.5 ± 11.7	36.7 ± 11.3	33.7 ± 11.2	33.6 ± 11.7	32.4 ± 12.0
	Q1	26.7 ± 11.1	33.5 ± 11.5	40.0 ± 11.6	36.2 ± 11.8	36.4 ± 10.7	35.1 ± 11.6
	Q2	28.4 ± 11.4	34.4 ± 11.7	40.3 ± 11.2	38.0 ± 11.4	36.9 ± 11.6	34.5 ± 11.9
	Q3	29.7 ± 11.7	36.1 ± 12.5	40.8 ± 11.7	38.1 ± 12.0	37.7 ± 12.9	35.2 ± 12.3
	Q4	32.2 ± 11.7	38.1 ± 12.8	41.8 ± 12.2	40.0 ± 12.1	38.4 ± 12.3	37.0 ± 12.4

Table C.14.: AF, CABG &/or PCI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with previous CABG &/or PCI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	38.8 ± 14.2	38.8 ± 14.2	40.9 ± 12.4	41.0 ± 12.6	40.9 ± 12.9	41.4 ± 13.1
	Best	38.8 ± 14.1	38.8 ± 14.2	41.0 ± 12.4	41.0 ± 12.7	40.9 ± 12.9	41.4 ± 13.1
	Q1	41.1 ± 12.4	41.3 ± 12.4	46.1 ± 12.0	45.6 ± 12.1	45.9 ± 11.4	46.2 ± 11.8
	Q2	41.2 ± 12.6	41.2 ± 12.6	45.8 ± 12.4	45.3 ± 12.2	45.1 ± 11.7	46.2 ± 12.0
	Q3	40.7 ± 12.8	40.7 ± 12.8	44.8 ± 12.1	45.2 ± 12.6	45.0 ± 12.6	46.0 ± 12.2
	Q4	41.3 ± 13.0	41.3 ± 13.0	45.9 ± 12.2	45.3 ± 11.8	45.7 ± 11.7	46.2 ± 12.1

Table C.15.: SR, non CABG &/or PCI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients without previous CABG or PCI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	28.3 ± 11.1	32.8 ± 11.7	35.1 ± 10.8	34.2 ± 11.3	34.0 ± 11.4	32.4 ± 11.3
	Best	29.0 ± 10.2	34.7 ± 10.7	37.8 ± 9.9	37.3 ± 10.2	36.0 ± 10.7	34.4 ± 10.1
	Q1	28.5 ± 9.3	35.8 ± 9.5	40.1 ± 10.0	38.7 ± 9.2	38.2 ± 8.8	36.6 ± 9.1
	Q2	29.9 ± 10.0	36.7 ± 10.6	41.1 ± 10.0	39.8 ± 10.2	39.2 ± 10.2	37.6 ± 10.0
	Q3	31.4 ± 10.4	37.8 ± 11.0	42.3 ± 9.9	40.6 ± 10.5	40.0 ± 11.0	38.1 ± 10.5
	Q4	33.7 ± 10.9	39.8 ± 11.8	44.2 ± 11.3	42.5 ± 11.3	41.8 ± 11.1	39.9 ± 11.1

Table C.16.: AF, non CABG &/or PCI, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients without previous CABG or PCI using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	47.7 ± 10.5	47.7 ± 10.5	47.6 ± 10.7	48.4 ± 10.2	48.0 ± 10.9	49.0 ± 11.2
	Best	47.7 ± 10.5	47.7 ± 10.5	47.7 ± 10.8	48.6 ± 10.3	48.1 ± 10.9	48.8 ± 11.2
	Q1	47.6 ± 10.9	47.9 ± 10.7	50.7 ± 10.3	50.7 ± 10.1	51.2 ± 9.4	51.4 ± 10.4
	Q2	48.3 ± 10.7	48.3 ± 10.7	51.2 ± 10.5	51.4 ± 10.2	49.8 ± 9.8	51.1 ± 10.0
	Q3	47.9 ± 11.1	47.9 ± 11.1	49.8 ± 10.6	50.5 ± 10.9	50.1 ± 10.2	50.5 ± 11.5
	Q4	48.7 ± 10.8	48.8 ± 10.6	50.7 ± 10.1	50.7 ± 10.3	50.1 ± 9.8	52.1 ± 10.4

Table C.17.: SR, normal coronary perfusion, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with normal coronary perfusion using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	37.0 ± 9.1	42.1 ± 9.3	41.7 ± 9.4	42.4 ± 9.7	42.4 ± 9.7	40.5 ± 9.9
	Best	35.8 ± 9.6	42.6 ± 8.8	44.3 ± 8.4	44.0 ± 8.7	44.0 ± 9.2	41.1 ± 8.7
	Q1	34.6 ± 7.7	41.9 ± 8.1	46.4 ± 8.3	44.4 ± 6.6	44.1 ± 8.3	41.2 ± 8.3
	Q2	36.3 ± 9.4	43.8 ± 9.0	48.8 ± 8.2	46.8 ± 9.3	45.4 ± 8.8	44.9 ± 8.5
	Q3	37.9 ± 8.8	44.0 ± 9.6	48.4 ± 6.9	47.7 ± 9.5	47.6 ± 9.1	44.7 ± 9.1
	Q4	41.9 ± 9.2	46.7 ± 10.1	51.2 ± 10.0	50.5 ± 9.9	47.7 ± 9.7	47.3 ± 10.2

Table C.18.: AF, normal coronary perfusion, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with normal coronary perfusion using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	36.2 ± 14.6	36.2 ± 14.6	38.3 ± 13.0	38.3 ± 13.2	38.4 ± 13.6	38.5 ± 13.7
	Best	36.2 ± 14.5	36.2 ± 14.6	38.2 ± 13.0	38.4 ± 13.2	38.4 ± 13.6	38.5 ± 13.7
	Q1	38.6 ± 12.9	38.6 ± 13.1	43.7 ± 12.5	43.7 ± 12.6	44.0 ± 11.7	44.7 ± 12.1
	Q2	38.4 ± 13.3	38.3 ± 13.4	43.9 ± 12.6	42.6 ± 12.8	43.3 ± 12.3	44.1 ± 12.6
	Q3	38.1 ± 13.5	38.1 ± 13.6	43.1 ± 12.6	42.8 ± 12.8	42.9 ± 12.8	43.8 ± 12.3
	Q4	38.4 ± 13.6	38.5 ± 13.5	43.5 ± 12.6	42.7 ± 12.3	43.9 ± 12.6	44.0 ± 12.6

Table C.19.: SR, ischaemic, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with ischaemia using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	27.4 ± 11.0	31.7 ± 11.7	33.9 ± 10.9	32.9 ± 11.4	32.7 ± 11.4	31.1 ± 11.3
	Best	27.9 ± 10.3	33.3 ± 10.8	36.7 ± 10.0	35.6 ± 10.4	34.5 ± 10.6	33.2 ± 10.4
	Q1	27.4 ± 9.6	34.4 ± 9.9	39.1 ± 10.3	37.3 ± 9.9	36.8 ± 9.1	35.5 ± 9.7
	Q2	28.8 ± 10.1	35.3 ± 10.7	39.8 ± 10.0	38.4 ± 10.2	37.8 ± 10.4	36.0 ± 10.4
	Q3	30.3 ± 10.6	36.7 ± 11.2	41.1 ± 10.4	39.2 ± 10.7	38.6 ± 11.3	36.6 ± 10.8
	Q4	32.6 ± 10.9	38.6 ± 11.9	42.7 ± 11.4	41.0 ± 11.2	40.2 ± 11.4	38.4 ± 11.1

Table C.20.: AF, ischaemic, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with ischaemia using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	45.4 ± 9.60	45.4 ± 9.61	45.1 ± 9.73	45.9 ± 9.43	45.9 ± 10.20	46.6 ± 9.9
	Best	45.4 ± 9.63	45.4 ± 9.61	45.2 ± 9.79	46.0 ± 9.54	45.9 ± 10.20	46.5 ± 9.89
	Q1	45.3 ± 9.75	45.5 ± 9.59	50.5 ± 9.52	49.5 ± 8.38	50.0 ± 7.99	49.9 ± 8.57
	Q2	45.9 ± 9.47	45.9 ± 9.46	49.8 ± 9.69	50.5 ± 9.29	49.2 ± 8.03	50.5 ± 9.11
	Q3	45.7 ± 10.20	45.7 ± 10.30	48.9 ± 8.87	48.8 ± 8.67	49.2 ± 9.29	49.6 ± 9.10
	Q4	46.3 ± 9.85	46.3 ± 9.77	49.1 ± 9.09	47.9 ± 8.39	50.3 ± 9.52	50.2 ± 9.85

Table C.21.: SR, negative ETT, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with negative ETT using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	29.0 ± 11.6	33.3 ± 12.0	36.7 ± 10.8	35.7 ± 11.5	35.2 ± 11.3	33.1 ± 12.2
	Best	30.1 ± 11.0	35.6 ± 11.3	41.0 ± 9.9	40.8 ± 10.5	38.4 ± 11.5	37.4 ± 11.7
	Q1	29.3 ± 10.7	37.5 ± 10.5	45.9 ± 13.4	42.1 ± 13.5	39.6 ± 13.2	42.2 ± 12.8
	Q2	31.5 ± 11.3	38.3 ± 12.1	42.8 ± 14.1	44.5 ± 12.2	43.0 ± 11.6	40.7 ± 13.4
	Q3	31.7 ± 11.0	39.7 ± 11.0	45.9 ± 13.6	43.7 ± 11.8	43.0 ± 11.8	40.6 ± 12.6
	Q4	34.2 ± 11.5	41.0 ± 12.1	47.9 ± 12.2	46.1 ± 12.0	43.3 ± 10.9	42.2 ± 12.4

Table C.22.: AF, negative ETT, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with negative ETT using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	41.8 ± 10.10	41.8 ± 10.10	42.0 ± 11.60	42.8 ± 10.90	42.19.78	41.4 ± 9.44
	Best	41.8 ± 10.10	41.8 ± 10.10	42.0 ± 11.50	42.9 ± 10.90	42.29.79	41.4 ± 9.53
	Q1	41.9 ± 11.40	41.9 ± 11.40	49.4 ± 11.00	55.4 ± 1.12	55.02.56	51.1 ± 9.77
	Q2	42.8 ± 10.00	42.7 ± 10.00	48.4 ± 8.95	47.1 ± 8.85	46.87.43	44.4 ± 6.08
	Q3	42.2 ± 10.20	42.2 ± 10.20	47.0 ± 6.25	45.9 ± 7.78	45.68.24	45.9 ± 8.83
	Q4	41.5 ± 9.33	41.4 ± 9.23	46.8 ± 8.15	44.9 ± 8.36	42.49.47	44.1 ± 9.60

Table C.23.: SR, positive ETT, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with positive ETT using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	28.8 ± 11.4	34.5 ± 13.1	36.3 ± 12.0	35.2 ± 12.0	35.1 ± 12.0	33.6 ± 11.3
	Best	28.2 ± 11.2	35.6 ± 11.4	41.4 ± 9.9	38.7 ± 9.6	36.9 ± 10.9	34.8 ± 10.4
	Q1	29.9 ± 8.9	39.9 ± 8.2	44.3 ± 8.1	42.8 ± 9.4	42.0 ± 7.1	37.8 ± 8.9
	Q2	30.3 ± 10.4	38.2 ± 10.8	45.5 ± 7.9	43.4 ± 8.4	42.7 ± 8.5	38.1 ± 8.8
	Q3	32.1 ± 11.0	39.8 ± 11.9	46.8 ± 7.9	46.3 ± 8.5	44.0 ± 10.9	40.0 ± 10.2
	Q4	34.7 ± 11.2	41.7 ± 13.1	48.2 ± 9.8	45.9 ± 11.9	43.7 ± 12.3	40.1 ± 11.7

Table C.24.: AF, positive ETT, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with positive ETT using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	12.9 ± 4.52	12.9 ± 4.52	15.8 ± 3.64	15.5 ± 3.13	15.3 ± 3.54	15.5 ± 3.47
	Best	13.1 ± 4.39	12.9 ± 4.52	15.7 ± 3.62	15.6 ± 3.10	15.3 ± 3.55	15.5 ± 3.37
	Q1	16.0 ± 3.45	15.9 ± 3.48	18.2 ± 3.10	19.1 ± 4.25	18.3 ± 2.77	22.5 ± 8.51
	Q2	15.3 ± 3.14	15.1 ± 3.32	21.5 ± 4.34	17.6 ± 2.55	18.4 ± 2.26	18.5 ± 2.02
	Q3	15.5 ± 3.47	15.5 ± 3.43	20.6 ± 5.67	18.0 ± 2.50	17.8 ± 3.11	17.5 ± 1.31
	Q4	15.8 ± 3.72	15.9 ± 3.75	17.9 ± 5.23	17.6 ± 1.58	19.1 ± 2.12	17.1 ± 3.54

Table C.25.: SR, poor & very poor function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with poor and very poor function using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	13.4 ± 3.5	15.2 ± 3.5	16.6 ± 3.4	16.1 ± 3.1	16.5 ± 3.7	15.1 ± 3.9
	Best	13.4 ± 3.6	16.1 ± 3.5	18.5 ± 2.6	17.3 ± 2.9	18.0 ± 3.0	16.9 ± 3.2
	Q1	13.3 ± 2.8	16.9 ± 3.4	NA	$18.7 \pm NA$	$29.1 \pm NA$	$15.9 \pm NA$
	Q2	14.4 ± 3.1	16.4 ± 2.8	$19.2 \pm NA$	18.6 ± 3.0	19.2 ± 3.5	20.6 ± 3.8
	Q3	15.5 ± 3.5	17.9 ± 3.2	21.2 ± 1.3	20.7 ± 3.5	20.8 ± 4.7	19.8 ± 4.1
	Q4	17.4 ± 4.1	20.0 ± 4.4	22.6 ± 3.7	22.3 ± 5.0	22.2 ± 5.2	20.5 ± 5.1

Table C.26.: AF, poor & very poor function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with poor and very poor function using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	32.1 ± 5.93	32.1 ± 5.94	32.2 ± 6.32	32.5 ± 6.45	32.5 ± 6.24	32.8 ± 6.17
	Best	32.1 ± 5.94	32.0 ± 5.94	32.2 ± 6.15	32.6 ± 6.51	32.4 ± 6.20	32.9 ± 6.25
	Q1	32.2 ± 6.14	32.2 ± 6.20	34.6 ± 7.81	34.5 ± 6.91	34.5 ± 6.34	34.9 ± 5.93
	Q2	32.7 ± 6.27	32.7 ± 6.24	35.4 ± 8.04	34.0 ± 6.56	34.7 ± 6.84	35.2 ± 6.91
	Q3	32.3 ± 6.08	32.3 ± 6.06	34.3 ± 6.49	34.2 ± 6.44	34.4 ± 6.74	34.0 ± 6.35
	Q4	32.7 ± 6.15	32.7 ± 6.12	34.2 ± 6.41	34.7 ± 6.55	34.1 ± 5.97	34.7 ± 6.57

Table C.27.: SR, moderate & mildly impaired function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with moderate and mildly impaired function using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	26.7 ± 5.7	30.5 ± 5.7	31.2 ± 5.8	31.2 ± 5.8	31.0 ± 5.9	29.5 ± 6.0
	Best	26.2 ± 5.8	30.8 ± 5.9	32.9 ± 5.7	32.0 ± 5.8	31.2 ± 5.8	30.0 ± 5.8
	Q1	24.3 ± 5.5	29.5 ± 5.5	32.8 ± 7.5	31.3 ± 5.9	31.7 ± 5.5	29.8 ± 5.6
	Q2	26.7 ± 5.5	31.7 ± 5.7	33.6 ± 5.7	33.7 ± 6.3	32.8 ± 6.0	31.6 ± 6.1
	Q3	28.6 ± 5.6	33.5 ± 6.1	35.5 ± 6.3	34.9 ± 6.3	34.2 ± 6.4	32.5 ± 6.0
	Q4	31.5 ± 5.8	35.9 ± 6.5	38.0 ± 6.5	37.2 ± 6.9	36.5 ± 6.5	35.3 ± 6.7

Table C.28.: AF, moderate & mildly impaired function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with moderate and mildly impaired function using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	49.8 ± 8.30	49.8 ± 8.31	49.4 ± 8.57	50.0 ± 8.43	50.4 ± 8.60	50.9 ± 8.57
	Best	49.8 ± 8.34	49.8 ± 8.33	49.5 ± 8.58	50.0 ± 8.53	50.4 ± 8.53	50.8 ± 8.54
	Q1	49.8 ± 8.60	49.9 ± 8.52	51.9 ± 8.70	51.8 ± 8.88	51.7 ± 8.16	52.5 ± 9.03
	Q2	50.1 ± 8.48	50.1 ± 8.52	52.1 ± 9.12	52.1 ± 8.60	51.8 ± 8.27	52.6 ± 8.72
	Q3	50.2 ± 8.76	50.2 ± 8.77	51.4 ± 9.15	52.1 ± 8.93	52.0 ± 8.31	52.2 ± 8.73
	Q4	50.6 ± 8.50	50.6 ± 8.45	51.7 ± 9.01	51.7 ± 8.51	52.4 ± 8.48	52.5 ± 8.40

Table C.29.: SR, normal function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in SR patients with normal function using variable time formatting.

		Current beat					
		All	Best	Q1	Q2	Q3	Q4
Preceding beat	All	42.1 ± 6.5	47.5 ± 6.3	47.4 ± 6.2	47.9 ± 6.3	47.9 ± 6.7	45.9 ± 7.0
	Best	40.8 ± 6.7	46.5 ± 6.0	47.2 ± 5.9	47.0 ± 6.2	47.0 ± 6.8	45.1 ± 7.0
	Q1	37.9 ± 7.0	44.2 ± 6.7	47.3 ± 7.2	45.5 ± 7.4	45.2 ± 7.4	43.8 ± 7.5
	Q2	41.5 ± 6.7	47.4 ± 6.3	49.4 ± 6.9	48.8 ± 6.5	48.5 ± 6.7	47.0 ± 7.2
	Q3	43.8 ± 6.6	49.6 ± 6.6	50.9 ± 6.4	50.9 ± 6.4	50.9 ± 7.2	48.3 ± 7.2
	Q4	46.7 ± 6.4	52.4 ± 6.9	54.6 ± 7.2	53.4 ± 7.2	52.9 ± 7.0	51.2 ± 6.7

Table C.30.: AF, normal function, LVEF: $Mean \pm StDev$ LVEF for different beat selection criteria in AF patients with normal function using variable time formatting.

C.3. Patient-by-patient regression by time

In the body of the text patient-by-patient regression has been done against quartile which matches the group regression; however, on a patient-by-patient basis it is also possible to regress by time. A summary of this is given in tables as follows:

- *LVEF* in Table C.31
- *PSV* in Table C.32
- *EDV/PSV* in Table C.33
- *Systolic time* in Table C.34
- *FTFF* in Table C.35
- *PFR* in Table C.36

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.81 ± 0.14	128	0.78 ± 0.13	40	4
Best (Fixed)	Q1 - Q4	0.80 ± 0.14	130	0.76 ± 0.14	47	4
Q1 - Q4	All (Fixed)	0.77 ± 0.15	108	0.77 ± 0.16	51	7
Q1 - Q4	Best (Fixed)	0.78 ± 0.15	100	0.76 ± 0.15	56	6
Q1 - Q4	Q1 - Q4	0.58 ± 0.14	34 (p), 36(i)		48 (p), 22(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.72 ± 0.16	28	0.76 ± 0.15	116	7
Best (Fixed)	Q1 - Q4	0.71 ± 0.13	16	0.78 ± 0.14	90	26
Q1 - Q4	All (Fixed)	0.86 ± 0.12	299	NA	0	13
Q1 - Q4	Best (Fixed)	0.84 ± 0.13	192	0.64 ± 0.04	2	34
Q1 - Q4	Q1 - Q4	0.73 ± 0.14	171 (p), 26(i)		0 (p), 147(i)	55

(b) AF

Table C.31.: LVEF: showing the regression results by time on a patient-by-patient basis for PSV in (a) SR, and (b) AF. Mean regression coefficient is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant (at $p < 0.05$). In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.87 ± 0.13	200	0.79 ± 0.15	34	4
Best (Fixed)	Q1 - Q4	0.87 ± 0.13	201	0.78 ± 0.15	34	4
Q1 - Q4	All (Fixed)	0.84 ± 0.14	167	0.76 ± 0.15	48	7
Q1 - Q4	Best (Fixed)	0.83 ± 0.14	160	0.76 ± 0.15	46	6
Q1 - Q4	Q1 - Q4	0.72 ± 0.16	60 (p), 106(i)		55 (p), 9(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.96 ± 0.07	334	$0.99 \pm NA$	1	7
Best (Fixed)	Q1 - Q4	0.95 ± 0.07	243	NA	0	26
Q1 - Q4	All (Fixed)	0.81 ± 0.13	128	0.81 ± 0.12	34	13
Q1 - Q4	Best (Fixed)	0.77 ± 0.14	69	0.76 ± 0.16	34	34
Q1 - Q4	Q1 - Q4	0.90 ± 0.10	149 (p), 227(i)		76 (p), 0(i)	55

(b) AF

Table C.32.: PSV: showing the regression results by time on a patient-by-patient basis for PSV in (a) SR, and (b) AF. Mean regression coefficient shows is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant. In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.76 ± 0.14	53	0.76 ± 0.14	91	4
Best (Fixed)	Q1 - Q4	0.75 ± 0.15	56	0.77 ± 0.15	100	4
Q1 - Q4	All (Fixed)	0.78 ± 0.14	74	0.78 ± 0.13	56	7
Q1 - Q4	Best (Fixed)	0.78 ± 0.14	73	0.77 ± 0.14	57	6
Q1 - Q4	Q1 - Q4	0.61 ± 0.17	29 (p), 16(i)		22 (p), 35(i)	38

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.79 ± 0.13	281	NA	0	
Best (Fixed)	Q1 - Q4	0.79 ± 0.14	191	0.74 ± 0.09	4	26
Q1 - Q4	All (Fixed)	0.81 ± 0.09	4	0.80 ± 0.13	210	13
Q1 - Q4	Best (Fixed)	0.77 ± 0.15	15	0.80 ± 0.15	118	34
Q1 - Q4	Q1 - Q4	0.69 ± 0.14	12 (p), 164(i)		151 (p), 0(i)	55

(b) AF

Table C.33.: EDV/PSV: showing the regression results by time on a patient-by-patient basis for EDV/PSV in (a) SR, and (b) AF. Mean regression coefficient shows is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant. In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.85 ± 0.16	120	0.68 ± 0.13	30	5
Best (Fixed)	Q1 - Q4	0.89 ± 0.15	122	0.68 ± 0.12	25	5
Q1 - Q4	All (Fixed)	0.83 ± 0.15	101	0.70 ± 0.12	48	9
Q1 - Q4	Best (Fixed)	0.84 ± 0.15	103	0.71 ± 0.13	47	8
Q1 - Q4	Q1 - Q4	0.61 ± 0.18	13 (p), 23(i)		15 (p), 5(i)	40

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.77 ± 0.15	69	0.74 ± 0.16	52	7
Best (Fixed)	Q1 - Q4	0.78 ± 0.14	36	0.74 ± 0.14	33	26
Q1 - Q4	All (Fixed)	0.77 ± 0.14	91	0.76 ± 0.15	41	13
Q1 - Q4	Best (Fixed)	0.77 ± 0.15	71	0.80 ± 0.13	32	36
Q1 - Q4	Q1 - Q4	0.55 ± 0.16	14 (p), 5(i)		11 (p), 8(i)	55

(b) AF

Table C.34.: Systolic time: showing the regression results by time on a patient-by-patient basis for systolic time in (a) SR, and (b) AF. Mean regression coefficient shows is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant. In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.77 ± 0.15	117	0.72 ± 0.13	25	4
Best (Fixed)	Q1 - Q4	0.77 ± 0.14	114	0.73 ± 0.14	23	4
Q1 - Q4	All (Fixed)	0.74 ± 0.14	95	0.70 ± 0.13	26	8
Q1 - Q4	Best (Fixed)	0.74 ± 0.13	89	0.69 ± 0.13	28	6
Q1 - Q4	Q1 - Q4	0.51 ± 0.23	76 (p), 107(i)		78 (p), 46(i)	21

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.85 ± 0.12	305	$0.99 \pm NA$	1	7
Best (Fixed)	Q1 - Q4	0.85 ± 0.12	219	NA	0	27
Q1 - Q4	All (Fixed)	0.82 ± 0.15	22	0.76 ± 0.15	95	14
Q1 - Q4	Best (Fixed)	0.79 ± 0.15	30	0.79 ± 0.15	68	34
Q1 - Q4	Q1 - Q4	0.71 ± 0.18	64 (p), 221(i)		158 (p), 4(i)	28

(b) AF

Table C.35.: FTFF: showing the regression results by time on a patient-by-patient basis for FTFF in (a) SR, and (b) AF. Mean regression coefficient shows is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant. In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.68 ± 0.12	50	0.69 ± 0.13	21	4
Best (Fixed)	Q1 - Q4	0.65 ± 0.12	57	0.70 ± 0.12	21	4
Q1 - Q4	All (Fixed)	0.68 ± 0.09	46	0.61 ± 0.09	23	8
Q1 - Q4	Best (Fixed)	0.68 ± 0.11	44	0.63 ± 0.09	26	6
Q1 - Q4	Q1 - Q4	0.41 ± 0.19	58(p),49(i)		35(p), 42(i)	21

(a) SR

Preceding	Indexed	Mean ± SD (+ve)	N (+ve)	Mean ± SD (-ve)	N (-ve)	NC
All (Fixed)	Q1 - Q4	0.71 ± 0.12	108	0.75 ± 0.16	17	7
Best (Fixed)	Q1 - Q4	0.71 ± 0.13	56	0.73 ± 0.18	13	27
Q1 - Q4	All (Fixed)	0.74 ± 0.13	61	0.70 ± 0.09	12	14
Q1 - Q4	Best (Fixed)	0.77 ± 0.14	42	0.72 ± 0.11	14	34
Q1 - Q4	Q1 - Q4	0.49 ± 0.21	79 (p), 89(i)		29 (p), 22(i)	28

(b) AF

Table C.36.: PFR: showing the regression results by time on a patient-by-patient basis for PFR in (a) SR, and (b) AF. Mean regression coefficient shows is divided into those which showed a positive association ("+ve") and those which showed a negative association ("-ve"). The mean is calculated only for those patients for whom the result was significant. In multiple regression line "(i)" and "(p)" represented indexed and preceding respectively in multiple regression and the mean R^2 value calculated for all patients. Total numbers of patients: 371 in SR (308 for multiple regression), 357 in AF (303 for multiple regression).

Appendix D.

Rhythm vs. Function Appendix

D.1. Correlations

The correlation between rhythm and variation in functional indices reported in chapter 6 (§6.2) was calculated using the standard deviation as the index of variation for the functional indicies. An alternative would be to consider the range (max - min), the results of such a calculation shown in Figure D.1 for SR and Figure D.2 for AF are similar but not the same.

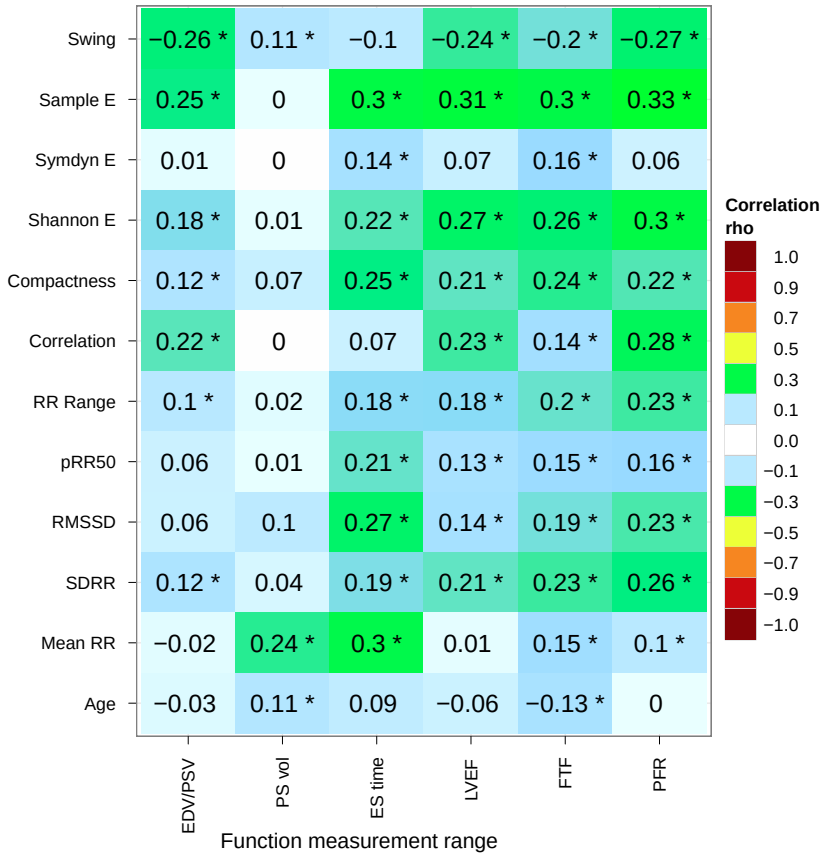


Figure D.1.: Showing the correlation between measures of RR variability and the range of measures of function (per patient) in SR.

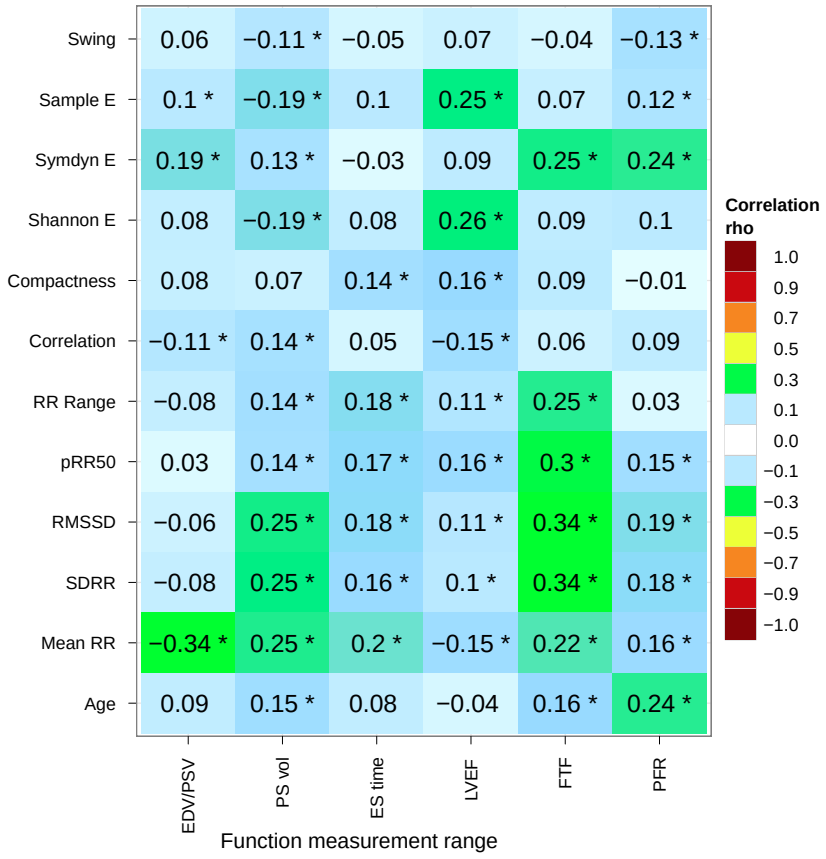


Figure D.2.: Showing the correlation between measures of RR variability and the range of measures of function (per patient) in AF.

Glossary

SampEn Calculation of entropy based on the conditional probability of matching a sequence of beats of length m within the beat interval stream. Each beat must match within a window of width r.

awk A data driven programming language designed for processing text based data files, generally applying the same transformation to each line of a file.

compactness factor A number indicating the spread of density over a plot. The smaller the number the more concentrated the points are in the Poincaré plot.

compactness factor by log As with compactness factor this is a number indicating the spread of density over a plot but the calculation of the integral is against $\log(area)$ instead of against the area. This gives more emphasis to changes in density over a smaller area. The smaller the number the more concentrated the points are in the Poincaré plot.

delta Poincaré A plot of the difference between the indexed beat and the preceding beat ($RR_i - RR_{i-1}$) against the difference between the preceding beat and the one before that ($RR_{i-1} - RR_{i-2}$).

ectopic Abnormal; in this thesis it refers to a beat which does not have the standard morphology for that patient.

Ejection Fraction The fraction of end-diastolic volume expelled from the relevant cardiac chamber during systole.

gated A multi-frame image file which shows the change in the heart in several image frames over a representative beat.

Lorenz plot An alternative name for Poincaré plot.

Mean NN The mean NN interval, where NN is the RR interval between adjacent QRS complexes from normal sinus node depolarisations.

NN range The difference between the longest and shortest NN interval (as described for mean NN).

NN50 The number of differences greater than 50ms between sucessive intervals.

pNN50 The percentage number of differences between sucessive intervals of greater than 50ms as a fraction of the notal number of NN intervals.

Poincaré plot Plot of indexed RR interval against the next RR interval.

RMSSD The square root of the mean squared difference between sucessive NN intervals.

SDANN*x* The standard deviation of the average of NN intervals over x beats.

SDNN The standard deviation of the NN interval.

sinus rhythm Normal regular cardiac rhythm.

symbolic dynamics Mathematical technique for "coarse graining" a system whereby states of the system are represented by symbols. The sequence of symbols represents the dynamic variation of the system.

Bibliography

[1] H-W. M. Breuer et al. "Heart rate variability and circulating catecholamine concetrations during steady state exercise in healthy volunteers." In: *Br. Heart J.* 70 (1993), pp. 144–149.

[2] D.E. Newby and N.R. Grubb. *Cardiology: an illustrated colour text*. Elsevier, 2005.

[3] A. G. Wallace et al. "Duration of the phases of left ventricular systole." In: *Circ. Res.* 12 (1963), pp. 611–619.

[4] B. C. Maciel et al. "Autonomic nervous control of the heart rate during dynamic exercise in normal man." In: *Clin. Sci.* 71.4 (1986), pp. 457–460.

[5] H Willacy. *Epidemiology of coronary heart disease*. 2010. URL: http://www.patient.co.uk/doctor/Epidemiology-of-IHD.htm.

[6] R. W. Nesto and G. J. Kowalchuk. "The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia." In: *Am. J. Cardiol.* 59.7 (1987), p. 2330.

[7] F. Grothues et al. "Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy". In: *Am. J. Cardiol.* 90.1 (2002), pp. 29–34.

[8] N. G. Bellenger et al. "Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance. Are they interchangeable?." In: *Eur. Heart J.* 21.16 (2000), pp. 1387–1396.

[9] B.L. Zaret. "Clinical nuclear cardiology: State of the art and future directions (4th Edition)". In: ed. by B.L. Zaret and G.A. Beller. Mosby Elsevier, 2010. Chap. Cardiac performance, pp. 183–193.

[10] A. J. Moss. "Risk stratification and survival after myocardial infarction. The multicenter postinfarction research group." In: *N. Eng. J. Med.* 309.6 (1983), pp. 331–336.

[11] Barry L. Zaret et al. "Value of Radionuclide Rest and Exercise Left Ventricular Ejection Fraction in Assessing Survival of Patients After Thrombolytic Therapy for Acute Myocardial Infarction: Results of Thrombolysis in Myocardial Infarction (TIMI) Phase II Study". In: *J. Am. Coll. Cardiol.* 26.1 (1995), pp. 73–79.

[12] A.C. McCulloch. "The stress radionuclide assessment of diastolic function". PhD thesis. The University of Glasgow, 2009.

[13] *Atrial fibrillation: national clinical guideline for management in primary and secondary care*. Tech. rep. Royal College of Physicians (London), 2006.

[14] *Prevalence of AF in England 2008/2009*. 2011. URL: http://www.nchod.nhs.uk/NCHOD/compendium.nsf/2217490fcc66bd94802573a30020fcd6/829b610b171c094280257851000fb40a!OpenDocument.

[15] S. Stewart et al. "Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study". In: *Heart* 86 (2001), pp. 516–521.

[16] N. F. Murphy et al. "A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland." In: *Heart* 93 (2007), pp. 606–612.

[17] P.A. Wolf, R.D. Abbott, and W.B. Kannel. "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study". In: *Stroke* 22 (1991), pp. 983–988.

[18] P.A. Wolf, J.B. Mitchell, C.S. Baker, et al. "Impact of atrial fibrillation on mortality, stroke, and medical costs." In: *Arch. Intern. Med.* 158 (1998), pp. 229–234.

[19] E.J. Benjamin et al. "Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study". In: *Circulation* 98 (1998), pp. 946–952.

[20] J. L. Cox. "Atrial fibrillation I: a new classification system." In: *J. Thorac. Cardiov. Sur.* 126.6 (2003), pp. 1686–1692.

[21] A.J. Camm et al. "Guidelines for the management of atrial fibrillation." In: *Eur. Heart J.* (2010).

[22] M. Haissaguerre et al. "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins". In: *N. Eng. J. Med.* 339 (1998), pp. 659–666.

[23] H. Oral et al. “Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation.” In: *Circulation* 105 (2002), pp. 1077–1081.

[24] A. Natale et al. “First human experience with pulmonary vein isolation using a through-the ballon- circumerential ultrasound ablation system for recurrent atrial fibrillation.” In: *Circulation* 102 (2000), pp. 1879–1882.

[25] L-F. Hsu et al. “Catheter ablation for atrial fibrillation in congestive heart failure.” In: *N. Eng. J. Med.* 351 (2004), pp. 2373–2383.

[26] V. Corino et al. “Understanding atrial fibrillation: the signal processing contribution”. In: ed. by L. Mainardi, L. Sornmo, and S. Cerutti. Synthesis lectures on biomedical engineering. Morgan & Claypool, 2008. Chap. Analysis of ventricular response during atrial fibrillation. Pp. 105–120.

[27] M. Malik et al. “Heart rate variability. Standards of measurement, physiological interpretation, and clinical use.” In: *Eur. Heart J.* 17.3 (1996), pp. 354–381.

[28] G. R. Sandercock and D. A. Brodie. “The role of heart rate variability in prognosis for different modes of death in chronic heart failure”. In: *Pacing. Clin. Electrophysiol.* 29.8 (2006), pp. 892–904.

[29] Helene Otzenberger et al. “Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men”. In: *Am. J. Physiol.: Heart Circ. Physiol.* 275 (1998), H946–H950.

[30] M. Eiselt et al. “Heart-rate variability in low-risk prematurely born infants reaching normal term: A comparison with full-term newborns.” In: *Early Hum. Dev.* 32.2-3 (1993), pp. 183–195.

[31] J. Nolan et al. “Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-Heart).” In: *Circulation* 98.15 (1998), pp. 1510–1516.

[32] F. Lombardi et al. “Heart rate variability and early recurrence of atrial fibrillation after electrical cardioversion.” In: *J. Am. Coll. Cardiol.* 37 (2001), pp. 157–162.

[33] H. Poincaré. “Mémoire sur les courbes définies par une équation différentielle.” In: *Journal de Mathematique* 7 (1881), pp. 375–442.

[34] E. N. Lerenz. “Deterministic nonperiodic flow”. In: *J. Atmos. Sci.* 10 (1963), p. 130.

[35] T. Anan et al. “Arrhythmia analysis by successive RR plotting.” In: *J. Electrocardiol.* 23.3 (1990), pp. 243–248.

[36] H. V. Huikuri et al. “Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction.” In: *Circulation* 93.10 (1996), pp. 1836–1844.

[37] M. Brennan, M. Palaniswami, and P. Kamen. “Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate variability?.” In: *IEEE Trans. Biomed. Eng.* 48.11 (2001), pp. 1342–1347.

[38] C. Lerma et al. “Poincare plot indexes of heart rate variability capture dynamic adaptations after haemodialysis in chronic renal failure patients.” In: *Clin. Physiol. Funct. Imaging* 23.2 (2003), pp. 72–80.

[39] H. V. Huikuri et al. “Impaired low-frequency oscillations of heart rate in patients with prior acute myocardial infarction and life-threatening arrhythmias.” In: *Am. J. Cardiol.* 76.1 (1995), pp. 56–60.

[40] J. Park, S. Lee, and M. Jeon. “Atrial fibrillation detection by heart rate variability in Poincare plot.” In: *Biomed. Eng* 8 (2009), p. 38.

[41] S. Garrigue, P. J. Tchou, and T. N. Mazgalev. “Role of the differential bombardment of atrial inputs to the atrioventricular node as a factor influencing ventricular rate during high atrial rate.” In: *Cardiovasc. Res.* 44.2 (1999), pp. 344–355.

[42] M. P. Van Den Berg et al. “Clustering of RR intervals predicts effective electrical cardioversion for atrial fibrillation.” In: *J. Cardiovasc. Electr.* 15.9 (2004), pp. 1027–1033.

[43] A. -L Smith and K. Reynolds. “Survey of Poincare indices for measuring heart rate variability.” In: *Australas. Phys. Eng. Sci. Med.* 29.1 (2006), pp. 97–101.

[44] M. Toichi et al. “A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval.” In: *J. Autonom. Nerv. Syst.* 62.1-2 (1997), pp. 79–84.

[45] H. Otzenberger et al. “Dynamic heart rate variability: A tool for exploring sympathovagal balance continuously during sleep in men.” In: *Am. J. Physiol.: Heart Circ. Physiol.* 275.3 (1998), H946–H950.

[46] K. Hnatkova et al. “Numeric processing of Lorenz plots of R-R intervals from long-term ECGS. Comparison with time-domain measures of heart rate variability for risk stratification after myocardial infarction.” In: *J. Electrocardiol.* 28s (1995), p. 74.

[47] C.K. Karmakar et al. “Complex correlation measure: a novel descriptor for Poincare plot”. In: *Biomed. Eng* 8 (2009), p. 17.

[48] S. L. Raetz et al. “Dynamic characteristics of cardiac R-R intervals during sleep and waking states.” In: *Sleep* 14.6 (1991), pp. 526–533.

[49] M.V. Volkenstein. *Entropy and information*. Ed. by R.G. (Translators) Shenitzer A. Burns. Vol. 57. Progress in mathematical physics. Birkhauser Verlag AG, 2009.

[50] Steven M Pincus, Igor M Gladstone, and Richard A Ehrenkranz. “A regularity statistic for medical data analysis”. In: *J. Clin. Monit.* 7 (1991), pp. 335–345.

[51] Joshua S. Richman and J. Randall Moorman. “Physiological time-series analysis using approximate entropy and sample entropy”. In: *Am. J. Physiol.: Heart Circ. Physiol.* 278 (2000), H2039–H2049.

[52] A. Porta et al. “Measuring regularity by means of a corrected conditional entropy in sympathetic outflow.” In: *Biol. Cybern.* 78.1 (1998), pp. 71–78.

[53] J. A. Palazzolo, F. G. Estafanous, and P. A. Murray. “Entropy measures of heart rate variation in conscious dogs.” In: *Am. J. Physiol.* 274.4 Pt 2 (1998), pp. 1099–1105.

[54] C. E. Shannon. “A Mathematical Theory of Communication”. In: *Bell Syst. Tech. J.* 27.3 (1948), pp. 379–423.

[55] Bai-lin Hao. “Sumbolic dynamics and the characterization of complexity”. In: *Physica D* 51 (1991), pp. 161–176.

[56] A. Voss et al. “The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death.” In: *Cardiovasc. Res.* 31 (1996), pp. 419–433.

[57] S.M. Pincus. “Approximate entropy as a measure of system complexity”. In: *Proc. Natl. Acad. Sci. U.S.A.* 88 (1991), pp. 2297–2301.

[58] S. M. Pincus and A. L. Goldberger. “Physiological time-series analysis: What does regularity quantify?.” In: *Am. J. Physiol.: Heart Circ. Physiol.* 266.4 35-4 (1994), H1643–H1656.

[59] Douglas E Lake et al. “Sample entropy analysis of neonatal heart rate variability”. In: *Am. J. Physiol.: Regul., Integr. Comp. Physiol.* 283 (2002), R789–R797.

[60] M. V. Green et al. “Ejection fraction by count rate from gated images.” In: *J. Nucl. Med.* 19.8 (1978), pp. 880–883.

[61] J. A. Parker et al. “A new technique for the calculation of left ventricular ejection fraction.” In: *J. Nucl. Med.* 13.8 (1972), pp. 649–651.

[62] I. McGhie et al. “The detection of coronary artery disease: a comparison of exercise thallium imaging and exercise equilibrium radionuclide ventriculography.” In: *Eur. J. Nucl. Med.* 13.1 (1987), pp. 18–23.

[63] M. L. Freeman et al. “Time–domain analysis in gated cardiac blood pool studies.” In: *Int. J. Nucl. Med. Biol.* 9.1 (1982), pp. 37–41.

[64] N. Honda et al. “Two dimensional polar display of cardiac blood pool SPECT.” In: *Eur. J. Nucl. Med.* 15.3 (1989), pp. 133–136.

[65] E. Mate et al. “Three-dimensional presentation of the Fourier amplitude and phase: a fast display method for gated cardiac blood-pool SPECT.” In: *J. Nucl. Med.* 33.3 (1992), pp. 458–462.

[66] J. Schneider et al. “Beat-to-beat left ventricular performance in atrial fibrillation: radionuclide assessment with the computerized nuclear probe”. In: *Am. J. Cardiol.* 51.7 (1983), pp. 1189–1195.

[67] A. T. Gosselink et al. “Left ventricular beat-to-beat performance in atrial fibrillation: contribution of Frank-Starling mechanism after short rather than long RR intervals.” In: *J. Am. Coll. Cardiol.* 26.6 (1995), pp. 1516–1521.

[68] S. M. Hardman, M. I. Noble, and W. A. Seed. “Postextrasystolic potentiation and its contribution to the beat-to-beat variation of the pulse during atrial fibrillation.” In: *Circulation* 86.4 (1992), pp. 1223–1232.

[69] J. S. Karliner et al. “Factors influencing the ejection fraction and the mean rate of circumferential fibre shortening during atrial fibrillation in man.” In: *Cardiovasc. Res.* 8.1 (1974), pp. 18–25.

[70] T. Tomotsugu et al. “Determinants of LV diastolic function during atrial fibrillation: beat to beat analysis in acute dog experiments.” In: *Am. J. Physiol.: Heart Circ. Physiol.* 286 (2004), H145–H152.

[71] M. Tanabe et al. “Assessment of left ventricular systolic function in patients with chronic atrial fibrillation and dilated cardiomyopathy using the ratio of preceding to prepreceding R-R intervals.” In: *Int. J. Cardiol.* 108.2 (2006), pp. 197–201.

[72] R. Wassenaar et al. “Optimization and validation of radionuclide angiography phase analysis parameters for quantification of mechanical dyssynchrony.” In: *J. Nucl. Cardiol.* 16.6 (2009), pp. 895–903.

[73] Y. -H Li et al. “Clinical significance of fibrillatory wave amplitude: A clue to left atrial appendage function in nonrheumatic atrial fibrillation.” In: *Chest* 108.2 (1995), pp. 359–363.

[74] Manfred M. D. Thurmann and James G. Jr M. D. Janney. "The Diagnostic Importance of Fibrillatory Wave Size". In: *Circulation* 25.6 (1962), pp. 991–994.

[75] Bulent Mutlu et al. "Fibrillatory wave amplitude as a marker of left atrial and left atrial appendage function, and a predictor of thromboembolic risk in patients with rheumatic mitral stenosis". In: *Int. J. Cardiol.* 91.2-3 (2003), pp. 179–186.

[76] A. Smith and K. Reynolds. "Survey of Poincare indices for measuring heart rate variability". In: *Australas. Phys. Eng. Sci. Med.* 29 (2006), p. 97.

[77] R. Alcaraz and J.J. Rieta. "A review on sample entropy applications for the non-invasive analysis of atrial fibrillation electrocardiograms". In: *Biomed. Signal Process. Control* 5 (2010), pp. 1–14.

[78] N. M. Segerson et al. "Heart rate variability measures during sinus rhythm predict cycle length entropy during atrial fibrillation." In: *J. Cardiovasc. Electr.* 19.10 (2008), pp. 1031–1036.

[79] *Sample Entropy estimation using sampen*. 2004. URL: http://www.physionet.org/physiotools/sampen/.

[80] A. L. Goldberger et al. "PhysioBank, PhysioToolkit, and PhysioNet: Components of a New Research Resource for Complex Physiologic Signals". In: *Circulation* 101.23 (2000), e215–e220.

[81] V. Tuzcu et al. "Decrease in the heart rate complexity prior to the onset of atrial fibrillation". In: *Europace* 8 (2006), pp. 398–402.

[82] J. Cohen. *Statistical power analysis for behavioural sciences (2nd ed.)* Lawrence Erlbaum, 1988.

[83] W.G. Hopkins. *A scale of magnitudes for effect statistics*. 2002. URL: http://sportsci.org/resource/stats/effectmag.html.

[84] J.M. Bland and D.G. Altman. "Measuring agreement in method comparison studies." In: *Stat. Methods. Med. Res.* 8 (1999), p. 135.

[85] J. M. Bland and D. G. Altman. "Statistical methods for assessing agreement between two methods of clinical measurement." In: *Lancet* 1.8476 (1986), pp. 307–310.

[86] R. H. J. A. Slart et al. "Gated blood-pool SPECT automated versus manual left ventricular function calculations". In: *Nucl. Med. Comm.* 25 (2004), pp. 75–80.

[87] Stephen L. Bacharach et al. "Left-ventricular Peak Ejection Rate, Filling Rate, and Ejection Fraction - Frame Rate Requirements at Rest and Exercise: Concise Communication". In: *J. Nucl. Med.* 20.3 (1979), pp. 189–193. eprint: http://jnm.snmjournals.org/content/20/3/189.full.pdf+html. URL: http://jnm.snmjournals.org/content/20/3/189.short.

[88] R. Fisher. *Convolution*. 2011. URL: http:\/\/homepages.inf.ed.ac.uk.rbf\/HIPR2\/convolve.htmon01.03.2011.

[89] W. Martin, I. McGhie, and A. C. Tweddel. "Geometrical dependence of radionuclide ejection fraction." In: *Physics in Medicine and Biology* 32.2 (1987), pp. 253–257.

[90] J.A. Rumberger and J.E. Reed. "Quantitative dynamics of left ventricular emptying and filling as a function of heart size and stroke volume in pure aortic regurgitation and in normal subjects." In: *Am. J. Cardiol.* 70 (1992), pp. 1045–1050.

[91] R.J. Carrol and D. Ruppert. *Transformation and Weighting in Regression*. Chapman and Hall, 1988.

[92] M. Crawley. "The R Book". In: John Wiley & Sons, 2007. Chap. Chapter 14: Count data, pp. 527–548.

[93] M. Crawley. "The R Book". In: John Wiley & Sons, 2007. Chap. Chapter 10: Regression, pp. 387–448.

[94] M.R. MacDonald et al. "Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular dysfunction: a randomised controlled trial." In: *Heart* 97.9 (2011), pp. 740–747.

[95] M.S. Chen, N.F. Marrouche, Y. Khaykin, et al. "Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function." In: *J. Am. Coll. Cardiol.* 43 (2004), pp. 1004–1009.

[96] C. Tondo, M. Mantica, G. Russo, et al. "Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function." In: *Pacing. Clin. Electrophysiol.* 29 (2006), pp. 962–970.

[97] P.J. Gentlesk, W.H. Sauer, E.P. Gerstenfeld, et al. "Reversal of left ventricular dysfunction following ablation of atrial fibrillation". In: *J. Cardiovasc. Electr.* 18 (2007), pp. 9–14.

[98] M.N. Khan, P. Jais, J. Cummings, et al. "Pulmonary vein isolation for atrial fibrillation in patients with heart failure". In: *N. Eng. J. Med.* 359 (2008), pp. 1778–1785.

[99] B. Richter et al. "Is inducibility of atrial fibrillation after radio frequency ablation really a relevant prognostic factor?." In: *Eur. Heart J.* 27.21 (2006), pp. 2553–2559.

[100] B. De La Cruz Torres, C. L. Lopez, and J. N. Orellana. "Analysis of heart rate variability at rest and during aerobic exercise: A study in healthy people and cardiac patients." In: *Br. J. Sports Med.* 42.9 (2008), pp. 715–720.

[101] S. Carrasco et al. "Reproducibility of heart rate variability from short-term recordings during five manoeuvres in normal subjects." In: *J. Med. Eng. Tech.* 27.6 (2003), pp. 241–248.

[102] L. Sornmo, M. Striddh, and J.J. Rieta. "Understanding atrial fibrillation: the signal processing contribution". In: ed. by L. Mainardi, L. Sornmo, and S. Cerutti. Sythesis lectures on biomedical engineering. Morgan & Claypool, 2008. Chap. Atrial activity extraction from the ECG, pp. 53–76.

[103] A. Bollmann and F. Lombardi. "Electrocardiology of atrial fibrillation: current knowledge and future challenges". In: *IEEE Eng. Med. Biol. Mag.* 25 (2006), pp. 15–23.

[104] M.P. Van den Berg et al. "Clustering of RR intervals predicts effective electrical cardioversion for atrial fibrillation". In: *J. Cardiovasc. Electr.* 15 (2004), pp. 1027–1033.

[105] A. M. Climent et al. "Role of the Atrial Rate as a Factor Modulating Ventricular Response during Atrial Fibrillation". In: *Pacing. Clin. Electrophysiol.* 33.12 (2010), pp. 1510–1517.

[106] J. Park, S. Lee, and M. Jeon. "Atrial fibrillation detection by heart rate variability in Poincare plot." In: *Biomed. Eng* 8 (2009), p. 38.

[107] K.C. Chua et al. "Computer-based analysis of cardiac state using entropies, recurrence plot and Poincare geometry". In: *J. Med. Eng. Tech.* 32 (2008), pp. 263–271.

[108] R. Alcaraz et al. "Optimized assessment of atrial fibrillation organization through suitable parameters of sample Entropy." In: *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society.* (2010), pp. 118–121.

[109] J. Billette, R.A. Nadeau, and F. Roberge. "Relation between the minimum RR interval during atrial fibrillation and the functional refractory period of the AV junction". In: *Cardiovasc. Res.* 8 (1974), pp. 347–351.

[110] Z. Blanck et al. "Characterization of atrioventricular nodal behavior and ventricular response during atrial fibrillation before and after a selective slow- pathway ablation." In: *Circulation* 91.4 (1995), pp. 1086–1094.

[111] G. K. Feld et al. "Control of rapid ventricular response by radiofrequency catheter modification of the atrioventricular node in patients with medically refractory atrial fibrillation." In: *Circulation* 90.5 (1994), pp. 2299–2307.

[112] S. B. Olsson et al. "Noninvasive support for and characterization of multiple intranodal pathways in patients with mitral valve disease and atrial fibrillation." In: *Eur. Heart J.* 7.4 (1986), pp. 320–333.

[113] T. Oka et al. "Double-sector Lorenz plot scattering in an R-R interval analysis of patients with chronic atrial fibrillation: Incidence and characteristics of vertices of the double-sector scattering." In: *J. Electrocardiol.* 31.3 (1998), pp. 227–235.

[114] K.M. Stein et al. "Ventricular response in atrial fibrillation: random or deterministic?" In: *Am. J. Physiol.: Heart Circ. Physiol.* 277 (1999), H452–H458.

[115] D.G. Wyse. "Therapeutic considerations in applying rate control therapy for atrial fibrillation." In: *J. Cardiovasc. Pharm.* 52.1 (2008), pp. 11–17.

[116] R. Cervigon et al. "Ventricular rhythm in atrial fibrillation under anaesthetic infusion with propofol." In: *Physiol. Meas.* 30.8 (2009), pp. 833–845.

[117] A. Nicol et al. "Procedure guideline for planar radionuclide cardiac ventriculogram for the assessent of left ventricular systolic function". In: *Nucl. Med. Comm.* 30 (2009), pp. 245–252.

[118] N. B. Schiller et al. "Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms." In: *J. Am. Soc. Echocardiogr.* 2.5 (1989), pp. 358–367.

[119] M. A. Schmidt et al. "Real-time three-dimensional echocardiography for measurement of left ventricular volumes." In: *Am. J. Cardiol.* 84.12 (1999), pp. 1434–1439.

[120] S. L. Mulvagh et al. "Contrast echocardiography: Current and future applications." In: *J. Am. Soc. Echocardiogr.* 13.4 (2000), pp. 331–342.

[121] S. Malm et al. "Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: A comparison with magnetic resonance imaging." In: *J. Am. Coll. Cardiol.* 44.5 (2004), pp. 1030–1035.

[122] S. Malm et al. "Real-time Simultaneous Triplane Contrast Echocardiography Gives Rapid, Accurate, and Reproducible Assessment of Left Ventricular Volumes and Ejection Fraction: A Comparison with Magnetic Resonance Imaging." In: *J. Am. Soc. Echocardiogr.* 19.12 (2006), pp. 1494–1501.

[123] J. H. McGowan and J. G. F. Cleland. "Reliability of reporting left ventricular systolic function by echocardiography: A systematic review of 3 methods." In: *Am. Heart J.* 146.3 (2003), pp. 388–397.

[124] R. M. Lang et al. "Recommendations for chamber quantification: A report from the American Society of Echocardiography's guidelines and standards committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology." In: *J. Am. Soc. Echocardiogr.* 18.12 (2005), pp. 1440–1463.

[125] C. Jenkins et al. "Comparison of Two- and Three-Dimensional Echocardiography With Sequential Magnetic Resonance Imaging for Evaluating Left Ventricular Volume and Ejection Fraction Over Time in Patients With Healed Myocardial Infarction." In: *Am. J. Cardiol.* 99.3 (2007), pp. 300–306.

[126] P. K. Woodard et al. "ACR Practice Guideline for the Performance and Interpretation of Cardiac Magnetic Resonance Imaging (MRI)". In: *J. Am. Coll. Radiol.* 3.9 (2006).

[127] F. Saremi, J.D. Grizzard, and R.J. Kim. "Optimizing cardiac MR imaging: practical remedies for artefacts." In: *Radiographics* 28 (2008), pp. 1161–1187.

[128] A. L. Jones et al. "Management of cardiac health in trastuzumab-treated patients with breast cancer: Updated United Kingdom National Cancer Research Institute recommendations for monitoring." In: *Br. J. Cancer* 100.5 (2009), pp. 684–692.

[129] National Institute for Health and Clinical Excellence. *Technology Appraisal 107: Trastuzumab for the adjuvant treatment of earlystage HER2-positive breast cancer*. Tech. rep. TA107. National Institute for Health and Clinical Excellence, 2006. URL: http://www.nice.org.uk/TA107.

[130] P. P. Sengupta et al. "Trastuzumab-induced cardiotoxicity: Heart failure at the crossroads." In: *Mayo Clin. Proc.* 83.2 (2008), pp. 197–203.

[131] P. E. Urena et al. “Ejection fraction by radionuclide ventriculography and contrast left ventriculogram: A tale of two techniques.” In: *J. Am. Coll. Cardiol.* 33.1 (1999), pp. 180–185.

[132] I. McGhie et al. “The detection of coronary artery disease: A comparison of exercise thallium imaging and exercise equilibrium radionuclide ventriculography.” In: *Eur. J. Nucl. Med.* 13 (1987), pp. 18–23.

[133] G. McMaster et al. “Effect of repositioning gamma camera on measured LVEF”. In: *Nucl. Med. Comm.* 28 (2007), A36.

[134] F. Grothues et al. “Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance.” In: *Am. Heart J.* 147.2 (2004), pp. 218–223.

[135] F. Grothues et al. “Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy.” In: *Am. J. Cardiol.* 90.1 (2002), pp. 29–34.

[136] N. G. Keenan and D. J. Pennell. “CMR of ventricular function.” In: *Echocardiography* 24.2 (2007), pp. 185–193.

[137] W. G. Hundley et al. “Comparison of quantitation of left ventricular volume, ejection fraction, and cardiac output in patients with atrial fibrillation by cine magnetic resonance imaging versus invasive measurements.” In: *Am. J. Cardiol.* 78.10 (1996), pp. 1119–1123.

[138] R. G. Pai and P. Varadarajan. “Prognostic significance of atrial fibrillation is a function of left ventricular ejection fraction.” In: *Clin. Cardiol.* 30.7 (2007), pp. 349–354.

[139] J. W. Wallis, J. E. Juni, and L. Wu. “Gated cardiac blood pool studies in atrial fibrillation: role of cycle length windowing.” In: *Eur. J. Nucl. Med.* 18.1 (1991), pp. 23–27.

[140] T. Ono et al. “Beat-to-beat evaluation of systolic time intervals during bicycle excercise using impedance cardiography.” In: *Tohoku J. Exp. Med.* 203.1 (2004), pp. 17–29.

[141] C. W. Parrott et al. “Comparison of changes in ejection fraction to changes in impedance cardiography cardiac index and systolic time ratio.” In: *Congestive heart failure (Greenwich, Conn.)* 10.2 Suppl 2) (pp 11-13 (2004), ate of Pubaton: 2004 Mar–Ar.

[142] P. Reant et al. “Systolic time intervals as simple echocardiographic parameters of left ventricular systolic performance: Correlation with ejection fraction and longitudinal two-dimensional strain.” In: *Eur. J. Echocardiogr.* 11.10 (2010), pp. 834–844.

[143] S. L. Bacharach et al. “Measurement of ventricular function by ECG gating during atrial fibrillation.” In: *J. Nucl. Med.* 22.3 (1981), pp. 226–231.

Colophon

Image processing was done using the Link Medical MAPS 10000 system. The thesis was written using the "Hepthesis" package on the LaTeXtext processing system running on Fedora and Red-Hat Linux systems. Statistics were calculated using "R" running on Fedora and Red-Hat Linux systems. Most of the plots were produced using the "ggplot2" package within the "R" environment; additional plots were produced using GNUplot. Figures were created using Xfig.