THE RECOGNITION AND MANAGEMENT OF ISCHAEMIC VENTRICULAR DYSFUNCTION

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ATTRIBUTIONS

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This "big book" is dedicated to my father, mother and daughter Jane.

DECLARATION

Although I have personally collected the majority of the data and collated this, in studies of this nature where haemodynamic data, myocardial flow and exercise testing are being performed simultaneously, these cannot be performed by a single individual. I am therefore indebted to the following for their collaboration.

The clinical classification: Dr. W.S. Hillis and Dr. K. Fearon. The exercise testing and assessment of physical work capacity: Dr. R. Carter. The ventricular volumes and function: Dr. I. McGhie and Dr. W. Martin; right ventricular function: Dr. Martin, Dr. McGhie and Dr. B. Neilly; myocardial perfusion: Dr. I. Hutton, Dr. McGhie and Dr. Martin.

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ABSTRACT

The high incidence of obstructive coronary artery disease in the West of Scotland has resulted in a clinical problem of increasing magnitude, namely ischaemic ventricular dysfunction and its clinical correlate "heart failure". In this thesis, the history of the identification of heart failure is traced, reflecting the still present confusion as to what constitutes "heart failure" and how this should be managed.

This thesis documents the use and limitations of the accepted clinical and haemodynamic measures for the identification of these patients with heart failure and the prediction of their subsequent mortality. Various non-invasive and invasive measurements were made and the overall conclusions from this work are that the appropriate differing tests require to be performed to address specific aspects, namely

a) The identification of the patient with heart failure requires a combination of symptoms and the demonstration of impaired ventricular function (radionuclide angiography in this thesis).

b) The assessment of the patients' clinical status, as reflected by the impact of the disease on his capacity to work is optimally assessed by measurement of gas exchange on exercise.

c) The prediction of subsequent death cannot be made on the basis of clinical or haemodynamic indices, but is dependent on the extent of myocardial "loss", measured in this thesis acutely by perfusion imaging and in the chronic state by the impact on systolic function (left ventricular ejection fraction).

d) Right ventricular dysfunction plays an important role for subsequent mortality, where there is associated left ventricular dysfunction.

In the patient with left ventricular dysfunction as a consequence of coronary artery disease, treatment should encompass an appreciation of the absolute requirement of the myocardium for perfusion and of the factors that determine myocardial flow. These factors are often disregarded, resulting in further jeopardy of the already ischaemic myocardium. In this thesis, it is these aspects that in general have been examined with the commonly applied therapy, such as diuretics. From the work presented, it is evident that diuretics, smooth muscle relaxants, such as calcium channel blockers and inotropic agonists, exert an overall beneficial effect by maintaining myocardial perfusion whereas, for example, nitrates need to be prescribed with care as they may reduce myocardial perfusion (by reducing the blood pressure).

Heart failure is easy to recognise but difficult to define. Hopefully this thesis has cast some light on the complexities of definition and management of heart failure.

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PART 1

HISTORICAL INTRODUCTION

Our concepts of heart disease and heart failure have evolved gradually over centuries. Treatment did not wait upon knowledge of anatomy, physiology and pathophysiology.

The earliest herbals, the pharmacopoeia of our forebears, date from 3000 B.D. - the tablet from Summner and the Pen T'Seo Ching composed by Emperor Shan Nung in China around 2700 B.C. and the Papyrus Ebers dated 1550 B.C., but containing material from the previous 5-20 centuries (1). Much of the skill and knowledge of the ancients has undoubtedly been lost to us. Atherosclerosis, for example, has been found in mummies of the 21st dynasty (circa 1000 B.C.) and was certainly known to the Egyptians. Angina was described in the Babylonian Talmund. The Chinese were well versed in the importance of examining the pulse.

The concept of "pneuma", which was important to Greek medicine appeared at about 600 B.C. with Anaximenes (2). The whole period of Greek medicine is marked by a wealth of both information and dis-information. As early as 500 B.C. (circa) Alcamaeon, a pupil of Pythagoras in Croton in southern Italy, was dissecting animals (Exerctato Anatomica de Mortu Cordis et Sanguinis in Animalibur). He talked of "vessels" but it was Herophilus in about 300 B.C. who understood that vessels contained blood and studied the rhythm and rate of arterial pulsation with the assistance of a clepsydra (3). This knowledge was not appreciated and in the 18th century, interest in the arterial pulse was re-awakened with the pulse watch.

Erasistratus understood that the heart's ventricles act as a pump (particularly the left ventricle), and described the valves. He was cited by Galen as having "invented" capillaries, "arteries and veins, the vessels carrying respectively pneuma and blood are each successively divided up into a great number of smaller and smaller branches, and are spread to all parts of the body so that there is no part in which their terminations are not present" **(4)**. It was not until 1661 that the existence of capillaries was demonstrated by Malpighi - and that blood flowed through these, by Leeuwenhoek. The experimental proof of blood flow from arteries to veins was provided by Walaeus de Wale at Leiden **(5)**.

The dexographer, Caelius Aurelianus (5th century A.D.) **(6)** recorded Herophilus had earlier attributed sudden death for which no cause could be found, to paralysis of the heart - "repentintam mortem nulla ex manifesta causa venientum, fieri inquit paralysis cordis". He seems personally to have observed cases of shock accompanying the onset of atrial fibrillation and to have had a clear idea of the signs and symptoms of acute myocardial infarction - praecordial heaviness, pain (especially in the "left side near the mamilla"), the choking sensation, the collapse with clear mind and the poor prognosis. This pre-dates by several centuries the careful clinical observations of Heberden in 1768 and the subsequent controversy of the pathophysiological implications of calcification of the coronary arteries finally established by Jenner (18th Century).

Aretaeus, a contemporary of Galen (circa 150-200 A.D.), described death due to "cardiac passion" clearly identifying the heart rather than the stomach as was originally believed as the cause. Symptoms were described as including a small and weak pulse, a noisy heart beat where the heart is leaping powerfully, fainting, blackouts, numbness and

paralysis of the limbs, profuse ungovernable sweating, coldness of the whole body, and loss of sensation and speech (**7**). However, it was undoubtedly the teaching of Galen which dominated thinking over the following centuries, particularly in the matter of circulation of blood which was thought to ebb and flow by the power of pulsation generated as the heart acting as a bellows (**8**). This was disputed by Praxagoras, who distinguished arteries from veins and asserted that the power of pulsation possessed by the arteries was quite independent of the heart, a view that was rejected not only by Galen but also Herophilus. Galenic doctrine is apparent throughout the Middle Ages and well into the Renaissance. Medicine was dominated by dogma, supposedly based on a theoretic approach. The disciplines of personal observation and experimentation had yet to have their day.

Anatomy and Physiology

In Avicenna's Cannon (**9**) he notes in his chapter on "Suffocation and Angina" that "cyanche" sometimes goes to the heart and kills. The Latin commentators Andrea Alpago (died 1521) and Joannes Costaeus (died 1603), in their discussions of this confusing chapter (**10**), cite the Galenic statement that a variety of "cyanche" exists in which there are no signs of inflammation in the mouth or upper structures but the patient feels suffocation of his throat - a reference perhaps to congestive heart failure (**11**). In his next chapter, Avicenna describes "pernicious suffocation" in which "respiration is difficult when the body is erect and is worse in recumbency. In contriving to breathe, the restless patient keeps extending his neck. When foam appears, the case is usually hopeless, especially if the colour of the face is unfavourable". Although Avicenna, in his chapters on the heart discusses diseases that affect the pericardium, the causes of syncope and palpitation and indeed how the heart may be

affected by other structures such as the transfer of matter from quinsy or pneumonia, the discussion on dyspnoea is confined to the section on pulmonary disease in accordance with Greek tradition **(12)**. The entirely humoralistic approach of Avicenna is faithfully reproduced by Jean Fernel (1507-1558) with his ancient and mediaeval concept of "down dropping catarrh" [destillabo, called katarrhous by the Greeks] that was formed in the large cerebral sinuses or ventricles and discharged in large volumes causing numerous symptoms and diseases, including obstruction of the lung with dyspnoea and suffocation **(13)**. From Capivaccius's text book **(14)**, with the notes made by Dodonaeus (1581) **(15)** and Schenckius (1665) **(16)**, it is clear that in the 16th and 17th centuries the suffocative catarrh theory of Fernel applied both to pulmonary oedema and to severe inflammation of the respiratory tract. The heart was considered to be an organ of respiration. The understanding of its physiology was that of Hippocrates and Galen and owed little to direct observation. Dropsy (hydrops), an abnormal swelling of the abdomen, was defined as a hepatic disorder, due chiefly but not solely, to "cold dyscrasia". The difference between hepatic concavity and convexity was stressed - "the abdomen is weakly resistant to palpitation and pressure on the diaphragm causes dyspnoea ..., the patient can not readily climb stairs and is dyspnoeic on the slightest exertion". Ludovicus Mercatus (?1520-?1606) clearly distinguished between dropsy of the thorax (hydrops thoracus) and dropsy of the lung (hydrops pulmonis) and suggested that fluid might reach the chest by precipitation from the head or by upward migration from an ascitic abdomen, fluid being attracted back to the chest by suction passed through branches of the pulmonary artery into the pleural cavity **(17,18)**. The anatomy might be correct, at least in part, but the physiology was entirely mythical. Even the writings at the end of the 16th century, including that of Mercatus, recorded little

of the 'new anatomy', gleaned from pathological dissection. For example, Annafis who died in 1288 had described a "lesser circulation" **(19)**, that is the coronary circulation, and challenged the Galenic theory that blood passed through pores from the right to the left ventricle - but the Galenic theory held sway until Harvey, centuries later, described the third circulation.

With Carolus Piso (1563-1633) who described paroxysmal nocturnal dyspnoea and its anatomical counterpart, hydrothorax, we can see the beginnings of clinical and anatomical empiricism **(20)**. The clinical syndrome began to be correlated with observation, albeit based on Galenic concepts of physiology. With Fabrizio Bartoletti (1576-1633) **(21)** we see an attempt to arrange old and new knowledge in an intelligible order, although his book was published some 90 years after that of Vesalius ("De Humani Corporis Fabrica", 1543) **(22)** which marked the beginnings of anatomy as a modern science. Bartoletti comments on dropsy of the chest (hydrothorax), he felt doubtful if Galen knew of hydrothorax; contrary to Mercatus he believed that the disease was one of the thoracic cavity rather than the lung, that fluid migrates in diseased lungs and is squeezed out into the pleural cavity, and that "unless there has been a passage of water from the lung into the cavity of the thorax it does not assume the form of dropsy". He noted from personal observation that the fluid was the same as that of ascites, and by asserting that it was produced in the lung he discounted Mercatus's theory that it resulted from suction of stagnant urine by the lungs. Melchior Sebezius (1578-1674) published a beginner's handbook in 1661 **(23)**. He described respiratory difficulty in three grades of severity - dyspnoea, asthma and orthopnoea - but for explanation returned to the old Galenic theory of obstruction, caused mainly by "precipitation of

fluid from the brain": the feet became swollen by "overflow of fluid from the chest" and weakness was caused by "sympathy with the heart, which became damaged by its immersions in harmful fluids".

The 16th century was the age of anatomy. Vesalius refuted the Galenic theory of pores in the right ventricle **(22)**. Canano described valves in veins **(24)** in 1541. Michael Servetus (1546) **(25)** and Recaldo Colombo (1558) **(26)** each independently described the pulmonary circulation. With William Harvey, and later Richard Lower, came the concept of circulation and the advent of cardiovascular physiology. Harvey explains "that the source and store-house of blood and the place for its perfections is in the lungs and heart". By accurately describing in "De Motu Cordis" that in the dying heart **(27)** the atria survive the ventricles and the right atrium survives the left, he laid the foundation for much of the present knowledge on cardiac impulse conduction. The clinical implications of Harvey's experiments are often not stated, but they can be divined. In his second letter to Riolen **(28)** he suggested that "many dangerous kinds of illness and surprising symptoms" ensue "if the circulation is hindered, perverted or overstimulated", including descriptions of suffocation, asthma and "suffocative catarrh" suggesting perhaps congestive heart failure. He also noted that if the ventricles became distended to the limit of their capacity the heart ceases to beat and death by suffocation ensues. Lower's work, essentially a continuation of Harvey's, relied similarly on direct observation and experiment. In 1669 he published Tractus de Corde Item de Motu et Colore Sanguinis and Chyli in Eum Transitu **(29)**, describing how the colour of blood changes as it passes through the lungs and obtains "a nitrous spirit" from the air. In the second chapter, he maintains that the two sides of the heart should have "like strength in order to maintain a

constant circulation", noting that inequality occurred rarely but the "cardiac parenchyma is subject to various illness:.., which interfere with its pulsation. Hence it gives out blood feebly and slowly". Although Lower did not develop the idea further for the left ventricle, he speculated on the underlying pathophysiology of the right ventricle when discussing the arrangement of the ventricular muscle and the action of the "moderator band". This can be translated as "But it (the right ventricle) might be spread apart so far beyond its proper stretch that its fibres could no longer contract and return to normal. This could be brought about by the onrushing torrent of blood (since the wall is thin) or by suppression of the heart's movement (if the quantity of blood is excessive)" **(30)**.

Marcello Malpighi (1628-1694), who never published, but whose "consultations" have been preserved, had demonstrated as early as the 1660's the implication of the pulmonary circulation in dyspnoea. His ideas were based on earlier experiments, conducted with Fracassati and which included ligation of pulmonary vessels together with minute anatomical studies using a microscope **(31)**. The first demonstration of circulating erythrocytes within the capillaries belongs, however, to Antony van Leeuwenhoek **(32)**. Giorgio Baglivi, a pupil of Malpighi, provides the clinical picture of "stagnation and sudden coagulation of blood in the lungs and praecordium", with "foaming" as a symptom for which blood letting is an "instant remedy" though it must sometimes be done repeatedly **(33)**. Further, in his writings on asthma, he describes a sleeping patient who "is suddenly aroused by severe asthma or is taken with suffocation and opens the windows and wants fresh air". Baglivi indicates that this is dropsy of the chest and is best treated by phlebotomy and diuretics **(34)**. A similar clinical picture of paroxysmal nocturnal dyspnoea, recognised as a "maldistribution of intrathoracic fluid" that

could be treated with diuretics and purges, was described by Carolus Piso in 1618 **(35)**.

THE HISTORY OF TREATMENT

This recognition that the underlying pathophysiology of breathlessness may be treated pharmacologically with specific agents leads directly on to the modern management of heart failure.

Cardiovascular Drugs

1. Cardiac Glycosides

In 1775 William Withering's opinion was sought as to the merits of a herbal tea, commonly used in Shropshire for the relief of dropsy. Withering, a talented botanist, recognised foxglove from over 20 or so ingredients as being the cause of the violent vomiting and purging that accompanies its use **(36)**. This plant had a long history of folk use having been listed in many of the herbals of Edward III's reign (1327-1377) **(37)**. Originally known as "foxglove" it was named Digitalis Purpurea in 1542 by the German botanist Leonard Fuchs and described as "a violent medicine" **(38,39)**.

In 1785 Withering published "An Account of the Foxglove and Some of Its Medical Uses: With Practical Remarks on Dropsy and Other Diseases" **(36)**. In this he described in detail how to determine the correct dosage (highly relevant as it was known to be a deadly poison - "dead men's bells" in Scotland). Withering was of the opinion that digitalis acted directly against dropsy since it did not increase urinary flow in people who did not have fluid retention. He did not realise that it was a cardiac stimulant, although he recognised that it had "power over the motion of the heart, to a degree yet unobserved in other medicine, and that this power may be converted to salutory ends". In 1799 a Manchester physician, John Ferrier, felt that the production of

urine was of secondary importance in comparison to the reduction of pulse rates. Thomas Beddoes noted that digitalis increased the contractile action of cardiac muscle fibres **(38)**.

Richard Bright in reports of medical cases (1827) was the first to distinguish between dropsy of cardiac origin and that due to renal disease, where the "urine was albuminous" **(38)**. Despite this the misuse of digoxin continued and as late as 1911 Potter's Materia Medica and Pharmacopoeia recommended digitalis as an aphrodisiac.

In the early 1900s the effects of digitalis on the heart began to be elucidated with the introduction of the polygraph in 1902 by James McKenzie **(40)** and the electrocardiograph by William Einthoven in 1903 at Leiden University **(41)**. Work carried out by Cushing and McKenzie in London and by Karl Wenckebach in Holland suggested the correct indications for the use of digitalis were atrial fibrillation and for heart failure in sinus rhythm.

Attempts to isolate the active principle in digitalis met with no success and in 1820 the Societé de Pharmacie in Paris offered a prize of 500 francs, which doubled after five years. This was not awarded until 1841 when Homolle and Quevenne, pharmacists at the Hôpital de la Charité in Paris, isolated the impure but active crystalline material, probably mainly digitoxin, which they called digitaline. Digitaline crystalliseé was isolated in 1869 by Claude Alphonse Nativelle. In the late 1920s the powdered leaves of digitalis lanata were found to have a greater pharmacological activity than digitalis purpurea, and Sidney Smith of Burroughs Wellcome isolated and separated the glycosides and thus identified a new glycoside which he called digoxin **(42)**.

In 1888 Ouabain was isolated by Arnaud from the bark and roots of the ouabaio tree (Acocanthera sp.) from which the Somalis of East Africa prepared their arrow poison. It was also present in the infusions of the barks and seeds of Strophanthus gratis used by the Pahouins. Thomas Fraser, working in Edinburgh, investigated a variety of arrow poisons from different varieties of Strophanthus, thus renewing interest in the isolation of cardiac stimulants. In 1933 Arthur Stoll and co-workers isolated a crystalline cardiotonic glycoside from squill ("the bulb of the sea onion"- Urginea maritime) which technically was similar to that of digitalis and was used by the ancient Egyptians and Greeks **(43)**.

2. Nitrates

Amyl nitrate had originally been synthesised at the Sorbonne in1844 by Balard who noted that its vapour gave him a severe headache. In 1865 Sir Bernard Ward Richardson showed that the facial flushing was due to dilatation of the capillaries. Gamgee showed that nitrate induced dilatation of blood vessels led to a drop in blood pressure.
In 1867, Thomas Brunton, working as a newly qualified physician at Edinburgh Royal Infirmary and faced with a patient with paroxysmal nocturnal angina, found that cupping and venesection proved consistently helpful. His friend, Arthur Gamgee, who had been using amyl nitrate to lower blood pressure in animals suggested that this might be tried and Brunton found this to be immediately effective in relieving chest pain **(44)**. In the following years Brunton examined other nitrates, including the readily available nitroglycerin whose explosive properties had been discovered by Alfred Nobel, but found that it caused such severe headaches that he pursued it no further (St. Bartholomew's Reports 1876). Nitroglycerin itself was discovered in 1847 by the French chemist Ascagne Sobrero and to avoid the intense headache, which he

attributed to overdosage, William Murrell developed a tablet containing 0.5 - 1.0 mg. of nitroglycerin to be dissolved slowly in the mouth (with larger doses for oral or topical preparations) and published in the Lancet in 1879 **(45)**.

Analogues and nitroglycerin have been synthesised and the first of these, pentaerythritol tetranitrate, was introduced in 1896. More recently, isosorbide dinitrate and isosorbide mononitrate have been manufactured. It was some time before it became appreciated that nitrates induce relaxation of smooth muscle throughout the body.

3. Alternative Vasodilators

In attempts to find alternatives to nitrates, and in the context of growing understanding of several of the underlying mechanisms, drugs which block calcium ion influx into ventricular smooth muscle have been developed. In 1942 Max Bochnuhl and Gustav Erhardt of Hoechst synthesised fenpiparane, an anologue of methodone, which could be used as a papaverine substitute. In 1958, Erhardt synthesised prenylamine (Synadrin) and in 1965 Janssen synthesised nidaflazine which incorporated a lignocaine residue, in an attempt to confer anti-arrhythmic activity. The Richardson Merrell company developed perhexilene (Pexid), a fenpiparane analogue, with a reduced diphenylhydryl ring. In 1962 Knoll and company developed an open chain papaverine analogue - verapamil **(46)**. In 1965 Bernard Loev for Smith Kline and French synthesised a series of dihydropyridines and published the discovery of a relatively long lasting compound that dropped the blood pressure in animals but in 1967, before Loev's work was protected by patent, Vosser and Wagner working for Bayer patented nifedipine **(47)**.

4. Diuretics

The removal of oedema relied on the removal of blood, sweat or urine: blood - by cupping or leeches; sweat - by herbal diaphoresis; and diuresis - again by herbs. Diuretic herbs were known to the ancients, particularly Rhu and Figwort, and the last herbal diuretic appeared in the British Pharmacopoeia in 1932 (Infusum Bachu). Xanthine alkaloids, present in tea, coffee and cocoa, all had diuretic properties and Bronne in his doctoral dissertation at the University of Strasbourg in 1886, investigated the diuretic action of caffeine. His supervisor, von Schroeder, looked at a chemically similar alkaloid in cocoa (theobromine). Shortly afterwards, theophylline was isolated from tea extract though not properly characterised until it was synthesised by Wilhelm Traube in 1902 **(39)**. Minkowsky established that it was three times more potent than caffeine. It is however very insoluble so that it was not until it was bound to ethylene-diamine that it become universally available as aminophylline.

The first of the more modern diuretics was discovered accidentally when Arthur Vogl, a medical student at the Wenckebach Clinic in Vienna University, was instructed to give a syphilitic patient mercury salicylate. Not realising how insoluble this was in water, he ordered a solution to be prepared but a colleague, to save his embarrassment, offered a soluble mercurial antisyphilitic - merbaphen - and this he gratefully accepted. On the carefully charted recording of urinary output he noted that the patient had a diuresis. He therefore gave merbaphen to another syphilitic patient with aortic valve disease and gross congestive failure in whom conventional diuretics had failed. This produced a 10 litre diuresis. It soon became evident, however, that merbaphen could produce fatal colitis or nephrotoxicity **(48,49)**. In 1924 mersalyl was introduced. This

was often life saving although it was known to be toxic and had to be given parenterally. In 1941 Walker, Bott and Oliver, using micro-analytical techniques, showed that the reabsorption of water from the glomerular filtrate depended largely on the efflux of sodium ions across the tubule wall and that mercurial diuretics probably acted on inhibiting dehydrogenase enzymes, thus diminishing the movement of sodium and chloride ions. They then set out to synthesise a mercury-free dehydrogenase inhibitor and eventually in 1962 ethacrynic acid emerged. This however was five years after the discovery of thiazide diuretics. In 1940 Mann and Keilin, working in Cambridge on antibacterial sulphonamides, noted that sulphonamides which retained both hydrogen ions were carbonic anhydrase inhibitors. These included sulphanilamide which produced an alkaline diuresis when given in massive doses **(50)**. In 1945 Pitt and Alexander established that inhibition of carbonic anhydrase in the kidney blocked reabsorption of sodium in the distal tubule. This property of naturesis subsequently shown to be secondary to blocking of the bicarbonate excretion was exploited by Schwarz who induced diuresis in patients with congestive heart failure with large oral doses of sulphanilamide. Roblin and Clapp synthesised hetero-cyclic sulphonamides in the belief that being more acidic than conventional sulphonamides they would better compete with carbon dioxide for the active site of the enzyme: acetazolamide was one such. Karl Bayer, working for Sharp and Dohme, thought a carbonic anhydrase inhibitor that acted in the proximal portion of the tubule might increase chloride excretion and thus promote loss of sodium chloride which would be useful in the treatment of hypertension which was currently being treated by reduced dietary salt intake. Sprague and Novello synthesised several aromatic sulphonamides for Bayer and his colleagues to test, eventually producing dichlorphenamide. The attachment of an amino group to the

benzene ring of compounds similar to dichlorphenamide together with various other substitutions led to the development of benzothiadiazine which was marketed as chlorothiazide in 1957. Thiazide diuretics herewith replaced the toxic mercurial diuretics. In attempts to enhance diuretic potency other analogues of dichlorphenamine were synthesised, such as the open chain substituted derivative where the second acidic group was replaced by a carboxyl group. This led to the introduction of frusemide by Hoechst in 1962 and its structual analogue, bumetanide, in 1972. These drugs act on the loop of Henle to induce a brisk intense diuresis. They are powerful drugs which remain the mainstay of diuretic therapy for heart failure today though thiazides retain an important role for milder diuresis in patients in the "diuretic" treatment of high blood pressure.

5. Angiotensin Converting Enzyme Inhibitors

In 1934 Goldblatt published his work on renal ischaemia producing persistent elevation of systolic blood pressure and, three years later, Juan Fasciolo showed that transplantation of a kidney from a hypertensive animal into one with hypertension induced by bilateral nephrectomy that the ischaemic kidney was a potent source of renin **(51,52)**. In 1939 Clifford Wilson and Frank Byron **(53)** demonstrated renal arteriolar degeneration associated with hypertension, laying the foundation for two further papers in 1940 - Eduardo Braun-Menendez, Juan Fasciolo et al "The Substance Causing Renal Hypertension" **(54)** and Irving Page and O.M. Helmer "A Crystalline Substance (Angiotensin) Resulting from the Reaction Between Renin and Renin-Activator" **(55)**.

In 1956 Skeggs et al **(56)** discovered the enzyme that converts angiotensin I to angiotensin II, but it was not until 1967 that the key role of angiotensin conversion was described in the lungs (Ng and Vane, 1967, 1968) **(57,58)**.

In 1965 Ferreira described a bradykinin potentiating factor present in the venom of the Brazilian arrowhead viper (Bothrops jararaca) and in 1968 Bakhle showed that this venom also inhibited the conversion of angiotensin I to angiotensin II, but it was not until 1972 until Engel et al appreciated that both actions of the venom were caused by the same components. Subsequently Ferreira et al isolated nine peptides, one of which was a nonapeptide called teprotide which was tested in vivo and was synthesised by Ondetti et al. In 1977 David Cushman, Hong Son Cheung and Emily Sabo and Miguel Ondetti of the Squibb unit developed captopril, which supplanted teprotide and is a nonapeptide possessing at least ten times the activity.

In 1978 two groups (Curtis et al and Gavras et al) **(59,60)** simultaneously reported on the use of intravenous teprotide for chronic congestive heart failure, both papers demonstrating improved cardiac function with reduced systemic vascular resistance. The following year two papers appeared on the use of captopril in congestive heart failure (Davis et al, Turini et al) **(61,62)** showing increased cardiac output, reduced pulmonary wedge pressure and systemic vascular resistance. Although captopril is undoubtedly effective it does have side effects, which may be associated with the presence of a sulfhydryl group.

6. Other Inotropic Drugs

The theory of competitive drug antagonism was first formulated by Sir John Henry Gaddum (1900-1965), working at the Wellcome Physiological Research Laboratories, with his paper "The Action of Adrenaline and Ergotamine on the Uterus of the Rabbit" (1926) **(63)**. This work showed that when the response to a drug was plotted against the logarithm of drug concentration, an S-shaped curve was obtained. A later paper "The Quantitative Effect of Antagonistic Drugs" (1937) showed that the effects of competitive drug antagonism could be expressed mathematically. Sune Bergström, working with US von Enler and U Hamberg, reported the "isolation of noradrenaline from the adrenal gland" (1949) **(64)**. Noradrenaline was also independently isolated by BF Tullar (1950). Noradrenaline is an alpha agonist which causes vasoconstriction.

Earlier James Gunn (1822-1958) **(65)** wrote on the pharmacological actions and therapeutic uses of some compounds related to adrenaline - ß phenylamine, tyramine, benzedrine and ephedrine - and concluded that one action which is retained by compounds based on phenyl-ethylamine, even with a modified structure, are its action on smooth muscle with pressor hypertensive effects. In 1946 Ulf von Enler showed that noradrenaline is the predominant transmitter of the post-ganglionic sympathetic nerve fibres **(66)**. It had been known for some time that the peripheral vasoconstrictive effects of adrenaline could be prevented by using antagonists (ergot alkaloids, phenoxybenzamines) whereas peripheral vasodilation could not. In 1948 RP Ahlquist introduced a hypothesis which accounted for these differing effects by postulating the existence of two different types of receptors - alpha and beta **(67)**.

For something like ten years, only alpha antagonistic effects were known then in 1958 dichloroisoprenaline was discovered, which was the first substance to selectively and competitively prevent beta receptor effects. In 1962 Sir James Whyte Black and JB Stephenson reported the development of pronethalol, a specific adrenergic beta receptor antagonist. A large number of compounds were made and tested and in 1949 the paper "A New Adrenergic Beta-Receptor Antagonist" - propranolol was published. Propranolol has now been augmented by an extensive range of adrenergic beta blocking drugs with differing degrees of cardioselective action **(68)**. In 1967 AM Lands and co-workers discovered that variations in sensitivity of the beta receptors to stimulant and blocking drugs (depending on their chemical composition) allowed the differentiation of two types of receptors - B_1 in the heart and small intestine and B_2 in the bronchi, vascular beds and uterus **(69)**. Levy and Wilkenfield (1969) showed that there are drugs available able to selectively block either B_1 or B_2 receptors without affecting the other type of B receptors **(70)**. Similarly, as shown by Choon-Kang et al (1970), salbutamol selectively activates B_2 receptors and relaxes bronchial smooth muscle, without producing unwanted cardiac stimulation **(71)**. This led to the development of selective beta antagonists in the form of prenalterol (1-[4-hydroxyphenoxy]-3-isopropyl-amino-2 propranol) which is essentially a B_1 agonist and pirbuterol which has a greater effect on B_2 receptors than on B_1 receptors (2-hydoxy-methyl-3-hydroxy-6-[1-hydroxy-2-test-butylamino-ethyl=pyridine 2HCl]). These drugs can be expected to produce different degrees of vasodilatation and inotropic stimulation of the myocardium.

HISTORY OF CLINICAL RECOGNITION OF HEART FAILURE

On the sound basis of new anatomical knowledge - a process begun in the 16th Century, came the "clinicians" of the following centuries. Raymond Vieussens (1641-1716) was according to Senec "an earnest student of anatomy". He wrote "the smallness, weakness and irregularity of the pulse can be ascribed to the small amount of blood that flowed from the left ventricle into the aorta as well as to the lessened force with which that ventricle pushed the blood into the artery, and to the irregularity of its contraction. As to the leaden colour of the lips, the dimmed lustre of the eyes, the dropsical swelling of the legs and thighs, and their lowered temperature, I would say that these symptoms can be viewed as the result of the disturbed circulation" **(72)**. Lancisi of Rome (1654-1720) had a wider view than Vieussens and in the second part of De Motu Cordis et Aneurysmatibus **(73)** there was an attempt at classification of "aneurysm" or dilatation of the heart - citing causes as heredity, mechanical obstruction from inside the heart as from calcified or leaking valves or calcified arteries, or from outside the heart as from chronic catarrh, asthma, palpitation, nervous and psychic conditions. His contemporary who also and independently studied heart disease - Hippolito Francesco Albertini was a pupil of Malpighi, a colleague of Valsalva and a teacher of Morgagni. In 1726, five years after its presentation, a paper was published in the transactions of the Bologna Scientific Society **(74)** which commented on the respiratory difficulties that depended on damage to the heart and praecordium. Albertini systematically employed palpation as an aid to diagnosis, recognising the quality of the heart's impulse, its extent, the presence of thrills and the location of the heart, particularly if it was enlarged and whether it was thin walled or thick walled (hypertrophied). He also discussed "remoter"

symptoms of heart disease such as pains in the shoulders and arms, and recognised difficulties in breathing as being accumulation of fluid due to obstruction to the circulation through the heart (clearly differentiating this from "hydrops" of the pleura).

Giovanni Battista Morgagni (1681-1771) in his monumental work De Sedibus et Causis Moriborum et Anatomes Indignatis - Libri Quinque (Venice 1761), in which he freely admits he borrows from many sources Albertini, Valsalva and Senec, laid the foundation for the anatomic concept. This was not discovered by Morgagni but he communicated it in a uniquely clear way - the value of careful case histories, various aetio-logical and therapeutic features, and the clinical symptoms in the light of revelation after death - that is a method of diagnosing and explaining disease in terms of pathological anatomy **(75)**. These methods became more general, especially after their adoption by Corvisart and Laennec. In the latter part of the 18th Century in England, interest in heart disease was kindled by William Heberden (1710-1801) the consummate physician of the Hippocratic type, whose bedside observations were keen and discriminating. In 1768 he described with remarkable clarity the clinical picture of what we now recognise as angina pectoris, of which he reported 20 cases **(76)**. Indeed his description has not been surpassed to date "but there is a disorder of the breath marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and the sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.

Those who are afflicted with it, are seized while they are walking (more especially if it be uphill and soon after eating) with a painful and most disagreeable sensation in the breast which seems as it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes. In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are more liable to this disease, especially such as have passed their fiftieth year". Heberden had little idea that his description of pain had any connection with the heart far less the coronary arteries but others in Britain had. A patient of John Fothergill's (1712-1780) with typical angina was sent to John Hunter for autopsy after his sudden death at the age of 63 because it was suspected by Fothergill that the heart was at fault **(77)**. The heart was of "ligamentous consistence and in many parts of the left ventricle almost white and hard". "The two coronary arteries from their origin to many of their ramifications upon the heart were become one piece of bone". In fact when Hunter himself died (1793) he was found to have extensively ossified coronary arteries and had been known to suffer from angina. His friends Edward Jenner and Caleb Hillier Parry refrained from discussing or publishing their thoughts on the association of angina with ischaemia of the heart muscle until after his death (Parry's Syncope Angiosa 1799) **(78)**. Following Parry's statements Alan Burns (1781-1813), working in Glasgow as an anatomy demonstrator, attempted to

demonstrate what he believed was the central mechanism of angina i.e. relative ischaemia of the muscle. The heart "has peculiar vessels set apart for its nourishment. In health, when we excite the muscular system to more energetic action than usual, we increase the circulation in every part, so that to support this increased action, the heart and every other part has its power augmented. If, however, we call in to vigorous action, a limb, round which we have with a moderate degree of tightness, applied a ligature, we find that the member can only support its action for a very short time; for now its supply of energy and its expenditure, do not balance each other; consequently, it soon from a deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence. A heart, the coronary vessels of which are cartilaginous or ossified, is in nearly a similar condition; it can, like the limb, ... with a moderately tight ligature, discharge its function so long as its action is moderate and equal. Increase, however, the action of the whole body, and along with the rest, that of the heart, and you will soon see it ..... the truth of what has been said; with this difference, but as there is no interruption in action of the cardiac nerves, the heart will be able to hold out a little longer than the limb. If a person walks fast, ascends a steep or mounts a pair of stairs, the circulation in their state of health is hurried, and the heart is felt beating more frequently against the ribs than usual. If, however, a person with the nutrient arteries of the heart diseased in such a way as to impede the progress of the blood along them, attempts to do the same, he finds, that the heart is sooner fatigued than the other parts are, which remain healthy. When, therefore, the coronary arteries are ossified, every agent capable of increasing the action of the heart, such as exercise, passion and ardent spirits, must be a source of danger" **(79)**.

The next notable advance came from France. Jean-Nicolas Corvisart (1755-1821), a clinician but an ardent advocate of autopsy control of diagnosis, was mainly interested in "aneurysm" which in the terminal stages resulted in "heart failure" **(80)**. He was able to distinguish between failure of the right and left heart. In addition he occasionally refers to the sounds of the heart being audible by listening "close by" in cases of "active aneurysm". In 1808 he translated and republished the "Investum Novum", published by Auenbrugger in 1761 adding his own comments **(81)**. Auscultation as a diagnostic method began to be accepted. Corvisart was also clearly conversant with the back pressure theory of the failing heart although his written explanations were not as clear as those of Vieussens almost 100 years earlier or of Hope some few years later.

In 1819 Laennec (1781-1826) published "De L'Auscultation Médiate" **(82)**. With the invention of the stethoscope the medical world awoke to the immense value to diagnosis of auscultation in addition to percussion, palpation and inspection. Laennec's main interest was in respiratory disease and he often misinterpreted sounds from the heart (eg of the two heart sounds he assigned the first to ventricular contraction and the second to auricular contraction). In Vienna Joseph Skoda (1805-1881) checked Laennec's work by experiment at the bedside and with autopsy, together with the clinician Carl Rokitansky (1804-1878). With these two clinicians, Vienna became renowned as the centre for clinical teaching and the teaching of the art of diagnosis **(83)**.

Ludwig Traube (1818-1876) twice visited Vienna to study under Skoda (1841 and 1843). In 1871 he published an article noting that the failing heart caused reciprocal changes in the kidney with congestion of that

organ **(84)**. He also discussed embolic infarction and primary contraction of the kidney which he believed was either causative or associated with hypertrophy of the heart.

Now was the age of physical diagnosis epitomised by the Irish clinicians, Graves, Corrigan, Cheyne and Adams, and above all William Stokes (1807-1878). Stokes, educated in Dublin, Glasgow and Edinburgh, was familiar with the work of Laennec and Skoda. In his major work "Diseases of the Heart and Aorta" (1854) **(85)** he sets forth the importance of judging the gravity of heart disease not only in the presence of a murmur but "it is in the vital and anatomical conditions of the muscular fibres that we find the key to cardiac pathology: for, no matter what the affection may be its symptoms mainly depend on the strength or the weakness, the irritability or the paralysis, the anatomical health or disease of the cardiac muscle. It was long ago observed by Laennec that valvular disease had but little influence on health when the muscular condition of the heart remained sound, and every day's experience confirms this observation". He advocated, only in passing, the use of digoxin but used mercury to strengthen "the weak myocardium" with favourable results - increasing urine output, decreasing the size of the liver and lessening dyspnoea.

Contemporary with Stokes, Peter Mere Latham (1789-1875) is of interest for his hypothesis of "pseudohypertrophy", which he named the temporary "distension" of the overfilled ventricle which returned to normal when the overload was removed **(86)**. When the muscular structure was damaged by disease and the elastic properties lost, he termed this dilatation and clearly described the secondary effects of congestion of the lungs, the venous system and oedema, which he

regarded as the body's way of attempting to drain the extra fluid and thus lessening the work of the heart. He also discussed five cases of angina which differed from the usual in that the pain was of sudden onset, lasted an inordinate time, recurred with the slightest provocation (status angiosus) and resulted in death. At autopsy in some of these patients not only were their coronaries found to be ossified but the heart muscle was "softened" **(87)**. James Hope (1801-1841), whose medical education started as a resident physician in Edinburgh, then a year in Paris and later hospitals in Italy, Bavaria and Holland, first published his Principles and Illustrations of Morbid Anatomy in 1834 **(88)**. In this he was the first to provide a clear exposition of the back pressure theory of heart failure **(89)**.

The term "chronic myocarditis" was appearing in the literature - often applied to processes that were not inflammatory - and indeed earlier Morgagni seems to have recognised this confusion - he thought that the process might often be degenerative rather than inflammatory **(90)**. Virchow taught that inflammation might start in the interstitial tissue which by contraction or exudation, by causing pressure, might damage muscle fibres **(91)**. This hypothesis was reversed by Carl Weigert (1847-1904) **(92)**. While investigating the effects of smallpox he noticed a fibrin-like change in the parenchymal cells with loss of nucleii, which he regarded as the first step in a process later termed "coagulation necrosis" by Cohnheim **(90,93)**. Subsequently there was proliferation and fibrous tissue formation as part of a reparative process. Weigert believed that initial damage in the case of the heart would affect the muscle cells. This damage may be caused by chemical or bacterial toxins, but also from excessive strain on muscle fibres that are overstretched, overworked and poorly nourished, as in aortic regurgitation or "lessened

circulation through the coronary arteries" (Dock's translation) "In atheromatous changes of the coronary arteries not infrequently thrombotic or embolic obstructions form in the branches of the arteries. If the obstruction forms slowly, or at least in such wise that the collateral channels exist, but not enough to keep up nutrition, a slow atrophy occurs with destruction of the muscle fibres without injury to the connective tissue. The muscle fibres that disappear are replaced by fibrinous connective tissue, and the so-called chronic myocarditis is nothing else than such a process" **(92)**.

In 1881 Cohnheim and von Schulthess-Rechberg published the results of experiments occluding coronary arteries in dogs and transferring these results to man concluded that ligation of larger branches was rapidly fatal **(93)**. They argued that in the extensive area of myocardium involved, the circulation became stagnant and with the accumulation of noxious chemical products this tended to paralyse the muscle.

There followed then a very exciting time in medicine - Pasteur's preventative vaccination (1880), Koch's discovery of the tubercle bacillus (1882), Lavereau's description of the parasite of malaria (1881), Lister's aseptic principles for surgery (1886), Fitz's operation for appendicitis and in 1896 Roentgen described the x-ray. Heart disease and its problems faded from the forefront until the early 20th Century when interest was reawakened with His, Keith and Flack, Gaitskell and Tawara, McKenzie's polygraph and Einthoven's electrocardiograph and Thomas Lewis's "The mechanisms of the Heart Beat" (1911).

This might be termed the era of the physiologists. Adolf Fick (1829-1901) developed the Fick principle for the measurement of cardiac output

- the principle of measurement of blood flow by dilution, being that the faster the blood flow the less oxygen is taken up per unit of flowing blood. In 1897 George Neil Stewart **(94)** published a series of experiments measuring circulation time using changes in conductivity and the principles of indicator dilution measurements. The control of cardiac output had been seen as an intriguing problem since the mid 19th century. Control of heart function involves both heart rate and stroke volume. The relationship between the length of the muscle fibre and its strength of contraction in skeletal muscle was known to Fick and was investigated by one of his former students - M. Blix (1891). Otto Frank (1865-1944) **(95)** formulated some of the fundamental principles of cardiac contraction. He says of isometric contraction "the peaks (maxima) of the isometric curve rise with increasing initial tension (filling). (I call this part of the family of curves the first part). Beyond a certain level of filling, the peaks decline (second part of the family of curves)". In 1914 Straub and Wiggers both published on the factors controlling pressure curves, but as with Frank they had difficulty demonstrating a quantitative relationship **(96,97)**. In 1912 Starling, Evans, Patterson and Piper began to work together which culminated in "the law of the heart" **(98,99)**.

"The law of the heart" is therefore the same as that of skeletal muscle namely that the mechanical energy set free on passage from the resting to the contracted state, depends on the area of "chemically active surfaces", i.e. the length of the muscle fibres. This formula serves to "explain" the whole behaviour of "the isolated mammalian heart". Starling's work emphasised the effects of venous flow - that increased cardiac output was determined by the increased venous inflow, until atrial pressure was considerably elevated and that there was a relationship between the

diastolic volume of the ventricle and the work developed in the following systole. But in the intact animal the law did not describe phenomena observed, such as a higher cardiac output in resting animals than in the heart lung preparation and the mechanisms by which cardiac output could increase above resting levels **(100,101)**. In 1878, A Waller **(102)** had the idea that increased output was accomplished by blood entering the heart from distended pulmonary veins at a higher pressure. Stanley Sarnoff and Erik Berglund confirmed that there is a consistent relationship between atrial pressure and ventricular stroke work and demonstrated series or families of ventricular function curves, by which concept changes in ventricular function could be understood. With regard to myocardial failure they state "The shape of the normal ventricular function curve does not confirm the interpretation that cardiac failure may result merely from stretching the muscle fibre beyond the point where an increased filling pressure causes a decrease in cardiac work. We consider myocardial failure to be an alteration of the contractility of the myocardial fibres resulting in a shift of the ventricle from a normal function curve to a depressed one. The increased filling pressures are not the cause of failure but a consequence of decreased myocardial contractility" **(103)**.

Historically the clinical manifestations of heart failure have been regarded as arising as a consequence of either inadequate cardiac output (backward failure hypothesis first proposed by Hope in 1832) **(104)** or the damming up of blood behind one or both ventricles (forward heart failure hypothesis proposed by McKenzie) **(105)**.

Backward failure - the overworked ventricle first hypertrophies and then dilates. As it dilates the blood gets dammed up behind it and an

increased venous pressure is transmitted ultimately to the capillaries where oedema is formed.

Forward failure, based on Starling's findings, that as the pressure in the great veins rose the pressure in the capillaries fell, thus Starling was forced to propose that the only explanation could be the loss of fluid with an increased capillary permeability ("The dropsy is entirely conditioned by the state of the capillary wall"). McKenzie championed this theory. "The blood passes through the capillaries at a slow rate, impairs their nutrition, and allows transudation to take place, which we call dropsy" **(105)**. It was several years before Landis' technique eventually demonstrated that capillary pressure was increased in heart failure **(106)**. It was not until after the introduction of cardiac catheterisation by Cournand and Richards, which allowed sampling of arterial and venous blood, that there was demonstrated there was a group of conditions in which there was undoubted cardiac failure, but the cardiac output was increased - the "high output failure" of anaemia, thyrotoxicosis, A-V fistula, cor pulmonale, beri-beri and Paget's disease.

This resulted in a small change in the definition which is now widely reproduced "a state in which the heart fails to maintain an adequate circulation for the needs of the body" (Paul Wood) **(107)**. What it leaves undefined are "the needs of the body". Peter Harris' St. Cyrus lecture of 1986 succinctly and logically deals with the various possibilities - glucose, fatty acids, oxygen, but there is no evidence for reduced uptake of any of these substances **(108)**. Peter Harris also discusses the control exerted by the autonomic nervous system, the central nervous system and endocrine mechanism and finally comes to the conclusion that evolution in warm blooded animals has produced a system to provide a high

cardiac output to support physical exercise, with the delivery of oxygen to exercising muscles together with a high resting arterial pressure which allows for this increase in cardiac output with a relatively unchanged left ventricular emptying pressure. "A damaged heart becomes progressively unable to maintain arterial pressure at first during exercise and ultimately at rest. When this happens the body responds in the stereo-typed manner for which it has been programmed by natural selection to maintain the arterial pressure during exercise or trauma".

The identification or diagnosis of heart failure is still problematical. Clinically the mechanisms of "forward and backward" heart failure operate to a greater or lesser degree in most patients with heart failure. Blood pressure measurement per se is not particularly helpful in identifying the patient with chronic heart failure, since by definition, blood pressure is maintained by a variety of compensatory mechanisms. Perhaps little has changed since Sir Thomas Lewis wrote "It is impossible thoughtfully to survey, in the light of early experience, the field of medical work covering diseases of the heart without realising the central problem to be failure of the heart to accomplish its work to a lesser or greater degree. The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure..... When a patient seeks advice and heart disease is suspected, or is known to be present, two questions are of chief importance. Firstly, has the heart the capacity to do the work demanded of it when the body is at rest? Secondly, what is the condition of the heart's reserve? These questions can be correctly answered in almost all cases by simple interrogations and by bedside signs" **(109)**.

REFERENCES FOR PART 1

1. Ebers Papyrus translated into German 1890 by H. Joachim, this version translated into English in 1930 C.P. Bryan. 1938 B. Ebbell, the only consecutive translation of the Ebers Papyrus in English. Also, An Illustrated History of the Herbals; Frank J. Anderson, 1977, Columbia University Press, New York.

2. A History of Medicine, Arturo Castiglonie; p. 47, 51 and 76, 1947. A.A. Knopfine in London by Routledge and Kegan Paul Ltd.

3. The battle against heart disease. P.E. Baldry. Cambridge University Press, 1971.

4. Erasistratus 4th Century A.D. in A Short History of Cardiology, p. 8. Garrison's translation in History of Medicine. Also in The Heart and the Vascular System in Ancient Greek Medicine. C.R.S. Hains. Clarendon Press, 1973. James B. Henck. Published by Chas C. Thomas 1942, Illinois.

5. Walaeus de Wale in History of Cardiology, p. 22. H.A. Snellen. Danker Academic Publications, Rotterdam, 1984.

6. Caelius Aurelianus 5th Century A.D., translated from Soranus 2nd Century A.D. Chapter on "The Cardiac Passion", English translation by Drabkin; 1950: p. 575.

7. De causis et signis acutorum morborum. Corpus medicorum graecorum, Vol 2, p. 21-23. Edited H. Diels, I. Mewaldt and J. Heeg, Leipzig/Berlin 1915, and the Extent and Works of Aretaeus, the Cappadcian ed. and trans. F. Adams, p. 429, London Sydenham Society 1856.

8. Why Galen and Harvey did not compare the Heart to a pump. Siegel R.E. A.J.C. 20; 117-121, July 1967.

9. Saul Jarcho. English translation of 8 sections of the Arabic Edition Ibn Sina 'Kikab al-ganum fi al-Tibb Rome Typographia Medicea 1593, with reference to corrections in the Bulag edition (1924 reproduced in Baghdad: Al-Muthanna Library of K.M. Ar-Rajab.

10. Corpus medicorum graecorum, Vol 5. Edited H. Diels, I. Mewaldt, and J. Heeg, Leipzig/Berlin 1915.

11. De locis affectis, Book 4, Chapter 1. Galen; Book 4, Chapter 4, p. 112-117. Siegel's translation. The Concept of Heart Failure, p. 3 and p. 127. Saul Jarcho, Harvard University Press, 1980.

12. Avicenna's Cannon. On the Signs [of Suffocation and Angina]. The Concept of Heart Failure from Avicenna to Albertini, p. 4, Saul Jarcho, Harvard University Press, 1980.

13. Medicina Jean Fernel - Symptoms of Discharges from the Head (Book 5, Chapter 4, p. 136-138. Published in Paris, 1554, reissued in 1577, under the title Universa Medicina.

14. Opera omnia - quinque sectionibus comprehensa - posthumously collected, edited and published in Frankfurt, 1603, Paltheniana. Hieronymus Capivaccus Practica Medicina. Ed. Ioannes Hartmannus Beyerus (Frankfurt: Paltheriana 1594).

15. Rembertus Dodonaeus. De catarrho, sive destillabione suffocante in medicinalium observationum expempla rava, recognita et aucta. Ch. 9, p. 24-25. Cologne: Cholinus, 1581.

16. Joannes Schenckius. Observationum medicarum rariorum, Book 1, Observabo 277, p. 224-229. Frankfurt, Paltheniana 1600.

17. De internorum morborum curatione, Book 2, Chap 4, p. 160-161. In Opera Ludovicus Mercatus. Frankfurt: Palthenius 1619-1620. English translation The Concept of Heart Failure. Saul Jarcho, p. 87-102. Harvard University Press 1980.

18. De internorum morborum curatione, Book 2, Chap 4, p. 175-182. In Opera Vol 3 Ludovicus Mercatus. Frankfurt: Palthenius 1619-1620. English translation The Concept of Heart Failure. Saul Jarcho, p. 87-102. Harvard university Press 1980.

19. A History of Medicine, p. 278. Arturo Castiglioni 1947. A.A. Knopfine and in London by Routledge and Keegan Paul Ltd.

20. Carolus Piso. Selectiorum observationum et consiliorum de praetervisis hacterus morbis affectibusque praeter naturam, ab aqua sem serosa colluvie et diluvie ortis, first published 1617 but recorded.

21. Fabrizio Bartoletti Methodus in dyspnoeam sem de respirationibus libri cum synopsibus quibus pro colophone accessit de curationibus, published posthumously Gologna 1633, Chap 9. Index-Catalogue of the Library of the Surgeon-General's Office, Series 1, Vol 12, p. 241.

22. Andreas Vesalius. De Fabrica Humani Corporis, 1543. Lindeboom G.A. Andreas Vesalius and His Opus Magnum 1975.

23. Melchior Sebezius. English translation:- Manual or Practical Mirror of Medicine, compiled from Good and Reliable Authors for the Use of Beginners in Medicine. Mancualis, sive speculi medicinae practici. Argertorati: Spoor 1661.

24. A History of Medicine. P. 418. Arturo Castiglioni. A.A. Knopfine and in London by Routledge and Keegan Paul Ltd. 1947.

25. Osler William, Michael Servetus Bull John Hopkins Hosp 21; 1-11: 1910.

26. A History of Medicine. P. 435. Arturo Castiglioni. A.A. Knopfine and in London by Routledge and Keegan Paul Ltd. 1947.

27. Exercitatio anatomica de motu cordis et sanguis in animalibus. Chap 4, p. 39-40. William Harvey trans. Chauncey D. Leake, 5th Ed. (Springfield, Illinois, Thomas 1970).

28. The Circulation of the Blood: Two Anatomical Essays by William Harvey. K.J. Franklin trans. and ed. Oxford Blackwell 1958, p. 42-43, 49, 64.

29. Tractus de corde, item de motu et calore sanguinis et chyli in eum transitu. Richard Lower, Facsimile and English translation K.J. Franklin in Early Science in Oxford, Vol 9, 1932. Ed. R.T. Gunther, Oxford, privately printed.

30. Richard Lower, translated by Saul Jarcho in The Concept of Heart Failure from Avicenna to Albertini, p. 363. Harvard University Press, 1980.

31. Liber primus de catarrhis consultations 30 and 33 in Chapter X. W. Schneider, Wittenberg, 1960; 61,62.

32. The Select Works of Antony van Leewenhoek 1632-1723, translated S. Hoole, London, Nicol 1798-1807 also, Facsimile ed. F.N. Egerton, New York Arno Press 1977; Vol 2: p. 323-326.

33. Opera omnia medico-practica et anatomica. G. Baglivi, Bassano 1732, translated Saul Jarcho - On Rare Affections of the Lungs, 87-89.

34. Opera omnia medico-practica et anatomica. G. Baglivi, Bassano 1732, translated Saul Jarcho - On Asthma, 96-97. The Concept of Heart Failure from Avicenna to Albertini, Harvard University Press 1980.

35. Carolus Piso. Selectorum observationum et consiliorum de praetervisis hacterus morbis affectibusque practer naturam, ab aqua sem serosa colluvie et diluvie ortis 1617, Pont-à-Monsson 1618. Translated Saul Jarcho p. 116. The Concept of Heart Failure from Avicenna to Albertini, Harvard University Press 1980.

36. Withering W
An account of the Foxglove and some of its medical uses: with practical remarks on dropsy, and other diseases.
1785 Birmingham. M. Swinney for GGY and Y Robinson, Paternoster-Row, London.

37. Anderson FJ
An illustrated history of the herbals.
1977 Columbia University Press, New York.

38. Castigloni A
A history of medicine.
1947 A A Knopfine and in London by Routledge and Kegan Paul Ltd.

39. Baldry PE
The battle against heart disease.
1971 Cambridge University Press.

40. Snelles HA
History of cardiology
1984 Donker Academic Publications, Rotterdam.

41. Herrick JB
A short history of cardiology.
1942. Charles C Thomas, Illinois and Maryland.

42. Smith S
Digoxin, a new digitalis glycoside
J Chem Soc 1930; 508-510.

43. BPC 1949
The British Pharmaceutical Codex 1949, London
Pharmaceutical Press.

44. Brunton TL
On the use of nitrate of amyl in angina pectoris.
Lancet 1867; 2: 97-98, 225-227..

45. Murrell W
Nitro-glycerine as a remedy for angina pectoris.
Lancet 1879; 1: 80-81.

46. Singh B, Ellrodt G, Peter CT
Verapamil: a review of its pharmacological properties and therapeutic uses.
Drugs 1978; 15: 169-197.

47. Guazzi M, Olivari MT, Polese A et al
Nifedipine, a new antihypertensive with rapid action.
Clin Pharmacol Ther 1977; 22: 528-532.

48. Brockbank W
Sovereign remedies, a critical depreciation of the 17th centuryLondon Pharmacopoeia.
Med Hist 1964; 8: 1-14.

49. Hamilton J
Observations on the use and abuse of mercurial medicines in various diseases.
1819 Edinburgh, Constable.

50. Loubatieres A
The hypoglycemic sulfonamides: history and development of the problem from 1942 to 1955.
Ann N Y Acad Sci 1957; 71: 4-11.

51. Goldblatt Harry et al.
Studies on experimental hypertension 1. The production of persistent elevation of systolic blood pressure by means of renal ischaemia.
J Exp Med 1934; 59: 347-379.

52. Honssay Berardo Alberto, Fasciolo Juan Carlos
Secreción hipertesora del actión isquemiado.
Rev Soc Argent Biol 1937; 13: 284-294.

53. Wilson Clifford, Byron Frank Barnett
Renal changes in malignant hypertension in experimental evidence.
Lancet 1939; 1: 136-139.

54. Braun-Menendez Eduardo et al
The substance causing renal hypertension.
J Physiol (London) 1940; 98: 283-298.

55. Page, Irving Heinly, Helmer OM
A crystalline substance (angiotonin) resulting from the reaction between renin and renin-activator.
J Exp Med 1940; 71: 29-42.

56. Skeggs LT, Khan JR, Shumway NP
Preparation and function of the hypertensin-converting enzyme.
J Expt Med 1956; 103: 295-299.

57. Ng KKF, Vane JR
Conversion of angiotensin I to angiotensin II.
Nature 1967; 216: 762-766.

58. Ng KKF, Vane JR
Fate of angiotensin I in the circulation.
Nature 1968; 218: 144-150.

59. Curtis C, Cohn JN, Vrobel T, Franciosa JA
Role of the renin-angiotensin system in the vasoconstriction of chronic congestive heart failure.
Circulation 1978; 58(5): 763-770.

60. Gavras H, Brunner HR, Turini GA, Kershaw GR, Tifft CP, Cuttelod S, Gavras I, Unkovitch RA, McKinstry DN
Antihypertensive effect of the oral angiotensin conventing-enzyme inhibitor SQ14225 in man.
N Engl J Med 1978; 298,28: 991-995.

61. Davis R, Ribner HS, Keung E, Sonnenblick EG, Le Jeuntes TH
Treatment of chronic congestive heart failure with captopril, an oral inhibtor of angiotensin-converting enzyme.
N Engl J Med 1979; 30(3): 117-121.

62. Turini GA, Brunner HR, Gribic M, Waeber B, Gavras H
Improvement of chronic congestive heart failure by oral captopril.
Lancet 1979; 1(8128): 1213-1215.

63. Gaddum Sir John Henry
The action of adrenaline and ergotamine on the uterus of the rabbit.
J Physiol (London) 1926; 61: 141-150.

64. Bergström Sune et al
Isolation of nor-adrenaline from the adrenal gland.
Acta Chem Scand 1949; 3: 305-306.

65. Gunn James Andrew.
The pharmacological actions and therapeutic uses of some compounds related to adrenaline.
Br Med J 1939; 2: 155-160, 214-219.

66. Enler Ulf Svante von
A specific sympathomimetic ergone in adrenergic nerve fibres (sympathin) and its relations to adrenaline and non-adrenaline.
Acta Phsyiol Scand 1946; 12: 73-97.

67. Alquist RP
A study of adrenotropic receptors.
Am J Physiol 1948; 153: 586-600.

68. Black James Whyte et al
A new adrenergic beta-receptor antagonist.
Lancet 1964; 1: 1080-1081.

69. Lands AM et al
Differentiation of receptor systems activated by sympatho-mimetic amines.
Nature (London) 1967; 214: 597-598.

70. Levy B and Wilkenfeld BE
An analysis of selective beta receptor blockade.
Eur J Pharmac 1969; 5: 227-234.

71. Choo-Kang YFJ et al
Response of asthmatics to isoprenaline and salbutamol aerosols administered by intermediate positive pressure ventilation.
Br Med J 1970; 4: 465-468.

72. Ralph H Major. Raymond Vieussens and his treatise on the Heart.
Ann M Hist 1932; 4: 147-154.

73. De Motu Cordis et Aneurysmatibus, Giovannie Maria Lancisi, published posthumously 1728, Rome.

74. Animadversiones super quibusdam difficilis respirationis vitiis a laesa cordis et praecordiorum structura pendentibus. Ippolito Francesco Albertini, published in De Bononiensi Scientiarum et Artium Instituto atque Academia Commentarii Vol 1, p. 382-404, 1748. Translated J.E. Erichsen, Observations on Aneurism, London Sydenham Society 1844; p. 237-242.

75. De Sedibus et Causis Moriborum et Anatomes Indignatis - Libri Quinque. Giovanni Morgagni, Venice, 1761.

76. William Heberden. Commentaries, 1802, p. 292-293, published and translated William Heberden (son).
A Short History of Cardiology. James B. Herrick, Charles C. Thomas, Illinois, 1942.

77. John Fothergill, Works, with Life and Notes by John Elliott, London 1781, p. 508 and 529.

78. Anderson HB, Caleb Hillier Parry and something of his contemporaries.
Canad M AJ 196; 16: 1531-1534.

79. Allan Burns.
Surgical Anatomy of the Head and Neck. Vol on Heart Disease 1809, p. 138-130. see Short History of Cardiology. James B. Herrick, p. 65-67. Charles C. Thomas, Illinois, 1942.

80. Jean-Nicolas Corvisart
Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux, 1806.

81. Investum Novum. Published by Auenbrugger in 1761, translated and comments added by Jean-Nicolas Corvisart 1808. Also translated into French Rozière de la Chausagne 1770, George Dolk Rozière and the Early History of Percussion of the Thorax Ann M Hist 1935; 57: 438-450

82. De L'Auscultation Médiate (Réné-Théophile-Hyacinthe) Laennec: Sir William Hale-White.
Selected passaged from the d'Auscultation Médiate, London, 1923.

83. James B. Herrick
A Short History of Cardiology.
Charles C. Thomas, Illinois, 1942: p. 96-100.

84. Ludwig Traube
Über der Zusammerharg von Herz-und Niesen-Krankheiton in Gesammelte Beiträge zur Pathologie und Physiologie, Vol 2, p 290-350. Berlin, Hirschwald 1891.

85. Diseases of the Heart and Aorta.
William Stokes 1854; P. 131.

86. Latham P M
Lectures on subjected connected with clinical medicine comprising Diseases of the Heart
London 1845-1846, Vol 2.

87. James B. Herrick
A Short History of Cadiology.
Published by Charles C. Thomas, Illinois, 1942; p. 187.

88. Principles and Illustrations of Morbid Anatomy.
James Hope, 1834.

89. Jane Sands Robb
A Historical Survey of Studies of Ventricular Stricture
Med Woman's J 1934; 41: 203-209.

90. Wearn in Levy's Diseases of the Coronary Arteries
Gross's Blood Supply to the Heart 1921.

91. Rudolf Virchow
Cellular Pathology 1858, p. 236

92. Dock's translation
Karl Weigert
Veber die pathologischen Gerinnungs-Vorgünge
Virchow Arch path Anat 1880; 79: 87-123.

93. Cohnheim J, von Schulthess-Rechberg A
Ueber die Folgen der Kranzarterienverschliessung für das Herz
Virchow Arch path Anat 1881; 85: 503-537.

94. Stewart G N
Researches on the circulation time and in the influences which affect it.
J Physiol (London) 1897; 22: 159-183.

95. Frank O
On the dynamics of cardiac muscle (translated by C B Chapman, E Wasserman).
Am Heart J 1959; 58: 282-317.

96. Wiggers C J
Some factors controlling the shape of the pressure curve in the right ventricle.
Am J Physiol 1914; 33: 382-396.

97. Straub H
Dynamik des sängetierherzens II dynamik des rechten Herzens
Disch Arch Klin Med 1914; 116: 409-436.

98. Patterson S W, Starling E H
On the mechanical factors which determine the output of the ventricles.
J Physiol (Lond) 1914; 48: 357-379.

99. Patterson S W, Piper I H, Starling E H
The regulation of the heart beat.
J Physiol (Lond) 1914; 48: 465-503.

100. Wiggers J H C
Cardiac output and total peripheral resistance measurements in experimental dogs.
Am J Physiol 1944; 140: 519-534.

101. Stead E A, Warren J V
Cardiac output in man: an analysis of the mechanisms varying the cardiac output based on recent clinical studies.
Arch Intern Med 1947; 80: 237-248.

102. Sarnoff S J
Myocardial contractility as described by ventricular function curves and observations on Starling's law of the heart.
Physiol Rev 1955; 35: 107-122.

103. Sarnoff S J, Mitchell J H
The regulation of the performance of the heart.
Am J Med 1961; 30: 747-777.

104. Hope J
A treatise on the diseases of the heart and great vessels, and on the affectations which may be taken for them: comprising the authors view of the physiology of the heart's action and sounds.
London, John Churchill, 1832.

105. McKenzie J
Diseases of the Heart.
3rd Ed Oxford Medical Pub, 1913: 26.

106. Fahr J, Esshler I
Studies of factors concerned in edema formation. II. The hydrostatic pressure in the capillaries during edema formation in right heart failure.
Ann Intern Med 1941; 15: 798-810.

107. Wood P W
Diseases of the heart and circulation.
Philadelphia, Lippincott, 1956.

108. Peter Harris
Congestive cardiac failure: central role of the arterial blood pressure.
Br Heart J 1987; 58: 190-203.

109. Sir Thomas Lewis
Diseases of the Heart, 1933.

PART 2

WHAT IS HEART FAILURE?

Introduction

Paul Wood in 1956 stated that "heart failure may be defined as a state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure" **(1)**. The limitations of such a definition are now recognised, particularly in respect to defining and measuring "adequacy", "needs" and "satisfactoriness". In patients, if the circulation is inadequate to supply the needs of the body, oxygen uptake should be diminished. Yet in early studies, using the Fick principle **(2)**, this was clearly not the case and in the face of evidence that resting cardiac output may be normal in untreated patients with undoubted features of clinical heart failure.

The clinical features which comprise the syndrome of congestive heart failure are well recognised. It is now appreciated that they reflect an altered setting of cardiovascular control mechanisms that may be regarded as "compensatory" **(3)** responses to a chronic (cardiac) reduction in cardiac output, and that they are manifest predominantly as the consequences of salt and water retention. The changes may affect every aspect of the cardiovascular system, fluid balance and their interactive neurohumoral control mechanisms. "Cardiac reserve" is encroached upon and reduced, with clinical implications in respect of exercise. Therapy readjusts one or more of these mechanisms, thus the overall cardiovascular status to net symptomatic benefit (with also some improvement in life expectancy).

The scope of this thesis is restricted to those patients with "heart failure" secondary to coronary artery disease, thus the impairment of cardiac performance is the consequence of **(a)** ischaemic necrosis with loss of myocardium - either as a major event as in myocardial infarction where a large mass of myocardium is lost, or as the cumulative loss of small regions of myocardium from recurrent ischaemic episodes; **(b)** acute ischaemia which is a potent reversible negative inotropic influence, or **(c)** myocardial "stunning" which represents the delay in full contractile recovery, which may take some days following an episode of severe ischaemia. Acute reduction of ventricular function causes an acute reduction in cardiac output, a rise in end diastolic pressure and pulmonary venous pressure, incipient or actual pulmonary oedema, and the acute neurohumoral responses, predominantly of the adrenergic or the sympathetic system that are responsible for the clinical features of shock where the perturbation (and associated pain and anxiety) are sufficiently severe. Chronic, or repeated and prolonged (eg "stunning") acute reduction of overall ventricular function leads to the chronic "compensatory" changes of heart failure involving (a) the heart, (b) the rest of the body.

Most of the experimental work on heart failure has been carried out on animal models of either mechanical overload, rapid pacing, or myocardial poisoning. In overload models; "ventricular failure" is produced either by abnormal volume or pressure loads. These lead to differing cardiac compensatory responses. Chronic volume or "diastolic" overload (A-V shunting or mitral regurgitation) leads to chronic dilatation with slippage of fibres, such that sarcomere lengths remain normal and diastolic chamber compliance is increased. Increased systolic wall tension, associated by the Laplace relationship with volume, leads to

secondary hypertrophy, explaining how wall thickness is unaltered while the total mass of the left ventricle increases. Chronic pressure "systolic overload" (eg by aortic banding or high blood pressure) leads to hypertrophy, with thickening of the ventricular wall; diastolic volume tends not to change. Much is known about the changes that occur in cardiac chamber geometry, myocytes, collagen matrix and vasculature in hypertrophy, and in overt congestive heart failure where the simplest interpretation of the voluminous literature is that these changes become more severe. Experimental coronary artery occlusion and infarction has also been used as a model of heart failure and compensatory hypertrophy where remodelling of the residual myocardium is observed. This is particularly relevant when it comes to interpreting the effects of exercise which are an integral part both of the symptoms and the evaluation of heart failure, given also that clinical ischaemia may be "silent". This thesis describes only clinical studies - in all their uncontrolled complexity but relevant uniquely to the clinical problem, its evaluation and its treatment.

"Heart failure" is becoming the major cardiovascular problem of this decade, its prevalence is increasing. Milton Packer (4) estimates that there are nearly 12 million people in the world with symptoms of heart failure, an "additional 40 million with important degrees of left ventricular dysfunction", and that "the numbers of persons hospitalised for heart failure has risen nearly four-fold during the past 15 years". The reason for the increase is partly due to the more effective management of acute events - with increased numbers of patients surviving acute myocardial infarction, albeit with impaired ventricular function. It may be due partly to the increased longevity of the general population: most patients with heart failure are older than 65 years and

heart failure is a common reason for hospital admission in this age group. Heart failure is a huge, expensive and growing problem.
In any evaluation of heart failure, it is important to distinguish subgroups with differing prognosis, differing characteristics and potentially different responses to treatment - if such subgroups exist and can be practically identified. This is likely to be particularly important when heart failure is secondary to coronary disease because of the potential contribution to impaired contractile function of stress induced ischaemia (which may be "silent") and also the potential contribution to overall cardiac performance of right ventricular ischaemia/infarction (which may be unrecognised), as well as differences in the neurohumoral and cardiac compensatory responses in relation to the severity of the condition.

This thesis describes a number of studies of heart failure from coronary disease, that are directed to these ends and whether there is a component that can be identified which may be influenced by therapy. There is therefore a need to classify patients accurately so that differing populations may be correlated and the effects of pharmacological intervention assessed. As all patients have significant coronary atherosclerotic disease, pharmacological interventions have been restricted to those drugs which might be expected to influence "ischaemia". Alterations of neurohumoral mechanisms have not been studied.

Conventionally, as cardiac failure is a disease of "symptoms", these are classified clinically using a variety of schemes, of which the most widely employed is the New York Heart Association. There is a great deal of doubt as to whether this is the most effective method of classifying

patients, either with respect to the degree of impairment or to risk of mortality.

Published studies have required differing inclusion criteria for the diagnosis of 'heart failure'. The simplest require the presence of cardiomegaly on chest x-ray, while others require the demonstration of raised left ventricular end diastolic pressure or reduced cardiac index. There is no universal agreement as to what constitutes 'heart failure' and how this may be best identified in the clinical setting. In the following chapter, conventional methods of classifying patients with heart failure are examined and compared. Since conventional clinical assessments are clearly not optimal in identifying the patient with 'heart failure', other non-invasive techniques, such as perfusion imaging, have been employed to assess other factors which may be important in this group of patients, where heart failure is secondary to coronary artery disease.

The experimental work of this thesis comprises of two parts - the first examining various methods by which the patient with heart failure may be identified, and the second in which the effects of pharmacological interventions are examined in small groups of these patients.

REFERENCES FOR WHAT IS HEART FAILURE?

1. Wood PW
Diseases of the heart and circulation.
Philadelphia, Lippincott, 1956.

2. Hickman JB, Carghill WH
Effect of exercise cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema.
J Clin Invest 1948; 27: 10-23.

3. Harris P
Congestive cardiac failure: Central role of the arterial blood pressure.
Br Heart J 1987; 58: 190-203.

4. Packer M
Advances in the pathogenesis and treatment of heart failure.
Current Opinion in Cardiology 1989; 4: 339-341.

CLINICAL CLASSIFICATION

Introduction

The opening paragraph of Sir Thomas Lewis' Diseases of the Heart **(1)** identifies the diagnosis and assessment of heart failure as the cardinal problem in clinical cardiology. The principal complication of almost all forms of heart disease is heart failure. Thomas Lewis states that two questions are of importance "Firstly, has the heart the capacity to do the work demanded of it when the body is at rest? Secondly, what is the condition of the heart's reserve?".

Lewis also wrote "These questions can be correctly answered in almost all cases by simple interrogations and by bedside signs".

Symptoms and Signs and Attempts at Classification

Braunwald's text book identifies the following (a) symptoms, breathlessness, effort intolerance; (b) signs, raised jugular venous pulse, peripheral oedema, tachycardia, third heart sound, cardiomegaly and basal crepitations, as being associated with "heart failure" **(2)**. There are various ways in which symptoms and signs may be classified but the most widely accepted is that of the New York Heart Association (Table 1) **(3)**. The importance of attempting to classify patients lies in identifying those characteristics that might identify the patient more likely to die, so that interventions may be judged to be more or less successful.

A small series of studies are presented in which the New York Heart Association grading is examined in detail, for the prediction of subsequent mortality and the degree of ventricular impairment. Clinical

Table 1

New York Heart Association (3)

Grade	Symptoms
I	No limitation
II	Breathless on normal exertion
III	Breathless on minimal exertion
IV	Breathless at rest

Table 2

NEW YORK HEART ASSOCIATION GRADING

GRADE	% TOTAL POPULATION	% MORTALITY
II	27%	26%
III	51%	38%
IV	22%	43%

signs and symptoms, usually employed for the diagnosis of heart failure, are then examined in a similar manner.

a) Introduction

The efficacy of the New York Heart Association Grading System, for the prediction of subsequent mortality, was assessed in patients with heart failure secondary to coronary artery disease.

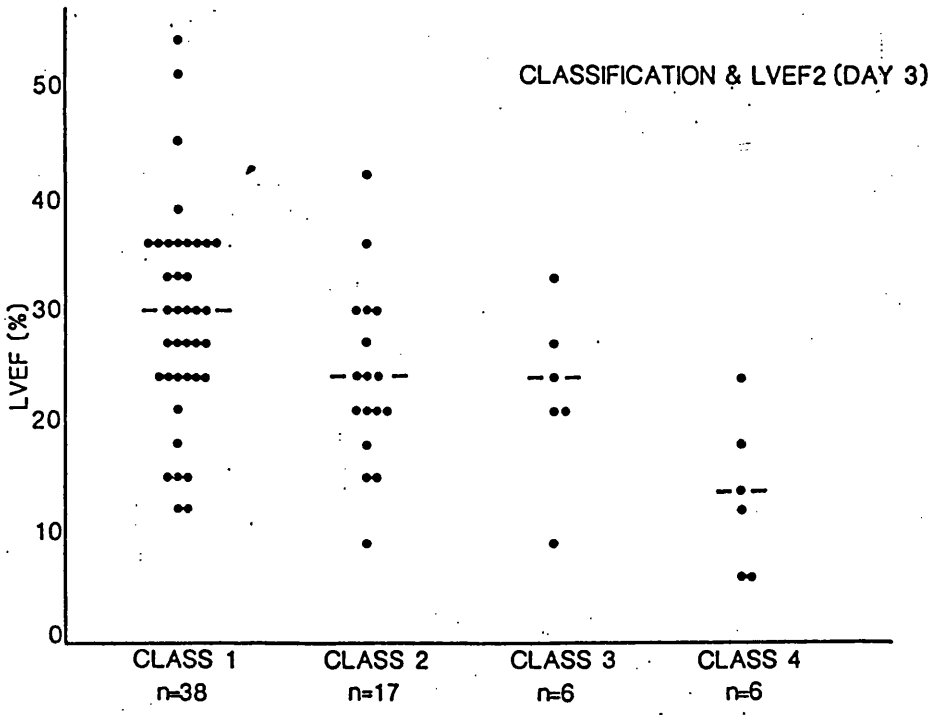
Methods

Patient Population

Sixty four patients who were clinically judged to have congestive heart failure by at least two experienced cardiologists were included. Congestive heart failure was thought to be secondary to significant coronary artery disease, based either on coronary arteriography or past history of myocardial infarction. Patients were followed for a mean of 19 $\pm$ 4 months and all deaths recorded. Deaths were classified as (a) cardiac, if the symptoms and signs preceding death suggested myocardial infarction, progressive heart failure or if the death was sudden and unwitnessed with an absence of symptoms or signs of other diseases, or (b) non-cardiac. The aetiology of the heart failure was confirmed by echocardiography and coronary angiography. Classification of the symptoms was according to the New York Heart Association (NYHA) **(3)** and was made by two clinicians.

Results

Sixty four patients were evaluated, eight were female with an age range 32-71 years. Total mortality was 36%. The percentage of patients assigned each of the NYHA gradings is seen in the Table 2, with the largest mortality (43%) occurring in the group with NYHA grade IV.


CLASSIFICATION & LVEF2 (DAY 3)
LVEF (%)
50
40
30
20
10
0
CLASS 1
n=38
CLASS 2
n=17
CLASS 3
n=6
CLASS 4
n=6

b) Introduction

The New York Heart Association grading is a subjective assessment of patients' symptoms. The degree of left ventricular impairment that underlies these symptoms may vary. Left ventricular ejection fraction, a measure mainly of systolic performance, is an accepted measure of left ventricular function and is known to be predictive of subsequent mortality following myocardial infarction.

Methods

Patient Population

Eighty consecutive patients admitted to the Coronary Care Unit of Glasgow Royal Infirmary were subsequently shown to have sustained a myocardial infarction on the basis of sequential electrocardiographic changes and enzymes. A clinical grading, using the conventional NYHA grading system, was made at 7-10 days by two clinicians.

Left Ventricular Function

Left ventricular function was measured using radionuclide angiography (see Appendix). In brief, following in vivo labelling of red blood cells with technetium$_{99}$m pyrophosphate scans were obtained gated to the electrocardiogram using a Gamma camera fitted with a high sensitivity parallel collimator. Data was obtained in listmode using a Link MAPS computer and reformatted into a 24 frame representative cardiac cycle. Left ventricular ejection fraction (LVEF) was calculated (see Appendix). Normal left ventricular ejection fraction $>40\%$.

Results

The correlation of New York Heart Association grading and left ventricular ejection fraction are seen in Figure 1 opposite. LVEF

obtained on the third day following myocardial infarction is used, as this has previously been shown to be the most stable (see Appendix). Although those patients with the lowest ejection fractions tended to have been graded NYHA IV, there is considerable overlap. Indeed, many patients graded NYHA I have substantial left ventricular dysfunction (LVEF $<30\%$).

c) Introduction

Conventionally, the diagnosis of heart failure (as with any disease process) is based on patients' signs and symptoms. The predictive value of individual signs and symptoms for the identification of heart failure has been calculated. To do this, an entirely arbitrary measure of pulmonary capillary wedge pressure $\geq$ 15 mm.Hg. has been employed to indicate significant left ventricular decompensation, and thus 'heart failure'.

Methods

Patient Population

Sixty four patients were judged to have congestive cardiac failure, secondary to coronary artery disease (proven either by coronary arteriography or consequent upon myocardial infarction). A detailed clinical history and examination were obtained by two experienced cardiologists. NYHA grading was assigned to each patient.

Non-Invasive Measurements

Chest x-rays were performed on full inspiration in a standard manner. Cardiothoracic ratio was obtained by drawing the largest diameter of the heart and dividing by the largest diameter of the expanded chest,

Table 3

PREDICTION OF HEART FAILURE

	SENSITIVITY	SPECIFICITY	PRED VALUE
NYHA	86%	45%	75%
Angina	33%	27%	67%
Palpitations	27%	71%	33%
Ankle oedema	48%	100%	100%
Orthopnoea	62%	67%	72%
PND	67%	55%	74%
Cyanosis	24%	100%	100%
HR > 100/minute	29%	100%	100%
SBP < 90 mm.Hg.	10%	100%	100%
JVP	48%	82%	83%
Apex displaced	43%	82%	82%
S3	10%	91%	66%
MR/TR	21%	91%	83%
Crepitations	57%	73%	80%
Effusion	5%	100%	100%
Ascites	5%	100%	100%
CTR > 48%	91%	64%	83%
Cardiac output	50%	64%	71%

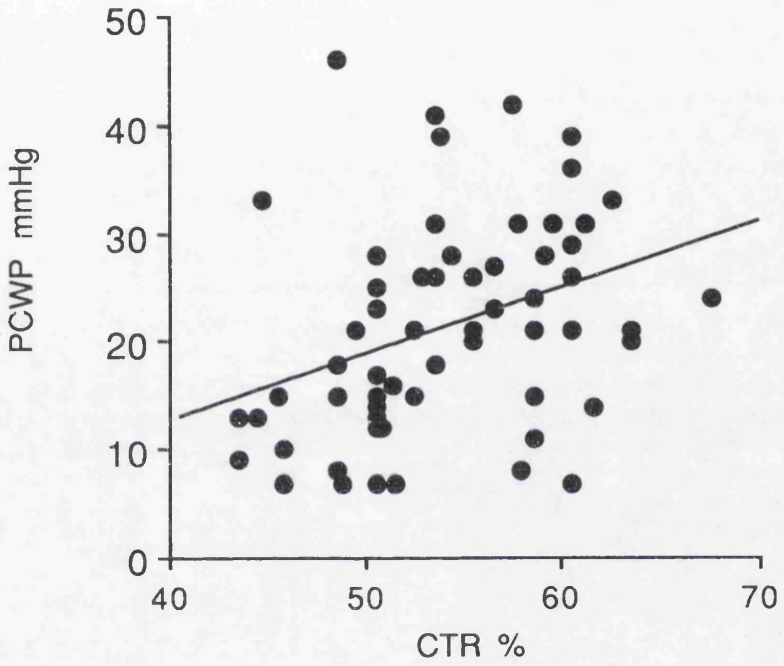


Fig. 2 Cardiothoracic Ratio vs PCWP

corrected for height and weight, as is described in Radiological Anatomy of the Heart (**4**).

Invasive Data

A Swan-Ganz thermodilution catheter was inserted percutaneously for the measurement of pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and cardiac output. A pulmonary capillary wedge pressure ≥ 15 mm.Hg. was taken as indicative of heart failure. Cardiac output was obtained in triplicate and cardiac index and stroke volume index calculated (see Appendix).

Statistical Methods

Sensitivity, specificity and predictive accuracy were calculated, using Stepwise multidiscriminant analysis, based on diagnosis of heart failure with a PCWP of ≥ 15 mm.Hg.

Results

NYHA, grade III and IV, have a predictive value of 75% for heart failure, based on a diagnosis by increased PCWP. Not surprisingly, symptoms and signs associated with high venous pressure (ankle oedema, ascites, pleural effusion) have a high specificity, with a lower sensitivity (Table 3). Increased cardiothoracic ratio, reflecting increased left ventricular volume as an adaptive response was sensitive, but not specific. Cardiothoracic ratio, plotted against PCWP is shown in Figure 2. 18% of patients with a cardiothoracic ratio >48% had a 'normal' PCWP (<14 mm.Hg.).

Table 4

PREDICTION OF DEATH

	SENSITIVITY	SPECIFICITY	PRED VALUE
NYHA	85%	32%	46%
Angina	38%	56%	46%
Palpitations	63%	67%	38%
Ankle oedema	50%	64%	38%
Orthopnoea	61%	86%	55%
PND	58%	85%	85%
Cyanosis	40%	59%	15%
HR > 100/minute	67%	65%	30%
SBP < 90 mm.Hg.	100%	63%	15%
JVP	50%	65%	46%
Apex displaced	36%	57%	31%
S3	67%	62%	15%
MR/TR	67%	65%	31%
Crepitations	64%	78%	69%
Effusion	0%	58%	0%
Ascites	0%	58%	0%
CTR > 48%	52%	80%	85%
Cardiac output	43%	53%	46%

d) Introduction

The predictive value of individual signs and symptoms, generally associated with heart failure, for subsequent cardiac mortality has been calculated.

Methods

Patient Population

The patients described in the previous study (c) were followed for a mean of 19 $\pm$ 4 months, and all deaths recorded. The total mortality was 36% with one death due to lung carcinoma.

Classification of signs and symptoms, calculation of cardio-thoracic ratio and measurements made from Swan Ganz catheter were identical to those in Section c).

Results

The sensitivity, specificity and predictive value of the clinical descriptions for mortality is seen opposite (Table 4). In general, clinical signs and symptoms are not predictive. However, an increased cardiothoracic ratio had a predictive accuracy of 85%, being specific but not sensitive. Measurements such as cardiac output, made by thermodilution, were neither sensitive nor specific for subsequent mortality.

Discussion

(1) Clinical Classifications

In 1949 when the Framingham Study was initiated, the organisers devised a system of major and minor criteria (Table 5), by which the diagnosis of heart failure was classified as certain, probable or unlikely,

Table 5

Framingham Study (5)

Major Criteria

Paroxysmal nocturnal dyspnoea or orthopnoea
Neck vein distension
Râles
Cardiomegaly
Acute pulmonary oedema
S_3 gallop
Increased venous pressure ≥ 16 cm. (of water)
Circulation time ≥ 25 sec.
Hepatojugular reflux.

Minor Criteria

Ankle oedema
Night cough
Dyspnoea on exertion
Hepatomegaly
Pleural effusion
Vital capacity one third from maximum
Tachycardia (rate > 120/minute)

Major or Minor Criteria

Weight loss ≥ 4.5 Kg. in 5 days in response to treatment

Table 6

Harlan et al (6)

Chronic Congestive Heart Failure in Coronary Artery Disease

Clinical Criteria

	SEN %	SPEC %	P VALUE %
Dyspnoea	66	52	23
Orthopnoea	21	81	2
PND	33	76	26
Oedema history	23	80	22
Inotropic treatment	47	77	34
HR > 100	7	99	6
Râles	13	91	27
Oedema	10	93	3
S3	31	95	61
Neck vein distension	10	97	2
HJR	17	91	-
Cardiomegaly by x-ray	62	67	32

PND = paroxysmal nocturnal dyspnoea
HR = heart rate
S3 = third heart sound
HJR = hepatojugular reflux

Sen = sensitivity
Spec = specificity
P Value = predictive value

and using this inferences have been drawn as to the presence of heart failure in the population (**5**). In a study by WR Harlan et al (**6**) the sensitivity, specificity and predictive accuracy of clinical signs were presented. This suggested that when the classical signs of cardiac de-compensation were present (tachycardia, oedema and neck vein distension) these were very specific but their predictive accuracy was low (Table 6) which is very similar to the findings in our study, presented earlier. The only clinical sign that had an acceptable accuracy in Harlan's study was the presence of a third heart sound (predictive accuracy 61%) which was somewhat surprising as the authors made no attempt to verify its reproducibility. A more recent study (**7**) has demonstrated low agreement as to the presence or absence of a third heart sound in a range of patients using clinical observers of varying experience.

The need for a classification system, whereby patients could be graded and the effect of drug therapy assessed, was clear. The American Heart Association published their four point scale (**3**) based on the patient's perception of his own ability to exercise. This has major faults, in that it is based on the patient's perception, life styles can be altered so that the patient can underestimate the degree of impairment or overestimate impairment if the patient does not indulge in exercise that may precipitate the symptoms. The subjective nature of this classification is shown by Franciosa et al (**8**) where, in comparison to measured maximal oxygen uptake (VO_2 max), there was little correlation with American Heart Association grading. In a study by JR Wilson et al (**9**), comparing the ability of the New York Heart Association grading measurements to predict subsequent mortality, New York Heart Association grades III and IV were the strongest (p 0.05). The New York Heart Association

(NYHA) grading does not easily discriminate between patients with different degrees of left ventricular impairment **(10)**.

In the study presented in this thesis, where left ventricular function was assessed by LVEF and correlated with NYHA grading of left ventricular function there was considerable overlap of results. Those patients with the lowest left ventricular ejection fractions tended to have the highest New York Heart Association gradings. However, looking at those patients with New York Heart Association grading I and II, 55% of patients had substantial left ventricular impairment (left ventricular ejection fraction <30%). Maranz et al **(11)** have shown that three other types of clinical scoring systems provide similar, but not identical, results. Mean left ventricular ejection fraction for patients with heart failure, according to the Framingham scale, was 45% compared to 53% in patients who had no failure. For the Duke scale, left ventricular ejection fractions were 43% versus 58% and the Boston scale, which classified heart failure as definite, possible or unlikely, had a mean left ventricular ejection fraction of 41% versus 51% versus 55%. When left ventricular ejection fraction was <40%, taken to indicate significant left ventricular dysfunction, sensitivity and specificity of clinical diagnosis using the Framingham scale was 0.63 and 0.62, for the Duke scale was 0.73 and 0.54 and 0.50 and 0.78 for the Boston scale. In patients with a normal left ventricular ejection fraction, 51% had heart failure diagnosed by at least one of the scoring system criteria and in those with low left ventricular ejection fractions 20% of patients met none of the clinical criteria. Thus, although clinical scoring systems may identify patients with ventricular dysfunction, the sensitivities and specificities vary **(12)**.

(2) Chest X-Ray

Enlargement of the heart is usually assumed to be due to left ventricular enlargement. An enlarged right ventricle, or an enlarged chest diameter due to, for example, emphysema can make the cardio-thoracic ratio abnormal. Cardiothoracic ratio (CTR) bears some relationship to PCWP (see Figure 2), but in 17% of patients with an abnormal CTR (>48%) PCWP was normal (<14 mm.Hg.). Demonstration of cardiac enlargement or cardiac dysfunction is not adequate for the diagnosis of overt congestive heart failure which is a clinical syndrome. In a series of 66 patients with heart failure Franciosa **(7)** found a cardiothoracic ratio of >50% in 75% of patients. Similarly, in the patients in this study, a cardiothoracic ratio of >48% was present in 75% of patients. In a study by Harlan et al **(6)** using 40 x-rays, the cardiothoracic ratio was analysed by two observers six weeks apart with a mean difference that was significant ($p<0.05$) and the major difference was in the long diameter of the heart. However, also in this study, a cardiothoracic ratio of >48% was the most valid descriptor of subsequent heart failure whether measured by left ventricular end diastolic pressure, AVO_2 (arterio-venous oxygen) differences or ejection fraction.

Heart volume can also be calculated **(13)**.

where $v = \frac{L \times B \times D \times k \times M}{A}$

where v = volume of the heart in ml per sq m of body surface area

L = long diameter
B = broad diameter
D = greatest horizontal depth
A = body surface area m^2
k = constant 0.63 **(14)**
M = magnification factor

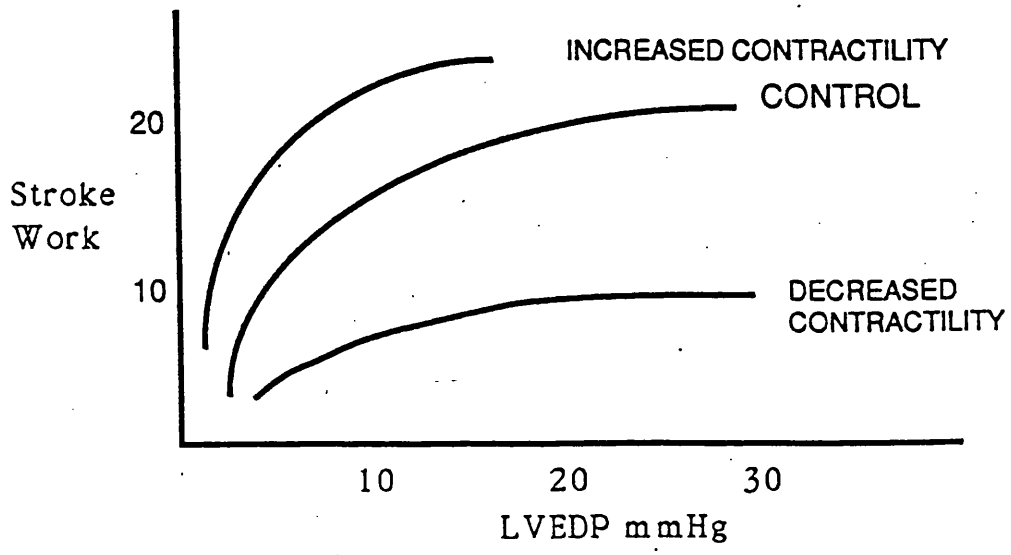
However this is time consuming and the measurements are very variable. Heart volume (left ventricular volume from contrast ventriculogram) was the most accurate ($n = 329$, $p < 0.001$) in patients in whom heart failure had been defined as left ventricular end diastolic pressure > 15 mm.Hg. **(6)**. Heart size was the most important predictor of death over the subsequent three year period **(6)**. In the Coronary Artery Surgery Study, of 24,959 subjects, 339 patients were found to have severe impairment as a result of heart failure (NYHA Class IV); 39.8% had normal heart size on chest x-ray.

(3) Haemodynamic Measurements

Left ventricular filling pressure:- Pulmonary capillary wedge pressure (PCWP) and pulmonary diastolic pressure have been shown to correlate well with left ventricular end diastolic pressure (LVEDP) ($r = 0.8$) **(16,17,18)** in the absence of mitral valve disease. The upper limit of normal for left ventricular end diastolic pressure is usually regarded as 12 mm.Hg. but Harlan et al **(6)** arbitrarily defined 15 mm.Hg. to be associated with heart failure. In their population of 273 patients with clinical heart failure and 1033 without, 53% of patients with heart failure

(cardiomegaly or S3) had a left ventricular end diastolic pressure > 15 mm.Hg. and 20% of those with clinical heart failure had an end diastolic pressure of < 15 mm.Hg. Thus, an enlarged heart on chest x-ray is specific but not sensitive. In our study, 61% had a pulmonary capillary wedge pressure ≥ 15 mm.Hg. Wedge pressure did not correlate with the left ventricular ejection fraction (r = 0.08). This was not really surprising as pressure measurements are very subject to influence, eg changing preload with diuretic therapy. The change of filling pressure with changes of pre-load are well known and were demonstrated by Sarnoff et al **(19,20)**. As seen in Figure 3, increasing ventricular filling pressure is a compensatory mechanism whereby output can be maintained. Thus, where a large volume of myocardium is lost (such as following myocardial infarction) and contractility is decreased, an isolated measurement of LVEDP or PCWP may not on its own be helpful in defining the patient with heart failure.

Patients with capillary wedge pressures >20 mm.Hg. tend to have poorer ventricular function. Patients with higher wedge pressures tend to have a higher death rate **(21)**.



Cardiac Output

Haemodynamic measurements have been the main tool by which our understanding has advanced of the pathophysiology of acute cardiac events, such as acute infarction and cardiogenic shock. Haemodynamic measurements have also been the main therapeutic end points of studies of interventions.

Resting haemdodynamic measurements, in the acute situation, may be predictive of subsequent events. Swan and Ganz **(22)** suggested that patients with a cardiac index that exceeded 2.2 l/min/m^2 have a favourable prognosis, a cardiac index of 1.8 - 2.2 l/min/m^2 represents a cardiac output that is barely adequate to meet ordinary needs and a cardiac index of less than 1.7 l/min/m^2 is associated with an extremely poor prognosis (unless there is an instantly reversible cause such as hypovolaemia).

In chronic cardiac failure, resting haemodynamic measurements such as cardiac index or stroke volume index, tend to be lower than normal values. Franciosa et al **(21)** found the cardiac index significantly reduced in patients with most reduced exercise capacity compared to normals (1.81 ± 0.12 versus 2.53 ± 0.18, $p<0.01$), but there was no significant difference between groups differentiated by degrees of limitation of physical work capacity. This is in keeping with our findings.

Earlier studies suggested that patients with the most abnormal haemodynamic measurements were most likely to die during long term follow-up **(23-26)**. Patients with markedly elevated values of pulmonary capillary wedge pressure, left ventricular end diastolic pressure, and systemic vascular resistance and markedly reduced cardiac output, had

the highest mortality, e.g. Franciosa **(27)**. In 182 patients it was found that the highest mortality was associated when the left ventricular filling pressure was greater than 27 mm.Hg., systemic vascular resistance greater than 23 Wood units, and survival longer when cardiac index was greater than 2.25 l/min/m^2.

In general, most investigators have noted a poorer long term prognosis in patients with high left ventricular filling pressures in association with low cardiac output (or measures incorporating cardiac output such as stroke work) **(26,28,29,30)**, although not all **(9,31)** suggesting that high risk of death in these patients may be related to other factors than abnormal haemodynamic measurements. Many of these studies use univariate analysis which does not take into account potential inter-relations between haemodynamic variables. The patient populations in these studies were often skewed as abnormal haemodynamics were required as an entry criteria to the study. Thus, the population represents only those with abnormal haemodynamics and not all patients with symptomatic heart failure. Only left ventricular filling pressure has a weak correlation ($r = -0.31$) with duration of survival in non-survivors. Higher values for systemic vascular resistance may reflect neurohumoral abnormalities, particularly of the sympathetic system **(32,33)**. High values for right atrial pressure have also been related to poor prognosis but this may reflect pulmonary artery pressure elevation and right ventricular dysfunction **(29,30,34)**.

Thus, in chronic heart failure, resting haemodynamic measurements do not correlate with symptoms or the functional capacity of patients and they are of little value in predicting the long term clinical responses to treatment **(27)**.

Summary

There is a clear need for a classification system whereby patients can be graded and the effects of drug therapy assessed. The New York Heart Association's four point system is based on the patient's perception of his own ability to exercise and as such has major limitations. The subjective nature of this classification has been shown by Franciosa et al **(8)** to have little relation to measured physical work capacity. From our own work (predictive value 46%) and that of JR Wilson et al **(9)** New York Heart Association classification does not predict subsequent death. Mortality was more strongly associated with New York Heart Associations grades III and IV ($p = 0.01$). Similarly, New York Heart Association grading cannot discriminate between patients with differing degrees of left ventricular impairment although patients with grade III and IV classifications tend to have the lowest left ventricular ejection fraction. Similar findings are observed using the Framingham data, Duke and Boston scales.

The chest x-ray is readily available and simple and cheap to perform. A cardiothoracic ratio of $>50\%$ is relatively sensitive and specific but has a relatively low predictive value for the diagnosis of heart failure. In our study, an increased cardiothoracic ratio was not predictive of death. This was in contrast to Harlan et al **(6)** who found that using a cardiothoracic ratio of $>48\%$ this was the most valid descriptor of death in the subsequent three years (compared to left ventricular end diastolic pressure, AVO_2 differences and ejection fraction).

Haemodynamic measurements, particularly pulmonary capillary wedge pressure, left ventricular end diastolic pressure >15 mm.Hg., are often used as a requirement for the diagnosis of heart failure. There are two

major disadvantages in using this as a criteria for the identification of patients with heart failure. Firstly, it requires a catheter measurement (either right heart catheter to measure pulmonary capillary wedge pressure or left heart catheter for left ventricular end diastolic pressure) which is invasive. Secondly, measurement of left ventricular filling pressure is sensitive to changes in preload, thus as a single measurement can well be misleading. Although not surprisingly patients with more extensive left ventricular dysfunction and damage tend to have higher filling pressures, as this classically is a ventricular compensatory mechanism to maintain cardiac output. Although haemodynamic responses do not relate closely to exercise capacity, they are predictive of survival, reflecting more extensive ventricular dysfunction (7).

Similarly, with other haemodynamic measurements, at rest, these parameters do not correlate with either symptoms or functional capacity in patients with chronic heart failure; nor are they of value in predicting the long term clinical response to treatment. In general, abnormal haemodynamic variables are associated with poorer long term prognosis, again reflecting the extent of ventricular dysfunction.

EXERCISE TESTING

Introduction

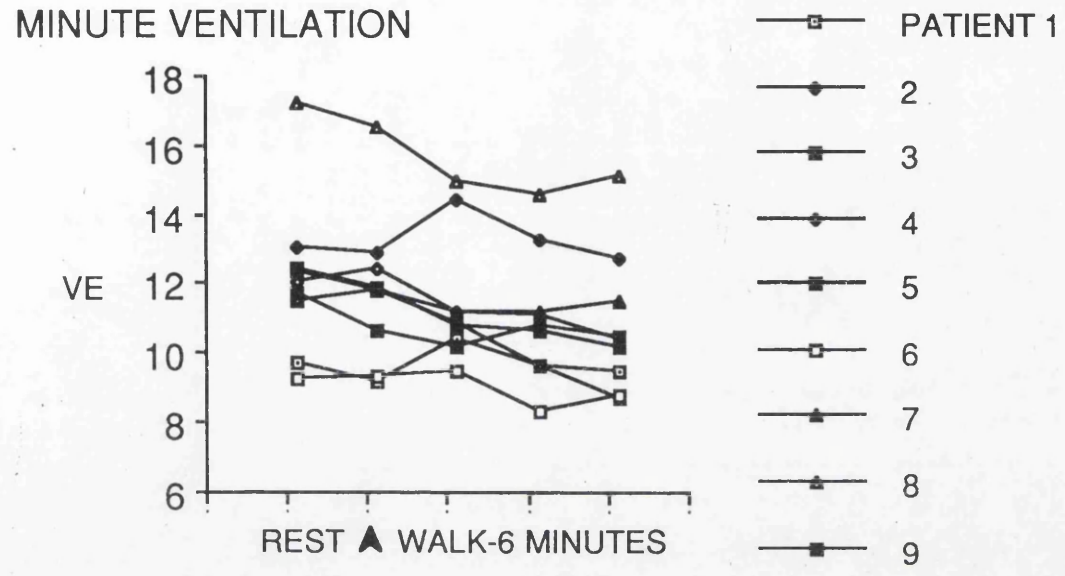
Control of the heart rate, cardiac output and blood pressure is mediated by regions of the mid brain, hypothalamus and cerebral cortex, resulting in activation of the sympathetic nervous system and the arterial baroreceptors some of which have been described by Hilton as organising the "defence reaction" **(35)**. This physiological response comprises an increased arterial pressure with an increased cardiac output together with vasoconstriction in the gut, skin and kidney and vasodilatation in the skeletal muscle. During exercise, afferents from the exercising limbs and messages from higher centres of the brain reset the medullary cardiovascular control system to permit an increased heart rate and blood pressure. In the patient with heart failure the damaged ventricle is progressively unable to increase its output normally in response to sympathetic drive and thus increase arterial pressure **(36)**.

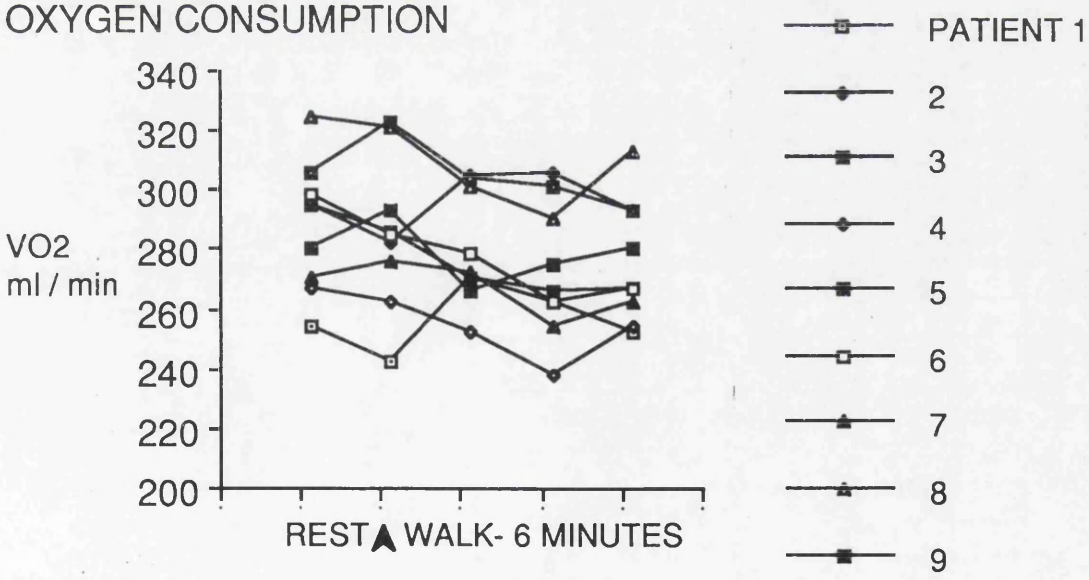
Patients with cardiovascular failure are usually more symptomatic during exertion, being limited by dyspnoea or fatigue. Exercise testing can objectively assess the degree of "exercise intolerance" and quantify the degree of impairment when the patient is symptomatic. Exercise capacity can also be used to evaluate effective therapeutic intervention.

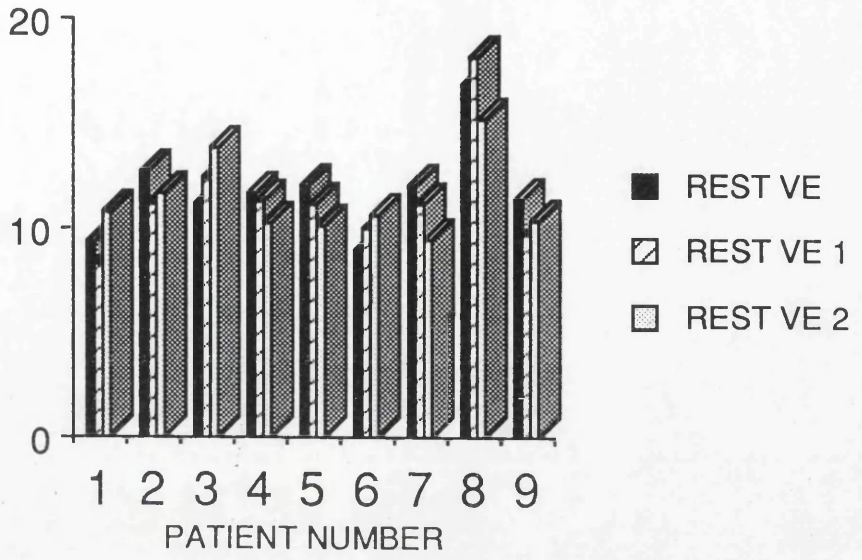
Which Test and Which Measurement

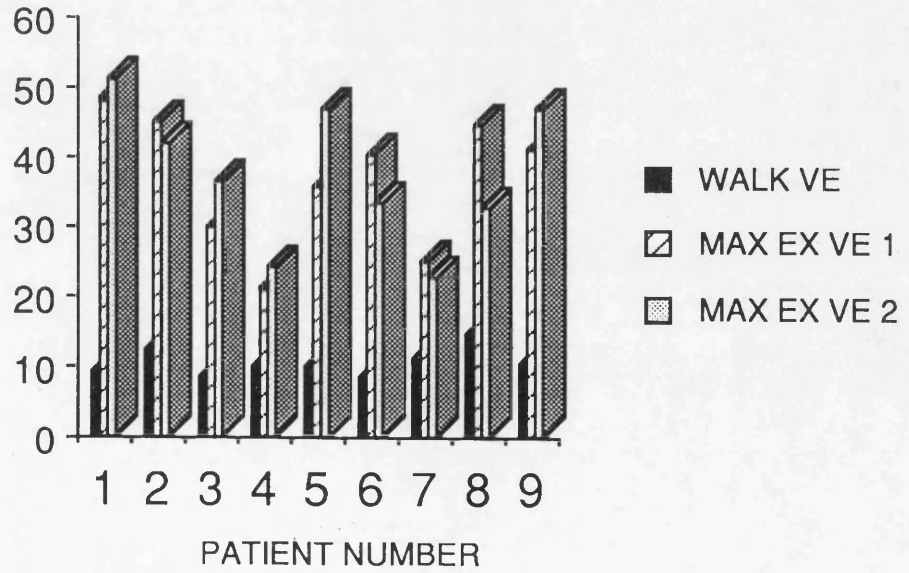
(a) Subjective Testing

All muscle activity demands extra energy and will test to a greater or lesser extent the oxygen carrying capacity of the body. Undoubtedly the simplest way of assessing exercise capacity is to ask the patient. The New York Heart Association classification, discussed earlier, is an


MINUTE VENTILATION
VE
18
16
14
12
10
8
6
REST
WALK-6 MINUTES
PATIENT 1
2
3
4
5
6
7
8
9


OXYGEN CONSUMPTION
VO2
ml / min
340
320
300
280
260
240
220
200
REST
WALK- 6 MINUTES
PATIENT 1
2
3
4
5
6
7
8
9


20
10
0
1 2 3 4 5 6 7 8 9
PATIENT NUMBER
REST VE
REST VE 1
REST VE 2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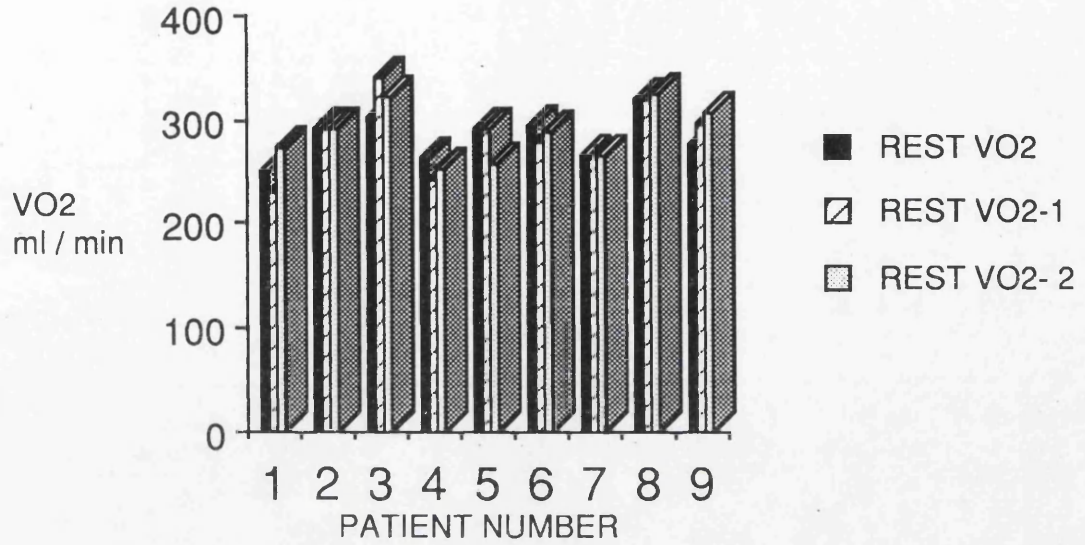
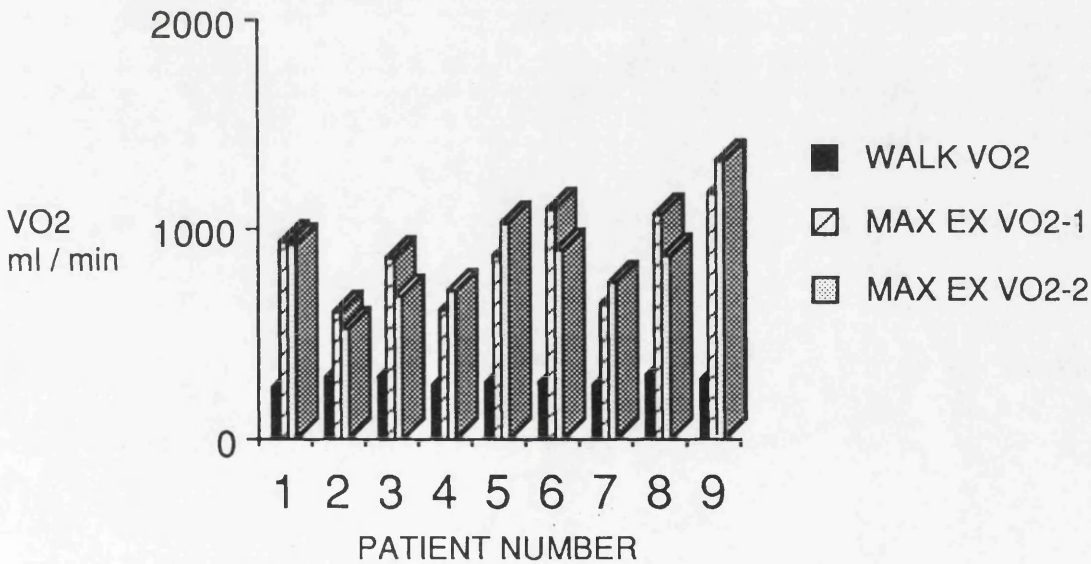
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9
PATIENT NUMBER
WALK VE
MAX EX VE 1
MAX EX VE 2


400
300
200
100
0
VO2
ml / min
1 2 3 4 5 6 7 8 9
PATIENT NUMBER
REST VO2
REST VO2-1
REST VO2- 2


2000
1000
0
VO2
ml / min
1 2 3 4 5 6 7 8 9
PATIENT NUMBER
WALK VO2
MAX EX VO2-1
MAX EX VO2-2

attempt to quantify this. Breathlessness, a symptom common in cardiovascular failure, is also difficult to measure as it depends on the patient's perception and assessment as a symptom is usually judged by clinical interview using questions such as "How far can you walk?" but this depends on how fast the patient walks and his judgement of distance, for which there is enormous inter-observer variation **(37)**. To provide an indirect measure of symptoms, the 12 and 6 minute walk tests have become popular **(38,39)**. This involves asking the patient to set his own walking rate and to measure how far he walks within the specified time, usually six minutes, and is thought to be more typical of "normal activity".

Methods

In order to assess the amount of work carried out in such a test, we studied nine male patients, very similarly matched both for left ventricular dysfunction and for symptoms, who all had New York Heart Association grade III and IV heart failure, and who had been stabilised on an optimal treatment with diuretic and vasodilators. They were asked to walk on a treadmill at a rate and incline which they chose as being comfortable and could be instantly increased or decreased by request by a pre-determined set of hand signals for six minutes. During the test, no vocal instructions or encouragement were given. Electrocardiogram was required continuously and blood pressure measured intermittently by cuff sphygmomanometer. Respiratory gas exchange was measured with the patient breathing from the low dead space and low resistance valve box, with which the patient was familiar. The valve box incorporates a turbine ventilometer on the inspired limb, for measurement of ventilation. The expired limb is fed through a mixing chamber from which samples of air are analysed for carbon dioxide by an infra-red

spectrometer and oxygen by a paramagnetic analyser. Throughout each test minute ventilation (VE), oxygen consumption (VO2) and carbon dioxide production (VCO2) were measured by online ventilation and expired gas analysis (PK Morgan, Rainham, Kent) using standard equations, further details of which are given in the Appendix. Arterial blood gas values were monitored during the test with a transcutaneous system (TCM3 Radiometer Limited, Copenhagen) which continuously monitors transcutaneous oxygen and carbon dioxide tension. Indices of gas exchange could thus be calculated. The non-invasive anaerobic threshold on exertion was calculated using a plot of oxygen consumption against carbon dioxide production (see Appendix). Comparisons were made with similar measurements made on symptom limited maximal exercise on two occasions - once when treated only with diuretics (maximal exercise 1) and secondly with the addition of vasodilator therapy (maximal exercise 2).

Results

Heart rate initially increased as one would expect and remained fairly stable as did systolic and diastolic blood pressure. Oxygen consumption initially tended to increase in patients but the variation was large with no patients walking at a level which was close to their predetermined maximal oxygen consumption. The large individual variation in minute ventilation and oxygen consumption can be seen in Figures 4a and 3b. There was no difference in resting minute ventilation or oxygen consumption at rest with any of the three tests (Figures 4c,4e). On exercise, walking tests in all cases had a lower VO_2 than maximal exercise although as a percentage of maximum this was very variable (Figures 4d,4f).

Discussion

These results suggested to us that the six minute walk test reflected the patient's motivation rather than as a test of his ability to exercise. Although the methodology used to replicate that described by the original authors **(40)** the distance walked during the six minute walk test has been reported to discriminate better than measurement of maximal oxygen consumption between patients with severe chronic heart failure, where differences in distance walked are small compared to differences in maximal oxygen consumption in contrast to patients with "mild heart failure" **(41)**. In our small number of patients who were similar from the point of view of left ventricular dysfunction, symptom severity, drug therapy and maximal oxygen consumption, measured oxygen consumption during walking and the percentage of maximal oxygen consumption varied enormously. In addition, on maximal exercise testing the response to vasodilator therapy was variable. More recently Parameshwar et al **(42)** have reported that in patients with mild heart failure, the distance travelled in 12 minutes on the self powered treadmill correlated significantly with maximal oxygen consumption. It remains to be seen whether this approach gives the better method of assessing the patient with "heart failure".

(b) Maximal Exercise Testing

Symptom limited maximal exercise testing is used extensively to evaluate the patient's ability to perform work. It is arguable whether this provides true objective evidence of maximal exercise without actual measurements of gas exchange or lactate accumulation **(43,44)**. However, in the hands of experienced operators the maximal exercise time was highly reproducible (0.9 $\pm$ 5% standard error of mean) in six patients exercised two weeks apart to obviate any training effect (see

Appendix). Either a bicycle ergometer or treadmill can be used. A treadmill has the advantage that the highest VO2 max can be achieved with healthy subjects (95-98% maximum running horizontally with 100% running uphill) **(45)**. The disadvantages include that at peak workloads whether the subject is running or walking greatly affects the maximal oxygen consumption **(46,47)** and that in subjects with heart failure walking technique is important and inefficient gait may also affect maximal oxygen consumption **(48)**. If maximal oxygen consumption is estimated rather than measured, practical details such as the patient's weight and whether they are holding on to the handrails **(49)** can greatly affect the values obtained. Upright bicycle ergometry produces oxygen uptake of 93-95% of maximum with 60 revolutions/minute as the optimum for most normal subjects **(43)** and if prediction of maximal oxygen consumption is used rather than measured oxygen consumption, the coefficient of variation is lower than with the treadmill **(50)**. The disadvantage that is usually quoted is premature leg fatigue **(51)** but many Scots have had bicycles as children and are familiar with this form of exercise.

Methods

Thirty six male patients with clinical evidence of heart failure were studied. In all patients left ventricular dysfunction was secondary to coronary heart disease, 34 of those 36 patients having suffered a previous myocardial infarction and the remaining two patients having blocked coronary artery vein bypass grafts. All patients complained of breathlessness on exertion and were graded II-IV by the New York Heart Association. Ages ranged from 38 to 63 years. All patients were receiving optimal doses of diuretics and all other concomitant therapy was withdrawn (including Digoxin) except for potassium supplements.

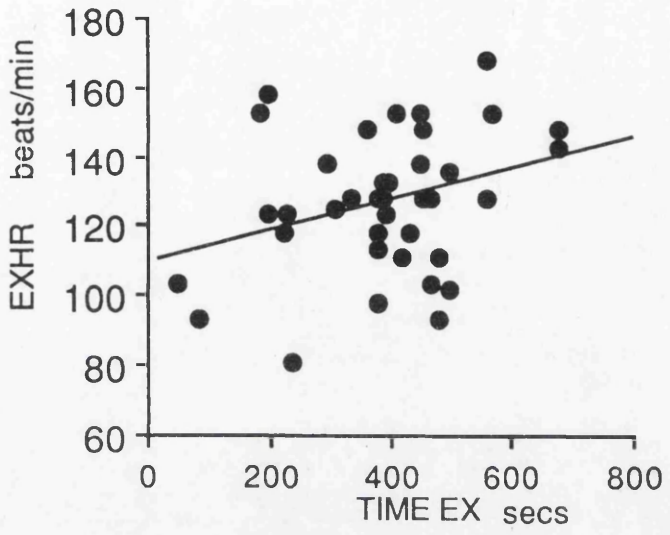
Table 7

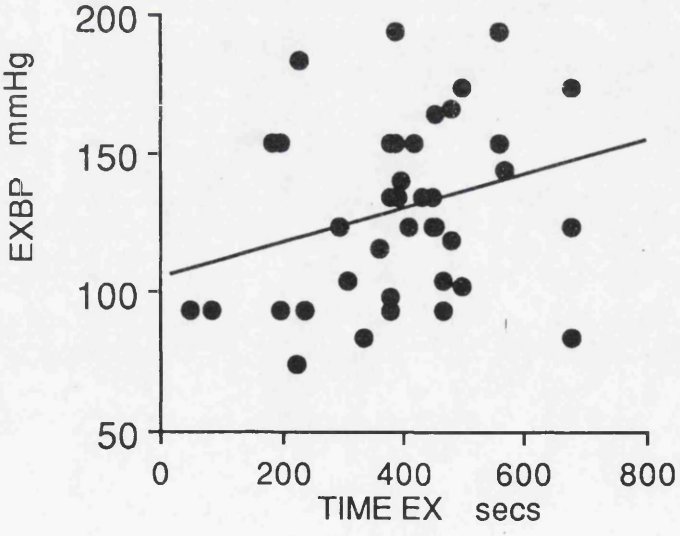
HAEMODYNAMIC MEASUREMENTS

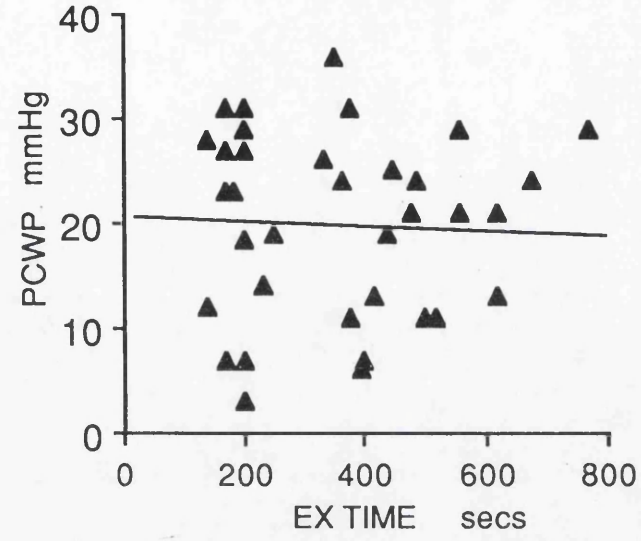
(mean ± SEM)

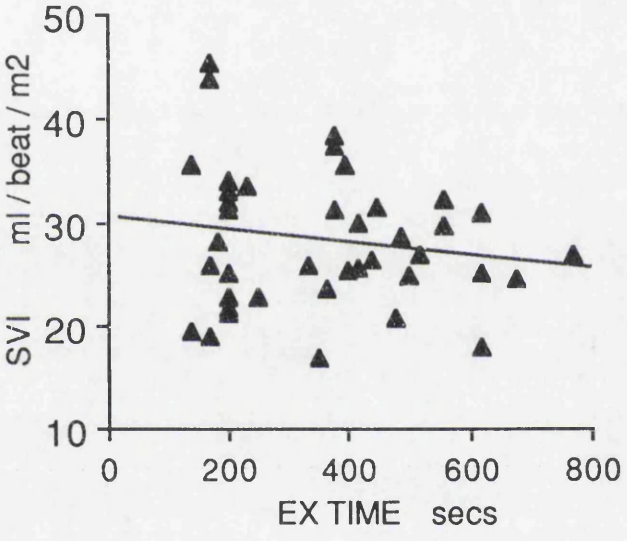
		Rest	Exercise
Heart Rate	beats/minute	79 ± 9	124 ± 8
Systolic BP	mm.Hg.	120 ± 6	152 ± 7
Diastolic BP	mm.Hg.	79 ± 5	85 ± 3
Mean BP	mm.Hg.	93 ± 5	106 ± 4
PCWP	mm.Hg.	21.6 ± 4	36.2 ± 4
Cardiac Index	$l/min/m^2$	2.16 ± 0.2	3.88 ± 0.3
Stroke Volume Index	$ml/beat/m^2$	28.3 ± 3	31.2 ± 3
SVR	$dyne\text{-}s\text{-}cm^{-5}$	1956 ± 163	1274 ± 77
LVEF	%	14 ± 2	16 ± 3

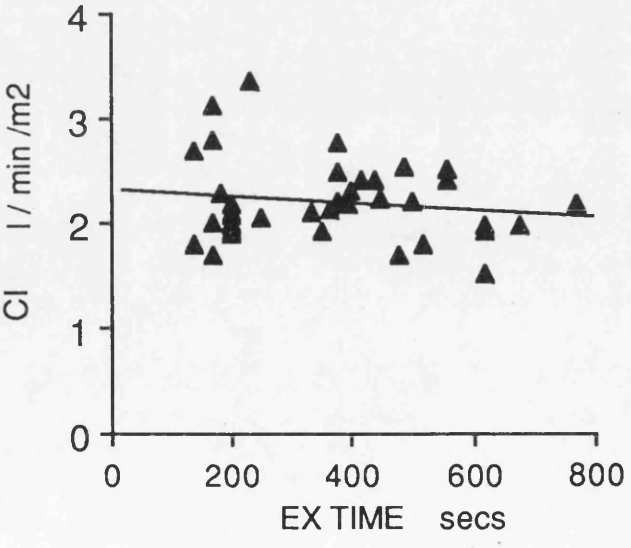
BP	Blood pressure
PCWP	Pulmonary capillary wedge pressure
Stroke Vol Index	Stroke volume index
SVR	Systemic vascular resistance
LVEF	Left ventricular ejection fraction

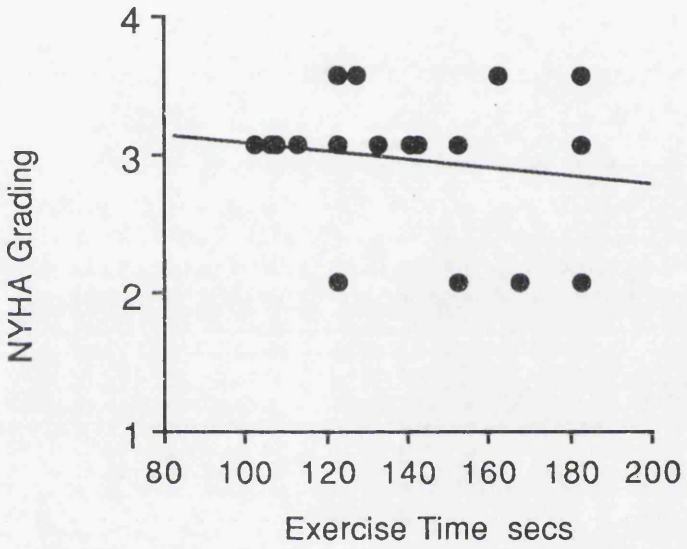

EXHR beats/min
180
160
140
120
100
80
60
0
200
400
600
800
TIME EX secs


EXBP mmHg
200
150
100
50
0
200
400
600
800
TIME EX secs


40
30
20
10
0
PCWP mmHg
0
200
400
600
800
EX TIME secs


50
40
30
20
10
SVI ml / beat / m2
0
200
400
600
800
EX TIME secs


4
3
2
1
0
CI l / min /m2
0
200
400
600
800
EX TIME secs


4
3
2
1
NYHA Grading
80
100
120
140
160
180
200
Exercise Time secs

Heart rate was obtained from the electrocardiogram, monitored continuously, and blood pressure by cuff sphygmomanometer. A Swan-Ganz thermodilution catheter was inserted percutaneously via the internal jugular vein for the measurement of pulmonary capillary wedge pressure and pulmonary artery pressure. Cardiac output was obtained in triplicate by the automatic technique (IL 702) using 10 ml of cooled dextrose injected via an automatic injector (OMP thermodilution injector 3700) (see Appendix). All measurements were made between the hours of 8 a.m. and 12 p.m. at rest and during upright dynamic exercise on a bicycle ergometer. Exercise was initially against no load, then increments of 25 watts every three minutes to a symptom limited maximum.

Results

Detailed results are seen in Table 7 opposite. Heart rate increases on exercise as does blood pressure although both are substantially lower at maximum than normal volunteers or age matched normals (heart rate 124 $\pm$ 8 beats/minute in patients, 149 $\pm$ 11 beats/minute in normal age matched; blood pressure 152/87 mm.Hg. and in normal age matched 180/78 mm.Hg.) **(52,53)**. Pulmonary capillary wedge pressure is elevated at rest and increases substantially with exercise although the range was very wide (15-53 mm.Hg.). Cardiac index increased on exercise but again not as much as any normals (3.88 versus 8.8 litres/min/m^2). Similarly stroke volume index does not increase normally (31.2 $\pm$ 3 in patients versus 59 $\pm$ 5 ml/m^2 in normals). Exercise time does not correlate with exercise heart rate, blood pressure, pulmonary capillary wedge pressure, cardiac index or stroke volume index. Exercise time did not differentiate patients with differing New York Heart Association gradings.

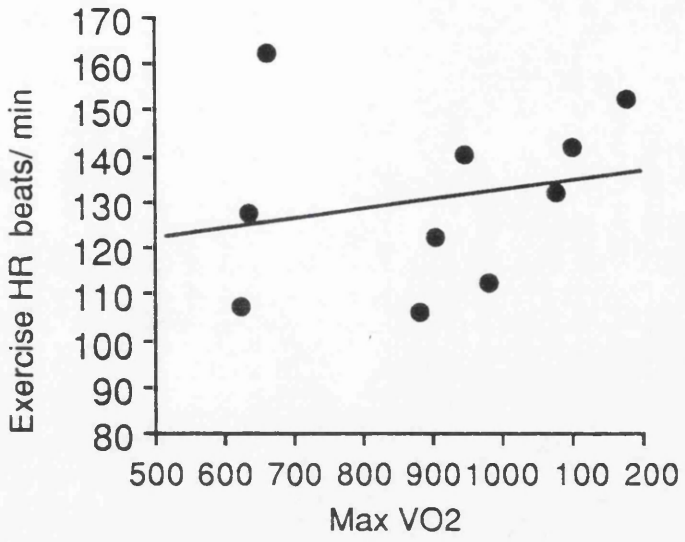
Table 8 mean ± SD

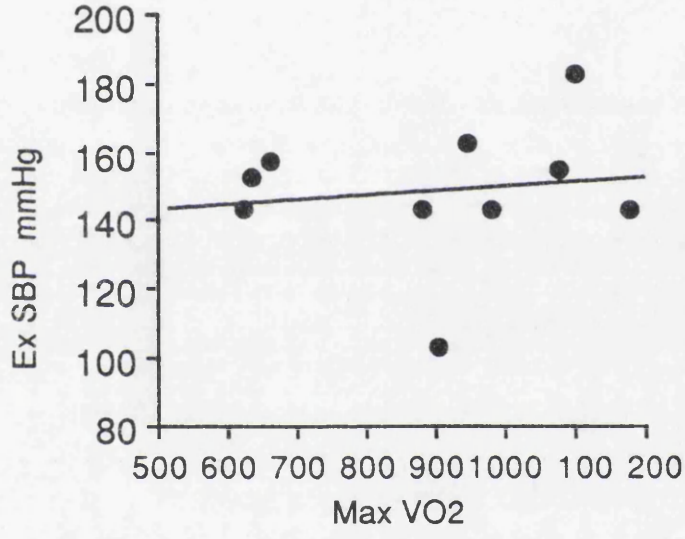
		Rest	Exercise
HR	beats/minute	92.3 ± 11.7	128.2 ± 19.0
SBP	mm.Hg.	115.5 ± 16.7	145.6 ± 20.3
DBP	mm.Hg.	79.2 ± 8.8	85.0 ± 10.8
SMPA	mm.Hg.	32.3 ± 13.8	60.6 ± 27.0
DMPA	mm.Hg.	21.3 ± 8.1	37.4 ± 18.9
CI	$l/min/m^2$	2.21 ± 0.45	4.29 ± 1.07
SVI	$ml/beat/m^2$	25.5 ± 5.2	33.8 ± 8.0
DP	HR x SBP	10286 ± 2577	18809 ± 4523
SVR	$dyne\text{-}s\text{-}cm^{-5}$	1864 ± 429	1139 ± 330
PVR	$dyne\text{-}s\text{-}cm^{-5}$	467 ± 226	436 ± 319
LVEF	%	11 ± 5	13 ± 5

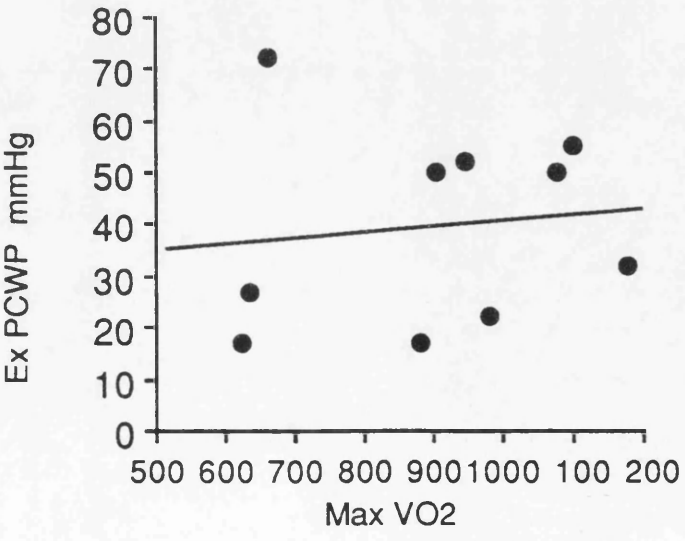
HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
SMPA = systolic mean pulmonary artery pressure
DMPA = diastolic mean pulmonary artery pressure
CI = cardiac index
SVI = stroke volume index
DP = double product
SVR = systemic vascular resistance
PVC = pulmonary vascular resistance
LVEF = left ventricular ejection fraction

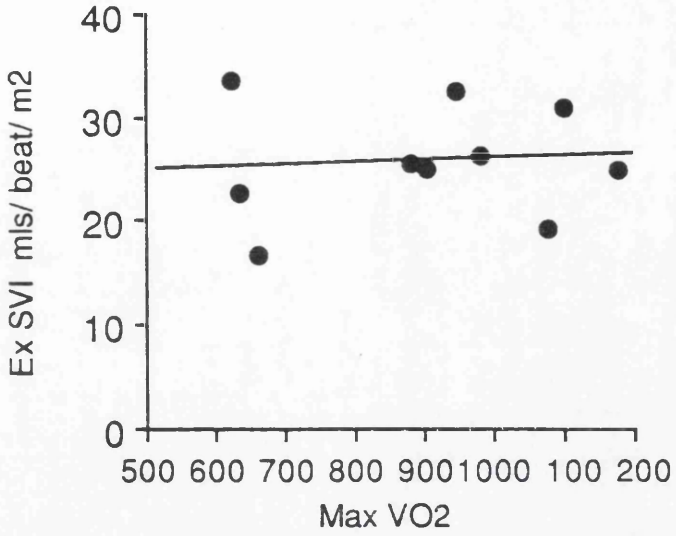
Respiratory Gas Analysis

	Rest	Exercise
VO_2 oxygen consumption	285.1 ± 33.5	881.4 ± 200.5
VE minute ventilation	11.4 ± 2.6	33.9 ± 9.3
PAO_2 arterial oxygen	87.7 ± 8.3	91.1 ± 11.5
$A\text{-}aO_2$ arterial-alveolar oxygen gradient	16.26 ± 8.10	18.13 ± 6.72
Vd/vt dead space/tidal volume ratio	47.8 ± 8.2	42.3 ± 17.3
Exercise time (mins)	-	7.8 ± 2.89


Exercise HR beats/ min
170
160
150
140
130
120
110
100
90
80
500 600 700 800 900 1000 100 200
Max VO2


Ex SBP mmHg
200
180
160
140
120
100
80
500 600 700 800 900 1000 100 200
Max VO2


Ex PCWP mmHg
80
70
60
50
40
30
20
10
0
500 600 700 800 900 1000 100 200
Max VO2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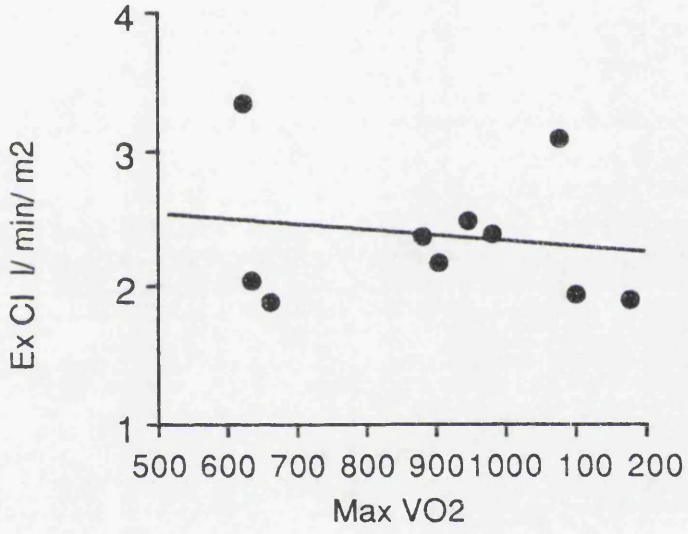
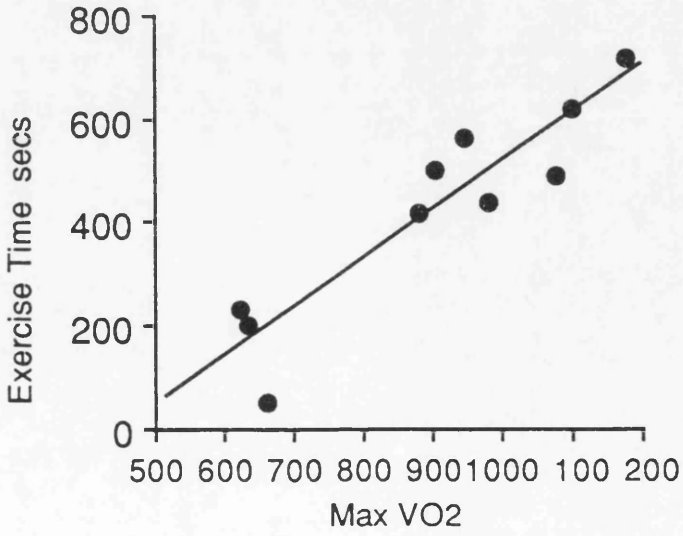
40
30
20
10
0
500 600 700 800 9001000 100 200
Max VO2


Ex CI l/ min/ m2
4
3
2
1
500 600 700 800 9001000 100 200
Max VO2


Exercise Time secs
800
600
400
200
0
500 600 700 800 9001000 100 200
Max VO2

(c) Measurements of Gas Exchange on Exercise

In 10 of the above patients, maximal oxygen consumption was measured simultaneously with haemodynamic variables. In a further 10 similar patients with coronary artery disease and heart failure, respiratory gas exchange was measured during exercise using a similar exercise protocol. The patients breathed through low dead space in a resistance valve box and this incorporated a turbine ventilometer on the inspired limb for measurement of ventilation and the expired limb was fed through a mixing chamber to allow analysis of carbon dioxide and oxygen partial pressures. Throughout the test minute ventilation (VE), oxygen consumption (VO2) and carbon dioxide production (VCO2) were measured by online ventilation expired gas analysis (PK Morgan, Rainham, Kent) using standard equations (further details are given in the Appendix). Arterial blood gas values were monitored throughout using trans-cutaneous system (TCM3 Radiometer Limited, Copenhagen) which continuously monitors transcutaneous oxygen and carbon dioxide tensions. Indices of gas exchange could then be calculated and the non-invasive anaerobic threshold on exertion were calculated using a plot of oxygen consumption against carbon dioxide production (see Appendix).

Results

Mean exercise time, heart rate and blood pressure were similar to the previous group and are shown in Table 8. Details of maximal oxygen consumption and anaerobic threshold are shown in Tables opposite. In the 10 patients in whom haemodynamic variables were measured simultaneously, there was no correlation between VO_2 max and heart rate, blood pressure, pulmonary capillary wedge pressure, stroke volume index or cardiac index. VO_2 max does correlate to a degree with exercise time.

Discussion

The exact mechanisms that underlie the exertional fatigue and dyspnoea experienced by patients with heart failure remain unclear. Originally, simplistically, the fatigue was thought to be a direct consequence of the inability of the heart to act efficiently as the pump and the breathlessness resulted from increased reflected left atrial pressure and "stiff" lungs. More recently it has been suggested that there is a complex interplay between the central and peripheral mechanisms that are activated in response to pump dysfunction that become more significant in the presence of peripheral oedema. In the presence of reduced oxygen delivery to working muscle **(43,54)** there is evidence of impaired vasodilation **(55,56)**, altered skeletal muscle metabolism **(57-59)** and possibly also loss of muscle bulk.

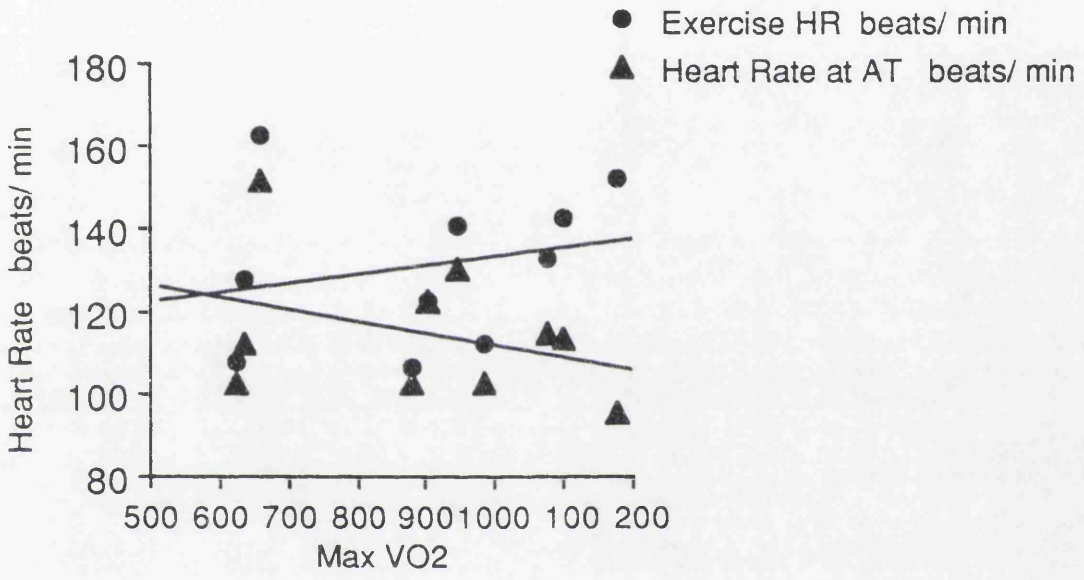
The mechanisms underlying the sensation of breathlessness are undoubtedly more complex. Recent data suggests that ventilation/ perfusion mismatch **(60)** with an increase in physiological dead space necessitates an increased minute ventilation to maintain normal arterial carbon dioxide partial pressure. In addition, in chronic heart failure, even moderate workloads are associated with increased carbon dioxide production and these two abnormalities are additive, resulting in an increased ventilatory requirement even for moderate workloads. This together with decreased lung compliance, which increases the intrinsic work of breathing, results in increased central respiratory drive to maintain eucapnia and appreciation of this at a conscious level could result in the sensation of breathlessness **(61-63)**.

The ventilation/perfusion mismatch does not appear to correlate with pulmonary capillary wedge pressure **(60)**. However pulmonary

microvascular permeability is significantly reduced in heart failure, possibly as an adaptive process to protect against pulmonary oedema **(48)** and it may well be that this is a further adaptive process in the lungs which determine the level at which patients develop both pulmonary oedema and the sensation of breathlessness. This would be in keeping with the very wide range of pulmonary capillary wedge pressures experienced by our patients during exercise who were all limited with the symptom of breathlessness.

The assessment of functional capacity by means of exercise testing has received increasing attention from investigators with the perceived need for objective measures to allow criteria to be established to institute therapy and to monitor the effects of these interventions. Clinical classifications of symptomatic status are too subjective and do not correlate well with measured exercise ability (see Figures 5,6) **(8,64,65)**. Table 8 shows that resting haemodynamic variables do not correlate with measured functional capacity in patients with chronic left ventricular failure as has been demonstrated by numerous other investigators **(8,10,65,66)** as resting haemodynamic measurements cannot be used to assess the severity of symptoms or clinical efficacy of treatment. Exercise haemodyamic measurements correlate more closely with symptoms but there is considerable overlap although other workers with a wider range of patients have shown a closer correlation **(67)**.

Exercise testing protocols for patients with heart failure are usually modified to accommodate a reduced exercise capacity, to allow the patient to exercise long enough to attempt to discriminate different grades of severity of exercise limitation **(8,64)**. In patients with chronic heart failure, the design of the test can influence the limiting symptom -


Exercise HR beats/ min
Heart Rate at AT beats/ min
Heart Rate beats/ min
180
160
140
120
100
80
500 600 700 800 900 1000 100 200
Max VO2

breathlessness limiting exercise tests with rapid increases in workload while if the work load is increased slowly the exercise is usually terminated by fatigue **(68)**. Thus it is preferable to measure the amount of exercise in terms of metabolic cost to the body - that is, as total oxygen consumption. Symptom limited maximum oxygen consumption (VO2 max) is reproducible and correlates well with exercise time (Figure 6). The reduction in VO2 max, associated with increasing severity of heart failure, correlates well with reduced exercise, cardiac index and stroke volume index **(69)**.

Oxygen consumption increases linearly with increasing workload and tends to plateau at maximal exercise **(70)** which approximates maximal aerobic capacity. If carbon dioxide production is measured simultaneously this can be used as the ratio to oxygen consumption (ventilatory exchange ratio) to more accurately indicate the achievement of the anaerobic threshold, which correlates well with the onset of systemic lactate production **(69,71)** (see Appendix). Measurements of VO2 max and anaerobic threshold are less subjective than reliance on symptoms at peak exercise. Anaerobic threshold relates to exercise duration and in patients with chronic heart failure occurs at a lower heart rate than normals (112 $\pm$ 17 versus 124 $\pm$ 7 beats/minute) (Figure 7) **(69)** and is less subject to variability with different exercise protocols **(72)**.

An important advantage of using measurements of respiratory gas analysis is that it allows patients to be classified on the basis of their "functional exercise capacity". Franciosa **(8)** using a four class system based on VO2 max (1: VO2 greater than 20 ml/min/kg; 2: 15-19 ml/min/kg; 3: 10-14 ml/min/kg; 4: below 10 ml/min/kg) showed that

patients could be differentiated in a manner that was not possible by either exercise capacity or New York Heart Association grading. However, maximum oxygen uptake is equally reduced in patients with cardiac failure who survive and non-survivors (7).

There is fairly extensive literature on the value of anaerobic threshold, but there is little correlative or prognostic information on some of the other measurements such as change in VO2 relative to the change in work rate (δ VO2/δ WR 73) and the slope of the VCO2/VO2 ratio above the anaerobic threshold (which reflects the rate of lactic acid buffering by HCO3) (74). Sietsema et al (75) in patients with cyanotic congenital heart disease and Nery et al (76) in patients with chronic obstructive airways disease have shown that VO2 is markedly attenuated during the first 20 seconds of exercise, which depends critically on cardiovascular function. There is as yet insufficient literature to judge whether these measurements will be of value in the assessment of the patient with heart failure.

In summary, exercise testing appears to be a useful tool for assessing the severity of chronic heart failure and following progress. Functional capacity in metabolic terms, can provide an objective measurement which is useful to assess responses to pharmacological and other interventions.

VENTRICULAR FUNCTION

Introduction

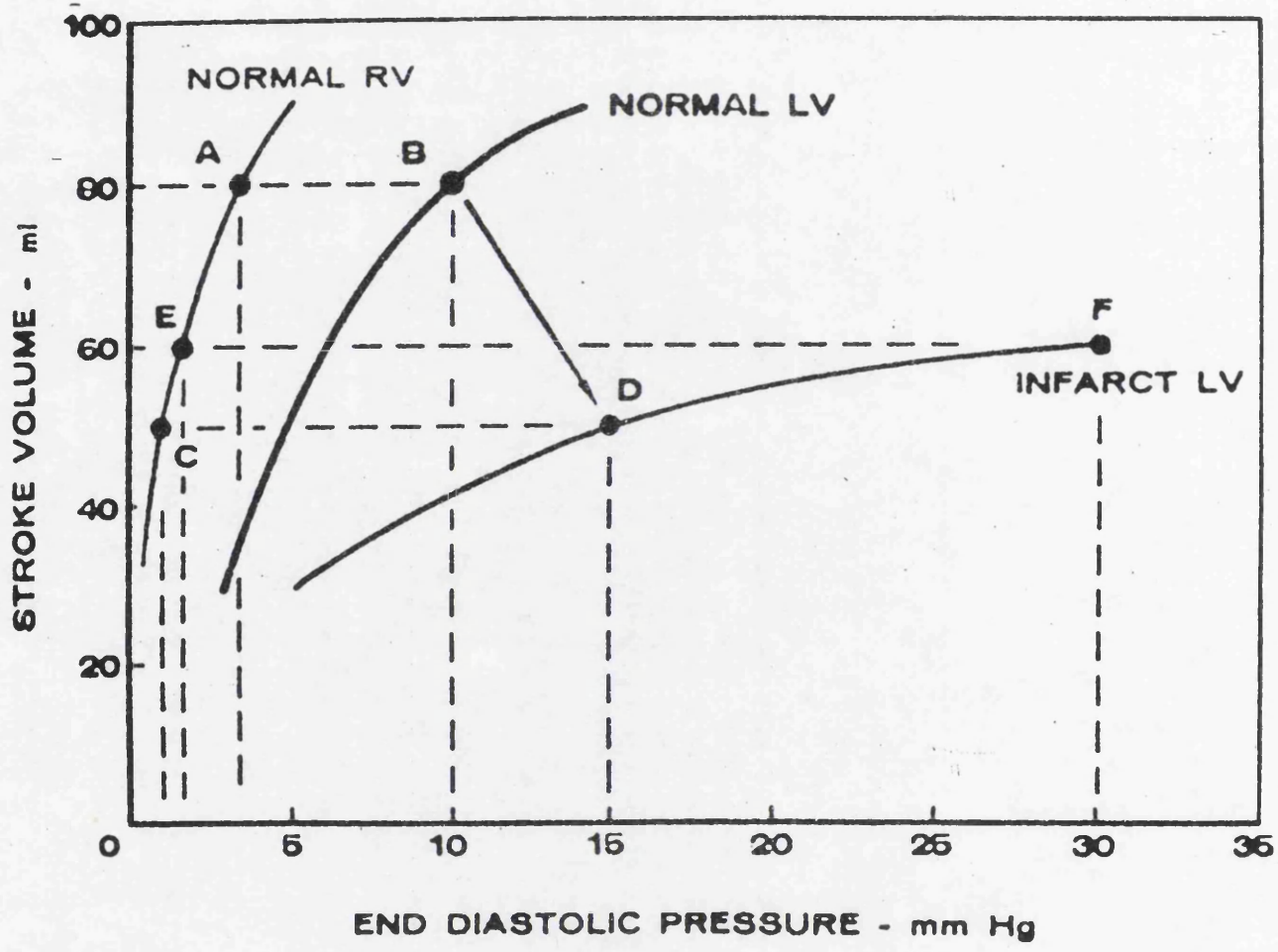
The ultimate importance of coronary disease is the impact of ischaemia upon the ventricle with ultimately the loss of muscle tissue. By assessing

symptoms of the oxygen carrying capacity of the body or exercise tolerance one is, in effect, looking at the end result or the efficiency of compensatory mechanisms rather than the organ that is damaged. It would therefore be logical to assess the function of the ventricle, or rather the degree of dysfunction when attempting to classify patients.

Left Ventricular Function Measurements

The common, and most widely known, are those measurements made during angiography. This allows determination of chamber dimensions, volume, wall thickness and mass. Combined with the intraventricular measurements and cardiac output, angiography can provide a very detailed assessment of ventricular function at any one instance in time **(77,81)**. With the use of specially adapted catheters specific measurements may be made, such as the Miller catheter providing dp/dt, but as with any invasive technique these measurements may be made only at one, or at most, a few points during the course of the cardiac catheterisation and are therefore not ideal for the assessment of out-patients or long term pharmacological intervention.

Other methods are available to assess many of the measurements that are made during cardiac catheterisation. Ventricular end diastolic pressure can be estimated either from pulmonary capillary wedge pressure or pulmonary diastolic pressure, as discussed earlier. Ventricular volume, wall thickness, ejection fraction and regional function can be obtained either by echocardiography or radionuclide techniques. Echocardio-graphy is non-invasive but requires considerable operator skill. Radionuclide techniques require intravenous injections of radio-active tracers but have the advantage of being less operator dependent, particularly during stress and when assessing right ventricular function.


NORMAL RV
NORMAL LV
INFARCT LV
A
B
C
D
E
F
100
80
60
40
20
0
5
10
15
20
25
30
35
STROKE VOLUME - ml
END DIASTOLIC PRESSURE - mm Hg

Studies on Ventricular Function

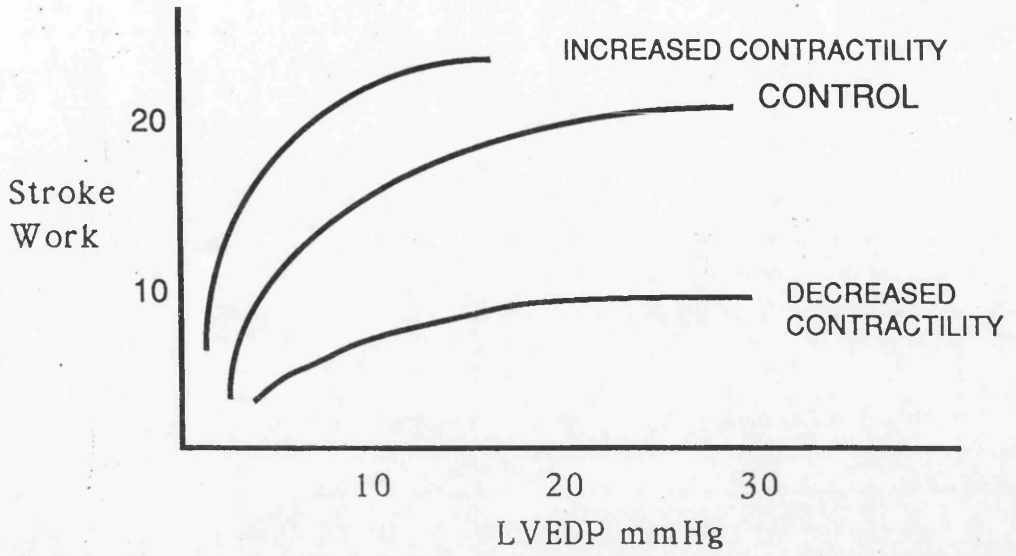
(a) Left Ventricular End Diastolic Pressure

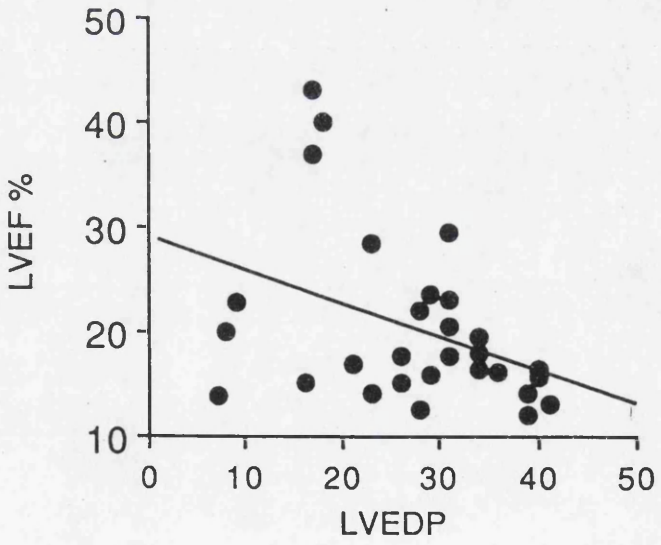
Normally left ventricular end diastolic pressure is defined as less than 12 mm.Hg. (see Appendix) and as the ventricle dilates so the left ventricular end diastolic pressure tends to rise although this is not inevitable. The Frank-Starling mechanism, described in the intact isolated dog heart, demonstrates the ability of increasing pre-load (filling pressure) in maintaining cardiac output (Figure 8a). In 1954 Sarnoff and Berglund combined stroke volume in a reflection of "flow work" by the heart and systemic pressure, cardiac "pressure work", to describe ventricular function curves (Figure 8b) **(82)**. Sarnoff then went on to describe a "family of ventricular function curves" relating stroke work to filling pressure depending on the level of contractility of the heart.

In the last 30 years there has been conflicting literature as to the importance of left ventricular end diastolic pressure in the limitation of exercise tolerance in the patient with heart failure **(83,84)**.

Methods

Thirty patients New York Heart Association graded II-IV heart failure, aged 36-66 years, underwent routine cardiac catheterisation. Left ventricular end diastolic pressure (LVEDP) was measured prior to the ventriculogram using a fluid filled catheter. Recordings were made at a range of 50 cm equals to 50 mm.Hg. at a speed of 50 mm/second and diastole was taken concurrently with the R wave of lead II of the electrocardiogram recorded simultaneously, after the a wave of atrial contraction. Ejection fraction was measured from the contrast ventriculogram (as determined in the Appendix) (LVEF).


INCREASED CONTRACTILITY
CONTROL
DECREASED
CONTRACTILITY
20
10
Stroke
Work
10
20
30
LVEDP mmHg


50
40
30
20
10
LVEF %
0
10
20
30
40
50
LVEDP

Results

The lack of correlation of end diastolic pressure and systolic function, measured as left ventricular ejection fraction is seen in Figure 9.

Discussion

As an isolated measurement, left ventricular end diastolic pressure may not be on its own helpful in defining the patient with heart failure and does not predict the measurement of systolic left ventricular performance (LVEF), although where LVEF was lowest left ventricular end diastolic pressure tended to be highest.

It has been suggested that left ventricular filling pressure is the primary haemodynamic abnormality during exercise in patients with heart failure **(85)**. Evidence cited to support this includes

(a) that exercise capacity is more closely related to left ventricular filling pressure than cardiac output or limb blood flow, as many patients have normal increases in skeletal muscle blood flow on exercise **(86,87)** and that pulmonary wedge correlates with the maximal exercise capacity **(84,88)**. However this is not our experience (see data on PCWP in this thesis), although the number of patients studied was small.

(b) changes in exercise capacity are more closely related to changes in LVEDP than to cardiac output.

(c) exercise capacity is more closely related to right ventricular ejection fraction than to left ventricular ejection fraction. It was presumed that this occurred because only right ventricular systolic function is correlated with the levels of pulmonary wedge pressure **(89)**. In a group of patients

with chronic obstructive airways disease we found only a weak correlation with right ventricular function and pulmonary pressure but a good correlation with pulmonary vascular resistance **(90)**.

Another explanation that might be considered is that ventricular filling pressure may be altered if there is a change in ventricular volume or if the pressure-volume relationship is altered by, for example, increasing muscle stiffness, as may occur with ischaemia **(85)**.

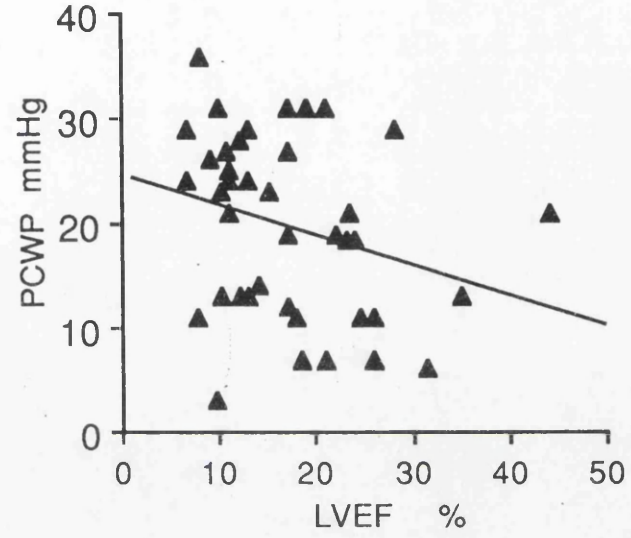
Ventricular Volumes and Function

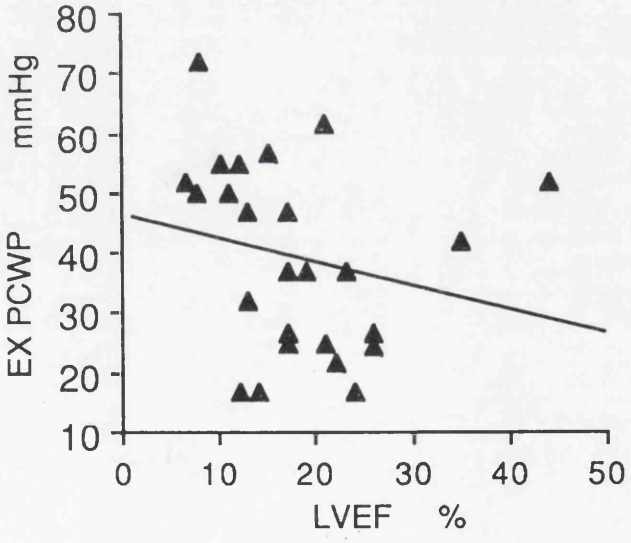
Following myocardial infarction, the most important determinant of survival is reported to be left ventricular ejection fraction (LVEF, see Appendix) **(5,91-94)** although end systolic volume and end diastolic volume may also be important **(96)**. Where heart failure is present nearly all the patients have abnormal ventricular function and the prognostic value of measurements of ventricular function are less clear as are the relationships between other measurements used for assessment of heart failure.

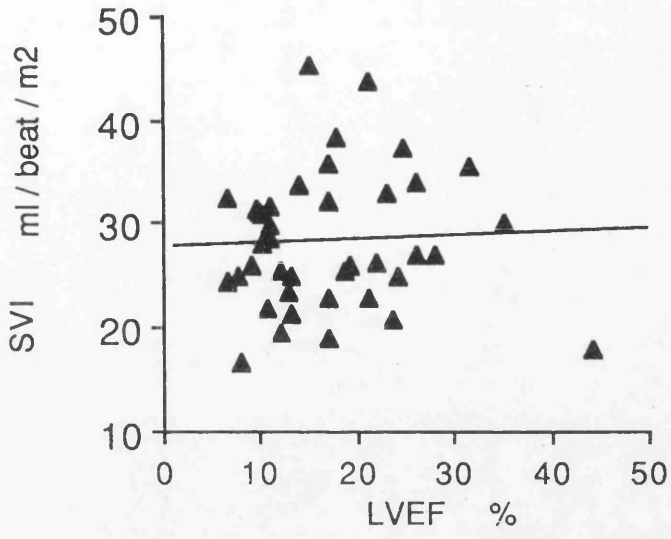
Methods

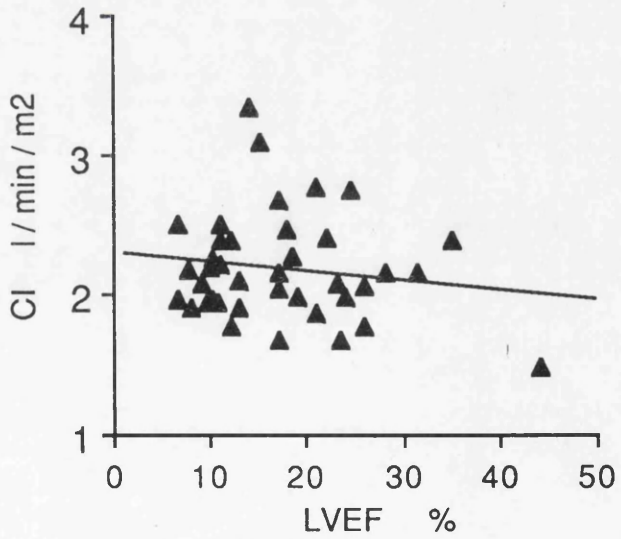
Thirty six patients with documented chronic heart failure New York Heart Association grade II-IV were studied. In all patients active drug therapy, apart from stable dosages of diuretics and potassium supplements, were withdrawn for at least 14 days.

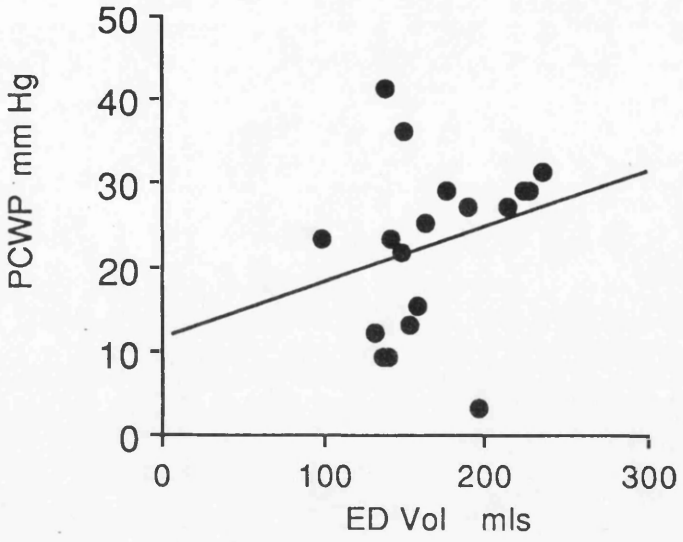
Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometer. Pulmonary capillary wedge pressure was obtained by Swan-Ganz catheter. Cardiac output was obtained in

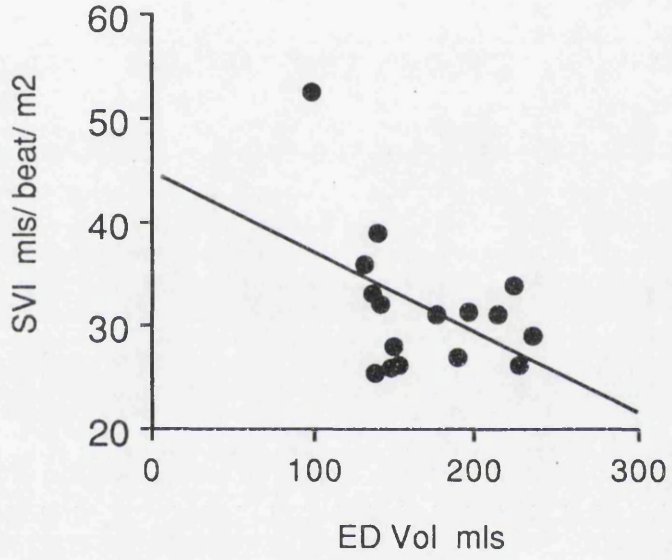

PCWP mmHg
40
30
20
10
0
0
10
20
30
40
50
LVEF %

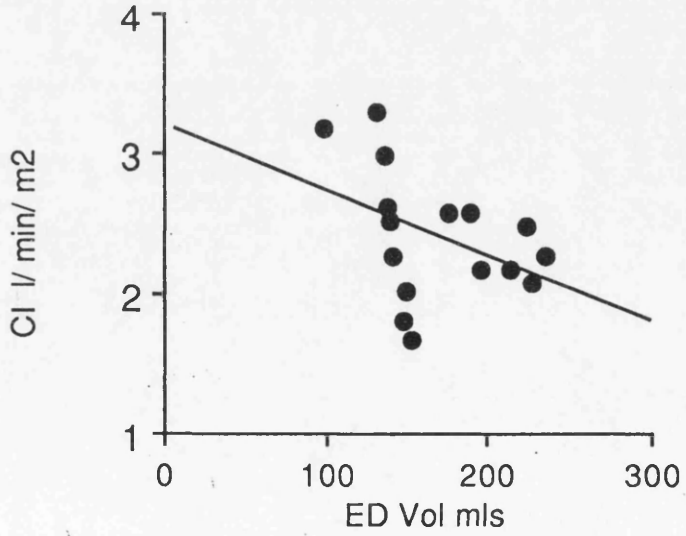

EX PCWP mmHg
80
70
60
50
40
30
20
10
0
10
20
30
40
50
LVEF %

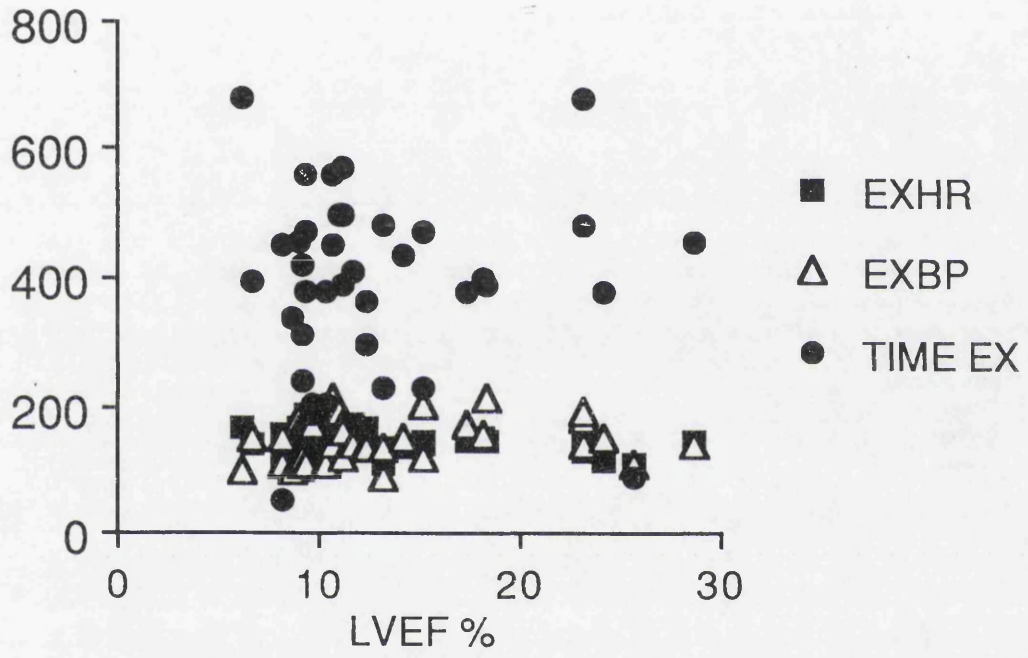

SVI ml / beat / m2
50
40
30
20
10
0
10
20
30
40
50
LVEF %

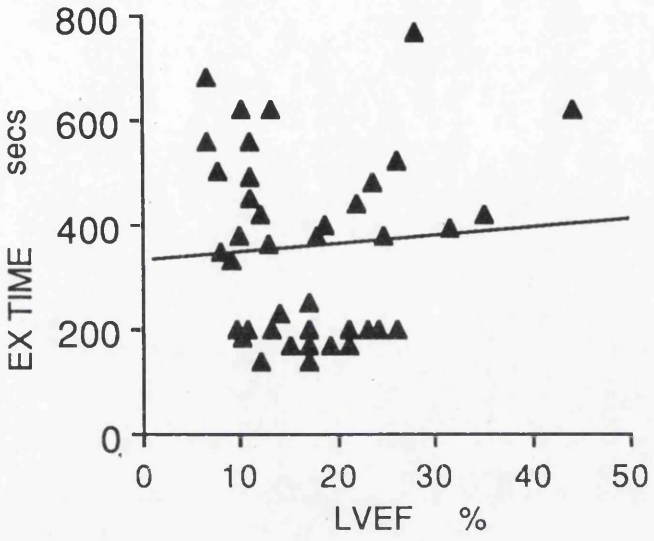

CI l / min / m2
4
3
2
1
0
10
20
30
40
50
LVEF %

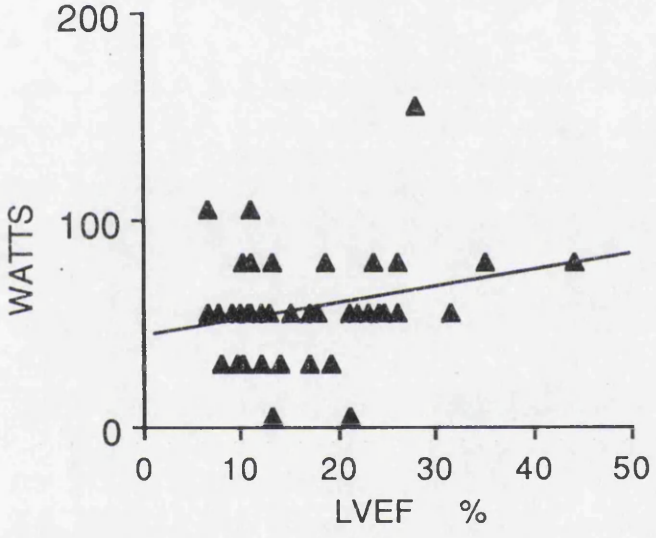

PCWP mm Hg
50
40
30
20
10
0
0
100
200
300
ED Vol mls

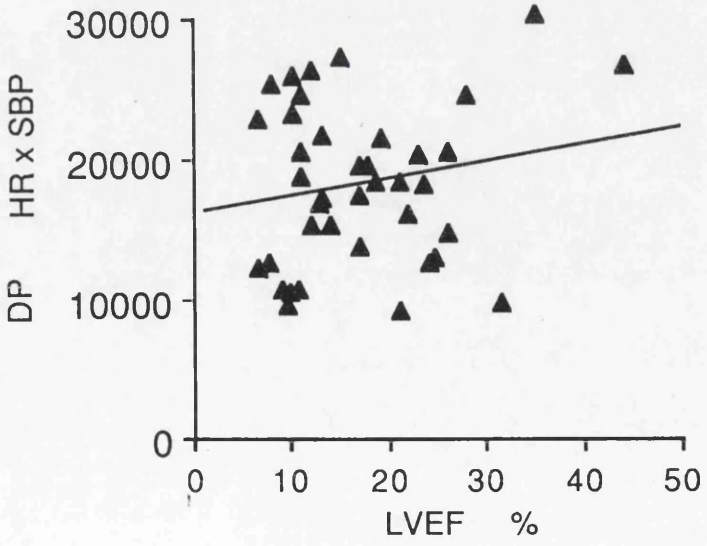

SVI mls/ beat/ m2
60
50
40
30
20
0
100
200
300
ED Vol mls

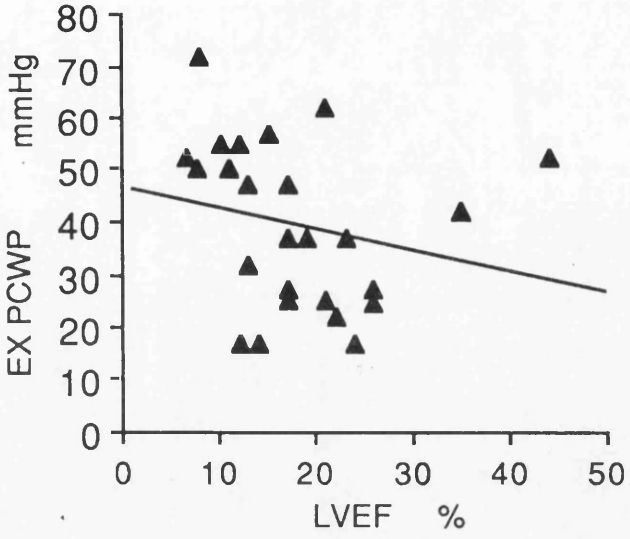

CI l/ min/ m2
4
3
2
1
0
100
200
300
ED Vol mls

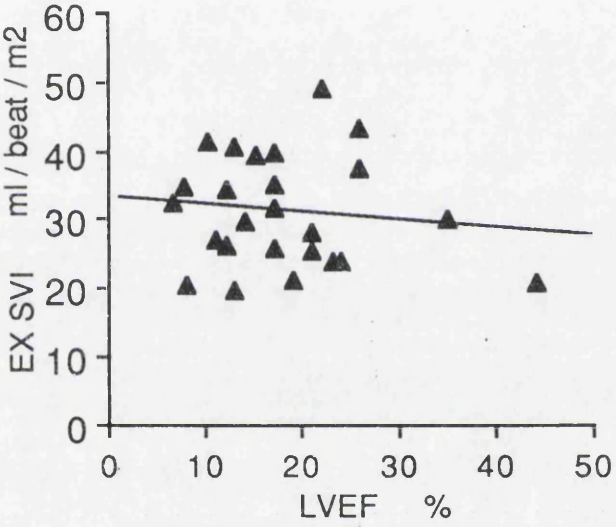

800
600
400
200
0
0
10
20
30
LVEF %
EXHR
EXBP
TIME EX

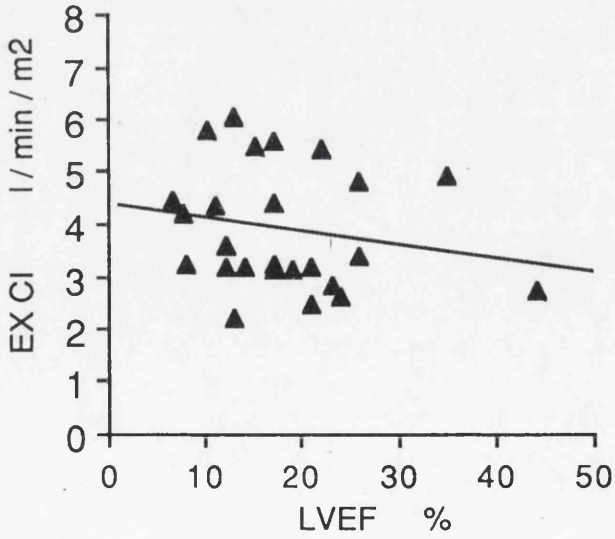

800
600
400
200
0
EX TIME secs
0
10
20
30
40
50
LVEF %

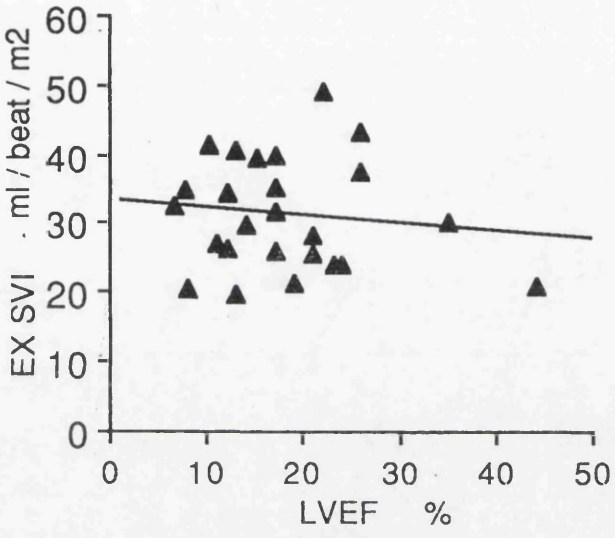

200
100
0
WATTS
0
10
20
30
40
50
LVEF %

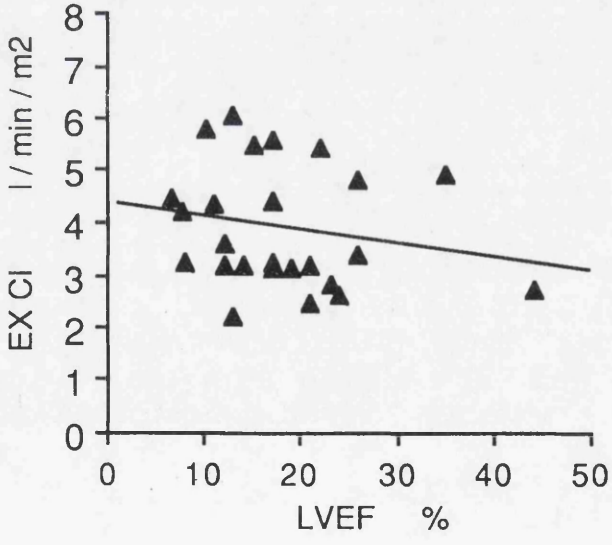

30000
20000
10000
0
DP HR x SBP
0
10
20
30
40
50
LVEF %


EX PCWP mmHg
80
70
60
50
40
30
20
10
0
0 10 20 30 40 50
LVEF %


EX SVI ml / beat / m2
60
50
40
30
20
10
0
0 10 20 30 40 50
LVEF %


EX CI l / min / m2
8
7
6
5
4
3
2
1
0
0 10 20 30 40 50
LVEF %


EX SVI . ml / beat / m2
60
50
40
30
20
10
0
0
10
20
30
40
50
LVEF %


EX CI l / min / m2
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
LVEF %

triplicate by thermodilution. Cardiac index and stroke volume index were calculated (see Appendix). Maximal symptom limited exercise testing was performed on a bicycle ergometer using an adjusted protocol (see Appendix). Respiratory gas analysis was carried out online in 10 patients as previously described. Ventricular function was assessed by technetium-99m radionuclide angiography. Left ventricular volume and left ventricular ejection fraction were calculated.

Results

The results are seen in the Figures opposite. There was no correlation between LVEF and wedge pressure, stroke volume index or cardiac index, although there was a tendency for the lowest LVEF to occur with the highest resting wedge pressure and lowest stroke volume index and cardiac index (Figure 10).

End diastolic and end systolic volume as shown in Figures opposite. Similarly, there was no correlation with haemodynamic parameters (Figure 11). LVEF % is shown, plotted against exercise parameters (Figure 12). There was no correlation with exercise heart rate, blood pressure, double product, exercise time or work load achieved. Similarly, there was no correlation between LVEF and exercise haemodynamic parameters - pulmonary capillary wedge pressure, cardiac index and stroke volume index (Figures 9,12).

Discussion

These results are not entirely surprising since the haemodynamic measurements are made at one instance in time and may be affected by other factors than ventricular performance. Conversely, ejection fraction is affected by changes in loading conditions, independent of changes in

muscle function. This confirms early reports by Dougherty et al **(96)** and Franciosa et al **(10)** on the little correlation between haemodynamic assessment and measurements of left ventricular function.

Although left ventricular dysfunction may alter exercise capacity, many compensatory mechanisms could preserve exercise tolerance despite severe left ventricular dysfunction. Exercise capacity has been reported to be preserved in patients with severe left ventricular dysfunction **(96)** and in this study there was no correlation between left ventricular ejection fraction and maximal symptom limited exercise capacity. In 10 patients exercise VO2 showed little correlation with left ventricular ejection fraction. There was a trend for the lower exercise anaerobic threshold to correlate with lower left ventricular ejection fraction and these are the patients who are symptomatically most impaired. Exercise capacity has previously been shown to correlate poorly with LVEF and has no correlation with VO2 max **(8, 84)**.

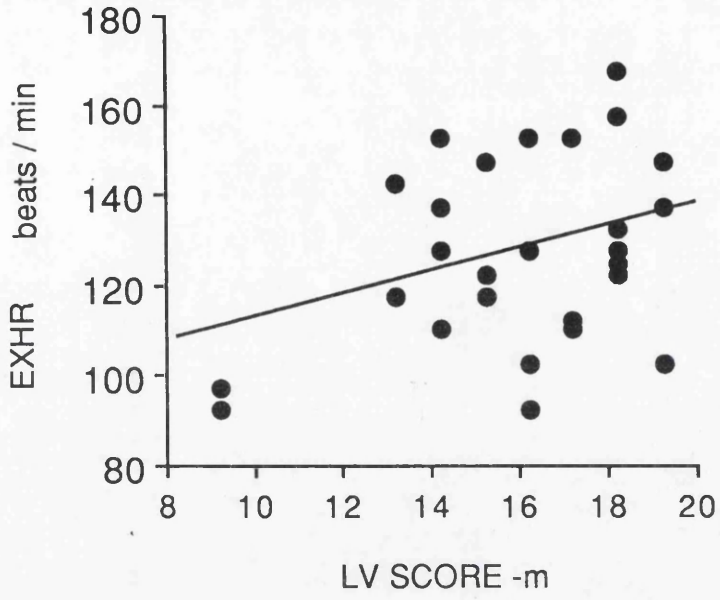
Maranz et al **(11)** compared clinical criteria with left ventricular ejection fraction in 407 patients. The clinical criteria were those used by the Framingham Study **(93)**, a study performed at Duke University **(6)** and those of a third group in Boston **(98)**. Of 133 patients with low ventricular ejection fractions (greater or equal to 40%) 20% met the criteria for chronic heart failure, and conversely of 204 patients with normal left ventricular ejection fractions (greater equal to 50%) 51 met at least one of the criteria for heart failure. These results suggest that a combination of clinical assessment and objective measure of left ventricular performance may be essential in the definition of patients with heart failure **(97)**.

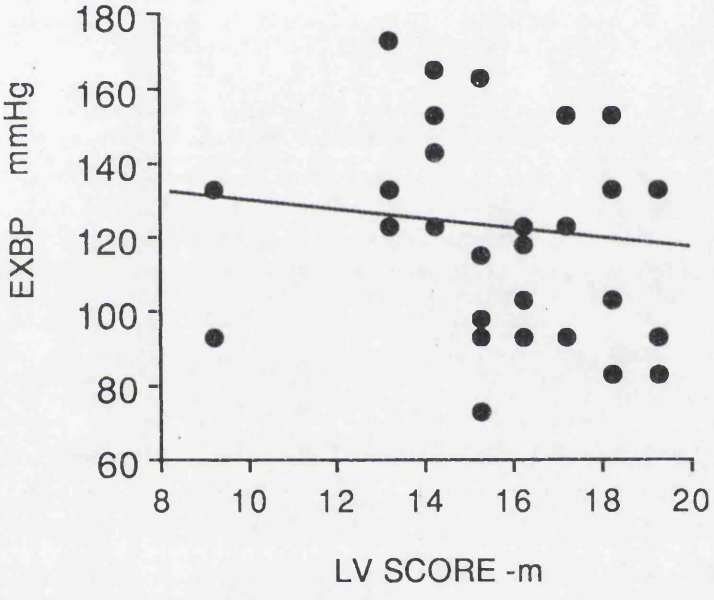
Global measures of left ventricular function appear to be of prognostic value in some patients with heart failure **(12,21,30,98)** but neither left ventricular systolic or diastolic dimensions or volumes discriminate between survivors and non-survivors in patients with ischaemic "cardiomyopathy" **(27)**.

(c) Regional Function

Measurements of global ventricular function may remain normal even when large portions of the ventricle are damaged due to hypertrophy and hyperfunction of the "normal segment". As coronary artery disease tends to produce regional ischaemia assessment of regional wall motion abnormalities may be a more accurate reflection of the degree of damage within the ventricle. It is true, however, where there is extensive coronary artery disease there is extensive ventricular involvement, thus producing a low ejection fraction which is presumably why this is a good predictor of subsequent death following myocardial infarction.

Regional function can be assessed in several ways. The commonest, and probably the most reliable, is the visual detection of regional wall motion abnormalities by an experienced observer. Sector analysis of regional ejection fraction **(99)**, functional or phase/amplitude images provide little advantage in the accuracy of detection of abnormalities **(100)** but may provide a more accurate measure of extent **(101,102)**. Similarly with regional ejection fraction images **(103)** or the stroke volume image which we have found to be most useful **(104)** (see Appendix).


EXHR beats / min
180
160
140
120
100
80
8
10
12
14
16
18
20
LV SCORE -m


EXBP mmHg
180
160
140
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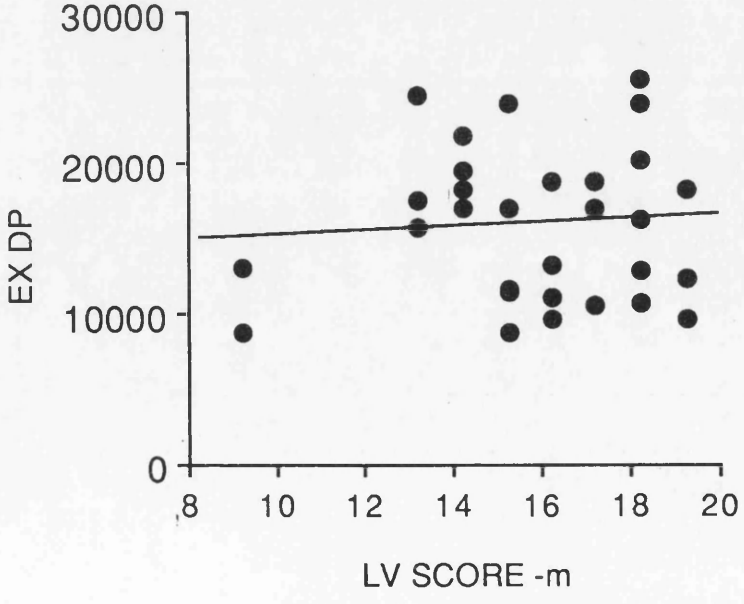
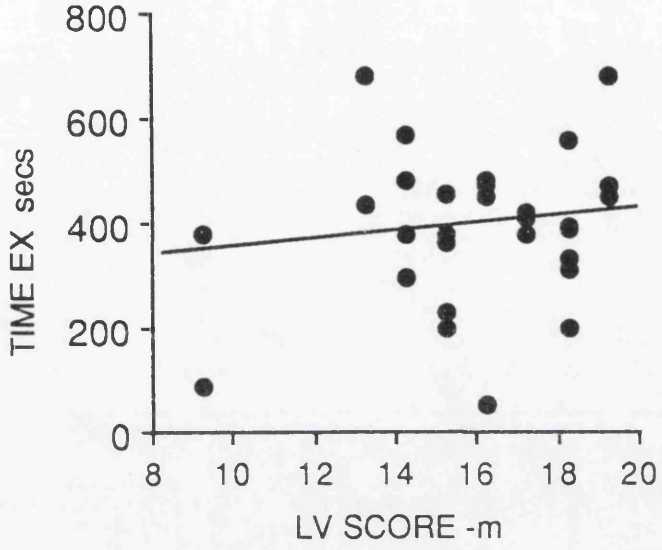
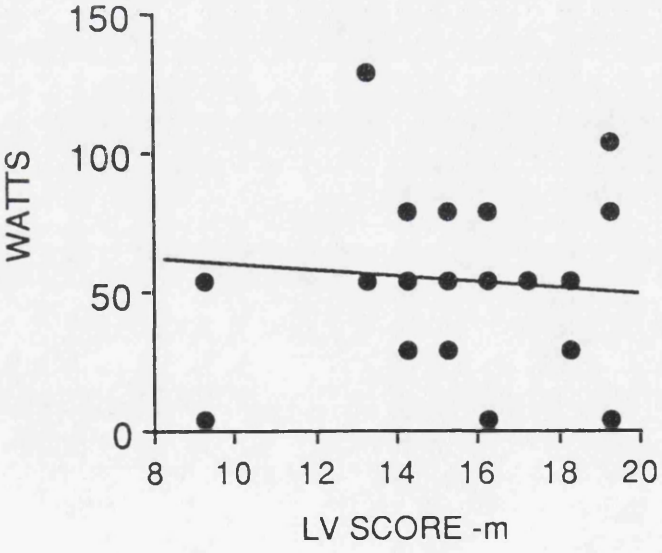
10
12
14
16
18
20
LV SCORE -m


EX DP
30000
20000
10000
0
8
10
12
14
16
18
20
LV SCORE -m


800
600
400
200
0
TIME EX secs
8
10
12
14
16
18
20
LV SCORE -m


150
100
50
0
WATTS
8
10
12
14
16
18
20
LV SCORE -m

Methods

In 40 patients with New York Heart Association grade II-IV heart failure resting technetium99m radionuclide ventriculo-graphy was performed. Regional function was assessed visually by two experienced observers using a five point scoring system (1=normal; 5=aneurysmal) applied to the left ventricle, divided into five regions of interest, and by standard functional images (stroke volume image and paradox image) and by phase analysis (see Appendix). Using this scoring system a score of 5 was normal, to a maximum of 25 with all regions aneurysmal.

Results

There was no correlation between regional dysfunction, as measured by total score, exercise heart rate, systolic blood pressure double product (HR x SBP), exercise time or work load achieved (Figure 13).

(d) Ventricular Function on Exercise

Radionuclide scans during exercise have been shown to be an accurate and reproducible method of detecting ischaemia and coronary artery disease **(109-111)** and provide prognostic information following acute myocardial infarction **(112)**. Exercise tests are usually performed supine to minimise the effect of chest wall motion, but exercise tests performed upright provide very similar information **(113)**.

Methods

Ten patients with chronic heart failure secondary to coronary artery disease were studied. All drug therapy including Digoxin and vasodilators had been withdrawn for at least 14 days and patients were

receiving a stable dose of diuretic with potassium supplements. Patients were symptomatically New York Heart Association grade III or IV. Heart rate was obtained from a 12 lead electrocardiogram, monitored at rest and continuously throughout exercise. Blood pressure was obtained intermittently every two minutes and at peak exercise using a cuff sphygmomanometer. A Swan-Ganz thermodilution catheter was inserted percutaneously through the internal jugular vein and measurements of right atrial pressure, pulmonary artery pressure and pulmonary capillary wedge pressure were obtained at rest. Pulmonary artery pressure was monitored continuously throughout exercise. Cardiac output was obtained by a thermodilution technique using an automatic injector (OMP thermodilution injector). Measurements were obtained at rest in triplicate continuously throughout exercise and for five minutes following exercise. Exercise was performed on an upright bicycle ergometer using a standard protocol previously described. Respiratory gas analysis was performed online to ensure that the patient achieved their anaerobic threshold. Ventricular function was measured at rest and continuously during exercise and for five minutes post exercise using technetium-99m radionuclide ventriculography. Scans were obtained with the patient seated comfortably on the bicycle with his left arm positioned on top of the camera. The camera was positioned in a 40° left anterior oblique projection to provide optimal separation between the right and left ventricles. Careful positioning of the bicycle, the Gamma camera and the patient ensures that there is little motion of the patient's chest during exercise. Scans obtained by this method show acceptable reproducibility (see Appendix).

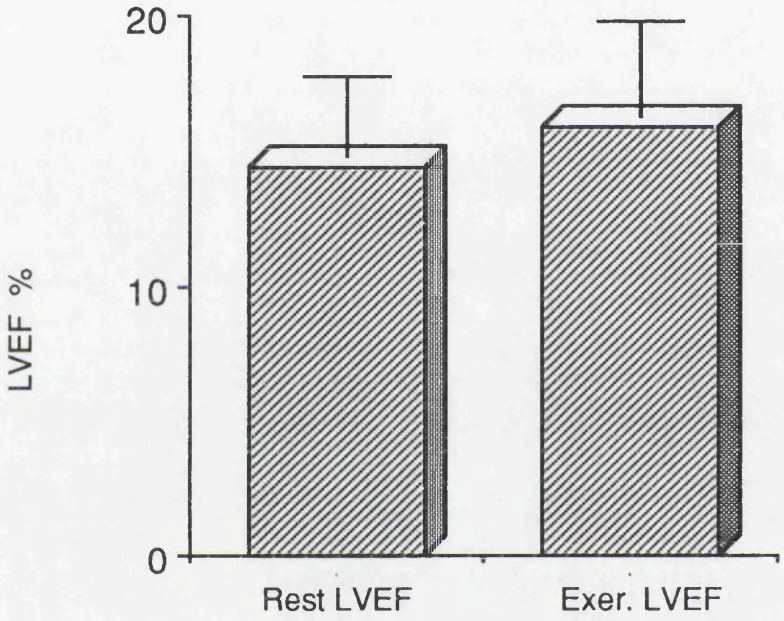
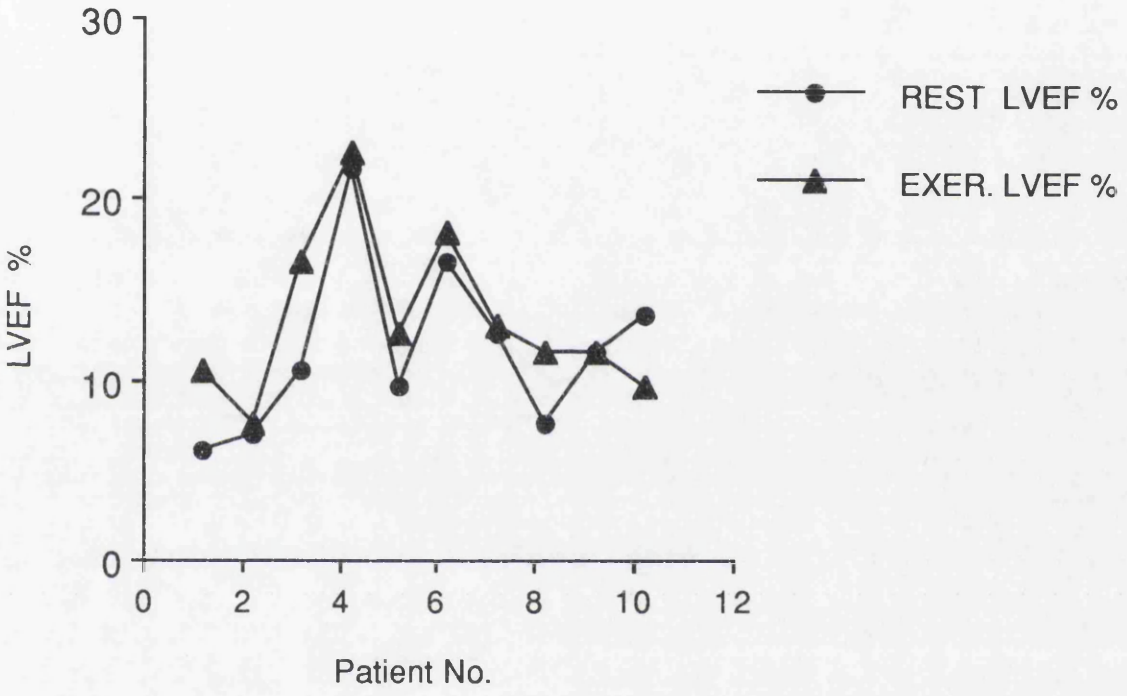
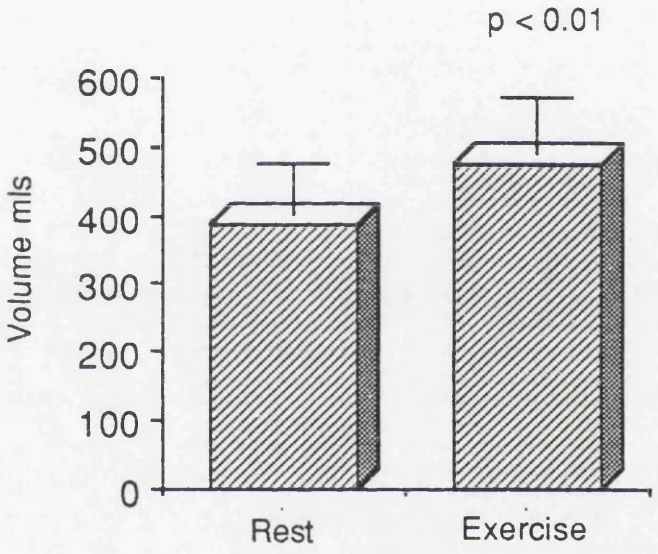
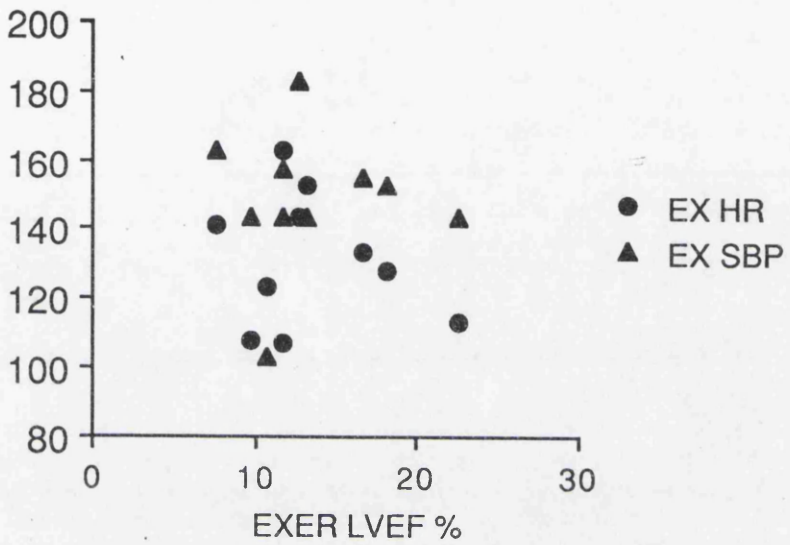
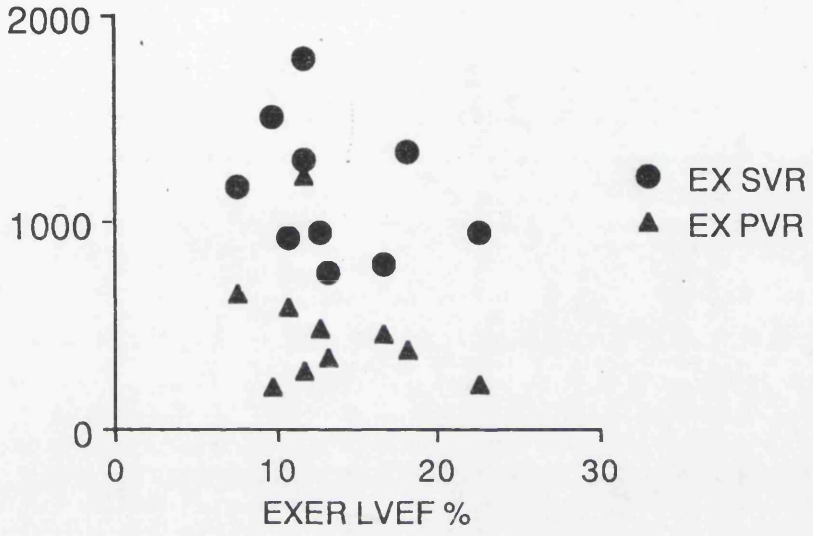


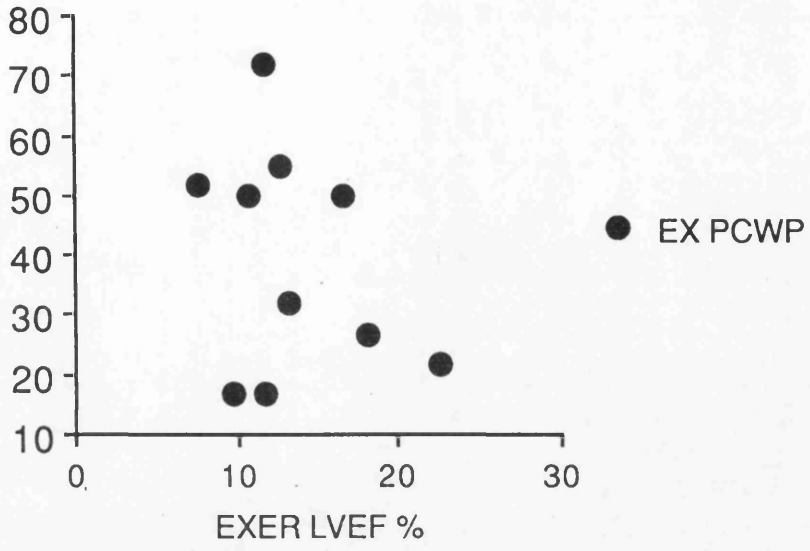
Fig. 14 (a) Change in LVEF % rest to exercise n = 36

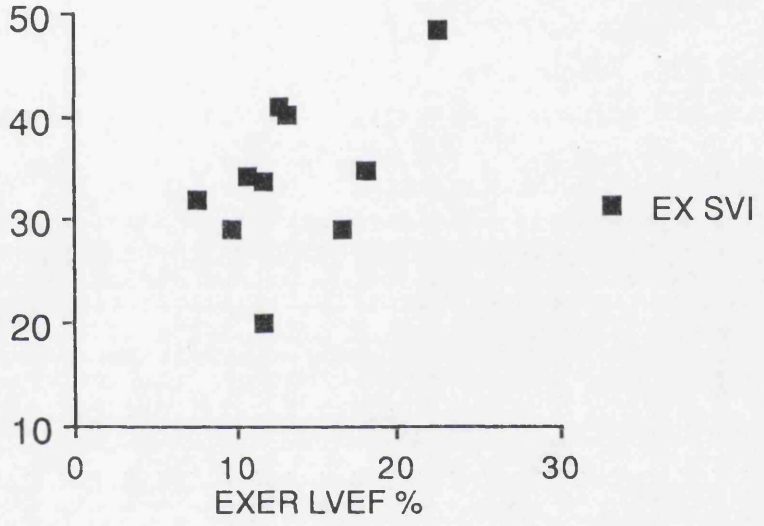

30
20
10
0
LVEF %
0
2
4
6
8
10
12
Patient No.
REST LVEF %
EXER. LVEF %

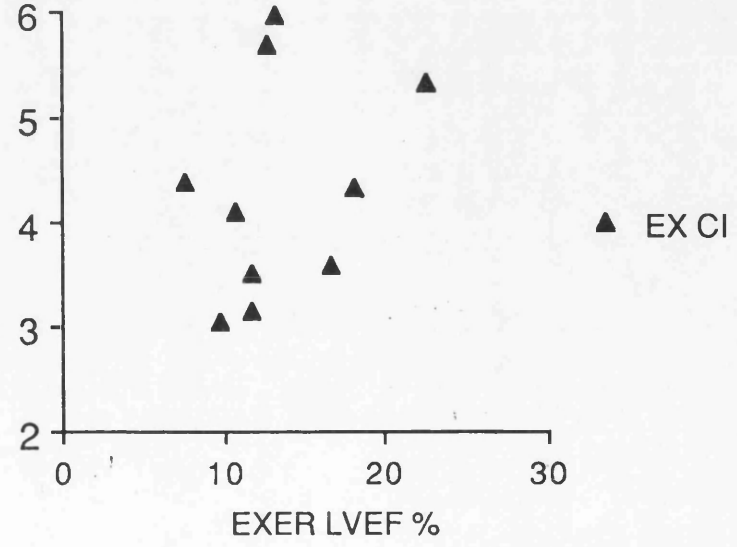

p < 0.01
600
500
400
300
200
100
0
Volume mls
Rest
Exercise

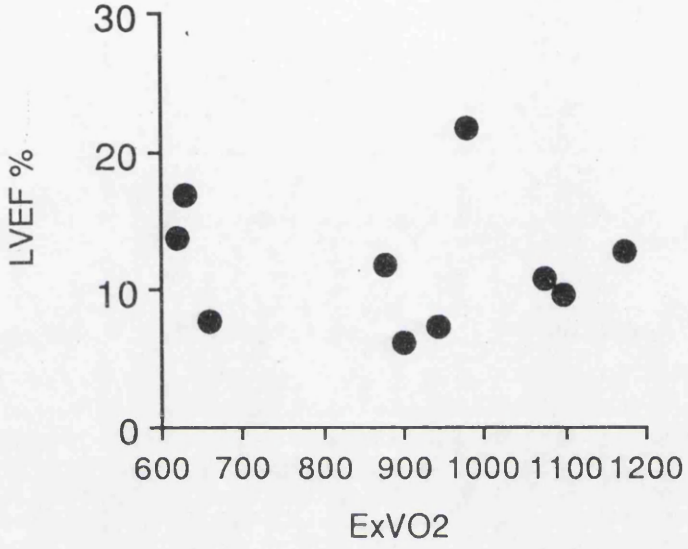

200
180
160
140
120
100
80
0
10
20
30
EXER LVEF %
EX HR
EX SBP


2000
1000
0
0
10
20
30
EXER LVEF %
EX SVR
EX PVR


80
70
60
50
40
30
20
10
0
10
20
30
EXER LVEF %
EX PCWP


50
40
30
20
10
0
10
20
30
EXER LVEF %
EX SVI


6
5
4
3
2
0
10
20
30
EXER LVEF %
EX CI


30
20
10
0
LVEF %
600
700
800
900
1000
1100
1200
ExVO2

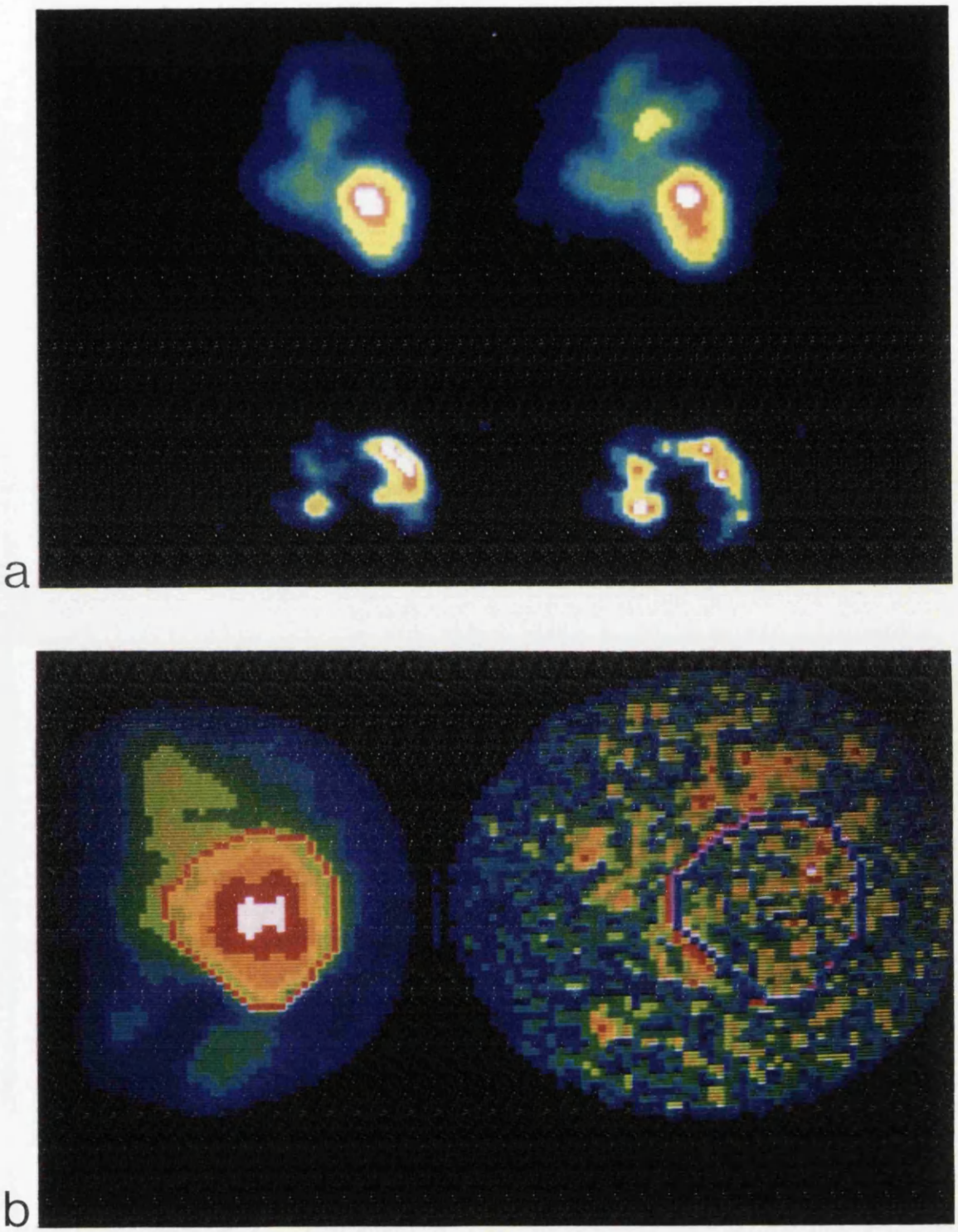


Figure 15: a) Rest and peak exercise end diastolic images, with stroke volume images, showing increasing anterior wall motion abnormality

b) Abnormal, dilated left ventricle; phase image showing totally inco-ordinate contraction (LV outlined in blue)

Results

The 10 patients had similar degrees of severe left ventricular dysfunction with resting left ventricular ejection fractions between 6 and 21% and all patients had sustained a previous myocardial infarction. Exercise time and maximal oxygen consumption (VO2 max) were reduced in all patients. Heart rate, blood pressure, cardiac index and stroke volume index all increased on exercise as would be expected. Calculated systemic vascular resistance and pulmonary vascular resistance fell. Ejection fraction was essentially unchanged (11.1 ± 4.73 to $12.8 \pm 4.5\%$). End diastolic volume increased significantly from 389 ± 72 to 475 ± 81 ($p<0.01$). Diastolic pulmonary artery pressure increased from 21.3 ± 8.1 to 37.4 ± 18.9 but this change was not significant (Figure 14).

Left ventricular contraction became less coordinate with exercise (Figure 15) with more extensive regional wall motion abnormalities. At peak exercise contraction becomes totally incoordinate.

Discussion

Many mechanisms have been proposed for the limitation of exercise in patients with chronic heart failure. In general the perceived wisdom is that left ventricular end diastolic pressure is the primary determinant of exercise intolerance in heart failure **(85)**. This seems unlikely in these patients, since although diastolic pulmonary artery pressure increases, this was not significant. Systolic function as reflected by left ventricular ejection fraction was unchanged. Cardiac index appeared to be sustained by a combination of increased heart rate and increasing volume.

It is generally reported that left ventricular function is abnormal if left ventricular ejection fraction fails to increase by 5% or declines during stress **(114,115)** but other reports suggest that for the detection of coronary artery disease, the exercise radionuclide angiogram may have limited specificity **(114)**. It is our experience that with upright exercise that a normal left ventricular ejection fraction tends to increase and wall motion score does not alter. In these patients with severe left ventricular dysfunction LVEF was either unchanged or fell, in agreement with published work **(116)**. Immediately post exercise left ventricular ejection fraction can increase, presumably secondary to catecholamine stimulation **(115)** which is maximal in the 30 seconds after exercise.

As exercise progressed in each patient, left ventricular contraction became increasingly discoordinate until at peak exercise there was no coordinate left ventricular function. Various factors should be considered that might underlie these changes. Ventricular filling pressure may alter as a consequence of changing ventricular volume with impairment of diastolic function **(117)**. Certainly diastolic function is altered as can be seen by the changing shape of the ventricular time activity curves **(118)**. Increased left ventricular volume increases left ventricular wall tension in accordance with the Laplace equation **(119)**

$$\text{wall tension} = \frac{\text{left ventricular systolic pressure x diastolic volume}}{\text{2 times wall thickness}}$$

Left ventricular wall tension is closely related to myocardial energy utilisation. In addition, increasing sympathetic drive during exercise will stimulate myocardial contractility which further increases myocardial

oxygen consumption **(120)**. Heart rate, another determinant of myocardial oxygen consumption, usually plays a relatively unimportant role. Tachycardia is usually associated with a decrease in intracardiac volume and myocardial shortening which results in a substantial decline in chamber wall stress **(121)**. However, in this group of patients clearly intracardiac volume increases and heart rate on exercise must therefore be a determinant of myocardial oxygen consumption **(122)**. Another factor which may be contributory is the reactive myocardial hypertrophy which occurs following myocardial infarction **(123,124)** as patients in this study had sustained substantial previous myocardial infarctions presumably with normal compensatory mechanisms. Ventricular hypertrophy can result in compromised blood flow during stress with a reduced vasodilatory reserve.

These increased demands in myocardial oxygen consumption would usually be met by increased coronary flow. In patients with coronary artery disease, as in this group of patients, increased demands cannot be met resulting in myocardial ischaemia **(125,126,127,128)**. Myocardial ischaemia induces reduced performance of the local myocardium **(125,129)**. If the extent of the myocardial involvement is sufficient the uninvolved myocardium cannot cope with the increased demands.

In these patients with extensive coronary artery disease and extensive previous myocardial damage, it is difficult to convincingly demonstrate further myocardial ischaemia. Exercise induced regional wall motion abnormalities have previously been demonstrated to be associated with ischaemia, reversible on revascularisation **(123,130,131)**. New regional wall motion abnormalities on exercise have been demonstrated in these patients with chronic heart failure without accompanying angina **(130)**.

This does not exclude myocardial ischaemia, as wall motion abnormalities usually precede symptoms and ischaemia may be "silent" **(131)**.

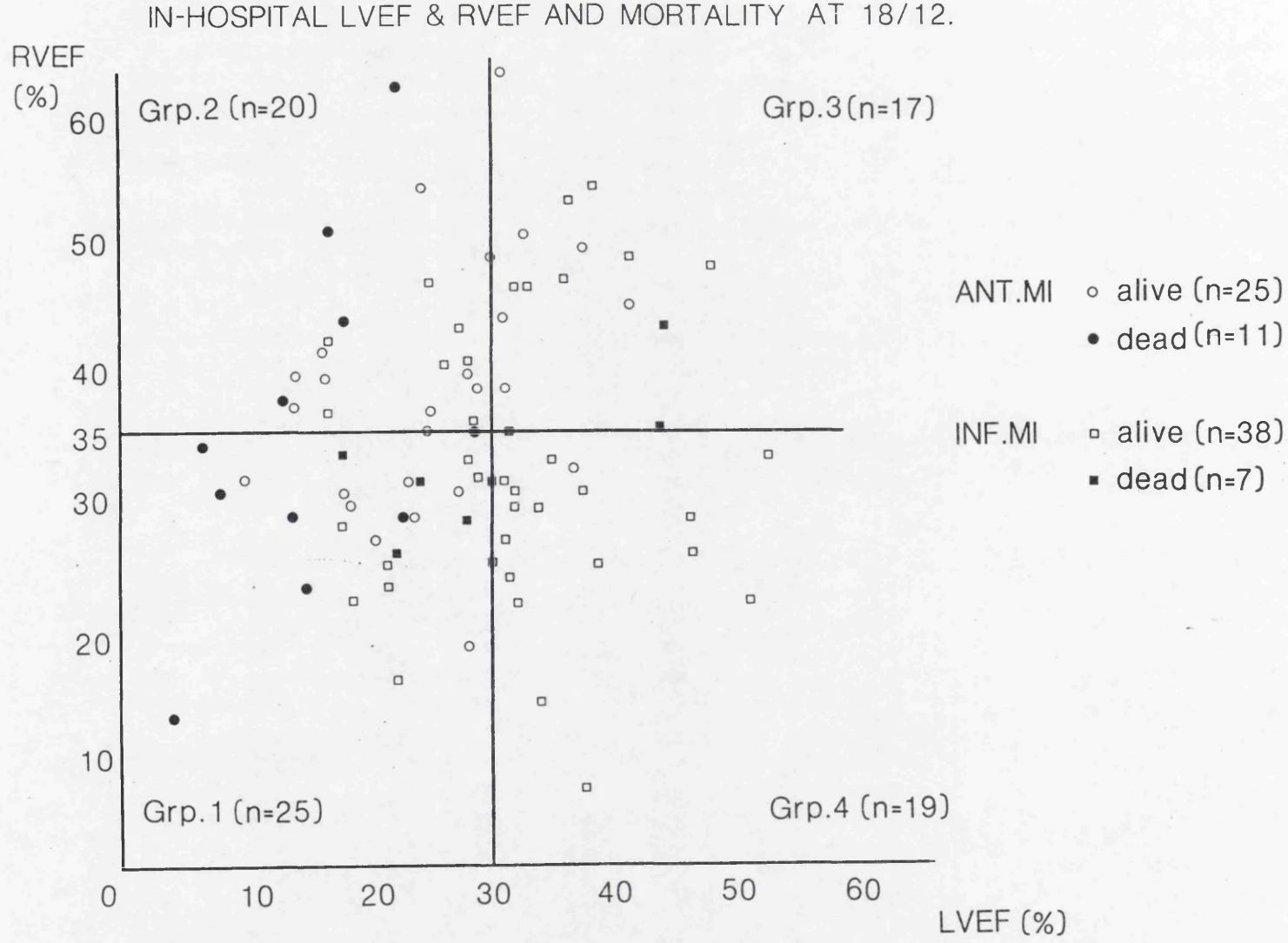
What is most striking is loss of coordinate contraction at peak exercise and it is difficult to imagine how the heart can fulfil its function as a pump if the heart cannot eject efficiently. Stroke volume must be limited and blood pressure cannot be further increased.

In summary, in patients with severe left ventricular dysfunction secondary to coronary artery disease myocardial stress, such as exercise, can induce incoordinate ventricular function, which may reflect underlying myocardial ischaemia induced by the stress which limits the heart's ability to eject.

RIGHT VENTRICULAR FUNCTION

(a) Introduction

In 1910 Bernheim **(132)** suggested that left ventricular dilatation could embarrass right ventricular function, producing systemic venous congestion and congestive heart failure and in 1914 Henderson and Prince **(133)** demonstrated inter-dependence between the two ventricles in an ejecting heart. The interplay between the function of the two ventricles has been reviewed in detail by Bove and Santamore in the American Journal of Physiology **(134)** and Sibald and Driedger in Critical Care Medicine **(135)**. In essence, experimental data suggests that ventricular interdependence is important in systolic function of the ventricles, but that responses to changes in volume and compliance are more complex and not completely understood.


IN-HOSPITAL LVEF & RVEF AND MORTALITY AT 18/12.
RVEF (%)
Grp.2 (n=20)
Grp.3 (n=17)
Grp.1 (n=25)
Grp.4 (n=19)
60
50
40
35
30
20
10
0
10
20
30
40
50
60
LVEF (%)
ANT.MI
alive (n=25)
dead (n=11)
INF.MI
alive (n=38)
dead (n=7)

In patients with coronary artery disease, the right ventricle is commonly involved. A prospective study of 107 autopsies from a Coronary Care Unit demonstrated right ventricular infarction in 80% and a 3% incidence of isolated right ventricular infarction **(136)**. This is in keeping with our own findings that of 100 patients with coronary artery disease right ventricular perfusion defects were seen in 67% and 90% of the patients with right ventricular perfusion defects had significant right coronary artery disease **(137)**. The role of right ventricular dysfunction in patients with "ischaemic cardiomyopathy" is less well documented.

Contrast right ventricular angiography is difficult to quantitate due to the geometry. The advantages of using radionuclide techniques are that they are count dependent and less critically dependent on the geometry. Technetium-99m scanning allows assessment of the right ventricle but when the right ventricle is dilated it can be difficult to obtain optimum septal separation, especially at the apex. We have developed a method of assessing right ventricular function using a short (20 seconds intra-venously) infusion of Xenon-133 **(132)**. Ninety per cent of the Xenon is excreted by the lungs allowing the right ventricle to be assessed in isolation. The method is simple, reproducible and repeatable and can be performed on exercise (see Appendix).

Methods

Of 120 consecutive patients admitted to the Coronary Care Unit, 81 were subsequently demonstrated to have sustained a myocardial infarction, based on serial electrocardiographic and enzyme criteria. Fifty nine (73%) were male and the mean age was 56 years (range 24-74 years). Thirty nine (48%) had had previous angina and 15 (18.5%) had sustained a previous myocardial infarction. Radionuclide scans were obtained

acutely (within 24 hours), at 3 days and at 18 months at follow-up. Data is presented from the 3 day scans as this time point was found to be most predictive of future events. Right ventricular function was assessed using Xenon-133 and left ventricular function obtained from gated technetium scans (see Appendix). Data was acquired from all patients at 18 months. In those that were dead, information as to the mode of death was obtained from the hospital notes, the general practitioner and the family as was appropriate. Deaths were either Hinkle Class I (abrupt loss of consciousness without prior circulatory collapse) or Hinkle Class II (gradual circulatory failure and collapsed circulation) and were therefore considered to be cardiac in origin **(139)**. Normal values for ventricular function were obtained from volunteers. The mean normal value for left ventricular ejection fraction (LVEF) is 50 $\pm$ 4.6% and a LVEF of greater than 40% was considered to be normal with a LVEF of less than 30% considered to be significant left ventricular dysfunction. The mean normal value for right ventricular ejection fraction (RVEF) is 47.3 $\pm$ 4.4% with a RVEF greater than 35% being considered normal and below this value right ventricular dysfunction.

Results

At three days following myocardial infarction left ventricular impairment was seen in 45/81 patients (56%) and right ventricular impairment in 44 (54%). Impairment of both ventricles was seen in 25 patients (31%). In the 18 months following myocardial infarction there were 18 deaths: ten (40%) occurred in Group 1 (see Figure 16), where there was both right and left ventricular impairment (n = 25); five (20%) in Group 2, with impaired left ventricular function and a normal right ventricle (n = 20); and two (12%) in Group 3 with preserved left and right ventricular function (n = 17); and one patient died in Group 4, with normal left

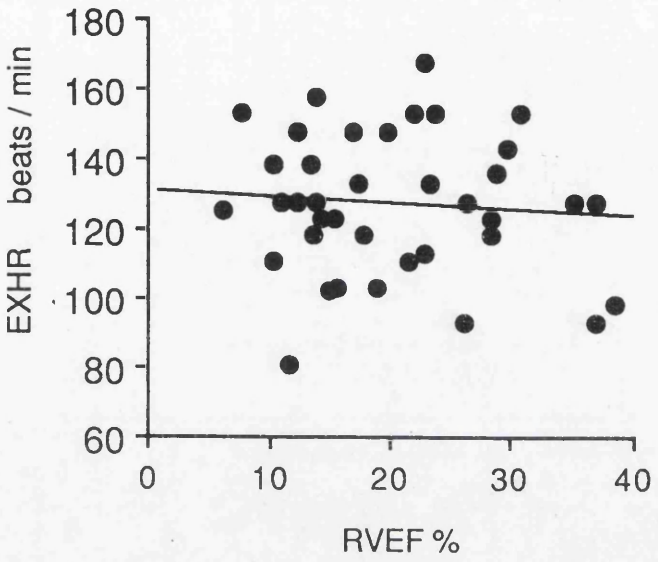
ventricular but impaired right ventricular function (n = 19). There were significantly more deaths in Group 1 where both right and left ventricular function were impaired ($p<0.01$) **(140)**.

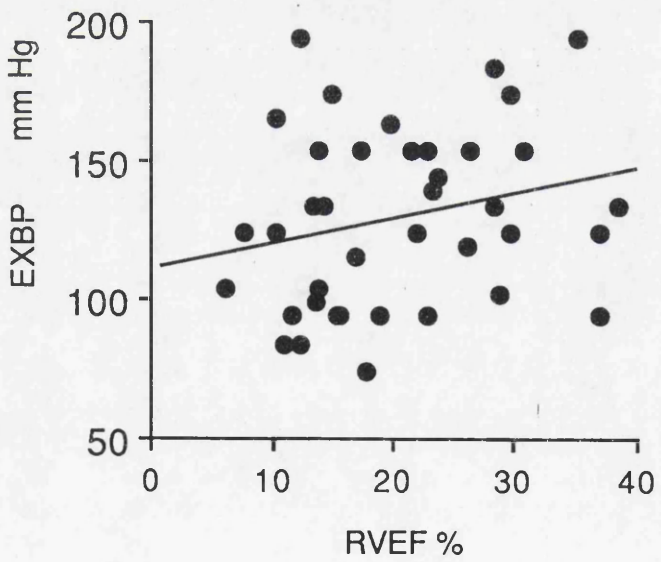
Discussion

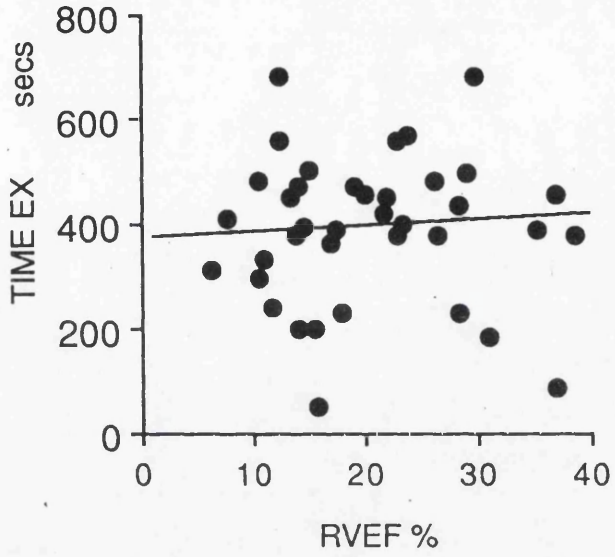
Right ventricular dysfunction following myocardial infarction is common but may be transient (due possibly to the fast recovery of the right ventricle following acute ischaemia). Right ventricular function assessed at three days was the least subject to variation, compared to measurements made at 24 hours and seven days. This is presumably because the right ventricle is sensitive to alterations in preload which acutely can change rapidly and at seven days is subject to alterations due to the patient's activity and the introduction of beta blockers etc. **(140)**.

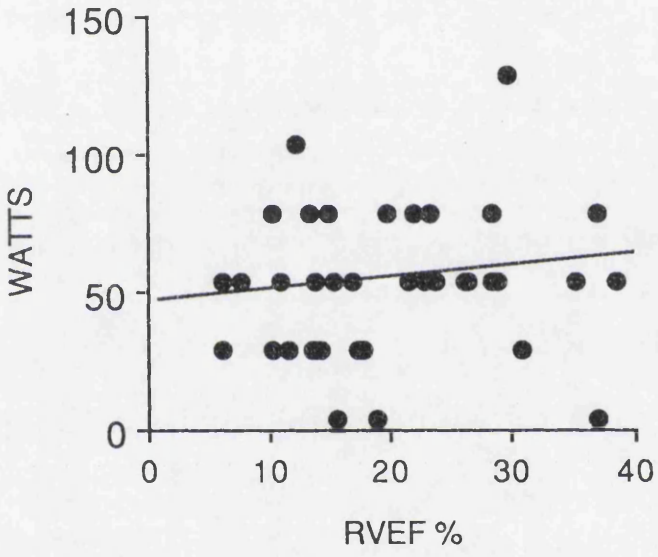
In a group of 34 patients with depressed left ventricular function and heart failure secondary to coronary artery disease, concomitant right ventricular dysfunction was found to have similar prognostic value in 16 patients (survivors of 19.9 month period) with a mean left ventricular ejection fraction of 18.7 $\pm$ 6.8% and right ventricular ejection fraction of 41.4 $\pm$ 23%. Eighteen non-survivors at 6.7 months, the mean left ventricular ejection fraction was similar (18.1 $\pm$ 10.3%) but right ventricular function was reduced (23.9 $\pm$ 10.2%, $p<0.01$) **(140,141)**. Actuarial survival curves confirmed this reduced survival in patients with right ventricular dysfunction (at 12 months 37% versus 84%, $p<0.05$).

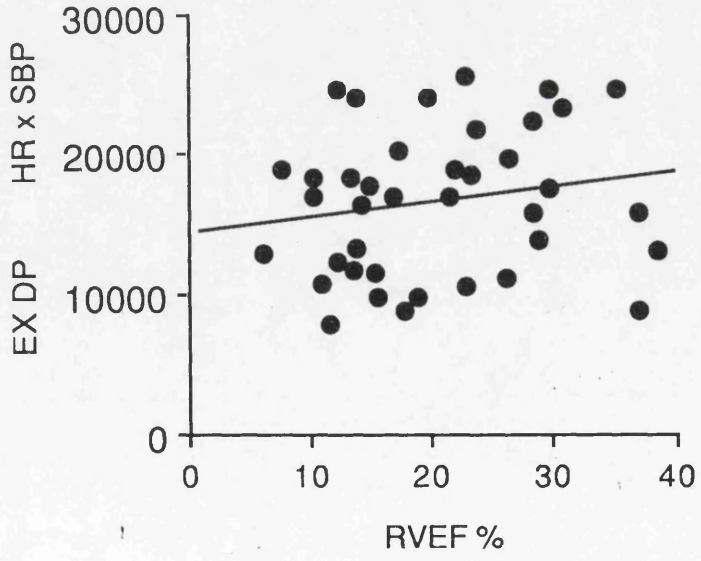
Right ventricular function appears to be an important determinant of survival in the patient with left ventricular dysfunction, secondary to coronary artery disease **(141,142)**. Function of the right ventricle is

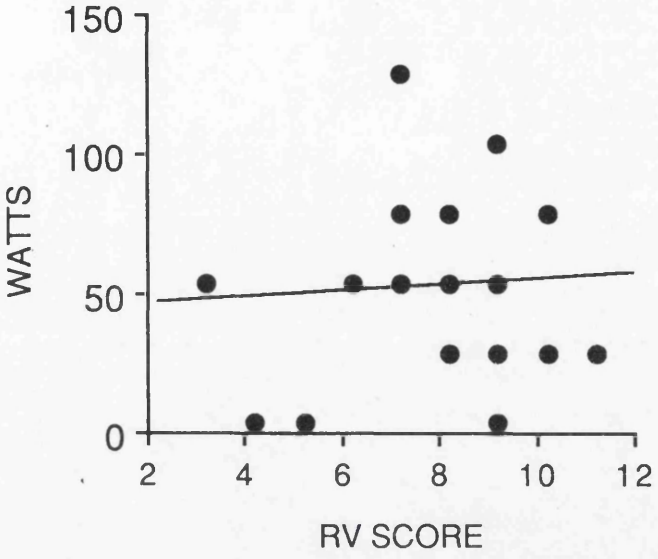

EXHR beats / min
180
160
140
120
100
80
60
0
10
20
30
40
RVEF %

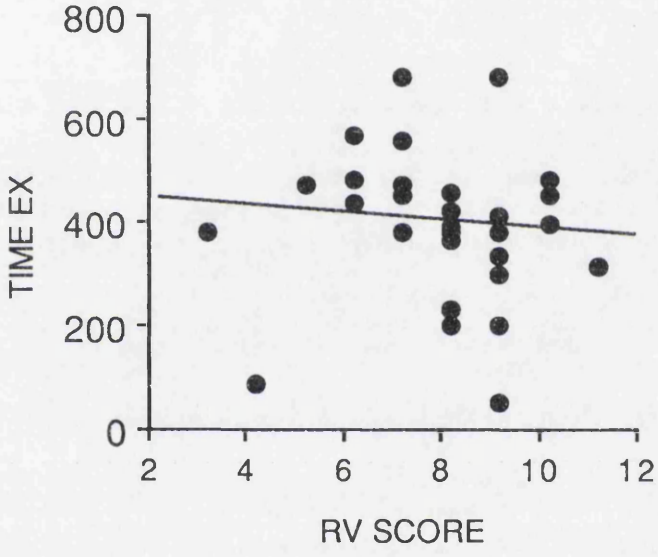

EXBP mm Hg
200
150
100
50
0
10
20
30
40
RVEF %

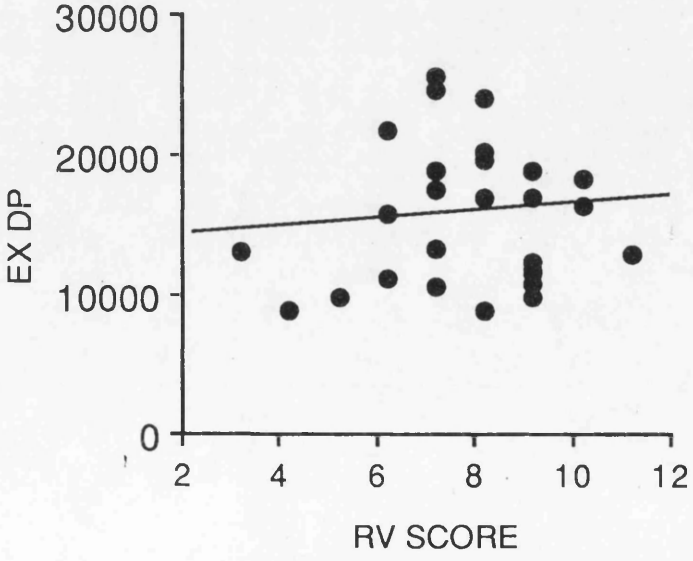

TIME EX secs
800
600
400
200
0
0
10
20
30
40
RVEF %


WATTS
150
100
50
0
0
10
20
30
40
RVEF %


EX DP HR x SBP
30000
20000
10000
0
0
10
20
30
40
RVEF %


150
100
50
0
WATTS
2
4
6
8
10
12
RV SCORE


800
600
400
200
0
TIME EX
2
4
6
8
10
12
RV SCORE


30000
20000
10000
0
EX DP
2
4
6
8
10
12
RV SCORE

probably most accurately and most conveniently assessed by radionuclide techniques.

Right Ventricular Function and Haemodynamic Parameters

In patients with left ventricular dysfunction, of a significant degree to cause the clinical signs of heart failure; often have associated right ventricular dysfunction. It is likely that in many cases this is as a consequence of right coronary artery disease and thus inferior infarction. Malfunction of the right ventricle may embarrass the pulmonary circulation and thus contribute to the patient's symptoms.

In 36 patients, known to have heart failure secondary to coronary artery disease, right ventricular function was obtained from $Tc_{99}m$ radionuclide angiography. Haemodynamic parameters, cardiac index and stroke volume index were calculated from cardiac output measurements made in triplicate, using a thermodilution catheter (see Appendix).

Exercise was performed to a symptom limited maximum, using an upright bicycle ergometer, with incremental loads of 25 watts, commending with no load, at 120 second intervals. Heart rate was obtained from the electrocardiogram which was recorded continuously and blood pressure by cuff sphygmomanometer.

Results

Detailed results are seen in Figure 17. There is little correlation of RVEF with exercise tolerance, expressed either as time of exercise or the work load achieved. Although exercise heart rate does not correlated with RVEF, there is some relationship with systolic blood pressure.

There was no correlation between right ventricular function and double product, which is an indirect measure of myocardial oxygen consumption. Similarly there was no correlation between the extent of wall motion abnormalities of the right ventricle as measure by right ventricular score (3 being normal to a maximum of 15 with all segments aneurysmal) with any of the measured parameters. These results are discussed in detail with the next section.

(b) Right Ventricular Function on Exercise

Left ventricular function can alter right ventricular function **(143,144)**. The factors that limit exercise in patients with left ventricular dysfunction are complex, and in patients with coronary artery disease, may well involve ischaemia of the ventricle. To assess the exercise response of the "failing" right ventricle, we therefore studied patients with chronic obstructive airways disease, although clearly pulmonary factors play a large part in the limitation of these patients.

Methods

Twenty five patients (seven female) aged 52 to 70 years, with severe irreversible airways limitation due to chronic bronchitis and emphysema, were studied. All patients were stable, as indicated by stable body weight, FEV_1, arterial gas tensions and the absence of respiratory infection in the previous three weeks. All were receiving diuretics and $Beta_2$ agonists, but none had been treated with digoxin or vasodilators. Left ventricular function was previously shown to be normal and no patient complained of angina.

Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometer. In 10 patients, simultaneous haemo-

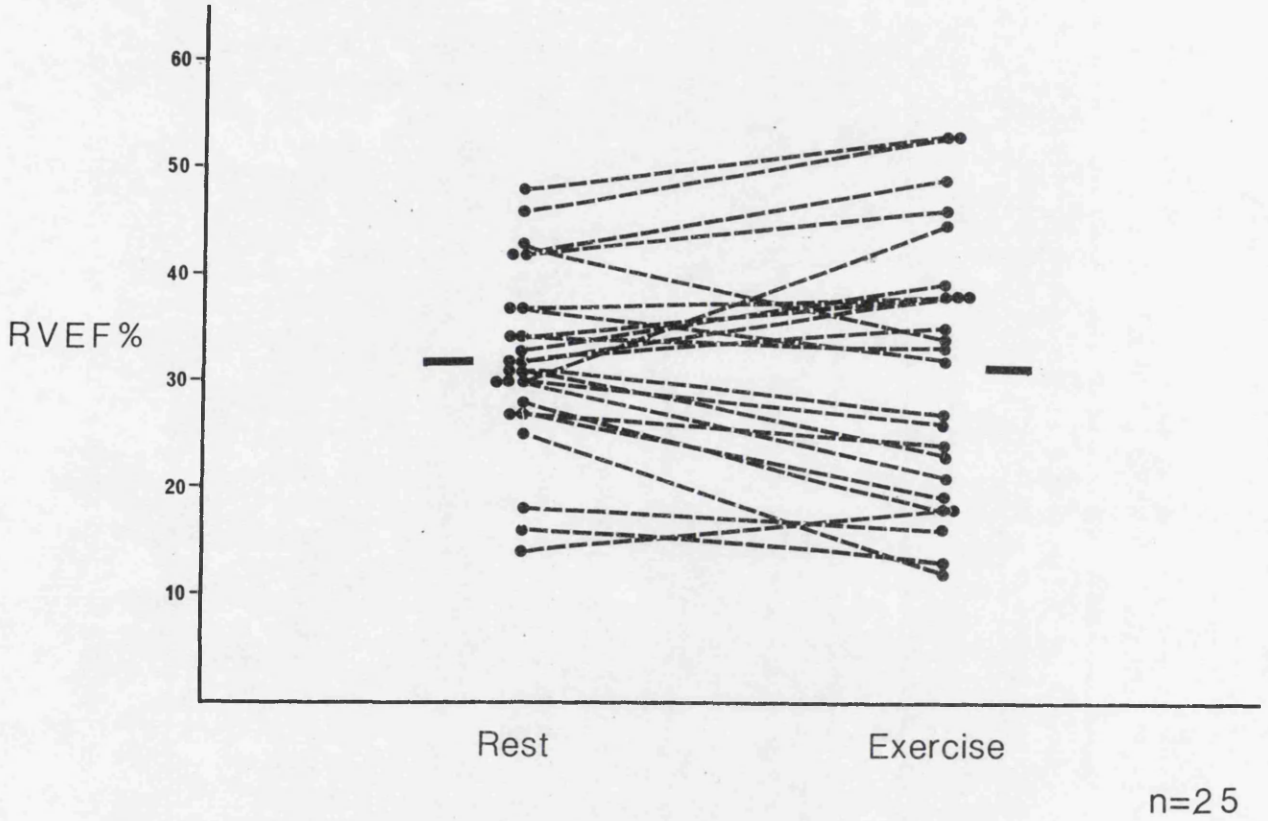
Table 9 **Chronic Obstructive Airways Disease (COAD)**

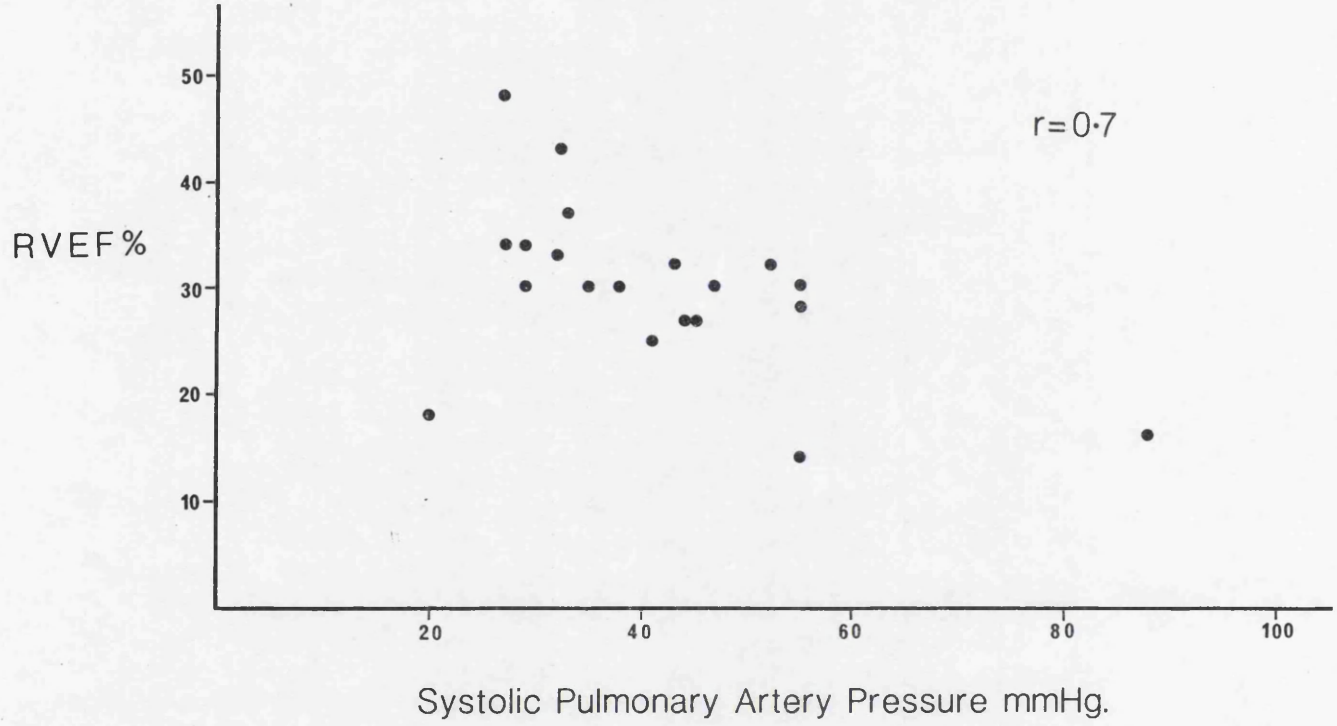
Haemodynamic changes (n = 20) ± SEM

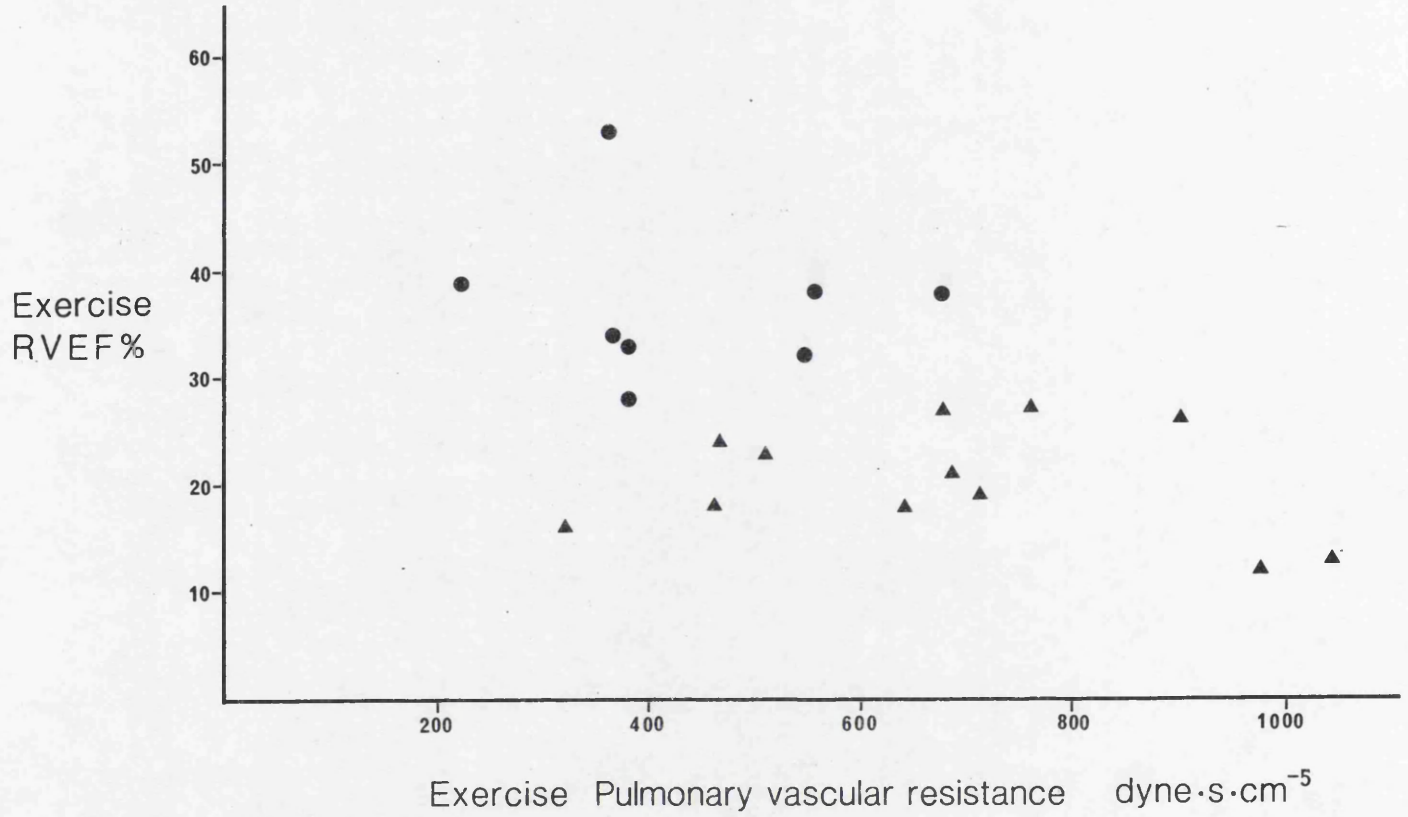
		Rest	Exercise
HR	beats/minute	88 ± 4	105 ± 5
SBP	mm.Hg.	143 ± 3	173 ± 9
DBP	mm.Hg.	81 ± 4	95 ± 5
Mean	mm.Hg.	103 ± 2	118 ± 5
CI	$l/min/m^2$	3.08 ± 0.19	4.05 ± 0.2
SI	$ml/beat/m^2$	35.1 ± 2	39.5 ± 3
SMPA	mm.Hg.	47 ± 6	71 ± 7
DMPA	mm.Hg.	23 ± 3	40 ± 2
Mean	mm.Hg.	32 ± 4	50 ± 4
PVR	$dyne\text{-}s\text{-}cm^{-5}$	524 ± 83	609 ± 72

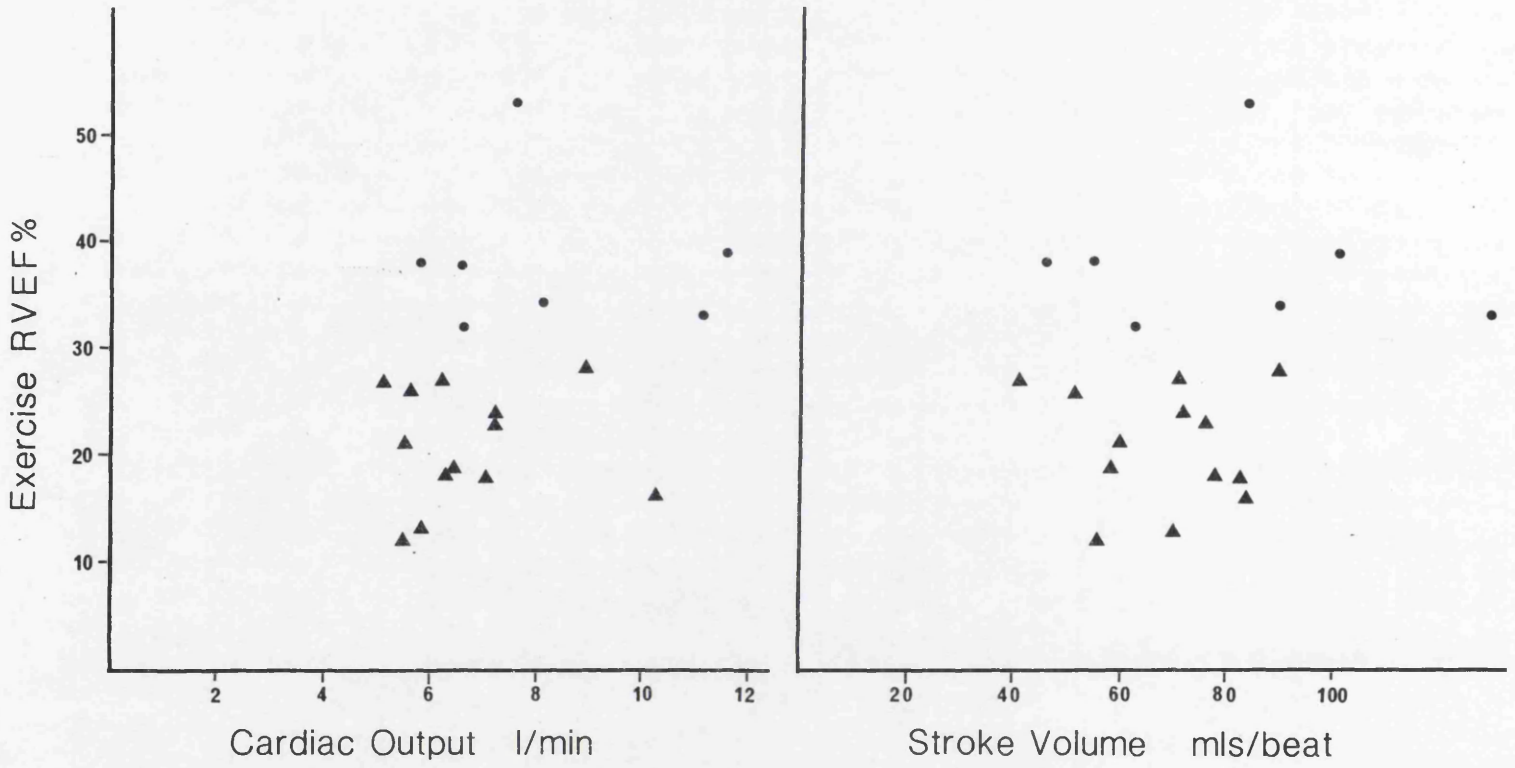
HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
CI = cardiac index
SI = stroke index
SMPA = systolic mean pulmonary artery pressure
DMPA = diastolic mean pulmonary artery pressure
PVR = pulmonary vascular resistance

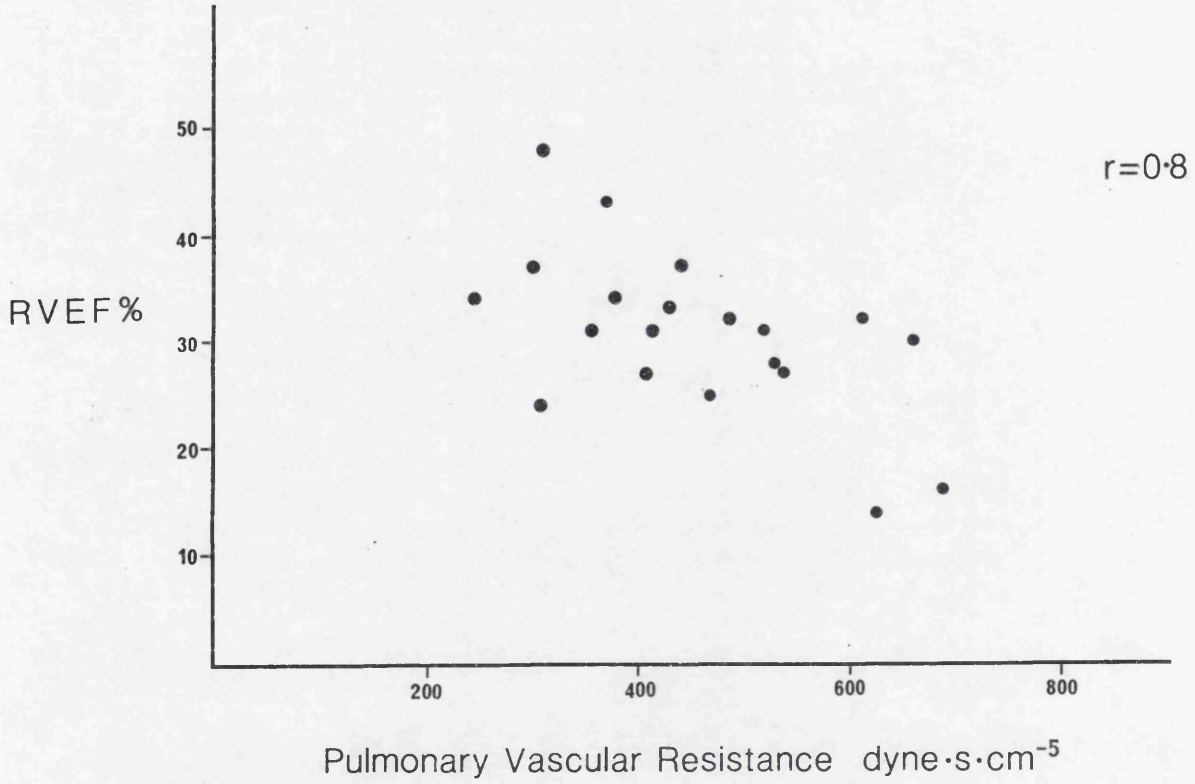
RVEF IN PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAYS DISEASE




RVEF%
50
40
30
20
10
r=0·7
20
40
60
80
100
Systolic Pulmonary Artery Pressure mmHg.


Exercise
RVEF%
60
50
40
30
20
10
200
400
600
800
1000
Exercise Pulmonary vascular resistance dyne·s·cm^{-5}


Exercise RVEF%
50
40
30
20
10
2
4
6
8
10
12
Cardiac Output l/min
20
40
60
80
100
Stroke Volume mls/beat


RVEF%
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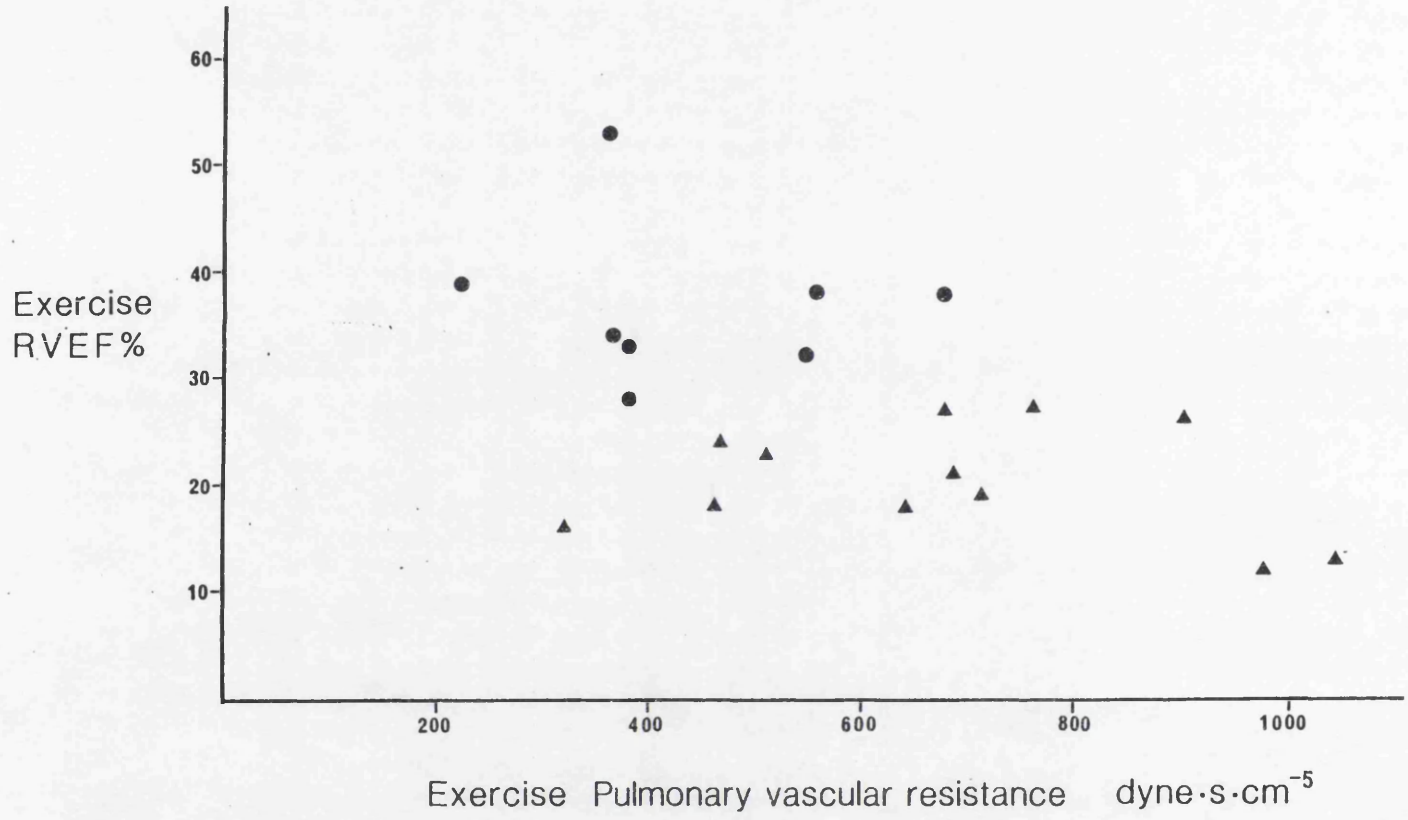
40
30
20
10
200
400
600
800
r=0·8
Pulmonary Vascular Resistance dyne·s·cm⁻⁵


Exercise
RVEF%
60
50
40
30
20
10
200
400
600
800
1000
Exercise Pulmonary vascular resistance dyne·s·cm^{-5}

dynamic measurements were obtained. Pulmonary artery pressure and pulmonary capillary wedge pressure were obtained from a Swan-Ganz catheter inserted percutaneously via a vein in the right antecubital fossa. Cardiac output was measured by the thermodilution technique in triplicate at rest and throughout exercise. Exercise was performed on an electronically braked supine ergometer using 25 watt increments in workload every three minutes.

Right ventricular function was assessed by the Xenon technique. Data were acquired with a mobile Gamma camera in the 5-10° left anterior oblique projection with a 6° caudal tilt to allow optimal separation of the heart from the lung fields. 400 MBq of Xenon-133 in 20 ml. of saline were injected intravenously and data were acquired from the time of first visualisation of activity within the right heart until activity was seen to leave it (average deposition time 25 seconds).

Cardiac index, stroke index and pulmonary vascular resistance were calculated and ejection fraction was obtained from the Xenon scans (see Appendix) **(138)**.

Results

Heart rate and blood pressure increased with exercise as did cardiac index and stroke index (see Table 9). Pulmonary artery pressure increased, with diastolic pulmonary artery pressure increasing from 23 $\pm$ 3 mm.Hg. to 40 $\pm$ 2 mm.Hg. Calculated pulmonary vascular resistance also increased with exercise.

Right ventricular ejection fraction at rest ranged from 15 to 46% with a mean of 32% and on exercise mean RVEF was 30% (range 11-53%). In

ten normal volunteers RVEF at rest was 40-55% rising by 5-15% during exercise (see Appendix). If an RVEF of below 30% was taken to represent impaired right ventricular function nine patients fell into this group. In patients with preserved right ventricular function (mean rest RVEF 39 $\pm$ 3%) with exercise RVEF increased (mean 43 $\pm$ 2%). However in patients with impaired right ventricular function (mean RVEF 26 $\pm$ 3%) mean RVEF fell with exercise (21 $\pm$ 2%).

Correlation of haemodynamic parameters with RVEF demonstrated a close relationship between RVEF and pulmonary vascular resistance (see Figure 18). However on exercise there was no definite correlation between any haemodynamic parameters and exercise RVEF response (see Figure 18).

Discussion

Although there is very extensive data regarding right ventricular function at rest in a variety of clinical conditions [for review see Ferlinz **(142)**] there is a paucity of data regarding the response of dysfunction in the right ventricle to stress. Possibly this is partly due to the early notion that the right ventricle was of little importance **(143,144,145)** but in the experiments of Rose et al **(146)** animals were unable to survive exclusion of the right ventricle from the circulation, and elevation of systemic pressure alone was unable to support pulmonary circulation, which also pertains to humans **(147)**. Problems and complications that occur following right ventricular damage are listed by Sade and Casteneda **(148)** and indeed even relatively minor injury to the right ventricle may compromise haemodynamic stability **(149)**.

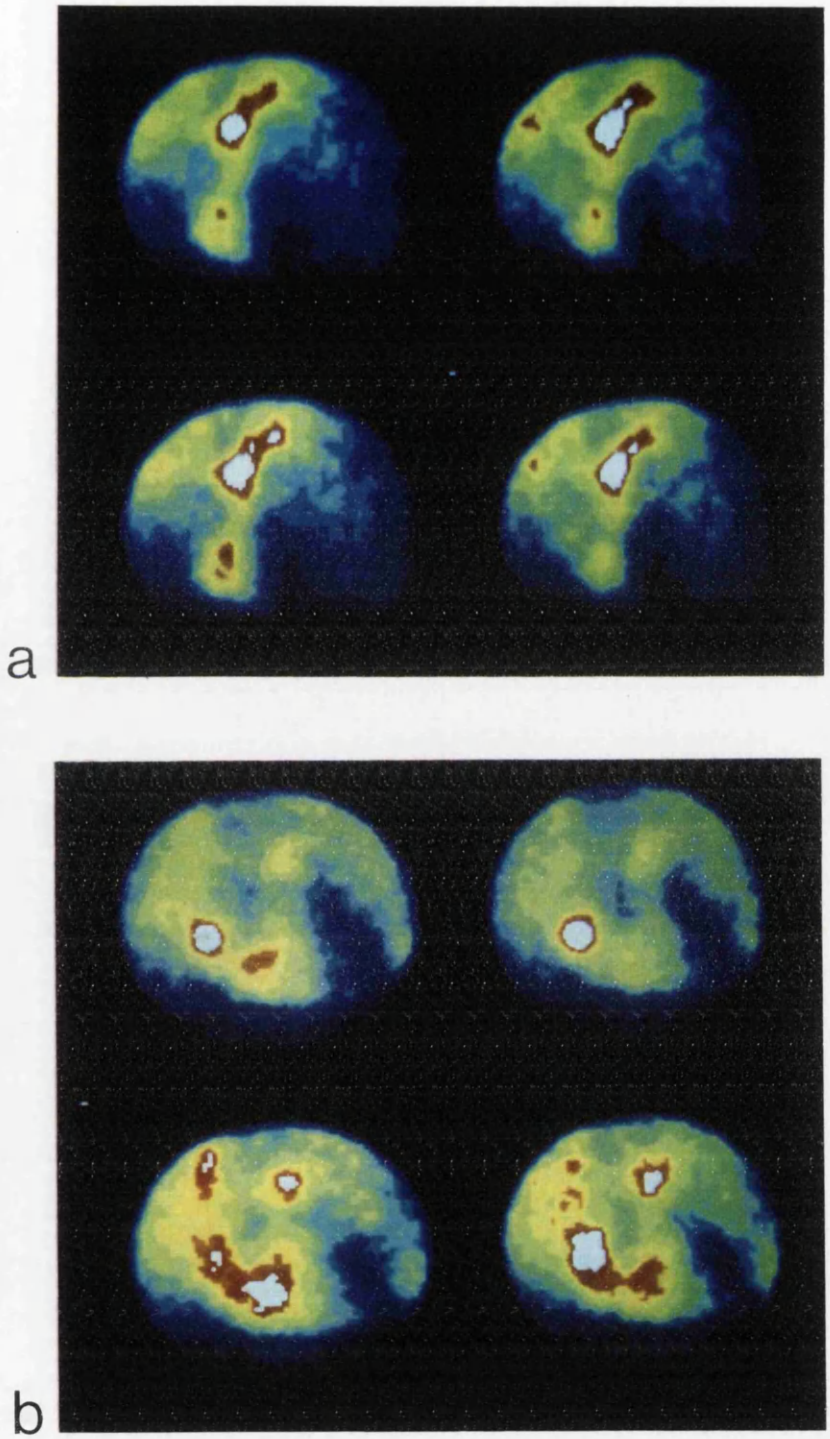


Figure 19: a) Rest end diastolic and end systolic images, normal right ventricular Xenon scan, with peak exercise images below

b) Rest and peak exercise images from a patient with COAD showing end systolic dilatation of the RV and RA

Studying right ventricular function is hampered by the shape of the right ventricle, which defies simple geometric analysis. In the normal right ventricle the shape is probably best approximated by an inverted pyramid, but with increasing dys-function this changes as the right ventricle dilates. Haemo-dynamic measurements do not reflect volume changes **(150)**. Echocardiography can provide useful information as to both right ventricular function and volume **(151,152)** but it can be very difficult to clearly identify the endocardial surface of the right ventricular free wall, especially on exercise. Radionuclides offer a method of assessing right ventricular function, which is less dependent on geometry, have been shown to be reproducible, and to correlate with angiography **(153)** and can easily be performed on exercise (see Appendix).

A previously reported study using technetium scanning demonstrated increased right ventricular ejection fraction in normal subjects and a right ventricular ejection fraction that was unchanged or decreased in 77% of patients with lung disease (including the 27% of patients with abnormal resting right ventricular function) **(154)**. Using technetium can result in difficulties in identifying the apex of the right ventricle especially if either chamber is dilated and the heart rotates with super-impostion of the left and right ventricles. The use of Xenon obviates many of these problems which is perhaps why we have been able to differentiate the response of the normal and dysfunctional right ventricle on exercise.

In patients with chronic obstructive airways disease exercise induces an increase in right ventricular afterload as reflected in the increased pulmonary vascular resistance **(155)**. The response of the right ventricle to increased pulmonary vascular resistance is initially dilatation with

consequent increase in stroke volume by the Frank Starling mechanism **(156)**. However the right ventricle is thin walled in comparison to the left ventricle and although initially contractile force increases for any given end diastolic volume the adaptive response is not as efficient as in the left ventricle, possibly limited by the availability of a compensatory increase in coronary blood flow **(157)**. Thus the increase in afterload is accompanied by depression of the right ventricular ejection fraction as is shown in this study **(135)**.

On exercise, in patients with right ventricular dysfunction end diastolic volume increased at peak exercise as did right atrial volume (see Figure 19). Changes in volume and dynamics within the right ventricle may induce tricuspid incompetence. Trivial amounts of tricuspid incompetence do not affect radionuclide measurements of right ventricular function, but where this becomes significant RVEF may be overestimated **(155)**. This, together with the small number of patients, may underlie the lack of correlation between haemodynamic measurements of afterload and right ventricular performance in these patients.

In summary, right ventricular dysfunction is exacerbated by exercise. The extent of right ventricular dysfunction appears to be related to after-load, which is in effect impedance within the pulmonary circulation.

MYOCARDIAL PERFUSION AND FLOW

(a) Introduction

Perfusion imaging has an established place in the identification and management of patients with coronary artery disease **(158)**. In patients with chronic heart failure the role is less well defined. If large

areas of myocardium are shown to have reversible ischaemia (e.g. on stress and then redistribution on a thallium scan) even patients with severe left ventricular dysfunction have been shown to benefit from revascularisation **(159)**. The ability of thallium imaging to identify viable myocardium has been called into question by some of the newer imaging modalities such as positron emission tomography but these are not widely available **(160.)**.

Using thallium, defects in regions remote from the site of myocardial infarction have been shown to be predictive of future events **(161)**. By using re-injection techniques thallium reperfusion in areas of infarct can demonstrate myocardial viability, within infarct areas. These areas are important in the clinical management of patients as they represent myocardial substrate for future ischaemic events **(162)**.

Thallium image defects on scans obtained acutely have been shown to correlate well with the site of infarction **(161)** and in animal models with size of infarction **(163)**. Other than for the assessment of the efficacy of thrombolysis, the prognostic value of imaging during the acute phase of infarction is not well documented.

Methods

One hundred and twenty consecutive patients with chest pain of cardiac origin were studied on admission to the Coronary Care Unit. Eighty two patients were subsequently shown to have sustained a myocardial infarction on the basis of electrocardiographic and enzyme changes (WHO criteria). Fifty five were male. No patient had received thrombolytic therapy.

Table 10

ALL INFARCTS

	mean	SD	COEFF VAR.(R)
Norris	6.47	2.8	0.42
I/M	25.89	10.7	0.41
P/M	33.87	14.6	0.43
EF	24.18	11.7	0.48
Vol	302.18	106.1	0.35
PCK	2242.28	1607.4	0.71
IGE	80.87	94.9	1.17

Norris = Norris Index; I/M = infarct perfusion defect; P/M = total perfusion defect in left ventricle; EF = left ventricular ejection fraction; Vol = left ventricular end diastolic volume; PCK = peak creatine kinase; IGE = infarct gram equivalents; SD = standard deviation; Coeff. var = coefficient of variation

		DEAD INFARCTS n = 24	**ALIVE n = 58**
SITE	ANT	14	22
	INF	6	32
	POST	1	1
	S/E	1	3
MEAN NORRIS		8.37	5.51
PREVIOUS MI		9	6
DEAD WITHIN 2 WEEKS			>2 WEEKS
n = 11			13
NORRIS MEAN		8.76 ± 3.4	8.04 ± 2.17
KILLIP	A	0	2
	B	3	5
	C	0	4
	D	8	2

ALL INFARCTS n = 82			DEAD INFARCTS n = 24	
	R.	P.	R.	
Norris vs IGE	-0.09		-0.23	
Norris vs P/M	0.34	$p<0.001$	0.60	$p<0.001$
I/M vs PCK	0.24		-0.13	
P/M vs PCK	0.18		0.01	
PCK vs EF	-0.04		0.02	
I/M vs IGE	0.24	$p<0.02$	-0.16	
Vol vs P/M	0.35		0.27	
EF vs IGE	-0.04		0.02	
EF vs P/M	-0.46	$p<0.001$	-0.49	$p<0.01$

DYING LESS THAN 14 DAYS n = 11

Norris vs P/M		0.8	$p<0.001$
	I/M	0.5	
	IGE	-0.29	
EF	IGE	0.29	
P/M	IGE	-0.12	
	PCK	-0.14	
P/M	IGE	0.007	

Norris = Norris Index; I/M = infarct perfusion defect; P/M = total perfusion defect in left ventricle; EF = left ventricular ejection fraction; Vol = left ventricular end diastolic volume; PCK = peak creatine kinase; IGE = infarct gram equivalents; SD = standard deviation; Coeff. var = coefficient of variation

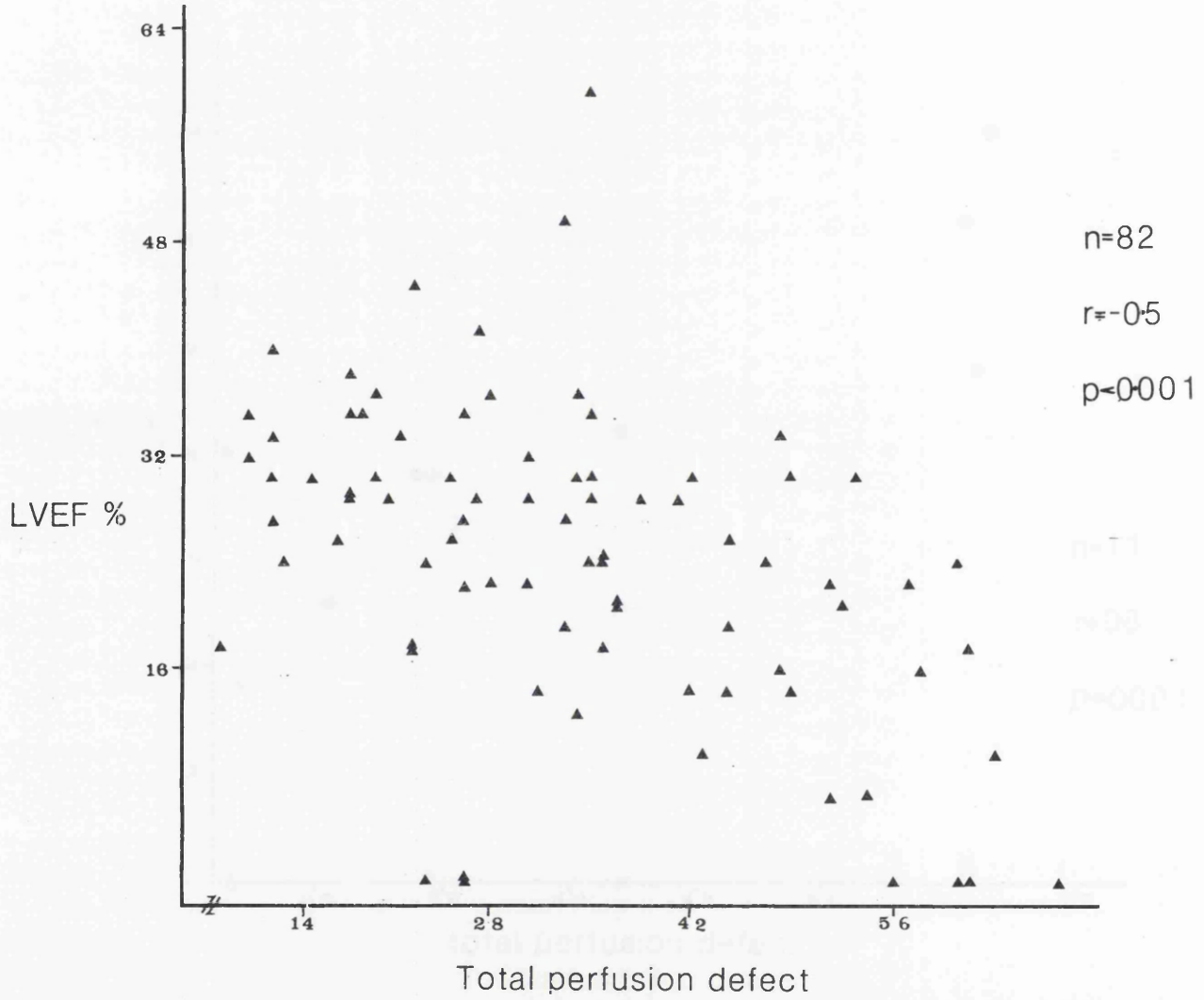
Scans were obtained following 60 MBq of intravenous thallium-201 using a mobile Gamma camera, fitted with a high sensitivity collimator, taken to the bedside. Scans were obtained in three projections (anterior, 40° left anterior oblique and 70° left anterior oblique). Acquisition was in listmode gated to the electrocardiogram and scans were obtained in all patients following relief of chest pain on admission to the Coronary Care Unit at a mean time of 86 minutes from arrival at the hospital.

Infarct severity was assessed using the Norris Index **(164)** and Killip Class **(165)**. Serial blood samples were taken for the estimation of creatine kinase and creatine kinase MB and infarct gram equivalents calculated **(166)**. All deaths were recorded and patients were re-assessed at one year. Cardiac failure was diagnosed on the basis of clinical criteria (dyspnoea on exertion, clinical signs and the use of diuretics $\pm$ admissions to hospital with heart failure or left ventricular failure).

Scans were analysed in duplicate by drawing a region of interest around the defect in the infarct site and expressing this as a percentage of the total left ventricle, infarct perfusion defect was obtained. Total perfusion defect was all areas of reduced perfusion expressed as a percentage of the total left ventricle. Ejection fraction was calculated from the gated thallium scan by the area length method (see Appendix).

Results

Of the 82 patients with myocardial infarction, in 36 the site was anterior, 39 inferior, 2 posterior and 2 subendocardial and in one patient the site was unidentified. In 65 patients this was their first documented infarct, 15 had a history of previous infarction and two possible previous


64
48
32
16
LVEF %
14
28
42
56
Total perfusion defect
n=82
r=-0·5
p<0·001

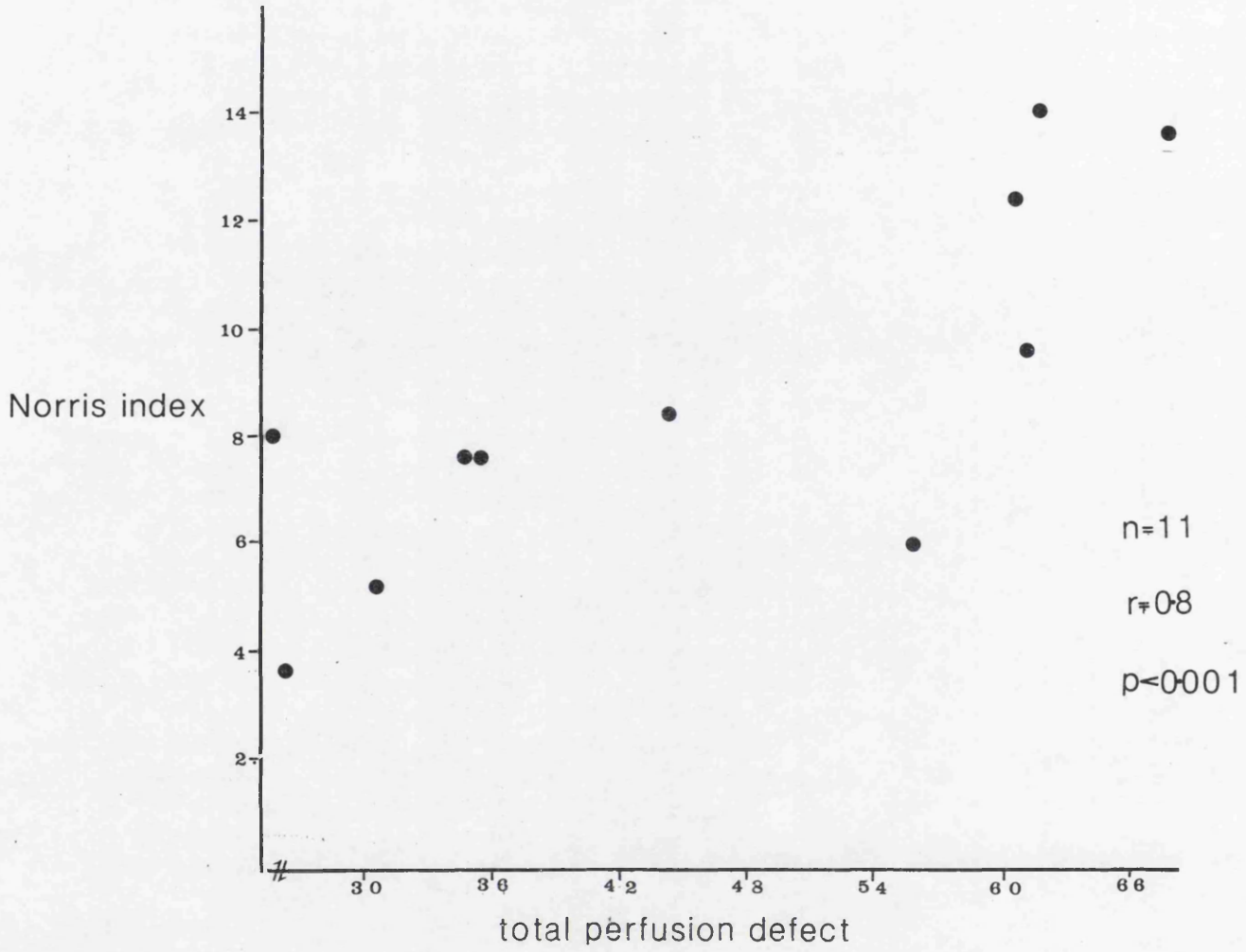

Norris index
14
12
10
8
6
4
2
3·0
3·6
4·2
4·8
5·4
6·0
6·6
total perfusion defect
n=11
r=0·8
p<0·001

Figure 21(a) **Sensitivity and specificity of Norris Index for prediction of acute and all deaths**

NORRIS INDEX > 7

	Acute deaths
Sensitivity	82%
Specificity	69%
Predictive accuracy	71%

NORRIS INDEX > 7

	All deaths
Sensitivity	71%
Specificity	76%
Predictive accuracy	74%

Figure 21(b) **Sensitivity and specificity of infarct perfusion defect for prediction of acute and all deaths**

INFARCT PERFUSION DEFECT > 30%

	Acute deaths
Sensitivity	73%
Specificity	72%
Predictive accuracy	73%

INFARCT PERFUSION DEFECT > 30%

	All deaths
Sensitivity	54%
Specificity	72%
Predictive accuracy	67%

Figure 21(c) **Sensitivity and specificity of infarct perfusion defect and Norris Index for prediction of acute and all deaths**

NORRIS INDEX & INFARCT PERFUSION DEFECT

	Acute deaths
Sensitivity	91%
Specificity	56%
Predictive accuracy	56%

NORRIS INDEX & INFARCT PERFUSION DEFECT

	All deaths
Sensitivity	91%
Specificity	56%
Predictive accuracy	56%

infarction. The mean values for Norris, volume of infarct, ejection fraction, are seen in Table 10 opposite.

Twenty four of the patients with myocardial infarction were dead at one year and 11 had died within 14 days of the index infarction. Details are seen in Table 10a. Deaths were all Hinkle Class I or Hinkle Class II **(139)** and were considered to be cardiac in origin.

Correlations between clinical indices (Norris Index), measurements of myocardial damage (CK MB infarct gram equivalents) **(166,167)**, infarct perfusion defect and total perfusion defect in the measurement of left ventricular function (LVEF) are seen in Table 10b. Ejection fraction was inversely correlated with total perfusion defect ($p < 0.001$) (Figure 20a). Similar correlations are shown for the 24 patients who died. Norris Index correlated with total perfusion defect. This finding is similar to that in the patients ($n = 11$) who died in less than 14 days from onset of infarction (Figure 20b).

From the data available as the patent was admitted to Coronary Care neither site of infarct nor a history of previous infarct were helpful in predicting subsequent deaths. Similarly peak creatine kinase, although not immediately available, was not predictive of subsequent deaths.

For all deaths where the Norris Index was greater than 7 this was predictive of subsequent mortality (predictive accuracy 74%). An infarct perfusion defect of greater than 30% of the left ventricle had a predictive accuracy of 67%. Both indices together gave an improved sensitivity (83%), but poorer specificity with an overall predictive accuracy of 63% (Figures 21a-c).

Looking at late deaths, Norris Index of greater than 7, was less sensitive but still specific. Overall predictive accuracy 73%. Infarct perfusion defects were less sensitive than specific. For acute deaths (those within 14 days) Norris Index greater than 7 and a perfusion defect of greater than 30% were both sensitive and specific but together were highly sensitive (91%) but less specific.

At one year, patients were considered to have developed heart failure on clinical criteria. Nine patients had been admitted to hospital with heart failure. Other events include two patients with infarct extension while in hospital, one reinfarction, 14 with post infarction angina, six who underwent coronary artery surgery, one who sustained ventricular tachycardia, one a cerebrovascular accident, one a brachial embolus and one renal carcinoma. Although Norris Index was helpful, total perfusion defect was the most sensitive and specific measure made acutely on admission to Coronary Care that was predictive of subsequent heart failure.

Discussion

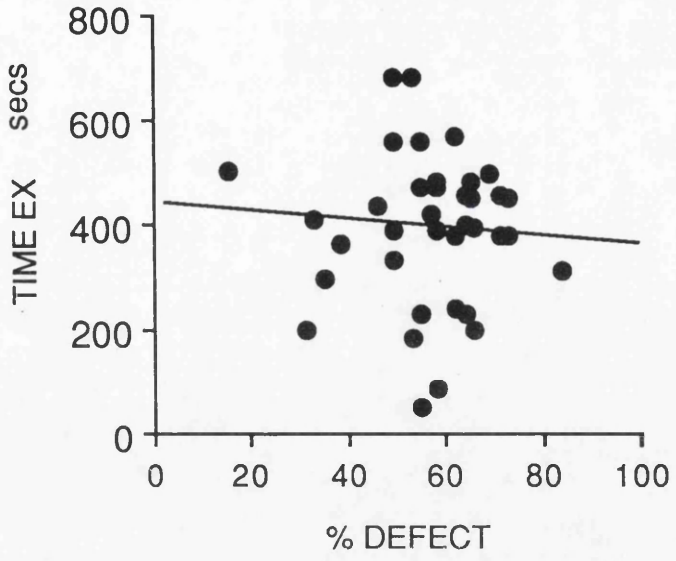
Left ventricular ejection fraction and clinical indices such as Norris Index have been established as predictive of mortality following myocardial infarction. What is less well documented is the place of perfusion imaging. Perfusion imaging has been used to establish the efficacy of acute intervention such as thrombolytic therapy **(158)** and to establish myocardium at risk following myocardial infarction **(159.160,162)**. Myocyte necrosis imaging with technetium pyrophosphate and more recently with anti-myosin antibody scintigraphy suggests that uptake in at least 50% of the myocardium was predictive of sudden death following infarct and was predictive of the severity of wall motion abnormality

(168,169). The disadvantage of necrosis imaging is the time required for optimal uptake of the tracer (48 hours). Gated thallium imaging was performed as the patient was admitted to Coronary Care. Our previous work in an animal model confirmed that in vivo perfusion imaging of infarct size correlated well with infarct extent using conventional staining techniques **(163)**. The extent of perfusion defect in patients (greater than 30%) was predictive especially of acute death (within 14 days). Presumably late deaths are less dependent on the extent of acute ischaemia. The choice of a total perfusion defect of greater than 30% of the left ventricle was based on the fact that this was the best discriminator of subsequent events. In the right model of heart failure Pfeffer et al noted an abrupt increase in left ventricular end diastolic pressure in 13 of 14 rats when the infarct size was greater than 46% and when the infarct size was greater than 30%, few rats could generate or develop pressure within two standard deviations of normal **(170,171)**.

Total perfusion defect, on admission to Coronary Care, was also predictive of the patients that would subsequently develop heart failure. Presumably myocardial infarction and its effective stress of the myocardium so that perfusion defects reflect the total myocardium at risk from ischaemia and it is this that provides the substrate of the myocardium that "fails".

(b) Perfusion Imaging in Heart Failure

Most perfusion imaging studies have concentrated on identifying viable myocardium within sites of myocardial infarction amenable to revascularisation **(172,173)**. There is little information as to perfusion patterns in patients with heart failure secondary to coronary artery disease. If exercise induced myocardial ischaemia is a significant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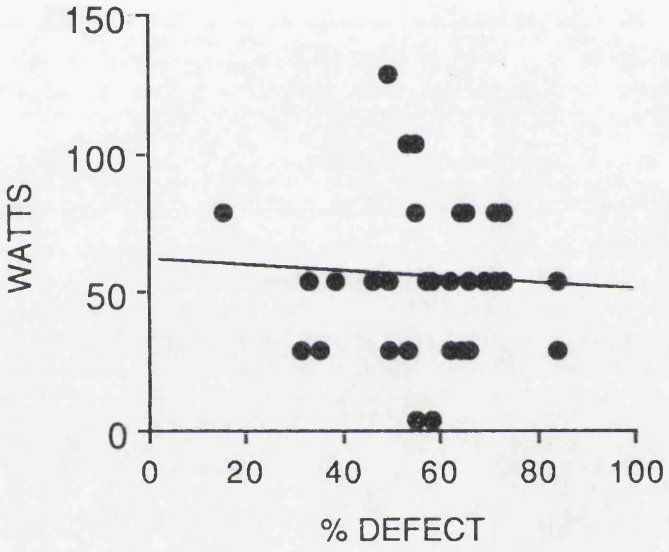
WATTS
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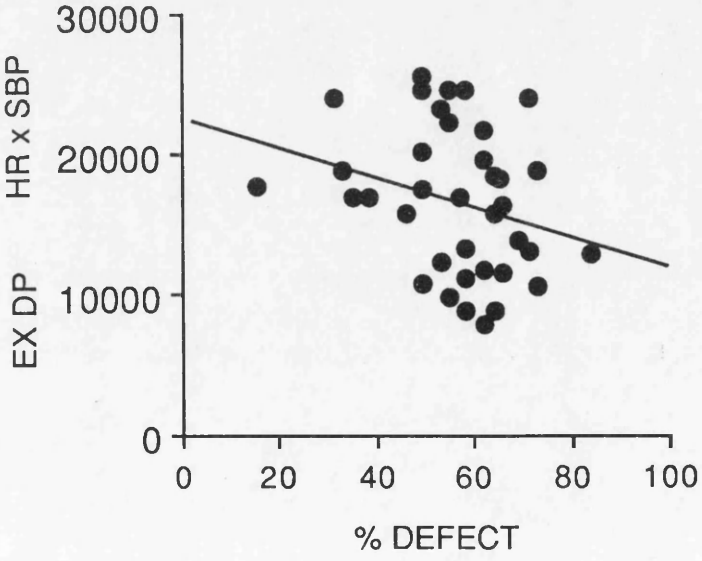
EX DP HR x SBP
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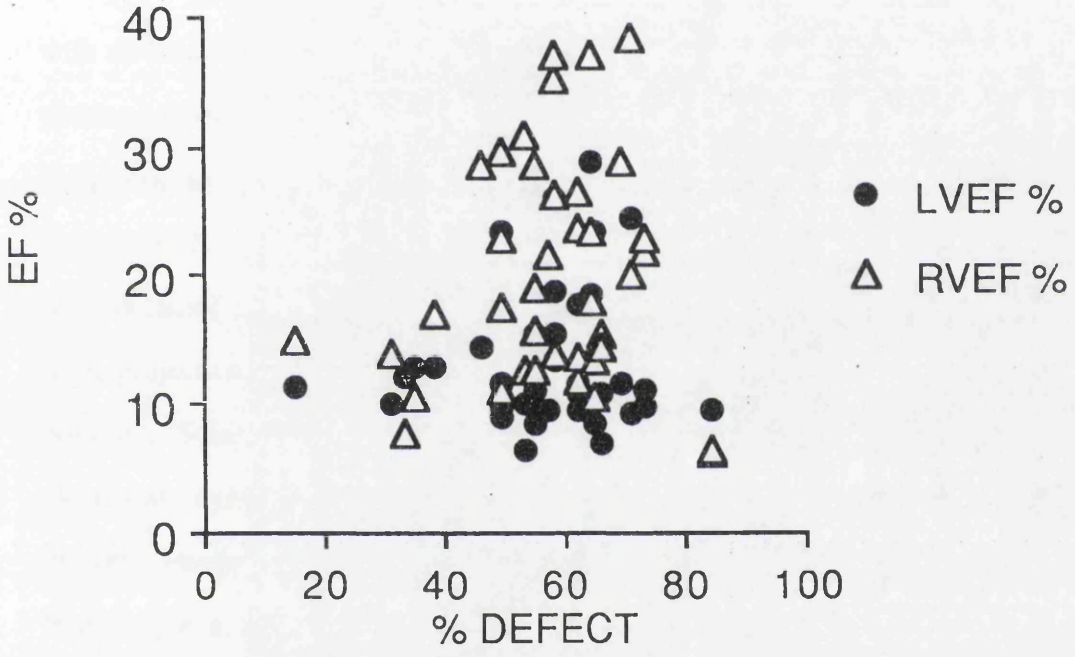
% DEFECT


40
30
20
10
0
EF %
0
20
40
60
80
100
% DEFECT
LVEF %
RVEF %

determinant of the limitation of patients, the extent of myocardial involvement may relate to exercise capacity.

Methods

Forty patients were studied with established heart failure secondary to angiographically documented coronary artery disease, and on optimal treatment with diuretics and vasodilators referred for consideration for transplantation. Patients performed upright symptom limited exercise on a bicycle ergometer, using a standard protocol already described (starting with no load, 25 watt increments every 2 minutes). Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometer. 60-80 MBq of thallous chloride were injected intravenously 20-30 seconds prior to the termination of exercise. Scans were obtained using a mobile Gamma camera for five minutes in each of three projections (anterior, 40° left anterior oblique and 70° left anterior oblique). Scintigraphic data was collected in listmode, gated to the electrocardiogram. Data was retrospectively constructed into eight images. Image analysis was reported from a cine group display of eight frame representations of the cardiac cycle using a 9 point spatial and 121 temporal smooth. Perfusion abnormalities were expressed as a percentage of the total left ventricle. Left ventricular ejection fraction was obtained from the technetium99m scan as previously described.

Results

Substantial perfusion defects were seen in most patients (range 13-82% of the left ventricle). Detailed results are seen in Figure 22. There is some relationship between exercise heart rate and blood pressure, but the closest, inverse relationship is with double product. Double product - the product of heart rate and systolic blood pressure is generally

recognised as an indirect measure of myocardial oxygen consumption. Interestingly, there was no relationship between total perfusion defect and either left or right ventricular ejection fraction.

Discussion

Total myocardial perfusion defects on exercise did not correlate with exercise capacity in our patients with heart failure but there was an inverse relationship with double product, which is an indirect measure of myocardial oxygen consumption. All these patients had previous angiographically documented coronary disease or myocardial infarctions and had various degrees of left ventricular dysfunction. Left ventricular systolic function has previously been shown not to correlate with exercise capacity **(175)**. Thus exercise induced ischaemia may play a part in exercise limitation.

Using radiotracers such as thallium-201 which reflect relative uptake rather than absolute flow in patients with previous myocardial infarction, regions of reduced uptake in areas remote from the infarction may not be identified. By using a gating technique blurring of the image due to cardiac motion is less obvious and the end diastolic image can be identified. In an animal model we have shown that the perfusion defect in the end diastolic image correlated best with conventional measures of myocardial damage and microsphere images **(163)**. Other imaging modalities such as positron emission tomography using F18 FDG, N13 ammonia or oxygen-15 or FDG/ammonia mismatch may provide a more accurate assessment of ischaemic myocardium but this technique is not widely available **(180)**. In summary, myocardial perfusion defects seen in patients with heart failure suggest that this may play a part in exercise limitation.

MYOCARDIAL FLOW

Myocardial flow in patients with chronic heart failure

With the declining incidence of rheumatic heart disease, the commonest cause of chronic heart failure is now coronary artery disease. There is evidence to suggest that this can be associated with different patterns of coronary arterial stenosis ranging from triple vessel disease to involvement of the microcirculation and "ischaemic cardiomyopathy" **(184)**. Rodgers et al investigated the patterns of coronary artery stenosis in 145 patients of whom 106 had chronic congestive heart failure **(185)**. Just over half (54%) had single vessel disease while the rest had double or triple vessel disease. In current cardiological practice, the vast majority of patients with heart failure have multiple vessel disease (often with previous coronary surgery) (unpublished observations).

In patients with cardiomyopathy myocardial perfusion may be decreased **(186)**. In the presence of normal epicardial vessels various explanations offered include the presence of myocardial fibrosis, the reduction of myocardial oxygen demand related to decreased contractility and possible changes in the microcirculation.

The measurement of myocardial flow and oxygen consumption in patients who have heart failure have been conflicting.

Methods

Eighteen patients (2 females) aged 37-61 years with a mean of 52 years with ischaemic left ventricular dysfunction (left ventricular ejection fraction $<30\%$) were studied. All patients had New York Heart Association Class III heart failure and had been stable on therapy with

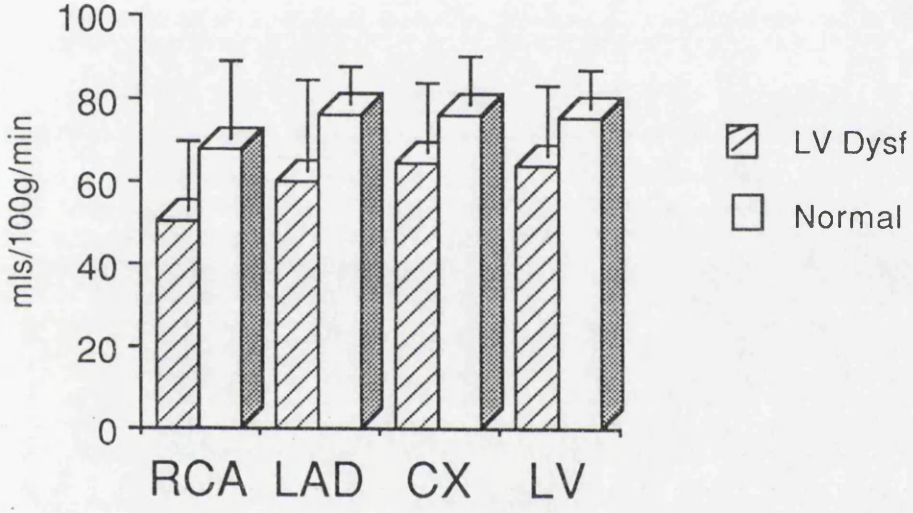
Table 11

XENON n = 18

		Mean ± SD		
HR	beats/min	75 ± 12.7	CSF	125 ± 34 ml/min
SBP	mm.Hg.	120 ± 24	A-V	11.45 ± 1.71 vol%
DBP	mm.Hg.	77 ± 10	MVO_2	1428.9 ± 429.5
Mean	mm.Hg.	94 ± 15		
DMPA	mm.Hg.	14 ± 5.5		
CI	l/min/m^2	2.63 ± 0.39		
SVI	ml/beats/m^2	35.8 ± 6.7		
SVR	dyne-s-cm^{-5}	1576 ± 503		

MYOCARDIAL FLOW		Normal
RCA	50.0 ± 16.8 ml/100 g/min	67.5 ± 19.1
LAD	60.2 ± 21.7	76.1 ± 9.1
Cx	64.7 ± 16.3	76.1 ± 11.7
LV	63.6 ± 16.9	75.5 ± 8.8

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; DMPA = diastolic mean pulmonary artery pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; CSF = coronary sinus flow; A-V = arteriovenous oxygen difference; MVO_2 = myocardial oxygen consumption


100
80
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40
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mls/100g/min
RCA
LAD
CX
LV
LV Dysf
Normal

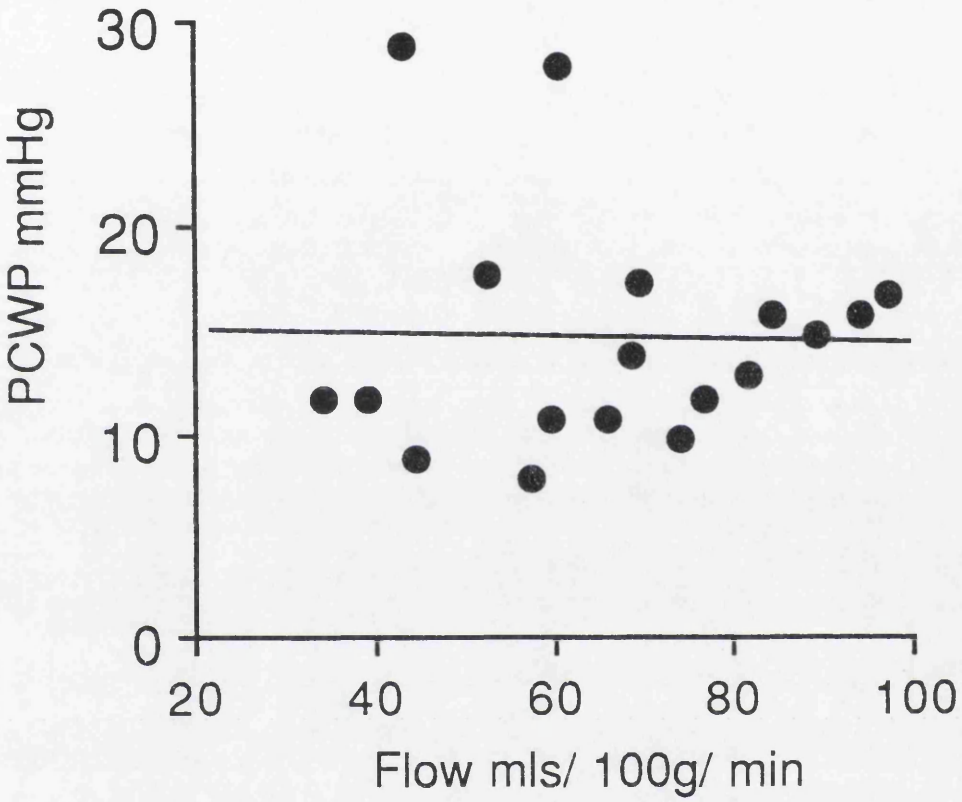


Fig. 24 Myocardial Flow vs PCWP

diuretics and vasodilators. Therapy was omitted for 24 hours prior to study. Patients were undergoing routine angiography for diagnostic purposes.

Heart rate was obtained from the electrocardiogram and blood pressure from an intra-arterial line in the ascending aorta. Pulmonary artery and pulmonary capillary wedge pressures were measured via a Swan-Ganz catheter inserted percutaneously via the femoral vein. Cardiac output was obtained by the thermodilution technique. Coronary sinus flow was also measured by thermodilution using a Wilton Webster catheter placed in the coronary sinus. This catheter has a sampling port and together with simultaneous arterial samples obtained via the femoral catheter myocardial oxygen consumption can be measured.

Myocardial flow was obtained by the Xenon-133 clearance technique. 200 MBq of Xenon-133 was injected intracoronary and images were acquired using a mobile Gamma camera fitted with a biplane collimator. Data were acquited in listmode and analysed retrospectively as outlined in the Appendix. In brief, a region of interest is described around the left ventricle and each of the territories supplied by the major coronary vessels. Washout curves are constructed and after suitable background subtraction a monoexponential is fitted from peak activity to 30 seconds. Curves can then be calculated using the Kety Schmidt formula **(190)**.

Results

Haemodynamic variables are shown Table 11, and as would be expected in this group of patients pulmonary artery end diastolic pressure is elevated and cardiac index is reduced. Resting coronary sinus flow, arteriovenous oxygen difference are also normal and mean left

ventricular flows from Xenon washout are also within normal (Figure 23). Myocardial flow is plotted against wedge pressure and, as can be seen, there is little correlation (Figure 24).

Discussion

In this group of patients resting myocardial flow was similar to normal values. Since a large proportion of coronary blood flow to the left ventricle occurs during diastole and raised end diastolic pressure could induce increased wall tension and thus reduce coronary flow, this was plotted against pulmonary capillary wedge pressure. However there was no correlation.

Henry et al **(191)** using helium found a decreased coronary flow in patients with ventricular dysfunction and with an associated decrease in myocardial oxygen consumption, but in contrast Porinn et al **(192)** demonstrated that coronary sinus flow was similar in patients with congestive cardiomyopathy to that found in patients with angina.

It is not altogether surprising that resting myocardial flow is normal as various compensatory mechanisms maintained cardiac flow. Even in areas of myocardial infarction, collateral flow will be induced and indeed can replace the native vessel (see Figure).

In summary, resting flow to the myocardium in patients with left ventricular dysfunction appears to be maintained presumably by a variety of compensatory mechanisms.

REFERENCES FOR IDENTIFICATION OF PATIENTS WITH HEART FAILURE

1. Lewis T
   Diseases of the Heart.
   1933

2. Braunwald E
   Clinical manifestations of heart failure. Chapter 15 in Heart Disease: A Textbook of Cardiovascular Medicine. Ed. Braunwald E. WB Saunders, Phildalphia, London, Toronto.

3. Criteria Committee New York Heart Association Inc: Diseases of the Heart and Blood Vessels Nomenclature and Criteria for Diagnosis. Ed 8. Boston Little Brown and Co. 1964; p114.

4. Ungerleider HE, Gubner R
   Normogram for prediction of transverse diameter of heart from height and weight 1942. In: Radiological Anatomy and Heart Size.

5. McKee PA, Castelli WP, McNamara, Karnes WB
   The Natural History of Congestive Heart Failure: The Framingham Study.
   N Engl J Med 1971; 285,26: 1441-1446.

6. Harlan WR, Oberman A, Grimm R, Rosah RA
   Chronic congestive heart failure in coronary artery disease: clinical criteria.
   Ann Int Med 1977; 86,2: 133-138.

7. Franciosa JA
   Epidemiologic patterns, clinical evaluation and long term prognosis in chronic congestive heart failure.
   Am J Med 1986; 80 (suppl 2B): 14-21.

8. Franciosa JA, Ziesches Wiles M
   Functional capacity of patients with chronic left ventricular failure: relationship of bicycle exercise performance to clinical and haemo-dynamic characterisation.
   Am J Med 1979; 67: 460-466.

9. Wilson JR, Schwartz JS, St John Smith M et al
   Prognosis in severe heart failure: relation to haemodynamic measurements and ventricular ectopic activity.
   J A C C 1983; 2,3: 403-410.

10. Franciosa JA, Park M, Levine TB
Lack of circulation between exercise capacity and indicies of resting left ventricular performance in heart failure.
Am J Cardiol 1981; 47: 33-39.

11. Maranz PR, Tobin JN, Wassertheil-Soller S et al
The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria.
Circulation 1988; 77: 607-612.

12. Carlson KJ, Lee DC-S, Goron AH
An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients.
J Chron Dis 1985; 38: 733-739.

13. Measurement of Cardiothoracic Ratio.
Radiological Anatomy and Heart Size, p 6-8.

14. Jonsell S
Method for dtermination of heart size by teleroentgenography (heart volume index).
Acta Radiol 1939; 20: 325-340..

15. Fischer LD, Alderman EL, Mock MB et al
Statistical considerations in evaluating treatment of advanced congestive heart failure. The principal investigators of CASS and their associates The National Heart Lung and Blood Institute Coronary Artery Surgery Study. American Heart Association Mingograph 79.
Circulation1963; Part II: 181.

16. Forrester JS, McHugh TJ, Diamond G et al
Rapid assessment of cardiopulmonary haemodynamics in acutely ill patients utilising a single right heart catheter.
Am J Cardiol 1970; 26: 633.

17. Swan HJC, Ganz W, Forrester JS et al
Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter.
New Engl J Med 1970; 283: 447.

18. Amsterdam E, Hughes JL, Iben A et al
Surgery for acute myocardial infarction. In: Shock in Myocardial Infarction. Ed Gunnar RM, Loeb HS, Rahimtoola SH. Grune & Statton 1974; p257: New York.

19. Sarnoff SJ, Berglund E
Starling's law of the heart studied by simultaneous right and left ventricular function curves in the dog.
Circulation 954; 9: 706.

20. Sarnoff SJ, Mitchell JH
The regulation of the performance of the heart.
Am J Med 1961; 30: 747.

21. Franciosa JA, Wilen M, Ziesche S, Cohn JN
Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy.
Am J Cardiol 1983; 51: 831-836.

22. Swan HJC, Ganz W
Haemodynamic measurements in clinical practice: A decade in review.
J Am Coll Cardiol 1983; 1: 103-113.

23. Hatle L, Stake G, Stortstein O
Chronic myocardial disease. II Haemodynamic findings related to long term prognosis.
Acta Med Scand 1976; 199: 407.

24. Yattean RF, Peter RH, Behar VS et al
Ischaemic cardiomyopathy: the myopathy of coronary artery disease.
Am J Cardiol 1974; 34: 520.

25. Hamby RI
Primary myocardial disease: a prospective clinical and haemodynamic evaluation in 100 patients.
Medicine 1970; 49: 55.

26. Fuster V, Gersh ER, Tajik AJ et al
The natural history of idiopathic dilated cardiomyopathy.
Am J Cardiol 1981; 47: 525.

27. Franciosa JA
Why patients with heart failure die: haemodynamic and functional determinants of survival.
Circulation 1987; 74(suppl IV) IV: 20-27.

28. Massie B, Ports T, Chatterjee K et al
Long-term vasodilator therapy for heart failure. Clinical response and its relationship to haemodynamic measurements.
Circulation 1981; 63: 269.

29. Creager MA, Faxon DP, Halperin JL
Determinants of clinical response and survival in patients with congestive heart failure treated with captopril.
Am Heart J 1982; 104: 1147.

30. Factors influencing the one year mortality of dilated cardiomyopathy.
Am J Cardiol 1984; 54: 147.

31. Lee WH, Packer M
Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure.
Circulation 1986; 73: 257.

32. Cohn JN, Levine TB, Olivari MT
Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure.
N Engl J Med 1984; 311: 819.

33. Viqieerat CE, Daly P, Swedberg K, et al
Endogenous catecholamine levels in chronic heart failure: relation to the severity of haemodynamic abnormalities.
Am J Med 1985; 78: 455.

34. Lee WH, Packer M
Importance of right ventricular function as the primary determinant of clinical response and long-term survival in patients with severe heart failure treated with converting-enzyme inhibitors.
J Am Coll Cardiol 1985; (abst) 5: 461.

35. Hilton SM
Central nervous origin of vasomotor tone.
Adv Physiol 1980; 8: 1-12.

36. Harris P
Congestive cardiac failure: central role of the arterial blood pressure.
Br Heart J 1987; 58: 190-203.

37. Cockcroft A, Adams L, Guz A
Assessment of breathlessness.
Quart J Med 1989; 72,268: 669-678.

38. McGavin CR, Gupta SP, McHardy GHR
Twelve-minute walking test for assessing disability in chronic bronchitis.
Br Med J 1976; 1: 822-823.

39. Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM
Two, six and 12 minute walking tests in respiratory disease.
Br Med J 1982; 2: 1607-1608.

40. Guyatt GH, Sullivan MJ, Thomson PI et al
The 6-minute walk a new measure of exercise capacity in patients with chronic heart failure.
Can Med Assoc J 1985; 132: 919-923.

41. Lipkin DP, Scriven AJ, Crake T, Poole Wilson PA
Six minute walking test for assessing exercise capacity in chronic heart failure.
Br Med J 1986; 292: 653-655.

42. Parameshwar J, Hedambrink J, Sparrow J et al
A new exercise test for the assessment of heart failure: use of a self powered treadmill.
Br Heart J 1989; 61: 421-425.

43. Astrand P-O, Rodahl K
Textbook of Work Physiology 1970, New York, McGraw-Hill.

44. Hermansen L, Ekblom B, Saltin B
Cardiac output during submaximal and maximal treadmill and bicycle exercise.
J Appl Physiol 1970; 29: 82.

45. Hermansen L, Saltin B
Oxygen uptake during maximal treadmill and bicycle exercise.
J Appl Physiol 1969; 26: 31.

46. Kamon E, Pandolf KB
Maximal aerobic power during laddermill climbing uphill running and cycling.
J Appl Physiol 1972; 32: 467.

47. Kaltenbach M, Bischofs W, Hopf R, Bohmer D
Physical and physiological work in treadmill testing compared with other types of ergometry.
Eur Heart J 1982; 3: 93-99.

48. Davies SW, Bailey J, Keegan J et al
Pulmonary capillary permeability in chronic left heart failure.
Br Heart J 1989; p477.

49. Haskell WL, Savin W, Oldridge N, Debusk R
Factors influencing estimated oxygen uptake during exercise testing soon after myocardial infarction.
Am J Cardiol 1982; 50: 299-304.

50. Blackburn H
Measurement in Exercise Electrocardiography 1969; Charles C Thomas, Springfield, Illinois. p269.

51. Naughton JP, Helterstein HK, Mohler K
Exercise Testing and Exercise Training in Coronary Heart Disease. 1973, New York, Academic Press.

52. McDonough JR, Kusumi F, Bruce RA
Variations in maximal oxygen intake with physical activity in middle-aged men.
Circulation 1970; 51: 743-751.

53. Higginbotham MB, Morris KG, Williams RS et al
Physiologic basis for the age-related decline in aerobic work capacity.
Am J Cardiol 1986; 57: 1374-1379.

54. Wilson JR, Martin JL, Schwartz D, Ferraro N
Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle.
Circulation 1984; 69,6: 1079-1087.

55. Zelis R, Nellis SH, Longhurst J, Lee G, Mason DT
Abnormalities in the regional circulations accompanyig congestive heart failure.
Prog Cardiovasc Dis 1975; 18: 181-199.

56. Wilson JR, Martin JL, Ferraro N
Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: Role of cardiac pump dysfunction as determined by the effect of dobutamine.
Am J Cardiol 1984; 53: 1308-1315.

57. Massie BM, Conway M, Rajagopalas B et al
Skeletal muscle metabolism during exercise under ischaemic conditions in congestive heart failure: evidence for abnormalities unrelated to blood flow.
Circulation 1988; 78: 320-326.

58. Massie BM, Conway M, Yonge R et al
Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow.
Circulation 1987; 5: 1009-1019.

59. Lipkin DP, Jones DA, Round JM, Poole Wilson PA
Abnormalities of skeletal muscle in patients with chronic heart failure.
Int J Cardiol 1988; 18: 187-195.

60. Mohserifar Z, Amin DK, Shah PK
Regional distribution of lung perfusion and ventilation in patients with chronic congestive heart failure and its relationship to cardiopulmonary haemodynamics.
Am Heart J 1989; 117,4: 887-891.

61. Reddy HK, McElroy PA, Janicki JS, Weber KT
Response in oxygen uptake and ventilation during stair climbing in patients with chronic heart failure.
Am J Cardiol 1989; 63: 222-225.

62. Buller N
Exercise testing in chronic heart failure.
Topics in Circulation 1987; 2,2: 2-3.

62. Leblanc P, Bowie DM, Summers E, Jones NL, Killian KJ
Breathlessness and exercise in patients with cardiorespiratory disease.
Am Rev Respir Dis 1986; 133: 21-25.

63. Rubin SA, Brown HV
Ventilation and gas exchange during exercise in severe chronic heart failure.
Am Rev Respir Dis 1984; 129: Suppl S63-64.

64. Patterson JA, Naughton J, Pietras RJ, Gunnar RM
Treadmill exercise in assessment of the functional capacity of patients with cardiac disease.
Am J Cardiol 1972; 30: 757-762.

65. Engles R, Ray R, Higgins CB et al
Clinical assessmentand follow-up of functional capacity in patients with chronic congestive cardiomyopathy.
Am J Cardiol 1982; 49: 1832-1837.

66. Rubin SA, Chatterjee K, Gelberg HJ et al
Paradox of improved exercise but not resting hemodynamics with short-term prazosin in chronic heart failure.
Am J Cardiol 1979; 43: 810-815.

67. Yamabe H, Kobayashi K, Fujitani K et al
Exercise capacity correlating to exercise haemodynamics in coronary artery disease.
Jpn Heart J 1985; 26,2: 143-154.

68. Poole Wilson PA
The origin of symptoms in patients with chronic heart failure.
Eur Heart J 1988; 9H: 49-53.

69. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP
Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure.
Circulation 1982; 65,6: 1213-1223.

70. Wasserman K, Whipp BJ
State of the art: exercise physiology in health and disease.
Am Rev Respir Dis 1975; 122: 219-249.

71. Naimark A, Wasserman K, McIlroy MB
Continuous measurement of ventilatory exchange ratio during exercise.
J Appl Physiol 1964; 19: 644-652.

72. Simonton CA, Higginbotham MB, Cobb FR
The ventilatory theshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and in patients with chronic congestive heart failure.
Am J Cardiol 1988; 62: 100-107.

73. Itoh H, Taniguchi K, Koike A, Doi M
Evaluation of severity of heart failure using ventilatory gas analysis.
Circulation 1990; 81: II 31-II 37.

74. Wasserman K, Beaver WL, Whipp BJ
Gas exchange theory and the lactic acidosis (anaerobic) threshold.
Circulation 1990; 81: II 14-II 30.

75. Sietsema KE, Cooper DM, Rosove MH et al
Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease.
Circulation 1986; 73: 1137-1144.

76. Nery LE, Wasserman K, Andrews JD et al
Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction.
J Appl Physiol 1982; 56: 1594-1602.

76. Cohn JN Arch
V-Heft Study
Circulation 1987; 74: 447.

LV Function

77. Dodge HT, Baxley WA
Haemodynamic aspects of heart failure.
Am J Cardiol 1968; 22: 24.

78. Hood WP Jr, Rackley CE, Rolelt EL
Wall stress in the normal and hypertrophied human left ventricle.
Am J Cardiol 1968; 22: 550.

79. Dodge HT, Baxley WA
Left ventricular volume and mass and their significance in heart disease.
Am J Cardiol 1969; 23: 528.

80. Hood WP Jr, Thomson WJ, Rackley CE et al
Comparison of calculations of left ventricular wall stress in man from thin walled and thick walled ellipsoidal models.
Circ Res 1969; 24: 575.

81. Rackley CE, Deer HD, Baxley WA et al
Left ventricular chamber volume, man and function in severe coronary artery disease.
Circulation 1970; 41: 605.

82. Sarnoff SJ, Mitchell JH
The regulation of the performance of the heart.
Am J Med 1961; 30: 747.

83. Fink LI, Wilson JR, Ferraro N
Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure.
Am J Cardiol 1986; 57: 249-253.

84. Szlachcic J, Massie BM, Kramer BL, Topic N, Tuban J
Correlates and prognostic implication of exercise capacity in chronic congestive heart failure.
Am J Cardiol 1985; 55: 1037-1042.

85. Packer M
Diastolic function as a traget of therapeutic interventions in chronic heart failure.
Eur Heart J 1990; II,C: 35-40.

86. Werner D, Fink LI, Maris J et al
Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow.
Circulation 1986; 73: 1127-1136.

87. Massie B, Conway M, Yonge R et al
Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow.
Circulation 1987; 76: 1009-1019.

88. Franciosa JA, Baker BJ, Seth L
Pulmonary versus systemic haemodynamics in determining exercise capacity of patients with chronic left ventricular failure.
Am heart J 1985; 110: 807-813.

89. Konstam MA, Weiland DS, Conlon TP et al
Haemodynamic correlates of left ventricular versus right ventricular radionuclide volumetric responses to vasodilator therapy in congestive heart failure secondary to ischaemic or dilated cardiomyopathy.
Am J Cardiol 1987; 59: 1121-1137.

90. Tweddel AC, Martin W, Neilly B, McGhie I, Stevenson R, Hutton I
Right ventricular function and haemodynamics in chronic obstructive airways disease at rest and exercise. In: Proceedings European Nuclear Medicine Congress, Goslar, September 1986. Nuklearmedizin. Eds Schmidt HAE, Emrich D. Schattauer Verlag 1987: 124-125.

91. Sanford CF, Corbett J, Nicool P et al
Value of radionuclide ventriculography in the immediate characterisation of patients with acute myocardial infarction.
Am J Cardiol 1982; 49,4: 637-644.

92. Weber KT, Ratshin RA, Janicki JS, Rackley CE, Russell RP
Left ventricular dysfunction following acute myocardial infarction.
Am J Med 1973; 54: 697.

93. White HD, Norris RM, Brown MA et al
Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction.
Circulation 1987; 76,1: 44-51.

94. Rigo P, Murray M, Strauus HW et al
Left ventricular function in acute myocardial infarction evaluated by gated scintigraphy.
Circulation 1974; 50: 678.

95. Schelbert HR, Henning H, Ashburn WL et al
Serial measurement of left ventricular ejection fraction by radionuclide angiography early and late after acute myocardial infarction.
Am J Cardiol 1976; 38: 407.

96. Dougherty AT, Nascarelli GV, Grey EL
Congestive heart failure with normal systolic function.
Am J Cardiol 1984; 54: 778.

97. Benge W, Litchfield RL, Marcus ML
Exercise capacity in patients with severe left ventricular dysfunction.
Circulation 1980; 61,5: 955-959.

98. Wilson JR, Schwartz JS, St John Sutton M et al
Prognosis in severe heart failure: relation to haemodynamic measurements and ventricular ectopic activity.
J Am Coll Cardiol 1983; 3: 403.

(Regional Function)

99. Maddox DE, Wynne J, Vren R et al
Regional ejection fraction: a quantitative radionuclide index of regional left ventricular performance.
Circulation 1979; 59: 1001-1009.

100. Vitale DF, Green MV, Bacharach SL et al
Assessment of regional left ventricular function by sector analysis: a method for objective evaluation of radionuclide blood pool studies.
Am J Cardiol 1983; 52: 1112-1119.

101. Warren Se, Bhargava V, Kieweg WVR et al
Semi-automated method for evaluation of left ventricular regional wall motion in coronary artery disease.
Am J Cardiol 1980; 46: 832-836.

102. Papapietro SE, Yester MV, Logic JR et al
Method for quantitative analysis of regional left ventricular function with first pass and gated blood pool scintigraphy.
Am J Cardiol 1981; 47: 618-625.

103. Maddox DE, Holman BL, Wynne J
Ejection fraction image, a non-invasive index of regional left ventricular wall motion.
Am J Cardiol 1978; 41: 1230-1238.

104. Johnston S, Tweddel AC, Martin W, McCartney A, Hutton I
A simple method of quantitating phase delay in an assessment of ventricular asynergy.
Nuclear Medicine Communications. British Nuclear Medicine Society, London, April 1988.

105. Carroll JD, Hess OM, Hirzel HO, Turina M, Krayenbuehl HS
Effects of ischaemia, bypass surgery and post infarction on myocardial contraction, relaxation and compliance during exercise.
Am J Cardiol 1989; 63: 65E-71E.

106. Karnegis JN, Matts J, Turia N et al
Directional ST-segment duration in graded exercise tests correlated with motion of the individual segments of the left ventricular wall.
Am J Cardiol 1983; 52: 449-452.

107. Stimson EB, Billingham ME
Correlative study of regional left ventricular histology and contractile function.
Am J Cardiology 1977; 39: 379-383.

108. Lee KL, Pryor DB, Pieper KS et al
Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease. A comparison with clinical and catheterization variables.

VENTRICULAR FUNCTION ON EXERCISE - REFERENCES

109. Pfisterer ME, Battler A, Swanson SM et al
Reproducibility of ejection fraction determinations by radionuclide angiography in response to supine bicycle exercise.
J Nucl Med 1979; 20: 491-495.

110. Borer JS, Kerk KM, Bacharach SL et al
Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography.
Circulation 1979; 60: 572.

111. Massie B, Botvinick E, Shames D, Brundage B
Correlation of myocardial perfusion with global and segmental ventricular function during exercise. Increased sensitivity of exercise blood pool scintigraphy for coronary disease.
Am J Cardiol 1979; 43: 343(abstract).

112. Corbett JR, Dehmer GJ, Lewis SE et al
The prognostic value of submaximal exercise testing with radionuclide ventriculography before hospital discharge in patients with recent myocardial infarction.
Circulation 1981; 64,3: 533-544.

113. Freeman MR, Berman DS, Stariloff H
Comparison of upright and supine bicycle exercise in the detection and evaluation of extent of coronary artery disease by equilibrium radionuclide ventriculography.
Am Heart J 1981; 102: 182-189.

114. Wieshammer S, Delagardelle C, Sigel HA et al
Limitations of radionuclide ventriculography in the non-invasive diagnosis of coronary artery disease: a correlation with right heart haemodynamic values during exercise.
Br Heart J 1988; 53: 603-610.

115. Schoer HR, Reid C, Arnold-Schneider M
Radionuclide assessment of a normal left ventricular response to exercise in patients without evidence of heart disease.
Eur Heart J 1986; 7: 118-126.

116. Hecht HS, Karahalios SE, Ormiston JA et al
Patterns of exercise response in patients with severe left ventricular dysfunction. Radionuclide ejection fraction and haemodynamic cardiac performance evaluations.
Am Heart J 1982; 104: 718-724.

117. Kronenberg MW, Brorson L, Smith CW et al
Radionuclide ventriculography: quantitative relationship to experimental ischaemia.
Am J Cardiol 1970; 43: 256(abstract).

118. McLaughlin PR, Kleiman JH, Martin RP
The effect of exercise and atrial pacing on left ventricular volume and contractility in patients with innervated and denervated hearts.
Circulation 1978; 58,3: 476-483.

119. Monroe RG, French GN
Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart.
Circ Res 1961; 9: 362-374.

120. Robard S, William CB, Robard D
Myocardial tension and oxygen uptake.
Circ Res 1964; 14: 139.

121. Sonnenblick EH, Ross J, Covell JW, Braunwald E
Velocity of contraction as a determinant of myocardial oxygen consumption.
Am J Physiol 1965; 209: 919.

122. Herman HV, Heinle RA, Klein MD, Gorlin R
Localized disorders in myocardial contraction asynergy and its role in congestive failure.
N Engl J Med 1967; 277: 222.

123. Amsterdam EA
Function of the hypoxic myocardium: Experimental and clinical aspects.
Am J Cardiol 1973; 32: 461.

124. Fox AR
Abnormalities in cardiac contractility associated with localized myocardial damage.
Ann Rev Med 1971; 22: 355.

125. Katz AM
Effects of ischaemia on the contractile processes of heart muscle.
Am J Cardiol 1973; 32: 456.

126. Sarnoff SJ, Braunwald E, Welch GH et al
Haemodynamic determinants of the oxygen consumption of the heart with special reference to the tension time index.
Am J Physiol 1958; 192(1): 148-156.

127. Braunwald E
Control of myocardial oxygen consumption. Physiologic and clinical considerations.
Am J Cardiol 1971; 27: 416-432.

128. Weber KT, Janicki JS
Myocardial oxygen consumption: the role of wall force and shortening.
Am J Physiol 1977; 233(4): H421-430.

129. Yamagishi T, Ozaki M, Kumada T et al
Asynchronous left ventricular diastolic filling in patients with isolated disease of the left anterior descending coronary artery: assessment with radionuclide ventriculography.
Circulation 1984; 69,5: 933-942.

130. Nakamura Y, Sasayama S, Nonogi H
Effects of pacing induced ischaemia on early left ventricular filling and regional myocardial dynamics and their modification by nifedipine.
Circulation 1987; 76,6: 1232-1244.

131. Rozanski A, Berman D, Gray R
Preoperative prediction of reversible myocardial asynergy by post exercise radionuclide ventriculography.
N Engl J Med 1982; 307: 212-216.

RV Function

132. Bernheim PI
De l'asystolie veineuse dans l'hypertrophie du coeur gauche par stenose concomitante du ventricle droit.
Rev Med 1910; 39: 785-794.

133. Henderson Y, Prince AC
The relative systolic discharges of the right and left ventricles and their bearing on pulmonary congestion and depletion.
Heart 1914: 217-226.

134. Bove AA, Santamore WP
Ventricular interdependence.
Progress in Cardiovascular Diseases 1981; 23,5: 365-387.

135. Sibald WJ, Driedger AA
Right ventricular function in acute disease states: Pathophysiologic considerations.
Crit Care Med 1983; 5: 339-345.

136. Andersen HR, Falk E, Nielsen D
Right ventricular infarction frequency, size and topography in coronary heart disease: a prospective study comprising 107 consecutive autopsies from a coronary care unit.
J Am Coll Cardiol 1987; 10: 1223-1232.

137. Tweddel AC, Martin W, McGhie I, Simpson I, McKillop JH, Hutton I
Ventricular function and perfusion by gated thallium scanning.
Proceedings of 16th International Symposium on Radioactive Isotopes in Clinical Medicine and Research, Badgastein, January 1984: p. 409-414.

138. Martin W, Tweddel A, McGhie I, Hutton I
Gated Xenon scans for right ventricular function.
J Nucl Med 1986; 27: 609-615.

139. Hinkle LE, Thaler HT
Classification of cardiac deaths.
Circulation 1982 65: 457-464.

140. McGhie I, Martin W, Tweddel A, Hutton I
Assessment of right ventricular function in acute inferior myocardial infarction using 133-xenon imaging.
Int J Cardiol 1989; 22: 195-202.

141. Polak JF, Holman L, Wynne J, Colucci WS
Right ventricular ejection fraction: An indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease.
JACC 1983; 2,2: 217-224.

142. Ferlinz J
Right ventricular function in adult cardiovascular disease.
Prog in Cardiovasc Dis 1982; XXV,3: 225-267.

143. Starr I, Jeffers WA, Meade RH
The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive heart failure and heart disease.
Am Heart J 1943; 26: 291.

144. Kagan A
Dynamic responses of the right ventricle following extensive damage by cauterization.
Circulation 1952; 5: 816.

145. Jamieson WL, Gemeinhardt W, Alaic J et al
Artificial maintenance of the systemic circulation without participation of the right ventricle.
Circ Res 1954; 2: 315.

146. Rose JC, Cosimano SJ, Hufnager CA et al
The effects of exclusion of the right ventricle from the circulation in dogs.
J Clin Invest 1955; 34: 1625.

147. Abe T, Kuriayashi R, Selo M et al
Congenital hypoplasia of the right ventricular myocardium (Uhl's anomaly). A case report and review of the literature.
J Cardiovasc Surg 1973; 14: 431.

148. Sade RM, Castaseda AR
The dispensable right ventricle.
Surgery 1975; 77: 624.

149. Guyton RA, Andrews MJ, Hickey PR et al
The contribution of atrial contraction to right heart function before and after right ventriculotomy. Experimental and clinical observations.
J Thorac Cardiovasc Surg 1976; 71: 1.

150. Prewitt RM, Ghignone M
Treatment of right ventricular dysfunction in acute respiratory failure.
Critical Care Medicine 1983; 2,5: 346-352.

151. Popp RL, Wolfe SB, Hirata T et al
Estimation of right and left ventricular size by ultrasound. A study of the echos from the intraventricular septum.
Am J Cardiol 1969; 24: 523.

152. Rogers EW, Feigenbaum H, Weymas AE
Echocardiography for quantitation of cardiac chambers. In: Progress in Cardiology. Ed Yu PN, Goodwin JF 1979; 8: 20. Lea and Febiger, Philadelphia.

153. Strauss HW, Pitt B
Gated blood pool imaging. In: Cardiovascular Nuclear Medicine. Ed Strauss HW, Pitt B 1979: 136. CV Mosby, St. Louis.

154. Berger HJ, Zaret BL
Noninvasive radionuclide assessment of right ventricular performance in man.
Cardiovascular Clin 1979; 10: 91.

155. Matthay RA, Berger HJ, Davies RA et al
Right and left ventricular exercise performance in chronic obstructive pulmonary disease. Radionuclide assessment.
Ann Intern Med 1980; 93: 234.

156. Matthay RA, Ellis JH, Steele PP
Methoxamine-induced increases in afterload. Effect on left ventricular performance chronic obstructive pulmonary disease.
Am Rev Respir Dis 1978; 117: 871.

157. Viahakes GJ, Turley K, Hoffman JI
The pathophysiology of failure in acute right ventricular hypertension: Haemodynamic and biochemical correlations.
Circulation 1981; 63: 87.

Myocardial Perfusion

158. Berger BL, Watson DD, Taylor GJ et al
Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease.
J Nucl Med 1981; 22: 585-593.

159. Kiat H, Berman DS, Maddahi J et al
Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability.
J Am Coll Cardiol 1988; 12: 1456-1463.

160. Dilsizian V, Rocco T, Freedman NMT, Leon MB, Bonow RO
Enhanced detection of ischaemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging.
N Engl J Med 1990; 323: 141-146.

161. Massie BM, Wisneski JA, Inouye IK et al
Detection and quantification of previous myocardial infarction by exercise redistribution tomographic thallium-201 scintigraphy.
Am J Cardiol 1984; 53: 1244-1249.

162. Freeman MR, Williams AE, Chisholm RJ et al
Role of resting thallium-201 perfusion in predicting coronary anatomy, left ventricular wall motion, and hospital outcome in unstable angina pectoris.
Am Heart J 1989; 117: 306-314.

163. Tweddel AC, Martin W, Winslow E, Campbell J, Marshall R, Hutton I
Infarct sizing by gated thallium scintigraphy in an animal model.
Proceedings of European Nuclear Medicine Congress, Budapest, August 1987. In: Nuklearmedizin. Eds Schmidt and Csernay.
Schattauer Verlag 1987: 175-179.

164. Norris RM, Brandt PWI, Caughey DE, Lee AJ, Scott PJ
A new coronary prognostic index.
Lancet 1969; 1: 274.

165. Killip T, Kimball JT
Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients.
Am J Cardiol 1967; 20: 457.

166. Grande P, Hansen BF, Christiansen C, Naeshoft J
Acute myocardial infarct size estimated by serum CK-MB. Clinical accuracy and prognostic relevance utilising a practical modification of the isoenzyme approach.
Am Heart J 1981; 101: 582-586.

167. Grande P, Christiansen C, Naeshoft J
Creatinine kinase isoenzyme MB assay by electrophoresis.
Scans J Clin Lab Invest 1979; 39: 607-612.

168. Berger HC
Prognostic significance of the extent of antimyosin uptake in unstable ischaemic heart disease early risk stratification.
Circulation 1988; 78 (4 Suppl II): II 31 (abst).

169. Taki J, Yasuda T, Gold HE et al
Prediction of extent of akinesis at 10 days from acute antimyosin scintigraphy.
J Nucl Med 1988; 29 (suppl): 851-852 (abstr).

170. Pfeffer MA, Pfeffer JM, Fishbein MC et al
Myocardial infarct size and ventricular function in rats.
Circ Res 1979; 44: 503-512.

171. Pfeffer JM, Pfeffer MAm Fletcher PJ, Braunwald E
Ventricular performance in rats with myocardial infarction and failure.
Am J Med 1984; 31: 99-103.

172. Pohost GM, Zir LM, Moore RH et al
Differentiation of transiently ischaemic from infarcted myocardium by serial imaging after a single dose of thallium-201.
Circulation 1977; 55: 294-302.

173. Gerwitz H, Beller GA, Strauss HW et al
Transient defects of resting thallium scans in patients with coronary artery disease.
Circulation 1979; 59: 707-713.

174. Rozanski A, Berman DB, Gray R et al
Use of thallium-201 redistribution scintigraphy in the pre-operative differentiation of reversible and non-reversible myocardial asynergy.
Circulation 1981; 64: 936-944.

175. Stratton JR, Speck SM, Caldwell JH et al
Relation of global and regional left ventricular ventricular function to tomographic thallium-201 myocardial perfusion in patients with prior myocardial infarction.
J A C C 1988; 12,1: 71-77.

176. Massie BM, Botvinick EH, Brundage BH, Greenberg B, Shames D, Gelberg H
Relationship of regional myocardial perfusion to sequential wall motion: a physiologic basis for understanding the presence and reversibility of asynergy.
Circulation 1978; 58: 1154-1163.

177. Liu P, Kiess MC, Okada RD et al
The persistent defect of exercise thallium imaging and its fate after myocardial revascularization: does it represent scar or ischaemia.
Am Heart J 1985; 110: 996-1001.

178. Gibson RS, Watson DD, Taylor RG et al
Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy.
J Am Coll Cardiol 1983; 1: 804-815.

179. Manyasi DE, Knudtson M, Kloiber R, Roth D
Sequential thallium 201 myocardial perfusion studies after successful percutaneous transluminal coronary angioplasty: delayed resolution of exercise induced scintigraphic abnormalities.
Circulation 1988; 77: 86-95.

180. Hashimoto T, Kambara H, Fudo T et al
Non Q wave versus Q wave myocardial infarction: Regional myocardial metabolism and blood flow assessed by positron emission tomography.
J A C C 1988; 12,1: 88-93.

181. Sinusas A, Watson Dd, Cannon JM, Beller GA
Effect of ischaemic and poor ischaemic dysfunction on myocardial uptake of technetium-99m labelled methoxy-isobutyl isonitrile and thallium-201.
J A C C 1989; 14,7: 1785-1793.

Xenon

182. See JR, Cohn PF, Holman BL, Adams DF, Maddox DE
Significance of reduced regional myocardial blood flow in asynergic areas evaluated with intervention ventriculo-graphy: results of studies combining washout of Xenon 133 and post extrasystolic potentiation.
Am J Cardiol 1979; 43: 179-185.

183. See JR, Cohn PF, Holman BL, Roberts BH, Adams DF
Angiographic abnormalities associated with alterations in regional myocardial blood flow in coronary artery disease.
Br Heart J 1976; 38: 1278-1285.

184. Burch GE, Giles TD, Colcolough HL
Ischaemic cardiomyopathy.
Am Heart J 1970; 79: 291-292.

185. Rogers WJ, Oberman A, Kouchnonkos L
Left ventricular aneurysmectomy in patients with single vs multi-vessel coronary artery disease.
Circulation 1978; 58 (suppl): 50-54.

186. Yattean RF, Peter RG, Behar VS et al
The myopathy of coronary artery disease natural history and results of medical versus surgical treatment.
Am J Cardiol 1974; 34: 520-525.

187. Betrand ME, Leblanche JM, Thieuleux FA, Tilmast PY
What is the role of the coronary circulation in congestive heart failure?
Eur Heart J 1983; 4,A: 131-135.

188. Weiss MB, Ellis K, Sciacca RR et al
Myocardial blood flow in congestive and hypertrophic cardiomyopathy.
Circulation 1976; 54: 484-494.

189. Pasternac A, Noble J, Streulens Y, Lesperance J, Bourassa MG
La perfusion myocardique dans les cardiomyopathies. Etude au repos et lors de tachycardie induite.
Arch Mal Coeur 1978; 71: 878-886.

190. Kety S
The theory and applications of the exchange of inert gas at the lungs and tissue.
Pharmacol Rev 1951; 3, 1-41.

191. Henry PD, Eckberg D, Gault JH, Ross I
Depressed inotropic state and reduced myocardial oxygen consumption in the human heart.
Am J Cardiol 1973; 31: 301-306.

192. Posin M, Sellier P, Lardoux H et al
Hemodynamique coronaire et metabolisme myocardique dans les myocardiopathies primitive a forme dilatee.
Arch Mal Coeur 1980; 73: 915-959.

PART 3

TREATMENT OF PATIENTS WITH HEART FAILURE

The literature on this subject is encyclopaedic. Small studies cannot attempt to answer questions about efficacy, morbidity or effect on mortality. Indeed there has been a profusion of large multicentre studies published with acronyms such as CONSENSUS, SOLVD and V-HeFT. Although much is known as to the effects of these drugs and overall mortality and morbidity, it is not always clear which is the optimal treatment for an individual patient. In the following section, using small numbers of patients but detailed measurements, I have attempted to address some of these uncertainties.

Diuretics

By far the commonest treatment for any patient with heart failure is diuretics. In plant form, these were well known to the Greeks, Romans, Arabians and Egyptians before them. A combination of emetics, purging, diuretics and bleeding were common practice among mediaeval physicians. Galega ossicinalias (goats rue), scrophularia nodosa (figwort) and scutellaria lateriflora (skullcap), all known for their diuretic action, can still be found in the Chelsea Physic Garden.

In modern cardiology practice, the introduction of diuretics was undoubtedly one of the major advances in the treatment of heart failure. They remain the commonest initial treatment. There is not a great deal of literature on the haemodynamic effects of diuretics. The majority of information is derived from haemodynamic studies in patients with acute myocardial infarction. Loop diuretics rapidly reduce left heart filling

pressures usually with a concomitant fall in cardiac output **(1,2)**. In patients with chronic heart failure the data is very sparse.

Methods

Eight male patients with severe left ventricular dysfunction (LVEF $<30\%$) secondary to coronary artery disease were studied. All were clinically classified as New York Heart Association Grade III and had received no drugs for 24 hours. Patients had been stable on a combination of diuretics and vasodilators and no patients was receiving digoxin.

Heart rate was obtained from the electrocardiogram which was monitored continuously. Intra-arterial pressure was obtained from a catheter placed in the ascending aorta. Pulmonary artery pressure and capillary wedge pressure were obtained from a Swan-Ganz catheter inserted percutaneously via the femoral vein. Cardiac output was obtained by the thermodilution technique in triplicate (see Appendix). Coronary sinus flow was also obtained by the thermodilution technique from a Wilton Webster catheter inserted in the coronary sinus. This catheter allows blood sampling from the coronary sinus for measurement of oxygen saturation and this, together with an arterial sample, allows myocardial oxygen usage to be calculated. Myocardial flow was measured using the Xenon washout technique by direct injection of Xenon-133 intracoronary and scans obtained by a mobile Gamma camera. Myocardial flow to the total left ventricle and in each of the major coronary artery distributions was calculated. Frusemide was given intravenously in a dose of 0.5 mg/ kg. All measurements were taken for a control period of 10-15 minutes prior to administration of frusemide and for 30 minutes thereafter.

Table 12(a) **Systemic haemodynamic changes with Frusemide**

Frusemide n = 8 Mean ± S.D.

			Post Frusemide		
		Control	**5 minutes**	**10 minutes**	**30 minutes**
HR	beat/minute	72.00± 9.0	74.00± 9.0**	74.00±10.0	78.00±10.0*
SBP	mm.Hg.	117.80±18.8	123.90±20.7**	125.80±24.8	135.00±24.4
DBP	mm.Hg.	75.80± 7.4	82.00± 8.0*	83.30± 7.7*	89.10± 9.6*
MAP	mm.Hg.	91.30±11.4	99.00±11.2**	100.80±15.0*	103.80±15.4*
DMPA	mm.Hg.	14.90± 8.3	17.40± 9.3	17.40± 9.9	16.60±10.5
CI	l/min/m^2	2.55± 0.38	2.43± 0.29	2.67± 0.27	2.53± 0.39
SVI	beat/min/m^2	36.00± 6.3	33.40± 6.1	36.40± 6.2	34.20± 6.1
SVR	dyne-s-cm^{-5}	1574.00±418	1650.00±462	1598.00±316	1786.00±509*

* $p < 0.02$ ** $p < 0.05$

Abbreviations:

HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
MAP= mean arterial pressure
DMPA = diastolic pulmonary artery pressure
CI = cardiac index
SVI = stroke volume index
SVR = systemic vascular resistance

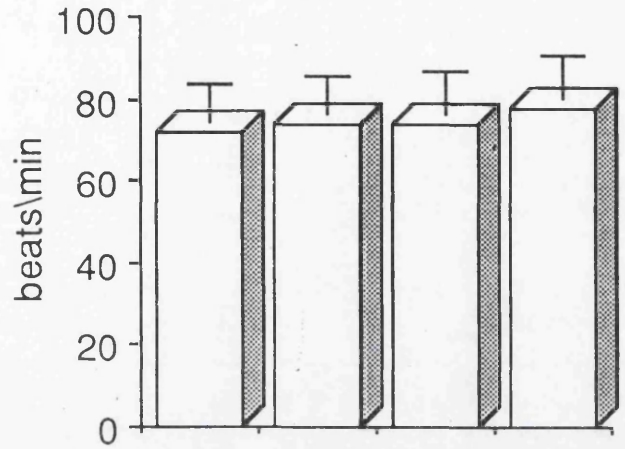
Table 12(b) **Coronary haemodynamic changes with Frusemide**

			Post Frusemide	
		Control	**5-10 Minutes**	**20-30 minutes**
	LV	54.7 ± 15.3	67.6 ± 11.2**	60.8 ± 10.1
	RCA	45.4 ± 18.6	38.8 ± 13.4**	39.2 ± 13.6
	LAD	51.4 ± 14.7	63.6 ± 13.1**	58.8 ± 15.6
	Cx	58.2 ± 14.9	70.8 ± 13.8**	65.4 ± 9.3
ml/min	CSF	130.3 ± 30.7	163.9 ± 51.3	172.9 ± 66.1**
vol %	A-V	11.0 ± 1.22	10.9 ± 1.65	11.9 ± 2.3
units	MVO_2	1433.3 ± 402	1786.5 ± 630	1785.0 ± 243

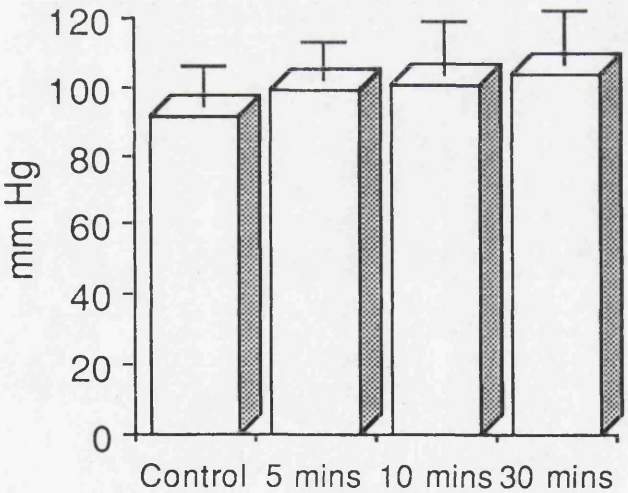
* $p < 0.02$ ** $p < 0.05$

Abbreviations:

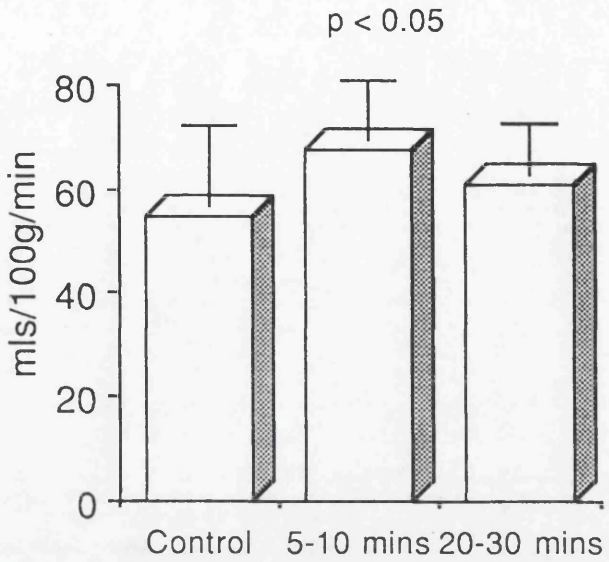
HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
MAP = mean arterial pressure
DMPA = diastolic pulmonary artery pressure
CI = cardiac index
SVI = stroke volume index
SVR = systemic vascular resistance



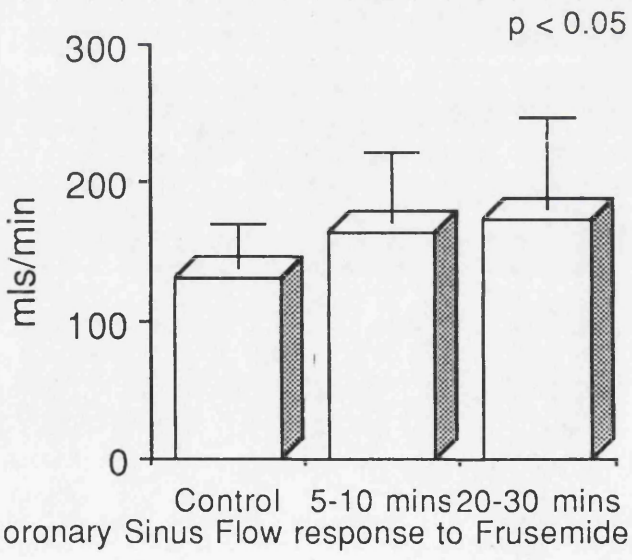
Heart rate response to Frusemide 40 mg IV



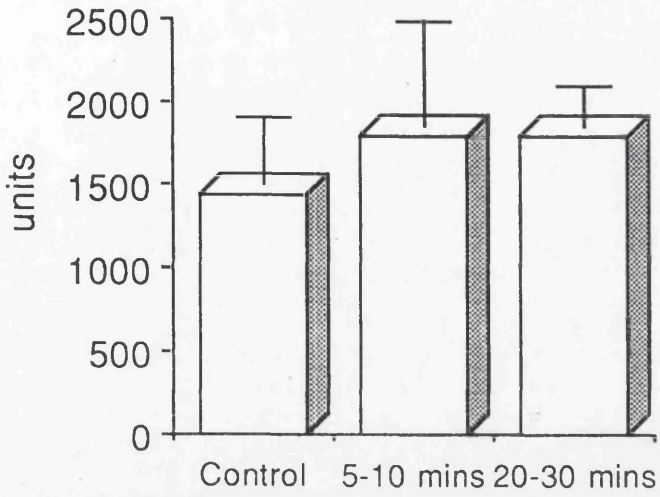
Mean Blood Pressure response to Frusemide 40mg IV



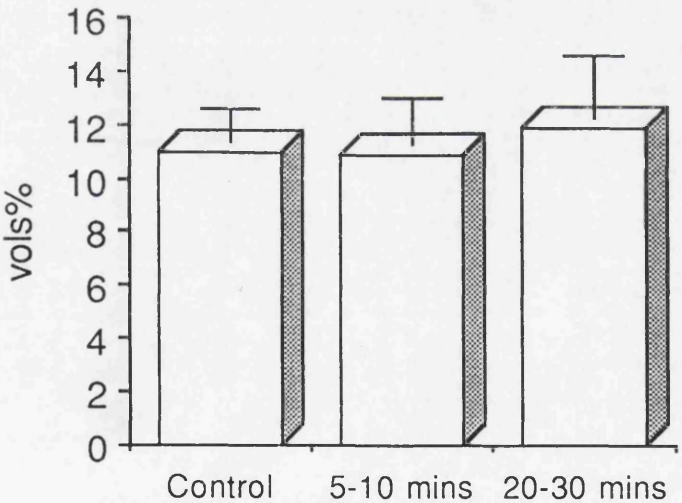
Left coronary artery flow response to Frusemide



Coronary Sinus Flow response to Frusemide



Calculated Myocardial Oxygen Consumption response to Frusemide



Arterio-venous Oxygen Difference response to Frusemide

Results

Heart rate increased by 5 minutes and remained elevated. Similarly there was a small but significant increase in systolic, diastolic and mean arterial pressure. Cardiac output and stroke volume were essentially unchanged. Pulmonary artery pressure and in particular pulmonary artery diastolic pressure, as a reflection of pulmonary capillary wedge pressure or left ventricular filling pressure, was unaltered.

With the increased blood pressure and unaltered cardiac output, calculated systemic vascular resistance was increased although this did not achieve statistical significance until 30 minutes after administration of the frusemide.

Coronary sinus flow measured by the thermodilution technique had increased significantly by 5-10 minutes and remained elevated at 20-30 minutes. There was a similar directional change in myocardial nutrient flow as measured by the Xenon clearance technique. This increase was mainly in the territory of the left coronary artery. This was achieved only with a widening of the arteriovenous oxygen difference and hence a small increase in calculated myocardial oxygen consumption.

Discussion

These haemodynamic changes are in keeping with those previously reported by Verma et al **(3)** but not with several studies reporting reduced cardiac output when diuretics are given in acute heart failure complicating acute myocardial infarction **(4-9)**. Given in acute heart failure left heart filling pressure is also universally lowered and this reduction in preload is thought to be its mode of action **(10)** with a reduced venous compliance due possibly to the release of prostacyclin or

kallikrein **(8,11,12)**. In acute situations, the acute elevation of systemic arterial pressure is thought to be mediated by activation of the renin-angiotensin system **(13,14)**.

In patients with chronic heart failure, diuretics undoubtedly produce symptomatic improvement, with increased exercise capacity, but with stimulation of the renin-angiotensin system **(15)** and probably also the sympathetic nervous system **(16)**. A study by Francis et al **(17)** demonstrated that, following the intravenous administration of frusemide to chronically diuresed patients with heart failure, systemic vascular resistance increased together with stimulation of the sympathetic nervous system, the renin-angiotensin system and anti-diuretic hormone, which is consistent with our findings. Similar findings were reported following an oral dose of frusemide with no change in cardiac output pulmonary pressure (measured by doppler) or blood pressure **(18)**.

Presumably, in our study, the resulting small increase in heart rate together with the increased blood pressure was sufficient to increase myocardial flow measured by the Xenon technique and also by cornary sinus flow. The unchanged arteriovenous oxygen difference with unchanged oxygen extraction results in an increased calculated myocardial oxygen consumption. Increased myocardial flow balanced by the increased myocardial oxygen consumption may well contribute to unchanging exercise tolerance with chronic diuretic therapy.

In summary, acute diuretic therapy in chronically diuresed patients appears to increase heart rate, blood pressure, and thus systemic vascular resistance but with no change in cardiac output or stroke volume. This results in an increased myocardial blood flow.

Nitrates

Oral nitrates, particularly isosorbide dinitrate, were the first oral vasodilators used in the management of patients with severe heart failure **(19)**. Nitrates act primarily by lowering right and left heart filling pressures by direct action on venous capacitance vessels **(20-22)** usually with a small increase in cardiac output, particularly in patients with a low cardiac index prior to treatment **(23,24)**. They have been found to be effective in alleviating dyspnoea and fatigue and to improve exercise tolerance **(25-28)**.

Theoretically, the potential efficacy of reducing preload is less certain. In isolated muscle preparations, when preload reserve is fully utilised, after-load mismatch can exist in steady state with heart function operating on an apparent descending limb. As long as venous return to the heart is not reduced, adaptive changes in preload probably have little effect **(29, 30)**. This may not be the case in patients with chronic heart failure, when small changes in left ventricular volume may be critical in determining the output from the failing heart **(31)**. However, nitrates also reduce left ventricular filling pressure, and thus left ventricular wall stress with subsequent improvement in myocardial subendocardial flow **(32,33)**.

Methods

Ten male patients with New York Heart Association Grade III heart failure (left ventricular ejection fraction $<30\%$) were studied at the time of routine coronary arteriography. All drug therapy was discontinued for 24 hours and no patient was receiving long acting vasodilators, ACE inhibitors or digoxin.

Table 13(a) **Systemic haemodynamic changes with Isosorbide Mononitrate (ISMN)**

Isosorbide Mononitrate n = 10 Mean ± S.D.

		Control	5 minutes	10 minutes	30 minutes
HR	beat/minute	78.40±16.1	84.80±18.7	83.20±20.2**	80.60±18.5
SBP	mm.Hg.	122.50±28.7	114.60±33.6	121.60±39.2	117.40±33.8
DBP	mm.Hg.	77.50±13.4	81.20±18.7	81.60±19.6	80.20±17.6
MAP	mm.Hg.	96.70±19.1	95.40±23.9	97.10±26.8	96.00±22.1
DMPA	mm.Hg.	13.10± 2.73	9.30± 3.86**	9.20± 3.04$^{\Delta}$	11.80± 6.1
CI	l/min/m^2	2.71± 0.39	2.66± 0.47	2.45± 0.54	2.33± 0.53
SVI	beat/min/m^2	35.60± 7.1	32.20± 6.0	30.50± 7.3**	30.00± 6.1*
SVR	dyne-s-cm^{-5}	1578.00±588	1595.00±579	1760.00±667**	1844.00±805*

$^{\Delta}$ $p < 0.01$ * $p < 0.02$ ** $p < 0.05$

Abbreviations:

HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
MAP = mean arterial pressure
DMPA = diastolic pulmonary artery pressure
CI = cardiac index
SVI = stroke volume index
SVR = systemic vascular resistance

Table 13(b) **Coronary haemodynamic changes with Isosorbide Mononitrate (ISMN)**

	Control	5-10 Minutes	20-30 minutes
LCA	72.5 ± 18.4	68.4 ± 27.1	66.8 ± 23.4
RCA	54.6 ± 15.0	55.4 ± 20.0	54.4 ± 17.2
LAD	69.0 ± 28.7	65.4 ± 25.3	64.2 ± 27.0
Cx	71.1 ± 17.7	71.2 ± 29.3	68.4 ± 21.2
CSF	119.7 ± 37.2	105.3 ± 29.4	108.6 ± 50.1
A-V	11.9 ± 2.2	10.4 ± 1.8**	10.7 ± 1.9*
MVO_2	1424.4 ± 457	1095.1 ± 425	1162.0 ± 225

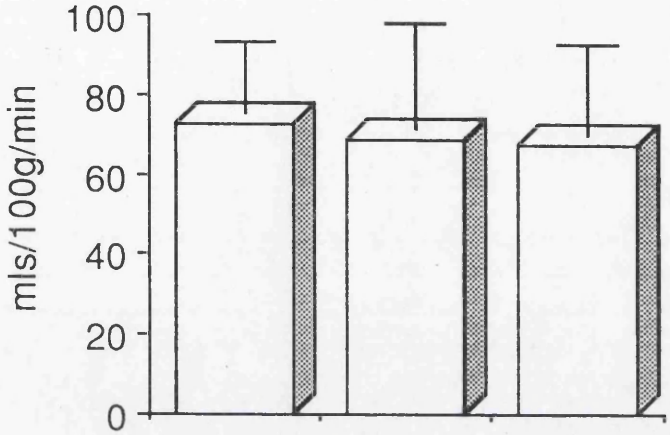
* $p < 0.02$ **$p < 0.05$

ISMN LEVELS Mean ± SD μg/ml
15 mg. into RA over 2 minutes

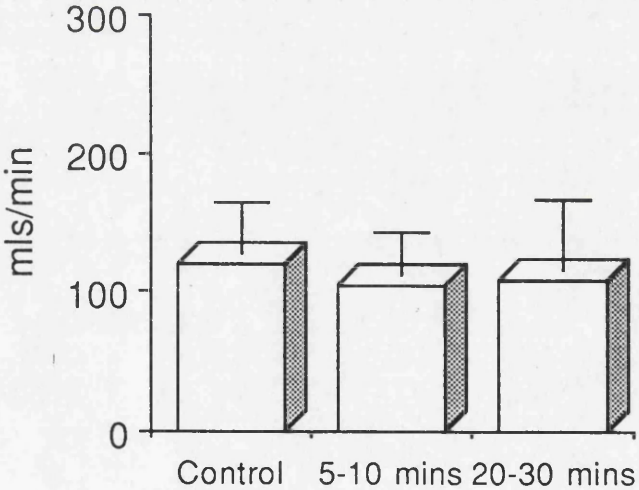
2 minutes (Peak)	739.5 ± 303
5 minutes	459.0 ± 192
20 minutes	296.0 ± 41
30 minutes	252.0 ± 42

Abbreviations:

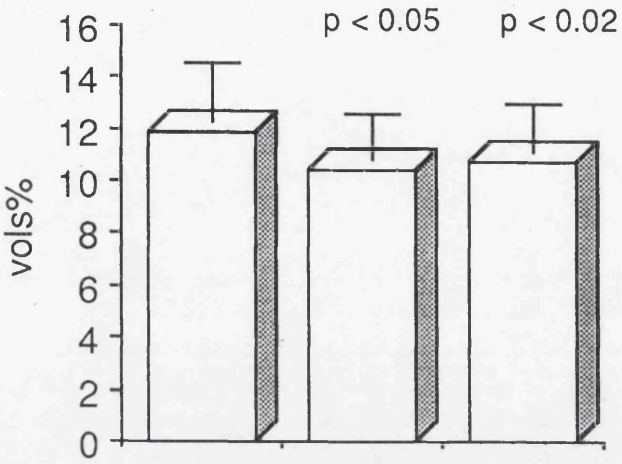
HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
MAP = mean arterial pressure
DMPA = diastolic pulmonary artery pressure
CI = cardiac index
SVI = stroke volume index
SVR = systemic vascular resistance



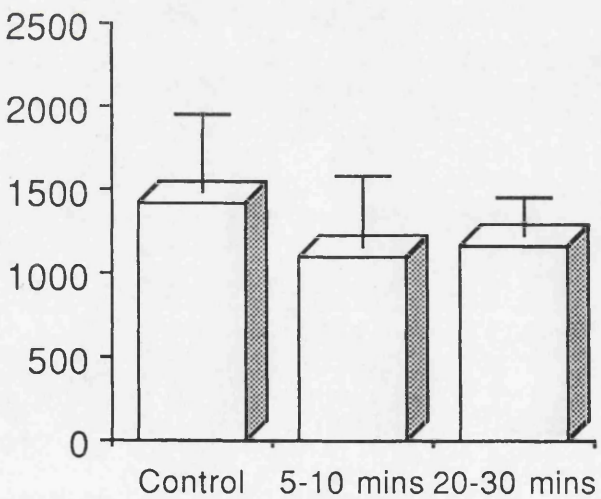
Left coronary artery flow respose to ISMN



Coronary Sinus Flow respose to ISMN



Arterio-venous Oxygen Difference response to ISMN



Calculated Myocardial Oxygen Consumption response to ISMN

Heart rate was obtained from the electrocardiogram and blood pressure from an intra-arterial line placed in the ascending aorta. Pulmonary artery pressure and pulmonary capillary wedge pressure were obtained by Swan-Ganz catheter inserted percutaneously into the femoral vein. Cardiac output was obtained by the thermodilution technique in triplicate. Coronary sinus flow was also measured by the thermodilution technique via a Wilton Webster catheter placed in the coronary sinus. Simultaneous sampling from the coronary sinus and aorta allowed myocardial oxygen consumption to be calculated. Myocardial flow was obtained from the Xenon clearance technique as previously described (see Appendix).

Isosorbide mononitrate 15 mg. was given intravenously into the right atrium over two minutes. Venous samples were obtained every minute for five minutes, at 10 minutes, 20 minutes and 30 minutes for drug levels.

Results

There was an initial small insignificant drop in blood pressure and reflex tachycardia though blood pressure returned to control values but the slight tachycardia persisted. Diastolic pulmonary artery pressure was reduced significantly but returned to control by 30 minutes. Cardiac output showed a small progressive decrease. Stroke volume was reduced and calculated systemic vascular resistance increased.

Myocardial flow by both the Xenon technique and coronary sinus flow were unchanged but arteriovenous oxygen difference was significantly narrowed reflecting decreased oxygen usage. However the combination of the slight reduction in myocardial flow (especially from the left

coronary artery) resulted in a small, non-significant drop in calculated myocardial oxygen consumption.

Blood levels of isosorbide mononitrate are shown with the peak occurring at two minutes following the end of the two minute infusion with adequate levels at 30 minutes.

In one patient systolic blood pressure dropped from 137 to 132 mm.Hg. with diastolic blood pressure dropping from 93 to 88 mm.Hg. and mean blood pressure 112 to 104 mm.Hg. with a small reflex tachycardia. At this point the patient developed chest pain, typical of his angina but without electrocardio-graphic change. Blood pressure was restored with intravenous fluid administration.

Discussion

Previous work would suggest that with the administration of intravenous nitrate one would expect a reduction in blood pressure with a reflex tachycardia. In this study there was an initial small decrease in systolic blood pressure which very quickly returned to control values although the minor tachy-cardia persisted. With the decrease in pulmonary artery diastolic pressure (left ventricular filling pressure) one might have expected the cardiac output and stroke volume to increase. This may have been a reflection partly of the dose chosen, which was fixed rather than titrated for each individual, and this has been shown to be required for isosorbide dinitrate **(34)** and partly that these were chronically treated patients, who had received no drugs for 24 hours, and no oral fluid for 12-15 hours and hence the initial the pulmonary artery diastolic pressure was not high. These patients undoubtedly had heart failure on the basis of clinical findings and the associated left ventricular dysfunction. The

action of nitrate is dependent on the prevailing haemodynamic findings **(35)**.

The increase in calculated systemic vascular resistance is interesting. Myocardial flow was unchanged, but myocardial arteriovenous oxygen difference narrows, suggesting decreased oxygen usage. In one patient chest pain developed, without electrocardiographic change, due presumably to subendocardial ischaemia which would be impossible to detect either with coronary sinus flow measurements or Xenon clearance.

In summary, it is possible therefore that the maintenance of cardiac output is more beneficial in patients with chronic heart failure, to maintain myocardial flow, and that agents that are predominantly venodilators should be reserved for situations where filling pressure has increased.

Calcium Channel Blockers

The only vasodilators employed in the treatment of patients with heart failure tended to be predominantly effective in reducing venous capacitance, or preload, with drugs such as nitrates or reducing systemic vascular resistance (afterload) using for example hydralazine. In animal models of the ischaemic myocardium, increased preload improved cardiac output but at the expense of aggravated ischaemia while increased afterload reduced cardiac output but tended to improve perfusion and lactate uptake of the ischaemic myocardium **(36)**.

Calcium antagonists are widely used for the treatment of angina and are known to reduce smooth muscle tone in the coronary and peripheral resistance vessels **(37,40)**. Nifedipine has also been shown to increase

	Post felodipine			
	Control	15 min	30 min	45 min
Heart rate (beats min^{-1})	76±4	82±4**	86±4^{+++}	84±5*
Systolic BP (mmHg)	126±5	123±5	104±4^{++}	107±5*
Diastolic BP (mmHg)	79±3	79±3	66±3^{+++}	66±4**
Mean BP (mmHg)	97±4	96±4	81±4^{+++}	82±4*
Cardiac index (l min^{-1})	2·61±0·13	3·10±0·17**	3·48±0·18^{+}	3·42±0·31***
Stroke volume index (ml $beat^{-1}$ m^{-2})	35·3±2·7	40·0±3·1***	41·4±2·4^{++}	40·9±5·2
Pulmonary artery diastolic pressure (mmHg)	19±2	19±2	19±2	17±2***
Systemic vascular resistance (dyne s cm^{-5})	1630±74	1357±96**	1024±53^{+}	1132±103***
Coronary sinus flow (ml min^{-1})	126±8	142±9	168±13^{+++}	167±8***
Coronary vascular resistance (units)	72·1±6·0	57·4±9·1	48·7±6·9^{+++}	46·3±5·1***
Myocardial AVO_2 difference (vol%)	12·3±0·7	11·4±0·3	9·7±0·6**	9·2±0·4***
Myocardial oxygen consumption MVO_2 (ml min^{-1})	16·5±1·3	16·8±1·3	17·2±1·5	16·0±1·4

*$P<0·01$, **$P<0·02$, ***$P<0·05$.
$^{+}P<0·001$, $^{++}P<0·002$, $^{+++}P<0·005$.

coronary blood flow to ischaemic regions **(41-43)**. Felodipine is a di-hydropiridine which inhibits the activation of intracellular calmodulin by calcium ions and in high concentrations acts as a slow calcium channel blocker **(44)**. It is a potent systemic vasodilator with no direct effect on left ventricular function **(45)**.

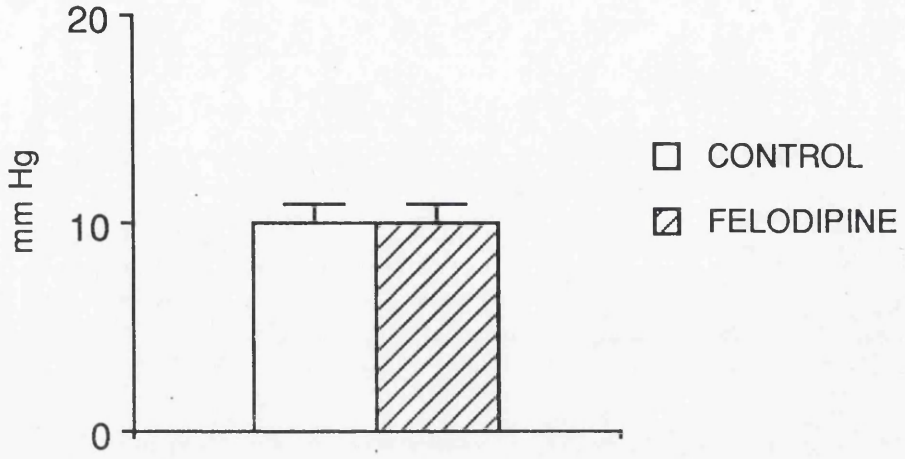
Methods

We studied 22 patients with left ventricular dysfunction secondary to arteriographically demonstrated coronary artery disease. Nineteen were male and the mean age was 46 years with a range of 29-66 years. Anti-anginal therapy was withdrawn for 72 hours prior to this study and the patients were premedicated with 10 mg. of oral diazepam.

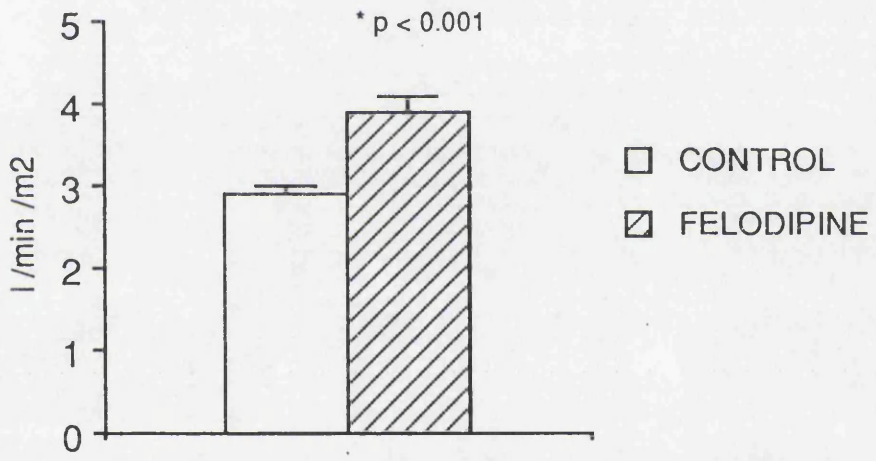
Heart rate was obtained from the electrocardiogram and blood pressure from an intra-aortic line placed in the descending aorta. A Swan-Ganz catheter was inserted percutaneously via a femoral artery for measurement of pulmonary artery pressure and pulmonary capillary wedge pressure. Cardiac output was obtained in triplicate using the thermodilution technique. Coronary sinus flow was also measured by thermodilution using a Wilton Webster catheter placed in the coronary sinus. Simultaneous aortic and coronary sinus samples were withdrawn for measurement of blood oxygen content (Instrumentation Laboratories 802). In eight patients heart rate was held constant by atrial pacing via the Wilton Webster catheter.

After the catheterisation procedure the patients were allowed to rest for 30 minutes when control measurements were obtained. They were then given a 10 mg. oral solution of felodipine and measurements repeated at 15, 30, 45 and 60 minutes.

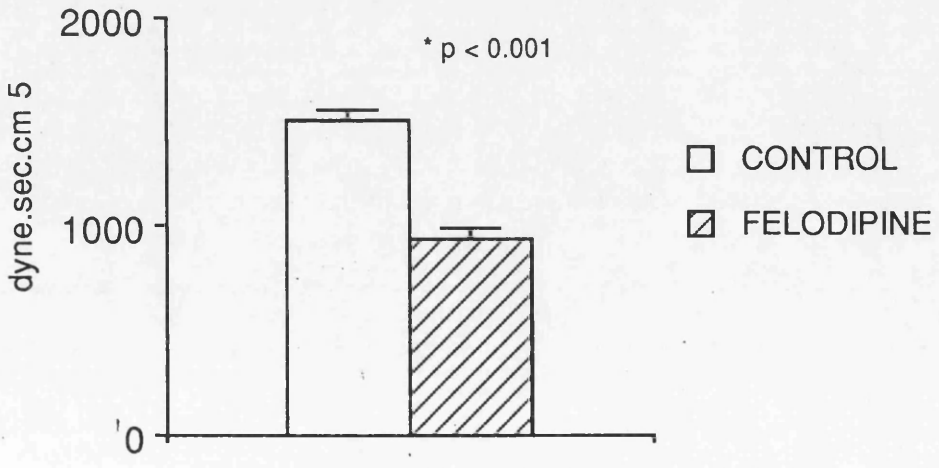
PULMONARY CAPILLARY WEDGE PRESSURE



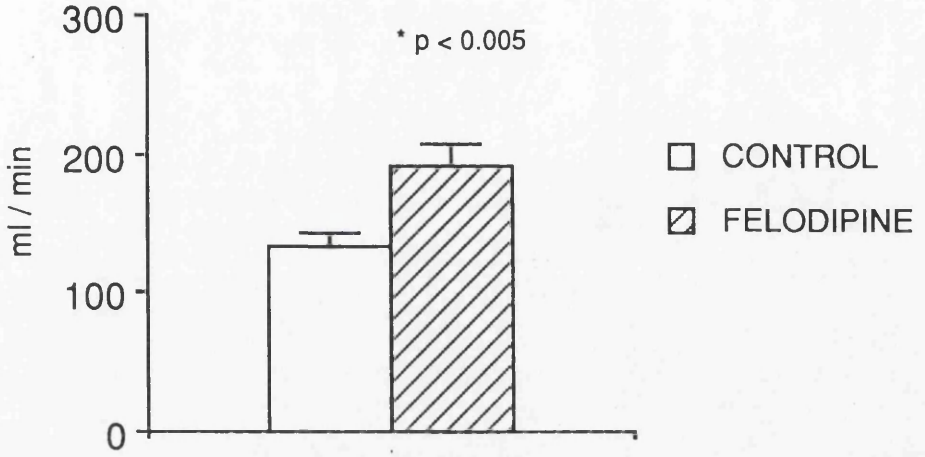
CARDIAC INDEX



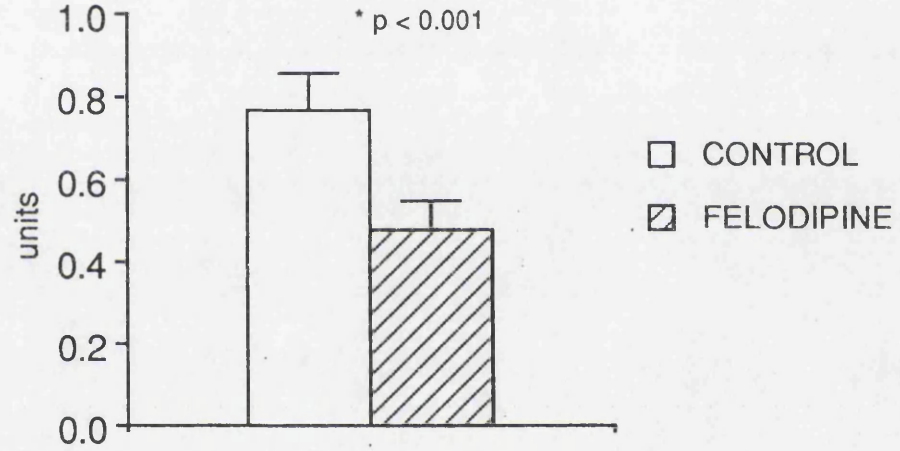
SYSTEMIC VASCULAR RESISTANCE



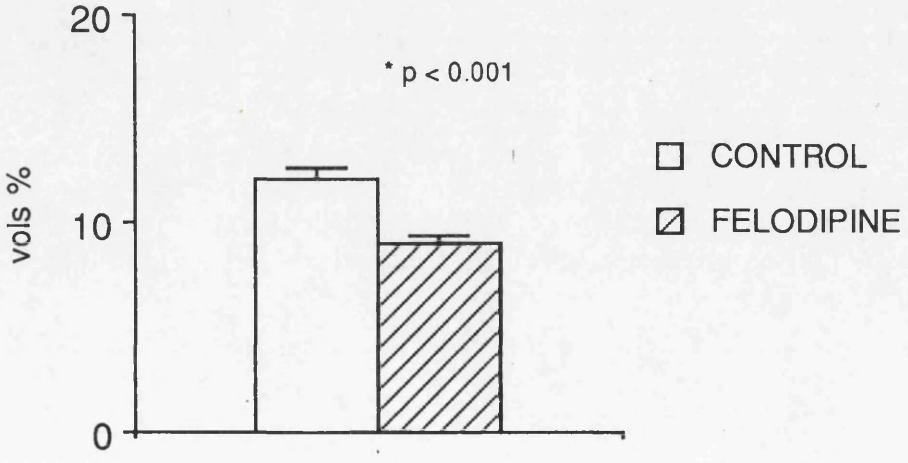
CORONARY SINUS FLOW

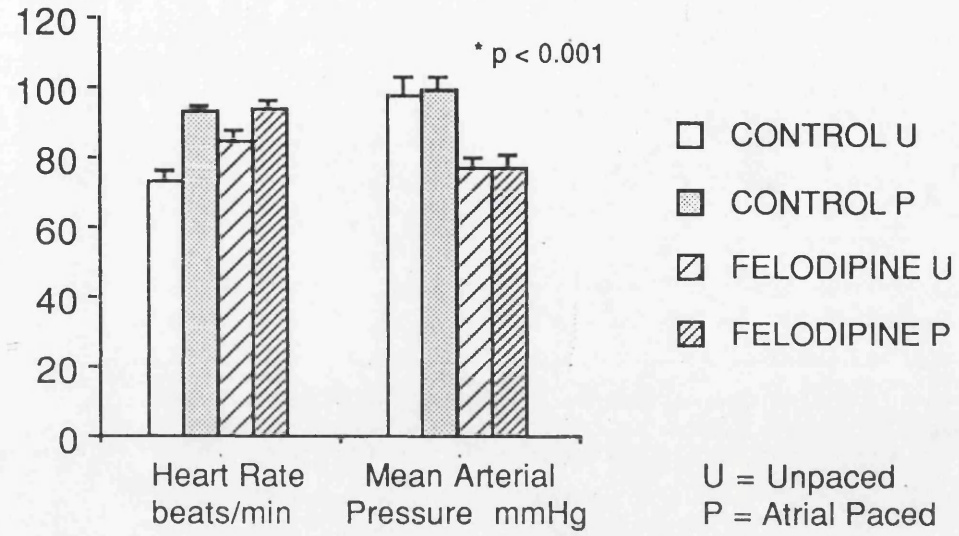


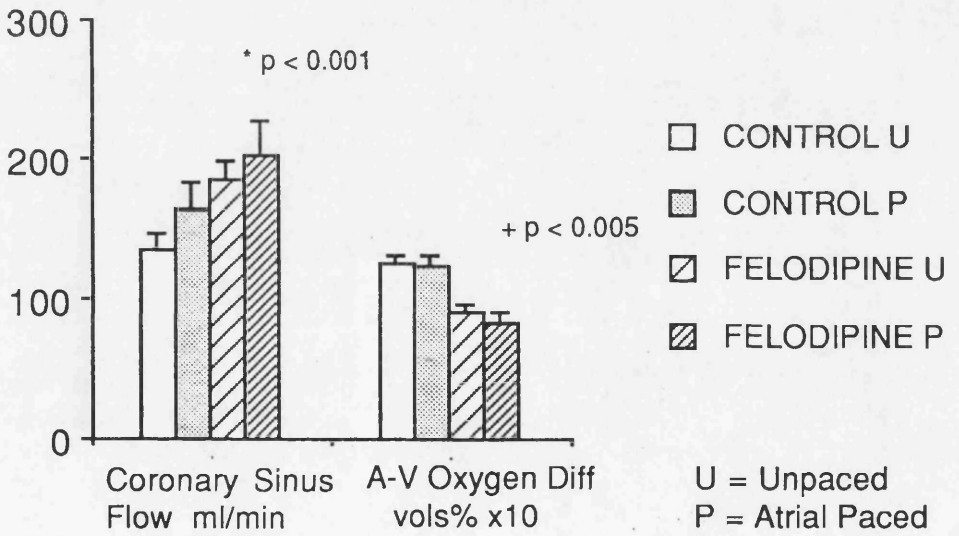
CORONARY VASCULAR RESISTANCE



ARTERIO - VENOUS OXYGEN DIFFERENCE




120
100
80
60
40
20
0
* p < 0.001
Heart Rate beats/min
Mean Arterial Pressure mmHg
CONTROL U
CONTROL P
FELODIPINE U
FELODIPINE P
U = Unpaced
P = Atrial Paced


300
200
100
0
* p < 0.001
+ p < 0.005
Coronary Sinus Flow ml/min
A-V Oxygen Diff vols% x10
CONTROL U
CONTROL P
FELODIPINE U
FELODIPINE P
U = Unpaced
P = Atrial Paced

Results

The results are shown in Table 14. There was a small decrease in blood pressure of 16% and a 38% decrease in systemic vascular resistance resulting in a reflex tachycardia. Stroke volume increased as did the cardiac index by 35%. Filling pressures were unchanged. Coronary sinus flow increased with a concomitant reduction in coronary vascular resistance and arteriovenous oxygen differences narrowed suggesting reduced myocardial oxygen consumption. In the eight patients in whom heart rate was held constant by atrial pacing, there was a similar reduction in blood pressure and systemic vascular resistance with a concomitant increase in cardiac index. Coronary haemodynamics showed similar changes in coronary sinus flow, coronary vascular resistance and again a narrowed arteriovenous oxygen difference.

Discussion

In these patients systemic blood pressure and the vascular resistance fell and when heart rate was held constant by atrial pacing the changes were maintained. Therefore it seems likely that afterload reduction (or impedance) was the major contributing factor. No effect on preload was seen as filling pressures remained unchanged. The oral felodipine gave rise to increases in both cardiac index and stroke volume index.

There was also dilatation in the coronary vasculature reflected as an increase in coronary sinus flow and a decrease in coronary vascular resistance. Myocardial arteriovenous oxygen differences narrowed on the combination of the increased coronary blood flow together with the fall in calculated left ventricular stroke work index would suggest this was due to less myocardial demand or work.

These haemodynamic changes resemble those found with hydralazine, but without the side effects **(47)**. It has been suggested that felodipine exerts its main vasodilating effect via calmodulin which has high concentrations in vascular smooth muscle with relatively low concentrations in the myocardium **(44)** providing an explanation for its predominantly peripheral action. In summary, the reduced impedance allows an increase in cardiac output and despite reduced blood pressure and reflex tachycardia coronary sinus flow increases with reduced myocardial oxygen usage.

Calcium Channel Blocker, Oral Administration

The advantageous effects of felodipine in reducing systemic vascular resistance and favourable coronary haemodynamic findings were tested with chronic administation in patients with chronic heart failure secondary to coronary artery disease.

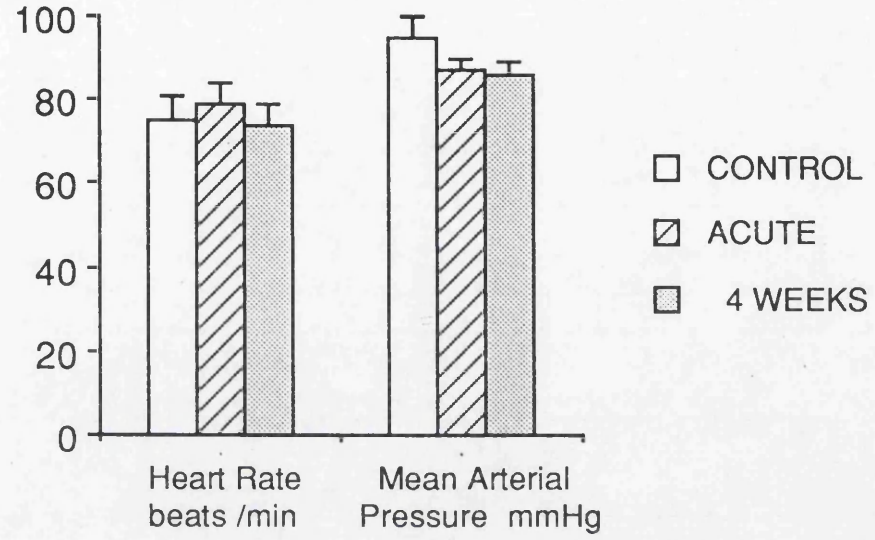
Methods

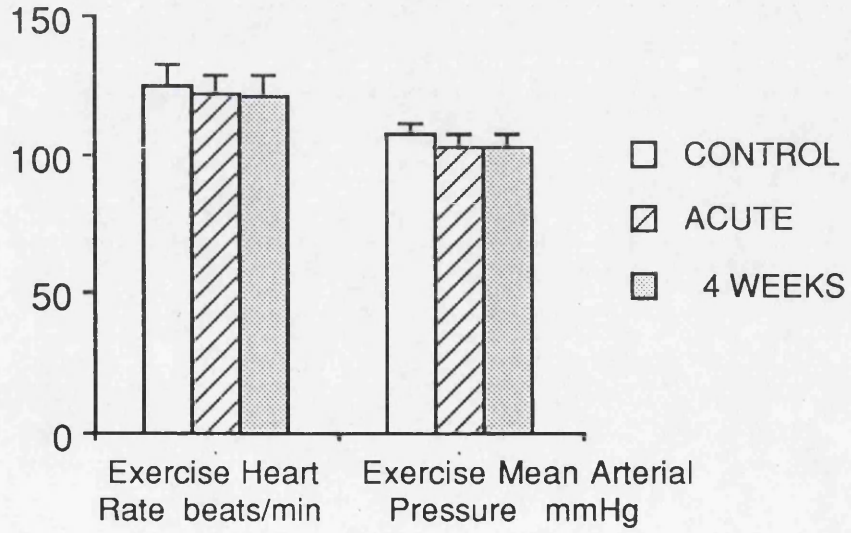
Ten patients (nine males) Grade III-IV New York Heart Association heart failure with a mean age of 55 years (range 42-63 years) were studied. Coronary artery arterial disease was confirmed at angiography and eight of the ten patients had sustained a previous myocardial infarction. The patients were maintained on a stable dose of diuretics and none had received vasodilators or digoxin.

Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometry. A Swan-Ganz catheter was inserted percutaneously via the neck for measurement of pulmonary artery pressure and pulmonary capillary wedge pressure. Cardiac output was

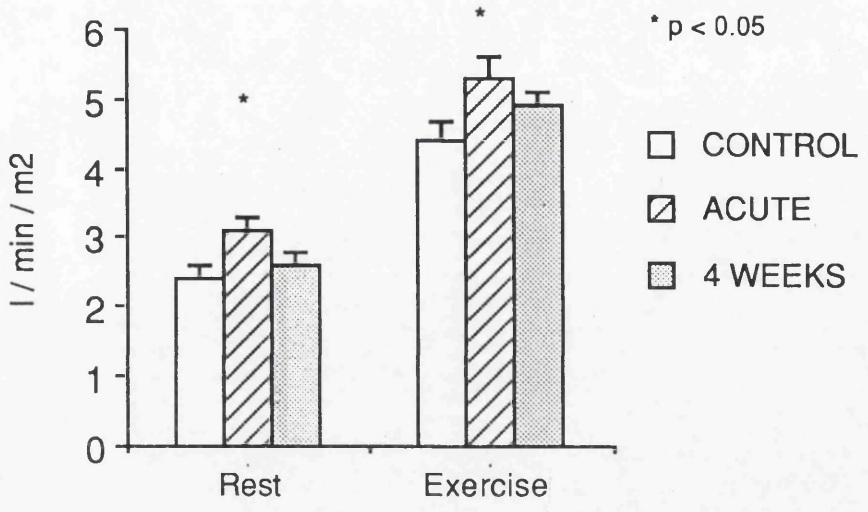
	Control	*Acute*	*4 weeks*
Heart rate (beats min^{-1})	124 ± 8	122 ± 7	121 ± 8
Systolic blood pressure (mm Hg)	154 ± 7	145 ± 6	147 ± 7
Diastolic blood pressure (mm Hg)	86 ± 3	83 ± 3*	81 ± 3*
Mean arterial pressure (mm Hg)	107 ± 4	103 ± 4	103 ± 4
Pulmonary capillary wedge pressure (mm Hg)	35 ± 4	27 ± 4**	31 ± 5
Cardiac index ($l\ min^{-1}\ m^{-2}$)	4.4 ± 0.3	5.3 ± 0.3*	4.9 ± 0.2
Stroke index ($ml\ beat^{-1}\ m^{-2}$)	36 ± 3	43 ± 4**	42 ± 4*
Systemic vascular resistance ($dyn\ s\ cm^{-5}$)	1113 ± 77	903 ± 65*	953 ± 57
Left ventricular ejection fraction (%)	15 ± 3	21 ± 4***	20 ± 3***

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.02$

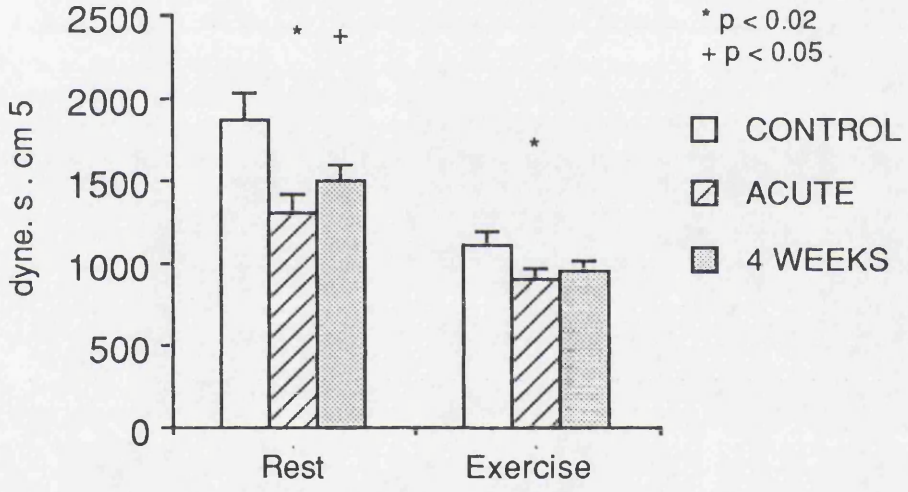

100
80
60
40
20
0
Heart Rate
beats /min
Mean Arterial
Pressure mmHg
CONTROL
ACUTE
4 WEEKS


150
100
50
0
Exercise Heart
Rate beats/min
Exercise Mean Arterial
Pressure mmHg
CONTROL
ACUTE
4 WEEKS

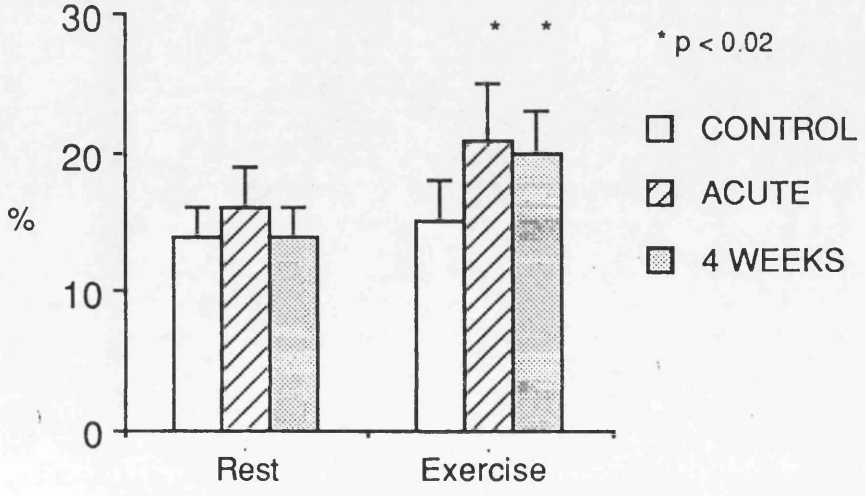
CARDIAC INDEX



SYSTEMIC VASCULAR RESISTANCE



LEFT VENTRICULAR EJECTION FRACTION



obtained by the thermodilution technique in triplicate. Ejection fraction was calculated from the radionuclide angiogram.

All haemodynamic measurements and radionuclide angiography were performed at rest and during upright dynamic exercise on a bicycle ergometer. The workload was predetermined for each individual as being near maximal and able to be sustained for two minutes. Two hours following the administration of placebo control data were obtained. The patient was then rested and depending on the haemodynamic response either 5 mg. or 10 mg. of felodipine were given six hourly. Rest and exercise measurements were repeated two hours after the fourth dose of felodipine, i.e. 24 hours after the initial control data. The patients were then given what appeared to be the optimal dose for four weeks and measurements were repeated at rest and during dynamic exercise two hours after the initial morning dose. In eight patients the dose was 10 mg. three times daily, in one 5 mg. three times daily and in one 5 mg. twice daily.

Results

The results are shown in Table 15. At rest there was no change in heart rate and very little change in blood pressure or pulmonary capillary wedge pressure. There was an initial increase in cardiac index but no change in stroke volume. Calculated systemic vascular resistance fell but left ventricular function measured by right and left ventricular ejection fractions was unchanged. During exercise heart rates were similar with felodipine treatment to control measurements as was systolic blood pressure. However diastolic blood pressure was significantly lower. Pulmonary capillary wedge pressure was lowered acutely but had returned to control values by four weeks. Exercise cardiac output and

stroke volume were both increased by felodipine with a reduction in calculated systemic vascular resistance. Exercise left ventricular ejection fraction improved and this improvement was maintained at four weeks.

Discussion

These results are in keeping with those of Timmis et al **(48)**. In patients with congestive cardiomyopathy and ischaemic heart disease felodipine would appear to be an effective arteriolar vasodilator with maintenance of the effect at four weeks. Systemic vascular resistance is reduced with subsequent changes in cardiac index, stroke volume index and ejection fraction. The fall in pulmonary capillary wedge pressure on exercise may well be secondary to the increase in stroke volume but an effect on capacitance vessels could not be excluded.

In patients with chronic heart failure increased cardiac output does not necessarily imply improved tissue perfusion. Skeletal blood flow may be normal at rest but fails to increase normally on exercise due partly to the inability of peripheral conductance vessels to dilate to appropriate stimuli and partly to the phenomenon of deconditioning which may result in structural changes in the muscles **(49,50)**. In a pig model of ischaemic heart failure nisoldipine (a calcium antagonist which 4-10 times the vasodilatory effect of nifedipine but with less cardiac depressant action) produces similar haemodynamic changes to felodipine. Blood flow to kidney, brain, liver and skin were unaffected but skeletal muscle flow increased by just over 350%. Blood flow also increased to normal myocardium by 60% and by nearly 50% to infarcted myocardium **(51)**.

Summary

Felodipine treatment for four weeks in patients with chronic heart failure produced maintenance of effect with reductions in systemic vascular resistance and cardiac index and increased left ventricular systolic function. Myocardial oxygen consumption was not increased, indeed myocardial flow may well improve and underlie the increased ventricular function.

Balanced Vasodilators

With the demonstrated advantageous effects of reduction impedance and the putative benefits of reduction in elevated filling pressure, a balanced vasodilator which acts on both arterial and venous sites should, theoretically, be the ideal therapeutic solution. Flosequinan (7-fluro-1-methyl-3-methyl-sulphinyl-4-quinolone, Boots) is a vasodilator which acts directly both on arterial and venous sites **(53)** and has previously been shown to be effective in prolonging exercise capacity, improving peak oxygen consumption and improving New York Heart Association grading **(54)**. Ten patients with exertional dyspnoea (New York Heart Association Grade III-IV) were studied. Heart failure was secondary to documented coronary artery disease and left ventricular function was severely impaired with resting left ventricular ejection fraction ranging between 6 and 22%. All patients were stabilised on optimal diuretic therapy for at least four weeks prior to the study.

Heart rate was obtained by the electrocardiogram and blood pressure by cuff sphygmomanometer. A Swan-Ganz thermodilution catheter was inserted percutaneously via the neck to give accurate measurements of pulmonary capillary wedge pressure and pulmonary artery pressure. Cardiac output measurements were by the thermodilution technique and

were in triplicate at rest, throughout exercise and post exercise for five minutes.

Symptom limited exercise tests were obtained using an electronically braked bicycle ergometer with the patient breathing a low dead space and low resistance valve box. The valve box incorporates a turbine ventilometer on the inspired limb for the measurement of ventilation. The expired limb is fed through a mixing chamber from which samples of air are analysed for carbon dioxide and oxygen by a infra-red spectrometer and paramagnetic analysis respectively. Ventilation and expired gas analysis were measured online throughout exercise and oxygen consumption and carbon dioxide production were calculated using standard equations. Arterial blood gas values were monitored using a transcutaneous system (TCM3 Radiometer Limited, Copenhagen) to measure transcutaneous oxygen ($tcpO_2$) and carbon dioxide ($tcpCO_2$) tensions. Indices of gas exchange, the alveolar oxygen gradient and dead space to tidal volume ratios were calculated. The patient exercised using a standard protocol already described. The non-invasive anaerobic threshold on exertion was calculated by the curve fitting method of Beever et al (see Appendix). Left and right ventricular function were obtained simultaneously from the technetium-99m radionuclide angiogram. Scans were obtained at rest and continuously throughout exercise and for five minutes post exercise by placing the Gamma camera close to the patient's chest in the left anterior oblique projection, with the left arm supported from the camera and the camera angled to give the best septal separation.

Table 16(a) Resting haemodynamics acutely and after 6 weeks' treatment with Flosequinan then Ouabain

Resting Haemodynamics

	Control	24 hours/Acute	6 Weeks		+ Ouabain	
HR	92.30 ± 11.7	95.20 ± 16.6	93.70 ± 11.3	nsd	89.7 ± 11.0	nsd
SBP	115.50 ± 16.7	106.80 ± 12.2	116.00 ± 16.3	$p<0.02$	119.3 ± 20.1	$p<0.02$
DBP	79.20 ± 8.8	69.80 ± 9.7	78.00 ± 9.9	nsd	82.2 ± 11.4	$p<0.02$
SMPA	32.30 ± 13.8	26.00 ± 11.2	25.70 ± 14.9	nsd	29.6 ± 13.2	nsd
DMPA	21.30 ± 8.1	17.40 ± 8.7	16.20 ± 9.9	nsd	19.6 ± 9.6	nsd
CI	2.21 ± 0.45	2.47 ± 0.595	2.42 ± 0.31	nsd	2.57 ± 0.59	nsd
S Vol I	25.50 ± 5.2	26.60 ± 8.6	25.90 ± 4.8	nsd	29.4 ± 7.9	nsd
LVEF	11.10 ± 4.73	14.50 ± 5.29	13.20 ± 4.8	nsd	14.9 ± 5.0	nsd
DP	10286.00 ± 2577	10084.00 ± 2541	10873.00 ± 1900	nsd	10679 ± 1982	nsd
SVR	1863.60 ± 429	1534.00 ± 405	1675.00 ± 342	nsd	1733 ± 635	nsd
PVR	466.60 ± 226	402.30 ± 322	338.80 ± 318	nsd	446.4 ± 317	nsd
VO_2	285.10 ± 33.5	284.70 ± 27.9	282.80 ± 20.2	nsd	289.8 ± 24.4	nsd
PaO_2	87.70 ± 8.29	86.70 ± 7.65	86.40 ± 8.53	nsd	89.67 ± 7.09	nsd

Table 16(b) Exercise haemodynamics acutely and after 6 weeks' treatment with Flosequinan then Ouabain

Exercise Haemodynamics

		Control	Acute	6 Weeks		+ Ouabain	
HR	beats/min	128.20 ± 19.0	137.90 ± 23.6	136.00 ± 18.2	nsd	130.20 ± 22.0	nsd
SBP	mm.Hg.	145.60 ± 20.3	155.20 ± 19.1	156.60 ± 25.7	nsd	161.80 ± 24.0	nsd
DBP	mm.Hg.	85.00 ± 10.8	84.00 ± 10.7	86.20 ± 14.2	nsd	91.30 ± 14.6	nsd
SMPA	mm.Hg.	60.60 ± 27.0	50.20 ± 24.2	56.10 ± 25.6	nsd	41.00 ± 22.1	nsd
DMPA	mm.Hg.	37.40 ± 18.9	34.70 ± 20.0	37.50 ± 13.9	nsd	30.40 ± 16.8	nsd
CI	l/m/m^2	4.29 ± 1.07	*5.26 ± 0.81	4.74 ± 1.49	$p<0.04$	5.09 ± 1.41	$p<0.06$
S Vol I	ml/beat/m^2	33.80 ± 8.0	38.90 ± 9.0	34.90 ± 10.8	nsd	38.20 ± 10.3	nsd
LVEF	%	12.80 ± 4.5	13.90 ± 6.2	14.70 ± 5.9	nsd	14.60 ± 7.43	nsd
DP	HR x SBP	18809 ± 4523	*21577 ± 5441	21886 ± 5190	$p<0.02$	21168 ± 4981	nsd
SVR	dyne-s-cm^{-5}	1139 ± 330	903 ± 158	*1082 ± 326	$p<0.04$	1064 ± 289	nsd
PVR	dyne-s-cm^{-5}	436 ± 319	310 ± 199	399 ± 238	nsd	325 ± 193	nsd

Table 16(c) **Ventilation and respiratory gas analysis acutely and after 6 weeks' treatment with Flosequinan then Ouabain on exercise**

VO_2	881.4	± 200.5	822.7	± 182.8	921.3	± 250.8	nsd	849.1 ± 224.4	nsd
VO_2	881.4	± 200.5	814.3	± 193.2	856.8	± 228.9	nsd	827.9 ± 184.0	nsd
VE	33.9	± 9.3	36.0	± 6.7	38.3	± 9.1	nsd	36.7 ± 9.6	nsd
PAO_2	99.1	± 11.46	90.0	± 11.96	93.5	± 9.64	$p<0.03$	95.4 ± 11.35	$p<0.01$
$A\text{-}aO_2$	18.13	± 6.72	18.30	± 10.52	17.24	± 6.66	nsd	16.34 ± 6.10	nsd
Vd/Vt	47.27	± 17.26	45.19	± 9.27	41.13	± 13.54	nsd	41.49 ± 15.6	nsd
Exercise time (mins)	7.8	± 2.89	8.0	± 2.53	8.8	± 2.74	nsd	8.33 ± 3.39	nsd

VO_2 = oxygen consumption
VO_2 same = oxygen consumption at same work load as control exercise test
VE = minute ventilation
PAO_2 = arterial oxygen on exercise
$A\text{-}aO_2$ = alveolar-arterial oxygen gradient
Vd/Vt = dead space/tidal volume ratio

Results

Detailed results are seen in the Tables opposite. There was a small change in the resting heart rate with flosequinan given acutely and a small drop in systolic blood pressure, consistent with vasodilatation. As might be expected in this group of patients with severely impaired left ventricular function, cardiac index and stroke volume index were reduced. During exercise, flosequinan given acutely produced an increase in exercise cardiac index but this was attenuated by six weeks as was a small and insignificant increase in stroke volume. Left ventricular ejection fraction and pulmonary artery diastolic pressure (pulmonary capillary wedge pressure) were unaltered. With intravenous ouabain exercise heart rate was similar to control but exercise systolic blood pressure was increased, producing a significant increase in double product with a small insignificant increase in left ventricular ejection fraction.

On exercise 9/10 patients achieved their anaerobic threshold. Oxygen consumption was unaltered by flosequinan therapy either at peak exercise or at the same watt load as the initial exercise test. Similarly, arterial blood gas values and indices of gas exchange were unaltered by treatment. Exercise was performed to a symptom limited maximum as indicated by the patient raising his hands and there was no difference in exercise times with treatment.

Discussion

Flosequinan is thought to modify the phosphoinositide pathway and have a weak non-selective inhibitory activity against phospho-diesterase. Previous work has suggested that the drug is effective long term in patients with chronic heart failure in both reducing filling pressure and

impedance and thus producing symptomatic improvement **(54-57)**. Results from the V-HeFT study, of the combination of prazosin and hydrallazine, showed significantly lower mortality compared to placebo which with the high incidence of side effects requiring withdrawal from the trial **(58)**. Conceptually a drug with venodilating action and effects on arteriolar resistance vessels is attractive.

In our patients at best, there were minor reductions in pulmonary artery diastolic pressure and small falls in blood pressure and systemic vascular resistance (and also pulmonary vascular resistance) with small increases in cardiac index and left ventricular ejection fraction. On exercise higher heart rate and systolic blood pressures were achieved with higher double product which is a reflection of myocardial oxygen consumption. Exercise systemic vascular resistance was reduced and cardiac index increased but there was no change in maximal oxygen consumption, exercise time or anaerobic threshold or indeed in ventricular function.

Ouabain given intravenously produced a further small increase in the exercise systolic blood pressure and increased cardiac output but with no change in ventricular function. These patients were undoubtedly substantially impaired and although exercise haemodynamics improved a little, there was no change in exercise capacity.

Summary

Although theoretically a balanced vasodilator would appear to be advantageous, in this group of patients with severely compromised left ventricular function, flosequinan had little effect.

Right Ventricular Function

Vasodilators can be effective in patients with chronic cardiac failure, but the benefits achieved in an individual patient vary considerably. It has been suggested that the response may depend on the extent of the reflex's constrictory action **(59)** or on the initial size of the left ventricle **(60)**. Clinical observations suggested that the response to afterload reduction was smaller in patients when right ventricular function was impaired.

Methods

Fifteen male patients with New York Heart Association Grade III-IV heart failure secondary to coronary artery disease were studied. The mean age was 53 years with an age range of 46-62 years. All were on stable diuretic therapy and none had received vasodilators or digoxin.

Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometer. A Swan-Ganz catheter was inserted percutaneously for the measurement of pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output. Right and left ventricular function were obtained from radionuclide scans using a mobile Gamma camera. Measurements were made at rest and 20-30 minutes following 10 mg. of oral felodipine when maximum haemodynamic changes are known to occur.

Results

Fifteen patients were arbitrarily divided on the basis of their right ventricular function (RVEF 25%). In 10 patients the right ventricular function was considered to be preserved with a mean RVEF of 33 $\pm$ 1%. Five patients were considered to have right ventricular dysfunction with a right ventricular ejection fraction of 20 $\pm$ 3%. Left ventricular

Table 17(a) **Haemodynamic variables in patients with preserved right ventricular function and right ventricular dysfunction**

Resting Measurements

		RVEF <25%	RVEF >25%	
HR	beats/minute	85 ± 6	71 ± 5	nsd
SBP	mm.Hg.	114 ± 2	129 ± 6	nsd
DBP	mm.Hg.	69 ± 8	83 ± 4	nsd
Mean	mm.Hg.	83 ± 5	100.5 ± 4	nsd
DPA	mm.Hg.	27 ± 7	17 ± 2	nsd
CI	l/min/m^2	2.25 ± 0.4	2.48 ± 0.08	nsd
SI	ml/beat/m^2	24.7 ± 3	37.2 ± 3	nsd
LVEF	%	12 ± 3	18 ± 2	nsd
RVEF	%	20 ± 3	33 ± 1	
Exercise time (seconds)		146 ± 15.5	168 ± 22	nsd

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; DPA = diastolic pulmonary artery pressure; CI = cardiac index; SI = stroke volume index; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.

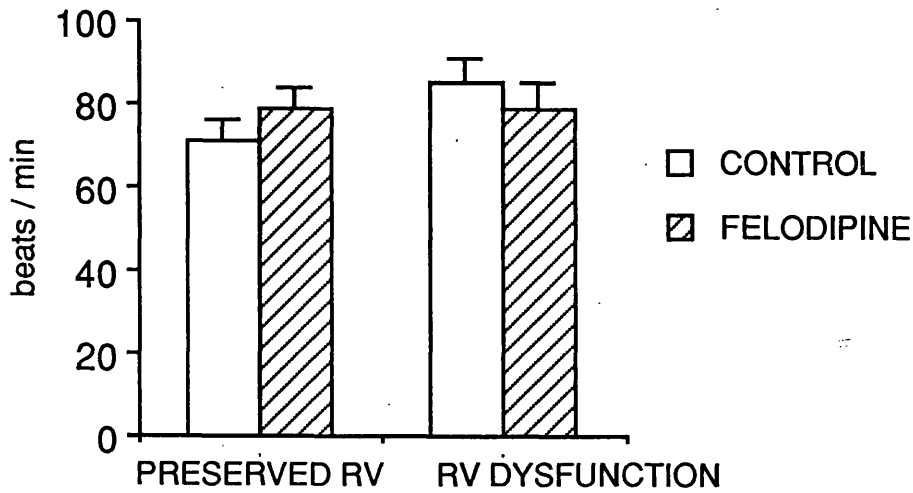
Table 17(b)

Treatment with Arteriolar Dilator

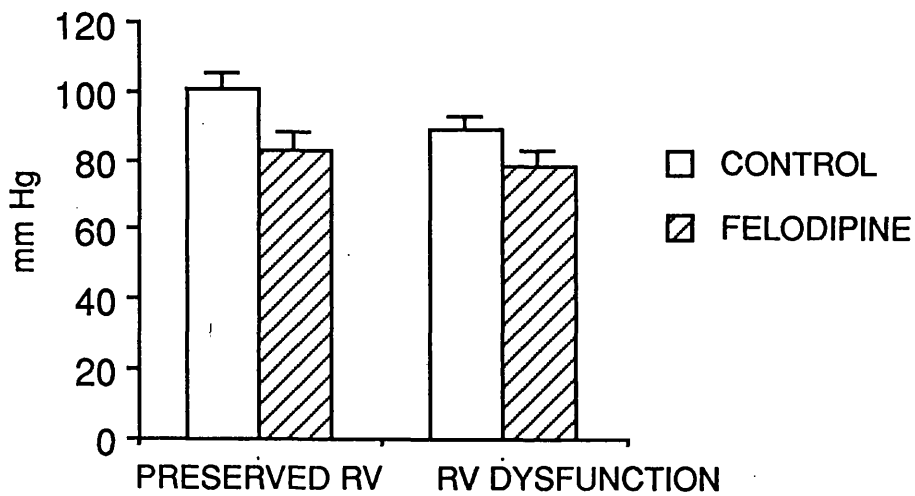
		RVEF <25%	RVEF >25%	
HR	beats/minute	79 ± 6	79 ± 5	nsd
SBP	mm.Hg.	108 ± 3	112 ± 7	nsd
DBP	mm.Hg.	67 ± 5	71 ± 4	$p<0.02$
Mean	mm.Hg.	78 ± 5	87 ± 3	$p<0.005$
DPA	mm.Hg.	18 ± 3	15 ± 2	nsd
CI	$l/min/m^2$	2.58 ± 0.4	3.29 ± 0.21	$p<0.02$
SI	$ml/beat/m^2$	30.7 ± 3	41.9 ± 2	nsd
LVEF	%	13 ± 4	20 ± 3	nsd

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; DPA = diastolic pulmonary artery pressure; CI = cardiac index; SI = stroke volume index; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.

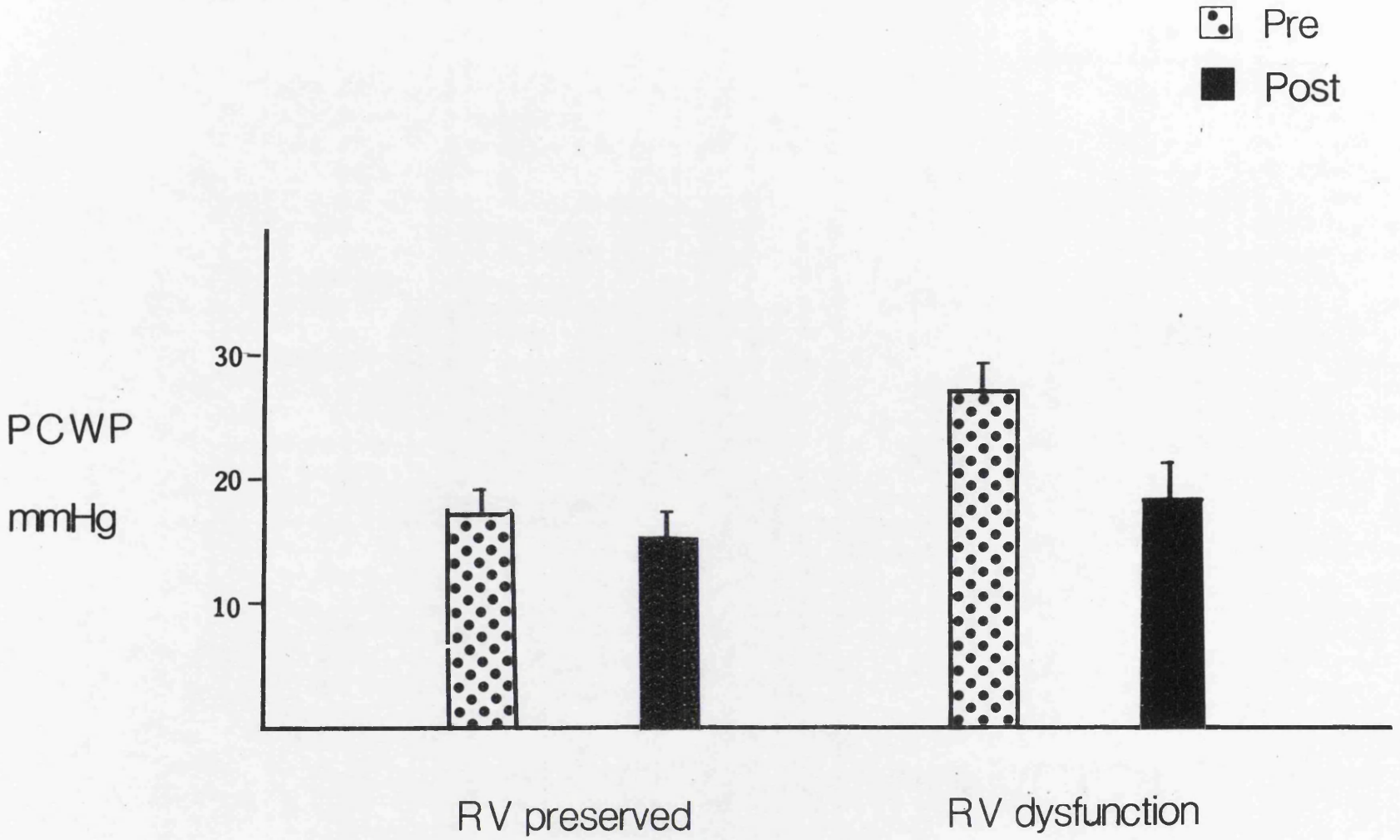
HEART RATE



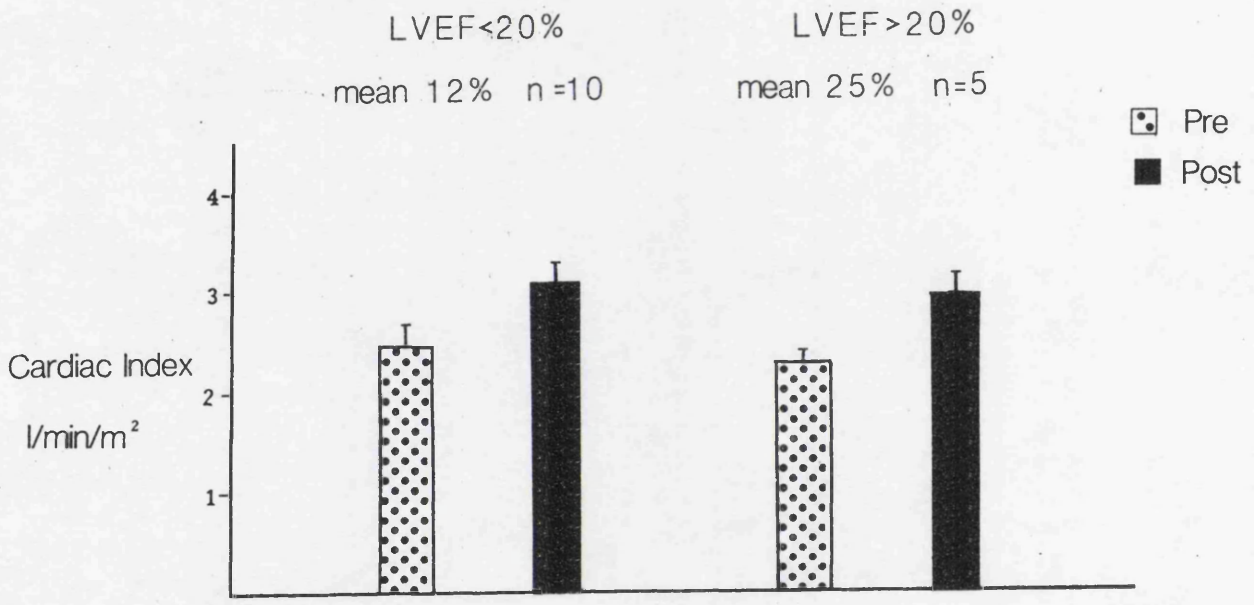
MEAN ARTERIAL PRESSURE



PULMONARY CAPILLARY WEDGE PRESSURE



10 patients		5 patients	
LVEF	Range 10-29% Mean 19%	LVEF	Range 10-23% Mean 13%
RVEF	Range 25-40%	RVEF	Range 12-24%
RV preserved		RV dysfunction	


LVEF<20%
mean 12% n=10
LVEF>20%
mean 25% n=5
Pre
Post
Cardiac Index
l/min/m²
4
3
2
1

ejection fraction in both groups was similar. In the 10 patients with preserved right ventricular function the range for left ventricular ejection fraction was 7-29% with a mean of 19 $\pm$ 2%. In those with right ventricular dysfunction left ventricular ejection fraction ranged from 7 to 23% with a mean of 12 $\pm$ 3% (nsd). Baseline haemodynamic measurements between the two groups were similar. Heart rate, blood pressure, diastolic pulmonary artery pressure, cardiac index, stroke volume index and systemic vascular resistance (not shown) were not statistically significantly different between the two groups. Exercise tolerance was similar in both groups. With treatment with felodipine in the group with right ventricular dysfunction heart rate fell whereas in those patients with preserved right ventricular function blood pressure fell and there was a small reflex tachycardia. Cardiac index increased significantly in those patients with preserved right ventricular function but did not change in those with right ventricular dysfunction.

To determine whether this effect was due to associated left ventricular dysfunction, the patients were re-divided on the basis of left ventricular ejection fraction. Ten patients had a left ventricular ejection fraction of less than 20% (mean 12 $\pm$ 2%) and five had a LVEF of greater than 20% (25 $\pm$ 2%). The mean increase in cardiac index induced by treatment with arteriolar vasodilators was similar in both groups 2.47 $\pm$ 0.2 to 3.14 $\pm$ 0.4 litres/minute/m^2 where left ventricular ejection fraction was less than 20% and 2.29 $\pm$ 0.15 to 2.96 $\pm$ 0.25 litres/minute/m^2 where the left ventricular ejection fraction was greater than 20%.

Discussion

There is very little information in the literature concerning chronic right ventricular dysfunction in patients with coronary artery disease, as opposed to those with chronic obstructive airways disease. In chronic pulmonary hypertension secondary to obstructive airways disease, generally drugs that reduce afterload increase cardiac output with minimal changes in pressure, whereas drugs that reduce preload markedly reduce right ventricular filling pressure with a minimal change in cardiac output with certain similarities to the situation in the left ventricle **(61)**. Since the right ventricular ejection fraction is highly dependent on afterload **(62)** effective arteriolar vasodilation would be expected to increase right ventricular systolic performance **(63)**. Right ventricular systolic function is linearly related to end systolic volume **(64)** above a right ventricular ejection fraction of 20%. Below this value there is little relationship.

Changes in right ventricular function are known to affect left ventricular pressure generation **(65)** and indeed there is inter-dependence between the damaged left ventricle and right ventricle if septal function is abnormal **(66)**.

In this study the patients had substantially impaired right and left ventricular function. The right ventricle dilates as it becomes increasingly dysfunctional but there must come a point at which it no longer acts as the pump but merely as a conduit and haemodynamic data would suggest that this may be in the region of a RVEF of 20% **(64)**. A dilated, grossly dysfunctional right ventricle may not be capable of improvement, whereas the right ventricle that is less damaged is capable

of improving which, in turn, due to inter-dependence between the ventricles would be translated into improved left ventricular ejection.

In a study of 29 patients with severe left ventricular dysfunction given nifedipine **(67)** the patients in whom cardiac index increased acutely, long term prognosis was better than in the 16 patients who exhibited haemodynamic deterioration with a marked hypotensive response. Patients were identical with respect to other haemodynamic measurements except that plasma renins were higher and serum sodiums lower in those whose haemodynamics deteriorated in response to nifedipine, and in fact this latter was the most powerful of those three variables in predicting the long term prognosis. Unfortunately in that study right and left ventricular ejection fractions were not measured. We know from previous work in acute myocardial infarction that right ventricular dysfunction in association with left ventricular dysfunction carries a grave prognosis (see under Right Ventricular Function).

In summary, in patients with left ventricular dysfunction the haemodynamic response to vasodilators may be partly dependent on right ventricular performance.

Inotropic Agents

The use of inotropic agents is based on the premise that although the myocardium is depressed, there is residual contractile reserve which is capable of contributing to improvement in myocardial performance. In heart failure, catecholamine stimulation is part of the heart's adaptive response to reduced output **(68,69)**. In the myocardium, catecholamines increase contractility by stimulation of the beta receptors on the myocardial cell surface, but also increase heart rate. The

HAEMODYNAMIC EFFECTS OF PRENALTEROL IN PATIENTS WITH L.V. DYSFUNCTION

	CONTROL	PRENALTEROL	
HEART RATE beats/min	74±4	90±6	***
SYSTOLIC BLOOD PRESSURE mmHg	115±7	116±2	
DIASTOLIC BLOOD PRESSURE mmHg	71±4	73±2	
MEAN BLOOD PRESSURE mmHg	87±6	88±3	
CARDIAC INDEX $L/min/m^2$	3.1±0.2	3.6±0.3	**
STROKE INDEX mls/m^2	42±4	41±4	
PULMONARY CAPILLARY WEDGE mmHg	9±1	7±1	
CORONARY SINUS BLOOD FLOW mls/min	107±4	133±12	*
MYOCARDIAL OXYGEN CONSUMPTION mls/min	11.6±1.2	14.5±2	

Results are mean ± S.E.M. of 6 patients

* $P < 0.05$ ** $P < 0.02$ *** $P < 0.005$

sympathomimetic amines dopamine and dobutamine are effective inotropic agents, with differing degrees of associated vasodilation due to dopaminaergic or $beta_2$ effects, but require to be given as an infusion.

Various attempts have been made to synethise agents that act as agonists to $beta_1$ or $beta_2$ receptors with various degrees of specificity. Prenalterol was a relatively selective $beta_1$ agonist which, in volunteers, produced an inotropic effect with a small increase in heart rate **(70)**. In patients with coronary heart disease it increased left ventricular dp/dt with no change in heart rate **(71)**.

Methods A

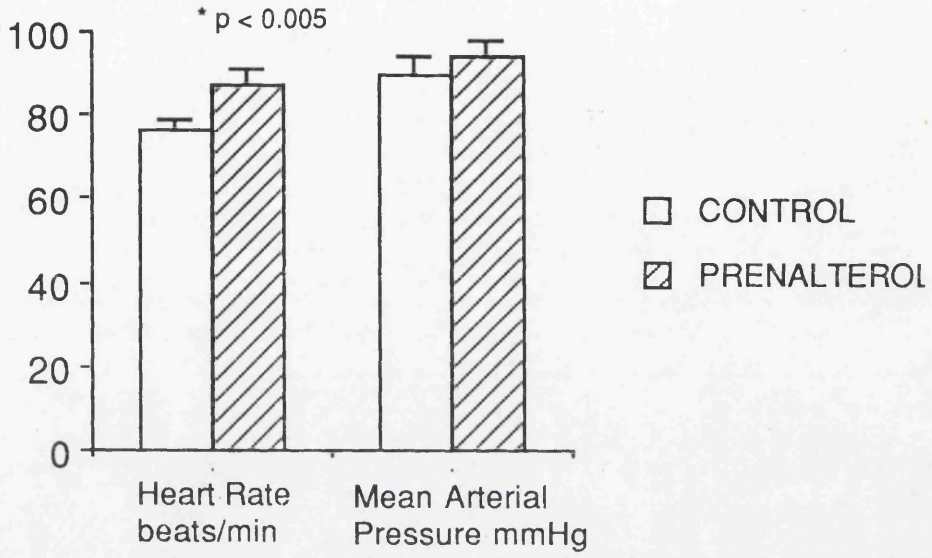
We studied six patients with left ventricular dysfunction secondary to coronary artery disease, all patients having sustained a previous myocardial infarction. The mean age was 47 years with a range of 37-59 years and no patient had taken any drug therapy for 48 hours. Heart rate was obtained from the electrocardiogram and blood pressure from an intra-arterial line placed in the descending aorta. A Swan-Ganz catheter was inserted percutaneously for the measurement of pulmonary capillary wedge pressure and pulmonary artery pressure. Cardiac output was obtained by thermodilution in triplicate. Coronary sinus flow was also obtained by the thermodilution technique via a Wilton Webster catheter placed in the coronary sinus. Simultaneous sampling from the arterial line and the coronary sinus allowed the measure of oxygen content and myocardial oxygen consumption to be assessed. Prenalterol was given in a dose of 1.5 mg. in 50 ml. over 30 minutes. Results are seen in the Table opposite. There was an increase in cardiac index but this was accompanied by a significant (20%) increase in heart rate. There was no change in blood pressure or filling pressure. Coronary sinus flow

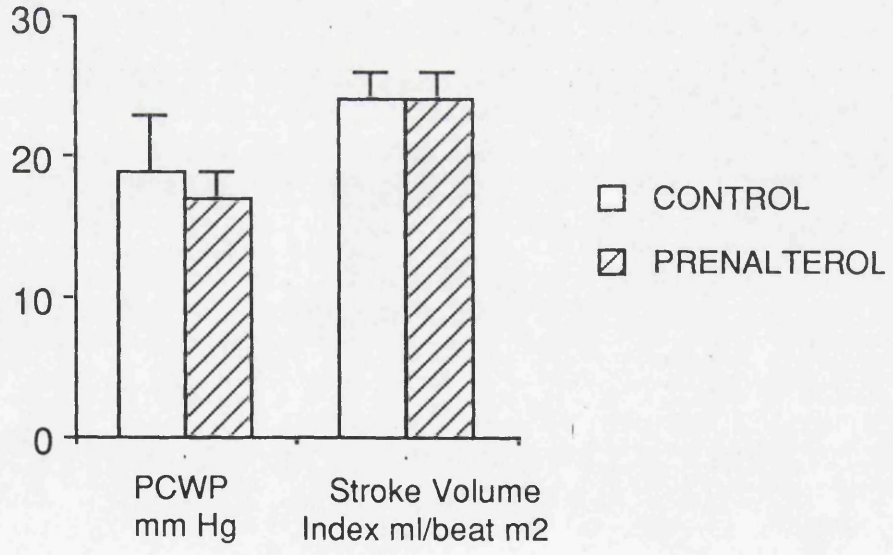
Table 19 **Haemodynamic effects of Prenalterol in patients with chronic cardiac failure**

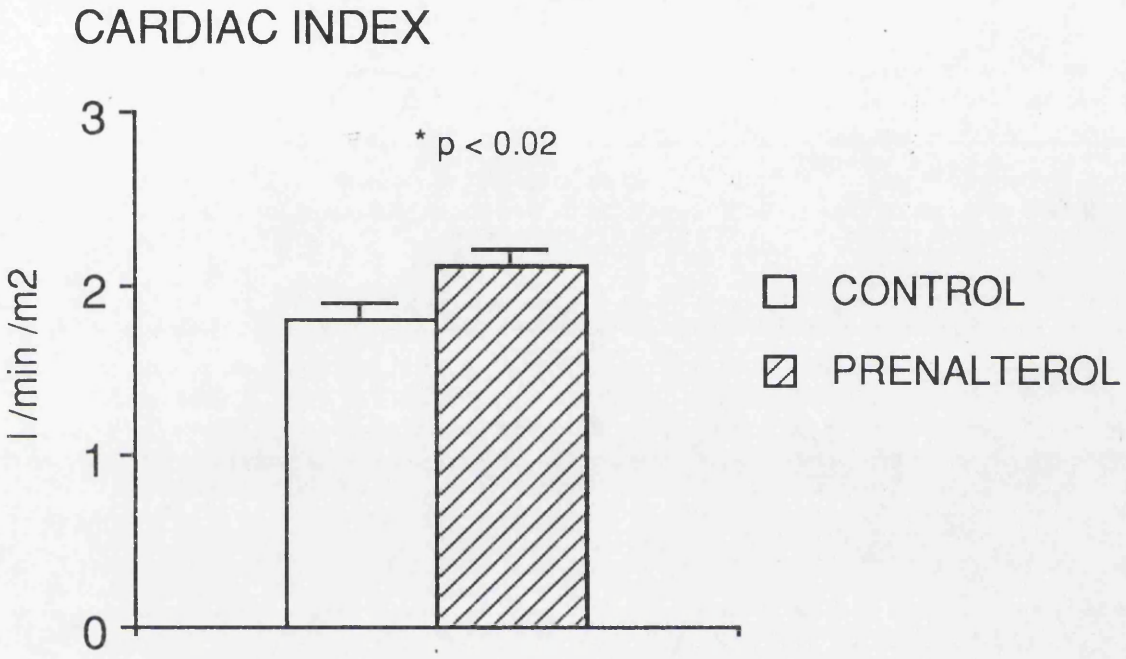
n = 9 Mean ± SEM

		Rest		Exercise	
		Control	Prenalterol	Control	Prenalterol
HR	beats/minute	76 ± 3	87 ± 4**	125 ± 10	120 ± 7
SBP	mm.Hg.	120 ± 6	130 ± 7∇	157 ± 12	163 ± 13
DBP	mm.Hg.	75 ± 3	75 ± 4		
Mean BP	mm.Hg.	90 ± 4	94 ± 4		
CI	$l/min/m^2$	1.8 ± 0.1	2.1 ± 0.1∇	3.0 ± 0.3	3.4 ± 0.2
SVI	$ml/beat/m^2$	24 ± 2	24 ± 2	25 ± 2	29 ± 3
PCWP	mm.Hg.	19 ± 2	17 ± 2	33 ± 6	26 ± 3*
EF	%	22 ± 3	28 ± 3∇		
SWI	$g/m/m^2$	23 ± 4	25 ± 3	25 ± 4	31 ± 5
SVR	$dynes\text{-}s\text{-}cm^{-5}$	2285 ± 193	2041 ± 201*	1733 ± 134	1414 ± 187*

* $p<0.05$ ** $p<0.005$ ∇ $p<0.02$


* p < 0.005
100
80
60
40
20
0
Heart Rate
beats/min
Mean Arterial
Pressure mmHg
CONTROL
PRENALTEROL


30
20
10
0
PCWP
mm Hg
Stroke Volume
Index ml/beat m2
CONTROL
PRENALTEROL


CARDIAC INDEX
* p < 0.02
l /min /m2
3
2
1
0
CONTROL
PRENALTEROL

increased but this was also accompanied by an increase in myocardial oxygen consumption although this was not significant.

Methods B

We studied nine patients with New York Heart Association Grade III heart failure with a mean of age of 51 years and an age range of 45 to 65 years. Heart rate was obtained from the electrocardiogram, blood pressure by cuff sphymomanometer and a Swan-Ganz catheter was inserted percutaneously via the neck for measurement of pulmonary artery pressure and pulmonary capillary wedge pressure. Cardiac output was obtained by thermodilution. Left ventricular function was measured by radionuclide angiography. Prenalterol was infused at a dose of 1.5 ug/kg.

Results

Detailed results are tabulated opposite.

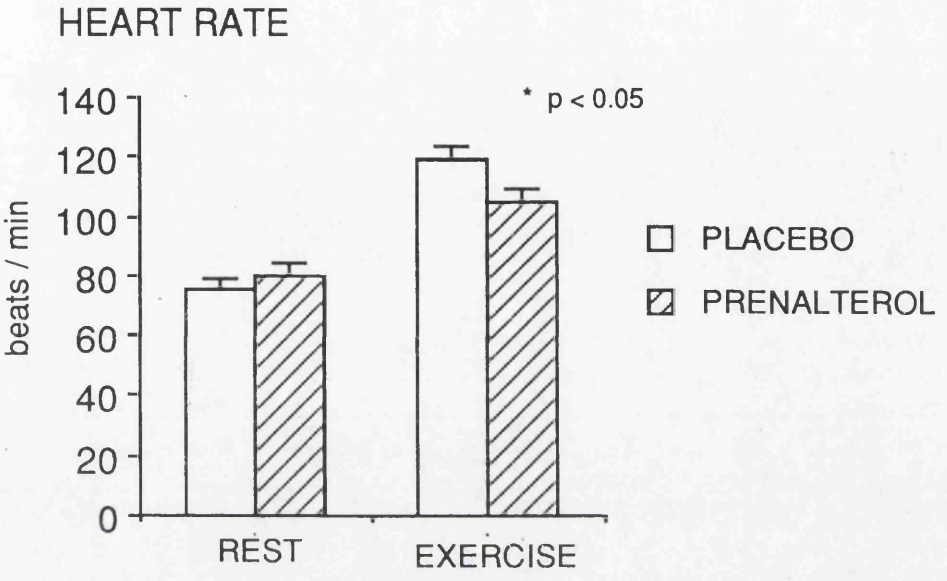
At rest there was a small increase in cardiac index from 1.8 to 2.1 litres/min/m^2, which was associated with an increase in heart rate and systolic blood pressure and a fall in calculated systemic vascular resistance. Filling pressure did not change. On exercise heart rate was unchanged as was blood pressure and filling pressure. Calculated systemic vascular resistance was lower and this was associated with a small (13%) increase in cardiac index.

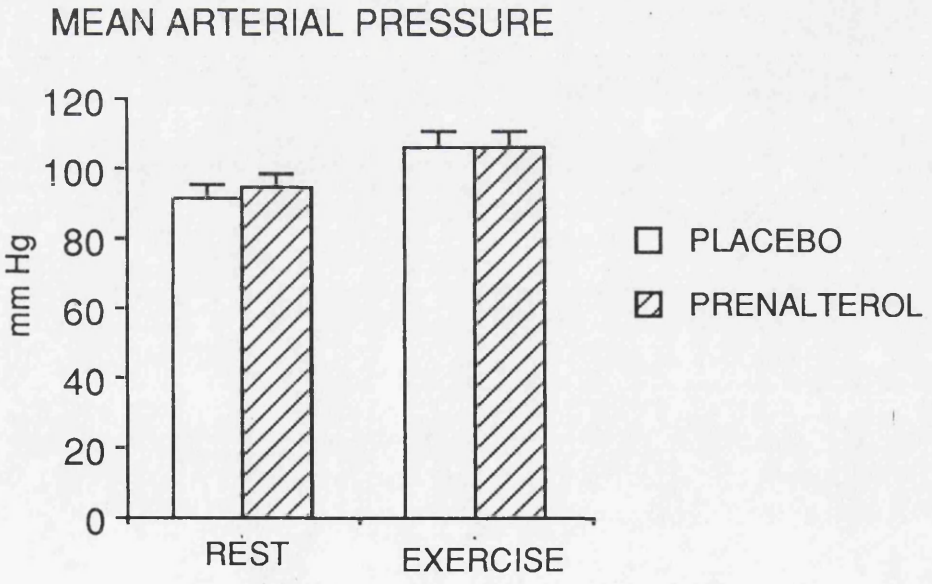
Methods C

We studied 10 male patients with New York Heart Association grade III-IV heart failure secondary to coronary artery disease. The mean age was 52 years with an age range of 47 to 57 years. The dose of Prenalterol to

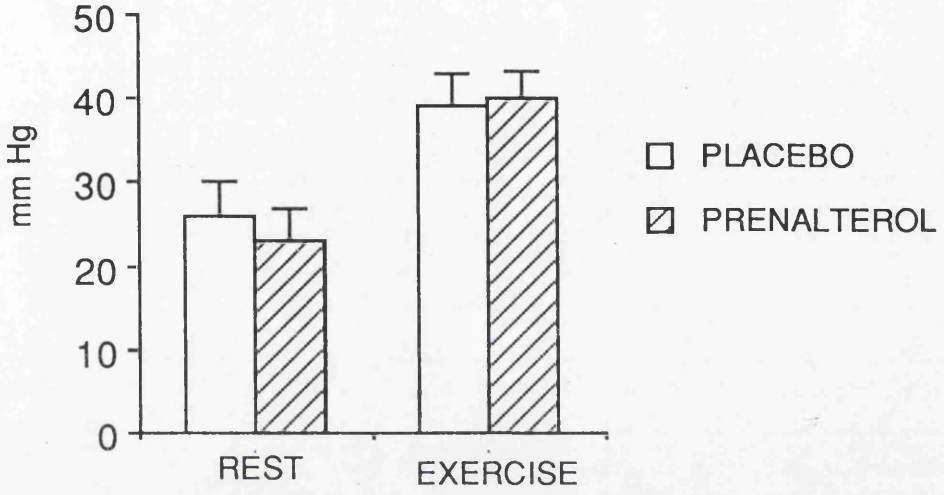
Table 20 **Systemic and coronary haemodynamic changes with oral prenalterol vs placebo at rest and on exercise**

		Rest		Exercise	
		Placebo	Prenalterol	Placebo	Prenalterol
HR	beats/minute	75 ± 4	80 ± 4	119 ± 5	104 ± 4
SBP	mm.Hg.	115 ± 5	124 ± 5	152 ± 11	147 ± 8
DBP	mm.Hg.	79 ± 4	81 ± 3	84 ± 3	84 ± 3
Mean	mm.Hg.	91 ± 4	95 ± 4	107 ± 5	105 ± 5
PCWP	mm.Hg.	26 ± 4	23 ± 4	38 ± 4	39 ± 4
CI	$l/min/m^2$	2.07 ± 0.19	2.50 ± 0.12	3.63 ± 0.41	3.47 ± 0.35
SVI	$ml/beat/m^2$	31 ± 3	33 ± 3	30 ± 3	33 ± 4
EF	%	18.4 ± 2.1	20.3 ± 2.1	21.1 ± 2.4	19.7 ± 2.5
DP	HR x SBP	8726 ± 710	9967 ± 577	18375 ± 1830	15306 ± 989
SVR	$dynes\text{-}s\text{-}cm^{-5}$	1883 ± 156	1701 ± 83	1396 ± 151	1520 ± 250

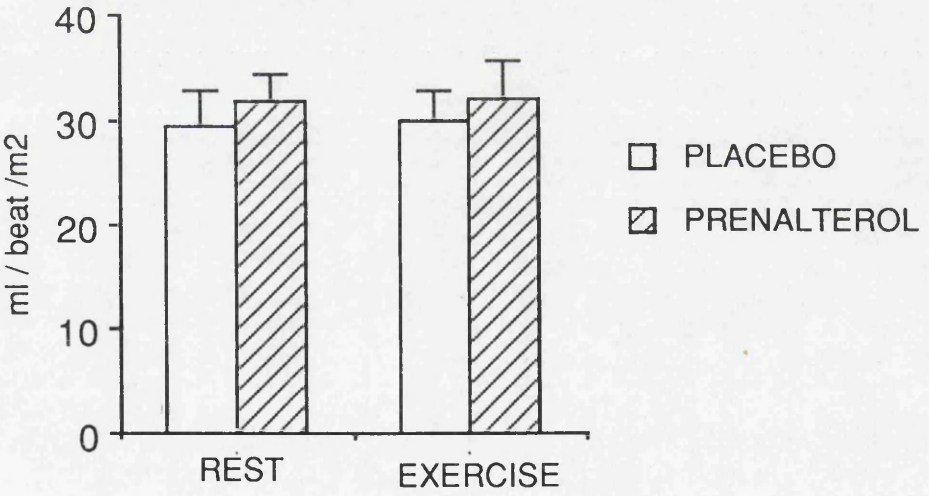

HEART RATE
* p < 0.05
beats / min
140
120
100
80
60
40
20
0
REST
EXERCISE
PLACEBO
PRENALTEROL


MEAN ARTERIAL PRESSURE
mm Hg
120
100
80
60
40
20
0
REST
EXERCISE
PLACEBO
PRENALTEROL

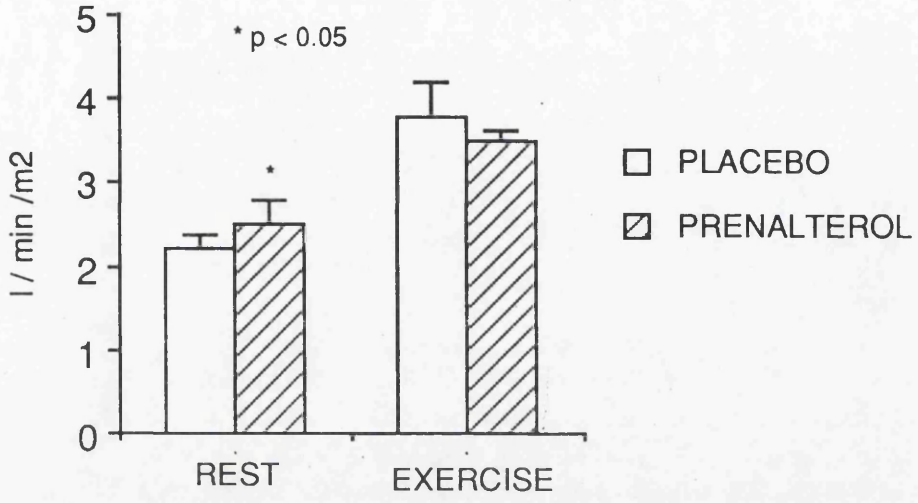
PULMONARY CAPILLARY WEDGE PRESSURE



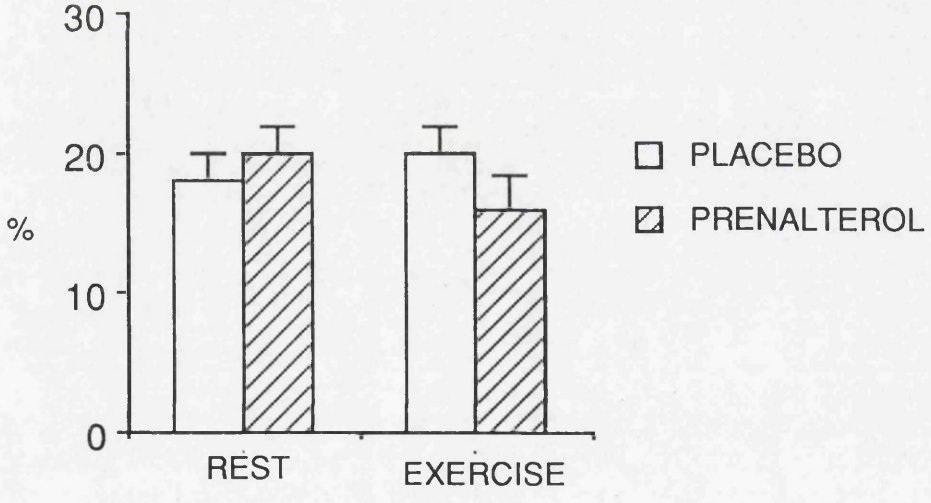
STROKE VOLUME INDEX



CARDIAC INDEX



LEFT VENTRICULAR EJECTION FRACTION



be given was predetermined by that which gave an increase in heart rate of 10 beats/minute or a maximum of 100 mg. Placebo or prenalterol were given in a randomised cross-over fashion for periods of four weeks. At the end of each four week period measurements were obtained at rest and throughout exercise using a bicycle ergometer at a predetermined near maximal workload which could be sustained for three minutes. Heart rate was obtained from an electrocardiogram, blood pressure by cuff sphygmomanometer. A Swan-Ganz catheter was inserted percutaneously for measurement of pulmonary capillary wedge pressure and pulmonary artery pressure and cardiac output which was obtained by the thermo-dilution technique. Left ventricular ejection fraction was obtained by radionuclide angiography.

Results

At rest heart rate was increased compared to placebo and although cardiac output measurements were significantly increased, cardiac index although higher was not significantly different. With exercise, heart rate with prenalterol treatment was lower than with placebo, thus the double product of heart rate and systolic blood pressure was 14% lower during exercise. However, systemic vascular resistance was elevated but left ventricular filling pressure was identical.

Discussion

Prenalterol, the relatively selective $beta_1$ agonist, which given as an infusion produces an increase in cardiac output but with an increased heart rate. Coronary sinus flow is enhanced but with an increased myocardial oxygen consumption. The increased cardiac output appears to be mainly dependent on a reduced calculated systemic vascular resistance presumably due to a vasodilatory action. With oral treatment

for four weeks resting heart rate effect was maintained and there was a small increase in cardiac output but no haemodynamic benefit on exercise. This loss of efficacy is thought to be due to "down-regulation", or a progressive decrease in the number of active beta-receptors, presumably as a protective response by the myocardium to over-stimulation from the sympathetic system **(72, 73)**.

Digoxin

Since Withering wrote his treatise on the use of digoxin, there has been controversy as to its efficacy where the controversy concerned types of patients who should receive digoxin **(74)**, much as today **(75)**. As in Withering's day, it is difficult to demonstrate efficacy when the drug is given inappropriately, the effects being of greater benefit as the heart failure becomes worse **(76)**. It produces a mild inotropic effect by inhibiting membrane sodium potassium ATPase activity resulting in enhanced calcium entry into the cells **(77)**.

Methods

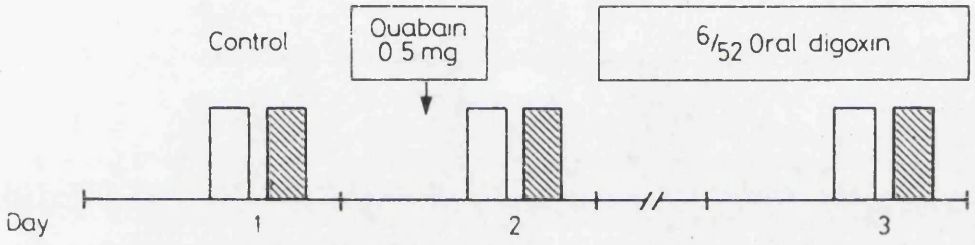
We studied 10 patients, nine of whom were male, of New York Heart Association grade III-IV heart failure with a mean age of 51 years and a range of 42 - 65 years. Heart rate was obtained from the electrocardiogram and blood pressure by cuff sphygmomanometer. A Swan-Ganz catheter was inserted percutaneously for the measurement of pulmonary capillary wedge pressure and pulmonary artery pressure and cardiac output which was obtained by the thermodilution technique in triplicate. Left ventricular function was measured by radionuclide angiography. Measurements were made at rest and during dynamic exercise at a fixed workload. Twenty four hours later a second set of measurements were made following 0.5 mg. of intravenous ouabain, again at rest and during

RESTING HAEMODYNAMIC DATA

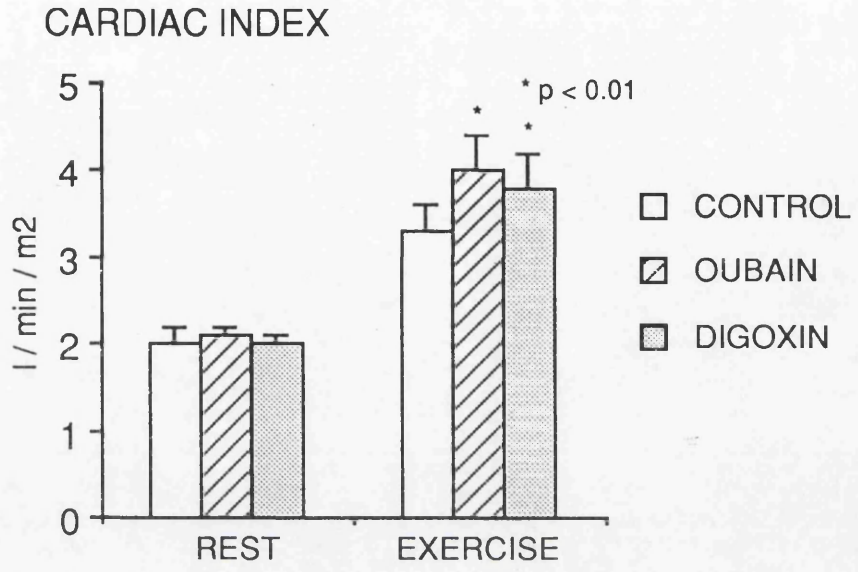
	Control	Ouabain	Digoxin
Heart Rate (beats/min.)	69 ± 3.6	67 ± 2.7	67 ± 2.9
Mean Arterial Pressure (mm Hg.)	89 ± 3.1	88 ± 3.5	91 ± 3.2
LVFP (mm Hg)	19 ± 2.6	17 ± 1.8	18 ± 1.8
Cardiac Index ($l/min/m^2$)	2.0 ± 0.2	2.1 ± 0.1	2.0 ± 0.1
Stroke Volume Index ($ml/beat/m^2$)	29 ± 3	32 ± 2	29 ± 2
Total Systemic Resistance ($dyn.sec.cm^{-5}$)	2080 ± 200	1849 ± 84	2121 ± 129
Stroke Work Index ($g.m/m^2$)	35 ± 4.2	38 ± 3.6	35 ± 3.2
LVEF (%)	33 ± 2.7	32 ± 2.3	35 ± 2.3

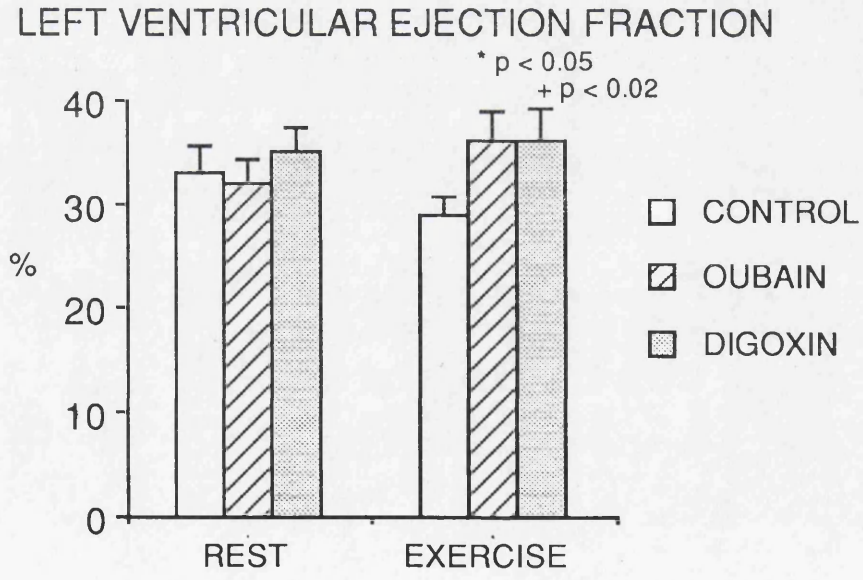
EXERCISE HAEMODYNAMIC DATA

	Control	Ouabain	Digoxin
Heart Rate (beats/min.)	125 ± 8.6	120 ± 7.3	122 ± 4.5
Mean Arterial Pressure (mm Hg.)	109 ± 4.5	111 ± 3.3	120 ± 8.0
LVFP (mm Hg)	39 ± 3.2	34 ± 2.6 ($P<0.05$)	33 ± 3.4 ($P<0.02$)
Cardiac Index ($l/min/m^2$)	3.3 ± 0.3	4.0 ± 0.4 ($P<0.01$)	3.8 ± 0.4 ($P<0.01$)
Stroke VolumeIndex ($ml/beat/m^2$)	27 ± 2	33 ± 3 ($P<0.01$)	31 ± 3 ($P<0.05$)
Total Systemic Resistance ($dyn.sec.cm^{-5}$)	1460 ± 112	1291 ± 131	1416 ± 140
Stroke Work Index ($g.m/m^2$)	36 ± 4.7	47 ± 5.6 ($P<0.01$)	49 ± 8.2 ($P<0.01$)
LVEF (%)	29 ± 1.7	36 ± 2.9 ($P<0.05$)	36 ± 3.1 ($P<0.02$)

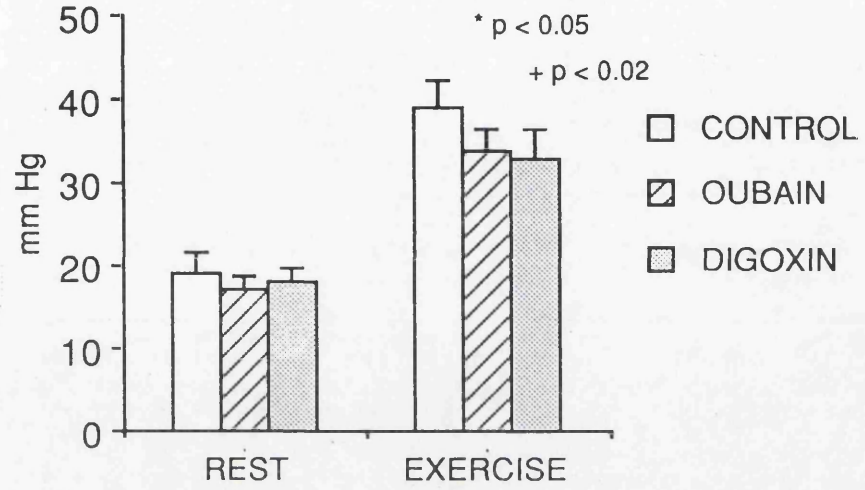


—Study design. Haemodynamic data and left ventricular ejection fraction measured at rest (open columns) and during dynamic exercise (shaded columns) after intravenous ouabain and after six weeks' maintenance with oral digoxin.

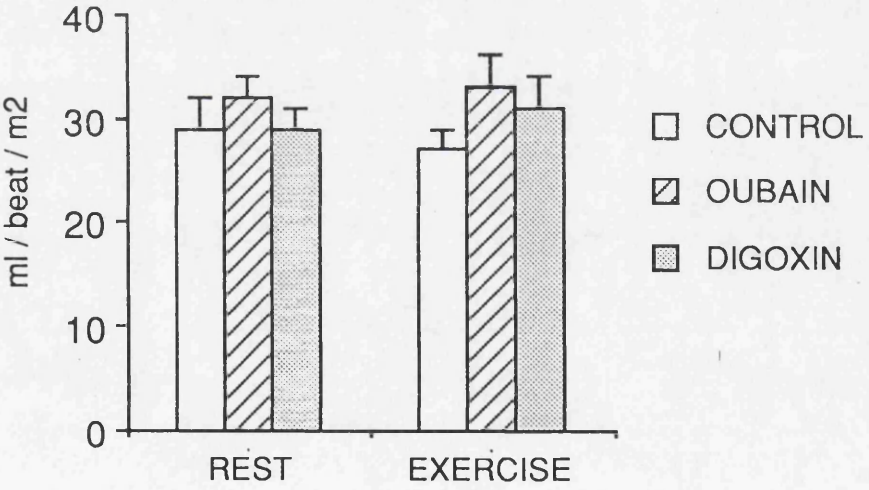

CARDIAC INDEX
l / min / m2
5
4
3
2
1
0
* p < 0.01
*
*
REST
EXERCISE
CONTROL
OUBAIN
DIGOXIN


LEFT VENTRICULAR EJECTION FRACTION
* p < 0.05
+ p < 0.02
%
40
30
20
10
0
REST
EXERCISE
CONTROL
OUBAIN
DIGOXIN

PULMONARY CAPILLARY WEDGE PRESSURE



STROKE VOLUME INDEX



exercise. Patients then received oral digoxin for six weeks and the measurements were repeated.

Results

The results are shown in the tables opposite. There was no change in any of the resting haemodynamic parameters and left ventricular ejection fraction was unchanged. Exercise was performed in only eight patients as two patients were unable to exercise for three minutes. Heart rate was unchanged compared to control with either the ouabain or digoxin therapy. Pulmonary capillary wedge pressure was reduced by 13% with ouabain and 15% by digoxin. Cardiac index increased by 21% with ouabain and by 15% with digoxin. Systemic vascular resistance was unchanged. Left ventricular ejection fraction increased both with ouabain and digoxin.

Discussion

These results suggest that there is haemodynamic improvement with digoxin manifest only during exercise with no changes at rest. Changes with ouabain were sustained at six weeks with digoxin. Since both systemic vascular resistance and blood pressure are unchanged it is likely that the improvement is related to increased contractility. In addition, pulmonary capillary wedge pressure on exercise fell which would reduce left ventricular wall tension and thus may reduce myocardial oxygen consumption.

The published data suggests that long term therapy with digoxin reduces symptoms, prolongs exercise tolerance and decreases the risk of clinical progression of heart failure **(78-80)**. In addition to its inotropic effects, in contrast to cyclic AMP dependent agents, digitalis reduces activation

of both the sympathetic nervous system and the renin angiotensin system **(81,82)**. This appears to be related to the ability of digoxin to restore the inhibitory effect of cardiac baroreceptors on sympathetic outflow from the central nervous system **(81)**.

In summary, in the appropriate patient, digitalis is effective in producing haemodynamic improvement which is manifest only during exercise. In recent studies long term therapy has reduced symptoms, improved exercise tolerance and decreased the risk of clinical deterioration due, presumably, to the complex interplay between the adaptive responses of the failing heart and the central and peripheral effects of the drug.

REFERENCES FOR PART 3

Diuretics

1. Anderson FJ
   An Illustrated History of the Herbals.
   New York: Columbia University Press: 1977.

2. Taylor SG, Storstein L
   Diuretics in the treatment of heart failure.
   Herz 1983; 8,1: 11-22.

3. Verma SP, Silke B, Hussain M et al
   First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function.
   J Cardiovasc Pharmacol 1987; 10: 38-46.

4. Nelson GIC, Silke B, Ahuja RC, Taylor SH
   Arterial dilatation or venodilation following frusemide in acute heart failure following myocardial infarction.
   Clin Sci 1982; 63: 3P.

5. Biddle TL, Yu PN
   Effect of furosemide on haemodynamics and lung water in acute pulmonary oedema secondary to myocardial infarction.
   Am J Cardiol 1979; 43: 86-90.

6. Mond H, Hunt D, Sloman G
   Haemodynamic effects of frusemide in patients suspected of having acute myocardial infarction.
   Br Heart J 1974; 36: 44-53.

7. Valette H, Herbert JC, Apoil H
   Acute haemodynamic effects of a single intravenous dose of piretanide in congestive heart failure.
   Eur J Clin Pharmacol 1983; 24: 163-166.

8. Dikshit K, Vyder JK, Forrester JS et al
   Renal and extra-renal haemodynamic effects of furosemide in congestive heart failure after myocardial infarction.
   N Engl J Med 1973; 288: 1087-1090.

9. Davidson RM, Goldman J, Whalen RE, Wallace AG
Haemodynamic effects of furosemide in acute myocardial infarction.
Circulation 1971; 44: 156.

10. Keily J, Kelly DT, Taylor DR, Pitt B
The role of furosemide in the treatment of left ventricular dysfunction associated with acute myocardial infarction.
Circulation 973; 48: 581-587.

11. Webster JA, Dollery CT
Antihypertensive action of bendroflumethazide: increased prostacyclin production.
Clin Pharmacol Ther 1980; 28: 751-758.

12. Abe K, Seino M, Yasujima M et al
Studies on renomedullary prostaglandin and serial kallikrein-kinin system in hypertension.
Jap Circ J 1977; 41: 873-880.

13. Rosenthal J, Boucher R, Newczynski W, Gerent J
Acute changes in plasma volume renin activity and free aldosterone levels in healthy subjects following frusemide administration.
Canad Physiol Pharmacol 1968; 46: 85-91.

14. Ikram H
Haemodynamic and hormone response to acute and chronic frusemide therapy in congestive heart failure.
Clin Sci 1980; 59: 443-449.

15. Bayliss J, Norell M, Canepa-Anson R
Untreated heart failure and neuro-endocrine effects of introducing diuretics.
Br Heart J 1987; 57: 17-22.

16. Carnella G, Galva MD, Campanini M et al
Sequential changes in plasma renin activity and plasma catecholamines in mildly hypertensive patients during acute furosemide induced body-fluid loss.
Eur J Clin Pharmacol 1983; 25: 299-302.

17. Francis GE, Siegel RM, Goldsmith Sr
Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure.
Ann Int Med 1985; 103: 106.

18. Cleland JGF, Gillen G, Dargie HJ
The effects of frusemide and angiotensin-converting enzyme inhibitors and their combination on cardiac and renal haemodynamics in heart faiure.
Eur Heart J 1988; 9: 132-141.

Nitrates

19. Bussman WD, Lohner J, Kalteinbach M
Orally administered isosorbide in patients with and without left ventricular failur due to acute myocardial infarction.
Am J Cardiol 1977; 39: 91-96.

20. Franciosa JA, Mikulic E, Cohn J, Jose E, Fabie A
Haemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure.
Circulation 1974; 50: 1020-1024.

21. Gray R, Chatterjee K, Vyder JK et al
Haemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure.
Am Heart J 1975; 90: 346-352.

22. Miller RR, Vismara LA, Williams DO, Mason DT
Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. Differential effects of nitroprusside, phentolamine and nitroglycerin on cardiac function and peripheral circulation.
Circ Res 1976; 39: 127-133.

23. Packer M
Vasodilator and inotropic therapy for severe chronic heart failure: Passion and Scepticism.
J A C C 1983; 2,5: 841-852.

24. Franciosa JA, Black RC, Cohn JN
Nitrate effects on cardiac output and left ventricular outflow resistance in chronic congestive heart failure.
Am J Med 1978; 64: 207-213.

25. Stephens J, Camm J, Spurrell R
Improvements in exercise haemodynamics by isosorbide dinitrate in patients with severe congestive cardiac failure secondary to ischaemic heart disease.
Br Heart J 1978; 40: 832-837.

26. Franciosa JA, Nordstrom LA, Cohn JN
Nitrate therapy for congestive heart failure.
J A M A 1978; 240: 443-446.

27. Franciosa JA, Goldsmith SR, Cohn JN
Contrasting immediate and long term effects of isosorbide dinitrate on exercise capacity in congestive heart failure.
Am J Med 1980; 69: 559-566.

28. Williams DO, Bommer WJ, Miller RR, Amsterdam EA, Mason DT
Hemodynamic assessment of oral peripheral vasodilator therapy in patients with refractory congestive heart failure: prolonged effectiveness of isosorbide dinitrate.
Am J Cardiol 1977; 39: 84-90.

29. Ross J
Mechanisms of cardiac contraction. What roles for pre-load, after-load and inotropic state in heart failure?
Eur Heart J 1983; 4,A: 19-28.

30. Carew TE, Corell JW
Left ventricular fuction in exercise-induced hypertrophy in dogs.
Am J Cardiol 1978; 42: 82-88.

31. Spenn JF
Vasodilators in congestive heart failure.
Clin Ther 1982; 4,5: 345-357.

32. Kjekshus JK
Mechanisms for flow distribution in normal and ischaemic myocardium during increased ventricular pre load in the dog.
Circ Res 1973; 33: 489-499.

33. Domenech RJ
Regional diastolic coronary blood flow during diastolic ventricular hypertension.
Cardiovasc Res 1978; 12: 639-645.

34. Baligadoo S, Ingrand JC, Savier Ch H, Derrida JP, Chiche P
Dose response study of acute haemodynamic effects of intravenous isosorbide dinitrate in patients with and without heart failure. In: Nitrates III. Cardiovascular Effects 1981: p. 495-504. Edited by Lichtler PR, Engel H, Schrey A, Swan HJC.

35. Parmley WW
Pathophysiology and current therapy of congestive heart failure.
J A C C 1989; 13,4: 771-785.

36. Wyatt HL, DaLuz PL, Waters DD, Swan HJC, Forrester JS
Contrasting influences of alterations in ventricular preload and afterload upon systemic haemodynamics, function, and metabolism of ischaemic myocardium.
Circulation 1977; 55,2: 318-323.

37. Andreasen F + 16 other authors
Assessment of verapamil in treatment of angina pectoris.
Eur J Cardiol 1975; 2: 443-452.

38. dePonti C, Mauri F, Aliberto GR et al
Comparative effects of nifedipine, verapamil, isosorbide dinitrate and propranolol on exercise-induced angina pectoris.
Eur J Cardiol 1979; 10: 47-58.

39. Harsack KP, Pool PE, Steele P et al
Efficacy of diltiazem in angina on effort; a multicentre trial.
Am J Cardiol 1982; 49: 567-572.

40. Jeeckenstein A
On the basic pharmacological mechanism of nifedipine and its relations to therapeutic effiacy. In: Jatene AD, Lichtler PR Eds. New therapy of ischemic heart disease: Third International Adalat Symposium. Amsterdam & Oxford. Excerpta Medica 1976: p. 1-13 (International Congress Series No. 388).

41. Clark RE, Christlieb IY, Henry PD et al
Nifedipine: A myocardial protective agent.
Am J Cardiol 1979; 44: 825-831.

42. Henry PD, Schuchleib R, Clark RE, Perez JE
Effect of nifedipine on myocardial ischemia: Analysis of collateral flow, pulsatile heart and regional muscle shortening.
Am J Cardiol 1979; 44: 817-824.

43. Engel HJ, Wolf R, Hundeshagen H, Lichtlen PR
Different effects of nitroglycerin and nifedipine on regional myocardial blood flow during pacing induced angina pectoris.
Eur Heart J 1980; 1,3: 53-58.

44. Boström SL, Ljung B, Mårdh SF, Forsew S, Trulin E
Interaction of the antihypertensive drug felodipine with Calmodulin.
Nature 1981; 292: 777-778.

45. Culling W, Ruttley MSM, Sheridan DJ
Acute haemodynamic effects of felodipine during beta blockade in patients with coronary artery disease.
Br Heart J 1984; 52: 431-434.

46. Perry JM
Late toxicity to hydrallazine resembling systemic lupus erythematosus or rheumatoid arthritis.
Am J Med 1973; 54: 58-72.

47. Massie B, Ports TA, Chatterjee K et al
Long-term vasodilator therapy for heart failure. Clinical response and its relationship to haemodynamic measurements.
Circulation 1981; 63: 267-278.

48. Timmins AD, Smyth P, Kenny JF, Campbell S, Jewit DF
Effects of vasodilator treatment with felodipine on haemodynamic responses to treadmill exercise in congestive heart failure.
Br Heart J 1984; 52: 314-320.

49. Wilson JR, Martin JL, Schwartz D, Ferraro N
Exercise intolerance in patients with chronic heart failure: role of impaired nutrative flow to skeletal muscle.
Circulation 1984; 69: 1079-1087.

50. Zelis R, Flasin SF
Alterations in vasomotor tone in congestive heart failure.
Prog Cardiovasc Dis 1982; 24: 437-459.

51. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA
Abnormalities of skeletal muscle in patients with chronic heart failure.
Int J Cardiol 1980; 18: 187-195.

52. van der Giessen WJ, van Woerkens LJ, Saxena PR, Roelandt JRTC, Verdonuw PD
Nisoldipine improves blood flow to skeletal muscles in conscious pigs with chronic heart failure.
Eur Heart J 1990; 11: 552-559.

53. Cowley AJ, Wynne R, Hampton JR
The effects of BTS49465 on blood pressure and peripheral arteriolar and venous time in normal volunteers.
J Hypertens 1984; 2: 547-549.

54. Elborn JS, Stanford CF, Nicholls DP
Effect of flosequinan on exercise capacity and symptoms in severe heart failure.
Br Heart J 1989; 61: 331-335.

55. Kessler PD, Packer M
Haemodynamic effects of BTS49465, a new long acting systemic vasodilator drug, in patients with severe congestive heart failure.
Am Heart J 1987; 113: 137-143.

56. Silke B, Verma SP, Taylor SG
A haemodynamic and treadmil exercise study with flosequinan in mild chronic heart failure.
Br J Clin Pharmacol 1987; 24: 250P-1P.

57. Cowley AJ, Wynne RD, Steiner K et al
Flosequinan in heart failure: acute haemodynamic and longer term symptomatic effects.
Br Med J 1988; 297: 169-173.

58. Cohn JN, Archibald DG, Ziesche S et al
Effect of vasodilator therapy on mortality in chroniccongestive heart failure. Results of a Veterans Administration Cooperative Study.
N Engl J Med 1986; 314: 5547-5552.

59. Packer M, Meller J, Median N, Yushak M, Gorlin R
Determinants of drug response in severe chronic heart failure 1. Activation of vasoconstrictor forces during vasodilator therapy.
Circulation 1981; 3: 64.

60. Packer M, Meller J, Median N, Gorlin R, Herman HV
Importance of left ventricular chamber size in determining the response to hydrallazine in severe chronic heart failure.
N Engl J Med 1980; 250: 303.

61. Jerzek V
The treatment of chronic pulmonary hypertension: hope and hesitation.
Eur Heart J 1988; J: 1-6.

62. Brest BN, Berger HJ, Matthay RA et al
Physiologic correlates of right ventricular ejection fraction in chronic obstructive pulmonary disease: A combined radionuclide and hemodynamic study.
Am J Cardiol 1982; 50: 255-261.

63. Massie B, Kramer BL, Topic N, hendry SG
Hemodynamic and radio-nuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise.
Circulation 1982; 65: 1374-1381.

64. Kenstam MA, Salem DN, Isner JM
Vasodilator effect on right ventricular function in congestive heart failure and pulmonary hypertension: end-systolic pressure-volume relation.
Am J Cardiol 1984; 54: 132-136.

65. Janicki JS, Weber KT
Ventricular interaction pre and post pericardectomy.
Fed Proc 1978; 37: 776.

66. Bove AA, Santamore WP
Ventricular interdependence.
Prog Cardiovasc Dis 1981; 23,5: 365-388.

67. Packer M, Lee WH, Medina N et al
Prognostic importance of the immediate hemodynamic response to nifedipine in patients with severe left ventricular dysfunction.
J A C C 1987; 10,6: 1303-1311.

68. Ferguson DW, Berg WJ, Sanders JS
Clinical and hemodynamic correlates of sympathetic nerve activity in normal humans and patients with heart failure; evidence from direct microneugraphic recordings.
J A C C 1990; 16,3: 1125-1134.

69. Francis GS, Goldsmith SR, Cohn JN
Relationship of exercise capacity to testing left ventricular performance and basal norepinephrine levels in patients with congestive heart failure.
Am Heart J 1982; 10,4: 725-731.

70. Johnsson G, Jordö L, Lundberg P et al
Haemodynamic and tolerance studies in man with a new orally active selective ß1 adrenoreceptor agonist H80/62.
Eur J Clin Pharmacol 1978; 13: 163-170.

71. Hutton I, Murray RG, Boyes RN, Rae AP, Hillis WS
Haemodynamic effects of prenalterol in patients with coronary heart disease.
Br Heart J 1980; 43: 134-137.

72. Colucci WS, Alexander RW, Williams CH et al
Decreased lymphocyte beta-adrenergic receptor density in patients with heart failure and tolerance to the beta-adrenergic agonist pirbuterol.
N Engl J Med 1981; 305: 185-190.

73. Bristow MR, Ginsberg R, Minobe M et al
Decreased catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts.
N Engl J Med 1982; 307: 205-211.

74. Withering W
An account of the Foxglove and some of its medical uses.
Birmingham,1785; M Swinney.

75. Taylor SH, Shustein L
Diuretics and digitalis in the treatment of chronic heart failure.
Eur Heart J 1983; 4,A: 153-159.

76. Parmley W
Pathophysiology and therapy of heart failure.
J A C C 1989; 13,4: 771-785.

77. Akera T, Brody TM
The role of Na^+ K^+ - ATPase in the inotropic actions of digitalis.
Pharmacol Rev 1977; 29: 187.

78. Guyett GH, Sullivan MJJ, Fallen EI et al
A controlled trial of digoxin in congestive heart failure.
Am J Cardiol 1988; 61: 371-375.

79. The Captopril-Digoxin Multicentre Research Group
Comparative effects of captopril and digoxin in patients with mild to moderate heart failure.
J A M A 1988; 259: 539-544.

80. DiBanco R, Shabetai R, Kostuk W et al
A comparison of oral intravenous digoxin, and their combination in the treatment of patients with chronic heart failure.
N Engl J Med 1989; 320: 677-683.

81. Ferguson DW, Berg WJ, Sanders JS et al
Sympatho-inhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings.
Circulation 1989; 80: 65-77.

82. Covit AB, Schaer GL, Sealey JE, Laragh JH, Cody RJ
Suppression of the renin-angiotensin system by intravenous digoxin in chronic congestive heart failure.
Am J Med 1983; 75: 445-447.

PART 4

CONCLUSIONS

"Heart failure" has a long history. Its recognition and management, or indeed its very nature, have intrigued physicians for centuries. In this thesis I have tried systematically to examine the different ways in which a patient with this condition may be identified. Implicit are questions about the condition itself, its characteristics and underlying mechanisms.

Peter Harris, St. Cyres Lecture of 1987, provided a penetrating insight into the condition and I have drawn heavily on the concepts outlined in the lecture to provide a broad framework of reference.

The function of the circulation is to perfuse tissues as appropriate to the varying metabolic needs. Although metabolic signals predominate in setting local tissue perfusion, overall cardiac output appears to be controlled primarily in response to sensors of arterial pressure which is maintained. This adaptive response developed during evolution to maintain the high cardiac output warm blood animals need to support physical activity fuelled by oxygen. Anything which impairs cardiac output such as increased systolic load or loss or ischaemia of myocardium will reduce arterial pressure. The resultant neurohumoral signals are unsurprisingly similar to those induced by exercise. A damaged or overloaded heart becomes progressively less able to maintain arterial pressue; at first during exercise and ultimately at rest. The body responds by a series of acute or chronic adaptive responses, programmed by natural selection to maintain the arterial pressure during exercise or trauma.

The neurohumoral signals result in resetting of fluid balance and they influence vascular and myocardial behaviour. Direct or secondary mechanical effects cause chronic adaptive changes in the vasculature, myocardial structure and the cardiac myocyte itself. The myocardium hypertophies, increasing its contractile protein and mass and normalises ventricular wall stress, with slower maximum velocity of contraction and lower energy requirements. Since cell division probably does not occur in mammalian myocardium after the neonatal period, this hypertrophy is due to increases in the size of individual myocytes. Genetic changes in the control of cytosolic calcium and the contractile proteins may be seen as improving metabolic efficiency in face of altered mechanical workload, as reflected by reducing energy requirements in relation to developed tension. At the myocyte level, these compensatory changes are appropriately adaptive. However, the cells are abnormally large, cell function is abnormal and this, ultimately, is associated with fibrosis which affects the mechanical properties of the heart, inevitably leading to progressive 'adaptive' hypertrophy and/or dilatation, thus the net benefits are over-ridden by functional deterioration.

Biological adaption represents a cascade of modifications to multiple physiological conditions and in general the adaption of any system not only has limits but potentially detrimental consequences. In characterising a patient with heart failure, there are clearly several aspects that require consideration. Firstly, the extent of damage that has initiated these adaptive processes; secondly, a measure of the results of this adaptation to characterise its adjustments and the stage of its development between initiation and ultimate "failure"; and thirdly, assessment of consequent processes which might contribute to further

deterioration, possibly through stimulating further the very process involved originating the adaptive process.

The commonest cause of heart failure in the West today is ischaemic heart disease. This is the group of patients addressed in this thesis. A co-existing potential for intercurrent episodic myocardial ischaemia and its functional consequences may not be clinically overt, but may contribute to the overall condition of heart failure. A further feature of heart failure due to coronary artery disease is the potential for implication in both the initial and further myocyte damage and detrimental consequences of the adaptive changes.

The first aspect to consider - the severity of the initiating cardiac insult appears to relate to prognosis. In this thesis I have tried to demonstrate that extent of damage can easily and practically by assessed by using a non-invasive measure of left ventricular ejection fraction. However in the setting of left ventricular dysfunction involvement of the right ventricle is also an important consideration. Mechanisms that would contribute to further damage - specifically the underlying coronary artery disease in the population of patients studied - are an often underestimated part of this equation. Secondly, I have approached the problem of measuring the degree of adaptation through its overall consequences. namely, physical work capacity which overall is testing the efficiency of all the adaptive processes to maintain blood pressure and transport oxygen during exercise. Other measures of the adaptive process, such as activation of the renin-angiotensin systems were not addressed in this thesis. Thirdly, processes that lead to further myocardial impairment, in what could be regarded as a vicious cycle of events, deserve greater recognition than they have generally received. These may act relatively

acutely with, for example, stress induced myocardial ischaemia resulting in further left ventricular dysfunction, as demonstrated in this thesis, ischaemia resulting in transient deterioration of cardiac function or more prolonged dysfunction as in myocardial stunning. When this occurs, the adaptive processes "fail" acutely but presumably are stimulated further by the resulting impairment in performance, particularly the inability to maintain the blood pressure

.

As Bernard Swynghendauw has said "heart failure is a disease of adaption", implying that it is a syndrome which results from the ultimate failure of the initially beneficial adaptive process.

APPENDIX

Introduction

Much of the methodology employed in this thesis is standard clinical practice. However, as with all measurements, in order to be able to judge the significance, the variability of the measurement must be determined. This degree of detail, although critically important, was felt to be intrusive within the body of this thesis. It is therefore presented in the Appendix. Standard measurements are presented with little detail other than to describe the precautions taken to produce reproducible results. Where methodology is less standard, or innovative, this has been compared with more standard measures.

Electrocardiography

Heart rate and ST segment changes were obtained from standard electrocardiograms, using a 6 lead Mingograph recorder at 25 mm/second. Electrocardiograms (ECGs) were recorded continuously throughout exercise at a slow speed (10 mm/second) and the speed increased to 25 mm/second each minute and at peak exercise. Mingograph recorders provide a good quality ECG with an ink jet recorder that has a good frequency response **(1)**. All measurements were made with a Mingograph 62 ECG amplifier/recording system which has a frequency response of 0.05 Hz to 1200 Hz with no filter selected. Tremor filter reduces frequency response to approximately 30 Hz.

Blood Pressure

Blood pressure was usually measured in the right arm, using a cuff sphygmomanometer, with a single observer. The reproducibility for

systolic blood pressure (SBP) was 5 $\pm$ 3% (standard error of estimate n = 20) and for diastolic blood pressure (DBP) 5 $\pm$ 5% on exercise.

An automatic blood pressure cuff was found to be less reproducible on exercise and was difficult to use in patients with chronic heart failure, where exercise blood pressure can drop very suddenly, and the cuff takes 10-15 seconds to inflate. Intra-arterial blood pressure recording could be more accurate but was not considered ethical.

As blood pressure is measured moving from central aorta to the periphery systolic blood pressure increases, diastolic blood pressure decreases and mean arterial pressure remains unchanged **(2)**. The relationship between central and peripheral arterial pressure is not constant and is critically dependent on peripheral vascular impedance.

Measurement of blood pressure by cuff sphygmomanometer introduces an additional variable. Sphygmomanometry underestimates direct brachial pressure by approximately 10-25 mm.Hg. **(3)**. Interestingly, although cuff blood pressure may still overestimate central aortic pressure to an extent, sphygmomanometry at the brachial artery more closely approximates central aortic systolic pressure, than does a direct arterial recording either from the same site or from the radial artery **(4)**.

It is therefore critical to appreciate why blood pressure is being measured. During exercise testing, an important warning sign is exercise induced hypotension. This may be a real fall in systolic blood pressure, or a failure of the blood pressure to increase with increasing workloads **(5)**. In patients with coronary artery disease, this usually indicates multi-

vessel disease or left main disease (**6**) and continued exercise may precipitate ventricular fibrillation (**7**).

Blood pressure may also be used to determine the effect of exertion on a number of physiological parameters. Indices such as heart rate-blood pressure product, designed to estimate myocardial oxygen demand, use systolic blood pressure for their calculation and are most accurate if central systolic measurements are used (**7**), hence the use of sphygmo-manometry. However if calculating systemic vascular resistance, the diastolic pressure must be employed to obtain mean arterial pressure, if this is not measured directly. As cuff measurement of diastolic blood pressure is notoriously less reliable than systolic pressure this inevitably will introduce errors.

Exercise Testing

The function of the circulation is to perfuse tissues. This requires adequate blood flow and gas transport between the lungs and cells of the body. With exertion, these requirements increase enormously and it is this inability of the cardiovascular system to sustain an increased demand that underlies the limitation in patients with heart failure.

Fick (**8**) in formulating his method of measuring cardiac output appreciated that the heart's output was intimately related to the body's oxygen consumption. It was some 70 years later before Harrison and Pilcher (**9**) examined gas exchange in patients with heart failure, showing that oxygen uptake was reduced but carbon dioxide output increased during exercise. The total oxygen (O_2) required to perform work was no different from normals but oxygen uptake at near maximal work rates was reduced and carbon dioxide (CO_2) output higher in patients with

heart failure compared to normal controls. They clearly realised that the increased CO_2 output was derived from bicarbonate (HCO_3), formed to buffer acid produced during exertion. Lactate was shown to increase with strenuous exercise by Barr and Himwich **(10)** and Brock et al **(11)**, who demonstrated the 'threshold behaviour' of acid-base balance. To understand the pathophysiological mechanisms in patients with heart failure, it is necessary to explain the normal physiological response to exercise.

Exercise capability and evaluations of physical work capacity in normals

At rest, human basal metabolic rate is usually 5500-7000 kilojoules/24 hours and muscular activity can increase this by as much as a factor of 50 with a concomitant increase in oxygen consumption, removal of heat, carbon dioxide, water and waste products **(12)**. At rest, and with moderate exertion, the necessary energy is provided by aerobic metabolism (oxygen converted to carbon dioxide) by mitochondrial oxidation of free fatty acids, carbohydrate and protein. With more vigorous exercise oxygen supplied to the working muscle is delayed, with a subsequent oxygen deficit, and at this point, part of the energy is supplied from anaerobic metabolism (produced predominantly from metabolic lactic acid, producing H^+ plus HCO_3 - producing H_2CO_3 producing H_2+CO_2) but also from the breakdown of ATP, CK and glycogen to pyruvic acid. This mechanism usually plays a relatively unimportant part of the energy supplied muscles and can be maintained only for a short period of time.

For many activities the individual energy cost is similar and this is true for exercise performed on a bicycle ergometer, whereas with the treadmill body weight is crucial for any given speed or slope, and the

energy costs differ for walking and jogging at a simialr incline **(13)**. By knowing the individual's potential ability to transport oxygen one can predict his potential to perform vigorous exercise (e.g. cross country skiing requires a maximal oxygen uptake of approximately 80 ml/kg/minute).

Normal limitations of oxygen transport during exercise

The Fick formula **(8)** for oxygen transport states that

VO_2 = heart rate x stroke volume x CaO_2-CvO_2

CO (cardiac output) x arterial and venous oxygen content = a-vO_2 difference

The increased oxygen demand during exercise is met by increased cardiac output and a wider a-vO_2 difference **(10,12,14)**. Pulmonary function does not limit oxygen uptake in normal individuals. Increasing cardiac output is reflected in an increased arterial-venous oxygen difference which provides an indirect evaluation, as during maximal exercise there is a linear relationship between maximum cardiac output and maximum oxygen uptake **(13)** irrespective of whether the subject is trained or untrained **(14)** and the form of exercise **(12,15,16)**.

With upright exercise, stroke volume increases by approximately 50% to a maximum at roughly 40% of the individual's maximal oxygen consumption (although stroke volume increases with training). Thereafter the main factor in providing the increased cardiac output is the linear increase in heart rate. Heart rate does tend to be somewhat higher for any given load of oxygen uptake or cardiac output when using small muscle groups (arm exercise) with isometric exercise than with dynamic exercise. If normal heart rate is altered by drug administration, e.g. beta blockers, normal maximum oxygen uptake is achieved but with

a shortened performance time and reduced blood pressure **(17)**. Normally during dynamic exercise, despite the reduced peripheral vascular resistance, intra-arterial blood pressure increases with aortic systolic levels approaching 175 mm.Hg. although it may be higher with isometric or arm exercise.

During strenuous exercise maximum oxygen consumption (VO_2) can attain maximal values varying from 22 to 50 ml/kg/minute, depending on age and fitness. VO_2 max declines with age by roughly 30% from the age of 40 to 65+ years **(18)** (40.5 $\pm$ 4.7 ml/kg/minute to 27.7 $\pm$ 4.2 ml/kg/minute in a 65+ year old) with a corresponding decrease in exercise time (10.3 $\pm$ 1.1 minutes to 7.5 $\pm$ 3.0 minutes at 65+ years of age). This represents a 3-8% decline per decade throughout adult life.

$$\% \text{ average normal } VO_2 \text{ max} = \frac{\text{observed } VO_2 \text{ max}}{\text{predicted } VO_2 \text{ max for age}} \times 100$$

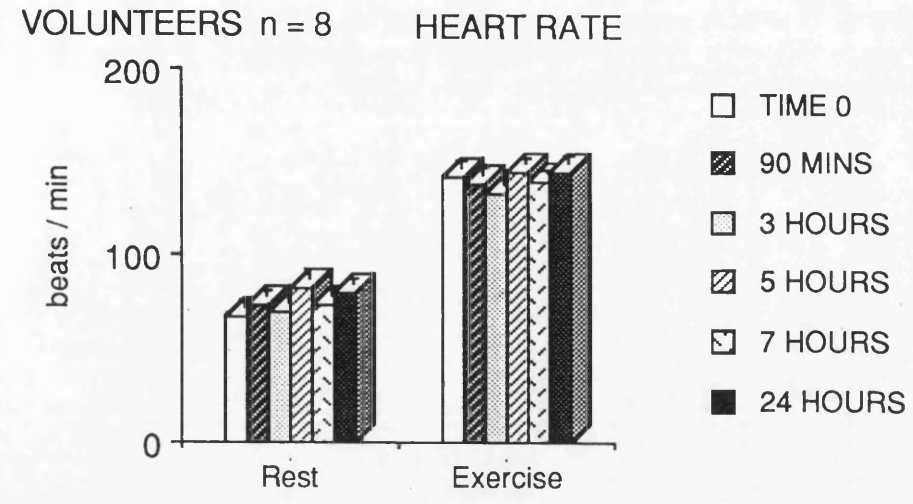
Fitness

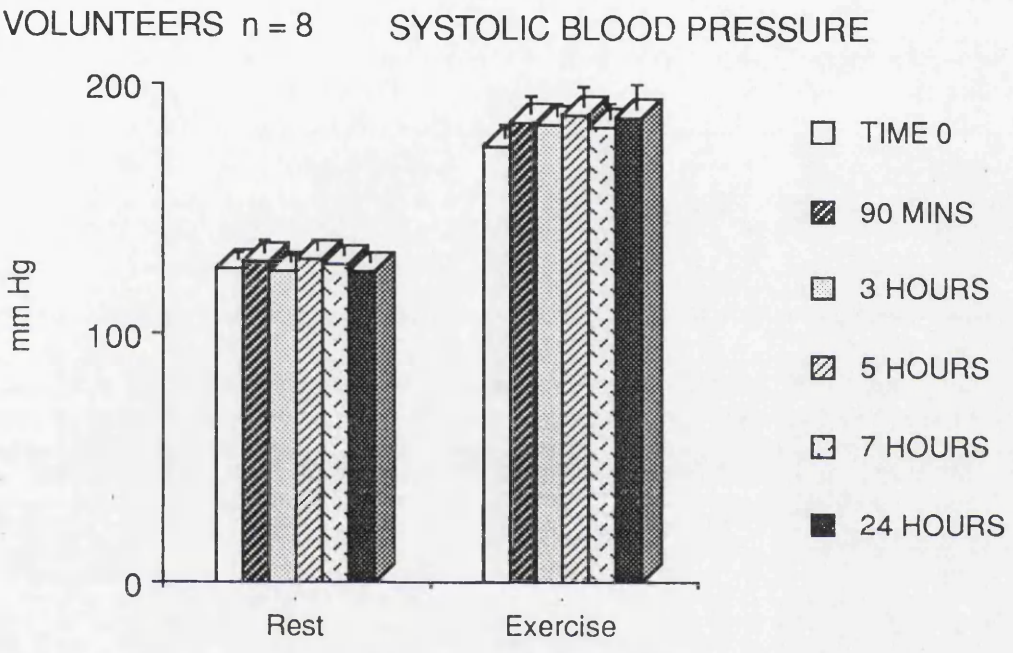
This age related decline in VO_2 max correlates inversely with the peak decreases in heart rate and decreases in peak cardiac index but not with a-vO_2 oxygen difference or stroke volume index. Thus, from the Fick equation, the only parameter affected by age is heart rate. The mechanisms for this decline with age are less clear, although it should be remembered that the changes are small when compared with overall variations in groups which are determined by other factors such as physical training. The cardiac output may be maintained by compensatory mechanisms, such as increased diastolic volume, calling into play the Frank-Starling mechanism. Left ventricular hypertrophy is a common ECG finding in elderly populations **(19)** and this may be

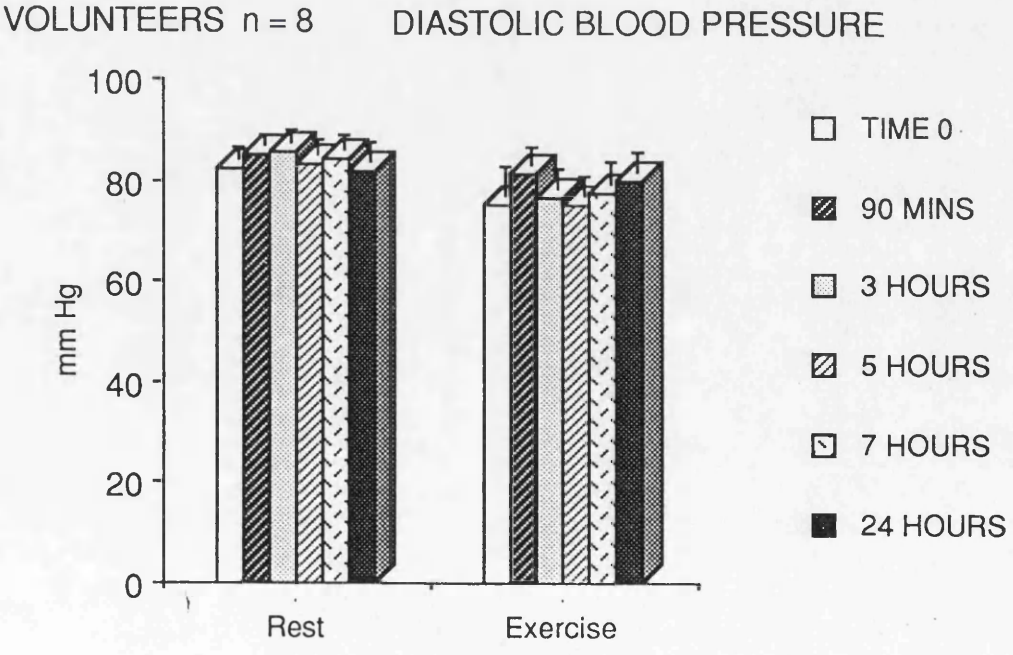
Table 22

Volunteers
(submaximal testing/HR 130-150) n = 8 ± SEM
fixed workload

HR Variations	Rest	Exercise
0	67.0 ± 4.1	142.0 ± 3.5
90 minutes	73.0 ± 3.5	138.0 ± 3.5
3 hours	70.0 ± 5.4	133.0 ± 2.4
5 hours	83.0 ± 5.0	145.0 ± 2.3
7 hours	74.0 ± 3.9	139.0 ± 2.1
24 hours	80.0 ± 2.8	145.0 ± 3.5
SBP		
0	125.8 ± 3.2	175.0 ± 4.6
90 minutes	129.3 ± 4.4	184.3 ± 6.7
3 hours	125.3 ± 3.0	183.3 ± 5.6
5 hours	130.0 ± 3.5	187.8 ± 7.8
7 hours	128.0 ± 4.1	183.0 ± 5.1
24 hours	125.0 ± 3.4	187.0 ± 8.8
DBP		
0	82.0 ± 2.4	75.0 ± 5.7
90 minutes	85.0 ± 2.2	81.3 ± 3.5
3 hours	85.5 ± 2.5	76.5 ± 3.7
5 hours	83.0 ± 3.0	75.0 ± 3.8
7 hours	84.0 ± 2.9	77.3 ± 4.2
24 hours	81.9 ± 3.5	79.8 ± 3.7


VOLUNTEERS n = 8
HEART RATE
200
100
0
beats / min
Rest
Exercise
TIME 0
90 MINS
3 HOURS
5 HOURS
7 HOURS
24 HOURS


VOLUNTEERS n = 8
SYSTOLIC BLOOD PRESSURE
200
100
0
mm Hg
Rest
Exercise
TIME 0
90 MINS
3 HOURS
5 HOURS
7 HOURS
24 HOURS


VOLUNTEERS n = 8
DIASTOLIC BLOOD PRESSURE
100
80
60
40
20
0
mm Hg
Rest
Exercise
TIME 0
90 MINS
3 HOURS
5 HOURS
7 HOURS
24 HOURS

another compensatory mechanism reflecting increased systemic vascular resistance.

Methodology used

Exercise testing was performed using a bicycle ergometer. Ergometers are calibrated regularly against a Kg weight so that work loads exerted are within 5% of measured and differences between ergometers are reduced as far as possible.

Exercise Protocol

Exercise testing protocols have to be modified in patients with heart failure to accommodate a reduced exercise capacity **(20,21)**. Multistage tests have to have stages that are long enough to accummulate data, but not so long that the end points change. There is some doubt as to whether metabolic and haemodynamic stability can be achieved **(22,23)**.

To Test Variation in Haemodynamic Variables

To test the variation in haemodynamic variables at rest and with exercise, eight volunteers were tested over a 24 hour period starting at 9 in the morning.

Heart rate was taken from the electrocardiogram, measured continuously, and blood pressure obtained by cuff sphygmomanometer by a single operator. Exercise was performed upright on a bicycle ergometer to an individual fixed work load, producing an exercise heart rate of 130-150 beats/minute. An incremental protocol was used, with 50 watt steps, to this fixed maximum. Volunteers performed at least two tests to familiarise them with the protocols and to obviate training effects.

Heart rates and blood pressures are shown in Table 1 and Figure 1. Heart rate both at rest and during exercise tends to be lower in the morning, whereas there is little difference with blood pressure. Because of this effect, exercise tests used for serial testing should be performed at roughly the same time of day.

It has been suggested that higher levels of physical work, heart rate and oxygen consumption, can be achieved using a treadmill rather than a bicycle **(24)**. We, and others **(21)**, have found no significant differences in peak performance and bicycle exercise, with simultaneous expired gas analysis, provides more reproducible results in our laboratory (unpublished data). Exercise testing was evaluated once patients had performed at least one previous test (greater than one week previously) in order to familiarise them with the equipment and this has been shown to provide more reproducible results **(25)**.

The protocol used in all testing was as follows:

2 minutes rest, sitting on bike, to allow collection of stable resting data. If respiratory gas analysis was being performed this was with a nose clip and mouthpiece attached to a low deadspace and low resistance valve box.

2 or 3 minutes at no load.

2 or 3 minute increments of 25 watts to a symptom limited maximum.

If expired gas analysis was being performed, the patient lifted his hand and thereafter was encouraged to continue to exercise for 20-30

seconds. If routine exercise testing was being performed, the patient had previously been given instructions to give warning when he felt he had to stop and again was encouraged to continue for 20-30 seconds.

Expired gas analysis and haemodynamic monitoring was continued for at least 1 minute post exercise, or until the patient was haemodynamically stable.

Measurement of Ventilation

Minute ventilation and respiratory rate were measured using a vane turbine placed on the inspiratory side of a non-rebreathing respiratory valve circuit and a ventilometer (PK Morgan). The rotating vane interrupts a beam of light and the number of pulses generated are integrated to measure inspired volume which can be converted to expired volume (VE) using the Haldane correction **(26)**.

Measurement of VO_2 and VCO_2

Expired gas was fed through a mixing chamber from which samples were analysed for carbon dioxide using an infra-red spectrometer and oxygen using a paramagnetic analyser. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured on line (PK Morgan Ltd, Rainham, Kent) using standard equations **(7,27)**

Arterial Gas Analysis

Arterial blood gas values were monitored throughout exercise testing using a transcutaneous system (TCM3 Radiometer Ltd, Copenhagen) which continuously monitors transcutaneous oxygen ($tcpO_2$) and CO_2 ($tcpCO_2$) tensions. This has been shown in our laboratory to be

reproducible, repeatable and to correlate well with direct brachial arterial sampling **(28)**. Indices of gas exchange - the alveolar-arterial oxygen gradient ($A\text{-}aO_2$) and dead space to tidal volume ratio (vd/vt) were calculated from expired gas analysis and transcutaneous oxygen gas tensions using standard formula **(27)**.

Measurements

Gas and flow measurements were corrected for ambient temperature, barometric pressure and water vapour. Measurements were made continuously, breath-to-breath.

Minute ventilation	VE litres/minute	
Oxygen uptake	VO_2 ml/min/kg	} compared to normal
Carbon dioxide production	VCO_2 ml/min/kg	} values of Jones & Campbell **(29)**

$A\text{-}aO_2$	Alveolar-arterial oxygen gradient
vd/vt	Dead space to tidal volume ratio

Anaerobic threshold (AT) was calculated by the curve fitting method of Beaver et al **(30)** using a plot of VO_2 against VCO_2.

Anaerobic threshold has been shown to correlate closely with the onset of lactate acid production **(31)** when the balance of oxygen supply and energy requirement is met by increased anaerobic glycolysis. Measurements of maximum oxygen consumption and anaerobic threshold therefore provide indices of the maximum ability of both aerobic and anaerobic mechanisms to supply energy to working skeletal muscle **(32)**. Weber and Janicki **(33)** have proposed a classification of severity of heart failure based on levels of oxygen consumption, as has Franciosa **(31)**, the classification assuming that maximal oxygen consumption has been

Table 23

Range Normal in Adult **Clinical Cardiology JTW & CA Sanders**

	Average	Range	Exercise
CI l/min/m^2	3.1	2.5 - 4.0	Increase x 2.3
Venous pressure mm.Hg.	5	3.0 - 8.0	Increase x 2.3
RA	2	-2 - +5	Increase x 2.3
RV systolic	25	18 - 30	Increase
end diastolic	2	-5 - +5	Increase
PA systolic	25	18 - 30	Increase
diastolic	10	6 - 12	Increase
mean	15	10 - 20	10 mm. increase
PCW	6	0 - 12	0-4 mm. increase
LA	6	0 - 12	0-4 mm. increase
LV systolic	120	100 - 140	Increase
LV diastolic	6	0 - 12	Increase
Brachial artery measurement	45	85 - 105	Decrease
LVEDP	12		
CTR	less than 50%	**Clinical Cardiology, page 177**	

reached. The relationship between oxygen consumption and work load during graded exercise is curvilinear - measurements are most reliable if a plateau of oxygen consumption is achieved **(34)**.

In general, the maximal oxygen consumption increases when anaerobic threshold increases. The use of anaerobic threshold to assess functional capacity is based on the evidence that inadequate blood supply or reduced oxidative capacity are the major determinants of limitation of exercise in patients with heart failure. Exercise at levels above the anaerobic threshold rapidly induces fatigue **(32)** in these patients and improved cardiac output during exercise may delay the anaerobic threshold but does not necessarily improve the exercise capacity **(35)**. Thus, anaerobic threshold is a marker of the success of the cardiovascular system in meeting the oxygen demands of working skeletal muscle **(36)**.

Cardiac Output

Cardiac output is the volume of blood ejected either from the left ventricle into the systemic circulation, or the right ventricle into the pulmonary circulation. It is usually measured in litres per minute, but to permit comparisons between output measurements of individuals of different body weight, cardiac index is usually employed.

$$\text{Cardiac index} = \frac{\text{cardiac output}}{\text{body surface area } (m^2)} \qquad l/min/m^2$$

Stroke volume is the volume of blood ejected per heart beat

$$\text{Stroke volume} = \frac{\text{cardiac output}}{\text{heart rate}} \qquad \text{mls/beat}$$

and stroke index = $\frac{\text{stroke volume}}{\text{body surface area } (m^2)}$ mls/beat/m^2

The theoretical principle enunciated by Adolph Fick in 1870 **(8)** states that the flow of blood in a given period of time is equal to the amount of substance entering the stream of flow in the same period of time divided by the difference between the concentrations of the substance in the blood upstream and downstream from its point of entry into the circulation.

The earliest studies of cardiac output were based on the Fick principle **(8,37,38,39)**, but as this requires the direct measurement of oxygen consumption and oxygen content of venous and arterial blood, this has largely been replaced by indicator dilution methods.

This technique, developed and refined by Stewart and Hamilton **(40)**, states that the volume of fluid in a container can be calculated if a known quantity of indicator (eg dye, cold saline, or radio-isotope) is added and the concentration of indicator measured after it has been uniformly dispersed throughout the fluid.

Q (flow ml s-1)= $\frac{\text{amount indicator injected}}{\text{mean concentration of indicator x time}}$

Specialised thermodilution catheters have been developed that allow injection of dextrose-saline, cooled to less than body temperature, into the right atrium. A thermistor incorporated into the distal end of the catheter, positioned in the pulmonary artery, allows measurement of the resultant change in blood temperature, which is proportional to blood

flow. Small dedicated computers allow curve integration and calculation of cardiac output, given by the equation

$$Q = \frac{Av\,(Tb-Tl)}{STbdt} \times \frac{Dc\,Sc - B}{Db\,Sb}$$

A and B are constants from the thermodilution/Fick regression equation of Braithwaite and Bradley (1968) **(41)**

V is the volume of dextrose-saline injected - the dead space of the catheter

T is temperature $^{\circ}C$

D is density

S is specific heat

subscripts b and c blood and injectate

STbdt is the interval of change in blood temperature with time, t in seconds.

This can be simplified **(42)** to

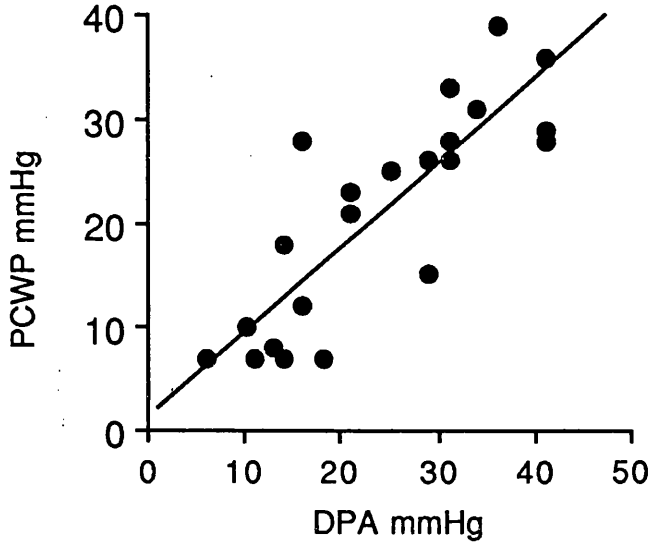
$$\text{Cardiac output} = \frac{V_I \times (T_B-T_I) \times 60 \times 1.08}{A\ (cmm^{-1})}$$

V_I = volume of injectate in ml; T_B = blood temperature; T_I = injectate temperature; 1.08 = correction factor for specific gravity and specific heat of blood and indicator; A = the area under the dilution curve multiplied by time for inscription of the curve.

To accurately assess blood flow requires that **(i)** the amount of indicator injected must be measured accurately and there should be no loss of indicator between the sites of injection and detection, **(ii)** the injection should be "instantaneous", **(iii)** there must be adequate mixing of the injectate with the volume flow and there must be no additional blood leaving or entering the circulation beyond the site of mixing and before the site of detection, **(iv)** steady-state conditions must apply.

It is clear that these perfect conditions cannot exist in the circulation in man, and therefore all measurements are subjects to error. The most signficant source of error is the accurate measurement of injected volume. This can be largely overcome by the use of injectors that are pre-set to inject exact volume. In this thesis all cardiac output measurements were made either with an electrically driven injector (IL 801 computer) or on exercise with a hand held gas cyclinder powered gun (OMP Thermodilution Injector 3700). The injectate (10 ml of dextrose) is cooled by storing the dextrose in iced water to reduce the variability of readings **(43)**.

Good correlation has been found between thermodilution and Fick methods (Fegler, 1954) **(44,45)** and between dye and thermodilution (Goodyear et al, 1959; Ginz et al, 1971) **(46,47)**.


PCWP mmHg
40
30
20
10
0
0
10
20
30
40
50
DPA mmHg

Results are reproducible over a wide range of measurements, reproducibility being ± 2%, and in our laboratory an r value of 0.95 was obtained against dye dilution.

Pressure measurement

The advantage of using a thermodilution catheter is that it also allows a measure of intra-cardiac pressure. Pulmonary "wedge" pressure is taken as an accurate reflection of left atrial pressure. Mean atrial pressure is thought to correlate well with the end diastolic pressure of the associated ventricle (1), thus mean wedge pressure correlates well with left ventricular end diastolic pressure in the presence of a normal mitral valve. Normal left ventricular end diastolic pressure is less than 12 mm.Hg. and does not rise with exercise.

Chest X-Ray

As the heart size increases, as an adaptive response in heart failure, this may be detected by chest x-ray. Heart size may be assessed by subjective grading, measurement of transverse diameter or volume measurements.

Subjective grading consists of grading heart size as normal, slight but definite, obvious or gross cardiomegaly. The accuracy of this form of grading may be increased by using a lateral view to assess whether the heart is deep or shallow.

Transverse diameter - This is the ratio between the maximum transverse diameter of the heart and the width of the thorax (the maximum width above the costophrenic angle measured from the inner ends of the ribs). In general, 50% is taken as the upper limit of normality. This may be

exceeded, without cardiac enlargement, if the heart is depressed (eg by sternal depression) or if the diaphragm is raised (eg obesity). Conversely, the cardiothoracic ratio may remain normal where the heart expands downwards (eg aortic regurgitation).

An alternative is to use a measurement of transverse cardiac diameter >15 cm. in an adult, or of more value, the transverse diameter predicted from height and weight **(49)** with a measurement of $>10\%$ outside of this being abnormal.

Heart volume - This is based on the assumption that the heart is ellipsoid and requires measurements from the anterior and lateral views **(50)**.

$$\text{Volume mls/m}^2 = \frac{L \times B \times D \times k \times M}{A}$$

where (L) is the long diameter, measured from the superior vena caval/ right atrial junction to the cardiac apex

B is the broad diameter, from diaphragm/right atrial junction to pulmonary trunk/left atrial appendix junction

D is the depth diameter, or the greatest horizontal depth of the heart

k is a constant of 0.63

M is the magnification factor (Jonsell, 1939 **(50)**)

A is the body surface area, derived from height and weight

The upper limit of normal for adult males is 550 ml/m^2 and 500 ml/m^2 for females **(51)**

Left Ventricular Function

Left ventricular function may be assessed by several methods, of which the commonest is left ventricular ejection fraction. By injecting contrast

medium into the left ventricle and recording on cine film, end diastolic and end systolic frames may be obtained. Left ventricular volumes and ejection fraction (LVEF) can then be calculated (Dodge and Sandler) **(52,53,54).**

Assuming the ventricle to be ellipsoid, the volume can be derived from

$$D = \frac{4A}{\pi L}$$

where D is the minor axis, A is the area of the ventricle and L is the long axis measured from the mid-aortic root to the apex of the ventricle. This becomes more accurate where a grid calibration correction for magnification is used, together with a correction for the right anterior oblique projection **(55)** or patient size **(56,57).**

Normal end diastolic volume index is 70 ± 20 (SD) ml/m^2 **(53).**
Left ventricular ejection fraction (LVEF) is given by the formula

$$LVEF = \frac{EDV - ESV}{EDV}$$ (Dodge and Sandler **(54)**)

where EDV = end diastolic volume
ESV = end systolic volume

Normal LVEF by angiography ranges from 52-64% **(57).**

Technetium Scanning

Radio-isotopic angiocardiography was developed in 1969 (Mason et al, 1969; Mullins et al, 1969 **(59,60)**) and in 1971 a non-invasive radionuclide method was described for gated blood pool imaging, using a scintillation camera for estimating ejection fraction and segmental contraction (Strauss et al, 1971; Zaret et al, 1971 **(61,62)**).

In vivo labelling is achieved by injecting intravenously sodium pertechnetate, followed 5-10 minutes later by 600-800 MBq of technetium (Tc99m). Images are obtained in listmode, gated to the electrocardiogram, using a mobile gamma camera fitted with a high sensitivity parallel collimator. Images may then be reconstructed into 24 frames. End diastolic and end systolic frames may be identified from the 40° left anterior oblique projection.

Calculation of Left Ventricular Ejection Fraction

By drawing a region of interest around the left ventricle in end diastole (Figure 35a) to encompass the whole of the left ventricle, taking care not to include left atrial activity, a background region of interest was drawn 3 pixels wide adjacent to the left ventricular region of interest. Using a semi-automated technique time activity curves (Figure 34d) were generated for both regions of interest, allowing ejection fraction to be calculated **(63,64,65)**.

$$LVEF = \frac{EDc - ESc}{EDc - B}$$

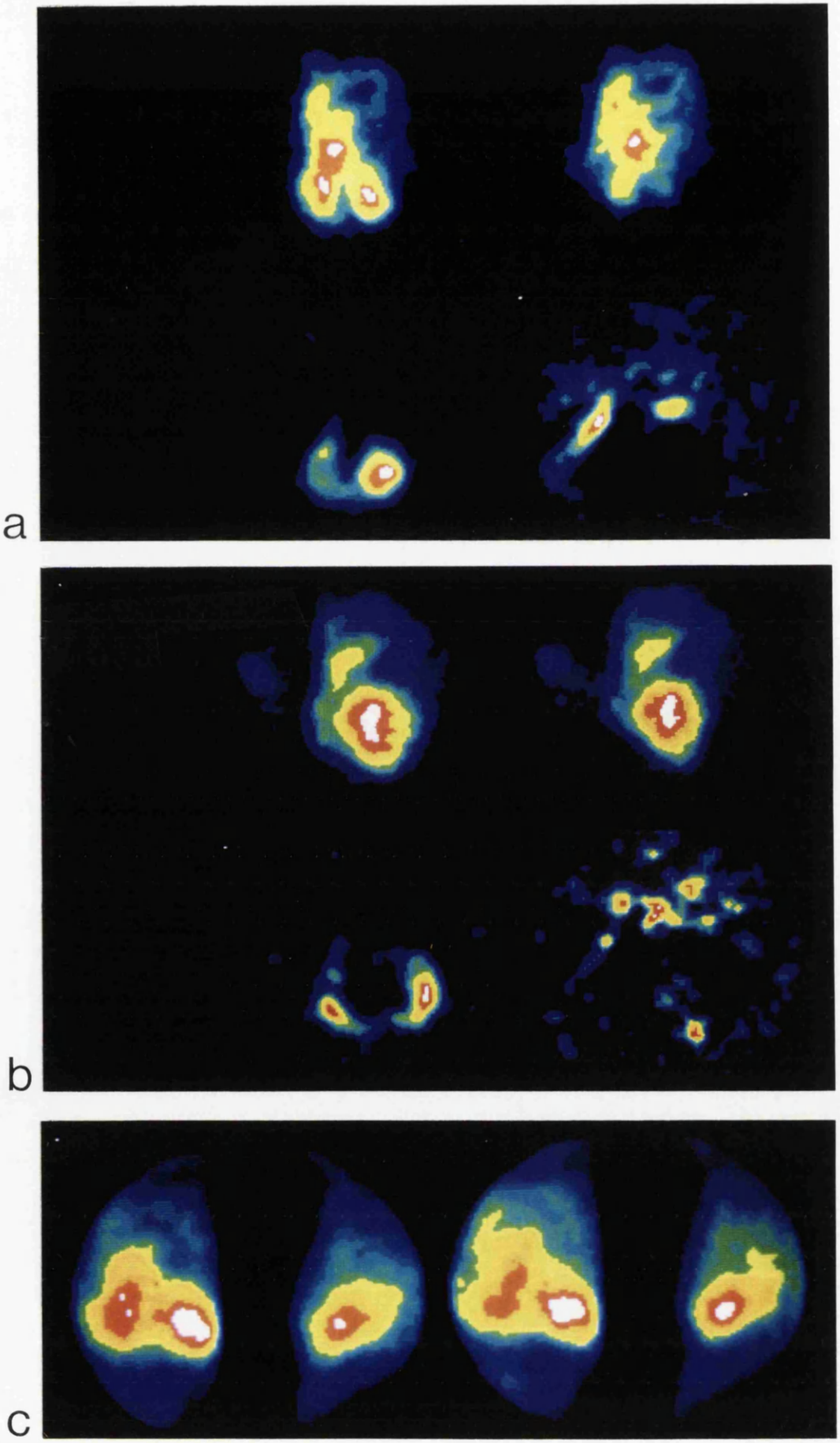
where EDc = end diastolic counts

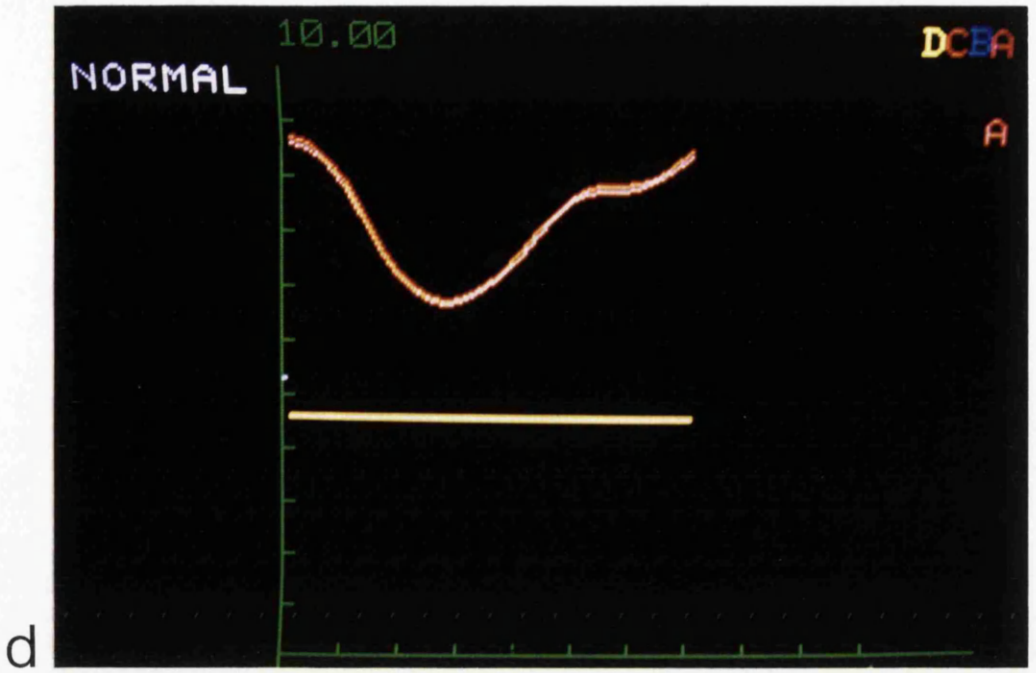
ESc = end systolic counts

B = background activity from mean counts throughout background activity curve.

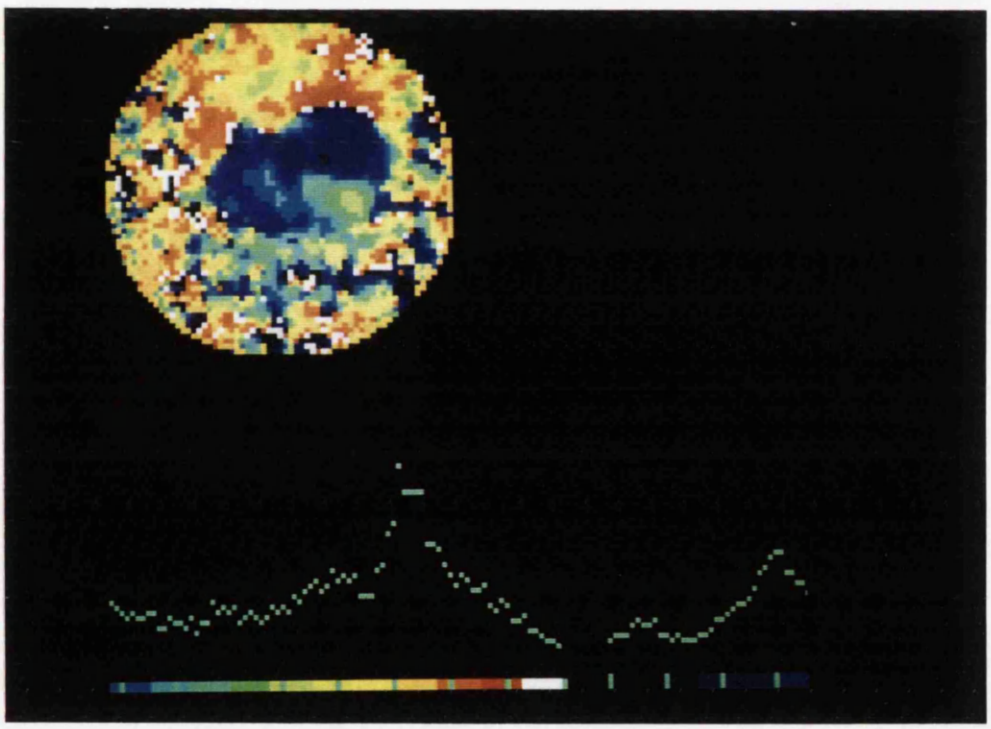
In 10 volunteers LVEF was above 45% with a mean standard deviation of 1.6%. The reproducibility of this measurement is high - both for repeatability with one observer, two and three observers. The day to day variation has been obtained in 20 subjects and was $\pm$ 2.2%. The

Figure 35:





d



e

Figure 35: a) Normal end diastolic and end systolic images from a technetium scan, with stroke volume and paradox images below

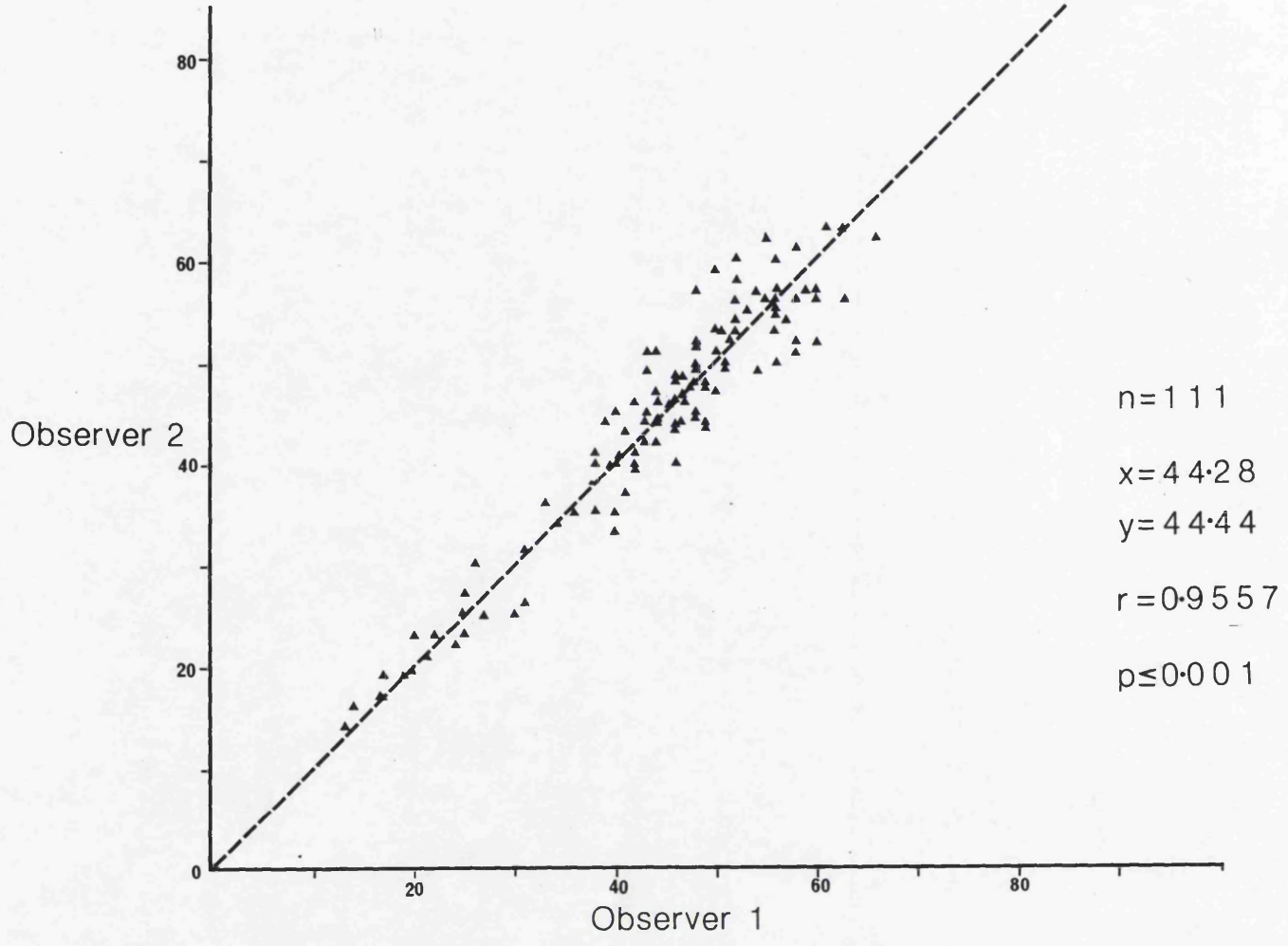
b) Abnormal technetium scan, with an apical aneurysm best seen on the paradox image

c) Abnormal end diastolic and end systolic images from a biplane technetium scan

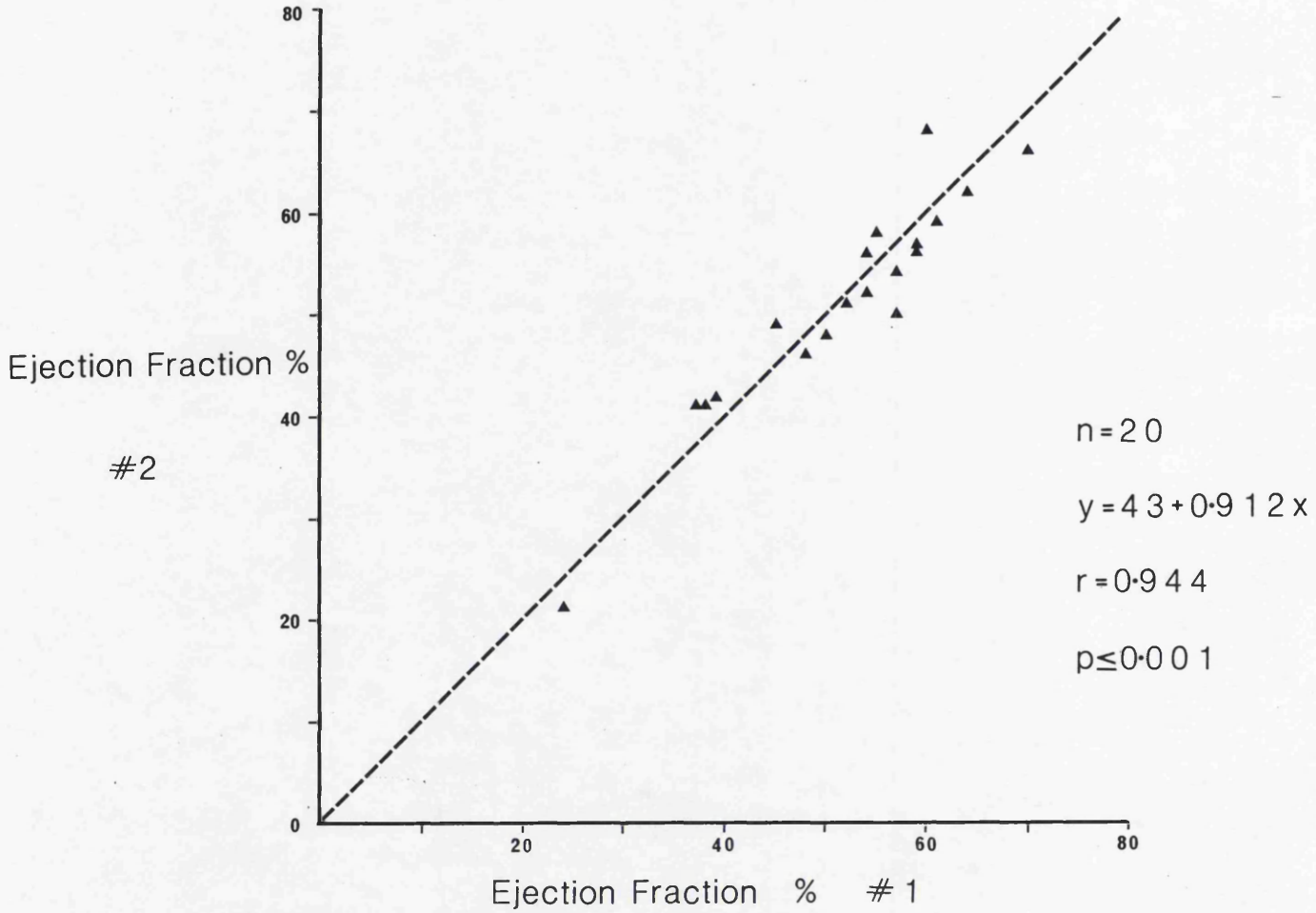
d) Normal ejection fraction curve

e) Phase image, showing an apical aneursym and curves, of phase delay

INTEROBSERVER VARIATION OF RADIONUCLIDE EJECTION FRACTION



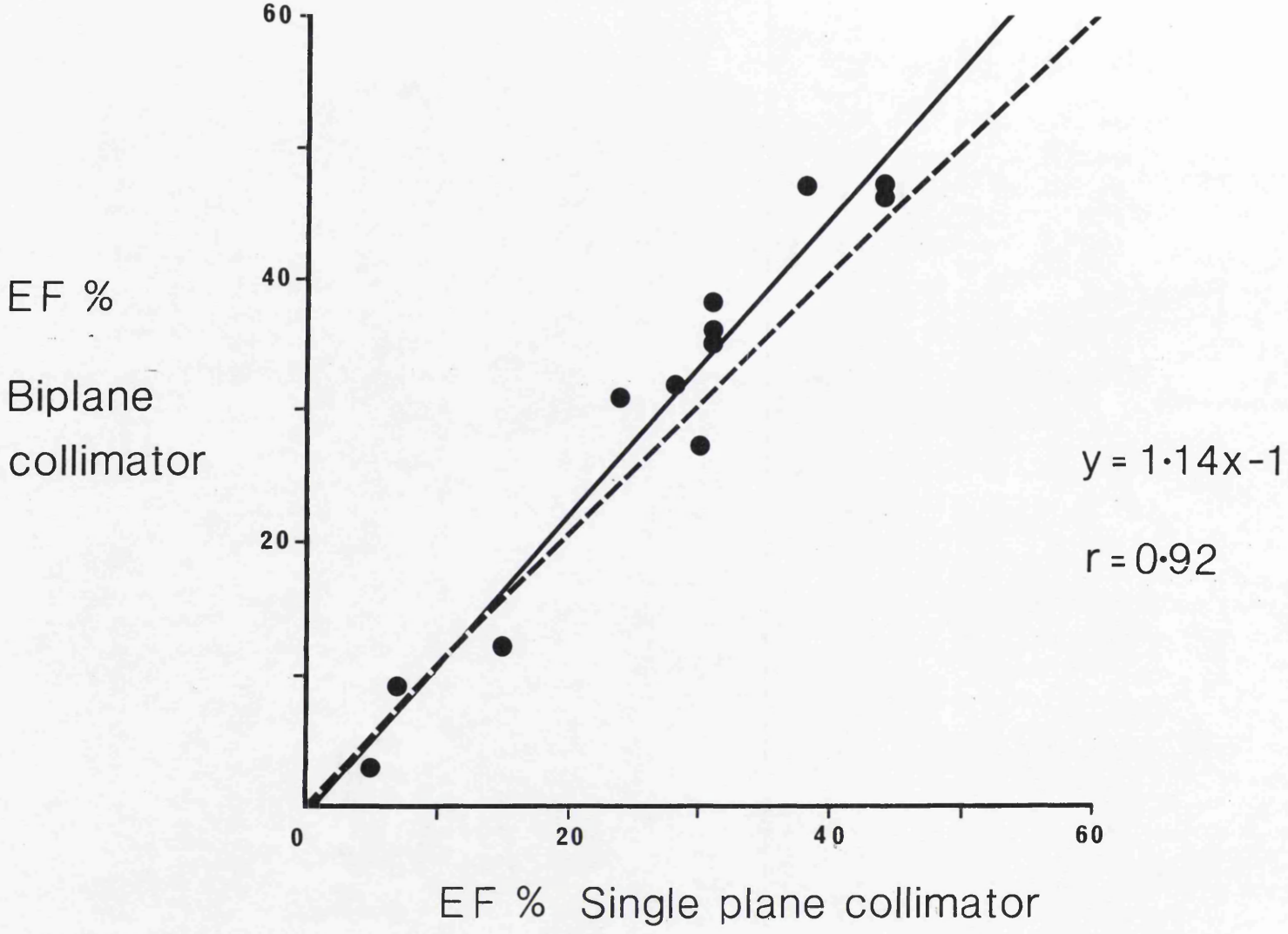
REPEATABILITY OF RADIONUCLIDE EJECTION FRACTION



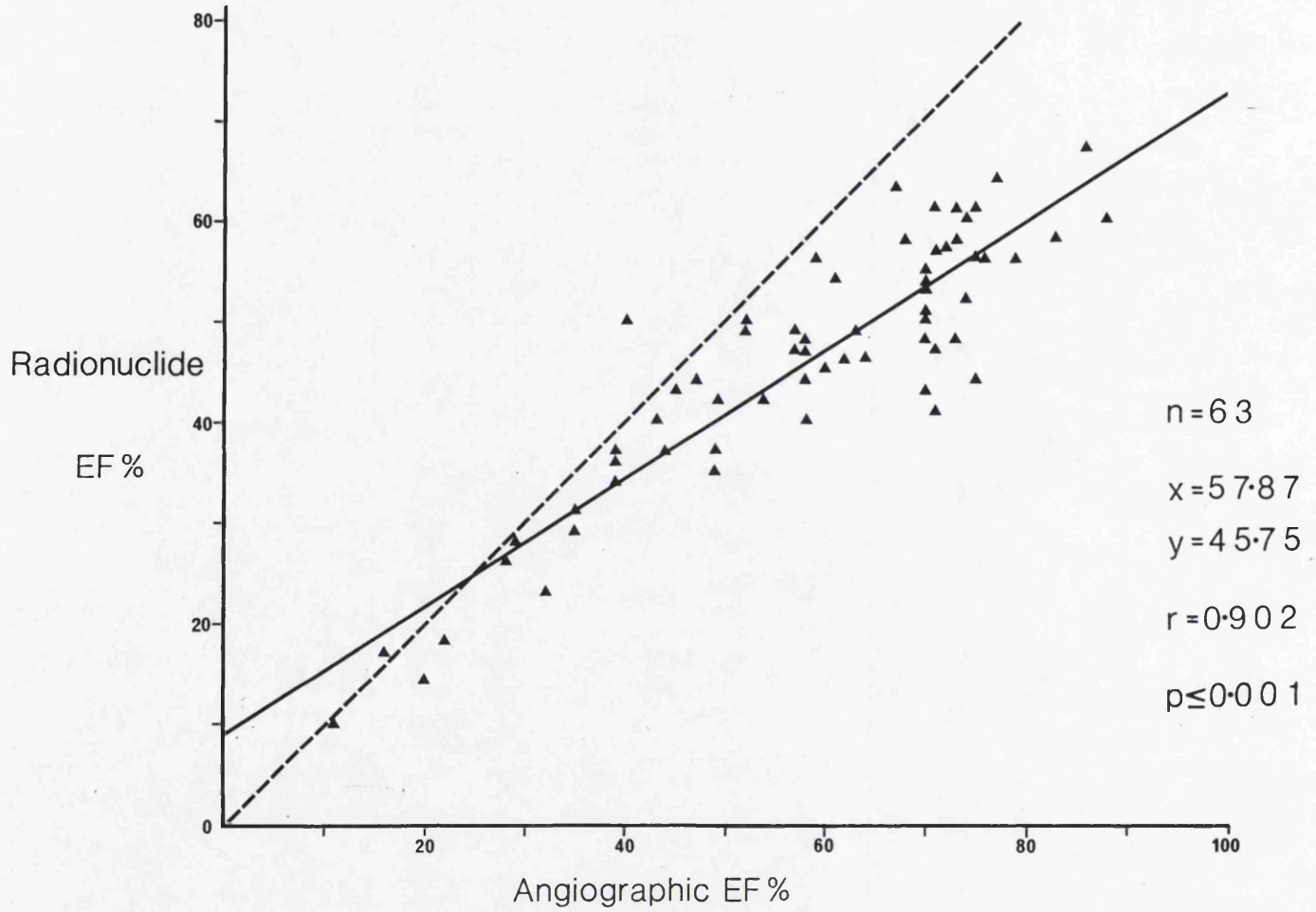
VALIDATION

Radionuclide E.F.

Reproducibility	a)	IHD	n = 111	mean SD 1·9%
		Normals	n = 10	mean SD 1·6%
	b)	2, 3, 4 observers		intra-observer variation 1·8% n = 50
	c)	Exercise	n = 10	mean SD 2·9%
Repeatability		1 hour ⇒ 28 days	n = 20	mean SD 2·2%


EF %
Biplane
collimator
60
40
20
0
20
40
60
y = 1·14x-1
r = 0·92
EF % Single plane collimator

CORRELATION OF RADIONUCLIDE & ANGIOGRAPHIC EJECTION FRACTION



CALCULATED AND TRUE LVEF OVER A RANGE
OF END DIASTOLIC VOLUMES FOR SYMMETRICAL CONTRACTION

EDV (ml)	EF(true)	EF(calculated)	%ERROR
144	48·8	49·3	0·9
180	48·8	49·4	1·1
221	48·8	49·5	1·2
268	48·8	49·6	1·4
322	48·8	49·7	1·6
382	48·8	49·8	1·8

reproducibility of the technique with either upright or supine exercise was 2.9% (Figure 36c).

Left ventricular ejection fraction obtained by technetium scanning was compared with angiography (calculated by the method of Dodge and Sandler). In 63 individuals, over wide range of LVEF r =0.9 (Figure 36c). Errors for calculated and true left ventricular ejection fraction for a range of end diastolic volumes are shown in Figure 36f. The inferior wall is best assessed using a 70° left anterior oblique or a lateral projection. Both a 30° and 70° left anterior oblique projection may be acquired simultaneously using a biplane collimator, for which LVEF may be calculated as seen in Figure 36d.

Volumes

End diastolic and end systolic volume may be calculated if a reference blood sample has been obtained **(66,67,68)**.

Normal ED Vol is 70 $\pm$ 20 (SD) ml/m^2

Reproducibility $\pm$ 4%

Functional images and Regional wall motion

Wall motion can be assessed by viewing the cine images and using a four point scoring system, ranging from 1 normal motion, 2 reduced motion, 3 little motion, 4 motion absent, and 5 aneurysmal motion, i.e. moving out of phase. With experienced observers, this is simple and very reproducible, cf. Figure 37. By simply adding the regional 'scores', normal = 5 ranging to a maximum of 25, with all segments aneurysmal.

In an effort to quantify the degree of regional abnormality, various methods have been employed **(69)**.

Functional images:-

The stroke volume image, Figure 35a, ED - ES image, gives a simple visual estimate of the degree of wall motion abnormality.

Estimation of the degree of abnormality from the stroke volume image gives a simple, reproducible measurement **(70)**.

The paradox image ES - ED allows identification of areas moving out of phase, or true aneurysm formation (Figure 35b).

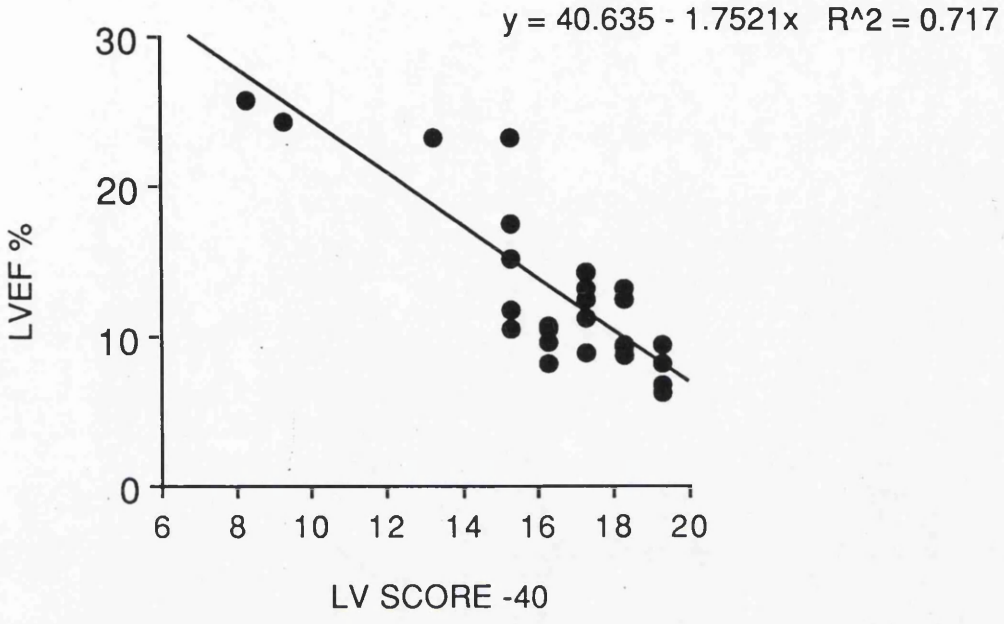
The phase image:-

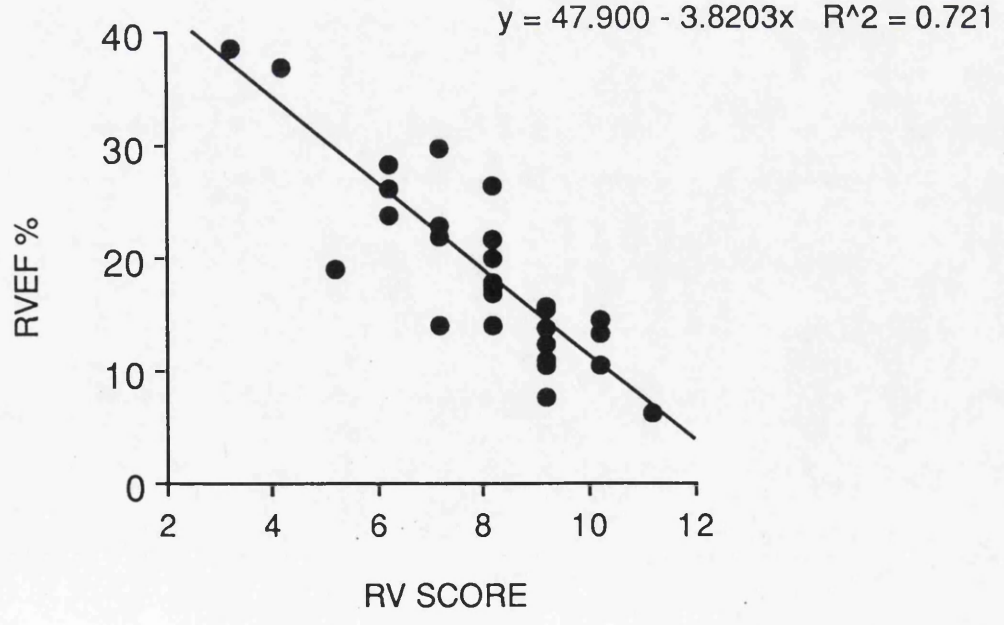
For each pixel, a time activity curve may be generated. If each pixel is coded for the time to end systolic counts, a phase image may be produced, which allows areas of ventricular motion which are delayed or "out of phase" to be identified, Figure 35e.

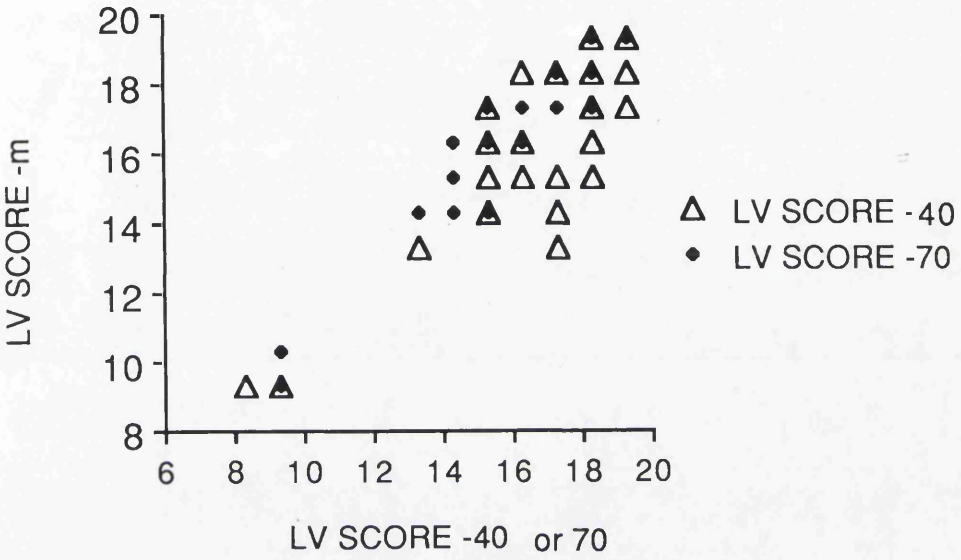
The degree of ventricular abnormal phase can be used to assess the extent of regional abnormality within the ventricle. Normal phase can occur

1 = Normal 2 = reduced
3 = little 4 = none

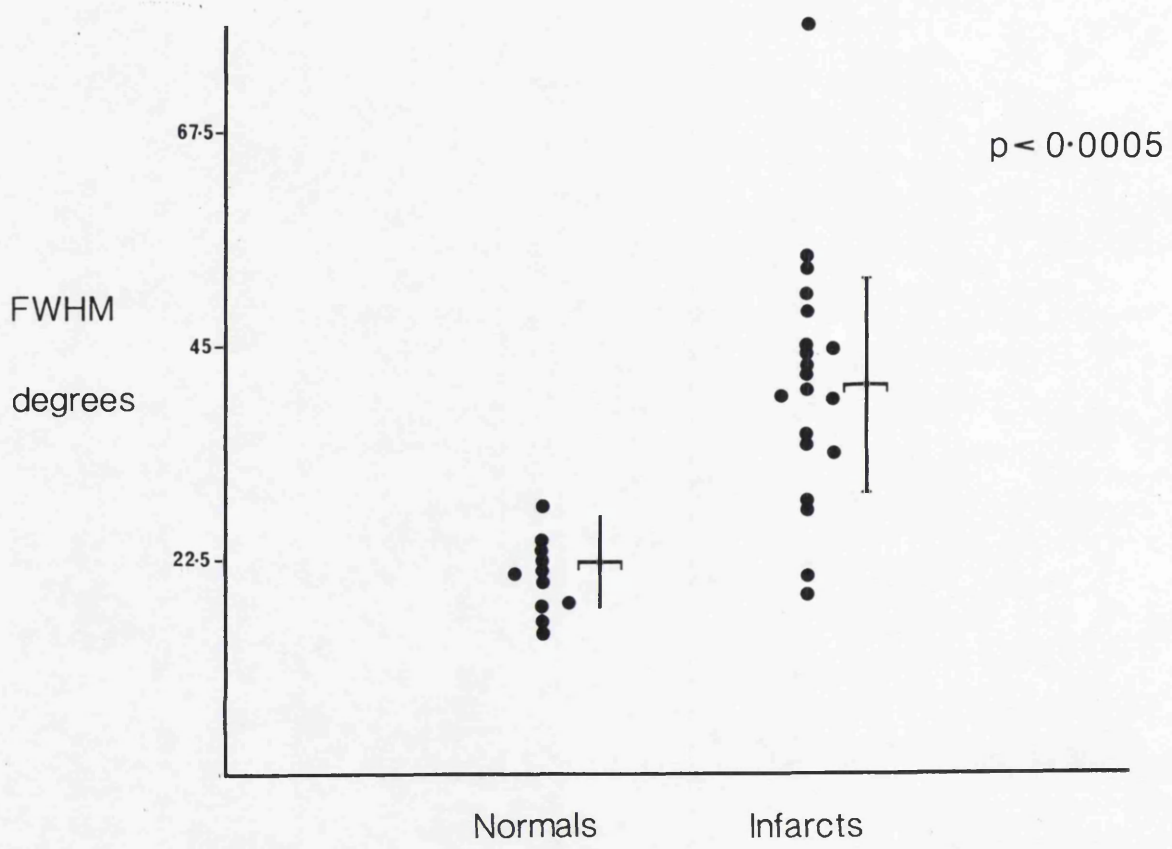
30 40 70

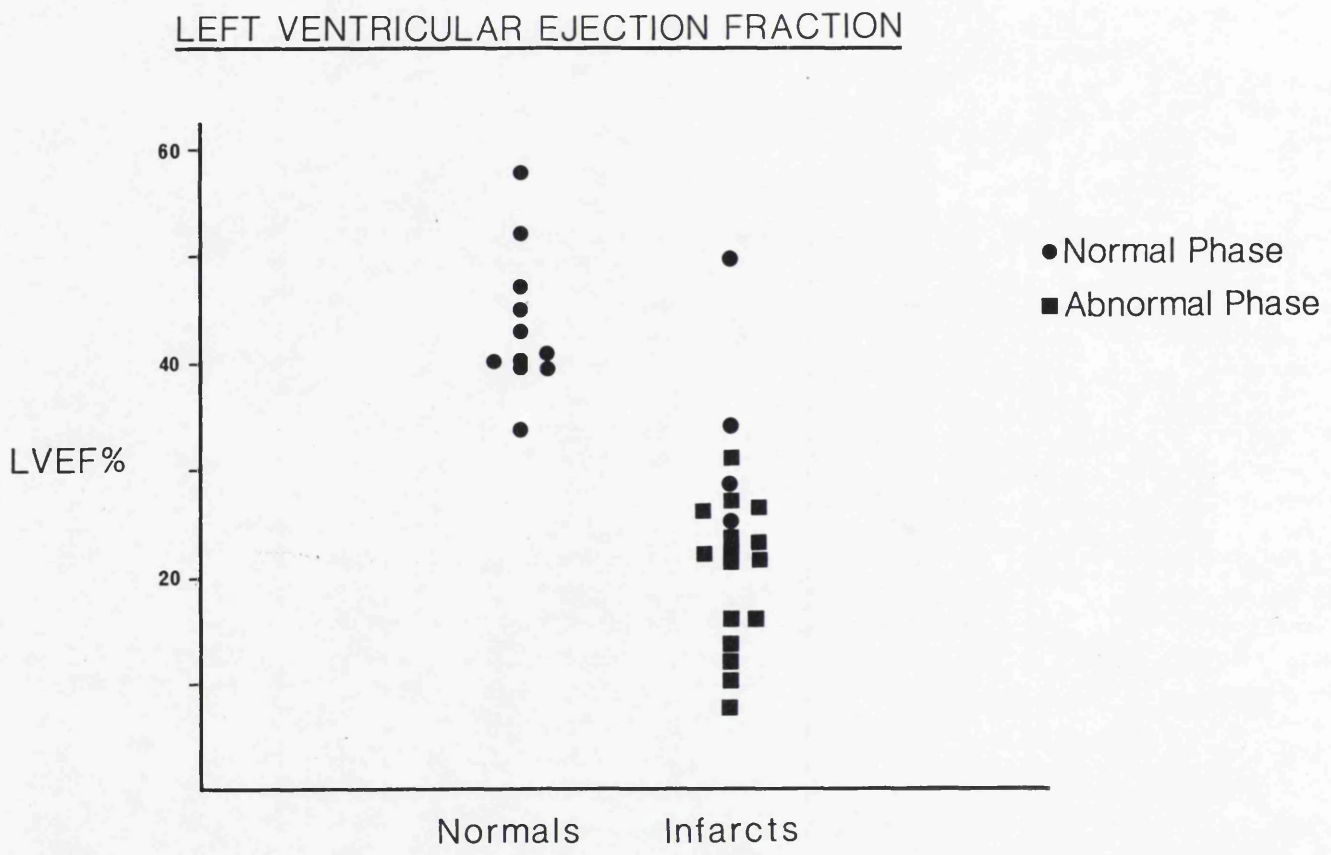

y = 40.635 - 1.7521x R^2 = 0.717
LVEF %
30
20
10
0
6
8
10
12
14
16
18
20
LV SCORE -40


y = 47.900 - 3.8203x R^2 = 0.721
RVEF %
40
30
20
10
0
2
4
6
8
10
12
RV SCORE

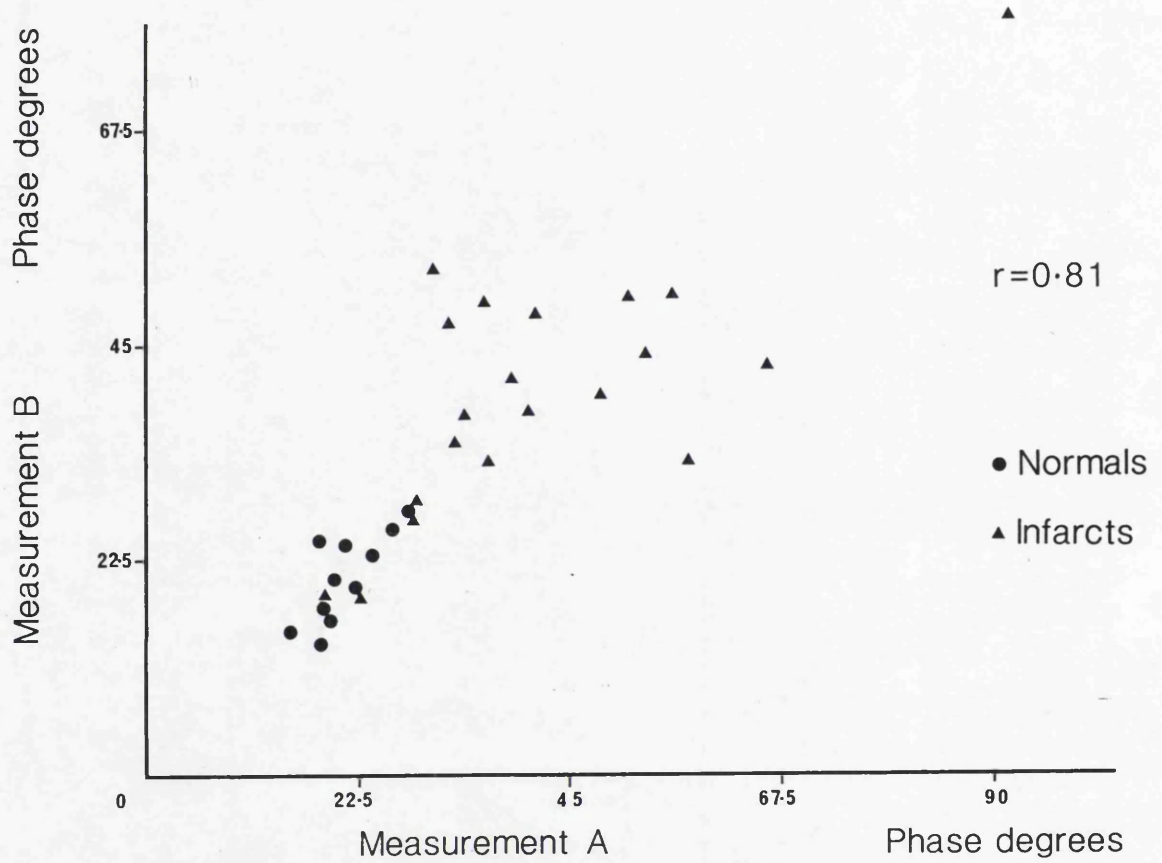

20
18
16
14
12
10
8
LV SCORE -m
6
8
10
12
14
16
18
20
LV SCORE -40 or 70
LV SCORE -40
LV SCORE -70

FULL WIDTH HALF MAXIMUM ~ NORMALS AND INFARCTS

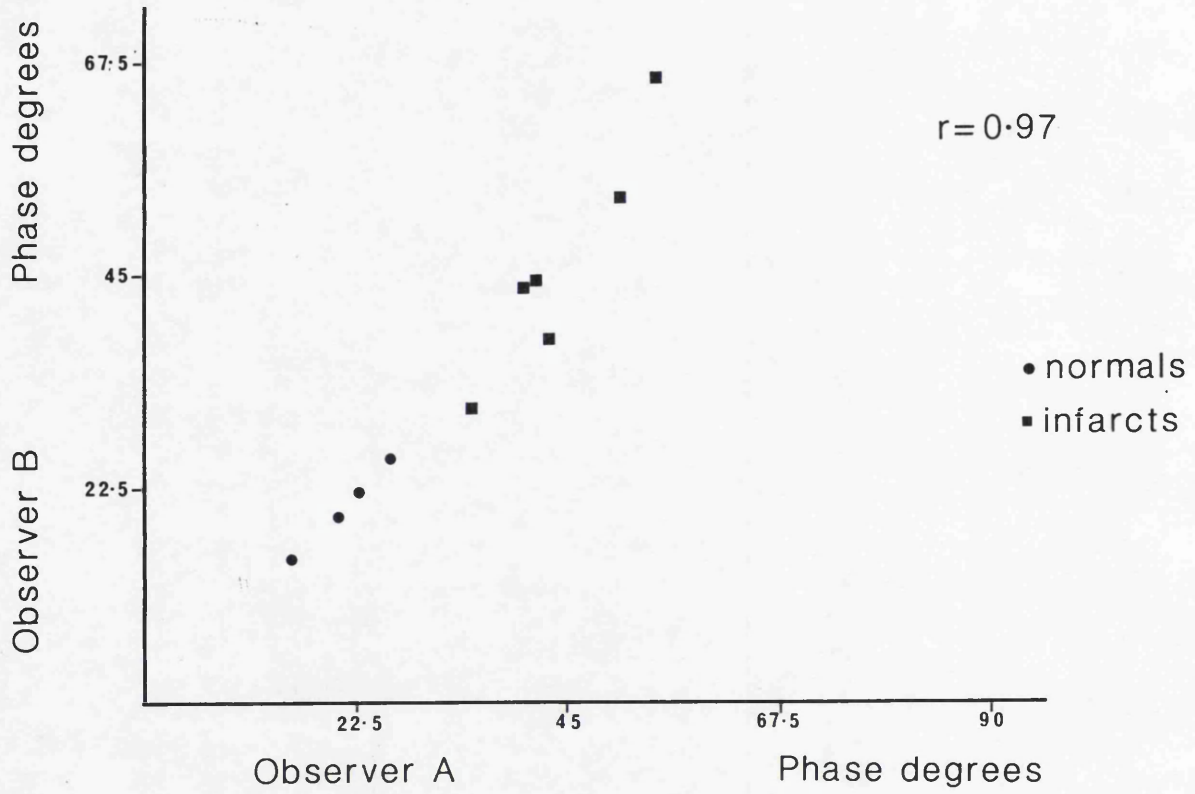



LEFT VENTRICULAR EJECTION FRACTION
60
40
20
LVEF%
Normals
Infarcts
●Normal Phase
■Abnormal Phase

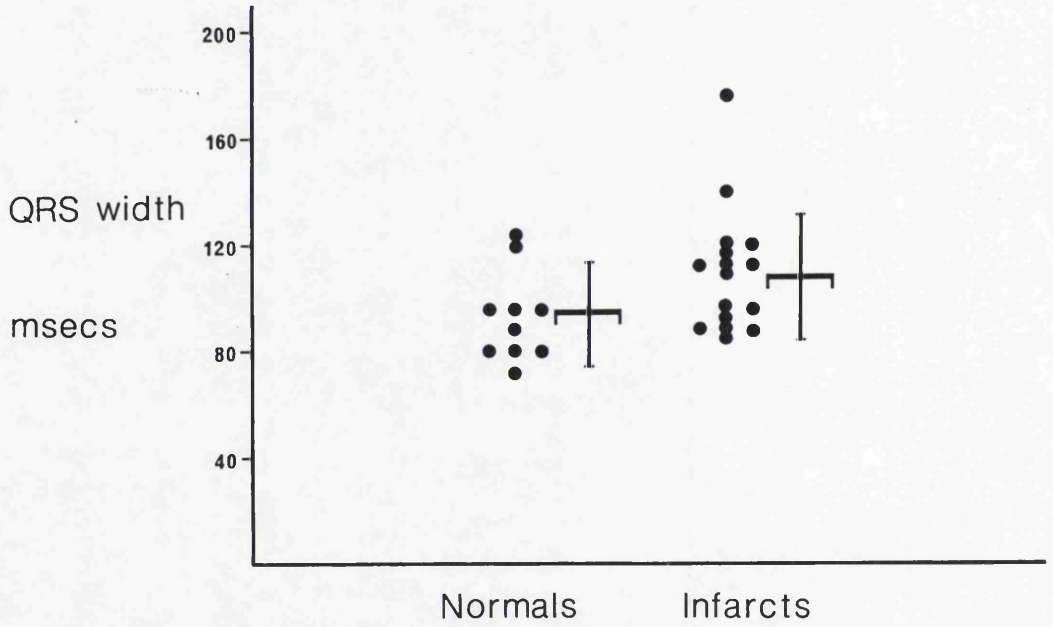
REPRODUCIBILITY OF FULL WIDTH HALF MAXIMUM MEASUREMENTS



REPEATABILITY OF FULL WIDTH HALF MAXIMUM MEASUREMENTS



QRS DURATION ~ NORMALS AND INFARCTS



where left ventricular ejection fraction is reduced, reflecting global rather than regional abnormalities (Figure 38). One of the ways in which the extent of phase abnormality may be simply assessed is to use measurements of full width half maximum (FWHM) of the phase degree. This is reproducible and repeatable and separates patients with normal ventricular function (n = 12, with normal coronary arterio-graphy) and patients with myocardial infarction (n = 20) (Figures 38 a-d). Conduction abnormalities may influence this measurement and this was excluded by measuring QRS duration on the ECG (Figure 38e).

Technetium Scans on Exercise

Technetium scanning may be performed on exercise, providing reproducible and repeatable data to assess ventricular function on exercise **(69-72)**. This may be performed using either a) a first pass technique which optimally employs a multi-crystal Gamma camera and allows a measurement over approximately 20 seconds at 'peak exercise', or b) the gated technique. The accuracy of the latter may be enhanced by the use of two modifications 1) a biplane collimator which simultaneously acquires a 30° and 70° LAO projection, and allows the inferior surface of the ventricle to be assessed, and 2) collecting data continuously in list mode, together with careful timing, then retrospective reconstruction allows the 30 seconds' data at peak exercise to be assessed (Figure 35c).

Exercise is usually performed supine, but where phsyiological parameters are to be tested that require normal ventricular filling, this is better performed upright **(73,74)**. This necessitates taking care in positioning the camera while the subject is seated on the bicycle and restraining the chest (best achieved by leaning on the patient's back).

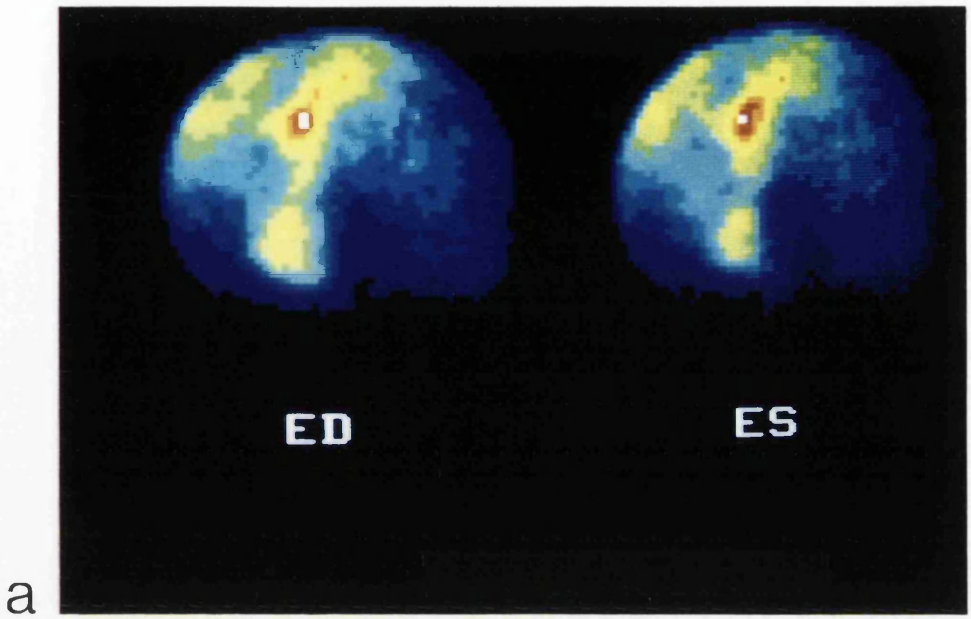
Global and regional function may then be assessed using various techniques already described. Exercise induced regional ventricular wall motion abnormalities correlate well with angio-graphic evidence of coronary disease **(75-79)** and electrocardio-graphic evidence of ischaemia **(80)**.

Summary

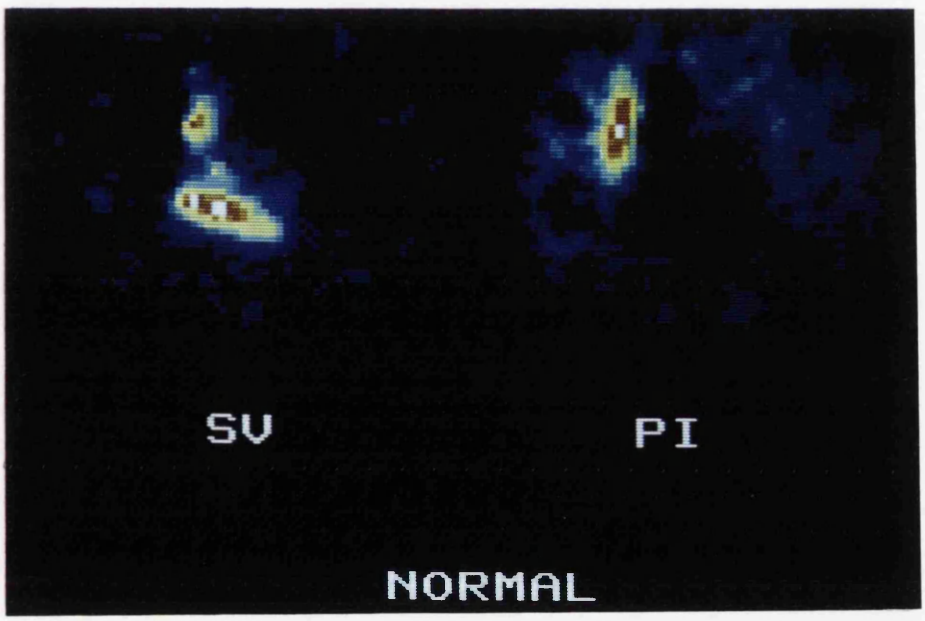
Regional wall motion is most easily assessed from cine images by experienced observers. For the quantification of the extent of regional wall motion abnormalities, the stroke volume image would appear to have advantages as the most reproducible, particularly on exercise.

Right Ventricular Function

The geometry of the right ventricle, with the lack of any approximation to known geometrical shape, makes angiographic measurements of right ventricular function subject to error. Radionuclides provide a count based assessment, which is less influenced by geometrical assumptions. Previously described methods include first pass techniques **(81,82)** and gated equilibrium technetium blood pool scanning **(83,84,85,86)**. However, as the right ventricle enlarges, or indeed as the left ventricle enlarges, it may be difficult to adequately separate the right and left ventricle. It is therefore an attractive idea to use a nobel gas, such as either Xenon-133 or Krypton-133, of which 90% is excreted by the lungs. Previous work using first pass techniques have shown this is feasible, but these images tend to be of poor quality due to reduced count density **(87,88,89,90)**. We therefore developed a method of assessing right ventricular function using gated Xenon133 imaging **(91)**.



a



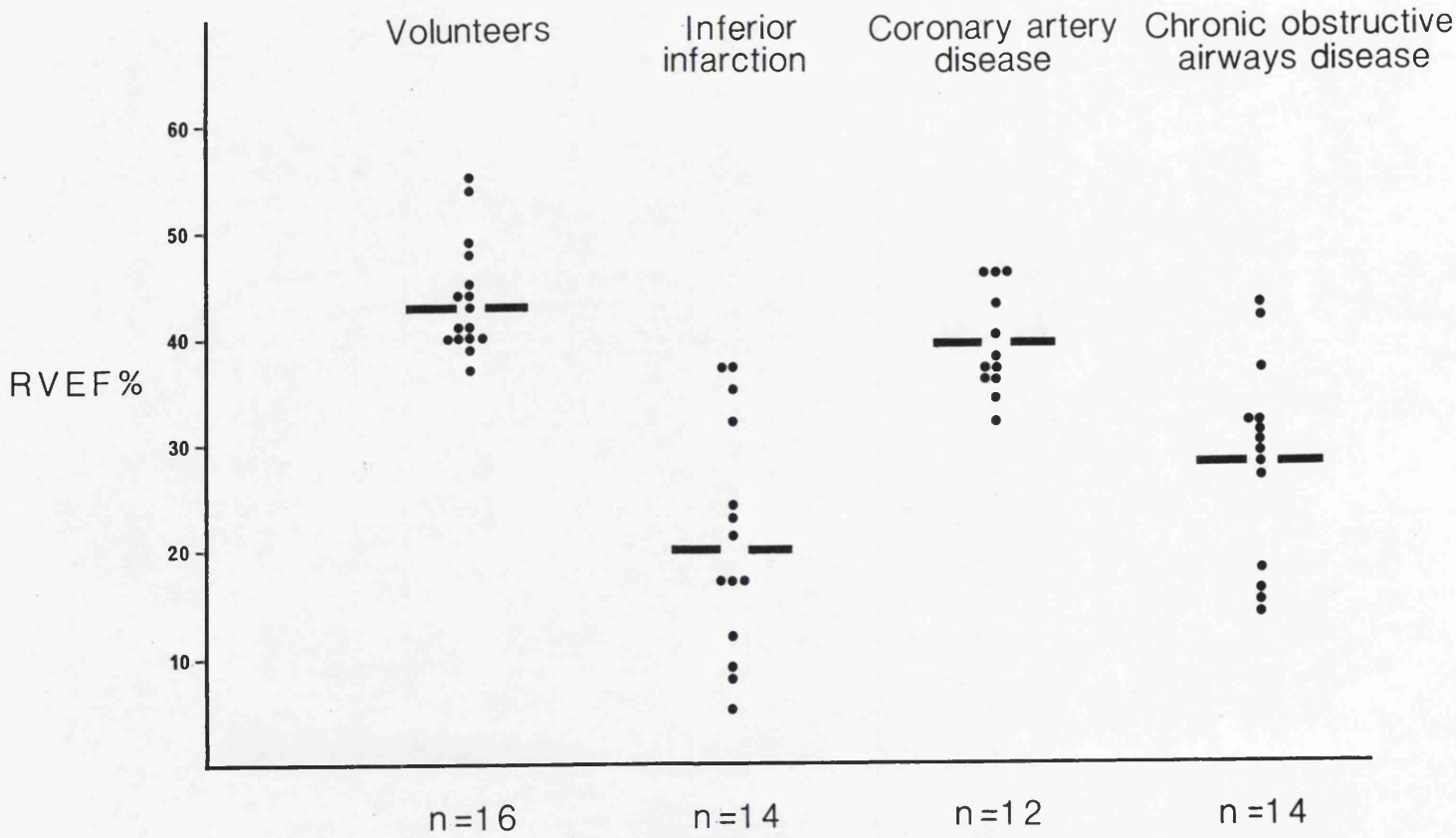
b

Figure 39: a) Normal right ventricular Xenon, end diastole and end systole

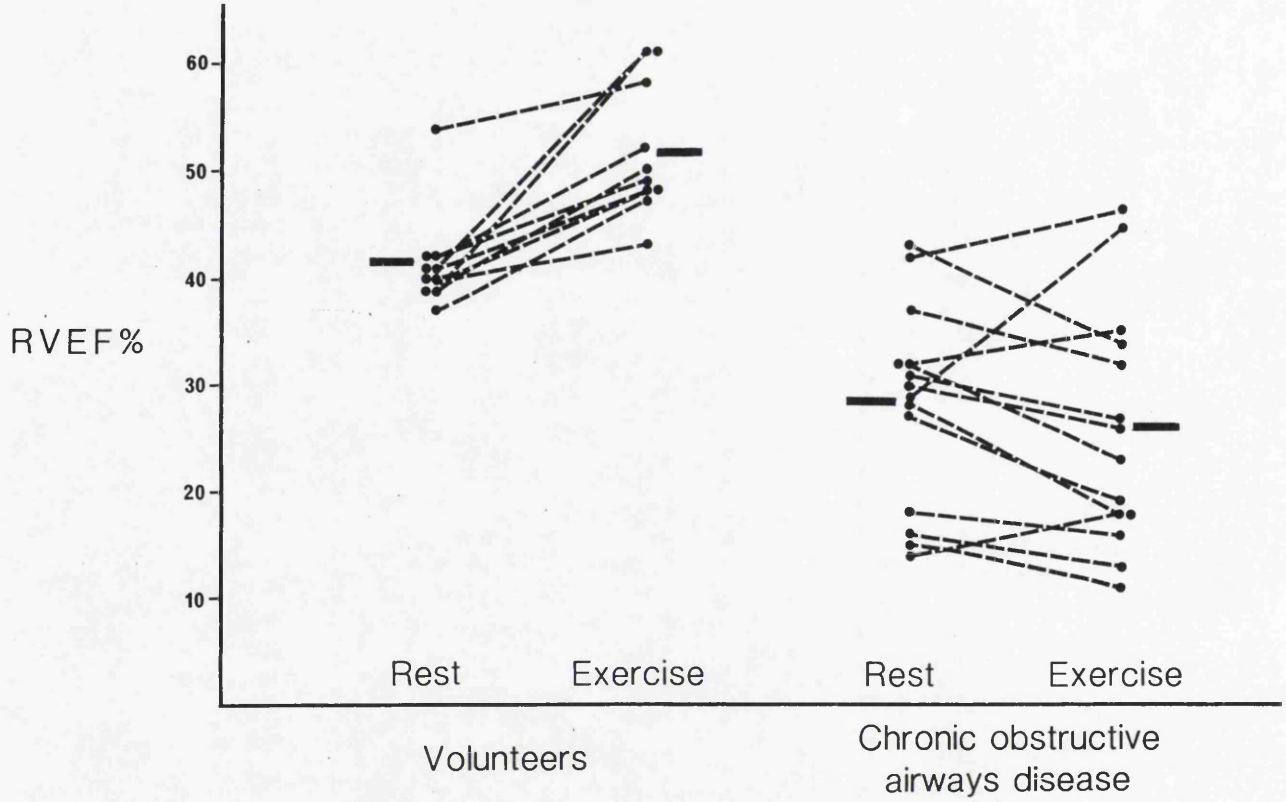
b) Normal stroke volume and paradox images

Data were acquired using a mobile gamma camera fitted with an ultra-high sensitivity parallel collimator. The camera was interfaced with a mobile computer system (Link MAPS). All data were acquired in listmode, to allow accurate retrospective construction of a representative cardiac cycle. The camera was positioned in 5-10° left anterior oblique projection with 6° caudal tilt, to allow optimal separation of the right atrium from the right ventricle, and isolation of right ventricular activity from the lung fields. 400-600 MBq of Xenon133 was injected intravenously over 20 seconds and data were acquired from time of first visualisation of activity within the right heart, until activity was seen to leave it. Average data acquisition time was 25 seconds and in 20 studies the average net end diastolic counts were 3620 $\pm$ 978 in 1/16 of a cardiac cycle.

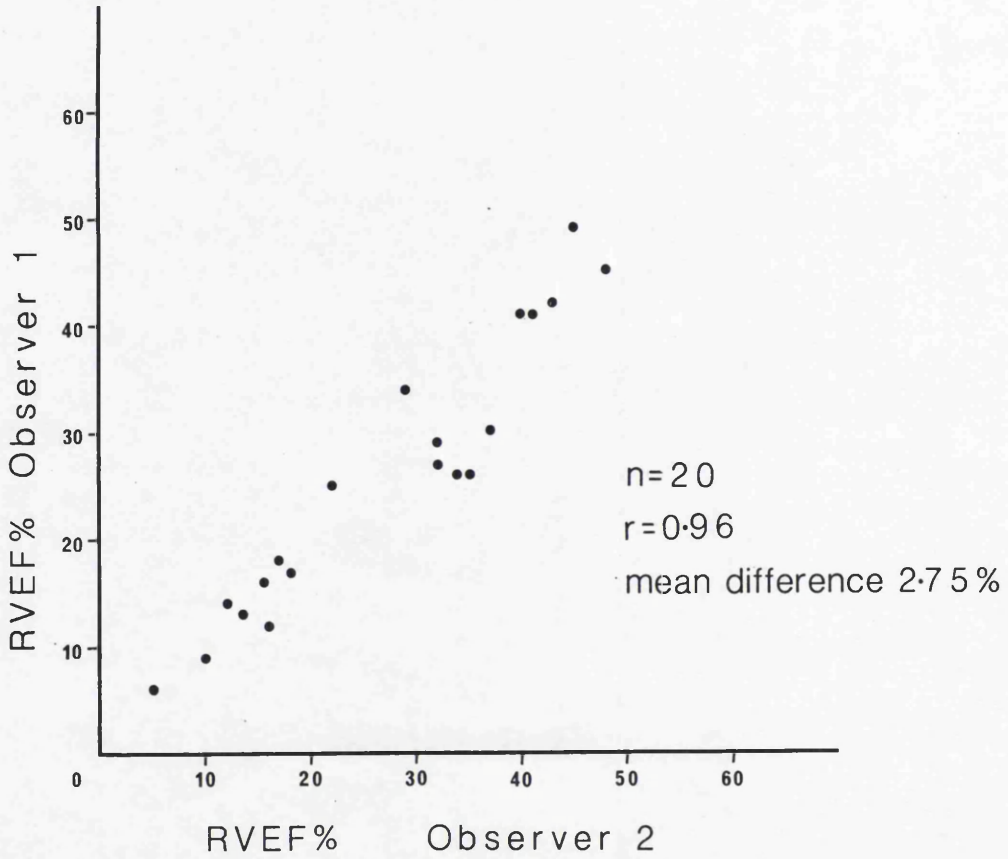
Data were processed to construct a cycle of 16 frames for analysis, with cycles with R-R intervals outwith 20% of the running average being discarded. After spatial and temporal smoothing, the end diastolic and end systolic frames are used to produce standard stroke volume and paradox images, Figure 39b, allowing definition of the tricuspid and pulmonary valve planes. The right ventricular region of interest was then extended from the valve planes to encompass the whole of the right ventricle. The region of interest was confirmed by superimposing the cine display and modifying as necessary. A background region of interest was drawn 3 pixels wide, adjacent to the right ventricular region of interest. Time-activity curves were then generated for both regions of interest, allowing right ventricular ejection fraction (RVEF) to be calculated.


Volunteers
Inferior infarction
Coronary artery disease
Chronic obstructive airways disease
RVEF%
60
50
40
30
20
10
n=16
n=14
n=12
n=14

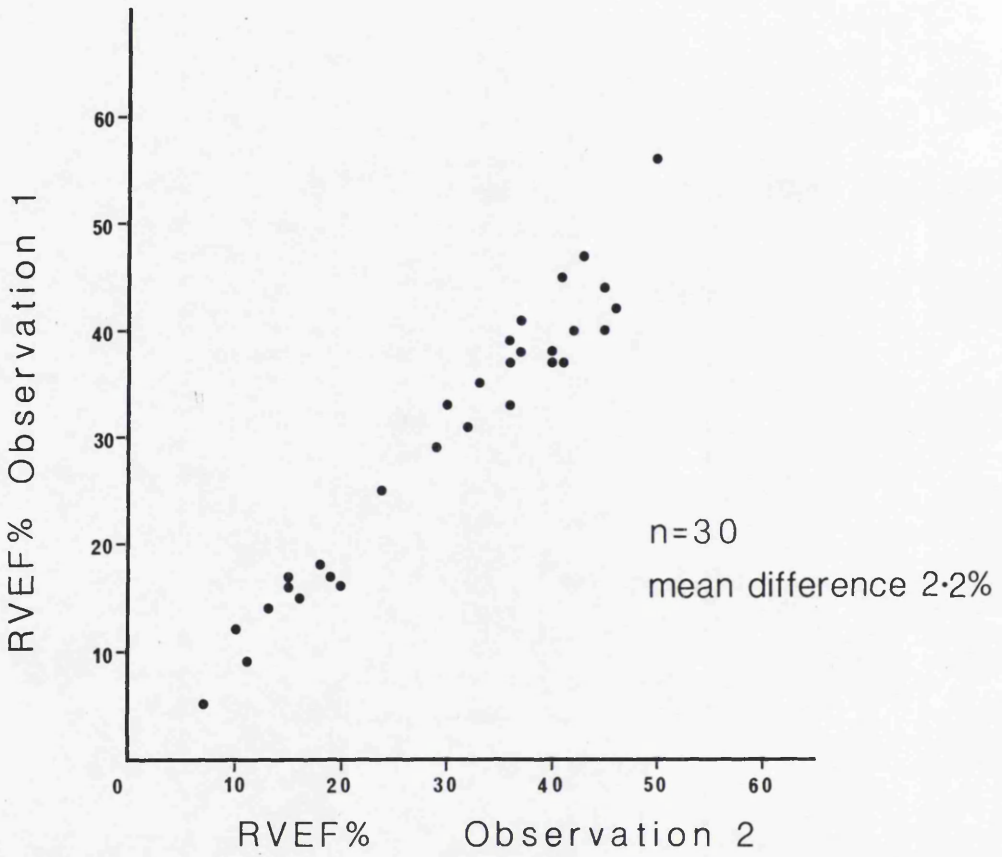
RVEF AT REST AND DURING EXERCISE

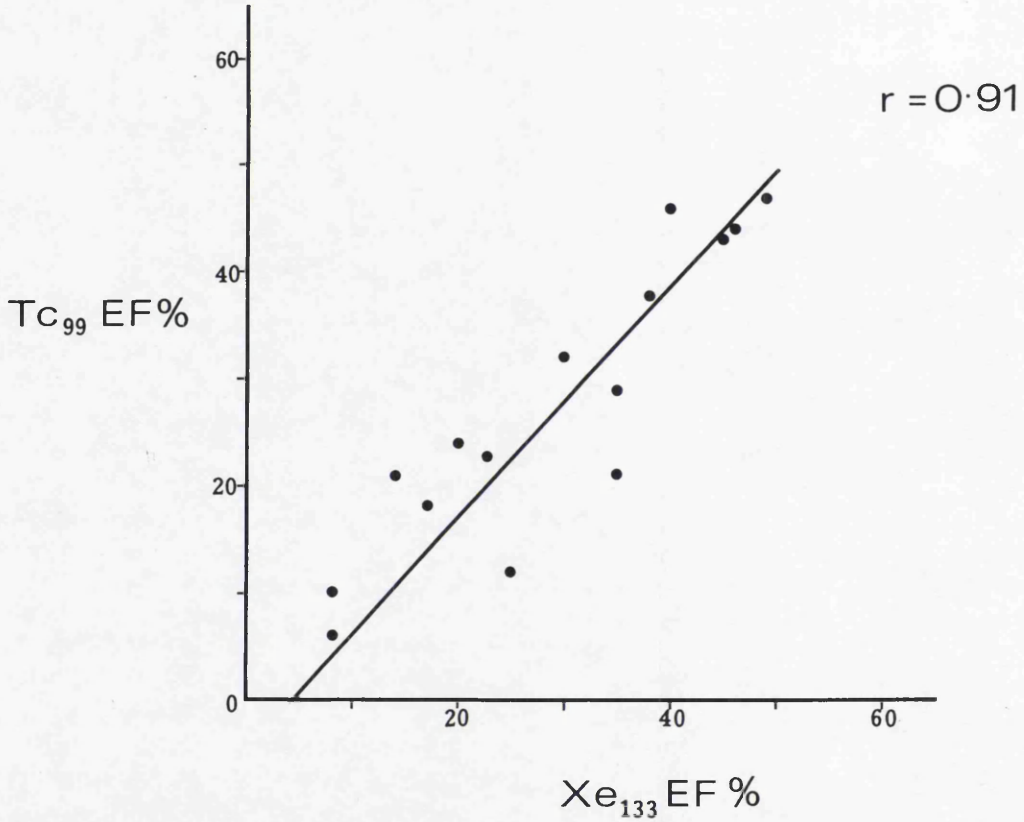


INTER-OBSERVER VARIATION



INTRA-OBSERVER VARIATION




r = 0·91
Tc99 EF%
Xe133 EF %
0
20
40
60
20
40
60

$$RVEF = \frac{EDc - ESc}{EDc - B}$$

where EDc = end diastolic counts

ESc = end systolic counts

B = background activity determined as mean counts throughout the time activity curve for the background region of interest.

Normal RVEF, in volunteers (n = 16,aged 23-36 years), was 35 - 55% with a mean 43 $\pm$ 5%. Gated Xenon133 scans were compared with first pass technetium scans performed in the right anterior oblique projection in 13 patients with a correlation coefficient of 0.80. In 15 patients, gated Xenon133 scans were compared with right ventricular ejection fraction obtained from standard gated technetium scans, with a correlation coefficient of 0.91 (Figure 40e).

Reproducibility and repeatability of the technique are also good with mean differences of 2.2 and 2.75% (Figures 40c,40d).

Coronary Flow

Coronary Sinus Flow

Coronary flow can be inferred from measurements of coronary sinus flow, which can be assessed during cardiac catheterisation by the thermodilution technique **(92)**. A catheter is inserted into the coronary sinus, most easily through the left antecubital vein and saline is infused continuously with the temperature of the injectate measured by a thermistor at the tip of the catheter. The temperature of the blood-saline mixture downstream in the coronary sinus measured by a thermistor

mounted on the catheter. The coronary sinus flow may be calculated (see below) by using samples of coronary sinus blood and simultaneous arterial samples, oxygen content and therefore oxygen usage may be calculated. A Wilton-Webster catheter also incorporates a pacing electrode that allows overdrive pacing within the right atrium.

$$\text{Coronary sinus flow (CSF) ml/min} = \frac{T_M - T_I}{T_B - T_M} \times k \times Q_I$$

T_M = temperature of mixture of blood and injectate, °C
T_I = temperature of injectate, °C
T_B = temperature of blood, °C
k = a constant 1.08
Q_I = rate of infusion of the injectate

Myocardial oxygen consumption (MVO_2) =

CSF x AV oxygen difference ml/min

$A\text{-}VO_2$ difference =

arteriovenous oxygen difference vols %
arterial - coronary sinus O_2 content

$$\text{Coronary vascular resistance} = \frac{\text{mean arterial pressure}}{\text{mean coronary sinus flow}} \times 80$$

dyne-s-cm^{-5}

Care must be taken to ensure that the flow of the inejctate is sufficiently fast - in this thesis 60 ml/minute, administered by a fast infusion pump (Sage Pumps) with a reproducibility of infusion rate ± 2%. This method allows repeated measurements of coronary flow, which are reproducible (± 5%) and are similar to coronary arterial flow (r = 0.9) **(92)**.

Myocardial Flow

Myocardial flow can also be assessed by using radioactive substances (a) radioactive diffusable substances that actively enter the cell, (b) distribution of radio-labelled particles, or (c) disappearance of radioactive diffusable gases.

(a) Radioactive isotopes of sodium, potassium and rubidium **(93,94,95)** all actively enter the cell, and clearance of these tracers from blood by myocardium measures nutritional (or effective capillary) flow. The validity of this technique is dependent on the premise that myocardial uptake is a flow dependent process, therefore

$$\text{Coronary blood flow} = \frac{\text{Myocardial uptake}}{\text{cardiac output total body uptake}}$$

However the extraction ratio of myocardium is not complete and re-circulation occurs. As the tracer is fixed in the myocardium, sequential measurements of flow are difficult.

(b) Radiolabelled particles.

This is the standard technique for the measurement of regional myocardial flow in animals **(96)**. Microspheres 8-10 λ in diameter, injected into the left atrium are trapped in the myocardium and may be quantitated by serial sectioning of the myocardium. Particles in the form of radiolabelled albumin macroaggregates may be injected directly intra-coronary in patients, but as they embolise the coronary capillary bed and have a biological half life of 4-8 hours, repeated measurements are difficult. In addition, recently it has been demonstrated that this

technique suffers from systematic errors due to the particulate nature of the microspheres **(97)**.

(c) Radioactive Nobel gases

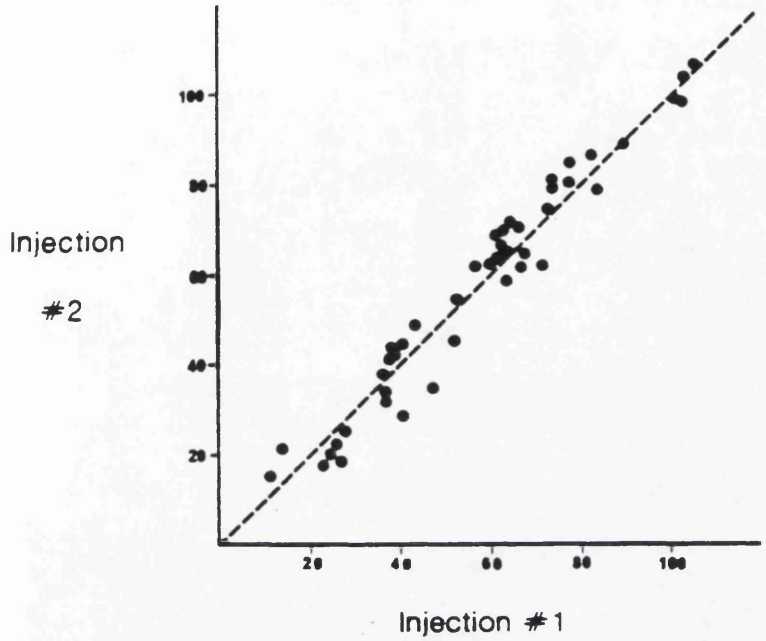
These agents have distinct advantages (i) as they are fat soluble they are capable of rapidly diffusing through the endothelium into surrounding tissue and thus can measure higher rates of flow than water soluble cations; (ii) approximately 95% of the gas tracer enters the alveolar air during first circulation through the lungs, thus there is little recirculation. As the gas is quickly cleared from the lungs, repeated measurements can be made. Krypton 85 has a very short half life (2-4 minutes) and requires to be infused continuously. Xenon133 with a half life of 5.27 days, being more stable, is more convenient to use. Xenon133, 1-200 MBq, is injected directly intracoronary and scans are obtained using a mobile gamma camera fitted with a biplane collimator, which allows the simultaneous acquisition of 30° and 70° left anterior oblique projections. Activity is acquired initially in 1 second, then 5 second frames, to produce washout curves. As the radioactivity reaches the capillary bed of the myocardium, Xenon leaves the capillary space and diffuses into the myocardium with the relationship.

$$\frac{\text{Solubility of Xenon133 in myocardial muscle (or fat)}}{\text{Solubility of Xenon133 in blood}} = \lambda$$

where λ is the partition coefficient - for myocardium this is 0.72 but for fat the coefficient is 8.0.

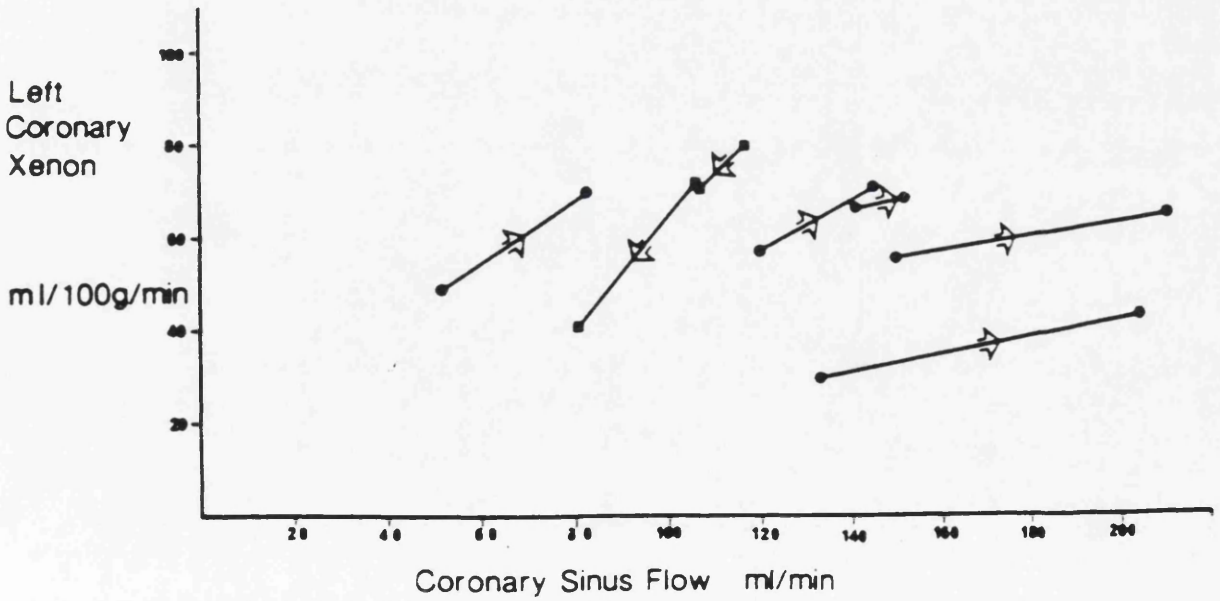
REPRODUCIBILITY OF REPEAT INJECTIONS~

SEGMENTAL PERFUSION



r = 0·8 2

y = 1 0·4 + 0·8 5 x



The blood flowing past the myocardium contains less tracer than the capillary bed, so the tracer begins to diffuse back into the vascular space at a rate proportional to blood flow. Blood flow can be calculated from the washout curve using the Kety-Schmidt formula **(98)**.

$$F = \frac{k\lambda\ 100}{\rho}\ \text{ml/min/100 g myocardium}$$

where

F = blood flow

k = rate constant, the slope of the washout curve

λ = partition coefficient for Xenon in myocardium 0.72 obtained in normal dog by Cohn **(99)**.

ρ = specific gravity of myocardium 1.05

(Volume = $\frac{\text{mass}}{\text{specific gravity}}$)

Blood flow is expressed in terms of an arbitrary 100 g of tissue, which is converted to volume by dividing by specific gravity.

The rate constant, k, is the slope of the washout curve and is derived from a semi-logarithmic data plot. By using only peak to 30 seconds of data, a monoexponential curve is obtained and factors which affect the latter end of the curve, such as washout of tracer from fat, are avoided as far as possible. The method is reproducible $\pm$ 2% (SD) and repeatable $\pm$ 5% (SD) **(100-103)** (Figure 41).

Direct comparison with other techniques, e.g. microspheres, has proved difficult. In a comparison with coronary sinus flow, measurements were similar but absolute values were different. Coronary sinus flow

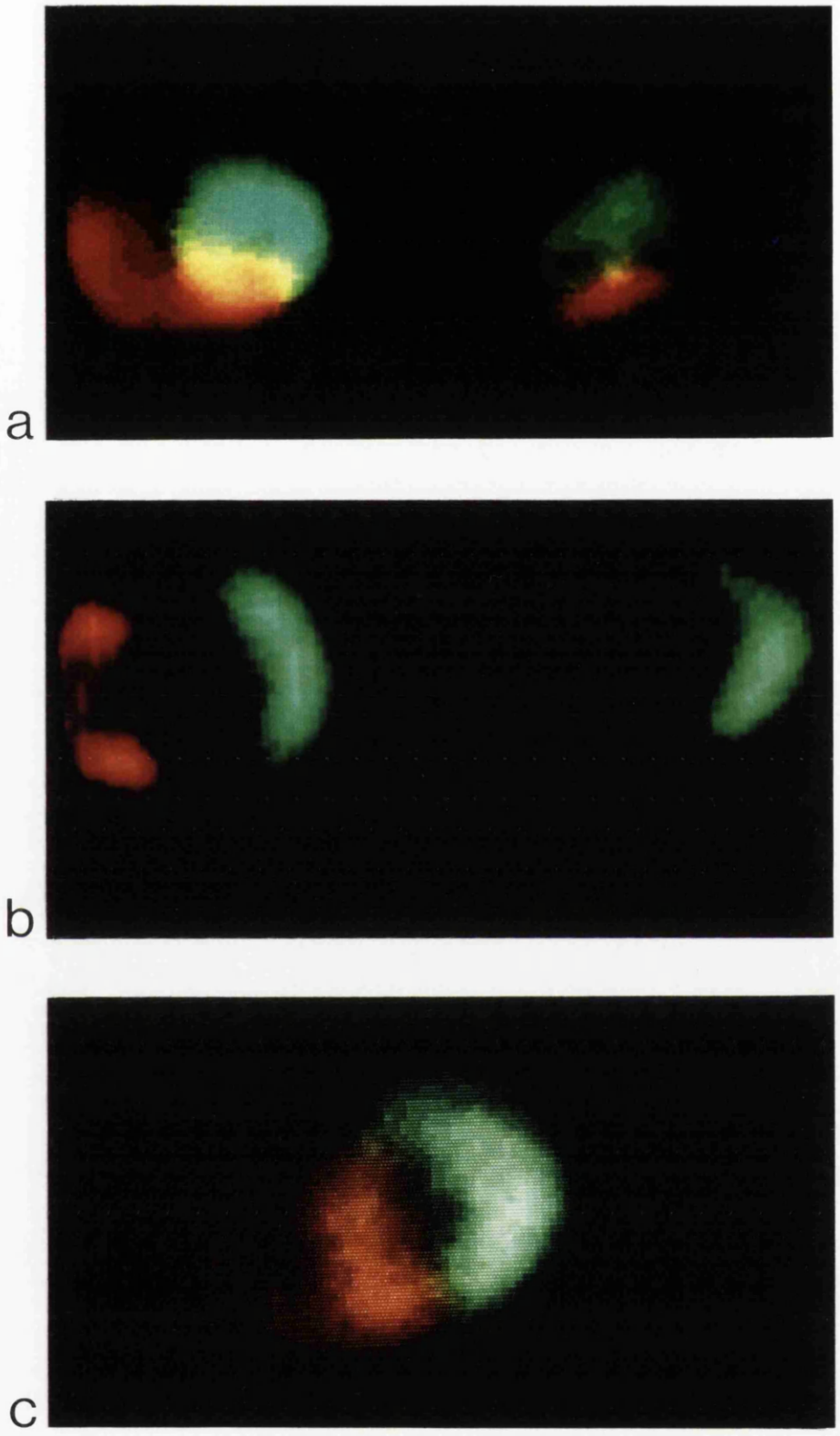


Figure 41: a) Normal intracoronary Xenon, right coronary artery red, left coronary artery green

b) Abnormal intracoronary Xenon, patient with triple vessel disease

c) Intracoronary Xenon, showing flow to septum from right coronary artery

measures drainage predominantly from the left coronary artery and the correlation between CSF and left coronary artery flow is shown in Figure 41.

In addition to flow, by imaging the myocardium, radio-tracer distribution can be followed. By knowing the normal variations (Figure 42a), distribution outside of these can be attributed to collateral flow (Figure 42c). The washout curves from a region of interest constructed around this distribution provides a measure of collateral flow.

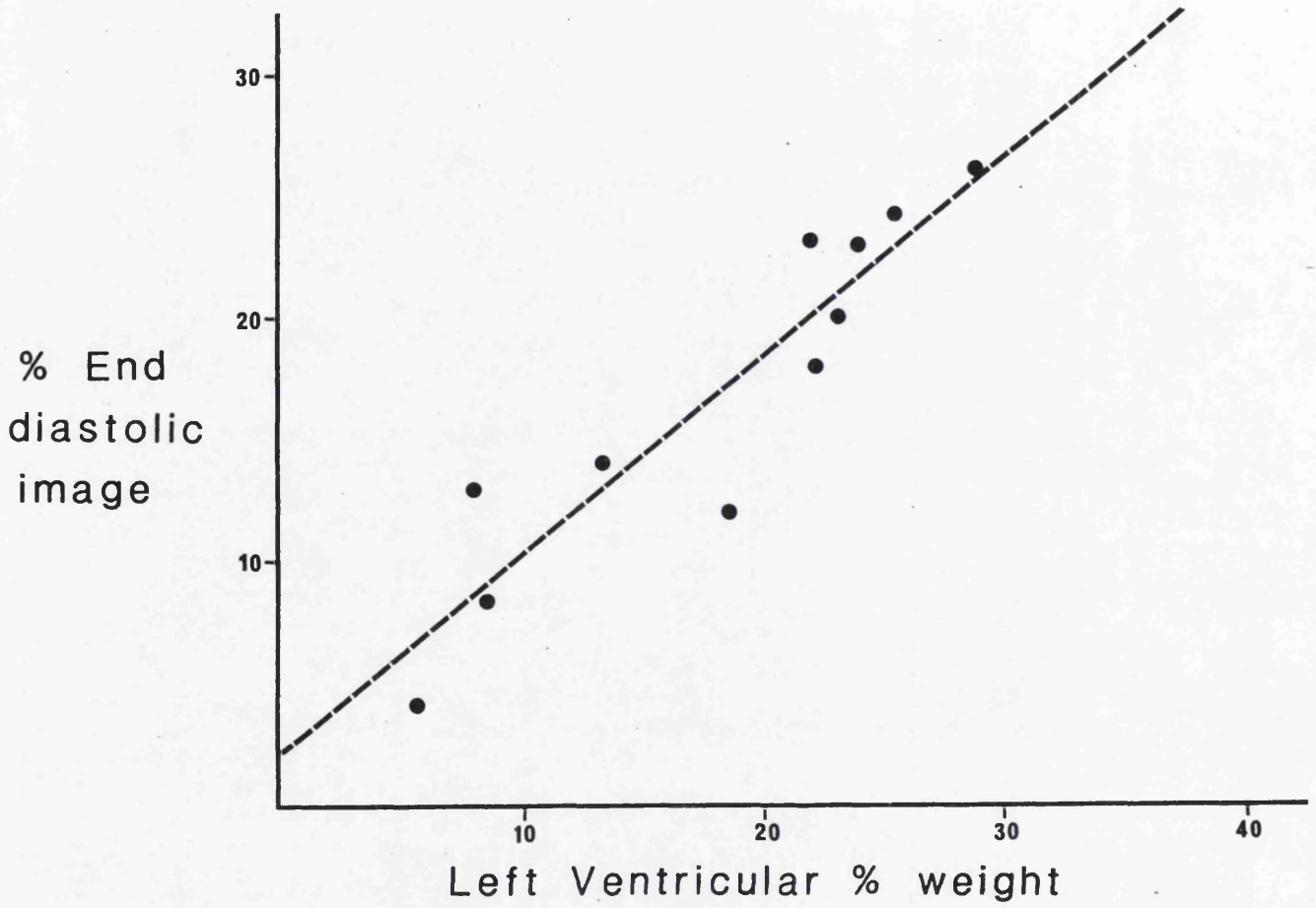
Perfusion Imaging

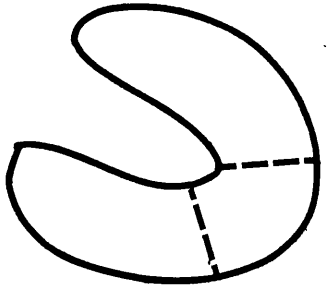
Direct measurements of coronary flow require invasive procedures and since 1973, thallium-201 has been used extensively as a marker of myocardial perfusion **(104-107)**.

Myocardial flow is reflected fairly closely by thallium-201.

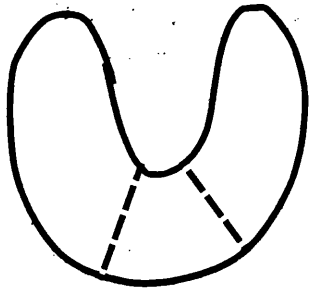
In a study of 19 pigs, where the left anterior coronary artery was ligated, gated thallium scans were obtained in the anterior projection. Infarct size was determined from the end diastolic image, by drawing a region of interest around the infarct, and expressing this as a percentage of the total left ventricle. Infarct perfusion defects ranged from 15-30%. The hearts were extracted and stained with tetrazolium and infarct expressed in terms of the percentage of the weight of the total left ventricle. This correlates well with the end diastolic image in vivo with $r = 0.94$ **(108)** (Figure 43).

In humans, thallium 201 imaging has various technical and fundamental limitations due primarily to the low energy emission of thallium 201 and

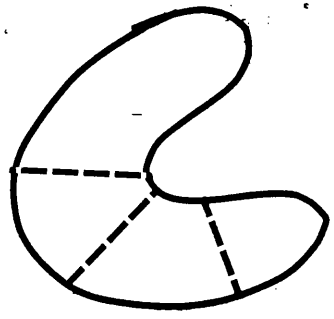

% End diastolic image
30
20
10
10
20
30
40
Left Ventricular % weight



Anterior



45°LAO



70°LAO

the inhomogeneity of normal myocardium **(109)**. Myocardial motion, due to contraction, results in blurring of static images while electro-cardiographic gating of images can produce motion free images with improved resolution of the myocardial wall **(110)** (Figure 45).

Thallium 201, maximum 60 MBq, is injected intravenously either at rest or during the last 15-30 seconds of symptom limited maximal exercise. Scans are obtained using a mobile gamma camera, fitted with a high sensitivity parallel collimator. A 20% window centred on the thallium 75 keV photopeak was used. Imaging was obtained in 3 projections, anterior, 40° and 75° left anterior oblique, each for five minutes, gated to the electrocardiogram. Data are acquired in listmode and reconstructed in to 8 frames representative cycle. R-R intervals outwith 20% of the running average are excluded. Typically between 6×10^5 and 1.2×10^6 counts were acquired in each projection.

Scans are reported by two experienced observers from static totalised images and the cine display in colour, using a 16 point colour scale and in black on white. Perfusion is reported as normal or abnormal in each of 15 segments as in Figure 46, wall motion is scored using a 4 point scoring system, with 1 considered normal, 2 reduced motion, 3 markedly reduced motion and 4 no visible or 5 paradoxical motion.

In 100 patients with angiographic data for the detection of coronary disease (Figure 45), the specificity was 88% with a sensitivity of 92% and an overall predictive accuracy of 91%. The interobserver variation for the reporting of perfusion defects varied from 9-16% and was most marked in the apical region. For wall motion, disagreement occurred in approximately 10% of segments between observers in comparison to the

PATIENT POPULATION

100 consecutive male patients undergoing coronary angiography

90 patients had significant coronary artery disease

≳50% reduction in luminal diameter of any major coronary vessel

10 patients had normal coronary arteries

12 normal volunteers

GATED THALLIUM SCANS

90 patients with coronary artery disease

50-75% stenosis of at least one major coronary artery in 24 patients

Abnormal GTI scan	18/24	75%

≥90% stenosis of at least one major coronary artery in 66 patients

Abnormal GTI scan	62/66	94%

SENSITIVITY FOR DETECTION OF CORONARY ARTERY DISEASE

Abnormal Perfusion ~		
Static Thallium scan	67/90	74%
Gated Thallium scan	80/90	89%
+ Abnormal wall motion ~		
Gated Thallium scan	86/90	95%

SPECIFICITY FOR DETECTION OF CORONARY ARTERY DISEASE

12 normal volunteers ~ normal Thallium perfusion scans

10 patients with normal coronary angiograms ~

8 normal perfusion scans

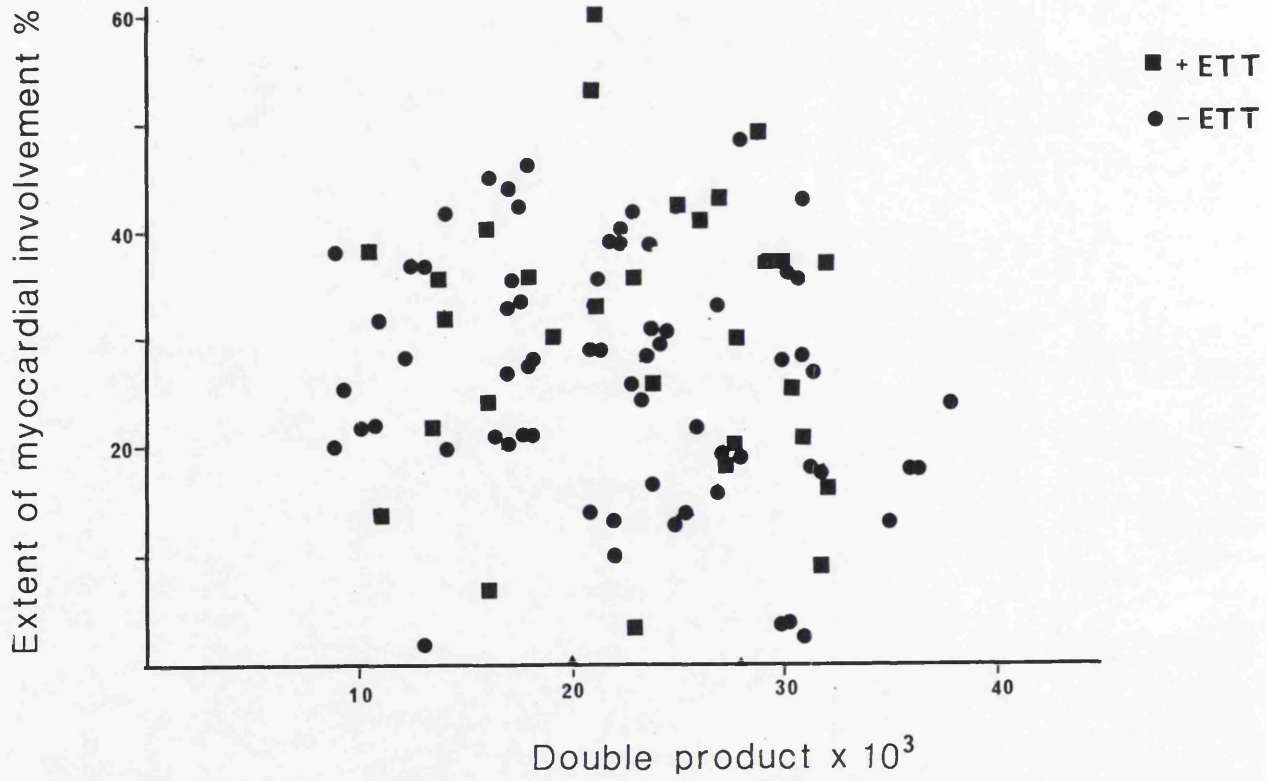
2 abnormal perfusion scans

1 abnormal wall motion

Specificity	20/22	91%

RIGHT VENTRICULAR PERFUSION DEFECTS

Left ventricular inferior perfusion defects	57/90	63%
All had ≥50% stenosis of RCA		
Right ventricular perfusion defects	20/57	35%
All had RCA disease, 80% ≥90% stenosis of RCA		


Extent of myocardial involvement %
60
40
20
10
20
30
40
Double product x 10^3
+ ETT
- ETT

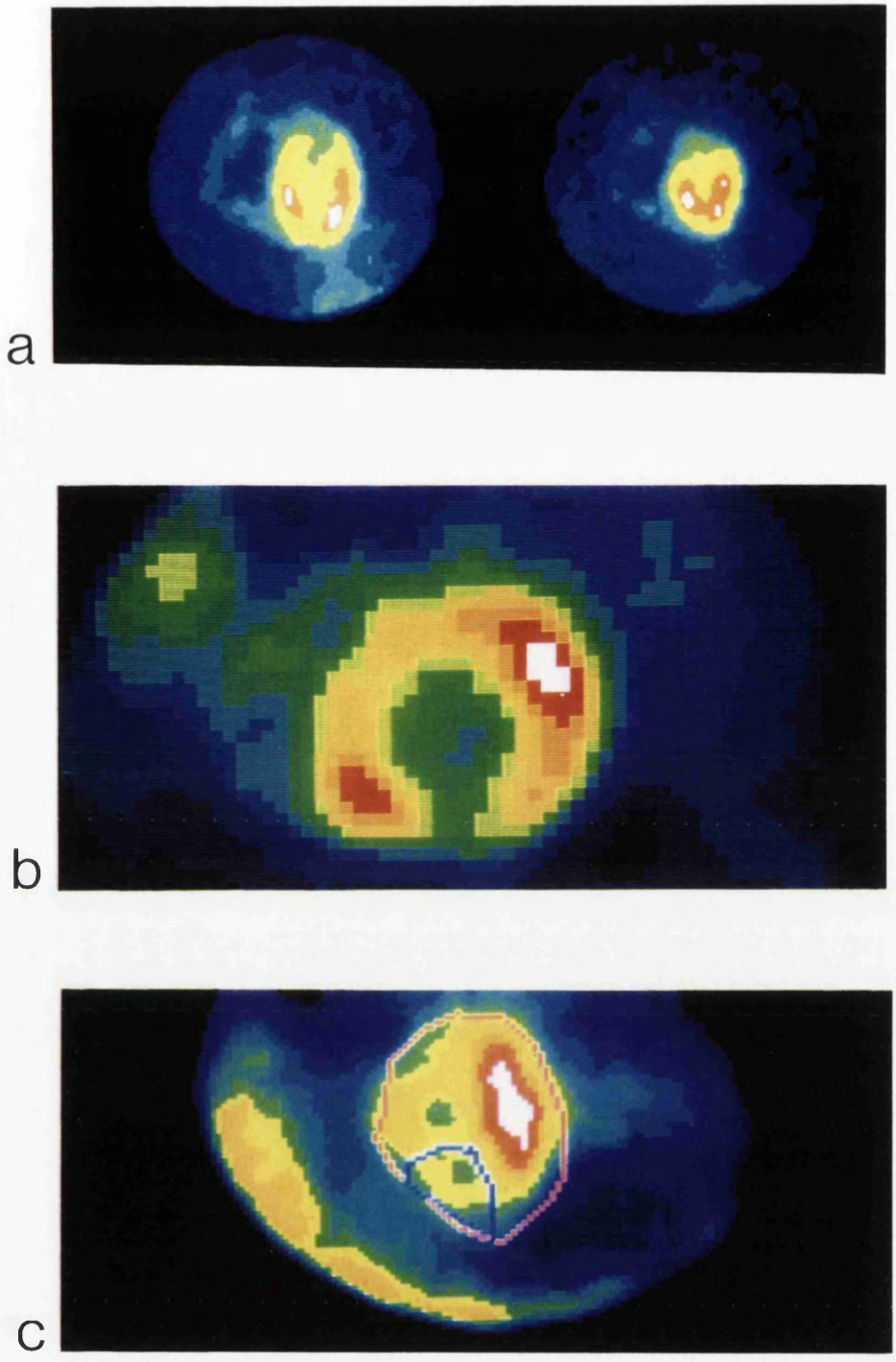


Figure 46: a) Normal end diastolic and end systolic images on a gated thallium scan

b) Abnormal end diastolic thallium image, 40° LAO showing an anterior defect in a patient with an inferior infarction

c) Region of interest around an infarct area (blue) to be expressed as a percentage of total left ventricular perfusion (red)

technetium-99m scan, in 25 patients, disagreements in regional wall motion abnormalities occurred in 4% **(110)**.

Summary

The extent of myocardial ischaemia and the physiological significance of coronary artery lesions are best assessed by perfusion imaging, performed following stress. Thallium-201 is a convenient, available isotope that can be imaged using a standard Gamma camera, providing clinically useful data.

REFERENCES

1. British Standards for Electrocardiography
Crown Office, British Standards, Milton Keynes, England
In Press

2. Kroeker EJ, Wood EH
Comparison of simultaneously recorded central and peripheral arterial pressure during rest, exercise and tilted position in man.
Circ Res 1955; 3: 623-632.

3. Gould SA, Hornung REs, Altman DG, Cashman PMM, Raftery J
Indirect measurement of blood pressure during exercise testing can be misleading.
Br Heart J 1985; 53: 611-615.

4. Gradman AH
Techniques of blood pressure monitoring during exercise.
Chest 1985; 87,6: 708-709.

5. Bruce RA, Robb LA, Katsura S et al
Exertional hypotension in cardiac patients.
Circulation 1959; 19: 543-551.

6. Morris SN, Phillips JF, Jordan JW, McHenry PL
Incidence and significance of decreases in systolic blood pressure during graded treadmill exercise testing.
Am J Cardiol 1978; 41: 221-226.

7. Nelson RR, Gobel FL, Jorgensen CR et al
Haemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise.
Circulation 1974; 50: 1179-1189.

8. Fick A
Uber dis Messung des Buntquantums in der Herzventikeln
Sitzungsb der Phys Med
Weirzburg Geselisch 1870, p. 16, in Glasser O Medical Physics Vol 3, Chicago, Chicago Year Book, Published 1960, p. 123.

9. Harrison TR, Pilcher C
Studies in congestive heart failure III. The respiratory exchange during and after exercise.
J Clin Invest 1930; 8: 291-315.

10. Barr DP, Himwich HE
Studies in the physiology of muscular exercise: Development and duration of changes in acid-base equilibrium.
J Biol Chem 1923; 58: 539-555.

11. Bock AV, Dill DB, Hurxthal LM et al
Blood gas as a physiochemical system V. The composition and respiratory exchange of normal human blood during work.
J Biol Chem 1927; 73: 749-766.

12. Astrand P-O, Rodahl K
Textbook of work physiology.
McGraw-Hill, New York, 1970: p. 669.

13. Astrand P-O
Quantification of exercise capability and evaluation of physical capacity in man.
Prog Cardiovasc Dis 1976; XIX,1: 51-67.

14. Rowell LB
Human cardiovascular adjustments to exercise and thermal stress.
Physiol Rev 1974; 54: 75.

15. Hermonsen L, Ekblom B, Saltin B
Cardiac output during submaximal and maximal treadmill and bicycle exercise.
J Appl Physiol 1970; 29: 82.

16. Holmer I
Physiology of swimming.
Acta Physiol Scand 1974; Suppl 40: 7.

17. Ekblom B, Goldberg AN, Kilbom A et al
Effects of atropine and propranolol on the oxygen transport system during exercise in man.
Scand J Clin Lab Invest 1972; 30: 35.

18. McDonough JR, Kusumi F, Bruce RA
Variations in maximal oxygen intake with physical activity in middle-aged man.
Circulation 1970; XLI: 743-751.

19. Savage DD, Garrison RJ, Kannes WB
The spectrum of left ventricular hypertrophy in a general sample: The Framingham Study.
Circulation 1987; 78, Suppl I: 26-33.

20. Patterson JA, McNaughton J, Pietras RD, Gunnar RM
Treadmill exercise in assessment of the functional capacity of patients with cardiac disease.
Am J Cardiol 1972; 30: 757-762.

21. Franciosa JA
Functional capacity of patients with chronic left ventricular fialure: relationship of bicycle exercise performance to clinical and haemodynamic characterization.
Am J Med 1979; 67: 460-466.

22. Donald KW, Bishop JW, Wade OL
A study of minute to minute changes of arterio-venous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of a steady state during exercise in rheumatic heart disease.
J Clin Invest 1954; 33: 1146-1167.

23. Franciosa JA, Wiles M
Delayed rise in oxygen uptake at onset of exercise in congestive heart failure (Abst)
Clin Res 1981; 29: 750A.

24. Astrand P-O
Quantification of exercise capability and evaluation of physical capacity in man
Prog Cardiovasc Dis 1977; 19: 51.

25. Elborn JS, Stanford CF, Nicholls DP
Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test.
Eur Heart J 1990; II: 75-81.

26. Weber KT, Janicki JS, Ward DM,McElroy PA
Measurement and interpretation of maximal oxygen uptake in patients with chronic cardiac or circulatory failure.
Adv Cardiol 1986; 35: 79-87.

27. Cotes JE
Lung function.
1978, 4th Edition, Oxford, Blackwell.

28. Carter R
The measurement of transcutaneous oxygen and carbon dioxide tensions during exercise testing.
Breath 1989; 38: 2-6.

29. Jones NL, Campbell EJM
Clinical exercise testing.
1982, 2nd Edition, Saunders, Toronto.

30. Beaver WL, Wasserman K, Whipps BJA
New method for detecting anaerobic threshold by gas exchange.
J Appl Physiol 1986; 60: 2020-2027.

31. Simonton CA, Higginbotham MB, Gibb FR
The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentrationin normal subjects and in patients with chronic congestive heart failure.
Am J Cardiol 1988; 62: 100-107.

32. Wasserman K
Determinants and detection of anaerobic threshold and consequences of exercise above it.
Circulation 1987; 76, Suppl VI: VI 29-VI 39.

33. Weber KT, Janicki JS
Cardiopulmonary exercise testing. In: Cardiopulmonary Exercise Testing. Physiological Principles and Clinical Applications. Weber K, Janicki J. Philadelphia, WB Saunders & Co. 1986.

34. Weber KT, Janicki JS, McElroy PA
Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure.
Circulation 1987; 76, Suppl VI: VI 40-VI 45.

35. Wilson JR, Martin JL, Ferraro N
Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: Role of cardiac pump dysfunction as determined by the effect of dobutamine.
Am J Cardiol 1984; 53: 1308-1315.

36. Jennings JL, Esler MD
Circulatory regulation at rest and exercise and the functional assessment of patients with congestive heart failure.
Circulation 1990; 81, Suppl II: II 5-II 13.

37. Guyton AC, Jones CE, Coleman TG
Measurement of cardiac output by the direct Fick method. In: Circulation Physiology: Cardiac Output and Its Regulation. 3rd Edition, Philadelphia, WB Saunders & Co. 1973: 21-39.

38. Harris P, Heath D
The measurement of flow in the human pulmonary circulation. Edinburgh, Churchill Livingstone, 1977: 78-96.

39. Janicki JS, Shroff SG, Weber KT
Instrumentation for monitoring respiratory gas exchange. In: Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Eds. Weber KT, Janicki JS. Philadelphia, WB Saunders & Co. 1986: 113-125.

40. Stewart GN
Researches on the circulation time and on the influences which affect it. IV The output of the heart.
J Physiol 1987; 23: 159

40a. Hamilton WF, Riley RL, Altyah AM et al
Comparison of Fick and dye injection methods of measuring cardiac output in man.
Am J Physiol 1948; 153: 309.

41. Braithwaite MA, Bradley RD
Measurement of cardiac output by thermal dilution in man.
J Appl Physiol 1968; 24: 434-438.

42. Conway J, Lund-Johansen P
Thermodilution method for measuring cardiac ouput.
Eur Heart J 1990; II, Suppl 1: 17-20.

43. Mackenzie JD, Haites NA, Rawles JM
Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers.
Br Heart J 1986; 55: 14-24.

44. Fegler G
Measurement of cardiac output in anaesthetized animals by a thermodilution method.
Quart J Exptl Physiol 1954; 39: 153-164.

45. Fegler G
The reliability of the thermodilution method for determination of the cardiac output and blood flow in central veins.
Quart J Exptl Physiol 1957; 42: 254-266.

46. Goodyear AVN, Huvoc A, Eckhardt WF, Ostberg RH
Thermal dilution curves in the intact animal.
Circ Res 1959; 7: 432-441.

47. Ganz W, Danoso R, Marcus HS, Forrester JS, Swan HJC
A new technique for measurement of cardiac output by thermodilution in man.
Am J Cardiol 1971; 17: 392-396.

48. Hawthorne JW, Saunders CA
The range of normal pressures and cardiac output in the adult in clinical cardiology. In: The Science and Practice of Clinical Medicine. Eds Willerson JT, Sanders CA. Grune & Stratton, New York, 1977: p.. 194.

49. Ungerleider HE, Gubner R
Evaluation of heart size measurements.
Am Heart J 1942; 24: 494-510.

50. Jonsell S
Methods for determination of heart size by teleroent-genography (heart volume index).
Acta Radiol 1939; 20: 325-340.

51. Keats TE, Enge IP
Cardiac mensuration by the cardiac volume method.
Radiology 1968; 85: 850-855.

52. Sandler H, Dodge HT
The use of single plane angiocardiograms for calculation of left ventricular volume in man.
Am Heart J 1968; 75: 325.

53. Kennedy JW, Baxley WA, Figley MM et al
Quantitative angiography. The normal left ventricle in man.
Circulation 1966; 34: 272.

54. Dodge HT, Sandler H, Ballew DW, Lord JD
The use of biplane angiocardiography for the measurement of left ventricular volume in man.
Am Heart J 1960; 60: 762.

55. Kennedy JW, Trenhole SE, Kasser IS
Left ventricular volume and mass from single-plane cineangiocardiogram - a comparison of an antero-posterior and right anterior oblique methods.
Am Heart J 1970; 80: 343.

56. Saskene BF, Saksena GB
Normogram for calculation of left ventricular volumes.
Br Heart J 1977; 39: 1143-1146.

57. Wynne J, Greer LH, Mann T, Levin D, Grossman W
Estimation of left ventricular volumes in man from biplane cineangiograms filmed in oblique projections.
Am J Cardiol 1978; 41: 726-732.

58. Mason T, Braunwald E
Haemodynamic techniques in the investigation of cardiovascular function in man. In: Clinical Cardiopulmonary Physiology, 3rd Edition. Ed Gordon B, New York, Grune & Stratton 1969: p. 153.

59. Mason DT, Ashburn WL, Harbert JC, Cohen LS and Braunwald E
Rapid sequential visualization of the heart and great vessels in man using the wide-field Anger scintillation camera.
Circulation 1969; 39: 19.

60. Mullins CB, Mason DT, Ashburn WL, Ross J
Determination of ventricular volume by radioisotope-angiography.
Am J Cardiol 1969; 24: 72.

61. Strauss HW, Zorer BL, Hurley PJ, Natarajan TR
A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterization.
Am J Cardiol 1971; 28: 575-580.

62. Zaret BL, Strauss HW, Hurley PJ et al
A noninvasive scintiphotographic method for detecting regional ventricular dysfunction in man.
N Engl J Med 1975; 284: 1165-1170.

63. Marshall RC, Berger HJ, Reduto LA, Gottschalk A, Zaret BL
Variability in sequential measures of left ventricular performance assessed with radionuclide angiography.
Am J Cardiol 1978; 41: 531-536.

64. Burow RD, Strauss HW, Singleton R et al
Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging: comparison to contrast angiography.
Circulation 1977; 56: 1024-1028.

65. Wackers FJT, Berger HJ, Johnstone DE et al
Multiple gated blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability.
Am J Cardiol 1979; 43: 1159-1166.

66. Starling MR, Dell'Italia LJ, Walsh R et al
Accurate estimates of absolute left ventricular volumes from equilibrium radionuclide angiographic count data using a simple geometric attenuation correction.
J A C C 184; 3,3: 789-798.

67. Slutsky R, Karliner J, Ricci D
Left ventricular volume by gated equilibrium radionuclide angiography: a new method.
Circulation 1979; 60: 556-564.

68. Massie BM, Kramer BL, Gertz EW, Henderson SG
Radionuclide measurement of left ventricular volume: comparison of geometric and count-based methods.
Circulation 1982; 65: 725-730.

69. Berman DS, Salel AF, DeNardo GL, Bogren HG, Mason DT
Clinical assessment of left ventricular regional contraction patterns and ejection fraction by high-resolution gated scintigraphy.
J Nucl Med 1975; 16: 865-874.

70. Johnston S, Tweddel AC, Martin W, McCartney A, Hutton I
A simple method of quantitating phase delay in an assessment of ventricular asynergy.
Nuc Med Communications, British Nuclear Medicine Society, London, April 1988.

71. Sharma B, Goodwin JF, Raphael MJ et al
Left ventricular angiography on exercise. A new method of assessing left ventricular function in ischaemic heart disease.
Br Heart J 1976; 38: 59-70.

72. Rerych SF, Scholtz PM, Newman GE, Sabiston DC, Jones RH
Cardiac function at rest and during exercise in normals and patients with coronary heart disease: evaluation by radionuclide angiography.
Ann Surg 1978; 187: 49-463.

73. Iskandrian AS, Hakki A, Kane SA, Segal BL
Quantitative radionuclide angiography in assessment of haemodynamic changes during upright exercise: observations in normal subjects, patients with coronary artery disease and patients with aortic regurgitation.
Am J Cardiol 1981; 48: 239-246.

74. Boucher CA, Binghm JB, Osbakker MD et al
Early changes in left ventricular size and function after correction of left ventricular volume overload.
Am J Cardiol 1981; 47: 991-1004.

75. Borer JS, Bacharach SL, Green MV et al
Real-time radionuclide cineangiography in the non-invasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease.
N Engl J Med 1977; 296: 839-844.

76. Berger HJ, Reduto CA, Johnstone DE, Borkowski H et al
Global and regional left ventricular response to bicycle exercise in coronary artery disease. Assessment by quantitative radionuclide angiocardiography.
Am J Med 1979; 66: 13-21.

77. Pfisterer ME, Ricci DR, Schuster G et al
Validity of left ventricular ejection fractions measured at rest and peak exercise by equilibrium radionuclide angiography using short acquisition times.
J Nucl Med 1979; 20: 48490.

78. Links JM, Douglass KH, Wagner HN
Patterns of ventricular emptying by Fourier analysis of gated blood-pool studies.
J Nucl Med 1980; 21: 978.

79. Vos PH, Vossepoel AM, Passwels EKJ
Quantitative assessment of wall motion in multiple-gated studies using temporal Fourier analysis.
J Nucl Med 1983; 24: 388-396.

80. Karnegis JN, Matts J, Thia N et al
Directional ST-segment duration in graded exercise tests. Correlated with motion of the individual segments of the left ventricular wall.
Am J Cardiol 1983; 52: 449-452.

81. Tobinick E, Schelbert HK, Henning H et al
Right ventricular ejection fraction in patients with acute anterior and inferior myocardial infarction assessed by radionuclide angiography.
Circulation 1978; 57,6: 1078-1084.

82. Dahlstrom JA
Radionuclide assessment of right ventricular ejection fraction: a comparison of first pass studies with ^{133}Xe and ^{99}Tcm.
Clin Physiol 1982; 2: 205-214.

83. Rigo P, Murray M, Taylor D et al
Right ventricular dysfunction by gated scintigraphy in patients with acute inferior myocardial infarctions.
Circulation 1975; 32: 268-274.

84. Slutsky R, Hooper W, Gerber K
Assessment of right ventricular function at rest and during exercise in patients with coronary heart disease: a new approach using equilibrium radionuclide angiography.
Am J Cardiol 1980; 45: 63-71.

85. Ferlinz J
Right ventricular function in adult cardiovascular disease.
Prog Cardiovasc Dis 1982; 25,3: 225-267.

86. Xue QF, MacNee W, Flenley DG, Hannan WJ, Adie CJ, Muir AL
Can right ventricular performance be assessed by equilibrium radionuclide ventriculography.
Thorax 1983; 38: 486-493.

87. Larsen NA
Assessment of tissue radiation dose in clinical use of radioactive inert gases with examples of absorbed doses from B-H_2, ^{85}-Kr, ^{133}Xe.
Minerva Nucl 1964; 8: 211-217.

88. Goldberg MJ, Mantel J, Freidin M, Ruskin R, Rubenstore M
Intravenous Xenon-133 for the determination of radionuclide first pass right ventricular ejection fraction.
Am J Cardiol 1981; 47: 626-630.

89. Ham HR, Piepsz A, Van de Vivere J et al
The evaluation of right ventricular performance using Krypton 81-m.
Clin Nucl Med 1983; 8: 257-260.

90. Knapp WH, Helus F, Lambrecht RM et al
Kr-81m for determination of right ventricular ejection fraction.
Eur J Nucl Med 1980; 5: 487-492.

91. Martin W, Tweddel A, McGhie I, Hutton I
Gated Xenon scans for right ventricular function.
J Nucl Med 1986; 27: 609-615.

92. Ganz W, Tamura K, Marcus HS, Danose R, Yoshida S, Swan HJC
Measurement of coronary sinus blood flow by continuous thermodilution in man.
Circulation 1971; 44: 181.

93. Hurley PJ, Cooper M, Reba M, Poggenburg KJ, Wagner HN
^{143}KCl, a new radiopharmaceutical for imaging the heart.
J Nucl Med 1971; 12: 516.

94. Carr EH, Beierwaltes WH, Wegst AV, Bartlett JD
Myocardial scanning with rubidium-86.
J Nucl Med 1962; 3: 76.

95. Martin ND, Zaret BL, McGowan RL, Wells HP, Fiamm MD
Rubidium-81: a new myocardial scanning agent.
Radiology 1974; 111: 651.

96. Domerech RJ, Hoffman JIE, Noble MIM et al
Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs.
Circ Res 1969; 25: 581.

97. Bassingthwaite JB, Malone MA, Moffett TC et al
Validity of microsphere depositions for regional myocardial flows.
Am J Physiol 1987; 253: H184-H193.

98. Kety S
The theory and applications of the exchange of inert gas at the lungs and tissue.
Pharmacol Rev 1951; 3: 1-41.

99. Conn HL
Equilibrium distribution of radioxenon in tissue-xenon-haemoglobin association curve.
J Appl Physiol 1960; 16: 1065-1070.

100. Morgan SM, Fisher JD, Horowitz LD
Comparison of regional myocardial blood flow measurements with scintillation camera detection of Xenon-133 and radioactive microspheres.
Clin Res 1976; 24: 232A.

101. Cannon PJ, Sciacci RR, Fowler DL et al
Measurement of regional myocardial blood flow in man: Description and critique of the method using Xenon-133 and a scintillation camera.
Am J Cardiol 1975; 36: 783-792.

102. Engel HJ
Assessment of regional myocardial blood flow by the praecordial ^{133}Xenon clearance technique. In: The pathophysiology of myocardial perfusion. Ed Schaper W. North Holland, Elsevier, 1979: p. 58-92.

103. Tweddel AC, Martin W, Hutton I
Perfusion imaging.
Br Med Bulletin 1989; 45,4: 896-921.

104. Bailey IK, Griffith LSC, Rouleau J, Strauss HW, Pitt B
Thallium-201 myocardial perfusion imaging at rest and during exercise: Comparative sensitivity to electro-cardiography in coronary artery disease.
Circulation 1979; 55: 79-87.

105. Okada RD, Boucher CA, Strauss HW, Pohost GM
Exercise radionuclide imaging approaches to coronary artery disease.
Am J Cardiol 1980; 46: 1188-1209.

106. Brown KA
Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age.
Circulation 1991; 83: 363-381.

107. Rigo P, Bailey IK, Griffith LSS, Pitt B, Wagner HN, Becker LC
Stress thallium-201 myocardial scintigraphy for the detection of individual coronary arterial lesions in patients with and without previous myocardial infarction.
Am J Cardiol 1981; 48: 209-216.

108. Tweddel AC, Martin W, Winslow E, Campbell J, Marshall R, Hutton I
Infarct sizing by gated thallium scintigraphy in an animal model.
Proceedings of European Nuclear Medicine Congress, Budapest, August 1987.
In: Nuklearmedizin. Eds Schmidt and Csernay. Published by Schattauer Verlag 1987: 175-179.

109. Ritchie JL, Zaret BL, Straus HW et al
Myocardial imaging with thallium-201. A multicentre study in patients with angina pectoris or acute myocardial infarction.
Am J Cardiol 1978; 345-350.

110. Martin W, Tweddel AC, McGhie AI, Hutton I
Gated thallium scintigraphy in patients with coronary artery disease: an improved planar imaging technique.
Clin Phys Physiol Meas 1987; 8,4: 343-354.