POTENTIAL PREDICTORS OF SUDDEN CARDIAC DEATH IN AORTIC VALVE DISEASE

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DECLARATION

I hereby certify that this thesis had been designed, composed and written entirely by myself and has not been submitted previously for any degree.

Signed:

Date: 10.4.91

DEDICATION

To my

Mother	Khadija
Wife	Salma
Sons	Wael and Ayham
Little daughter	Dania

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S U M M A R Y

Although sudden death continues to claim 15 to 20% of patients with aortic valve disease, the exact cause still remains speculative. It has been the assumption of many workers that these deaths result from ventricular tachyarrhythmias. The major aim of this thesis was therefore to assess the prevalence of ventricular arrhythmias in patients with aortic valve disease and to evaluate their significance by signal-averaged electrocardiography (SAECG).

A total of 100 patients, 55 with predominant aortic stenosis (AS) with a mean transaortic gradient of 81 ± 27 mmHg, 16 with predominant aortic regurgitation (AR) and 29 with combined AS and AR were studied prior to aortic valve replacement (AVR). Substantial left ventricular hypertrophy was present with a mean echocardiographic left ventricular mass index of 210 ± 72 g/m2. Left ventricular systolic and diastolic function were normal in 94% and 61% of patients respectively.

Coronary angiography was performed in 89 patients of whom 50 (56%) had chest pain typical of angina pectoris and 21 (24%) had significant coronary artery disease. Angina was present in 20 of these 21 patients (95%). Thus angina could predict the presence of significant coronary artery disease with 95% sensitivity and 54% specificity.

In agreement with previous work, this study has shown a high prevalence of complex ventricular arrhythmias. Nonsustained ventricular tachycardia (NSVT) was detected by ambulatory electrocardiographic monitoring in 9 (9%)

patients of whom only one had late potentials on SAECG. The frequency of ventricular arrhythmias was not related to the degree of left ventricular hypertrophy or the severity of aortic valve disease. Left ventricular function did not have any effect on ventricular arrhythmias.

A high prevalence of complex ventricular arrhythmias was also seen in the early (5 to 7 days post AVR) and late (121 ± 24 days post AVR) post-operative periods. The frequency of ventricular arrhythmias was not affected by AVR. In the late post-operative period, 4 patients had NSVT, but none of them had late potentials on SAECG. As with the pre-operative results, there was little to suggest the presence of an arrhythmogenic substrate in these patients in view of the absence of late potentials on SAECG. Furthermore, no sustained ventricular arrhythmias were detected in the 3 study periods.

Aortic valve replacement was accompanied by a significant regression in echocardiographic left ventricular hypertrophy in patients with predominant AS and those with combined AS and AR.

Of the total 100 patients in this study, 75 were on the cardiac surgical waiting list of whom 60 have already undergone operation. There have been 7 deaths (7%) during the study period, 3 of them occurring suddenly in patients awaiting surgery. Thus, the incidence of sudden death while awaiting operation was 4%.

It has been suggested that patients with decreased heart-rate variability have decreased vagal tone, increased sympathetic activity or both and hence are at a higher risk of developing ventricular fibrillation and sudden death. Cardiovascular autonomic function was assessed in 47 patients prior to AVR and repeated in 10 patients 3 months following AVR. Abnormal heart-rate variation during deep breathing was detected in 18 (38%) patients. AVR was not accompanied by any improvement in cardiovascular autonomic function at least in the short-term.

Thus, despite a high prevalence of ventricular arrhythmias in aortic valve disease patients with substantial left ventricular hypertrophy, there was little to suggest the presence of an arrhythmogenic substrate. The potential mechanism of sudden death in these patients could be speculated on the basis of impaired cardiovascular autonomic function.

CHAPTER ONE

LITERATURE REVIEW

1.1 Natural History of Aortic Valve Patients

An understanding of the natural history of aortic valve disease is very important because of the significant incidence of sudden death associated with this disease and the grave prognosis that appears to accompany the onset of certain symptoms (Contratto and Levine, 1937; Mitchell et al, 1954; Chizner, Pearle and de Leon, 1980). However, evaluation of the natural history of aortic valve disease has recently been difficult because of the development of objective means for assessment of its severity and the advent of corrective operations resulting in the interruption of the course of the disease. Thus the resultant lack of sufficient prospective information concerning the outlook of aortic valve patients has necessitated a largely retrospective view of the natural history.

About 100 years ago the diagnosis of aortic valve disease and in particular aortic stenosis was made solely on the basis of hearing a systolic murmur over the aortic area. This resulted in the dismissal of many army recruits during the first world war who were subsequently considered to have innocent murmurs. It was therefore felt by many workers that stringent diagnostic criteria should be developed in the diagnosis of aortic stenosis. In an excellent paper by Contratto and Levine (1937), 180 definite cases of aortic stenosis were studied. Definite evidence of aortic stenosis was based on the presence of a systolic thrill at the base of the heart, the detection of calcification in the aortic valve on fluoroscopic examin-

ation and post-mortem findings. In these 180 cases, the commonest aetiology was rheumatic fever and the male sex predominated. Angina pectoris was quite common, occurring in 22.7% of the cases, and of 9 sudden deaths that occurred, 5 of these cases had angina pectoris. Palpitation was an early complaint and survival after its onset was 8 years compared to 23 months for dyspnoea and only 9.1 months for syncope.

A total of 533 cases of aortic stenosis, half of which were diagnosed at post-mortem, were studied by Mitchell et al (1954). Mean survival in 159 cases with angina was 4.1 years after its onset. Sixty-seven patients had syncope and their mean survival after its onset was 3.3 years. The mean survival after the onset of congestive cardiac failure was 2.3 years. Sudden death occurred in 40 patients. There were only three cases of syncope in the sudden death group, while on the other hand 12 of these patients had a definite history of angina pectoris. It would follow from this series that angina pectoris is a fairly common precursor of sudden death in aortic valve patients and occurs not infrequently in the absence of significant coronary sclerosis as evident from post-mortems.

In a retrospective study involving 100 cases of pure aortic stenosis, life expectancy was markedly reduced with the onset of either cardiac pain, syncope or symptoms of congestive cardiac failure in isolation or in various combinations (Bergeron et al, 1954).

With the development of effective prosthetic devices for replacement of the aortic valve, the need for a greater understanding of the natural history of patients with aortic valve disease became even more important. However, the natural history of the patients is frequently interrupted by surgical intervention. In a follow-up study of 15 cases with pure aortic stenosis in whom surgery was not performed due to a variety of reasons, the average life expectancy was dependant upon the presence or absence of symptoms, notably angina pectoris, syncope and congestive cardiac failure (Frank, Johnson and Ross, 1973).

Chizner and his colleagues studied 42 adults with haemodynamically documented valvular aortic stenosis who did not undergo early surgical intervention due to various reasons (Chizner, Pearle and de Leon, 1980). Aortic stenosis was categorised into mild, moderate and severe stenosis according to the valve area or systolic peak-to-peak gradient. Not surprisingly, mortality was quite high in 23 symptomatic patients with moderate to severe aortic stenosis. Twenty-six percent were dead at one year, 48% at 2 years and 57% at 3 years. Fifty-six percent of all deaths were sudden. This high mortality was not seen in asymptomatic patients with moderate or severe stenosis. It was striking to note that the mortality was also high in symptomatic patients with mild stenosis. Four of 9 (44%) of these patients were dead by the end of the follow-up period.

Unlike aortic stenosis, patients with pure aortic regurgitation have been shown to remain asymptomatic for many years, sometimes decades, following the clinical diagnosis, and the progression of the disease is insidious (Goldschlager et al, 1973). Dyspnoea and fatigue are the common presenting symptoms, while chest pain and syncope occur less frequently. Sudden death is also not as common as in patients with aortic stenosis. However, progression of the natural course of aortic regurgitation becomes very rapid with a fatal outcome with the appearance of either angina or congestive heart failure (Bland and Wheeler, 1957; Massell, Amezcua and Czoniczer, 1966; Spagnuolo et al, 1971; Smith et al, 1976). In these excellent studies involving a total of 764 patients with pure aortic regurgitation who were followed up for up to 20 years, prognosis was found to be poor following the appearance of angina or congestive heart failure. In one series, 13 of 14 patients with congestive heart failure died within 2 years. Aortic valve replacement is therefore strongly indicated in such symptomatic patients. Other factors that led to a poor prognosis were an enlarged heart on chest radiography, the presence of extreme electrocardiographic left ventricular hypertrophy and cardiac arrhythmias.

It must be emphasised that the pattern of aortic valve disease in developed countries has been changing recently in view of the rapid decline in the incidence of rheumatic heart disease, increasing age of the patient population and the increase in the frequency of coronary artery disease. Aortic stenosis is now most commonly due to a

bicuspid valve. Rheumatic aortic stenosis has become much less common and calcific stenosis of valves in the elderly is a rapidly increasing cause. As a result of these changes, the natural history of the disease has altered to some extent. It would therefore be logical to base our understanding of the disease progression on the result of recent studies. In a recent study by Turina et al (1987), 190 adults with aortic valve disease who had undergone haemodynamic studies and in whom operation was not carried out due to a variety of reasons, were followed up for several years. Survival was poor in haemodynamically severe disease and patients with aortic stenosis fared worse than those with aortic regurgitation. In mild disease, the first year survival was 100% in both groups, while moderate disease showed an intermediate prognosis. Prevalence of symptoms was related to the degree of severity of the disease. In a prospective study reported by Kelly et al (1988), 90 patients with haemodynamically significant aortic stenosis, 39 with and 51 without symptoms, were followed up until the occurrence of either death or aortic valve replacement. Fifteen deaths (38%), all cardiac in origin occurred in the symptomatic group while only 8 deaths, 6 of which were non-cardiac, occurred in the asymptomatic group. In another long-term follow-up study involving 142 patients with aortic stenosis, prognosis was related to the occurrence of symptoms (Torstkotte and Loogen, 1988). Mean survival after the occurrence of angina pectoris was 45 $\pm$ 13 months, after syncope 27 $\pm$ 15 months and after the first occurrence of left heart failure 11 $\pm$ 10 months.

It would be reasonable to conclude from the above studies that the prognosis of patients with aortic valve disease can be largely determined by their symptoms and therefore the decision and timing of valve replacement should in most cases be based on the knowledge of the severity of symptoms.

1.2 Sudden Death in Aortic Valve Patients

Prior to aortic valve replacement, patients with severe aortic stenosis often died suddenly. In most cases, sudden death is usually preceded by angina, congestive heart failure or syncope (Contratto, and Levine, 1937; Mitchell et al, 1954; Chizner, Pearle, and de Leon, 1980). In a minority of cases, however, it may be the first and only symptom of severe aortic valve disease (Ross and Braunwald, 1968; Wagner et al, 1977). The association of aortic stenosis and sudden death was first noted by Cabot (1926). From a study of post-mortem records attention was drawn to the fact that in 6 of 28 cases of aortic stenosis, death was noted to be sudden and unexpected.

The paucity of reports in the medical literature and the failure of textbooks to mention either sudden death or syncope in connection with aortic stenosis, and by the occurrence of sudden and unexpected death in two of their patients with aortic stenosis within a week, prompted Martin and Sullivan (1935) to pioneer one of the earliest and most extensive reviews of the medical literature on sudden death in aortic stenosis. In this excellent review they gave detailed case histories of 11 patients with

aortic valve disease in 9 of whom death was witnessed and occurred suddenly. It is worth noting that all 11 patients had severe symptoms and in nearly half of them syncope was a common occurrence. Reynolds et al (1960) described the occurrence of sudden death in a four and a half year old child with congenital aortic stenosis with severe symptoms. In their paper they quoted from reported series an incidence of sudden death in aortic stenosis of between 4 and 18%. Glew et al (1969) reported from published data nearly the same incidence of sudden death in congenital aortic stenosis as that quoted by Reynolds et al. However, sudden death occurred in only 8 patients with congenital aortic stenosis in a 20 year period in their own practice, an incidence of 1%.

Schwartz et al (1969) studied the electrocardiograms of 9 adult patients with aortic stenosis and a history of syncopal attacks during and after development of syncopal seizures. They concluded that sudden death in such patients was due to ventricular standstill, flutter or fibrillation, or a combination of the three. They also reported 12 sudden deaths in patients with aortic stenosis that occurred in their hospital. Johnson (1971) reported quite a high incidence of death in his own series of 204 adult patients with aortic stenosis. Twenty-seven of 130 patients with severe aortic stenosis died suddenly, an incidence of 21%. In agreement with Johnson's findings, Chizner and his colleagues reported a high incidence of sudden death in those of their patients who had moderate to severe aortic stenosis (Chizner, Pearle and de Leon, 1980). In a recent study, Von Olshausen et al (1983)

reported the occurrence of sudden death in 2 of their patients with aortic valve disease while awaiting aortic valve replacement.

1.3 Ventricular Arrhythmias as Predictors of Sudden Death

Sudden death claims an estimated 350,000 lives per year in the United States and between 50,000 and 100,000 lives a year in the United Kingdom (Braunwald, 1988). When death occurs within one hour of the onset of symptoms, the majority are the result of ventricular tachyarrhythmias (Kremers, Black and Wells, 1989). Two of the commonly employed methods for detecting ventricular arrhythmias and hence predict to a certain extent sudden death, are electrophysiological studies and ambulatory recording of the electrocardiogram. The first is an invasive technique where arrhythmias are artificially induced thus detecting the potential substrate which may ultimately lead to lethal arrhythmias. This of course assumes that the lethal arrhythmias thus reproduced will occur as the final event leading to sudden death. The second is the more favoured method as it has the advantages of being both non-invasive and needing less expertise.

Previous reports of recorded sudden death involving 74 patients from 24 centres while on ambulatory electrocardiographic monitoring, indicated that 66 to 75% of deaths were related to ventricular tachyarrhythmias (Coumel, Leclercq and Leenhardt 1987). Several other examples of sudden death during ambulatory monitoring further confirm that the terminal event in the majority

was related to a tachyarrhythmia. In a case report by Gradman and his associates, an increase in the premature ventricular contraction frequency with couplets was noted one and a half hours before death, finally degenerating into ventricular fibrillation (Gradman, Bell and De Busk, 1977). Pool and his colleagues reported 2 cases of sudden death during ambulatory monitoring that showed an increase in complex premature ventricular contractions culminating into a tachyarrhythmia as a final event (Pool, Kurst and Van Wermeskerken, 1978). Lahiri's group reported 3 cases dying suddenly during ambulatory monitoring (Lahiri, Balasubramanian and Raftery, 1979). In 2, ventricular fibrillation was the terminal arrhythmia while in the third, the terminal event was slow, bizarre ventricular complexes at 30 to 40 beats per minute ending in asystole. In a 71 year old man who died suddenly, analysis of the ambulatory recording showed an increased frequency of complex premature ventricular contractions with short runs of ventricular tachycardia in the last hour prior to death (Salerno et al, 1981). In 6 instances of sudden cardiac death during ambulatory electrocardiographic monitoring reported by Nikolic and his colleagues, the terminal event was ventricular fibrillation in 5 of them (Nikolic, Bishop and Singh, 1982). Coincidentally, all the 6 patients had cardiac enlargement or left ventricular hypertrophy on objective grounds. In 15 cases of spontaneous ventricular fibrillation preceded by ventricular tachycardia during ambulatory electrocardiographic monitoring, 8 died and 7 survived cardiopulmonary resuscitation (Pratt et al, 1983). Again, left ventricular hypertrophy was present in 7 patients by electrocardiographic and 3 patients by

echocardiographic criteria. In a recent analysis of data from 5 patients who died suddenly during ambulatory electrocardiographic monitoring, an increased density of ventricular ectopic activity was noted in the hour before the final event (Martin et al, 1987). The final arrhythmia in all the 5 cases was ventricular tachycardia degenerating into ventricular fibrillation.

It is evident from these reports that in the majority of cases of sudden death as recorded by electrocardiographic monitoring, the final lethal event was a ventricular tachyarrhythmia. Another interesting finding was the occurrence of an increased density of ventricular ectopic activity including both isolated ventricular premature contractions and bouts of repetitive firing during the hour before the terminal dysrrhythmia. The R - on - T phenomenon in addition, was implicated in the onset of ventricular fibrillation in roughly half of the cases. These experiences provide a valuable glimpse at the terminal electrical event. It would therefore appear logical to search for these "warning arrhythmias" for the purpose of identifying those patients who may be at a high risk of sudden death.

There are very few cases of recorded sudden death in patients with aortic valve disease reported in the literature, despite the high incidence of sudden death in this disease. Von Olshausen et al (1982) reported a case of severe aortic stenosis with impaired left ventricular function who died suddenly while on an ambulatory electrocardiographic recording. This showed ventricular

tachycardia as the terminal event with no ventricular arrhythmias recorded in the last hour prior to death. In a recent case report, sudden cardiac death was documented on a Holter monitor electrocardiogram in a 71 year old man with calcific aortic stenosis where the terminal arrhythmia was ventricular fibrillation preceded by sinus tachycardia with broad QRS complexes (Siostrzonek et al, 1987). To further emphasize the role of ventricular arrhythmias as a major cause of sudden death in patients with aortic valve disease, Von Olshausen and his associates reported 4 patients with aortic valve disease who had died suddenly while being monitored on an ambulatory electrocardiogram (Von Olshausen et al, 1987). Three of the 4 patients had nonsustained ventricular tachycardia in the hour before death. In all the 3 patients, the ventricular tachycardia ended in ventricular fibrillation. In the fourth patient, the recording time was only 40 minutes and therefore not sufficient for any conclusions to be formed. Nevertheless, the final rhythm in this patient was ventricular fibrillation.

In a recent study reported by Luu and his colleagues, 21 cardiac arrests occurred in 216 patients with advanced heart failure while being monitored by telemetry electrocardiography (Luu et al, 1989). It is of interest to note that the final rhythm at the time of arrest was bradycardia or electromechanical dissociation in 13 (62%) arrests while ventricular tachycardia or fibrillation occurred in only 8 (38%) arrests. It should be noted that none of these patients had aortic valve disease.

1.4 Prevalence of Ventricular Arrhythmias in Left Ventricular Hypertrophy

Ventricular tachyarrhythmias have been implicated as the terminal event in the majority of cases of sudden death, and the studies described above indicate that many of the cases of sudden death occur in patients with left ventricular hypertrophy. It would obviously be of interest and importance to know the prevalence of ventricular arrhythmias in this group of patients.

In the Framingham Heart Study, both electrocardiographic and echocardiographic left ventricular hypertrophy have been shown to be associated with an increased risk of all grades of ventricular arrhythmias (Levy et al, 1987). Echocardiographic left ventricular hypertrophy, however, was more prevalent and sensitive for ventricular arrhythmias than electrocardiographic left ventricular hypertrophy. The association of echocardiographic left ventricular hypertrophy with arrhythmias persisted after controlling for confounding variables, thus acting as an independent contributing factor. Electrocardiographic left ventricular hypertrophy may result from various forms of cardiovascular diseases. By far the most common cause of left ventricular hypertrophy in the general population is hypertension (Messerli et al, 1984; Dunn et al, 1977; Savage et al, 1979). In a study by Messerli et al (1984) hypertensive patients with left ventricular hypertrophy had significantly more premature ventricular contractions than those without left ventricular hypertrophy or than normotensive subjects. McLenachan et al (1987)

investigated by 48 hour ambulatory monitoring, 100 hypertensive patients of whom 50 had electrocardiographic left ventricular hypertrophy. Salvoes of nonsustained ventricular tachycardia occurred in 28% of the patients with compared to 8% in those without electrocardiographic left ventricular hypertrophy. However, nonsustained ventricular tachycardia occurred in only 2% of 50 normotensive controls matched for age, sex and smoking habits. Pringle et al (1987) performed 24 hour electrocardiographic monitoring on 16 hypertensive patients with and 23 without electrocardiographic left ventricular hypertrophy. Nonsustained ventricular tachycardia occurred in 2 of the 16 patients with and in none of the 23 patients without electrocardiographic left ventricular hypertrophy.

In a study of 100 patients with hypertrophic cardiomyopathy investigated by 24 hour ambulatory electrocardiographic monitoring, more than 50% of the patients had multiform or repetitive ventricular premature contractions, including 19% who had ventricular tachycardia (Savage et al, 1979). McKenna et al (1980), studied 30 patients with hypertrophic cardiomyopathy by 48 hour ambulatory electrocardiographic monitoring. Multiform or paired ventricular extrasystoles were present in 43% and ventricular tachycardia occurred in 26% of the patients. Canedo and his colleagues studied the prevalence of arrhythmias in 33 patients with hypertrophic obstructive cardiomyopathy by 24 hour ambulatory electrocardiographic monitoring (Canedo, Frank and Abdulla, 1980). Eighty-two percent of their patients had

ventricular premature contractions with 39% of patients showing "potentially life-threatening rhythm disturbances". Short runs of ventricular tachycardia occurred in 15% and frequent couplets in 18% of the patients. In a study involving 50 patients with hypertrophic obstructive cardiomyopathy by periodic 24 hour Holter monitoring, the incidence of "potentially lethal arrhythmias" was 32% at 5 years and 81% at 10 years of follow-up (Frank et al, 1984). Kowly and his associates reported the occurrence of nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring in 4 out of 7 patients with hypertrophic cardiomyopathy that he investigated (Kowly, Eisenberg and Engel, 1984). In a large series involving 86 unselected patients with hypertrophic cardiomyopathy studied by 72 hour ambulatory electrocardiographic monitoring, 24 patients had ventricular tachycardia of whom 10 had more than 3 episodes (McKenna et al, 1981). Seven patients died suddenly during a follow-up period of one to 4 years, 5 of these patients belonging to the group that showed ventricular tachycardia as well as a combination of multiform and paired ventricular extrasystoles on the previous Holter recordings. In addition, they also had a significantly higher maximum ventricular extrasystolic count than the survivors, thus showing an association between arrhythmias and subsequent prognosis.

Few studies using ambulatory electrocardiography for detecting ventricular arrhythmias have been carried out in patients with idiopathic dilated cardiomyopathy. Huang and his colleagues studied 35 patients with idiopathic

dilated cardiomyopathy by 24 hour Holter monitoring (Huang, Messer and Denes, 1983). Frequent ventricular premature contractions were seen in 83%, of whom 93% had complex ventricular premature contractions. Nonsustained ventricular tachycardia occurred in 60% of the patients. In a similar study involving 74 patients with idiopathic dilated cardiomyopathy, frequent ventricular premature contractions were seen in 35%, complex ventricular premature contractions in 87% and nonsustained ventricular tachycardia in 49% of the patients (Meinertz et al, 1984). In both studies, the severity of ventricular arrhythmias was not related to the severity of clinical symptoms or to the impairment of left ventricular function. Further evidence for the high prevalence of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy is illustrated in a study involving 60 patients (Von Olshausen et al, 1984). Multiform extrasystoles were recorded by a Holter monitor in 95%, paired ventricular extrasystoles in 78% and nonsustained ventricular tachycardia in 42% of the patients.

There is scanty information about the incidence of ventricular arrhythmias in patients with aortic stenosis or aortic regurgitation despite the fact that sudden cardiac death is a well known complication in this group of patients (Ross and Braunwald 1968; Von Olshausen et al 1982; Von Olshausen et al, 1987). Von Olshausen et al (1983) investigated the incidence and severity of ventricular arrhythmias in 93 patients with isolated aortic valve disease (without coronary artery disease) by 24 hour ambulatory electrocardiographic monitoring.

Frequent and complex ventricular ectopic activity was noted in 55% of the patients out of whom 18% had ventricular tachycardia. It is interesting to note that 2 out of the 17 patients with ventricular tachycardia died suddenly, and in one of them who died while being monitored, the terminal arrhythmia was ventricular tachycardia. There are a few preliminary studies on preoperative ventricular arrhythmias in patients with aortic valve disease. Kennedy et al (1975) studied 8 patients with aortic valve stenosis and 7 with combined aortic stenosis/aortic regurgitation by 24 hour Holter recordings. Complex ventricular premature contractions were exhibited in 93% of the patients of whom 47% had ventricular tachycardia. In another preliminary study, Schilling et al (1982) investigated 38 aortic valve disease patients by 24 hour Holter monitoring. High grade ventricular arrhythmias occurred in 26 of the 38 patients. Hochreiter et al (1982) studied 28 patients with severe aortic regurgitation. Complex ventricular arrhythmias were detected in 10 out of the 28 patients (36%). Twenty-eight patients with aortic stenosis without significant coronary artery disease or aortic regurgitation were studied by 24 hour ambulatory electrocardiogram (Kostis et al, 1984). Ventricular ectopic activity was present in 27 of the 28 patients. Nineteen patients had complex premature ventricular contractions of whom 4 exhibited ventricular tachycardia. Klein (1984) performed 24 hour electrocardiographic monitoring in 52 patients with aortic stenosis and 50 patients with haemodynamically significant aortic regurgitation. The occurrence of ventricular arrhythmias in these patients was compared with that in

matched controlled subjects without aortic valve disease. Complex ventricular extrasystoles were detected in 46% of patients with aortic stenosis and 30% of patients with aortic regurgitation. There was no difference in the incidence of complex ectopy between aortic valve disease patients with normal coronary arteries and those with co-existing coronary artery disease. The incidence of complex arrhythmias in aortic valve disease patients with normal coronary arteries was significantly greater than control subjects. However, the incidence of complex ectopy in aortic valve disease patients with co-existing obstructive coronary artery disease was similar to that of patients with the same degree of coronary artery disease and normal aortic valves.

There do not appear to be many studies that have directly examined the relationship between ventricular arrhythmias and the degree of left ventricular mass. McLenachan et al (1987) have shown a more frequent occurrence of ventricular tachycardia as well as ventricular couplets in those hypertensive patients who had left ventricular hypertrophy. Although this relationship is even more marked with respect to echocardiographic left ventricular hypertrophy than to electrocardiographic left ventricular hypertrophy (Levy et al, 1987), they did not attempt to correlate the arrhythmias with the degree of left ventricular mass. In a study involving 554 elderly persons, complex ventricular arrhythmias occurred in 75% and paroxysmal ventricular tachycardia in 15% of the subjects with echocardiographic left ventricular hyper-trophy, compared to 44% and 6% respectively in those with-

out hypertrophy (Aronow et al, 1987). However, as in the previous study, the authors did not examine the occurrence of complex ventricular arrhythmias in relation to the degree of left ventricular mass. In a follow-up study of patients with hypertrophic cardiomyopathy, ventricular septa were thicker in patients who died compared to those in the survivors (Kowly, Eisenberg and Engel, 1984). Seventy-one percent of the patients who died had ventricular tachycardia on their previous ambulatory electrocardiographic recordings. Spirito and his colleagues compared the extent of echocardiographic left ventricular hypertrophy in 30 patients with hypertrophic cardiomyopathy in whom ventricular tachycardia had been documented on 24 hour ambulatory electrocardiographic monitoring, to a control group of 61 patients with hypertrophic cardiomyopathy who had normal ambulatory electrocardiographic recordings (Spirito, Walson and Maron, 1987). Severe left ventricular hypertrophy was significantly more common in patients with documented ventricular tachycardia than in those with normal ambulatory electrocardiographic recordings.

1.5 Effects of Left Ventricular Dysfunction on Ventricular Arrhythmias

The relationship between ventricular arrhythmias and left ventricular dysfunction can ideally be studied in patients following an acute myocardial infarction. About 30 years ago, the in-hospital mortality of patients with acute myocardial infarction was as high as 40% (Brown et al, 1963). The exact cause for this high mortality was

unclear at the time despite the treatment of patients with anticoagulant drugs, as this mode of therapy had been shown earlier by some workers to improve patient survival (Hilden et al, 1961).

It was with the introduction of the first coronary care units that the relationship between ventricular ectopic activity and sudden death in acute myocardial infarction patients was recognised (Brown et al, 1963). A few years later, Lown et al (1967) showed for the first time a reduction in mortality from arrhythmias in hospitalised patients with acute myocardial infarction. This was attributed to the improved organisation of the coronary care unit, thus providing continuous electrocardiographic monitoring under the supervision of highly trained nurses who could detect dangerous arrhythmias and promptly institute the appropriate therapy.

Sudden death however, continued to claim lives in survivors of acute myocardial infarction in the late post-infarction period. The exact prevalence and prognostic significance of ventricular arrhythmias during this period had not been adequately studied previously. Kotler et al (1973), studied 160 patients who had survived a recent infarct by at least 3 months. Repeated ambulatory electrocardiographic recordings were performed at 8 monthly intervals and the patients were followed up for up to 54 months. Eighty percent of the patients had ventricular ectopic activity on their recordings and sudden death was significantly more common in this group compared to those without ventricular ectopics. Four more

studies involving a total of 3,675 patients, further lend support to the prognostic significance of ventricular arrhythmias detected in the late post-infarction period (Ruberman et al, 1977; Anderson, De Camilla and Moss, 1978; Moss et al, 1979; Schulze, Strauss and Pitt, 1977).

Weaver et al (1976) were among the first workers who recognised the relationship between life threatening arrhythmias and left ventricular dysfunction. They studied 64 patients with coronary artery disease who had been resuscitated from out of hospital cardiac arrest. Cardiac catheterisation and coronary angiography were performed and patients were followed up for an average of 20.4 months. Recurrent ventricular fibrillation and/or death occurred in those patients with triple vessel disease and lower left ventricular ejection fraction. This study however did not look at the prevalence and severity of ventricular arrhythmias during the ambulatory state in these patients and therefore no firm conclusions can be drawn pertaining to the relationship of ventricular arrhythmias and left ventricular dysfunction. Two large studies have shown an independent effect of ventricular arrhythmias on mortality after adjustment is made for left ventricular dysfunction (Ruberman et al, 1977 and Moss et al, 1979). However, both studies used a short period of ambulatory electrocardiographic recording and clinical heart failure served as an indicator of left ventricular dysfunction. In contradiction to the above two studies, Calvert, Lown and Gorlin (1977) as well as Califf et al (1978) have shown a direct relationship between the frequency and complexity of ventricular arrhythmias and

the extent of left ventricular dysfunction. In the study by Califf et al, the relationship of ventricular arrhythmias to the extent of left ventricular dysfunction was shown to be independent to the number and/or severity of diseased vessels. Schulze, Strauss and Pitt (1977), studied 81 patients following an acute myocardial infarction by 24 hour ambulatory electrocardiographic monitoring and gated cardiac blood pool scan. Approximately 90% of their patients with complex ventricular arrhythmias had a left ventricular ejection fraction of less than 0.40. Forty-five patients had an ejection fraction of less than 0.40 and 26 of these 45 patients had complex ventricular arrhythmias. Sudden death occurred in 8 of these 26 patients while no sudden deaths were reported in the remaining 19 patients with a low ejection fraction, but with non-complex ventricular arrhythmias. They also showed a low prevalence of complex ventricular arrhythmias in the patients with an ejection fraction of more than 0.40, and none of these patients died suddenly.

In the multicentre post-infarction research group study, both left ventricular dysfunction defined as a radio-nucleide ejection fraction of less than 0.40 and ventricular ectopy of 10 or more per hour identified a group of patients with a higher two year mortality (Multicentre Post Infarction Research Group, 1983). A further analysis of the data from this study showed an independent contribution to mortality of ventricular arrhythmias and left ventricular dysfunction (Bigger et al, 1984). Thus these findings from a study that involved

866 patients do not support the presence of a direct effect of left ventricular dysfunction on ventricular arrhythmias. Although it is known that patients with left ventricular dysfunction can either die of heart failure, myocardial infarction or arrhythmia, it is of interest to note that a low left ventricular ejection fraction in this study was more strongly associated with arrhythmic than heart failure death. The same conclusion was reached in another large multicentre study involving 533 patients who survived 10 days after myocardial infarction (Mukharji et al, 1984). In a major U.K. study of patients with chronic ischaemic cardiac failure, mortality was very high in those patients with a combination of poor left ventricular function and high grade ventricular arrhythmias (Glover and Littler, 1987). Furthermore, they showed an inverse relationship between left ventricular ejection fraction and grade of ventricular arrhythmias. They thus came to the conclusion that the presence of severe ventricular arrhythmias acts as a marker of severe left ventricular impairment and that therapy should be aimed at both improving left ventricular function and abolishing complex ventricular arrhythmias.

In a study looking at factors responsible for high mortality in patients with severe cardiac failure due to ischaemic and non-ischaemic dilated cardiomyopathy, Chakko and Gheorghiade (1985) showed an association between high grade ventricular arrhythmias and in particular, nonsustained ventricular tachycardia, with more severe resting left ventricular dysfunction. The left ventricular ejection fraction among the patients with

complications were even more pronounced when left ventricular ejection fraction was less than 30%.

There are few studies that have looked at the relationship between ventricular arrhythmias and left ventricular function in patients with aortic valve disease. Von Olshausen et al (1983) showed a highly significant inverse correlation between left ventricular ejection fraction and frequency of ventricular premature contractions in their study involving 93 patients with aortic valve disease. Klein (1984), noted a significantly lower left ventricular ejection fraction in patients with aortic regurgitation who had complex ventricular arrhythmias compared to the ejection fraction of those with simple ventricular arrhythmias. In an elegant study, Von Olshausen et al (1984) looked at the influence of aortic valve replacement on the incidence of ventricular arrhythmias. Prior to surgery, frequent and complex ventricular arrhythmias were more prevalent in patients with impaired left ventricular function. Interestingly, following aortic valve replacement, the grade of ventricular arrhythmias improved significantly only in those patients who obtained an improvement in their left ventricular function which was assessed non-invasively. In a recent study involving 68 patients with mitral and 92 with aortic valve disease, the incidence and severity of ventricular arrhythmias showed a negative correlation to left ventricular ejection fraction (Meinertz et al, 1987). In addition, there was a positive correlation between the grade of ventricular arrhythmias and left ventricular end systolic volume index, as well as

to peak systolic left ventricular wall stress in the patients with aortic valve disease.

1.6 Effects of Aortic Valve Replacement on Cardiac Arrhythmias

In a number of long-term follow-up studies of patients following aortic valve replacement, sudden death was not an uncommon occurrence (Duvoisin et al, 1968; Shean et al, 1971; Lee et al, 1975; Barrat-Boyes, Roche and Whitlock, 1977; Samuels et al, 1979). However, the exact mechanism of sudden death remains speculative and is presumed to be secondary to an arrhythmic event. There are scant data available on the effect of aortic valve replacement on cardiac arrhythmias. Three studies involving a total of 55 patients with aortic valve disease, reported a low incidence of ventricular arrhythmias following aortic valve replacement (Smith et al, 1972; Angelini et al, 1974; Michelson, Morganroth and McVaugh, 1979). In all these three studies arrhythmia monitoring was performed within the first week following operation. In contradiction to these findings, other workers have reported a very high incidence of ventricular arrhythmias in studies involving a total of 141 aortic valve disease patients following valve replacement (Schilling et al, 1982; Gradman et al, 1981; Kostis et al, 1984; Von Olshausen et al, 1984). In 3 of these studies, the incidence of ventricular arrhythmias was assessed immediately before and following aortic valve replacement (Schilling et al, 1982; Kostis et al, 1984; Von Olshausen et al 1984). Schilling and his colleagues showed a high

incidence of complex ventricular arrhythmias in their patients with a further increase 2 weeks and one year after aortic valve replacement (Schilling et al, 1982). In contrast, Kostis et al (1984) although showing a high incidence of ventricular arrhythmias in their patients, did not observe significant effect of aortic valve replacement on the frequency or complexity of ventricular ectopic activity. An interesting but not surprising observation was noted by Von Olshausen and his colleagues when they studied the influence of aortic valve replacement on the incidence of ventricular arrhythmias (Von Olshausen et al, 1984). Following aortic valve replacement, the grade of ventricular arrhythmias improved significantly only in those patients who obtained an improvement in their left ventricular function.

1.7 Detection of Ventricular Late Potentials for the Identification of Patients with Ventricular Tachyarrhythmias

Reentry plays a major role in the genesis of ventricular tachyarrhythmias (El-Sherif et al, 1977; El-Sherif et al, 1977; El-Sherif et al, 1977; Williams et al, 1974; and Zipes, 1975). The prerequisites for reentry are unidirectional block, slow conduction and recovery of the tissue ahead of the wave front of excitation (Zipes, 1975). One of the most significant findings attributed to slow conduction was the detection of delayed fractionated electrical activity in regions of experimental infarction (El-Sherif et al, 1977) and since these potentials occur at and after the end of the QRS complex they have been called "late potentials". They are characterised by

multiple high frequency low amplitude spikes and it has been suggested that the presence of such signals indicate sites for potential reentrant circuits. It has recently been possible to record late potentials by signal-averaging of the surface electrocardiogram and this technique which is simple and non-invasive has gained popularity for identifying those patients who are prone to develop ventricular tachyarrhythmias. This technique is performed by feeding a number of electrocardiographic complexes through a high gain amplifier (X 1,000) and after dividing by the number of cycles, an average value of the electrocardiogram for each discrete point in time is obtained. The averaged electrocardiogram is then passed through a high pass filter which permits high frequency signals to pass without a loss of amplitude. By this method, ventricular late potentials can be identified. These potentials would not be expected to be recorded in the standard electrocardiogram since they are in the microvolt range.

Berbari et al (1978), demonstrated for the first time ventricular late potentials in the experimental animal, and Fontaine et al, in patients with idiopathic ventricular tachycardia (Breithardt and Borggrefe 1986). This has been confirmed by a growing number of further reports (Breithardt, Becker and Seipel, 1980; Simson et al, 1980; Rozanski et al, 1981; Simson, 1981; Denes et al, 1983; Denes, Uretz and Santarella, 1984). Eight patients with ventricular aneurysm and chronic recurrent ventricular tachycardia showed late potentials on signal-averaged electrocardiograms (Rozanski et al, 1981).

Disappearance of both ventricular tachycardia and late potentials was noted following aneurysmectomy thus suggesting that late potentials are related to the tendency to develop recurrent sustained ventricular tachycardia. Simson (1981) performed signal-averaging of the electrocardiogram on 66 patients who had a previous myocardial infarction. Ventricular late potentials were detected in 92% of 39 patients who had repeated episodes of symptomatic ventricular tachycardia and in only 7% of the remaining 27 patients without complex ventricular arrhythmias. All the ventricular tachycardia patients had sustained inducible ventricular tachycardia on electrophysiological studies. Denes et al (1983) by performing signal-averaging of the electrocardiogram could distinguish patients with documented ventricular tachycardia from normal subjects. All the ventricular tachycardia patients had a history of myocardial infarction and ventricular tachycardia was inducible by programmed electrical stimulation. In another larger study reported by Denes and colleagues on patients with coronary artery disease, 66% of patients with documented VT/VF had late potentials compared to 25% in those without VT/VF (Denes, Uretz and Santarelli, 1984). In a study involving 236 patients, ventricular late potentials were recorded in 45 of 63 patients (71%) with documented ventricular tachycardia or fibrillation while in 27 control subjects, no late potentials were recorded (Breithardt et al, 1982).

Several studies have shown a high incidence of life threatening ventricular arrhythmias in patients with dilated congestive cardiomyopathy (Huang, Messer and

Denes, 1983; Meinertz et al, 1984; and Von Olshausen et al, 1984). To assess whether signal-averaged electrocardiography could identify patients who are at a high risk of an arrhythmic death i.e. those with previously documented episodes of sustained ventricular tachycardia or fibrillation, Poll et al (1985) studied 41 patients with dilated congestive cardiomyopathy. Abnormal signal-averaged electrocardiograms occurred in 83% of the patients with previously documented sustained ventricular tachycardia/ventricular fibrillation, and in only 14% of the patients with no ventricular tachycardia/ventricular fibrillation. In a control group of 55 healthy individuals, abnormal signal-averaged electrocardiogram was detected in only 2%.

In addition to the above studies, several other investigators have shown a strong correlation between ventricular tachycardia inducible on electrophysiologic study and the presence of an abnormal signal-averaged electrocardiogram (Simson et al, 1983; Freedman et al, 1985; Lindsay et al, 1986; Dennis et al, 1987; Winters et al, 1988; Turitto et al, 1988; Borbola, Ezri and Denes, 1988; and Nalos et al, 1988). Simson et al (1983) studied 102 patients with prior Q wave myocardial infarction and reported a 78% agreement between inducible ventricular tachycardia and the presence of late potentials on the signal-averaged electrocardiogram. Freedman et al (1985) studied patients with a history of spontaneous ventricular fibrillation or spontaneous sustained ventricular tachycardia. Ventricular late potentials were present in 58% of those patients with inducible ventricular tachycardia

or ventricular fibrillation by electrophysiologic study. By performing signal-averaging of the electrocardiogram, Lindsay et al (1986) could correctly identify 88% of patients with inducible ventricular tachycardia on subsequent electrophysiologic study. A year later, Denniss et al (1987) showed a strong correlation between the ability to induce sustained ventricular tachycardia at programmed ventricular stimulation and the presence of abnormal signal-averaged electrocardiograms in patients following an acute myocardial infarction. The usefulness of signal-averaging of the electrocardiogram for selecting patients with nonsustained ventricular arrhythmias to undergo electrophysiological study was assessed by Winters and his colleagues (Winters et al, 1988). An abnormal signal-averaged electrocardiogram had a 91% sensitivity and a 56% specificity with respect to subsequent induction of tachycardia by programmed ventricular stimulation. Turitto et al (1988) studied 105 patients with nonsustained ventricular tachycardia detected by Holter monitoring and assessed the predictive accuracy of signal-averaged electrocardiogram for the induction of sustained monomorphic ventricular tachycardia by programmed ventricular stimulation. Signal-averaged electrocardiogram showed a sensitivity of 64%, specificity of 89% and predictive accuracy of 84% in predicting inducibility of sustained ventricular tachycardia. In 50 patients with coronary artery disease and documented spontaneous ventricular tachycardia or ventricular fibrillation, late potentials were present in 71% of those patients with inducible sustained monomorphic ventricular tachycardia at electrophysiological studies (Borbola, Ezri and Denes,

1988). In a study by Nalos et al (1988), signal-averaged electrocardiography could correctly identify those patients in whom sustained monomorphic ventricular tachycardia was induced by programmed ventricular stimulation with a sensitivity of 80% and a specificity of 92%.

The prognostic significance of late potentials in patients with coronary artery disease has been evaluated in a few prospective studies (Zimmermann et al, 1985; Denniss et al, 1983; Kuchar, Thorburn and Sammel, 1986). Zimmermann et al (1985) followed up 90 patients with coronary artery disease for a period of one to 22 months. There were 9 deaths (10%), 6 of them resulting from sustained ventricular arrhythmias. All these 6 patients had ventricular late potentials at the beginning of the study. Thus ventricular late potentials had a 100% sensitivity in predicting sudden arrhythmic death. Denniss et al (1983) had previously reported a similar positive prognostic value of late potentials in identifying patients with sustained ventricular tachycardia. In another study involving 165 patients who survived acute myocardial infarction signal-averaged electrocardiography predicted arrhythmic events with a 92% sensitivity and 62% specificity (Kuchar, Thorburn and Sammel, 1986).

The clinical setting of an acute myocardial infarction provides fertile ground for research in signal-averaged electrocardiography with the view of identifying patients with poor prognosis. McGuire et al (1988) performed signal-averaged electrocardiograms in 50 patients within the first 24 hours following acute myocardial infarction.

The presence of late potentials could predict the development of subsequent fatal ventricular arrhythmias with a sensitivity of 80% and specificity of 72%. Although this study was performed in a small group of patients, it nonetheless suggests that signal-averaged electrocardiography may well have an important role in identifying high risk patients prior to hospital discharge. These findings are further supported by data of Kienzle, Falcone and Simson (1988). They showed a significant decrease in voltage over the first 80 milliseconds of the signal-averaged QRS complex in patients with acute myocardial infarction compared with signal-averaged electrocardiograms of healthy volunteers. Interestingly, they found a further decline in voltage when comparing patients with previous myocardial infarction and sustained ventricular tachycardia with the patients with acute myocardial infarction without ventricular tachycardia.

Syncope is a commonly encountered clinical problem that frequently defies ready explanation. Signal-averaged electrocardiography provides a non-invasive tool in the initial evaluation of patients with unexplained syncope, particularly in the presence of organic heart disease before subjecting them to invasive electrophysiological studies. Kuchar and his colleagues studied 150 patients with recurrent syncope by signal-averaged electrocardiography in order to determine its role in identifying patients with ventricular tachycardia and hence determine their prognosis (Kuchar, Thorburn and Sammel, 1986). They found late potentials to have a predictive accuracy of 82% for identifying ventricular tachycardia in patients with

ischaemic heart disease and 54% in those with other forms of structural heart disease. It is interesting to note that patients without heart disease in whom late potentials were detected did not have ventricular tachycardia. This is because myocardial disease is a prerequisite for reentrant ventricular arrhythmias and in addition late potentials do not identify patients in whom ventricular tachycardia results from an automatic or triggered mechanism. In another smaller study involving 24 patients with unexplained syncope, signal-averaged electrocardiography provided an 89% sensitivity in detecting those patients with sustained ventricular tachycardia induced on subsequent electrophysiological studies (Gang et al, 1986). Winters and his colleagues studied 40 patients with unexplained syncope by signal-averaged electrocardiography followed by electrophysiologic studies (Winters, Stewart and Gomes, 1987). An abnormal signal-averaged electrocardiogram had a sensitivity of 82% and specificity of 91% in predicting the induction of sustained ventricular tachycardia at electrophysiologic testing.

A reduced incidence of ventricular tachyarrhythmias and sudden death has been observed in patients who receive thrombolytic therapy following an acute myocardial infarction. This observation prompted Gang et al (1989) to perform signal-averaged electrocardiograms in 106 patients within 48 hours of hospital admission following a first myocardial infarction. They noted a significant difference in the incidence of late potentials in patients who had, compared to those who had not received tissue

plasminogen activator (t - PA). Furthermore, in the only 2 patients with late potentials in the t - PA group, coronary angiography demonstrated continued occlusion of the infarct related artery in both of them.

In another interesting study involving 40 patients with chronic coronary artery disease, signal-averaged electrocardiography was performed immediately before and repeated within a mean of 10 days following coronary artery bypass grafting (Borbola et al, 1988). In 2 of 7 patients with previous myocardial infarctions and positive for late potentials before coronary artery bypass grafting, signal-averaged electrocardiograms became normal following surgery. In the 5 remaining patients with persistent late potentials, the mean values of the signal-averaged electrocardiographic variables improved after revascularisation.

As far as I am aware, there are no studies on signal-averaged electrocardiography in patients with aortic valve disease. However, in the only study on hypertensive patients with electrocardiographic left ventricular hypertrophy, 11 out of a total of 90 patients had nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring. Of these 90 patients, only one had ventricular late potentials on signal-averaged electrocardiography (Pringle et al, 1989).

1.8 Autonomic Dysfunction as a Potential Mechanism for the Development of Ventricular Tachyarrhythmias and Sudden Death

The importance of the autonomic nervous system has been relatively neglected until recent years simply by the fact that this system lies in the borderlands between cardiology, general medicine, neurology and endocrinology. Autonomic neuropathy and its resultant clinical manifestations may occur in a long list of diseases, and structural disturbances may affect different systems. However, I shall restrict myself here in reviewing some of the work that looks at the effects of autonomic failure on the cardiovascular system.

The first historical contribution on cardiovascular autonomic failure was pioneered by Bradbury and Eggleston (1925), when they reported three cases with orthostatic hypotension. However, it was in 1955 that one of the first large studies on cardiovascular autonomic disturbances was presented in the medical literature (Sharpey-Schafer, 1955). Sharpey-Schafer, who was then the Professor of Medicine at St. Thomas' Hospital, performed valsalva manoeuvre in 63 patients with heart failure resulting from a variety of cardiac conditions including aortic valve disease, and in 62 normal volunteers. He showed a marked difference in continuous arterial pressure records between normal subjects and patients with heart failure. The classical heart rate changes occurring in normal subjects were observed to be absent in the heart failure patients.

Diabetes mellitus is by far the commonest cause of autonomic neuropathy and its appearance is closely associated with peripheral neuropathy. Autonomic impairment can present in a variety of symptoms, but in some patients it may cause no symptoms. The first review on autonomic neuropathy in diabetes mellitus was contributed by Rundles (1945). Since then, several syndromes have been described, but it was in the early sixties that reports on abnormal circulatory reflexes began to appear in the literature. Sharpey-Schafer and Taylor (1960) studied 337 patients attending a diabetic clinic, for evidence of neuropathy. Sixty-nine patients (20%) showed evidence of neuropathy and all had an abnormal response to valsalva manoeuvre. Ewing et al (1973) studied 37 diabetics with symptoms or signs of autonomic neuropathy. The heart rate and blood pressure response to valsalva manoeuvre was abnormal in 62% of the patients and this showed a significant correlation with a fall in systolic blood pressure on standing. Beat to beat (R-R interval) variation in heart rate which is a sensitive test of autonomic cardiovascular reflexes, was studied in 42 young asymptomatic male diabetics (Murray et al, 1975). The mean R-R interval was significantly shorter in the diabetics compared to 25 age matched healthy controls. This was the first study to document abnormal autonomic cardiovascular reflexes in diabetics without any clinical features of autonomic neuropathy thus demonstrating that damage to the autonomic pathways controlling heart rate can occur without any accompanying symptoms. This is further supported by evidence from a study on 11 diabetics in whom abnormal autonomic functions were present in 7,

being more severe in 3 of them (Bennett et al, 1976). Despite the severity of cardiovascular autonomic dysfunction, no patient reported troublesome symptoms. Rubler, Chu and Bruzzone (1985), studied 25 adults with diabetes mellitus, but free from heart disease and with no symptoms of peripheral or autonomic nervous dysfunction. Heart-rate variation to deep breathing was abnormal in 52% of the diabetics compared to 23% in 13 healthy volunteers. On 24 hour ambulatory monitoring, the mean heart rate was significantly higher in the diabetics with abnormal, compared to those with normal, heart-rate variation to deep breathing. In addition, the mean of the 5 highest 24 hour systolic blood pressures was also greater in the diabetics with abnormal heart-rate variation to deep breathing than in healthy volunteers.

In a recent study, Hornung and his colleagues performed 24 hour ambulatory heart rate and blood pressure recordings in 42 patients with diabetes mellitus and 22 normal subjects (Hornung, Mahler and Raftery, 1989). There was little heart-rate variation in the diabetic patients thus giving a somewhat "flat curve" in the 24 hour profile. The smallest diurnal change in heart rate was observed in 6 of the 42 diabetics who had autonomic neuropathy.

The increased prevalence of myocardial infarction in diabetic patients has been attributed to autonomic neuropathy and it has been suggested that abnormal autonomic reflexes may account for some of the deaths, especially those occurring suddenly in these patients (Clarke, Ewing and Campbell, 1979). In a study by Niakan

et al, (1986) unrecognised myocardial infarction i.e. silent, was present in 20% of diabetic patients with documented cardiovascular autonomic neuropathy as opposed to 4.2% of patients with normal autonomic function. This lends further support to the hypotheses that sudden death which is common in diabetics, may be resulting from unrecognised myocardial infarction and simple bedside autonomic function tests may identify this high risk group of patients. Thirty-seven patients with diabetes mellitus and clinical features suggestive of autonomic neuropathy were followed up for 33 months (Ewing, Campbell and Clarke, 1976). There were 10 deaths (27%), all occurring in patients with previously documented abnormal autonomic function tests. In another larger study on patients with diabetes mellitus, 26 deaths occurred during a follow-up period of up to 5 years (Ewing, Campbell and Clarke, 1980). There were 21 deaths (53%) in 40 patients with initially abnormal autonomic function tests compared to only 5 deaths (15%) in 33 patients with initially normal tests. Two of these 5 patients had abnormal autonomic function tests on subsequent testing during the follow-up period. The mean duration of survival in those with initially abnormal autonomic function tests was 18.6 months compared to 28.6 months in the 5 patients with initially normal tests.

In a study to determine the predictors of intra-operative cardiovascular morbidity in diabetics, autonomic function tests were performed in 17 diabetic patients and 21 non-diabetic patients before undergoing elective ophthalmologic surgery (Burgos et al, 1989). A significantly

greater impairment in autonomic function was noted in diabetics needing intra-operative blood pressure support, thus indicating the usefulness of autonomic screening in identifying a subset of diabetics who are at an increased risk of intra-operative cardiovascular instability.

Ventricular fibrillation is regarded as the underlying mechanism of sudden death (Lown and Wolf, 1971). Neural inputs may play a role in the pathogenesis of ventricular fibrillation. Verrier and his associates provoked ventricular fibrillation in 60% of mongrel dogs following stimulation of the stellate ganglia, which are way stations for sympathetic neural discharge from the brain to the heart (Verrier, Thompson and Lown, 1974). The incidence of ventricular fibrillation and the time of its onset were comparable for left and right-sided stimulation. However, when stellate ganglia were sectioned or when the dog was pre-treated with reserpine, the changes in cardiac vulnerability were prevented. Brown (1967) demonstrated an increase in sympathetic discharge with the onset of acute myocardial infarction following occlusion of the left main coronary artery in anaesthetised cats. In a similar type of experiment, coronary occlusion was followed by increased firing from sympathetic fibres (Malliani, Schwartz and Zanchetti, 1969). If sympathetic neural discharge is a determining factor in cardiac susceptibility to ventricular fibrillation, pharmacologic adrenergic blockade would be expected to prevent the reduction in threshold for ventricular fibrillation that attends coronary occlusion. This is well established in patients following an acute

myocardial infarction (Wilhelmsson et al, 1974; The Norwegian Multicenter Study Group, 1981). Both these studies showed a significant reduction in sudden cardiac death presumably by preventing lethal arrhythmias in patients who received a beta-blocker.

Does the vagus nerve play any role in control of the threshold for ventricular fibrillation? This question was first addressed by Einbrodt in 1859, when he concluded from his experiments on dogs, that the vagus protected the heart against ventricular fibrillation (Bleich and Boro, 1976). More than a hundred years later, Kent et al, (1973), in agreement with Einbrodt's findings, demonstrated that a reduction in vagal tone led to an increase in the electrical instability of the heart. However, several other studies have indicated that vagal stimulation has indirect effects that are expressed by opposing the influence of heightened adrenergic tone on ventricular vulnerability (Kolman, Verrier and Lown, 1975; Bleich and Boro, 1976). This is further supported by the failure of vagal stimulation to influence the fibrillation threshold in dogs following beta-adrenergic blockade with propranolol (Bleich and Boro, 1976).

Schwartz and his co-workers have performed a number of animal experiments to explore the relationship between the autonomic nervous system, myocardial ischaemia and ventricular arrhythmias (Billman, Schwartz and Stone, 1982; Schwartz et al, 1988). In these series of experiments, dogs were experimentally infarcted by occluding the left anterior descending coronary artery and

after recovering from the acute myocardial infarction, baroreceptor reflex testing was performed. The baroreceptor slope was then constructed by plotting the R-R interval as measured from a continuous electrocardiogram, against systolic blood pressure that was either lowered or raised by 30 to 50 mmHg by injecting sodium nitroprusside or phenylephrine intravenously. Baroreflex sensitivity was measured as the slope of the $\Delta RR/\Delta BP$ relationship. Malignant arrhythmias were then induced by a combination of exercise so as to physiologically elicit a high sympathetic tone, and a brief episode of myocardial ischaemia induced by occluding the circumflex artery. The baroreceptor slope could identify those dogs that were likely to develop ventricular fibrillation and thus at risk of sudden death. Their slopes were noted to be significantly reduced when compared to the slopes in dogs that did not develop ventricular fibrillation.

It was in 1971 that the first study looking at the parasympathetic control of the human heart was reported (Eckburg, Drabinsky and Braunwald, 1971). They constructed baroreceptor slopes by plotting the R-R interval against systolic blood pressure after injecting phenylephrine in 22 patients with a variety of cardiac conditions and in 23 subjects free of heart disease. The heart rate response to autonomic agents was also tested by injecting propranolol and atropine intravenously. There was no difference in heart rate between the patients and controls after propranolol, while a significant increment in heart rate was noted after atropine injection in only the controls, thus indicating a marked disturbance of

parasympathetic function in patients with heart disease. The baroreceptor slope was also significantly diminished in heart disease patients.

The work by Webb and his associates represents another clinical milestone (Webb, Adgey and Pantridge, 1972). They studied 74 patients within the first 30 minutes of the onset of acute myocardial infarction and found a vast majority of them to have signs of autonomic disturbances. Signs of excessive sympathetic activity were more frequent in cases of anterior infarction, whereas signs of vagal overactivity were more frequent in inferior infarctions. Correction of these disturbances by pharmocologic means was followed by a noticeable reduction in the in-hospital mortality. About 12 years later, in agreement with these findings, Imaizumi et al (1984) reported an impairment in baroreflex control of heart rate in patients following an acute myocardial infarction. Interestingly, the baro-receptor slope assessed by plotting the R-R interval against systolic blood pressure was appreciably depressed in the acute convalescent phase becoming steeper when the test was repeated in the late convalescent phase. A few years earlier, Kirby had also reported abnormal blood pressure responses to the Valsalva manoeuvre in patients with acute myocardial infarction (Kirby, 1977). A number of recent studies have lended more support to the occurrence of significant autonomic dysfunction in patients following acute myocardial infarction (Bigger et al, 1988; McAreavey et al, 1989; Bhatnagar, Al-Yusuf and Al-Asfoor, 1987). Bigger et al (1988) and McAreavey et al (1989), used a more sophisticated technique and

demonstrated low cardiac parasympathetic activity in patients with acute myocardial infarction. This was done using 24 hour ambulatory electrocardiographic recordings, measuring the changes in R-R intervals and monitoring variations throughout the day and night. This technique was previously shown to provide a good measure of cardiac parasympathetic activity (Ewing, Neilson and Travis, 1984). In a study in patients with chronic coronary artery disease, significant impairment of cardiac parasympathetic function was demonstrated in the patients compared to healthy volunteers (Airaksinen et al, 1987).

The prognostic importance of cardiac autonomic dysfunction has been assessed by several workers (Kleiger et al, 1987; Martin et al, 1987; La Rovere et al 1988). In an elegant piece of work Kleiger et al (1987) studied the heart rate variability by performing 24 hour ambulatory electrocardiographic recording in 808 patients from 9 hospitals at an average of 11 days following an acute myocardial infarction. They showed the relative risk of mortality after a mean follow-up period of 31 months to be 5.3 times higher in patients with lower heart rate variability. The heart rate variability remained a powerful predictor of mortality after adjusting for other variables known to affect survival in patients following acute myocardial infarction. Martin et al (1987) reported a significantly lower heart rate variability in 3 patients who died suddenly during ambulatory electrocardiographic monitoring when compared to heart rate variability in normal subjects.

La Rovere et al (1988) studied baroreflex sensitivity in 78 patients following a first acute myocardial infarction by plotting R-R intervals against systolic blood pressure following an injection of phenylephrine. Six cardiovascular deaths, 4 of them sudden, occurred during a mean follow-up period of 24 months. Baroreflex sensitivity was remarkably lower in the patients who died than those of the survivors. Mortality significantly increased from 2.9% in patients with satisfactory baroreflex sensitivity to 40% in those with a markedly depressed baroreflex sensitivity.

An interesting study reported by Ellenbogen and his associates showed a striking improvement in baroreflex sensitivity in severe heart failure patients as early as 2 weeks after orthotopic cardiac transplantation (Ellenbogen et al, 1989). Baroreflex sensitivity was evaluated by plotting arterial pressure measurments against AA intervals in the recipient atrial intracavitary electrogram after intravenous phenylephrine bolus. This led to the speculation that neurohumoral rather than structural abnormalities of the baroreceptors account for depressed baroreflex sensitivity in patients with severe heart failure.

As sudden death is not an uncommon occurrence in aortic valve patients (Ross and Braunwald, 1968; Chizner, Pearle and de Leon, 1980; Lombard and Selzer, 1987) and as known from previous studies, the increased risk of sudden cardiac death associated with impaired autonomic function (Billman, Schwartz and Stone, 1982; Schwartz, Billman and

Stone, 1984; Kleiger et al, 1987; Martin et al, 1987; La Rovere et al, 1988), it would be interesting to assess the state of the autonomic nervous system in patients with aortic valve disease. However, I am aware of only one study that has systematically addressed this question (Airaksinen et al, 1988). These workers investigated heart rate responses to deep breathing and to standing up in 24 patients with aortic stenosis and 24 age-matched healthy controls. Heart-rate variation to deep breathing was significantly lower in patients with aortic stenosis than in healthy controls. This led to the suggestion that high left ventricular pressures seen in these patients may blunt the baroreceptors within the ventricle. However, aortic valve replacement which is expected to normalise the left ventricular pressure was not followed by improvement in the heart rate variability when the tests were repeated 6 weeks after surgery in 6 patients.

C H A P T E R T W O

A I M S O F T H E T H E S I S

Sudden cardiac death is a well known complication of patients with aortic valve disease (Ross and Braunwald, 1968; Von Olshausen et al, 1982; Von Olshausen et al, 1987). The exact mechanism responsible for this fatal outcome has remained speculative. However, many workers have presumed sudden death to occur secondary to an arrhythmic event in view of the high prevalence of complex ventricular arrhythmias in this group of patients (Schilling et al, 1982; Von Olshausen et al, 1983; Kostis et al, 1984; Klein, 1984). Electrocardiographic left ventricular hypertrophy which is found in 85% of patients with severe aortic valve disease (Braunwald, 1988) is associated with an eight-fold increase in cardiovascular mortality and a six-fold increase in coronary mortality. This cardiovascular risk is doubled when left ventricular hypertrophy is accompanied by repolarisation abnormalities (Kannel, 1983). The probability of dying within 8 years after developing this electrocardiographic pattern is more than half, which is at least 3 times the average mortality for this age-sex group. The mortality is in fact greater in persons with definite electrocardiographic left ventricular hypertrophy than in persons surviving an acute myocardial infarction (Kannel, Gordon and Offutt, 1969). Two explanations have been offered for the increased incidence of sudden death in this group of patients. One, is the increased incidence of ventricular arrhythmias as reported in a number of studies (Levy et al, 1987; Messerli et al, 1984; McLenachan et al, 1987), and the other is the decrease in coronary reserve, well recognised in patients with pressure induced left ventricular

hypertrophy thus leading to myocardial ischaemia (Borhani, 1987).

Most of the above studies have not looked at the relationship between left ventricular dysfunction and ventricular arrhythmias, as the presence of severe ventricular arrhythmias may merely act as a marker of severe left ventricular impairment. This fact is supported by a number of studies (see Chapter One).

The term "complex ventricular arrhythmias" quoted in most studies refers to a modified Lown grading system for ventricular arrhythmias described by Ryan et al, (1975) which also includes short runs of nonsustained ventricular tachycardia. However, there are no reports of sustained ventricular tachycardia, and therefore it cannot be assumed that these complex ventricular arrhythmias are a direct cause of death in these patients. It would therefore be worthwhile to verify their significance by the use of signal-averaged electrocardiography to detect ventricular late potentials. The presence of these late potentials has been shown to identify patients who are prone to develop sustained ventricular tachycardia either spontaneously or inducible by programmed ventricular stimulation (see Chapter One).

Other processes may be involved in the mechanisms leading to sudden death in patients with aortic valve disease. Several studies have reported an increased risk of sudden cardiac death associated with impaired cardiac autonomic function (see Chapter One). And in a study by Airaksinen

et al, (1988), patients with aortic valve disease were shown to have significantly impaired parasympathetic heart-rate control. Animal experiments had earlier shown that a reduction in vagal tone led to an increase in the electrical instability of the heart thus leading to a reduction in the ventricular fibrillation threshold.

In order to examine the various potential factors responsible for sudden death in aortic valve disease patients, this thesis was designed to address a number of points:-

1. What is the prevalence of ventricular arrhythmias in patients with aortic valve disease?

2. Is there a relationship between ventricular arrhythmias and the degree of left ventricular mass, the severity of aortic valve disease and the presence or absence of coexisting coronary artery disease?

3. What is the effect of left ventricular dysfunction on ventricular arrhythmias?

4. To assess the effect of aortic valve replacement on ventricular arrhythmias.

5. To evaluate the significance of ventricular arrhythmias detected by Holter monitoring by the use of signal-averaged electrocardiography.

6. To assess the status of cardiac autonomic nervous function in patients with aortic valve disease.

CHAPTER THREE

PATIENTS AND METHODS

3.1 Patient Selection and Recruitment

The University Department of Cardiology of the Glasgow Royal Infirmary is a referral centre for invasive cardiological investigations and has a wide catchment area. Patients with significant aortic valve disease were identified from the cardiac catheterisation waiting list. The other main source of patient identification was the surgical waiting list. The majority of the patients enrolled into the study had left ventricular hypertrophy and strain on the 12 lead electrocardiogram. This was defined as the sum of the amplitudes of the R-wave in V_5 or V_6 and S-wave in V_1 equal to or exceeding 3.5 mV in the presence of T-wave inversion of 0.1 mV or more in leads V_5 or V_6 (Sokolow and Lyon, 1949; Kannel 1983) (Figure 3.1). The only exclusion criteria for entering the study was either patient's refusal due to personal reasons or if the investigating Cardiologist felt that the patient was too unwell to be able to participate in the study. The distance of the patient's residence from the hospital was also taken into consideration before recruitment. Having identified the patients in this way, the patient was either interviewed in the hospital while awaiting cardiac catheterisation or an explanatory letter was sent asking the patient to attend a special out-patient clinic. In either case, an informed consent was obtained. A total of 100 patients with significant aortic valve disease were studied before surgery.

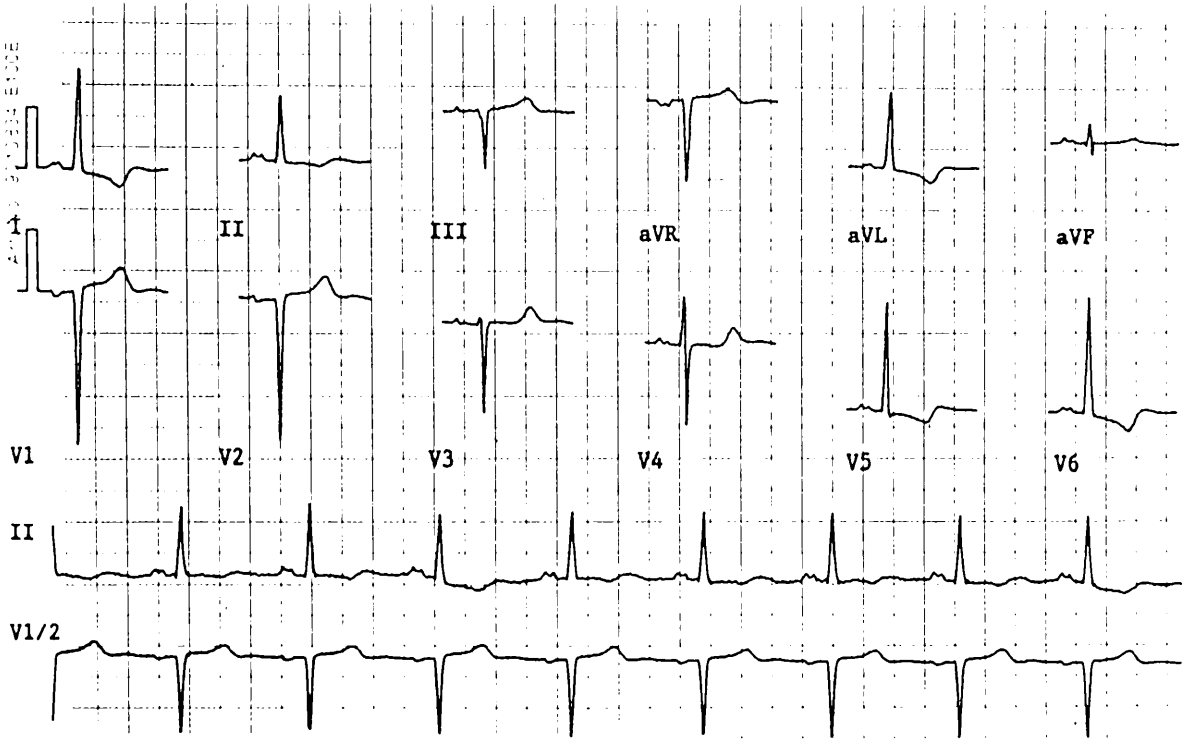

Figure 3.1: An electrocardiogram showing left ventricular hypertrophy and strain.

3.2 Study Protocol

Day 1

On the first day of the study a detailed history was obtained with particular reference to:-

- Past history of rheumatic fever, hypertension, angina, myocardial infarction and diabetes mellitus.

- Present medical history, especially exertional chest pain, breathlessness, palpitations, syncope, black-outs or dizziness and intermittent claudication.

- Cigarette smoking and alcohol intake.
- Current and past drug therapy.

Physical examination was carried out with particular reference to:-

- Height and weight.
- Cardiac failure.
- Added heart sounds and murmurs.

Investigations

- Haematology: haemoglobin and haematocrit.
- Biochemistry: urea and electrolytes, urate, gamma GT and total cholesterol.
- 12 Lead electrocardiogram.

Signal-averaging of the electrocardiogram was performed and finally an Oxford Medilog II frequency-modulated tape recorder was fitted. The patient was then asked to return to the hospital after 48 hours.

Day 3

The Oxford Medilog II frequency-modulated tape recorder was removed and a detailed cardiac ultrasound examination was performed. In 47 of the hundred patients, bedside autonomic function tests were also carried out.

Early post-operative study

The prevalence of arrhythmias during the immediate post operative period was assessed in 38 patients. Twenty-four and, whenever feasible, 48 hour ambulatory electrocardiographic recordings were made between the 5th and 7th post-operative days using the same equipment as that for the pre-operative study. Details of the operative procedure were obtained with particular emphasis on the type of aortic prosthetic valve inserted as well as any other additional surgical procedure e.g. mitral valve replacement or coronary artery bypass grafting. Haematological and biochemical results of the patients during the period of ambulatory electrocardiographic monitoring were also obtained.

Late post-operative study

The full study protocol as that for the pre-operative study was repeated about 3 to 6 months post-operatively in 30 patients. Once again an informed consent was obtained and after a detailed history with particular emphasis on the presence or absence of the cardinal symptoms i.e. exertional chest pain, palpitations, syncope and breathlessness, a thorough physical examination was carried out.

Blood was obtained for haematological and biochemical investigations. Signal-averaging of the electrocardiogram was then performed and finally the patient was fitted with the ambulatory electrocardiographic recorder and asked to return to the hospital 48 hours later. On the return appointment, the patient underwent a detailed cardiac ultrasound examination and in 10 of the 30 patients bedside autonomic function tests were performed.

3.3 Echocardiography

Echocardiograms were recorded using an Advanced Technology Laboratory Ultramark 8 system with a 3.0 mHz transducer at a paper speed of 50 mm/s. The patients were studied in the supine or left lateral position with the transducer placed in the third to fifth left intercostal space to demonstrate the long axis view. Whenever necessary, the transducer was manipulated laterally until both the mitral valve leaflets could be visualised with the transducer perpendicular to the chest wall and adequate echoes of the interventricular septum and left ventricular posterior

wall were simultaneously visualised. M-mode recordings were obtained under 2-D guidance. Left ventricular dimensions were measured at or slightly below the tips of the mitral valve leaflets at the peak of the R-wave of the simultaneously recorded electrocardiogram. Measurements of the interventricular septum (IVST), left ventricular internal dimension (LVID) and posterior wall thickness (PWT) were made according to the Penn convention (Figure 3.2) (Devereux and Reichek, 1977). By this method, the thickness of both the septal and left ventricular posterior wall endocardial echoes are included in the left ventricular internal dimension measurement and excludes these echoes from the septal and left ventricular posterior wall thickness measurements. By this method, echocardiographic left ventricular mass was shown to correlate well with anatomic left ventricular mass (Devereux and Reichek, 1977). Left ventricular mass (LVM) was calculated using an anatomically validated formula:- $LVM = 1.04([LVID+PWT+IVST]^3 - [LVID]^3) - 13.6$; where 1.04 is the specific gravity of the myocardium. Left ventricular mass index was then calculated by dividing the LVM with body surface area derived by using the formula of Dubois and Dubois (1916). Left ventricular hypertrophy was considered to be present when the LVMI exceeded 134 g/m^2 in males and 110 g/m^2 in females (Devereux et al, 1984).

Left ventricular systolic wall stress was determined non-invasively in all patients using echocardiographic parameters. Two previously validated methods for the calculation of wall stress were employed:-

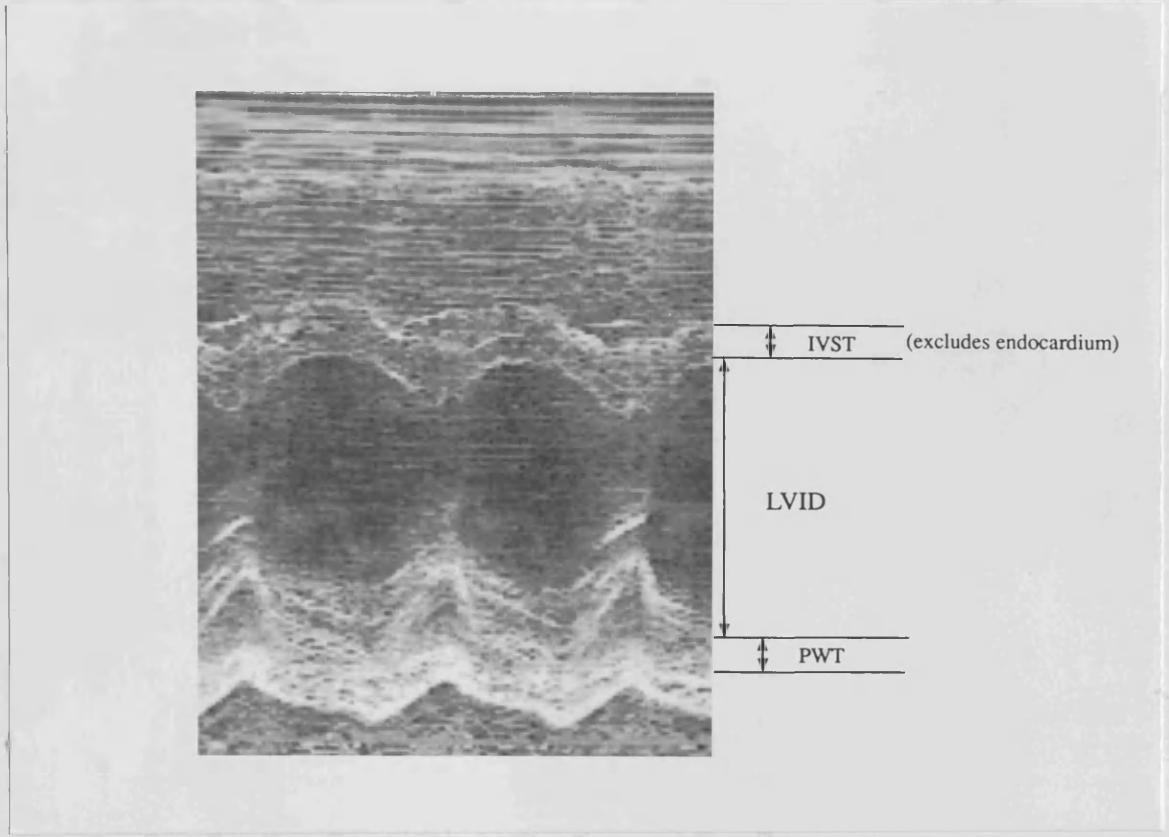

Figure 3.2:

Measurements of left ventricular dimensions according to the Penn Convention.

1. Reichek et al's method (1982)

By this method LV wall stress was determined by using the angiographically validated method of Grossman and his colleagues (Grossman, Jones and McLaurin, 1975):-
(0.334 P (LVID)/PWT [I+PWT/LVID]) where P = LV systolic pressure, LVID = LV diameter in endsystole and PWT = LV posterior wall thickness in endsystole.

2. Quinones et al's method (1980)

P (r/WT)

Where P = LV systolic pressure, r = intracavitary radius in cm, taken as half the echocardiographic left ventricular diameter in endsystole (LVID/2) and WT = the average of septal and posterior wall thicknesses in end-systole (IVST + PWT/2, where IVST = interventricular septal thickness).

In both the above methods, LV systolic pressure was estimated by adding cuff systolic blood pressure and doppler derived peak systolic gradient across the aortic valve, both done during the echocardiographic examination. Endsystole was identified as the time of smallest LVID. Fractional shortening was calculated using the equation:- FS = LVIDd - LVDS (McDonald, Feigenbaum and Chang, 1972).

Left atrial dimension was measured as the maximal distance between the posterior aortic root wall and the posterior left atrial wall.

All measurements were averaged from three consecutive sinus beats by the use of a tracker-ball manipulated cursor. In addition to the measurements made by the use of a digitizer contained in the image system, manual measurements were also made from hard copy.

3.4 Doppler Echocardiography

Doppler echocardiographic studies were performed using the same equipment as that for the echocardiographic studies. Continuous wave doppler examinations were performed using a 2.25 mHz transducer. The subjects were examined supine or in the left lateral position during quiet respiration. The transducer was placed at or slightly medial to the apex and its position altered until the highest peak flow velocities in early and late diastole and the best possible graphic quality of the doppler wave forms were obtained. Tracings of the four cardiac cycles with the highest velocity profile of early diastolic left ventricular filling were analysed and an average was taken for the peak velocity of early left ventricular filling (peak E) and peak velocity of late ventricular filling due to atrial contraction (peak A) (Figure 3.3). The ratio of peak E/peak A was calculated as was the pressure half time, which is the time required during diastole for the pressure difference across the mitral valve to fall to one half of its initial value at the onset of diastole (Hatle, Angelson and Tramsdal, 1979). To record aortic flow velocity, the transducer was placed at or slightly medial to the apex with the patient lying in the supine or left lateral position. Whenever necessary, other transducer

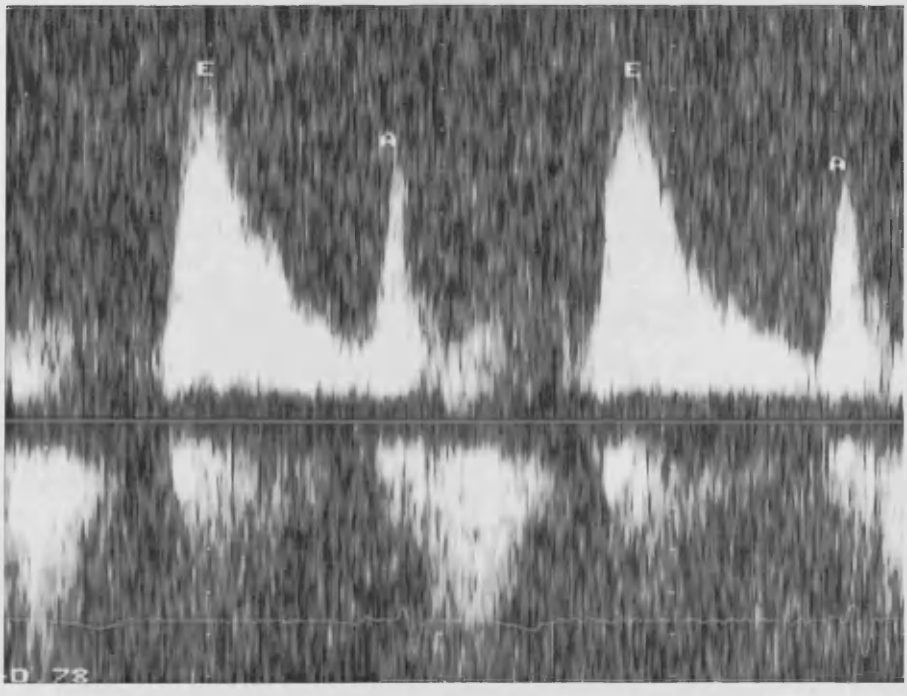

FIGURE 3.3: Normal Doppler mitral flow pattern. The maximal early diastolic flow velocity (E) is high relative to maximal late diastolic flow velocity (A) giving an E/A ratio of ›1.

positions were sought e.g. the first or second right intercostal space with the patient turned over to the right side or the suprasternal notch. Measurement of the maximum velocity was made after obtaining the optimal aortic flow recording from the ascending aorta. The recordings were considered optimal only after systematic examination to locate the signal of highest audible frequency, maximal velocity, and most clearly defined spectral velocity envelope. Optimal signals were assumed to be in a near-parallel orientation to the direction of maximal blood flow across the stenosis. The systolic pressure gradient across the aortic valve was then calculated automatically using the software contained in the system which applied the modified Bernoulli equation (Hatle, 1980) as follows:- Gradient = $4V^2$, where V^2 = maximum velocity squared (in m/sec). In several recent studies, a general and close correlation between the continuous-wave doppler derived pressure gradient and the catheterisation gradient has well been established (Hatle, 1981; Stamm and Martin, 1983; Currie et al, 1985).

The degree of aortic regurgitation was estimated from the maximum and clearest diastolic velocity profile. This was accomplished by estimating the shape of the deceleration slope which is defined as the line joining the peak diastolic velocity to the end-diastolic velocity, the slope being steepest in patients with severe regurgitation. Previous studies have shown a good correlation between the severity of aortic regurgitation obtained by continuous-wave doppler and that obtained by supravalvular aortography (Masuyama et al, 1986; Grayburn

et al, 1987; Beyer et al, 1987). Any other coexisting valvular lesions were also documented.

The predominant aortic valve lesion of the patients was determined from doppler ultrasound and when available cardiac catheterisation studies. Patients with a transvalvular gradient of more than 25 mmHg and aortic regurgitation of less than grade 2+ of 4+ grades were classified as having aortic stenosis (AS). Patients with aortic regurgitation of $\geq$ 2+ and a transvalvular gradient of $<$25 mmHg, were classified as having predominant aortic regurgitation (AR). Those who did not meet these criteria were classified as having combined AS and AR.

3.5 Ambulatory Electrocardiographic Monitoring

Ambulatory electrocardiographic recordings were made on TDK acoustic dynamic cassettes over two consecutive 24 hour periods using calibrated Oxford medilog II frequency-modulated tape recorders where channel I recorded lead CM5 and channel II recorded lead V2. After careful skin preparation the patients were connected to the tape recorders using standard disposable silver-silver chloride electrodes. The electrodes were placed over bony prominences to avoid muscular artifacts. These sites were the manubrium sternum, right sixth rib over the anterior axillary line, the left subclavicular space, the left sixth rib in the anterior axillary line (lead CM5) and a modified V2.

The patients were then provided with a diary and instructed to note down any significant cardiac symptom, e.g. chest pain or discomfort, breathlessness, palpitations or dizziness. The complete 48 hour records were analysed by the author by replaying at 60 times normal speed on an Oxford unit to the high speed analyser (Pathfinder) produced by Reynolds Medical Electronics. The outputs from the pathfinder were interfaced to a PDP8A mini computer (MacFarlane, 1979) which prints a detailed report. By this method, a tabulation of the heart rate, incidence of ventricular extrasystoles as well as episodes of ST - segment depression were automatically produced for both the 24 hour periods. Further verification was achieved by visual inspection of the monitor during play back of the tapes and examination of hard copy printouts of areas of interest. In cases of doubt, the hard copy printouts were interpreted by two experienced Cardiologists and a consensus of opinion was taken as the final result. The use of a manual back up has been shown to improve the reproducibility of the computer assisted technique (Khurmi and Raftery, 1987).

The arrhythmias were classified into the different categories:

- less than 10 ventricular extrasystoles per hour.
- 10 to 30 ventricular extrasystoles per hour.
- More than 30 ventricular extrasystoles per hour.
- The presence or absence of couplets.
- The presence or absence of ventricular tachycardia.

Ventricular tachycardia was defined as 3 or more consecutive uniform or multiform ventricular beats at a rate of more than 120 beats per minute, with nonsustained ventricular tachycardia lasting less than 30 seconds.

In order to allow comparisons to be made with previous work, arrhythmias were also analysed using the Lown's grading (Lown and Wolf, 1971).

- Grade 0 - No ventricular ectopic beats.

- Grade 1 - Infrequent ventricular ectopic beats (less than 30 per hour).

- Grade 2 - Frequent ventricular ectopic beats (more than 30 per hour).

- Grade 3 - Multiform ventricular ectopic beats.

- Grade 4a - Couplets (two consecutive ectopic beats).

- Grade 4b - Salvos of nonsustained ventricular tachycardia (three or more consecutive ventricular beats occurring at a rate of greater than 120 per minute and lasting for not more than 30 seconds).

- Grade 5 - Early ectopic beats
(when the R - wave of the ectopic beat commenced before the end of the preceding T - wave).

3.6 Signal-Averaged Electrocardiography

Recordings were carried out with a commercially available machine (Arrhythmia Research Technology 1200 EP X high resolution electrocardiogram). This system uses the method described by Simson for the detection of late potentials (Simson, 1981). After preparation of skin with an alcohol swab and careful abrasion, pre-gelled electrodes were applied in the orthogonal lead configuration using the bipolar X,Y,Z leads. The X lead was between the right and left mid axillary lines at the fourth intercostal space. The Y electrodes were placed at the superior aspect of the manubrium and the proximal left leg. The anterior Z electrode was at the V2 position and the other was at the identical position on the posterior chest. Positive electrodes were left, inferior and anterior. Recordings were made while the patient was fully relaxed and lying flat in the supine position. The whole process of signal-averaging of the electrocardiogram took approximately 5 minutes. The electrocardiogram was recorded during basic rhythm and about 300 beats were averaged to achieve a noise level of less than 1.0 uV. The signals were amplified, averaged and filtered with a bidirectional filter at frequencies of 25 to 250 Hz. The filtered leads were then combined into a vector magnitude ($X^2 + Y^2 + Z^2$), a measure that sums the high frequency

information contained in all leads (Simson, 1981). A computer programme algorithm determined the onset and offset of the QRS complex and calculated the total filtered QRS duration, the root mean square voltage of the signals in the last 40 milliseconds of the filtered QRS (RMSV 40) and the duration of low amplitude signals of less than 40 uV (LAS 40).

Signal-averaged electrocardiogram was considered to be abnormal in the presence of 2 or more of the following:-

a) Filtered QRS duration of more than or equal to 120 milli-seconds.

b) Root mean square voltage of the signals in the last 40 milliseconds. (RMSV40) of less than or equal to 25 uV.

c) Low amplitude signals under 40 uV (LAS 40) of more than or equal to 38 milliseconds.

These normal ranges were derived by combining the most discriminatory features from previous studies (Simson, 1981; Winters, Stewart and Gomes, 1987; Turitto et al, 1988; Borbola, Ezri and Denes, 1988; Nalos et al, 1988; Cripps et al, 1988). Recordings with a noise level › 1 uV were rejected. Patients with left bundle branch block on the 12 lead electrocardiogram were excluded from analysis of the filtered QRS duration.

3.7 Autonomic Function Tests

1. Heart-rate response to valsalva manoeuvre

The valsalva manoeuvre was first described by Antonio Valsalva, an Italian surgeon from Bologna, who originally used the technique to help inflate the middle ear. It consists of a forced expiration against resistance. This is accompanied by circulatory responses provided the forced expiration is maintained for at least 7 seconds.

Hamilton, Woodbury and Harper (1936), described the physiological changes and defined the phases of the valsalva manoeuvre:-

Phase 1

Following the onset of straining, there is an initial increase of blood pressure resulting from an increase in the intrathoracic pressure. This results in a reflex fall in the heart rate.

Phase 2

As a result of the continuous strain, there is a progressive fall in blood pressure due to a reduction in the venous return producing a fall in cardiac output. This in turn causes a progressive increase in heart rate.

Phase 3

After release of the strain, there is an initial fall in blood pressure for about 2 - 3 seconds caused by the release of intrathoracic pressure and consequent rise in pulmonary venous capacitance resulting in a momentary fall in cardiac output. This is accompanied by an increase in heart rate.

Phase 4

This is the phase of a rebound hypertension normally referred to as the "overshoot", which is caused by an increase of a raised systemic vascular resistance in response to the baroreflex stimulation produced by the fall in blood pressure during Phase 2. This is accompanied by a marked bradycardia.

In the sitting position, the patient is instructed to blow into a 10 ml syringe connected to a mercury sphygmomanometer and is asked to hold a pressure of 40 mmHg for 15 seconds while a continuous electrocardiogram is recorded. The manoeuvre is performed three times with one minute intervals between.

The result is expressed as a "valsalva ratio" first described by Levin, (1966), which is a ratio of the longest R - R interval after the manoeuvre to the shortest R - R interval during the manoeuvre. In normal subjects, the R - R interval shortens during the strain thus reflecting the tachycardia that occurs and lengthens after

release reflecting the bradycardia resulting in a ratio of greater than 1.00.

The valsalva ratio has been shown to be reproducible in normal subjects and to decline very slightly with age in a number of studies (Levin, 1966; Baldwa and Ewing, 1977; Kalbfleisch, Stowe and Smith, 1978).

2. Heart-rate (R - R interval) variation during deep breathing

In the sitting position, the patient is asked to breathe deeply at 6 breaths a minute, i.e. 5 seconds of deep inspiration followed by 5 seconds of forced expiration. This technique of breathing at 6 beats a minute has been shown by Ewing et al (1981) to be most convenient and reproducible. An electrocardiogram is continuously recorded during the test with a marker used to indicate the onset of each inspiration and expiration. The maximum and minimum R - R interval during each breathing cycle are measured with a ruler and converted to beats per minute. The result is then expressed as the mean of the difference between maximum and minimum heart rates for the 6 cycles in beats per minute.

This technique in measuring heart-rate variation on deep breathing was first performed by Wheeler and Watkins (1973) on diabetics by using an instantaneous rate-meter. They suggested that impaired beat to beat variation in heart rate may be due to loss of cardiac parasympathetic function that is mediated by the vagus nerve. They showed

a diminution in heart rate variation with age and that sympathetic blockade by propranolol did not affect the beat to beat variation in a normal subject, thus lending further support to the suggestion that it is the vagus nerve which is responsible for this physiological effect. The reproducibility of this method was shown by Hilsted and Jensen (1979). In normal subjects the heart rate difference is almost invariably more than 15 beats per minute (MacKay et al, 1980).

3. Immediate heart rate response to standing

This test is performed by asking the subject to lie down for 2 minutes and then stand up unaided and remain standing for about 2 minutes while a continuous electrocardiogram is being recorded. The point at starting to stand is marked on the electrocardiogram. The shortest R - R interval around the 15th beat and the longest R - R interval around the 30th beat after starting to stand are measured using a ruler and the response is expressed by the 30:15 ratio.

A number of cardiovascular reflexes occur on standing up. Blood tends to pool in the legs with a consequent momentary fall in blood pressure. But with normally functioning baroreflexes, this fall in blood pressure is rapidly corrected by peripheral and splanchnic vasoconstriction as well as tachycardia (Ewing, 1978). This reflex tachycardia is maximal at around the 15th beat after standing which is followed by a relative overshoot

bradycardia maximal at around the 30th beat, and normally the 30:15 ratio will be 1.04 or more (Ewing et al, 1978).

4. Blood pressure response to standing

The test is performed by measuring the patient's blood pressure with a sphygmomanometer after 10 minutes of lying down quietly and repeated after a minute of standing up. The postural fall in blood pressure is taken as the difference between the lying and standing systolic pressures. This test can be performed simultaneously with the heart rate response to standing thus making it more convenient for the patient.

3.8 Cardiac Catheterisation

Diagnostic left heart catheterisation and coronary angiography was performed in 89 patients by their respective treating Cardiologists. The films were then reviewed by the author and an independent observer for the assessment of left ventricular function and the presence of coronary artery disease. Significant coronary artery disease was defined as 70% or more reduction in luminal diameter seen in at least one angiographic view. Contrast left ventriculography in a single plane right anterior oblique view (RAO) was utilised for the calculation of ejection fraction (EF). End-systolic and end-diastolic volumes of the left ventricle were calculated by Dodge et al's method (1960) utilising the area length measurements of RAO views. After projecting the ventriculograms frame by frame onto the screen of the Cipro projector, suitable

end-systolic and end-diastolic frames were identified for analysis. Only sinus beats were included taking care to exclude enhanced post-ectopic beats. The end-systolic and end-diastolic outlines of the left ventricle and aortic root were drawn by hand onto tracing paper clipped in position on the projector screen. The longitudinal axis and the surface area of the end-systolic and end-diastolic frames were then measured from the tracings by a Cherry digitising tablet interfaced to a Commodore personal computer for analysis with reference to the external diameter of the catheter that was simultaneously traced during the projection of the film. The short axis was then calculated from the following formula:-

$$D = \frac{4\,A}{3.14\,L}$$

where D is the short axis

A is the surface area

L is the long axis

The volumes of the end-systolic and end-diastolic frames were respectively calculated from the RAO view from the following equation (Rackley, 1976):

$$V = \frac{3.14\,L \cdot D^2 \quad cm^3}{6}$$

where V is the volume

L is the long axis

D is the short axis

The ejection fraction was finally derived by using the following formula:-

$$\text{Ejection fraction (\%)} = \frac{\text{end-diast vol - end-syst vol}}{\text{end-dast vol}} \times 100$$

It is the policy of our catheter laboratory not to try too hard to cross the aortic valve if there was clinical, echocardiographic and Doppler evidence of severe AS. Thus 30 left ventriculograms were performed but only 23 were suitable for assessment of left ventricular function. Coronary angiograms were evaluated from all the 89 patients.

3.9 Statistical Methods

After estimating the distributions by constructing histograms, group values were expressed as means ± one standard deviation or as frequencies. Differences between two groups were examined by paired or unpaired t - test or Mann-Whitney test as appropriate. A chi-square test was performed when comparing proportions. In cases of small numbers where the chi-square test is not valid, Fisher's exact test was performed.

Comparisons between more than two groups were made by either a one-way analysis of variance or Kruskall-Wallis test as appropriate. Correlation between two variables was assessed by Pearson's product moment correlation if the data were normally distributed and Spearman's rank correlation if they were skewed.

Statistical significance was defined as a p-value of less than 0.05.

3.10 Ethical Approval

The study was approved by the ethical committee of the Glasgow Royal Infirmary. Patients provided verbal consent for the investigations, which were all non-invasive.

CHAPTER FOUR

CLINICAL, ECHOCARDIOGRAPHIC AND ANGIOGRAPHIC CHARACTERISTICS OF PATIENTS

4.1 Clinical Particulars

A total of 100 patients with haemodynamically significant aortic valve disease was studied before aortic valve replacement. Their age, weight and body surface area (BSA) distributions are shown in figures 4.1 to 4.3. Fifty-three of the patients were males with an average age of 58 ± 11 years (range 32 - 78 years) and 47 females with an average age of 62 ± 10 years (range 32 - 77 years). The mean age of the whole group was 60 ± 11 years (range 32 - 78 years) (Table 4.1).

Using the criteria defined in Chapter 3, 55 patients were classified as having predominant AS with a mean transvalvular gradient of 81 ± 27 mmHg (range 38 - 178 mmHg), 16 predominant AR and 29 combined AS and AR. Eleven patients had mitral valve disease in addition to the aortic valve lesion. Of these 11 patients, the predominant aortic valve lesion was AS in 4, AR in 3 and combined AS and AR in 4 patients.

The clinical characteristics of patients are outlined in table 4.2. The mean age of the patients with AS was 61 ± 12 years, of those with AR was 58 ± 10 years and of those with combined AS and AR was 60 ± 9 years. These differences in age were insignificant. Diastolic blood pressure was significantly higher in patients with AS than in those with AR (83 ± 11 mmHg Vs 69 ± 18 mmHg; $p<0.03$). Mean systolic blood pressure tended to be lower in AS patients compared to that in AR and combined AS and AR patients, but this did not reach statistical significance.

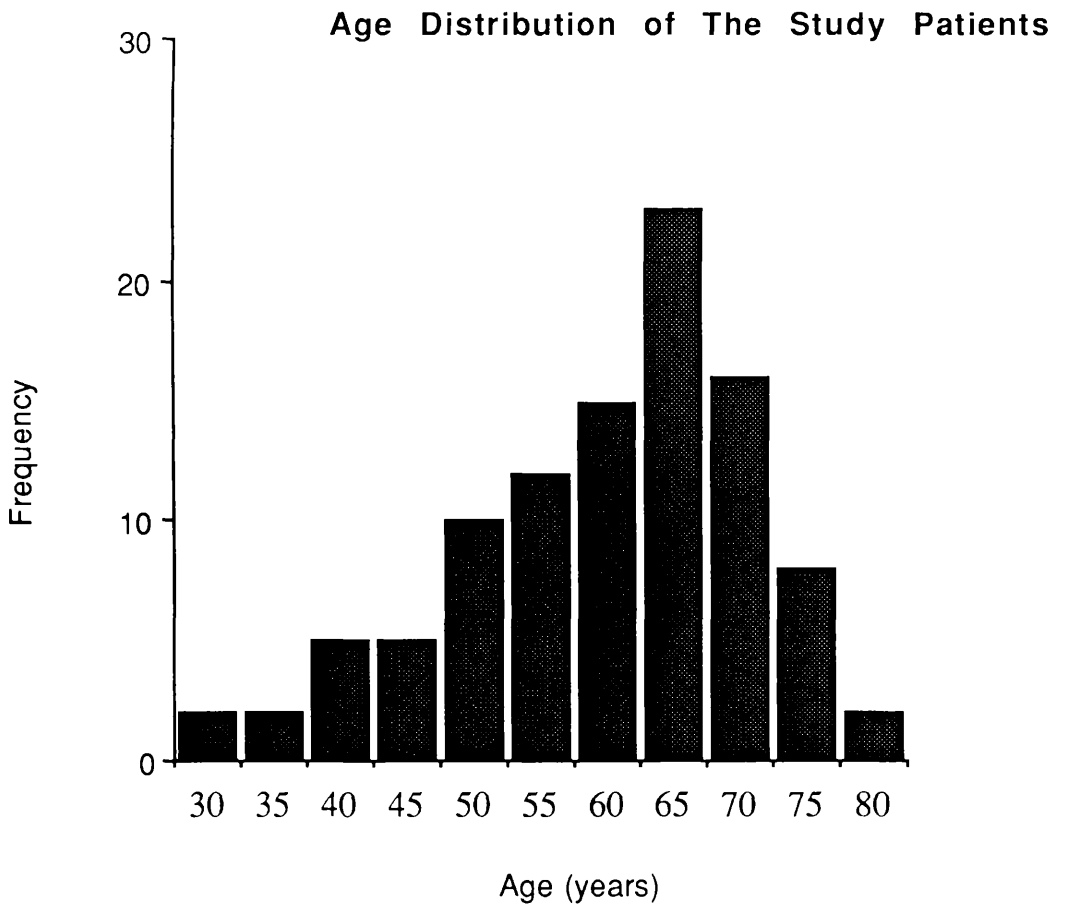

Figure 4.1: Distribution of age (years) in the 100 study patients.

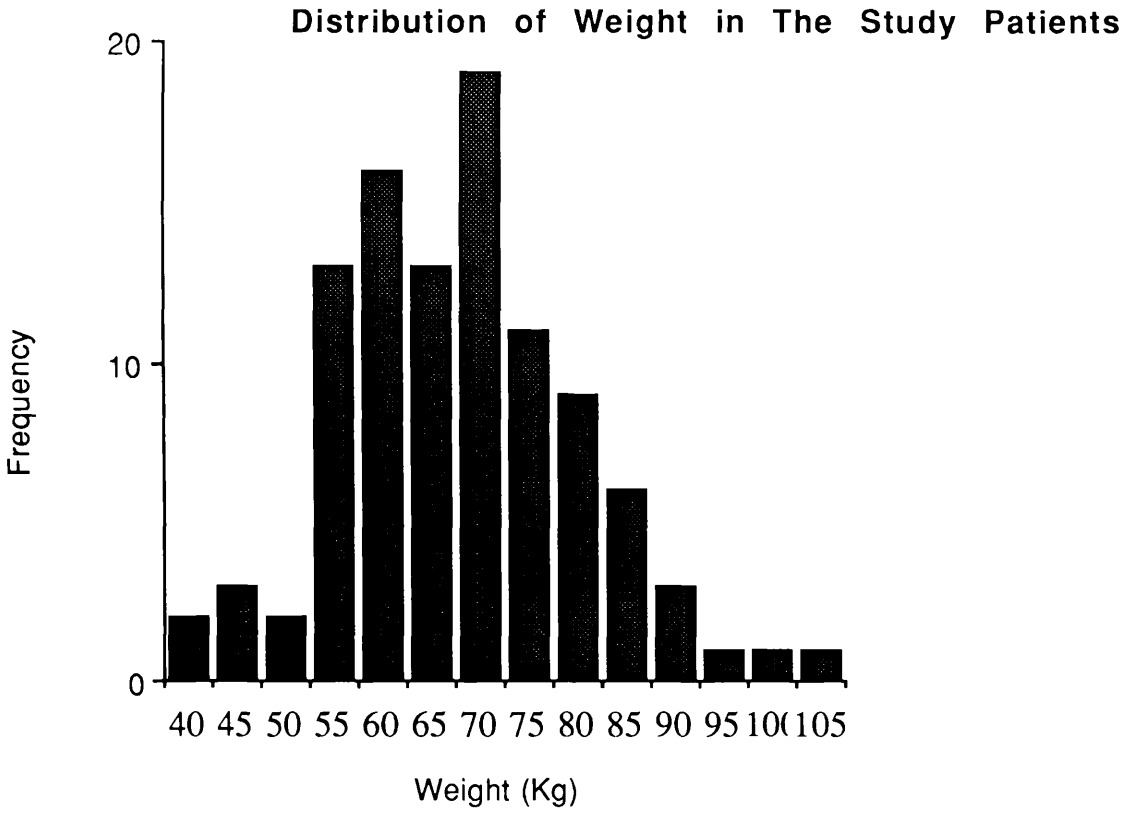

Figure 4.2: Distribution of weight (kg) in the 100 study patients.

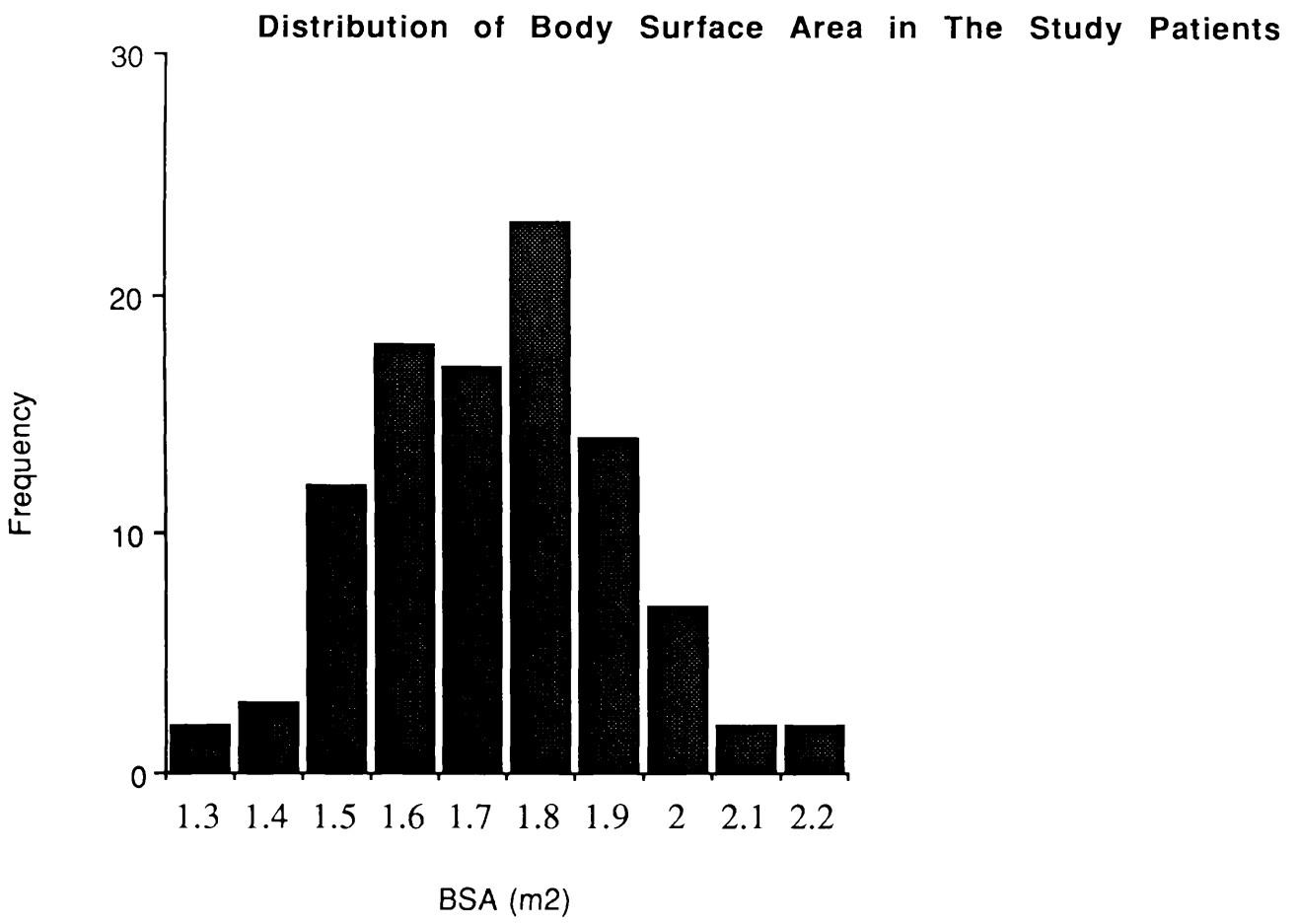

Figure 4.3: Distribution of body surface area derived by using the formula of Dubois and Dubois (1916).

Table 4.1

Characteristics of Study Patients

Characteristics	Men (n=53)	Women (n=47)
Age (yr)	58 ± 11 (32-78)	62 ± 10 (32-77)
Height (m)	1.69 ± 0.06 (1.51-1.81)	1.58 ± 0.06 (1.44-1.75)
Weight (kg)	72.5 ± 11.6 (49.0-103.5)	62.1 ± 11.2 (39.5-89.0)
Body surface area (m^2)	1.82 ± 0.15 (1.52-2.19)	1.62 ± 0.15 (1.31-2.04)

Mean ± SD (range)

Table 4.2

Clinical Characteristics of Patients

	All (n=100)	AS(n=55)	AR (n=16)	AS+AR (n=29)
Age (yr)	60 ± 11 (32-78)	61 ± 12 (32-78)	58 ± 10 (37-73)	60 ± 9 (41-74)
Sex M/F (F%)	53/47 (47)	30/25 (45)	8/8 (50)	15/14 (48)
BSA (m^2)	1.73 ± 0.18	1.74 ± 0.18	1.70 ± 0.20	1.72 ± 0.18
Systolic BP (mmHg)	148 ± 26	142 ± 25	154 ± 24	156 ± 27
Diastolic BP (mmHg)	79 ± 16	83 ± 11*	69 ± 18	77 ± 19
Smoking	39 (39%)	21 (38%)	10 (63%)	8 (28%)
Digoxin	23 (23%)	11 (20%)	6 (38%)	6 (21%)
Diuretics	48 (48%)	24 (44%)	12 (75%)	12 (41%)
Atrial fibrillation	18 (18%)	8 (15%)	4 (25%)	6 (21%)
NYHA I	22 (22%)	13 (24%)	3 (19%)	6 (21%)
II	64 (64%)	33 (60%)	10 (62%)	21 (72%)
III	14 (14%)	9 (16%)	3 (19%)	2 (7%)
Angina	51 (51%)	31 (56%)	8 (50%)	12 (41%)
CAD	21 (21%)	11 (20%)	5 (31%)	5 (17%)
Palpitations	53 (53%)	31 (56%)	11 (69%)	11 (38%)
Syncope	23 (23%)	15 (27%)	3 (19%)	5 (17%)

Mean ± SD
AS = aortic stenosis AR = aortic regurgitation BSA = body surface area
NYHA = New York Heart Association functional Class CAD = coronary artery disease

*$p < 0.03$ difference in diastolic BP between AS and AR

Smoking was more prevalent in AR patients when compared to AS and combined AS and AR patients, but this did not reach statistical significance.

The basic rhythm was sinus in 82 patients and atrial fibrillation (AF) in 18, 11 of whom had concomitant mitral valve disease. Twenty-three patients were on digoxin with no significant differences in the three groups and while diuretics were prescribed to proportionally more patients with AR compared to those with AS or combined AS and AR, but this did not reach statistical significance. As would be expected, the plasma potassium of patients taking diuretics was significantly lower than that of patients not on diuretics (4.11 $\pm$ 0.37 mmols/L Vs 4.26 $\pm$ 0.33 mmols/L; $p < 0.05$).

There were no significant differences noted in the haematological and biochemical parameters between the 3 groups although the total blood cholesterol tended to be higher in patients with AS than in patients with AR or combined AS and AR (Table 4.3).

The functional class of the patients was determined according to the New York Heart Association Classification (1979). Accordingly 22 patients were determined to be in Class I, 64 in Class II, 14 in Class III and none in Class IV (Table 4.4). Patients in NYHA Class III were significantly older than those in Class I (66 $\pm$ 9 years Vs 56 $\pm$ 10 years; $p < 0.03$). There was no significant difference in weight, body surface area (BSA) or systolic

Table 4.3

Blood Results

	All (n=100)	AS (n=55)	AR (n=16)	AS+AR (n=29)
Haemoglobin (g/dl)	13.8 ± 1.6	13.9 ± 1.7	14.1 ± 1.3	13.6 ± 1.5
Haematocrit	0.405 ± 0.05	0.404 ± 0.05	0.421 ± 0.04	0.397 ± 0.04
Potassium (mmol/L)	4.19 ± 0.36	4.15 ± 0.41	4.24 ± 0.32	4.24 ± 0.27
Urea (mmol/L)	6.6 ± 2.1	6.7 ± 2.3	6.8 ± 2.3	6.1 ± 1.7
Creatinine (umol/L)	101 ± 36	103 ± 43	100 ± 27	97 ± 24
Gamma GT (u/L)	40 ± 42	41 ± 46	51 ± 48	34 ± 29
Total Cholesterol (mmol/L)	6.19 ± 1.39	6.40 ± 1.59	5.76 ± 0.96	6.01 ± 1.10

Mean ± SD
AS = aortic stenosis AR = aortic regurgitation

Table 4.4

Distribution of Clinical Characteristics of Patients According to NYHA Functional Class

	NYHA I (n=22)	NYHA II (n=64)	NYHA III (n=14)
Age (yr)	56 ± 10*	60 ± 11	66 ± 9
Weight (kg)	67.6 ± 9.0	69.1 ± 12.4	60.8 ± 15.8
BSA (m^2)	1.75 ± 0.15	1.74 ± 0.17	1.62 ± 0.24
Systolic BP (mmHg)	152 ± 28	147 ± 24	145 ± 34
Diastolic BP (mmHg)	82 ± 15	78 ± 16	78 ± 14

Mean ± SD
BSA = Body surface area
NYHA = New York Heart Association functional Class

* $p < 0.03$ difference in age between NYHA I and NYHA III

and diastolic blood pressure between the 3 functional Classes.

Chest pain typical of angina pectoris, defined as sub-sternal left precordial pain, tightness or discomfort precipitated by effort, emotional stress or exposure to cold and promptly relieved by rest or nitrates, was present in 51 patients, 31 with AS, 8 with AR and 12 with combined AS and AR (Figure 4.4). There was no significant difference in age, weight, BSA, systolic and diastolic blood pressure, total blood cholesterol and smoking status in patients with compared to those without angina pectoris (Table 4.5).

A total of 89 coronary angiograms was available for analysis. Eleven patients did not undergo cardiac catheterisation. In 7 patients, cardiac catheterisation was not indicated due to the presence of mild asymptomatic aortic valve disease. In 3 patients, cardiac catheterisation was not performed due to a variety of reasons including one patient who had other medical conditions that influenced the investigating Cardiologist's decision in not investigating the patient invasively. None of these 3 patients had angina pectoris. The remaining patient who was a 65 year old woman with haemodynamically severe AR and exertional angina, refused to give consent for cardiac catheterisation. Significant coronary artery disease defined as 70% or more reduction in luminal diameter seen in at least one angiographic view was present in 21 of the 89 patients who had undergone cardiac catheterisation; 11 (20%) with AS, 5 (31%) with AR and 5

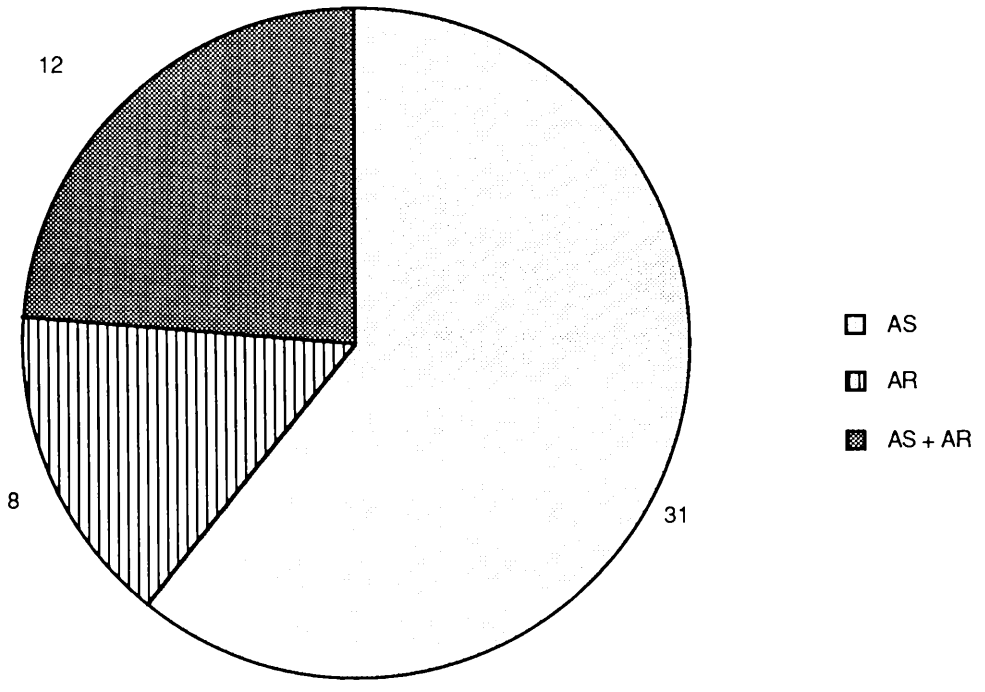

Figure 4.4: **Prevalence of Angina Pectoris According To The Predominant AV Lesion**

Table 4.5

Distribution of Clinical Characteristics of Patients According to Presence or Absence of Angina

	Angina (n=51)	No angina (n=49)
Age (yr)	61 ± 11	59 ± 10
Weight (kg)	68.2 ± 11.8	66.5 ± 13.3
BSA (m^2)	1.72 ± 0.17	1.73 ± 0.19
Systolic BP (mmHg)	146 ± 27	150 ± 26
Diastolic BP (mmHg)	80 ± 13	78 ± 18
Total Cholesterol (mmols/L)	6.37 ± 1.53	5.99 ± 1.19
Smoking n(%)	16 (31)	22 (45)

Mean ± SD

BSA = body surface area

(17%) with combined AS and AR (Table 4.2, Figure 4.5). Of those 21 patients with significant coronary artery disease 9 had one vessel disease, 5 had 2 vessel disease and 7 had 3 vessel disease (Table 4.6). Angina pectoris was present in all but one patient with significant coronary artery disease. There was no significant difference in age, weight, BSA, systolic and diastolic blood pressure, total blood cholesterol and smoking status of patients with compared to those without significant coronary artery disease (Table 4.7).

A total of 53 patients had palpitations; 31 with AS, 11 with AR and 11 with combined AS and AR (Table 4.2). There was no significant difference in age, weight, BSA, systolic and diastolic blood pressure, plasma potassium, total blood cholesterol and haemoglobin of patients with compared to those without palpitations. Coronary artery disease was equally prevalent in the 2 groups. However, angina was significantly more common in patients with palpitations ($p < 0.05$) (Table 4.8).

Syncope occurred in 23 patients; 15 with AS, 3 with AR and 5 with combined AS and AR (Table 4.2). There was no significant difference in the age, weight, BSA, systolic and diastolic blood pressure, plasma potassium and total blood cholesterol of patients with compared to those without a history of syncope. Although angina and coronary artery disease tended to be marginally more prevalent in patients with syncope, these differences failed to attain statistical significance (Table 4.9).

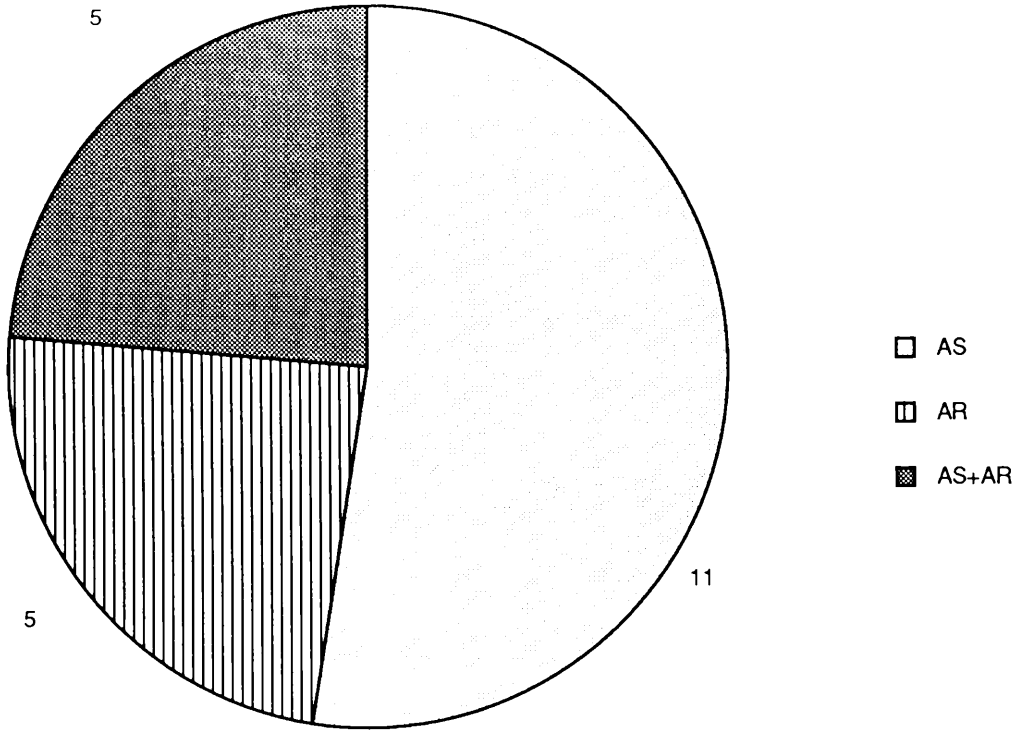

Figure 4.5:

Prevalence of Significant Coronary Artey Disease According To The Predominant AV Lesion

Table 4.6

Distribution of Patients According to the Number of Stenosed Coronary Arteries

	Number of Patients (n=21)	Anatomical Distribution
Single vessel disease	9	7 RCA 2 LAD
Two vessel disease	5	3 LAD + Cx 2 RCA + Cx
Triple vessel disease	7	

RCA = right coronary artery
LAD = left anterior descending coronary artery
Cx = left circumflex coronary artery

Table 4.7

Distribution of Clinical Characteristics of Patients According to the Presence or Absence of Coronary Artery Disease

	CAD (n=21)*	No CAD (n=68)
Age (yr)	63 ± 9	59 ± 11
Weight (kg)	67.9 ± 8.6	67.0 ± 12.7
BSA (m^2)	1.72 ± 0.13	1.72 ± 0.19
Systolic BP (mmHg)	155 ± 26	145 ± 27
Diastolic BP (mmHg)	84 ± 13	79 ± 16
Total Cholesterol (mmols/L)	6.82 ± 1.91	6.11 ± 1.18
Smoking n(%)	7 (33)	25 (37)

Mean ± SD
BSA = body surface area

*CAD is defined as 70% or more reduction in luminal diameter seen in at least one angiographic view

Table 4.8

Distribution of Clinical Characteristics of Patients According to the Presence or Absence of Palpitations

	Palpitations (n=53)	No palpitations (n=47)
Age (yr)	58 ± 11	62 ± 10
Weight (kg)	67.2 ± 12.8	68.1 ± 12.3
BSA (m^2)	1.71 ± 0.17	1.74 ± 0.19
Systolic BP (mmHg)	147 ± 27	149 ± 26
Diastolic BP (mmHg)	78 ± 14	80 ± 17
Potassium (mmols/L)	4.20 ± 0.34	4.18 ± 0.38
Total Cholesterol (mmols/L)	6.12 ± 1.18	6.27 ± 1.60
Haemoglobin (g/dl)	13.6 ± 1.5	14.1 ± 1.6
Angina n(%)	32 (60)~	19 (40)
CAD* n(%)	9 (19)	12 (29)

Mean ± SD
BSA = body surface area

~ $p < 0.05$

* of the 89 patients who had undergone cardiac catheterisation, 48 had palpitations and 41 had no palpitations

Table 4.9

Distribution of Clinical Characteristics of Patients According to the Presence or Absence of Syncope

	Syncope (n=23)	No syncope (n=77)
Age (yr)	62 ± 10	59 ± 11
Weight (kg)	65.3 ± 10.0	68.3 ± 13.1
BSA (m^2)	1.69 ± 0.15	1.74 ± 0.19
Systolic BP (mmHg)	147 ± 31	149 ± 25
Diastolic BP (mmHg)	82 ± 15	78 ± 16
Potassium (mmols/L)	4.17 ± 0.34	4.20 ± 0.36
Total Cholesterol (mmols/L)	6.38 ± 1.26	6.14 ± 1.42
Angina n(%)	16 (70)	35 (45)
CAD* n(%)	6 (29)	15 (22)

Mean ± SD
BSA = body surface area

* of the 89 patients who had undergone cardiac catheterisation, 21 had syncope and 68 had no syncope

4.2 Echocardiography

Ninety-eight of the 100 study patients had technically adequate echocardiograms. The distribution of inter-ventricular septal thickness (IVSTd), left ventricular internal dimension (LVIDd) and posterior left ventricular wall thickness (PWTd) in diastole, as well as left ventricular mass index (LVMI) in the study population, are shown in Figures 4.6 to 4.9. Table 4.10 presents echocardiographic and doppler ultrasound data of patients distributed according to sex and predominant aortic valve lesion. There was no difference between the sexes in echocardiographic and doppler ultrasound variables in patients with predominant AS. However, in patients with predominant AR, significant differences were noted between males and females in LVIDd (7.43 $\pm$ 1.18 cm Vs 5.01 $\pm$ 0.91 cm; $p < 0.001$), LVMI (310 $\pm$ 72 g/m^2 Vs 173 $\pm$ 48 g/m^2; $p < 0.001$), EF (44 $\pm$ 10% Vs 58 $\pm$ 12%; $p < 0.04$), FS (23 $\pm$ 7 Vs 31 $\pm$ 8; $p < 0.05$), aortic gradient (10 $\pm$ 7 mmHg Vs 21 $\pm$ 3 mmHg; $p < 0.004$), PSLVWS by Reichek's method (158 $\pm$ 61 dyn/cm^2 Vs 88 $\pm$ 34 dyn/cm^2; $p < 0.02$) and EDV (325 $\pm$ 47 cm^3 Vs 119 $\pm$ 50 cm^3; $p < 0.0001$) respectively. In patients with combined AS and AR, EDV was the only variable that was significantly larger in males compared to females (186 $\pm$ 58 cm^3 Vs 123 $\pm$ 28 cm^3; $p < 0.002$)

Table 4.11 outlines echocardiographic and doppler ultra-sound results of patients distributed according to the predominant aortic valve lesion. As expected, LVIDd was significantly smaller in AS (5.10 $\pm$ 0.82 cm) than in AR (6.22 $\pm$ 1.61 cm; $p < 0.03$) and combined AS and AR patients

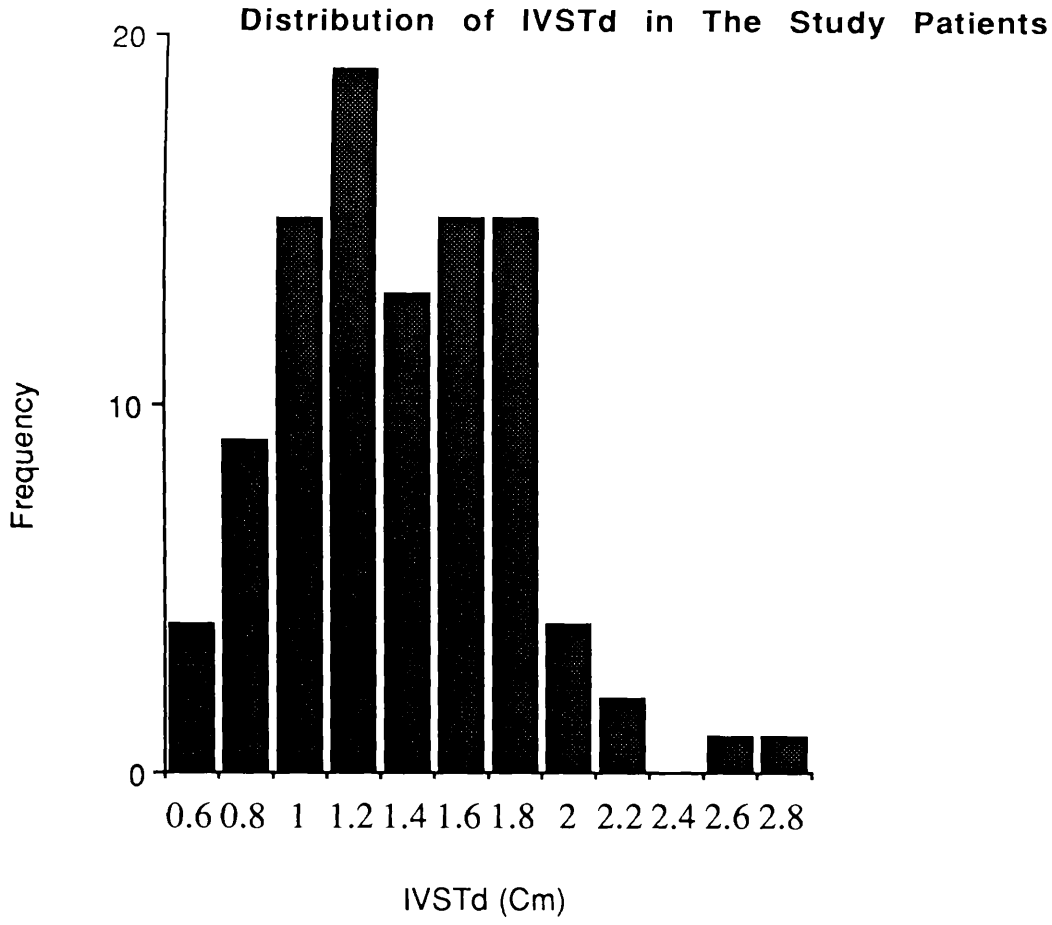

Figure 4.6: Distribution of IVSTd (cm) measured according to the Penn Convention in 98 patients with adequate echocardiograms.

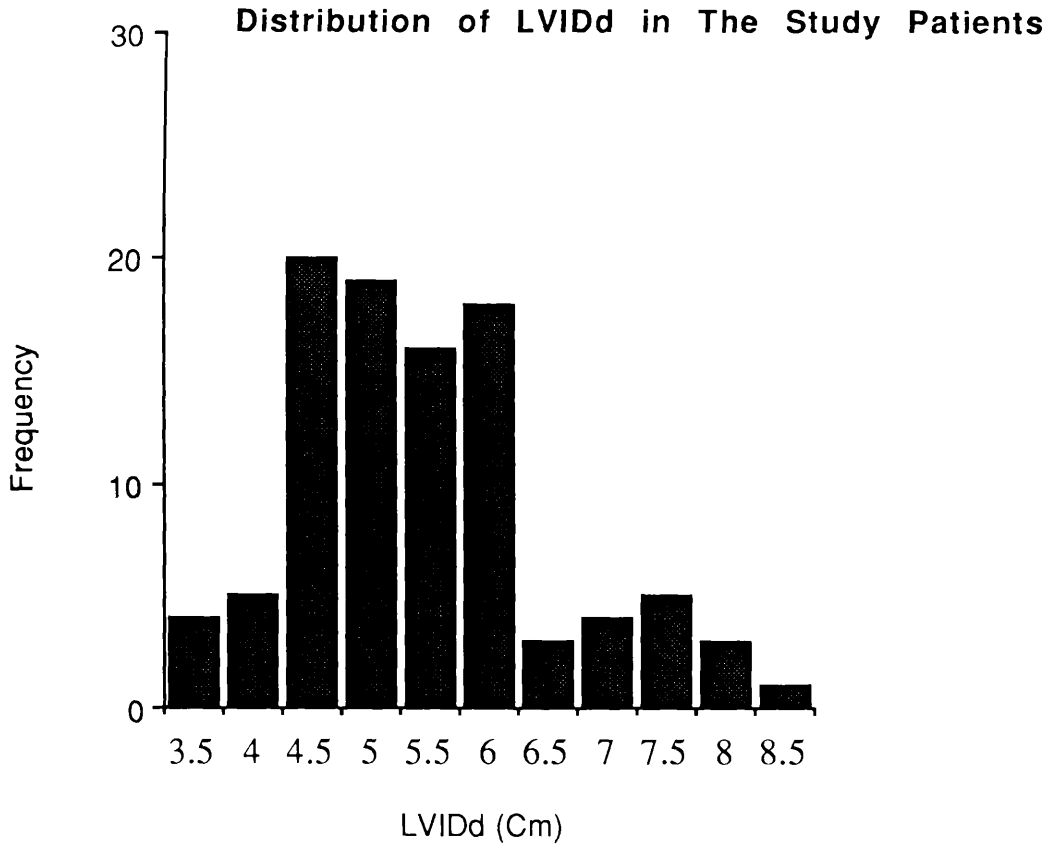

Figure 4.7: Distribution of LVIDd (cm) measured according to the Penn Convention in 98 patients with adequate echocardiograms.

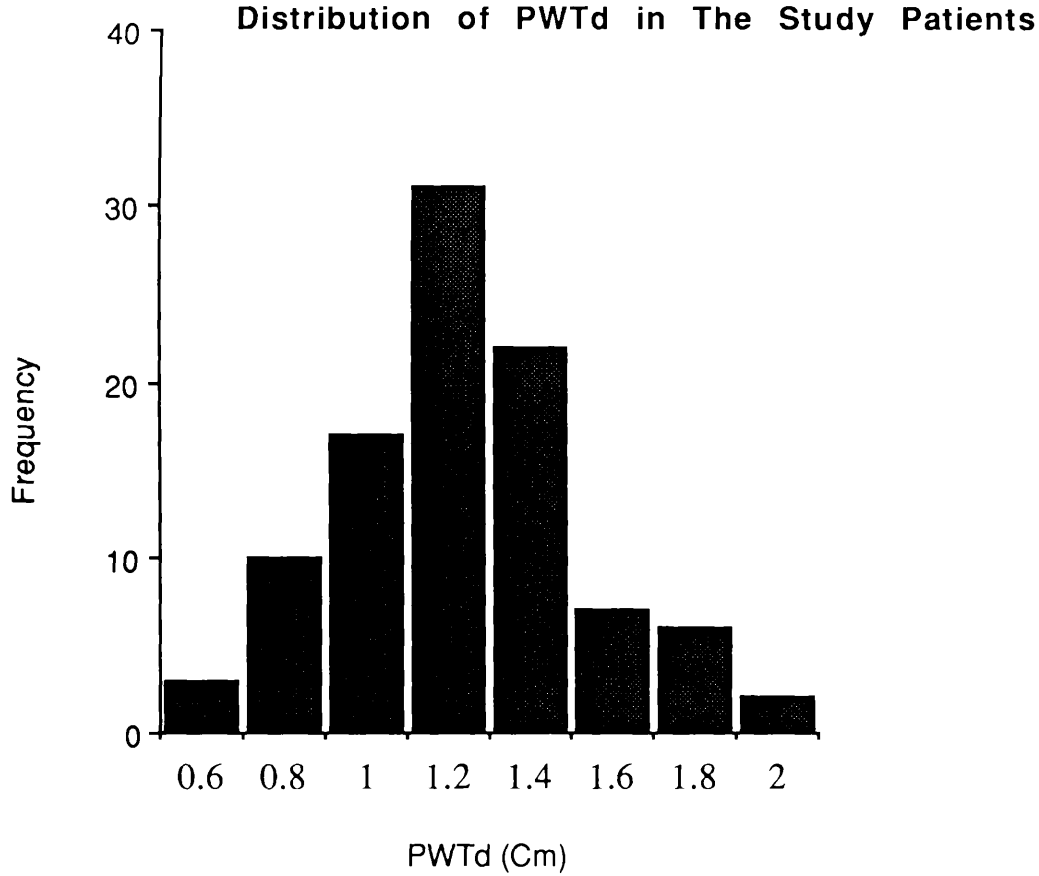

Figure 4.8: Distribution of PWTd (cm) measured according to the Penn Convention in 98 patients with adequate echocardiograms.

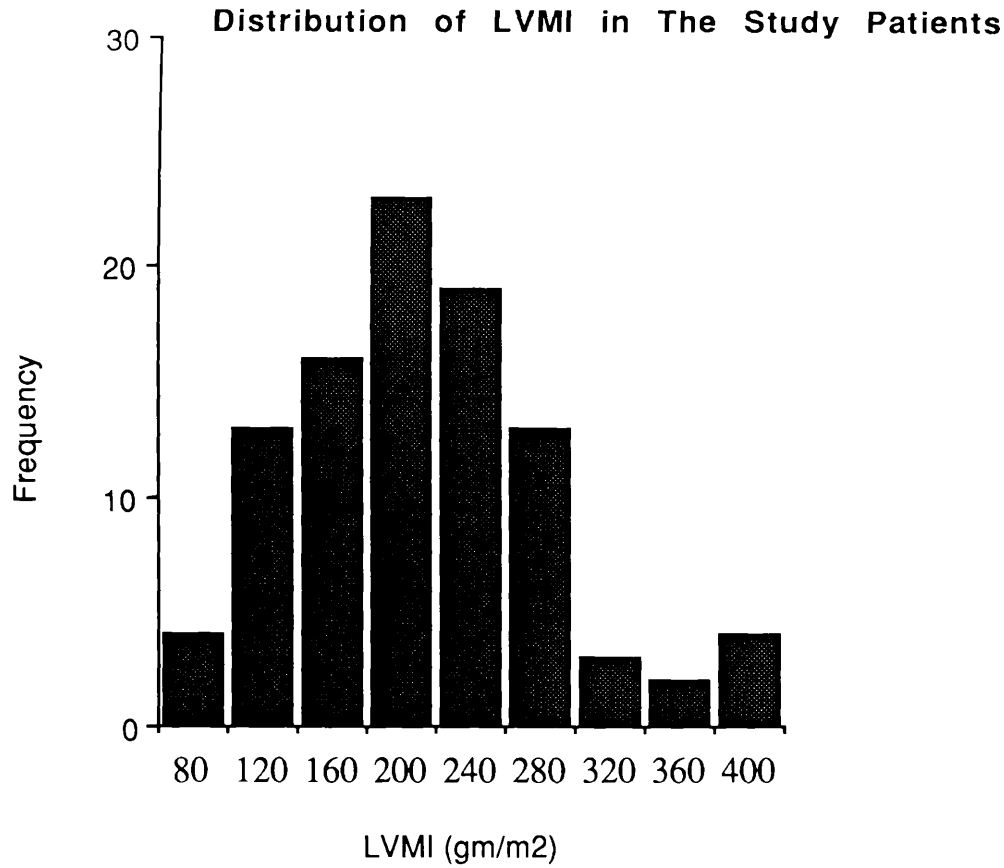

Figure 4.9: Distribution of LVMI (gm/m^2) calculated according to the Penn Convention in 98 patients with adequate echocardiograms.

Table 4.10

Echocardiographic Data of Patients According to Sex (n=98)

	AS (n=53)		AR (n=16)		AS + AR (n=29)	
	Male (n=31)	Female (n=22)	Male (n=6)	Female (n=10)	Male (n=15)	Female(n=14)
LVIDd (cm)	5.16 ± 0.78	5.02 ± 0.88	7.43 ± 1.18*	5.01 ± 0.91	5.99 ± 0.82	5.23 ± 0.83
PWTd (cm)	1.28 ± 0.35	1.14 ± 0.31	1.29 ± 0.31	1.22 ± 0.13	1.25 ± 0.28	1.23 ± 0.27
IVSTd (cm)	1.44 ± 0.43	1.32 ± 0.41	1.16 ± 0.18	1.14 ± 0.39	1.51 ± 0.55	1.33 ± 0.40
LVMI (g/m^2)	196 ± 53	183 ± 75	310 ± 72**	173 ± 48	250 ± 53	208 ± 71
LA (cm)	3.74 ± 0.73	4.00 ± 1.25	4.26 ± 0.45	4.31 ± 1.35	4.03 ± 1.19	4.17 ± 1.07
EF (%)	64 ± 16	62 ± 13	44 ± 10***	58 ± 12	57 ± 17	65 ± 11
FS	34 ± 12	33 ± 9	23 ± 7+	31 ± 8	29 ± 11	34 ± 7
Aortic Gradient (mmHg)	79 ± 29	83 ± 25	10 ± 7++	21 ± 3	70 ± 33	76 ± 22
LVSP (mmHg)	218 ± 34	230 ± 34	158 ± 19	179 ± 22	222 ± 40	236 ± 38
PSLVWS (dyn/cm^2) Reichek's method Quinones' method	 99 ± 73 211 ± 90	 111 ± 50 237 ± 85	 158 ± 61+++ 291 ± 82	 88 ± 34 209 ± 76	 143 ± 109 293 ± 160	 107 ± 37 234 ± 65
EDV (cm^3)	132 ± 46	123 ± 51	325 ± 47^	119 ± 50	186 ± 58^^	123 ± 28
E/A ratio	1.02 ± 0.39	1.01 ± 0.46	1.24 ± 0.52	0.87 ± 0.31	1.03 ± 0.27	1.03 ± 0.61

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

*	p <0.001	difference in LVIDd between males and females with AR.
**	p <0.001	difference in LVMI between males and females with AR.
***	p <0.04	difference in EF between males and females with AR.
+	p <0.05	difference in FS between males and females with AR.
++	p <0.004	difference in aortic gradient between males and females with AR.
+++	p <0.02	difference in PSLVWS (Reichek's method) between males and females with AR.
^	p <0.0001	difference in EDV between males and females with AR.
^^	p <0.002	difference in EDV between males and females with AS + AR.

Table 4.11

Echocardiographic Data of Patients According to the Aortic Valve Lesion Type

	All (n=98)	AS (n=53)	AR (n=16)	AS+AR(n=29)
LVIDd (cm)	5.44 ± 1.08	5.10 ± 0.82***	6.22 ± 1.61	5.63 ± 0.90
PWTd (cm)	1.23 ± 0.30	1.21 ± 0.34	1.25 ± 0.23	1.24 ± 0.27
IVSTd (cm)	1.36 ± 0.43	1.39 ± 0.42***	1.15 ± 0.29	1.42 ± 0.48
LVMI (g/m^2)	210 ± 72	190 ± 64^	242 ± 92	230 ± 65
LA (cm)	4.00 ± 1.03	3.86 ± 0.99	4.28 ± 0.97	4.10 ± 1.12
EF (%)	60 ± 15	63 ± 14^^	51 ± 13	61 ± 15
FS	32 ± 10	33 ± 10+	27 ± 8	32 ± 10
Aortic Gradient (mmHg)	68 ± 34	81 ± 27++	15 ± 8+++	73 ± 28
LVSP (mmHg)	216 ± 40	223 ± 34~	169 ± 23!	229 ± 39
PSLVWS (dyn/cm^2) Reichek's method	114 ± 70	104 ± 64	123 ± 60	126 ± 83
Quinones' method	240 ± 101	223 ± 88	250 ± 87	264 ± 125
EDV (cm^3)	151 ± 72	128 ± 48x	222 ± 117	156 ± 56
E (cm/s)	96 ± 40	90 ± 41	114 ± 38	98 ± 36
A (cm/s)	88 ± 30	82 ± 25	94 ± 27	97 ± 38
E/A ratio	1.03 ± 0.43	1.01 ± 0.41	1.09 ± 0.47	1.03 ± 0.45

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

*	p <0.03 difference in LVIDd between AS and AR.
**	p <0.03 difference in LVIDd between AS and AS + AR.
***	p <0.03 difference in IVSTd between AS and AR.
^	p <0.03 difference in LVMI between AS and AS + AR.
^^	p <0.03 difference in EF between AS and AR.
+	p <0.05 difference in FS between AS and AR.
++	p <0.03 difference in aortic gradient between AS and AR.
+++	p <0.03 difference in aortic gradient between AR and AS + AR.
~	p <0.03 difference in LVSP between AS and AR.
!	p <0.03 difference in LVSP between AR and AS + AR.
x	p <0.03 difference in EDV between AS and AR.

(5.63 ± 0.90 cm; p ‹0.03), while IVSTd was significantly thicker in AS (1.39 ± 0.42 cm) than in AR patients (1.15 ± 0.29 cm; p ‹0.03). Combined AS and AR patients also had thicker IVSTd (1.42 ± 0.48 cm) when compared to AR patients but this did not attain statistical significance. Left ventricular mass index was significantly lower in AS patients (190 ± 64 g/m^2) than in combined AS and AR patients (230 ± 65 g/m^2; p ‹0.03) but insignificantly so when compared to LVMI of patients with AR. Ejection fraction was significantly higher in patients with AS when compared to that of patients with AR (63 ± 14% Vs 51 ± 13%; p ‹0.03). The same was true when comparing FS of patients with AS to that of patients with AR (33 ± 10 Vs 27 ± 8; p ‹ 0.05). As expected peak systolic aortic gradient and hence left ventricular systolic pressure (LVSP) of patients with AR was significantly lower than that of patients with AS and combined AS and AR (p ‹0.03). On the other hand, the EDV of patients with AR was significantly larger (222 ± 117 cm^3) than that of patients with AS (128 ± 48 cm^3; p ‹0.03) and insignificantly so when compared to that of patients with combined AS and AR. The peak systolic left ventricular wall stress (PSLVWS) tended to be lower in AS patients compared to that in the other 2 groups by using Reichek's and Quinones' methods. However, these differences did not attain statistical significance. There were no significant differences in the E velocity, A velocity and E/A ratio between the 3 groups.

Table 4.12 presents echocardiographic and doppler ultrasound data of patients distributed according to the

Table 4.12

Distribution of Echocardiographic Data of Patients According to the Presence or Absence of Angina (n=98)

	AS (n=53)		AR (n=16)		AS + AR (n=29)	
	Angina (n=29)	No angina (n=24)	Angina (n=8)	No angina (n=8)	Angina (n=12)	No angina (n=17)
LVIDd (cm)	5.19 ± 0.85	4.99 ± 0.79	5.56 ± 1.77	6.88 ± 1.19	5.32 ± 0.62	5.84 ± 1.01
PWTd (cm)	1.17 ± 0.29	1.27 ± 0.38	1.32 ± 0.16	1.19 ± 0.28	1.29 ± 0.18	1.20 ± 0.32
IVSTd (cm)	1.30 ± 0.37	1.48 ± 0.46	1.24 ± 0.38	1.06 ± 0.14	1.41 ± 0.45	1.43 ± 0.52
LVMI (g/m^2)	186 ± 64	194 ± 64	217 ± 103	267 ± 78	214 ± 61	241 ± 66
LA (cm)	3.62 ± 0.69	4.13 ± 1.22	3.99 ± 0.56	4.58 ± 1.22	3.94 ± 1.16	4.21 ± 1.11
EF (%)	64 ± 16	62 ± 13	53 ± 13	49 ± 14	66 ± 13	57 ± 15
FS	34 ± 11	33 ± 10	27 ± 9	26 ± 8	36 ± 8*	28 ± 9
Aortic Gradient (mmHg)	82 ± 21	79 ± 34	16 ± 8	14 ± 7	79 ± 31	68 ± 26
LVSP (mmHg)	224 ± 35	222 ± 34	169 ± 21	168 ± 25	231 ± 38	227 ± 41
PSLVWS (dyn/cm^2) Reichek's method Quinones' method	 109 ± 73 228 ± 89	 99 ± 52 217 ± 88	 90 ± 37** 209 ± 79	 156 ± 63 290 ± 80	 97 ± 31 218 ± 64	 146 ± 102 298 ± 147
EDV (cm^3)	135 ± 53	121 ± 43	179 ± 132	265 ± 88	139 ± 38	169 ± 65
E/A ratio	0.94 ± 0.40	1.11 ± 0.42	1.15 ± 0.53	0.95 ± 0.34	1.15 ± 0.57	0.94 ± 0.34

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* $p < 0.03$ difference in FS between angina and no angina groups in patients with AS + AR.
** $p < 0.03$ difference in PSLVWS (Reichek's method) between angina and no angina groups in patients with AR.

prevalence of angina and predominant aortic valve lesion. In patients with combined AS and AR fractional shortening was the only variable that was significantly better in patients with compared to that of patients without angina pectoris (36 ± 8 Vs 28 ± 9; p ‹0.03). In patients with predominant AR, PSLVWS by Reichek's method was significantly lower in patients with compared to that of patients without angina pectoris (90 ± 37 dyn/cm^2 Vs 156 ± 63 dyn/cm^2; p ‹0.03).

Echocardiographic and doppler ultrasound data distributed according to the prevalence of coronary artery disease and predominant aortic valve lesion are shown in table 4.13. In patients with predominant AS, the aortic gradient was significantly lower in patients with compared to that of patients without coronary artery disease (71 ± 16 mmHg Vs 86 ± 29 mmHg; p ‹0.05). In patients with predominant AR, LVIDd, LVMI, PSLVWS, by both Reichek's and Quinones' methods and EDV were significantly better in patients with coronary artery disease. There were no differences in echocardiographic and doppler variables between the 2 groups in patients with combined AS and AR.

Table 4.14 outlines echocardiographic and doppler ultrasound data distributed according to the predominant aortic valve lesion and to the presence or absence of palpitations. Posterior left ventricular wall thickness in diastole was significantly thinner in patients with compared to that of patients without palpitations (1.16 ± 0.18 cm Vs 1.45 ± 0.22 cm; p ‹0.05) and LVSP was significantly lower in patients with compared to that of

Table 4.13

Distribution of Echocardiographic Data of Patients According to the Presence or Absence of Coronary Artery Disease (n=89)

	AS (n=48)		AR (n=14)		AS + AR (n=27)	
	CAD (n=11)	No CAD (n=37)	CAD (n=5)	No CAD (n=9)	CAD (n=5)	No CAD (n=22)
LVIDd (cm)	5.27 ± 1.04	4.95 ± 0.75	4.31 ± 0.52*	6.78 ± 1.42	5.48 ± 1.21	5.63 ± 0.84
PWTd (cm)	1.22 ± 0.38	1.23 ± 0.34	1.30 ± 0.21	1.23 ± 0.26	1.34 ± 0.24	1.22 ± 0.29
IVSTd (cm)	1.43 ± 0.33	1.39 ± 0.44	1.45 ± 0.35	1.08 ± 0.16	1.39 ± 0.49	1.43 ± 0.51
LVMI (g/m^2)	204 ± 80	185 ± 57	163 ± 51**	269 ± 96	227 ± 63	229 ± 68
LA (cm)	4.08 ± 0.67	3.59 ± 0.81	4.13 ± 0.65	4.47 ± 1.21	4.90 ± 1.25	3.83 ± 0.99
EF (%)	65 ± 18	63 ± 13	50 ± 10	52 ± 16	68 ± 12	59 ± 16
FS	35 ± 12	33 ± 10	23 ± 8	28 ± 10	32 ± 14	31 ± 9
Aortic Gradient (mmHg)	71 ± 16+++	86 ± 29	19 ± 2	14 ± 9	85 ± 51	72 ± 21
LVSP (mmHg)	222 ± 34	225 ± 35	183 ± 17	166 ± 25	245 ± 58	224 ± 35
PSLVWS (dyn/cm^2) Reichek's method Quinones' method	 117 ± 105 234 ± 116	 99 ± 52 209 ± 74	 75 ± 17*** 177 ± 46+	 139 ± 71 264 ± 94	 115 ± 61 265 ± 121	 128 ± 92 263 ± 134
EDV (cm^3)	140 ± 65	120 ± 43	77 ± 21++	259 ± 107	154 ± 82	153 ± 49
E/A ratio	1.00 ± 0.31	1.00 ± 0.45	0.79 ± 0.14	1.24 ± 0.63	1.39 ± 0.99	0.99 ± 0.34

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

*	p <0.002	difference in LVIDd between CAD and no CAD groups in patients with AR.
**	p <0.03	difference in LVMI between CAD and no CAD groups in patients with AR.
***	p <0.04	difference in PSLVWS (Reichek's method) between CAD and no CAD groups in patients with AR.
+	p <0.05	difference in PSLVWS (Quinones' method) between CAD and no CAD groups in patients with AR.
++	p <0.002	difference in EDV between CAD and no CAD groups in patients with AR.
+++	p <0.05	difference in aortic gradient between CAD and no CAD groups in patients with AS.

Table 4.14

Distribution of Echocardiographic Data of Patients According to the Presence or Absence of Palpitations (n=98)

	AS (n=53)		AR (n=16)		AS + AR (n=29)	
	Palpitations (n=31)	No palpitations (n=22)	Palpitations (n=11)	No palpitations (n=5)	Palpitations (n=11)	No palpitations (n=18)
LVIDd (cm)	5.14 ± 0.81	5.04 ± 0.85	6.61 ± 1.55	5.35 ± 1.54	5.34 ± 0.91	5.80 ± 0.87
PWTd (cm)	1.23 ± 0.37	1.20 ± 0.29	1.16 ± 0.18*	1.45 ± 0.22	1.18 ± 0.28	1.27 ± 0.27
IVSTd (cm)	1.34 ± 0.38	1.45 ± 0.48	1.10 ± 0.25	1.25 ± 0.38	1.64 ± 0.56	1.29 ± 0.39
LVMI (g/m^2)	188 ± 57	192 ± 74	248 ± 96	227 ± 91	229 ± 59	230 ± 70
LA (cm)	3.70 ± 0.90	4.07 ± 1.09	3.89 ± 0.42	5.14 ± 1.33	4.55 ± 1.41	3.82 ± 0.81
EF (%)	62 ± 14	64 ± 15	51 ± 14	51 ± 11	58 ± 19	62 ± 12
FS	33 ± 11	34 ± 10	27 ± 9	25 ± 6	31 ± 11	32 ± 9
Aortic Gradient (mmHg)	80 ± 24	82 ± 32	15 ± 8	15 ± 8	69 ± 19	75 ± 33
LVSP (mmHg)	225 ± 35	221 ± 35	160 ± 20**	189 ± 14	225 ± 32	231 ± 44
PSLVWS (dyn/cm^2) Reichek's method Quinones' method	 106 ± 72 224 ± 86	 101 ± 53 221 ± 92	 131 ± 66 262 ± 97	 106 ± 46 223 ± 61	 130 ± 98 254 ± 126	 124 ± 75 271 ± 127
EDV (cm^3)	131 ± 49	124 ± 48	236 ± 113	169 ± 140	142 ± 60	164 ± 53
E/A ratio	1.02 ± 0.48	1.01 ± 0.30	1.20 ± 0.52	0.83 ± 0.12	1.15 ± 0.28	0.98 ± 0.50

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* $p < 0.05$ difference in PWTd between palpitations and no palpitations groups in patients with AR.

** $p < 0.006$ difference in LVSP between palpitations and no palpitations groups in patients with AR.

patients without palpitations in the subgroup of patients with predominant AR (160 ± 20 mmHg Vs 189 ± 14 mmHg; p <0.006). There were no differences noted in echocardiographic and doppler ultrasound variables between patients with and those without palpitations in the subgroups with predominant AS and combined AS and AR.

Table 4.15 presents echocardiographic and doppler ultrasound data according to the predominant aortic valve lesion and prevalence of syncope. In patients with combined AS and AR, EF, FS and LVSP were significantly higher and PSLVWS by Reichek's method was significantly lower in those with syncope. There were no differences noted in echocardiographic and doppler ultrasound variables between patients with and without syncope in the subgroups with predominant AS and predominant AR.

4.3 Extent of Left Ventricular Hypertrophy

Left ventricular dimensions and in particular left ventricular mass (LVM) has been shown to be related significantly to body surface area and that when LVM is corrected for body surface area, the resultant left ventricular mass index (LVMI) has been shown to be 20% less in women than in men (Devereux et al, 1984). These workers have also shown that the range of variability in LVM in normal individuals can be greatly narrowed by indexation of the LVM and this results in clinically useful criteria of left ventricular hypertrophy (LVH). Thus LVH according to their well validated criteria which roughly corresponds to the 97th percentile in their normal

Table 4.15

Distribution of Echocardiographic Data of Patients According to the Presence or Absence of Syncope (n=98)

	AS (n=53)		AR (n=16)		AS + AR (n=29)	
	Syncope (n=15)	No syncope (n=38)	Syncope (n=3)	No syncope (n=13)	Syncope (n=5)	No syncope (n=24)
LVIDd (cm)	4.99 ± 0.75	5.14 ± 0.85	6.62 ± 2.67	6.13 ± 1.42	5.24 ± 0.64	5.71 ± 0.93
PWTd (cm)	1.12 ± 0.35	1.25 ± 0.33	1.41 ± 0.30	1.22 ± 0.21	1.32 ± 0.24	1.22 ± 0.28
IVSTd (cm)	1.33 ± 0.36	1.41 ± 0.44	1.34 ± 0.37	1.10 ± 0.27	1.36 ± 0.44	1.43 ± 0.50
LVMI (g/m^2)	174 ± 56	196 ± 66	307 ± 129	227 ± 80	209 ± 77	234 ± 63
LA (cm)	3.59 ± 0.66	3.97 ± 1.09	4.07 ± 0.78	4.33 ± 1.03	4.73 ± 1.36	3.97 ± 1.04
EF (%)	64 ± 14	62 ± 15	50 ± 7	51 ± 14	72 ± 7*	58 ± 15
FS	36 ± 11	32 ± 10	26 ± 6	27 ± 9	38 ± 4**	30 ± 10
Aortic Gradient (mmHg)	91 ± 35	77 ± 23	10 ± 9	16 ± 7	101 ± 45	67 ± 20
LVSP (mmHg)	228 ± 35	222 ± 35	182 ± 28	166 ± 21	264 ± 32+	221 ± 37
PSLVWS (dyn/cm^2) Reichek's method Quinones' method	 100 ± 48 214 ± 79	 106 ± 70 226 ± 92	 119 ± 58 224 ± 82	 124 ± 63 256 ± 91	 90 ± 22++ 231 ± 46	 133 ± 89 271 ± 135
EDV (cm^3)	119 ± 38	132 ± 52	251 ± 173	214 ± 107	134 ± 37	161 ± 59
E/A ratio	0.91 ± 0.28	1.06 ± 0.45	0.76 ± 0.05	1.17 ± 0.49	0.68 ± 0.27	1.08 ± 0.45

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. EDV = end diastolic volume. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* p <0.01 difference in EF between syncope and no syncope groups in patients with AS + AR.
** p <0.01 difference in FS between syncope and no syncope groups in patients with AS + AR.
\+ p <0.04 difference in LVSP between syncope and no syncope groups in patients with AS + AR.
++ p <0.05 difference in PSLVWS (Reichek's method) between syncope and no syncope groups in patients with AS + AR.

subjects, was defined as a LVMI greater than 134 g/m^2 in men and 110 g/m^2 in women.

In the present study 98 of the 100 patients had technically adequate echocardiograms and LVMI was normal in only 4 males (‹134 g/m^2) and 5 females (‹110 g/m^2). Substantial LVH was present with a mean LVMI of the study patients of 210 ± 72 g/m^2 (range 63 - 403). Left ventricular mass index was higher in AR patients (242 ± 92 g/m^2) and significantly so in combined AS and AR patients (230 ± 65 g/m^2; p ‹0.03) when compared to that in AS patients (190 ± 64 g/m^2) (Table 4.11). In agreement with Devereux et al's observations, the mean LVMI in females (189 ± 69 g/m^2)was approximately 17% less than that in males (229 ± 69 g/m^2). Also in keeping with these workers findings, LVM showed a direct relationship with body surface area (r = 0.47, p ‹0.002). There was no relationship observed between LVMI and age (r = 0.16, p ‹0.2), FS (r = $^{-}$0.11, p ‹0.2), EF (r = $^{-}$0.16, p ‹0.2), E/A ratio (r = 0.08, p ‹0.2), peak systolic left ventricular wall stress as determined by Reichek (r = 0.02, p ‹0.2) and Quinones' methods (r = 0.03, p ‹0.2); and peak aortic systolic gradient (r = 0.10, p‹0.2) and peak left ventricular systolic pressure (r = 0.20, p ‹0.1) in the patients with predominant aortic stenosis. On the other hand, a direct relationship existed between LVMI and left ventricular internal dimension in diastole (r = 0.53, p ‹ 0.002) and left ventricular end diastolic volume (r = 0.51, p ‹0.002).

In summary, the present study has shown a high prevalence

(91%) of echocardiographic left ventricular hypertrophy in patients with aortic valve disease, normal LVMI being seen in only 9 of the 98 patients with technically adequate echocardiograms. Left ventricular mass index was significantly higher in patients with predominant aortic regurgitation and this is probably due to a preponderance of these patients having more dilated left ventricles due to volume overload and consequently larger left ventricular end-diastolic volumes. This is suggested by the presence of a direct relationship between LVMI and left ventricular internal dimension during diastole as well as to left ventricular end diastolic volume. Most interestingly and contrary to expectation is the lack of a relationship between LVMI and the severity of aortic stenosis as assessed by the pressure gradient across the aortic valve. This would suggest that factors other than pressure overload of the left ventricle secondary to outlet obstruction play a role in the aetiology of left ventricular hypertrophy in this group of patients. Alternatively, it may be that a single measurement of pressure gradient at one point in time is an inadequate index of long-term left ventricular pressure overload.

This finding of substantial echocardiographic left ventricular hypertrophy in our study patients has important prognostic implications. In a follow up study of 3200 subjects in the Framingham Heart Study, an increase in left ventricular mass was associated with a higher incidence of clinical events including cardio-vascular deaths (Levy et al, 1990).

4.4 Left Ventricular Function

Left ventricular systolic function was assessed by echocardiographic EF in 97 patients and by echocardiographic FS in 98 patients. In 23 patients with suitable left ventriculograms, EF was calculated by using a well established method (see Chapter 3). Left ventricular function was considered to be impaired when the EF was less than 40% and severely impaired when EF was less than 30%. Corresponding figures for FS were 25 and 20 respectively. Left ventricular diastolic function was assessed in 79 patients by the doppler derived E/A ratio which is the ratio between early (E) and late (A) left ventricular diastolic filling velocities. An E/A ratio of less than 0.85 was considered to indicate abnormal left ventricular diastolic function. This figure was derived by considering the normal range as lying within two standard deviations from the mean of recordings in 90 normal subjects studied in our institution (0.85 - 1.65).

Thus using the above criteria 91 of the 97 patients studied (94%) had normal left ventricular systolic function by EF, while 6 (6%) had impaired systolic function of whom only 1 (1%) had severely impaired function (EF $<30\%$) (Table 4.16). The mean EF of the entire study group was 60 $\pm$ 15%. Aortic regurgitation patients had lower EF (51 $\pm$ 13%) than those of patients with combined AS and AR (61 $\pm$ 15%) but significantly so than those of patients with predominant AS (63 $\pm$ 14%; $p < 0.03$) (Table 4.11). Systolic function as assessed by FS was impaired in 27 (28%) patients and severely impaired in

Table 4.16

Left Ventricular Systolic and Diastolic Dysfunction in the Study Patients

	No. of patients with abnormal results	Total number studied	% abnormal
EF <40%	6	97	6
EF <30%	1	97	1
FS <25	27	98	28
FS <20	9	98	9
E/A ratio <0.85	31	79	39

EF = ejection fraction
FS = fractional shortening.
E/A = the ratio between early (E) and late (A) left ventricular diastolic filling velocity

9 (9%) patients. Fractional shortening of the whole group was 32 ± 10. As with EF, FS was significantly lower in patients with AR (27 ± 8) when compared to that of patients with AS (33 ± 10; $p < 0.05$) but insignificantly so when compared to that of patients with combined AS and AR (32 ± 10; $p < 0.1$) (Table 4.11).

Left ventricular diastolic function was abnormal (E/A ratio <0.85) in 31 (39%) of a total of 79 patients with technically adequate doppler studies. Figure 4.10 illustrates an abnormal mitral flow pattern showing a reversal of E/A ratio. The mean E/A ratio of the study group was 1.03 ± 0.43 with no differences noted between the 3 sub-groups (Table 4.11).

Impairment in both systolic (EF <40%) and diastolic (E/A ratio <0.85) function was seen in only 2 patients.

The mean EF of the 23 patients with technically adequate left ventriculograms was 65 ± 14%.

Impaired systolic function was present in only one (EF = 35%) of the 23 patients. This patient also had a marked impairment in systolic function as assessed by echocardiographic EF (32%) and FS (16).

4.5 Angina Pectoris and Coronary Artery Disease in Patients with Aortic Valve Disease

With the longer survival of the population, the pattern of aortic valve disease in the developed countries has

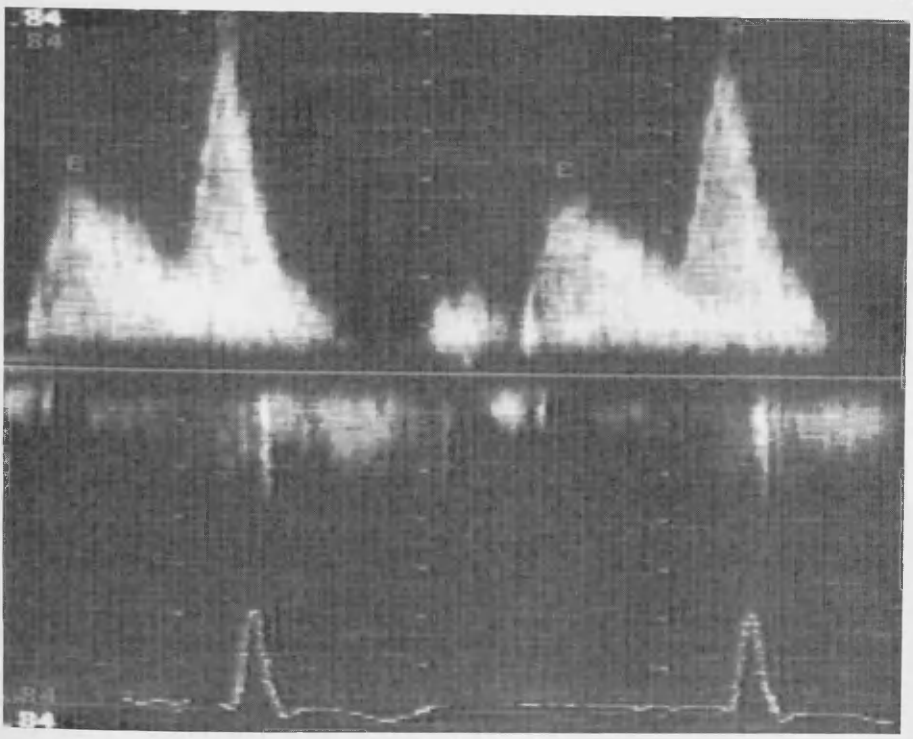

FIGURE 4.10: Abnormal Doppler mitral flow pattern. The maximal early diastolic flow velocity (E) is low relative to maximal late diastolic flow velocity (A) giving an E/A ratio of ‹0.85.

changed with the decline in the incidence of rheumatic heart disease and an increased incidence of calcific aortic valve disease (Selzer and Lombard, 1988). Increasing age of the patient population also leads to the increase in the frequency of coronary artery disease. Thus the presence of significant coronary artery disease in patients with aortic valve disease is not an uncommon finding. In adults with aortic valve disease, aortic valve replacement is nowadays typically performed in the sixth or seventh decade of life when the prevalence of coronary artery disease in the general population is 10% to 15% among men and 5% to 10% among women (Diamond and Forrester, 1979). Several studies have also shown an increase in the operative mortality of aortic valve replacement in the presence of coexisting coronary artery disease (Table 4.17). In these series, concomitant coronary artery bypass grafting had been shown to modulate surgical mortality. Long-term survival also improves following myocardial revascularisation (Mullany et al, 1987; Jones et al, 1989; Lytle et al, 1983). To complicate the issue further, angina pectoris is a common symptom of both aortic valve disease and coronary artery disease (Contratto and Levine, 1937; Mitchell et al, 1954; Wood, 1958). Does the presence of angina therefore necessitate coronary angiography before aortic valve replacement, or should the absence of angina in patients with significant aortic valve disease alleviate the need to perform a pre-operative coronary angiography? On the other hand, coronary angiography is associated with a small but definite risk and therefore should not be

Table 4.17

Operative Mortality Rates

Reference	No CAD		CAD			
	AVR		AVR, NO CABG		AVR + CABG	
	No. of patients	Deaths (%)	No. of patients	Deaths (%)	No. of patients	Deaths (%)
Mullany et al (1987)	73	1 (1.4)	32	3 (9.3)	99	4 (4.0)
Jones et al (1989)	428	18 (4.2)	51	9 (17.6)	68	9 (13.2)
Lytle et al (1989)	272	3 (1.1)	23	1 (4.3)		
Lytle et al (1983)					375	20 (5.3)
Total	773	22 (2.8)	106	13 (12.2)	542	33 (6.1)

CAD = coronary artery disease
CABG = coronary artery bypass grafting
AVR = aortic valve replacement

performed unnecessarily (Green, McKinnon and Rosch, 1972; Adams, Fraser and Abrams, 1973).

Of the major studies in the literature that have addressed this question, the majority (Paquay et al, 1976; Graboys and Cohn, 1977; Exadactylos, Sugrue and Oakley, 1984; Basta et al, 1975) favour the view that coronary angiography should only be performed in those patients with chest pain typical of angina pectoris as it is less likely to find significant coronary artery disease in patients free from chest pain, while other workers (Hancock, 1977; Hakki et al, 1980) stress the necessity of performing coronary angiography in all patients (see Table 4.18).

In the present study 89 of the 100 patients had undergone coronary angiography before aortic valve replacement. Of these 89 patients, chest pain typical of angina pectoris was present in 51 patients (57%), and a total of 21 (24%) had significant coronary artery disease. Angina pectoris was present in 20 of these 21 patients (95%). One patient with significant coronary artery disease was free of chest pain. This patient had predominant aortic regurgitation and 90% proximal stenosis of the left anterior descending coronary artery but with good collateral supply from a dominant right coronary artery. The prevalence of angina pectoris and coronary artery disease according to the predominant aortic valve lesion are shown in figures 4.4 and 4.5.

Table 4.18

Chest Pain in Relation to Coronary Artery Disease in Patients with Aortic Valve Disease (Present and Previous Studies)

		Patients with chest pain with CAD		Patients without chest pain with CAD		Patients without chest pain with CAD	
	Total No. of Patients studied	No.	%	No.	%	No.	%
Hancock (1977)	173	82/128	64	46/128	36	15/45	33
Hakki et al (1980)	90	33/60	55	27/60	45	2/30	7
Paquay et al (1976)	76	29/57	51	28/57	49	1/19	5
Graboys and Cohn (1977)	66	13/42	31	29/42	69	1/24	4
Exadactylos et al(1984)	88	22/62	35	40/62	65	0/26	0
Basta et al (1975)	70	12/51	24	39/51	76	0/19	0
Present Study	89	20/51	39	31/51	61	1/38	3
Total	652	211/451	47	240/451	53	20/201	10

Thus angina pectoris could predict the presence of significant coronary artery disease with a 95% sensitivity and a 54% specificity.

In the 55 patients with predominant aortic stenosis in this study, 31 (56%) had angina pectoris while 24 (44%) were free of chest pain. Aortic gradients were available in 54 patients and these patients were then divided into 3 groups according to their gradients: 20 to 50, 51 to 100 and >100 mmHg, which were considered mild, moderate and severe aortic stenosis respectively (Table 4.19). Approximately 97% of the patients with angina pectoris had moderate and severe aortic stenosis while, on the other hand, the majority of patients free from chest pain (83%) had mild to moderate aortic stenosis. This finding is in contradiction with that reported by Chobadi et al (1989). They showed a lower frequency of angina pectoris in the patients with severe aortic stenosis. Ninety-one percent of the patients with significant coronary artery disease in this study had moderate aortic stenosis and in only one (9%) patient was aortic stenosis severe. This is in agreement with Chobadi et al's finding of a higher incidence of coronary artery disease in patients with mild aortic stenosis and complete absence of coronary artery disease in 20 of their patients in whom aortic gradient was >110 mmHg. It must also be emphasised from the results of the present study that in 10 patients in whom the transaortic gradient was greater than 100mmHg only one had significant coronary artery disease (Table 4.19).

Table 4.19

Chest Pain and Incidence of CAD*
Relative to Aortic Pressure Gradient in Patients with Predominant Aortic Stenosis

Gradient (mmHg)	Patients (n)	Anginal pain n (%)	No angina n (%)	CAD n (%)
20 - 50	7	1 (14)	6 (86)	0 (0)
51 - 100	37	23 (62)	14 (38)	10 (91)
› 100	10	6 (60)	4 (40)	1 (9)
TOTAL	54	30 (56)	24 (44)	11 (100)

* CAD = coronary artery disease defined as the presence of 70% or more reduction in luminal diameter seen in at least one angiographic view.

These findings draw our attention to two important observations. Firstly, angina pectoris is very rare in patients with mild aortic stenosis occurring in only one out of 30 patients with chest pain (0.3%). Secondly, angina becomes more prevalent with increasing severity of aortic stenosis while the opposite is true for coronary artery disease as significant coronary artery disease was present in only one of the 10 patients with severe aortic stenosis. This patient was a 73 year old lady with a transaortic gradient of 101 mmHg which is at the borderline between the moderate and severe groups. Therefore, our study has shown a reverse relationship between aortic pressure gradient and frequency of coronary artery disease. In the groups with a lower pressure gradient, angina is more likely to be due to coronary artery disease, while in the groups with a higher pressure gradient it is more likely to be due to uncomplicated aortic stenosis. Furthermore, in patients with predominant AS, aortic gradient was significantly lower in the patients with compared to that of patients without coronary artery disease (71 $\pm$ 16mmHg Vs 86 $\pm$ 29mmHg; $p < 0.05$). In patients with predominant AR, those with coronary artery disease had less severe indices of AR compared to those with normal coronary arteries (Table 4.13). Thus, patients with less severe aortic valve disease are presumed to have come to early cardiac referral as a result of angina secondary to coronary artery disease. Hence, the occurrence of angina in patients with mild aortic stenosis should caution the investigating Cardiologist to the possible presence of concomitant coronary artery disease. Therefore all

workers agree without any reservation the necessity of performing coronary angiography in patients with aortic valve disease and chest pain. However it remains less clear whether coronary angiography should be performed in patients with aortic valve disease free from chest pain. Our results revealing only a 2% prevalence of coronary artery disease in patients without angina supports the view of those who favour the practice of not performing coronary angiography before operation in aortic valve disease patients free from chest pain (Paquay et al, 1976; Graboys and Cohn, 1977; Exadactylos, Sugrue and Oakley, 1984; Basta et al, 1975).

CHAPTER FIVE

PREVALENCE AND SIGNIFICANCE OF VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH AORTIC VALVE DISEASE

5.1 Introduction

Sudden death is a known complication of patients with aortic valve disease (Ross and Braunwald, 1968) but in most cases this is usually preceded by angina, congestive heart failure or syncope (Contratto and Levine, 1937; Mitchell et al, 1954; Chizner, Pearle and de Leon, 1980).

In a few cases however, sudden death may be the first and only symptom of severe aortic valve disease (Ross and Braunwald, 1968; Wagner et al, 1977). Reynold et al (1960) have quoted from reported series an incidence of sudden death in these patients of between 4 and 18%. Johnson (1971) reported a higher incidence (21%) of sudden death in his series comprising of 204 adult patients with aortic stenosis. With the advances in surgical techniques, aortic valve replacement is nowadays carried out with <5% mortality and hence surgical relief to patients with severe aortic valve disease is offered before the occurrence of left ventricular failure. Therefore left ventricular failure may now be regarded as an accidental occurrence in a patient with significant aortic valve disease. With the outlook after operation so much better than the natural history of aortic valve disease, the incidence of sudden death has assumed more importance. The exact cause of sudden death still remains speculative, but it has been partly attributed to ventricular arrhythmias. This speculation has been entertained by several workers who have shown an association between electrocardiographic as well as echocardiographic left ventricular hypertrophy and complex ventricular

arrhythmias in hypertension and hypertrophic cardiomyopathy (Levy et al, 1987; Messerli et al, 1984; McLenachan et al, 1987; Pringle et al, 1987; Savage et al, 1979; McKenna et al, 1980; McKenna et al, 1981). Furthermore, electrocardiographic left ventricular hypertrophy is found in 85% of patients with severe aortic valve disease (Braunwald, 1988). Several studies on patients with significant aortic valve disease have also shown a high incidence of complex ventricular arrhythmias (Von Olshausen et al, 1983; Kennedy et al, 1975; Schilling et al, 1982; Kostis et al, 1984; Klein, 1984).

In most of the above quoted studies however, ambulatory electrocardiographic monitoring had been used as a tool for predicting subsequent sudden death. Does the presence of these spontaneously occurring ventricular arrhythmias recorded during a limited ambulatory period necessarily indicate an ominous prognosis? In other words, do they indicate the presence of an underlying arrhythmogenic substrate that could support the genesis of fatal ventricular arrhythmias?

Several studies have shown the major role played by reentry in the genesis of ventricular tachyarrhythmias (El-Sherif et al, 1977; Williams et al, 1974; Zipes, 1975). The prerequisites for reentry are unidirectional block, slow conduction and recovery of the tissue ahead of the wavefront of excitation (Zipes, 1975). One of the most significant findings attributed to slow conduction was the detection of delayed fractional electrical activity in regions of experimental infarction (El-Sherif

et al, 1977) and since these potentials most frequently occur in the ST segment after the end of the QRS complex, they have been called "late potentials". They are characterised by multiple low-amplitude spikes, and it has been suggested that the presence of such electrocardiograms indicate sites for potential reentrant circuits. It has recently been possible to record late potentials by signal-averaging of the electrocardiogram and this technique which is simple and non-invasive has gained popularity for identifying those patients who are prone to develop ventricular tachyarrhythmias. We can therefore verify the significance of complex ventricular arrhythmias detected by ambulatory electrocardiographic recording by performing signal-averaging of the electrocardiogram to detect the presence of any late potentials. Furthermore, several studies have shown a strong correlation between ventricular tachycardia inducible on electrophysiologic study and the presence of an abnormal signal-averaged electrocardiogram (Simson et al, 1983; Freedman et al, 1985; Lindsay et al, 1986; Dennis et al, 1987; Winters et al, 1988; Turitto et al, 1988; Borbola, Ezri and Denes, 1988; Nalos et al, 1988). This part of the study therefore investigates the incidence and significance of ventricular arrhythmias in patients with aortic valve disease before undergoing aortic valve replacement. These findings were related to clinical, echocardiographic and to some extent cardiac catheterisation data of the patients.

5.2 Patients and Methods

The clinical characteristics of the study patients and methods are described in detail in Chapters 3 and 4. In brief, 100 patients with clinically significant aortic valve disease were studied. All patients underwent a thorough physical examination after obtaining a detailed history. Appropriate blood investigations were done and signal-averaged electrocardiograms were then performed. The patients were then fitted with an Oxford Medilog II frequency modulated recorder to wear for a period of 48 hours. During this period all patients were fully ambulatory and none was receiving anti-arrhythmic medications. On the return appointment, i.e. 48 hours later, detailed echocardiographic and doppler ultrasound examinations were performed. The data were analysed as described in Chapter 3.

5.3 Results

Ambulatory Monitoring

Technical problems with the recordings were encountered in 9 patients. Recordings were successfully repeated in 8 of them while it was not possible in the last patient as he had already undergone aortic valve replacement. Therefore, ambulatory electrocardiographic results of 99 patients are presented in this study.

Prevalence of Ventricular Arrhythmias (VA) (Table 5.1)

Eighty seven (88%) patients had infrequent ventricular extrasystoles (VES) (<10 VES/h). Of these 87 patients, 9 (9%) had no VES detected during the entire 48 hour period. Eight (8%) patients had 10-30 VES/h, while frequent VA (>30 VES/h) occurred in only 4 (4%) patients. Infrequent couplets (<10/24hrs) were seen more commonly, occurring in 21 (21%) patients. Nonsustained ventricular tachycardia (NSVT) was recorded in 9 (9%) patients.

Nonsustained Ventricular Tachycardia (Tables 5.2 and 5.3)

A total of 13 episodes of NSVT occurred in the 9 patients. A single episode of NSVT was recorded in 6, 2 episodes in 2 and 3 episodes in one patient. Eight of the episodes were triplets, 2 comprised 4 VES, one comprised 5 VES, one comprised 7 VES and the longest run comprised 10 VES (Figure 5.1). Nonsustained ventricular tachycardia was recorded in the first 24 hours in 6 patients while in the remaining 3 patients NSVT occurred in the second 24 hour period. These episodes were not associated with symptoms. However, a history of palpitations was volunteered in 4 patients while syncope was a symptom in 3. Frequent couplets as well as frequent VES occurred in only one patient with NSVT. It is noteworthy that 8 of the 9 patients with NSVT had aortic stenosis as their predominant lesion while in the remaining patient, the predominant lesion was aortic regurgitation. Two patients were in NYHA functional Class 1, 5 in Class 2 and only 2 were in Class 3. Angina pectoris occurred in 5 patients

Table 5.1

Prevalence of Ventricular Arrhythmias

	Number of Patients	%
‹10 VES/hr	87	88
10-30 VES/hr	8	8
›30 VES/hr	4	4
Frequent couplets (›10/24 hrs)	3	3
Infrequent couplets (‹10/24 hrs)	21	21
NSVT	9	9

VES = Ventricular extrasystoles
NSVT = Nonsustained ventricular tachycardia

Table 5.2

Episodes of Nonsustained Ventricular Tachycardia and their Relationship to Other Forms of Ventricular Arrhythmias

Patient I.D.	No. of episodes	No. of VES* in each episode	Period of occurrence	Couplets in 24 hrs	No. of VES /24 hrs
17	2	3	1st 24 hrs	19	4894
		3	1st 24 hrs		
26	1	4	2nd 24 hrs	2	30
33	1	3	1st 24 hrs	0	1
42	1	5	2nd 24 hrs	1	255
58	1	3	2nd 24 hrs	0	10
63	2	3	1st 24 hrs	3	8
		3	1st 24 hrs		
64	1	4	1st 24 hrs	0	0
77	3	3	1st 24 hrs	2	43
		10	1st 24 hrs		
		3	2nd 24 hrs		
85	1	7	1st 24 hrs	1	39

* VES = ventricular extrasystoles

Table 5.3

Summary of the Clinical and Echocardiographic Findings in 9 Patients with Nonsustained Ventricular Tachyardia

Case	Sex	Lesion	NYHA	Palpitations	Syncope	Angina	CAD	EF	PSLVWS Reich	PSLVWS Quin	EDV	LVMI	E/A
17	F	AS	1	-	-	-	-	48	133	316	108	129	-
26	M	AS	3	-	-	+	-	-	-	-	-	-	0.67
33	M	AS	2	+	-	-	-	77	28	90	75	270	0.85
42	M	AR	1	-	+	-	-	48	178	314	325	383	0.79
58	F	AS	3	+	+	+	-	71	56	155	75	210	0.69
63	F	AS	2	-	-	+	+	47	152	360	193	403	0.91
64	F	AS	2	+	-	+	-	60	173	373	193	176	0.89
77	F	AS	2	-	+	-	-	43	136	308	112	266	1.10
85	M	AS	2	+	-	+	+	30	413	489	138	135	1.23

AS = aortic stenosis. AR = aortic regurgitation. NYHA = New York Heart Association functional Class. CAD = coronary artery disease. EF = ejection fraction. PSLWVS = peak systolic left ventricular wall stress. LVMI = left ventricular mass index. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

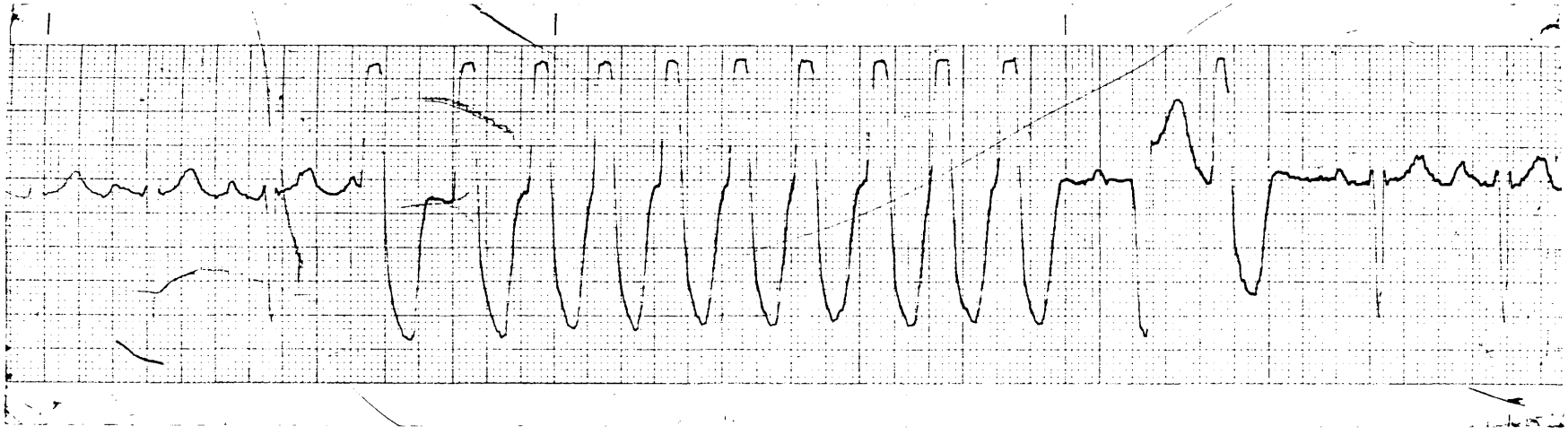

Figure 5.1: An episode of NSVT comprising 10 VES recorded in a 61 year old woman with predominant AS and a normal SAECG.

while significant coronary artery disease was present in only 2 patients, angina being a symptom of both. Left ventricular systolic function was satisfactory in all except one patient who had an EF of 30% while diastolic function showed some impairment in the majority of the patients. Substantial left ventricular hypertrophy was present in most of the patients. None of the patients had a normal LVMI. Peak systolic left ventricular wall stress was elevated in most of the patients while end diastolic volume was not surprisingly markedly increased in the patient with predominant A.R.

Table 5.4 presents the distribution of VA by their maximum Lown Grade. Eight (8%) patients were in Grade O, 18 (18%) in Grade 1, none in Grade 2, 5 (5%) in Grade 3, 4 (4%) in Grade 4A, 3 (3%) in Grade 4B and 61 (62%) in Grade 5. If for the purpose of analysis, we consider Lown Grades 0 to 2 as simple and Grade 3 to 5 as complex VES, the majority of the study patients (74%) had complex VES.

Table 5.5 presents clinical characteristics and echo-cardiographic findings of patients according to the frequency of VA. Patients with infrequent VA (‹10 VES/h) were significantly younger than those with frequent VA (›30 VES/h) (59 ± 11 years Vs 68 ± 3 years; p ‹0.03). The end diastolic volume of patients with ‹10 VES/h was significantly smaller than that of patients with 10-30 VES/h (144 ± 69 cm^3 Vs 248 ± 70 cm^3; p ‹0.03) but insignificantly so when compared to that of patients with ›30 VES/h.

Table 5.4

Distribution of Ventricular Arrhythmias According to the Lown's Grading[x]

	No. of Patients (n=99)	%
Grade 0	8	8
Grade 1	18	18
Grade 2	0	0
Grade 3	5	5
Grade 4A	4	4
Grade 4B	3	3
Grade 5	61	62

[x] Lown grades:
0 = no ventricular extrasystoles
1 = infrequent ventricular extrasystoles (<30/h)
2 = frequent ventricular extrasystoles (>30/h)
3 = multifocal ventricular extrasystoles
4A = ventricular couplets
4B = nonsustained ventricular tachycardia
5 = R on T phenomenon

Table 5.5

Clinical and Echocardiographic Characteristics of Patients According to the Frequency of Ventricular Arrhythmias

		4 AS 3 AR 1 AS+AR	3 AS 1 AR
	‹10 VES/h (n=87)	10-30 VES/h (n=8)	›30 VES/h (n=4)
Age (yr)	59 ± 11*	61 ± 7	68 ± 3
Weight (kg)	66.9 ± 12.3	72.0 ± 13.3	70.5 ± 10.8
BSA (m^2)	1.72 ± 0.18	1.79 ± 0.19	1.77 ± 0.13
Systolic BP (mmHg)	147 ± 26	157 ± 27	162 ± 23
Diastolic BP (mmHg)	78 ± 16	87 ± 16	75 ± 12
Potassium (mmols/L)	4.20 ± 0.33	4.19 ± 0.58	4.03 ± 0.53
Cholesterol (mmols/L)	6.23 ± 1.45	5.83 ± 0.86	6.05 ± 0.75
EF (%)	61 ± 14	58 ± 15	56 ± 22
FS	33 ± 10	27 ± 11	26 ± 9
LVMI (g/m^2)	209 ± 73	235 ± 73	197 ± 55
EDV (cm^3)	144 ± 69**	248 ± 70	171 ± 81
PSLVWS (dyn/cm^2) Reichek's method	107 ± 63	131 ± 47	158 ± 89
Quinones' method	229 ± 94	261 ± 101	324 ± 83
E/A ratio	1.05 ± 0.44***	0.85 ± 0.17	0.81 ± 0.08

Mean ± SD
BSA = body surface area. EF = ejection fraction. FS = fractional shortening. EDV = left ventricular end diastolic volume. PSLVWS = peak systolic left ventricular wall stress. E/A = the ratio between early (E) and late (A) left ventricular diastolic filling velocity. VES = ventricular extrasystoles.

* p ‹0.03 difference in age between ‹10 VES/h and ›30 VES/h
** p ‹0.03 difference in EDV between ‹10 VES/h and 10-30 VES/h
*** p ‹0.03 difference in E/A ratio between ‹10 VES/h and ›30 VES/h

The E/A ratio of patients with ‹10 VES/h was significantly higher than that of patients with ›30 VES/h (1.05 ± 0.44 Vs 0.81 ± 0.08; p ‹0.03). Left ventricular systolic function as assessed by both ejection fraction and fractional shortening appeared to be marginally better in patients with ‹10 VES/h when compared to that in the other 2 groups. However, this did not reach statistical significance. There was no difference in serum potassium levels of the 3 groups. Left ventricular mass index was also not statistically different in the 3 groups.

Table 5.6 compares clinical and echocardiographic data of patients with and without multifocal VES. Patients with multifocal VES had significantly larger left atria (4.33 ± 1.07 cm Vs 3.68 ± 0.89 cm; p ‹0.01), more impairment of left ventricular function by fractional shortening (30 ± 9 Vs 34 ± 10; p ‹0.05) and increased peak systolic left ventricular wall stress assessed by Reichek's method (129 ± 76 dyn/cm^2 Vs 94 ± 43 dyn/cm^2; p ‹0.02).

Patients with frequent couplets (›10 couplets/24hrs) had significantly lower serum potassium than those with infrequent couplets (‹10 couplets/24hrs) (3.73 ± 0.32 mmols/L Vs 4.30 ± 0.44 mmols/L; p ‹0.05) (Table 5.7).

Table 5.8 presents clinical and echocardiographic data of patients according to the prevalence of nonsustained ventricular tachycardia (NSVT). Although patients with NSVT tended to be older, had higher systolic blood pressure and total cholesterol, poorer left ventricular systolic function, slightly more dilated left ventricles

Table 5.6

Clinical and Echocardiographic Characteristics of Patients According to the Presence or Absence of Multifocal Ventricular Extrasystoles

		Multifocal VES (n=48)	Unifocal VES (n=51)
Age (yr)		60 ± 11	59 ± 11
Weight (kg)		68.6 ± 13.4	66.3 ± 11.4
BSA (m^2)		1.74 ± 1.33	1.71 ± 1.31
Systolic BP (mmHg)		151 ± 27	145 ± 26
Diastolic BP (mmHg)		79 ± 17	78 ± 14
Potassium (mmols/L)		4.21 ± 0.34	4.20 ± 0.38
Cholesterol (mmols/L)		6.40 ± 1.66	6.00 ± 1.08
LVIDd (cm)		5.62 ± 1.05***	5.24 ± 1.08
LA (cm)		4.33 ± 1.07***	3.68 ± 0.89
LVMI (g/m^2)		217 ± 78	204 ± 67
EF (%)		58 ± 15	63 ± 14
FS		30 ± 9*	34 ± 10
EDV (cm^3)		161 ± 71	140 ± 73
PSLVWS (dyn/cm^2)	Reichek's method	129 ± 76**	94 ± 43
	Quinones' method	261 ± 104	213 ± 80
E/A ratio		1.07 ± 0.42	0.99 ± 0.44

Mean ± SD
BSA = body surface area. LVIDd = left ventricular internal dimension in diastole. LA = left atrium. LVMI = left ventricular mass index. EF = ejection fraction. FS = fractional shortening. EDV = left ventricular end diastolic volume. PSLVWS = peak systolic left ventricular wall stress. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* $p < 0.05$
** $p < 0.02$
*** $p < 0.01$

Table 5.7

Clinical and Echocardiographic Characteristics of Patients According to the Frequency of Ventricular Couplets

		Frequent couplets (n=3)	Infrequent couplets (n=21)
Age (yr)		64 ± 4	64 ± 8
Weight (kg)		68.7 ± 10.4	65.7 ± 13.0
BSA (m^2)		1.76 ± 0.15	1.70 ± 0.20
Systolic BP (mmHg)		158 ± 30	152 ± 29
Diastolic BP (mmHg)		83 ± 25	77 ± 21
Potassium (mmols/L)		3.73 ± 0.32*	4.30 ± 0.44
Cholesterol (mmols/L)		5.88 ± 0.27	6.58 ± 2.11
EF (%)		70 ± 19	53 ± 13
FS		33 ± 9	27 ± 8
LVIDd (cm)		4.92 ± 0.43	5.32 ± 1.03
LA (cm)		5.25 ± 1.79	4.22 ± 0.87
LVMI (g/m^2)		186 ± 56	233 ± 85
EDV (cm^3)		102 ± 8	149 ± 73
PSLVWS (dyn/cm^2)	Reichek's method	96 ± 37	138 ± 87
	Quinones' method	216 ± 88	266 ± 99
E/A ratio		1.09 ± -	0.96 ± 0.28

Mean ± SD
BSA = body surface area. EF = ejection fraction. FS = fractional shortening. LVIDd = left ventricular internal dimension in diastole. LA = left atrium. LVMI = left ventricular mass index. EDV = left ventricular end diastolic volume. PSLVWS = peak systolic left ventricular wall stress. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* $p < 0.05$

Table 5.8

Clinical and Echocardiographic Characteristics of Patients According to the Presence or Absence of Nonsustained Ventricular Tachycardia

		NSVT (n=9)	No NSVT (n=90)
Age (yr)		64 ± 11	59 ± 11
Weight (kg)		68.3 ± 13.7	67.3 ± 12.4
BSA (m^2)		1.71 ± 0.23	1.72 ± 0.18
Systolic BP (mmHg)		160 ± 27	147 ± 26
Diastolic BP (mmHg)		81 ± 15	78 ± 16
Potassium (mmols/L)		4.29 ± 0.39	4.18 ± 0.36
Cholesterol (mmols/L)		7.46 ± 2.80	6.07 ± 1.14
EF (%)		53 ± 15	61 ± 14
FS		28 ± 10	32 ± 10
LVIDd (cm)		5.53 ± 1.23	5.41 ± 1.07
LA (cm)		4.32 ± 1.55	3.96 ± 0.98
LVMI (g/m^2)		247 ± 105	207 ± 69
EDV (cm^3)		152 ± 84	149 ± 71
LVSP (mmHg)		241 ± 38*	213 ± 40
PSLVWS (dyn/cm^2)	Reichek's method	158 ± 116	106 ± 55
	Quinones' method	301 ± 126	230 ± 90
E/A ratio		0.89 ± 0.19	1.04 ± 0.44

Mean ± SD
BSA = body surface area. EF = ejection fraction. FS = fractional shortening. LVIDd = left ventricular internal dimension in diastole. LA = left atrium. LVMI = left ventricular mass index. EDV = left ventricular end diastolic volume. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

* $p < 0.05$

(LVIDd) and left atria, increased end diastolic volume, left ventricular mass index and peak systolic left ventricular wall stress by both Reichek's and Quinones' methods and decreased E/A ratio, these findings did not reach statistical significance. Left ventricular systolic pressure was the only variable which was significantly higher in patients with NSVT than that of patients with no episodes of NSVT (241 ± 38 mmHg Vs 213 ± 40 mmHg; $p < 0.05$). This is not surprising in view of the fact that 8 of the 9 patients with NSVT had aortic stenosis as their predominant lesion. However, in the patients with predominant AS, there was no difference in the mean systolic gradient across the aortic valve between the group with compared to that without NSVT (91 ± 21 mmHg Vs 79 ± 28 mmHg; $p < 0.19$)

The total number of VES per 24 hours was correlated with clinical and echocardiographic findings in the study patients (Table 5.9). Left atrial size was the only variable that showed a weak but highly significant relationship with total number of VES per 24 hours ($r = 0.357$; $p < 0.002$).

Signal-Averaged Electrocardiography (SAECG)

Signal-averaged electrocardiography was technically satisfactory in 99 of the 100 patients. QRS duration was prolonged in 16 (16%) out of 97 patients, 2 patients being excluded due to the presence of left bundle branch block on their surface electrocardiograms. Five (5%) patients had prolonged low amplitude signals under 40 microvolts

Table 5.9

Relationship between Number of VES per 24 Hours and Clinical and Echocardiographic Findings of the Study Patients

	r - value	p - value
Age	0.138	NS
LVIDd	-0.008	NS
PWTd	-0.073	NS
IVSTd	-0.083	NS
LVMI	-0.089	NS
LA	0.357	‹0.002
EF	-0.039	NS
FS	-0.109	NS
EDV in all patients	-0.005	NS
EDV in AR patients	0.209	NS
LVSP	-0.169	NS
PSLVWS:- Reichek's method	0.076	NS
Quinones' method	0.139	NS
E/A ratio	0.098	NS
Aortic Gradient in AS patients	0.102	NS

VES = Ventricular extrasystoles. LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EF = ejection fraction. FS = fractional shortening. EDV = left ventricular end diastolic volume. LVSP = left ventricular systolic pressure. PSLVWS = peak systolic left ventricular wall stress. E/A ratio = ratio between early (E) and late (A) left ventricular diastolic filling velocity. NS = not significant.

(LAS40) while root mean square voltage of the signals in the terminal 40 milliseconds (RMSV40) was abnormally decreased in 6 (6%) patients. Late potentials were present according to the criteria previously described in Chapter 3, in 6 (6%) patients. Two of these 6 patients had all the 3 criteria positive on their SAECG's (Table 5.10). Figures 5.2 and 5.3 illustrate examples of a normal and an abnormal SAECG respectively.

Table 5.11 presents some clinical, echocardiographic and ambulatory electrocardiographic findings in the 6 patients with abnormal SAECGS. The predominant lesion was AR in 3, AS in 2 and combined AS and AR in one patient. Palpitations were reported in 2, syncope in one and angina pectoris in 3 patients. Significant coronary artery disease was present in 2 patients. None of the patients had a previous myocardial infarction. Left ventricular systolic function assessed by echocardiographic EF was satisfactory in all patients while diastolic function (E/A) was markedly abnormal in 2 of the 3 patients assessed. The remaining 3 patients were in atrial fibrillation. Ambulatory electrocardiographic monitoring showed frequent VES (4894 VES/24hrs), frequent couplets (19 couplets/24hrs) and the occurrence of nonsustained ventricular tachycardia (NSVT) in only one patient (Case 17). Thus, NSVT occurred in only one patient with an abnormal SAECG.

Signal-averaged electrocardiographic findings of patients in relation to their clinical characteristics are depicted in Table 5.12. Patients with predominant AS had a

Table 5.10

Prevalence of Abnormal Signal-Averaged Electrocardiograms

	Number of patients	%
QRS ($\geq$ 120 msec)	16	16
LAS 40 ($\geq$ 38 msec)	5	5
RMSV40 ($\leq$ 25 uV)	6	6
Abnormality by 2 criteria	4	4
Abnormality by 3 criteria	2	2

QRS = filtered QRS duration
LAS 40 = Low amplitude signals under 40 uV
RMSV = root mean square voltage of the signals in the terminal 40 milliseconds

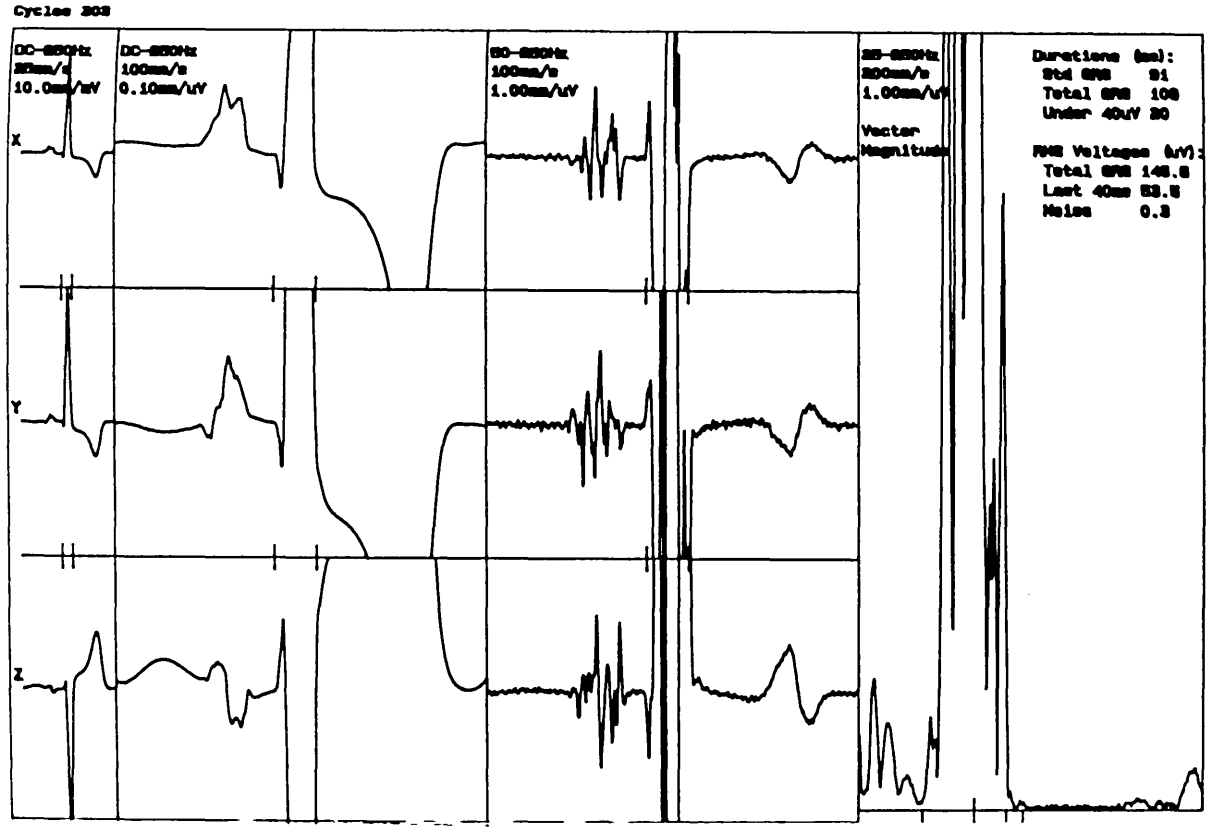

Figure 5.2: Normal SAECG recorded in a 44 year old woman with predominant AS.

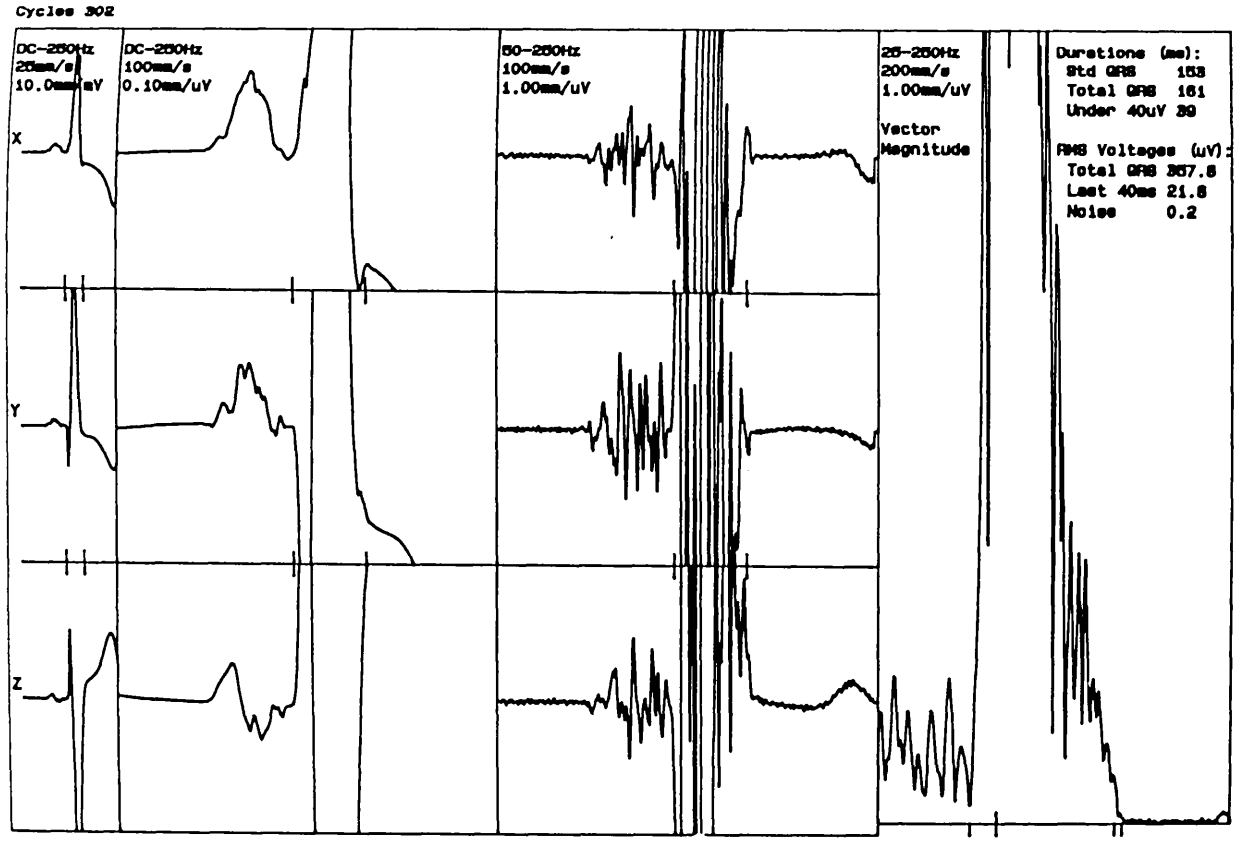

Figure 5.3: Abnormal SAECG recorded in a 54 year old man with predominant AR. It shows a prominent late potential. Ambulatory electrocardiographic monitoring showed infrequent VES with absence of couplets and NSVT.

Table 5.11

Summary of the Clinical, Echocardiographic and Ambulatory ECG Findings in 6 Patients with Abnormal SAECGS

Case	Sex	Lesion	NYHA	Palpitations	Syncope	Angina	CAD	EF	E/A	LVMI	No of VES /24hr	No of couplets /24hrs	Episodes of VT
15	F	AR	1	-	-	-	-	49	-	173	16	0	0
17	F	AS	1	-	-	-	-	48	-	129	4894	19	2
47	M	AS+AR	2	-	-	-	-	56	0.51	266	14	0	0
50	F	AR	3	+	-	+	+	52	_	103	8	0	0
55	M	AR	2	+	-	+	-	41	2.09	384	27	0	0
79	F	AS	2	-	+	+	+	86	0.40	126	8	0	0

SAECG = signal averaged electrocardiogram. CAD = coronary artery disease. EF = ejection fraction. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity. LVMI = left ventricular mass index. VES = ventricular extrasystoles. VT = nonsustained ventricular tachycardia. AS = aortic stenosis. AR = aortic regurgitation. NYHA = New York Heart Association functional Class.

Table 5.12

Signal-Averaged Electrocardiographic Findings of Patients in Relation to their Clinical Characteristics

	No. of patients	Filtered QRS duration (ms)	LAS 40 (ms)	RMSV40 (uV)
AS	55	101 ± 10***	15 ± 8^+	130 ± 87~
AR	16	122 ± 21	30 ± 20	64 ± 43
AS + AR	28	112 ± 16	20 ± 9	84 ± 63
NYHA I	22	108 ± 19	19 ± 10	101 ± 62
NYHA II	63	107 ± 14	18 ± 9	112 ± 86
NYHA III	14	109 ± 19	27 ± 23	84 ± 70
Angina	51	108 ± 19	20 ± 15	101 ± 81
No angina	48	107 ± 12	18 ± 9	111 ± 77
CAD	21	114 ± 18*	24 ± 17	75 ± 64**
No CAD	78	105 ± 16	17 ± 18	117 ± 79
Palpitation	53	106 ± 16	20 ± 14	103 ± 79
No palpitation	46	109 ± 16	18 ± 10	109 ± 80
Syncope	22	104 ± 16	17 ± 11	112 ± 77
No syncope	77	108 ± 16	18 ± 13	104 ± 80

AS = aortic stenosis. AR = aortic regurgitation. NYHA = New York Heart Association functional Class. CAD = coronary artery disease. LAS40 = low amplitude signals under 40 uV. RMSV40 = root mean voltage in last 40ms.

* $p<0.05$ difference in QRS duration between patients with and without CAD
** $p<0.02$ difference in RMSV40 between patients with and without CAD
*** $p<0.03$ difference in QRS duration bwtween AS and AR as well as between AS and AS + AR
^ $p<0.03$ difference in LAS40 between AS and AR
\+ $p<0.05$ difference in LAS40 between AS and AS + AR
~ $p<0.03$ difference in RMSV40 between AS and AR as well as between AS and AS + AR

significantly shorter QRS duration (101 ± 10 ms) than that of patients with AR (122 ± 21 ms; p <0.03) and patients with combined AS and AR (112 ± 16 ms; p <0.03). Low amplitude signals under 40 uV were also significantly shorter in AS patients (15 ± 8 ms) compared to that of AR patients (30 ± 20 ms; p <0.03) and that of patients with combined AS and AR (20 ± 9 ms; p <0.05). Root mean square voltage of the signals in the terminal 40 milliseconds in AS patients (130 ± 87 uV) was significantly higher than that of patients with AR (64 ± 43 uV; p <0.03) and combined AS and AR (84 ± 63 uV; p <0.03). Filtered QRS duration was significantly longer in patients with compared to that of patients without coronary artery disease (114 ± 18 ms Vs 105 ± 16 ms; p <0.05). Likewise RMSV40 of patients with coronary artery disease was significantly lower than that of patients without coronary artery disease (75 ± 64 uV Vs 117 ± 79 uV; p <0.02). Although LAS40 in patients with coronary artery disease was longer than that of patients without coronary artery disease, this did not reach statistical significance. There were no significant differences noted in the SAECG variables between patients with compared to those without symptoms of angina, palpitations or syncope. Signal-averaged electrocardiographic variables were also not significantly affected by NYHA functional classes of the patients.

Table 5.13 presents SAECG findings of patients in relation to the results of ambulatory electrocardiographic monitoring. There were no differences observed in the SAECG variables in relation to the frequency of VES or couplets,

Table 5.13

Signal-Averaged Electrocardiographic Findings of Patients in Relation to Ventricular Arrhythmias

	No. of patients	QRS duration (ms)	LAS 40 (ms)	RMSV40 (uV)
<10 VES/h	86	107 ± 16	19 ± 13	106 ± 79
10-30 VES/h	8	111 ± 15	19 ± 8	102 ± 71
>30 VES/h	4	109 ± 17	18 ± 13	130 ± 118
Frequent couplets (>10/24hrs)	3	113 ± 17	22 ± 13	89 ± 63
Infrequent couplets (<10/24hrs)	21	105 ± 10	15 ± 7	114 ± 92
VT	9	106 ± 14	14 ± 10	131 ± 108
No VT	89	108 ± 16	20 ± 12	104 ± 76
Multifocal VES	48	108 ± 17	20 ± 12	105 ± 81
Unifocal VES	50	107 ± 15	19 ± 13	107 ± 78

LAS40 = low amplitude signals under 40 uV. RMSV40 = root mean square voltage in last 40ms. VES = ventricular extrasystoles. VT = ventricular tachycardia (nonsustained).

and in relation to the presence or absence of nonsustained ventricular tachycardia or multifocal VES.

5.4 Discussion

Although sudden death claims 15 to 20% of patients with acquired aortic valve disease (Contratto and Levine, 1937; Dry and Willius, 1939; Mitchell et al, 1954), the exact cause of this remains unclear. However, these deaths have been assumed to result mainly from ventricular tachyarrhythmias. This is supported by studies that have demonstrated ventricular tachyarrhythmias as the terminal event in the majority of cases of recorded sudden deaths (see Chapter One, Section 1.3). Furthermore, the Framingham Heart Study has reported an association between both electrocardiographic and echocardiographic left ventricular hypertrophy and an increased risk of ventricular arrhythmias (Levy et al, 1987). It is also known from studies on hypertensive patients that significantly more complex ventricular arrhythmias occur in those patients with left ventricular hypertrophy (Messerli et al, 1984; McLenachan et al, 1987; Pringle et al, 1987). Several other studies have also reported an association between electrocardiographic and echocardiographic left ventricular hypertrophy which occur in the majority of patients with aortic valve disease (Braunwald, 1988) and the prevalence of complex ventricular arrhythmias (Savage et al, 1979; McKenna et al, 1981).

In the present study electrocardiographic and echocardiographic left ventricular hypertrophy were present in 90%

and 91% of patients respectively. Ventricular ectopic activity was present in 91% of patients. The majority (88%) of patients had infrequent VA (<10 VES/h) while frequent VA (>30 VES/h) occurred in only 4 (4%) patients (Table 5.1). In terms of complexity, 74% of patients had complex VA (Lown grades 3 to 5). The reported incidence of complex VA in patients with aortic valve disease varies between 36 to 93% (Table 5.14). These differing incidences in the complexity of VA reported by different studies may be explained by several factors. Firstly, the patients were not comparable in terms of their age, type of aortic valve disease, prevalence of concomitant coronary artery disease and the degree of impairment of left ventricular function amongst other factors. Secondly, the methods used for arrhythmia detection and quantification were not uniform. Thirdly, there was a marked variability in the size of the study population in the different studies. Furthermore, a spontaneous and marked variability in the frequency and complexity of VA of individual patients has been well documented (Morganroth et al, 1978; Michelson and Morganroth, 1980).

Prognostic Significance of Complex Ventricular Arrhythmias including Nonsustained Ventricular Tachycardia (NSVT)

Nonsustained ventricular tachycardia may be detected during ambulatory electrocardiographic monitoring in patients with heart disease and occasionally in those with structurally normal hearts (Kennedy et al, 1985). Does the presence of this arrhythmia indicate an increased risk of subsequent sudden death? The significance of this arrhythmia has been determined by electrophysiological

Table 5.14

Incidence of Complex Ventricular Arrhythmias in Patients with Aortic Valve Disease (Present and Previous Studies)

	Total no. of patients	Duration of ambulatory ECG monitoring (hr)	CVA (%)	NSVT (%)
Von Olshausen et al (1983)	93	24	55	18
Klein (1984)	102	24	38	NOT REPORTED
Kennedy et al (1975)	15	24	93	47
Schilling et al (1982)	38	24	68	NOT REPORTED
Hochreiter et al (1982)	28	24	36	NOT REPORTED
Kostis et al (1984)	28	24	68	14
Present Study	99	48	74	9

CVA = complex ventricular arrhythmias
NSVT = nonsustained ventricular tachycardia

studies by a number of workers. Buxton et al (1984), performed electrophysiological studies on 83 consecutive patients with spontaneous NSVT documented on ambulatory electrocardiographic monitoring. Thirty-three of these 83 patients had coronary artery disease, 18 had cardiomyopathy, 8 had mitral valve prolapse and 24 had no heart disease. Patients were followed up for a mean period of 33 months. There was a suggestion that the presence of NSVT on its own did not necessarily indicate an increased risk of sudden death. However, when this occurred in combination with severe left ventricular dysfunction, the risk of sudden death was high.

Gomes and his colleagues (Gomes et al, 1984) performed electrophysiological studies on 73 patients most of them with atherosclerotic heart disease and with previously documented high grade ventricular arrhythmias (Lown grades 3, 4A and 4B) on 48 hour ambulatory electrocardiogaphic monitoring. Ventricular tachycardia was inducible in 20 patients, all of whom had atherosclerotic heart disease. After a follow-up period of 30 $\pm$ 15 months, sudden death was significantly higher in the 20 patients who were inducible at electrophysiological study. Radionuclide ejection fraction of less than 40% was also associated with a poor survival. An interesting finding in this study is that the grade of ventricular extrasystoles (Lown grades 3 to 4B) was not significantly different between the patients with and those without inducible ventricular tachycardia or between survivors and non-survivors.

Zheutlin et al (1986) studied 88 patients with organic heart disease including 8 patients with valvular heart disease, who had ventricular ectopy ($\geq$ Lown grade 3). All patients underwent programmed electrical stimulation. Ventricular tachycardia was inducible in 33 patients and interestingly all the 8 patients with valvular heart disease were non-inducible. Patients with valvular heart disease tended to have higher left ventricular ejection fractions. In agreement with Gomes et al's findings, the grade of ventricular arrhythmias could not predict inducibility at electrophysiological study. After a 44 month follow-up period, no major arrhythmic events had occurred in the non-inducible group while there was a 12% incidence of major arrhythmic events in the inducible group.

In the present study, 9 patients (9%) had NSVT on 48 hour ambulatory electrocardiographic monitoring, and of these 9 patients, only one had late potentials on SAECG. Thus, there is little evidence to suggest the presence of an arrhythmogenic substrate in these patients. This is supported by the reported strong correlation between ventricular tachycardia inducible at electrophysiologic study and the presence of an abnormal SAECG (Simson et al, 1983; Freedman et al, 1985; Lindsay et al, 1986; Dennis et al, 1987; Winters et al, 1988; Turitto et al, 1988; Borbola, Ezri and Denes, 1988; Nalos et al, 1988). Furthermore, the prognostic significance of late potentials has been prospectively studied by Breithardt and his colleagues (Breithardt, Martinez-Rubio and Borggrefe, 1990). They showed a higher risk of major

arrhythmic complications including sudden cardiac deaths in patients with late potentials on SAECG.

The present findings are in agreement with those recently reported by Pringle et al (1989). Nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring occurred in 11 out of a total of 90 hypertensive patients with electrocardiographic left ventricular hypertrophy. Of these 11 patients, only one had ventricular late potentials on SAECG. I am aware of no other studies on SAECG in patients with left ventricular hypertrophy and especially in those with aortic valve disease.

5.5 Summary

This part of the study has documented the occurrence of infrequent, but complex ventricular arrhythmias in patients with aortic valve disease. Nonsustained ventricular tachycardia occurred in 9 patients (9%). However, there is little evidence from SAECG to suggest that these patients have an underlying arrhythmogenic substrate. Signal-averaged electrocardiography detected ventricular late potentials in 6 (6%) patients of whom only one had NSVT on ambulatory electrocardiographic monitoring. From these findings, the reported 15 to 20% incidence of sudden deaths in these patients cannot be entirely explained on the basis of ventricular tachyarrhythmias. There are probably other yet unexplained mechanisms responsible for sudden death in patients with aortic valve disease.

CHAPTER SIX

CLINICAL OUTCOME OF PATIENTS

Of the total 100 patients in the study, 75 were on the waiting list for cardiac surgery. The remaining 25 patients were being followed up by their investigating Cardiologists. The majority of these patients did not have sufficient clinical or haemodynamic indications for cardiac surgery while a few had other medical conditions that influenced the treating Cardiologists' decision in not referring them for operation. Two patients refused to undergo cardiac surgery due to personal reasons.

The waiting list for elective cardiac surgery in our institution is usually between 6 to 18 months. At the time of writing up this thesis, 60 patients had undergone cardiac surgery. Table 6.1 shows the distribution of patients according to the type of surgical procedure performed. Forty-two patients (70%) underwent aortic valve replacement (AVR) alone. In addition to AVR, 10 patients (17%) had coronary artery bypass graft surgery (CABG), 5 (8%) had mitral valve replacement (MVR), one (2%) had mitral valvotomy and two (3%) had MVR plus CABG.

There have been a total of 7 deaths in the study to date. Sudden death, defined as death that occurred within minutes of symptom onset or during sleep in a previously stable patient, occurred in 3 patients (Cases 24, 71 and 77; Tables 6.2. and 6.3). Case 71 was witnessed to have suddenly collapsed and died within minutes. She had combined AS and AR as well as severe mitral regurgitation with an enlarged left atrium (6.8 cm). Her basic rhythm was atrial fibrillation. In Cases 24 and 77 the deaths were unwitnessed, both occurring at home and thus assumed

Table 6.1

Type of Surgery Performed in the Study Patients

Type of surgery	No of patients (n=60)
AVR	42
AVR + CABG	10
AVR + MVR	5
AVR + Mitral Valvotomy	1
AVR + MVR + CABG	2

AVR = aortic valve replacement
MVR = mitral valve replacement
CABG = coronary artery bypass graft surgery

to have occurred suddenly. Both had severe calcific aortic stenosis accompanied with substantial echocardiographic left ventricular hypertrophy. All these 3 patients were on the surgical waiting list thus giving an incidence of sudden death of 4% in this study group.

Case 26 who was not yet referred for surgery died a few hours following an emergency hospital admission due to a prolonged episode of severe chest pain culminating in uncontrolled severe left ventricular failure. There was no electrocardiographic or cardiac enzyme evidence of myocardial infarction. Doppler transaortic gradient during this admission was 100 mmHg.

Two deaths occurred during or immediately after surgery. The first (Case 4) was a 77 year old lady who died during aortic valve replacement. Postmortem revealed severe 3 vessel coronary artery disease which was not suspected prior to surgery. The second patient (Case 43) failed to recover his heart pump function following AVR and CABG and died 8 days following surgery. Left ventricular function assessed immediately before operation showed echocardiographic ejection fraction of approximately 30%. Postmortem coincidentally revealed a large right renal carcinoma.

The remaining patient (Case 5) died of a gastric carcinoma 3 months following AVR.

Tables 6.2 and 6.3 outline clinical, echocardiographic, ambulatory electrocardiographic and signal-averaged

electrocardiographic (SAECG) findings in the 7 patients who have died. None of the 7 patients had frequent VES (›30/h) or couplets (›10 couplets/24hrs) on ambulatory electrocardiographic monitoring. Two patients had NSVT (Case 26 and 77). Case 26 had a single episode of NSVT comprising 4 VES while Case 77 had 3 such episodes, the longest one comprising 10 VES. All patients had entirely normal SAECGS.

Mortality Rate in the Study Population

There were 7 deaths (7%) in this study population, two of them occurring directly as a consequence of cardiac surgery. Three of these 7 deaths are of interest for a couple of reasons. Firstly, they all occurred suddenly and in patients who were already on the cardiac surgical waiting list, thus leading to the speculation that had the waiting list not been long, these deaths could have been preventable. This however is not entirely true as all these 3 patients died within the first 7 months of being on the waiting list (Figure 6.1). Case 24 died after 3.5 months, Case 77 after 4 months and case 71 after 7 months of being on the waiting list. As illustrated in Figure 6.1, the median waiting time for surgery in the operated patients was 7.5 months. Thus, in order to prevent all these 3 deaths, surgery would have had to be performed within the first 3.5 months of being on the waiting list. Hence, the incidence of sudden death while on the waiting list for cardiac surgery in this group of patients was 4%. This mortality rate is slightly higher when compared to the operative mortality following AVR quoted by different

Table 6.2

Summary of the Clinical and Echocardiographic Findings in 7 Patients Who Have Died During the Study Period

Case	Sex	Age	Lesion	NYHA	Syncope	Angina	CAD	EF	PSLVWS Reich	PSLVWS Quin	EDV	LVMI	E/A	Aortic Gradient	LVSP
4	F	77	AS	2	-	+	+	-	-	-	-	-	-	60	196
5	M	57	AS	2	-	+	-	-	102	209	-	154	0.64	45	203
24	M	68	AS	2	-	-	-	83	38	119	100	228	0.86	62	202
26	M	78	AS	3	-	+	-	-	-	-	-	-	-	68	188
43	M	64	AR	2	-	+	+	58	129	248	365	354	1.50	9	159
71	F	61	AS+AR +MVD	2	+	+	+	72	53	155	87	234	-	74	232
77	F	61	AS	2	+	-	-	43	136	308	112	266	1.10	110	260

NYHA = New York Heart Association functional Class. CAD = coronary artery disease. EF = ejection fraction. PSLWVS = peak systolic left ventricular wall stress. EDV = left ventricular end diastolic volume. LVMI = left ventricular mass index. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity. LVSP = left ventricular systolic pressure.

Table 6.3

Ambulatory Electrocardiographic and Signal-Averaged Electrocardiographic Findings in 7 Patients Who Have Died During the Study Period

Case	No of VES/24hrs	No of Couplets/24hrs	Episodes of NSVT	QRS	LAS40	RMSV40
4	29	0	0	109	13	197.3
5	518	4	0	87	10	253.0
24	1	0	0	116	22	28.0
26	30	2	1	102	8	98.7
43	6	0	0	126	26	70.6
71	41	0	0	96	19	61.5
77	43	2	3	99	5	340.3

VES = ventricular extrasystoles. NSVT = nonsustained ventricular tachycardia. QRS = filtered QRS duration. LAS40 = low amplitude signals under 40 uV. RMSV40 = root mean square voltage of the signals in the terminal 40 milliseconds.

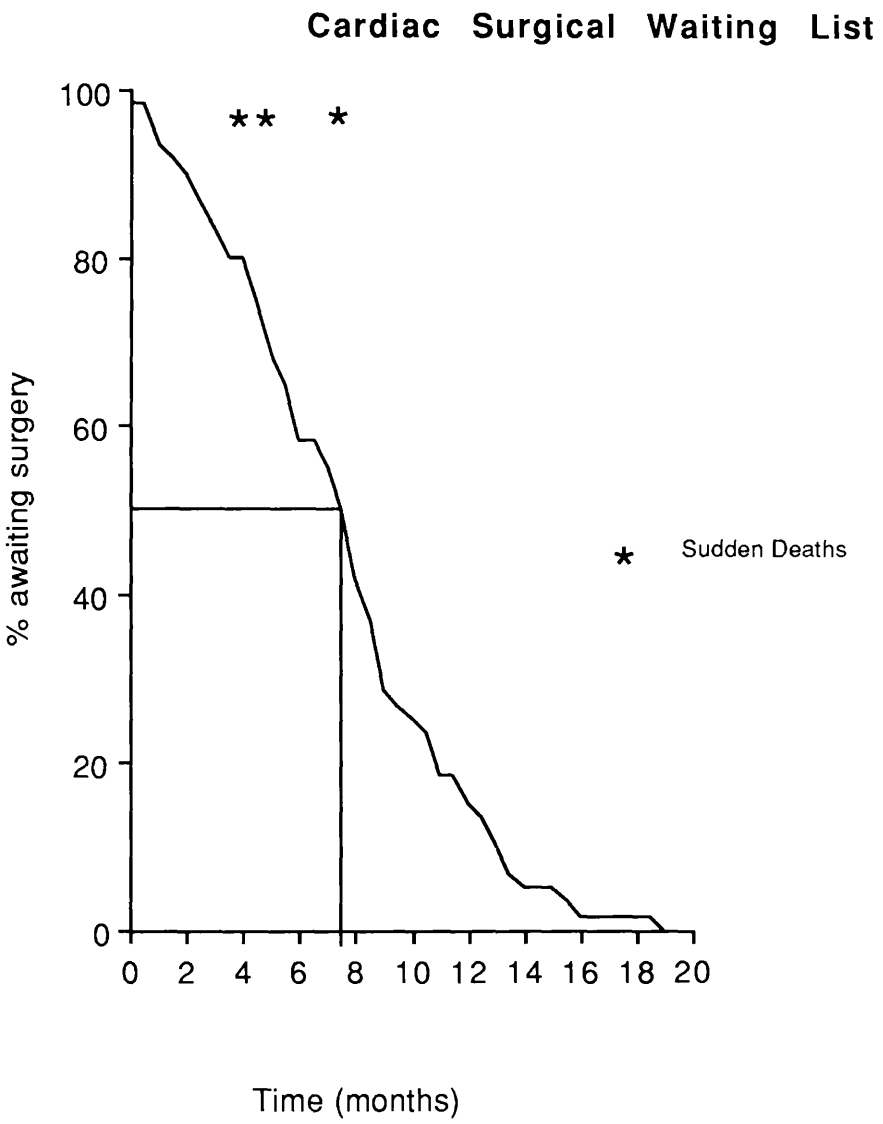

Figure 6.1 Waiting time for surgery in 60 operated and 3 sudden death patients. The median waiting time for surgery was 7.5 months. All the 3 sudden deaths occurred within the first 7 months.

workers (see Table 4.18, Chapter 4). Secondly, in all these 3 patients sudden death could not be predicted from either the ambulatory electrocardiographic monitoring or from SAECG. Although case 77 had 3 episodes of NSVT, the longest comprising 10 VES, the significance of this was not substantiated by SAECG results. However, these 3 patients were nevertheless at a high risk of sudden cardiac death due to the presence of severe echocardiographic left ventricular hypertrophy (Levy et al, 1990).

Summary

Of the total 100 patients in the study, 60 have had cardiac surgery to date. A total of 7 deaths (7%) occurred in this study population. Three of the deaths occurred suddenly and in patients on the surgical waiting list. Thus the incidence of sudden death while awaiting operation was 4% which is slightly higher compared to previously reported operative mortality following AVR. Both ambulatory electrocardiographic monitoring and SAECG could not predict these sudden deaths. However, all these 3 patients had severe echocardiographic left ventricular hypertrophy.

CHAPTER SEVEN

PREVALENCE OF VENTRICULAR ARRHYTHMIAS IN THE EARLY POST-OPERATIVE PERIOD

7.1 Introduction

Aortic valve replacement usually results in major clinical improvement and substantial reduction of the haemodynamic burdens imposed by aortic stenosis and regurgitation (Bristow et al, 1964; Kennedy, Doces and Stewart, 1977). However, successful aortic valve replacement does not completely eliminate the risk of death particularly sudden cardiac death in both the early and late post-operative periods (Shean et al, 1971; Hirshfeld et al, 1974; Barratt-Boyes, Roche and Whitlock, 1977; Rubin et al, 1977; Samuels et al, 1979). The underlying mechanism in these sudden deaths is still unclear and remains speculative, but it has been presumed by some workers to be secondary to malignant ventricular tachyarrhythmias (Rubin et al, 1977; Samuels et al, 1979).

Despite the widespread use of ambulatory electrocardiographic recording to detect arrhythmias in a variety of cardiac conditions, few data have been reported concerning the prevalence of ventricular arrhythmias in the early post-operative period following aortic valve replacement. In this study, therefore, ambulatory electrocardiographic monitoring was performed in patients with aortic valve disease in the immediate post-operative period following valve replacement to analyse for the presence and severity of ventricular arrhythmias.

7.2 Patients and Methods

Sixty of the 100 study patients have had cardiac surgery

to date. Of these 60 patients, 38 were studied by ambulatory electrocardiographic monitoring using the same equipment as that for the pre-operative study. The recordings were made between the 5th and 7th post-operative days before the patient was discharged home. Serum potassium levels were obtained during the monitoring period. The recordings were analysed as previously described in Chapter 3.

7.3 Results

Prevalence of Ventricular Arrhythmias (VA)

Five of the 38 patients studied had technical problems with their ambulatory ECG recordings. Therefore the results of the remaining 33 patients are presented here. None of the patients had hypokalaemia during the monitoring period and the mean serum potassium of the study group was 4.45 $\pm$ 0.32 mmols/L.

Twenty-two patients were monitored for 48 hours while 11 patients had recordings for only 24 hours. Table 7.1 outlines the results of ambulatory ECG monitoring of the 33 patients. Twenty-two patients (67%) had infrequent ventricular extrasystoles (<10 VES/h) and of these 22 patients no VES were detected in 2 patients. Five patients (15%) had 10-30 VES/h and frequent VA (>30 VES/h) occurred in 6 patients (18%). Two patients (6%) had frequent couplets (>10 couplets/24hrs) while infrequent couplets (<10 couplets/24hrs) were recorded in 9 patients (27%). Runs of nonsustained ventricular tachycardia were

Table 7.1

Prevalence of Ventricular Arrhythmias in the Early Post-operative Period

	Number of Patients	%
‹10 VES/hr	22	67
10-30 VES/hr	5	15
›30 VES/hr	6	18
Frequent couplets (›10/24 hrs)	2	6
Infrequent couplets (‹10/24 hrs)	9	27
NSVT	6	18

VES = Ventricular extrasystoles
NSVT = Nonsustained ventricular tachycardia

recorded in 6 patients (18%). None of the 33 patients suffered a cardiac arrest during the post-operative hospital stay.

Nonsustained Ventricular Tachycardia (NSVT)

Table 7.2 outlines episodes of NSVT and their relationship to other forms of VA. There were a total of 14 episodes of NSVT occurring in 6 patients. One patient in whom a single episode of NSVT occurred, had 24 hours of ambulatory ECG monitoring (patient number 40). In the 5 patients with 48 hours of monitoring, 5 of the episodes of NSVT occurred in the first 24 hour period, while 8 occurred in the second 24 hour period. Patient number 55 had 9 episodes of NSVT, all episodes consisting of 3 VES, while the remaining patients had a single episode each. The longest episode comprised of a run of 10 VES (patient number 40) (Figure 7.1). None of the patients reported any symptoms coinciding with these episodes of NSVT. All the patients except patient number 51 had couplets, occurring most frequently in patients number 6 and 55. It is noteworthy to point out that none of the 6 patients with NSVT had coronary artery disease.

Lown Grading (Table 7.3)

The majority of the patients (88%) were in Grade 5, two (6%) in Grade 0 and 2 (6%) in Grade 1. Thus, in terms of complexity (Grades 3 to 5) 88% of the patients had complex VA's.

Table 7.2

Episodes of Nonsustained Ventricular Tachycardia and their Relationship to Other Forms of Ventricular Arrhythmias

Patient I.D.	No. of episodes	No. of VES* in each episode	Period of occurence	Couplets in 24 hrs	No. of VES /24 hrs
6	1	3	2nd 24 hrs	36	1347
27	1	3	1st 24 hrs	2	485
40	1	10	24 hr monitoring only^	2	1053
41	1	7	2nd 24 hrs	2	239
51	1	5	2nd 24 hrs	0	38
55	9	3	1st 24 hrs	72	1519
		3	1st 24 hrs		
		3	1st 24 hrs		
		3	1st 24 hrs		
		3	2nd 24 hrs		
		3	2nd 24 hrs		
		3	2nd 24 hrs		
		3	2nd 24 hrs		
		3	2nd 24 hrs		

* VES = ventricular extrasystoles
^ patient number 40 had 24 hours only of ambulatory electrocardiographic monitoring

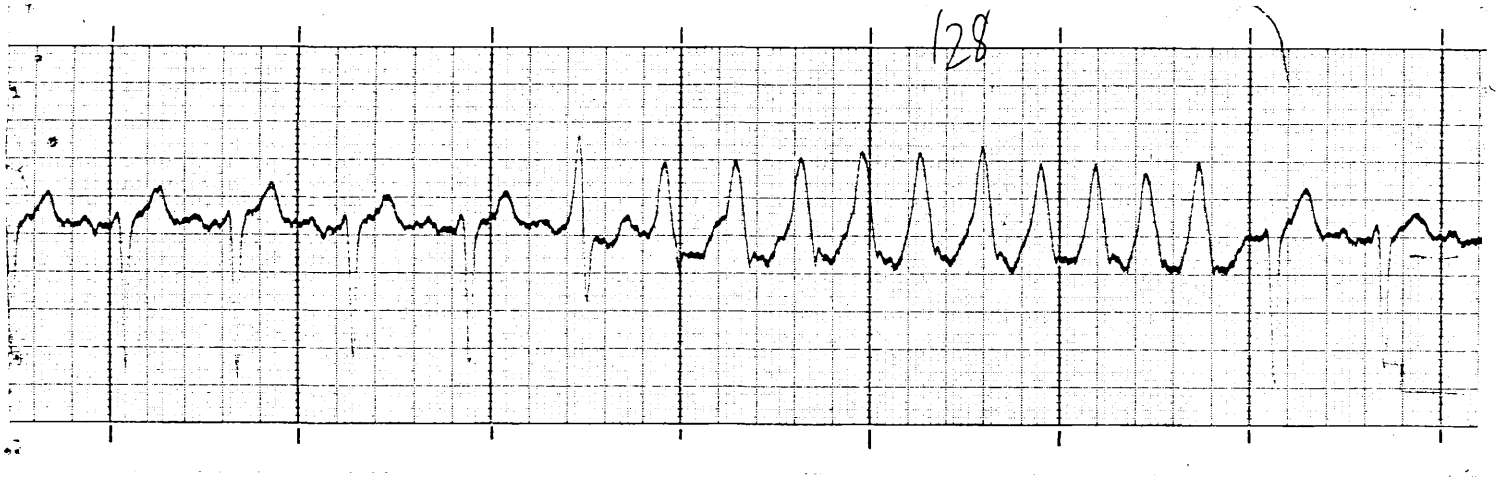

Figure 7.1: An episode of NSVT comprising 10 VES at a rate of 190 beats per minute recorded in a 66 year old man who had undergone AVR.

Table 7.3

Distribution of Ventricular Arrhythmias According to the Lown's Grading[x]

	No. of Patients (n=33)	%
Grade 0	2	6
Grade 1	2	6
Grade 2	0	0
Grade 3	0	0
Grade 4A	0	0
Grade 4B	0	0
Grade 5	29	88

[x] Lown grades:
0 = no ventricular extrasystoles
1 = infrequent ventricular extrasystoles (‹30/h)
2 = frequent ventricular extrasystoles (›30/h)
3 = multifocal ventricular extrasystoles
4A = ventricular couplets
4B = nonsustained ventricular tachycardia
5 = R on T phenomenon

7.4 Discussion

There is scant data in the literature concerning the incidence of ventricular arrhythmias in patients with aortic valve disease in the immediate post-operative period following aortic valve replacement. Three studies have reported a low incidence of ventricular arrhythmias (Angelini et al, 1974; Smith et al, 1972; Michelson, Morganroth and MacVaugh, 1979) while in another study (Schilling et al, 1982) a high incidence of ventricular arrhythmias occurred.

Angelini et al (1974) studied 178 unselected and consecutive patients undergoing heart surgery to assess the incidence of arrhythmias. Twenty-eight of these 178 patients were adults with aortic valve disease undergoing aortic valve replacement. They reported a very low incidence of ventricular arrhythmias in these 28 patients, ventricular extrasystoles (VES) occurring in only 4 patients (14%). No episodes of ventricular tachycardia were reported during the entire hospital stay (mean 12.3 days). There are two major setbacks in the design of this study. Firstly, detection of ventricular arrhythmias relied solely on clinical observations confirmed by electrocardiographic rhythm strips. The other method used for detecting arrhythmias was by routine electrocardiograms, generally one being done daily in the first 3 post-operative days and one before discharge. Secondly, ventricular arrhythmias of less than 2 VES per minute were excluded from analysis. This would obviously lead to an

underestimation of the true incidence of ventricular arrhythmias.

Smith et al (1972) studied 50 consecutive patients with a variety of valvular lesions and undergoing cardiac valve replacement. Arrhythmias were assessed by continuous monitoring using a bedside electrocardiographic monitor during the first 7 days following operation. Sixteen of the 50 patients had undergone aortic valve replacement. Ventricular arrhythmias were reported in 3 of these 16 patients (21%) who had undergone aortic valve replacement (AVR). Three patients out of the total of 50 patients enrolled in the study had episodes of ventricular tachycardia (VT). As the data was pooled together it was not clear as to how many of these 3 patients with VT belonged to the group of patients who had undergone AVR.

The only study in this series to use ambulatory electrocardiographic monitoring for the detection of arrhythmias was that by Michelson and his colleagues (Michelson, Morganroth and MacVaugh, 1979). They studied 70 consecutive patients undergoing cardiac surgery, 15 of whom underwent valve replacement. Of these 15 patients, 12 had aortic valve disease and were undergoing AVR. Twenty-four hour ambulatory electrocardiographic monitoring was performed on the 4th and 8th post-operative days. Ventricular arrhythmias were considered to be significant and hence reported, on the occurrence of VES more than or equal to 30 per hour, ventricular couplets, ventricular tachycardia ($\geq$3 consecutive VES) and multiform VES. Thus VES of less than 30 per hour were not included in the

analysis. Accordingly, significant ventricular arrhythmias occurred in 3 of 15 patients (20%) who underwent valvular replacement. No patient in this group had ventricular tachycardia.

Schilling et al (1982) using a different method of grading ventricular arrhythmias, reported a high incidence of ventricular arrhythmias in their patients. They studied 38 patients with aortic valve disease by 24 hour ambulatory electrocardiographic monitoring 2 weeks following AVR. Complex ventricular arrhythmias (Lown Grades 3, 4A and 4B) occurred in 33 of the 38 patients (87%).

In the present study, frequent ventricular arrhythmias (›30 VES/h) were present in 18% of the patients, couplets were also quite common, occurring in 33% and episodes of nonsustained ventricular tachycardia (NSVT) were recorded in 18%. The incidence of complex ventricular arrhythmias and in particular episodes of NSVT in the present study was higher than previously reported. This can be directly attributed to an increase in arrhythmia detection due to the use of a longer electrocardiographic monitoring period. Most of the patients in this study (22 out of 33) had 48 hours of ambulatory electrocardiographic monitoring. The usefulness of longer periods of ambulatory monitoring is clearly evident from this study. Of the 13 episodes of NSVT recorded in 5 of the 6 patients with NSVT who had 48 hours of ambulatory monitoring, 8 (62%) of them were detected in the second 24 hour period. Thus, the incidence of NSVT would have been greatly underestimated had 24 instead of 48 hours of monitoring

been performed. One must therefore be aware of this point when comparing the results of studies using different periods of ambulatory monitoring. This may explain the variation in the prevalence and severity of ventricular arrhythmias in different studies.

The clinical significance of these early post-operative ventricular arrhythmias following AVR is not known. Further follow-up of these patients may determine whether these arrhythmias contribute to sudden death or to other complications after discharge from hospital.

7.5 Summary

The incidence of complex VA including episodes of NSVT in the present study was higher than that reported by the majority of previous studies. Complex VA (Lown grades 3 to 5) occurred in 88% of patients. The importance and usefulness of longer periods of ambulatory electrocardiographic monitoring was demonstrated. Further follow-up of these patients will be needed in order to verify the prognostic significance of these early post-operative VA following AVR.

CHAPTER EIGHT

EFFECT OF AORTIC VALVE REPLACEMENT ON ECHOCARDIOGRAPHIC LEFT VENTRICULAR HYPERTROPHY AND CARDIAC ARRHYTHMIAS

8.1 Introduction

Left ventricular hypertrophy, irrespective of the criteria used to define it, whether by electrocardiography, chest x-ray or echocardiography, is associated with an increased risk of sudden death (Kannel, W.B, 1983). This increased risk has been speculated by various workers to be due to the increased incidence of frequent and complex ventricular arrhythmias (Levy et al, 1987; Siegel et al, 1990). Sudden death is also not an uncommon occurrence in patients with aortic valve disease (Ross and Braunwald, 1968). This may not be surprising given the fact that electrocardiographic left ventricular hypertrophy is found in 85% of patients with severe aortic valve disease (Braunwald, 1988). Furthermore, several studies on patients with significant aortic valve disease have shown a high incidence of complex ventricular arrhythmias (Kennedy et al, 1975; Schilling et al, 1982; Von Olshaussen, 1983; Kostis et al, 1984; Klein, 1984)

Regression of left ventricular hypertrophy either following a period of adequate control of blood pressure in cases of hypertension, or following valve replacement in patients with significant aortic valve disease, would be expected to lead to a decrease in ventricular ectopic activity and hence result in a reduction of the risk of sudden death in these patients.

Therefore, in this part of the study, 30 of the original 100 patients were investigated by echocardiography and doppler ultrasound, ambulatory electrocardiographic

monitoring and signal-averaged electrocardiography, an average of 121 ± 24 days following aortic valve replacement. The results of these investigations were compared with the pre-operative data. Twenty-one of the original 100 patients had ambulatory electrocardiographic recordings performed during the pre-operative, early post-operative (5-7 days post AVR) and late post-operative (121 ± 24 days post AVR) periods and the prevalence of arrhythmias during these 3 periods was compared.

8.2 Methods

8.2.1. Study Patients (Table 8.1)

The study group consisted of 30 of the 100 patients studied before surgery. These comprised of 18 men and 12 women with a mean age of 60 ± 10 years (range 36 to 77 years). The studies were performed 121 ± 24 days (range 85 to 199 days) following cardiac surgery. Twenty-two patients had undergone aortic valve replacement (AVR) alone. In addition to AVR, 3 patients had coronary artery bypass graft surgery (CABG), one had a mitral valvotomy, 3 had mitral valve replacements (MVR) and one had a MVR plus CABG. Eleven patients had received Bjork-Shiley mechanical prosthesis, 13 had received Carpentier-Edwards porcine xenografts and 6 had received bioflo pericardial bioprostheses in the aortic position. The native aortic valve was bicuspid in 14 and tricuspid in 16 patients.

Table 8.1

Operative Data of Patients

Case	Age	Sex	Type of surgery	Type of aortic valve	Native valve	Post-op day of study
11	41	F	AVR	BS	TRI	95
13	66	F	AVR+M. VALV.	CE	TRI	133
14	59	F	AVR+MVR	BS	BIC	135
20	56	F	AVR	CE	BIC	131
21	65	M	AVR	BS	TRI	131
23	68	M	AVR+MVR	CE	TRI	119
25	68	F	AVR	BIO	TRI	104
27	62	M	AVR+CABG	BIO	TRI	85
29	63	M	AVR	CE	BIC	125
31	66	F	AVR+MVR	BS	TRI	99
32	57	M	AVR	BIO	TRI	111
33	64	M	AVR	CE	BIC	142
34	66	F	AVR	BIO	BIC	124
36	58	F	AVR+CABG	BIO	BIC	104
38	48	M	AVR	CE	TRI	175
39	43	M	AVR	CE	TRI	128
40	66	M	AVR	CE	TRI	138
41	69	M	AVR	BIO	TRI	132
47	72	M	AVR+CABG	CE	BIC	199
48	36	M	AVR	BS	BIC	98
49	55	M	AVR	BS	BIC	139

CONTINUED/....

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Case	Age	Sex	Type of surgery	Type of aortic valve	Native valve	Post-op day of study
51	63	M	AVR	CE	BIC	103
55	54	M	AVR	BS	TRI	134
56	57	F	AVR	BS	TRI	95
57	51	F	AVR	CE	BIC	114
58	77	F	AVR	CE	TRI	108
66	46	M	AVR	BS	BIC	104
67	57	M	AVR	BS	BIC	101
70	66	F	AVR+MVR+CABG	BS	TRI	124
78	70	M	AVR	CE	BIC	136
Mean ± SD	60 ± 10					121 ± 24

AVR = aortic valve replacement. M.VALV. = mitral valvotomy. MVR = mitral valve replacement. CABG = coronary artery bypass graft surgery. BS = Bjork-Shiley. CE = Carpentier-Edwards. Bio = bioflo pericardial bioprostheses. BIC = bicuspid. TRI = tricuspid.

8.2.2. Study Protocol

Explanatory letters together with appointments were sent to the patients who were asked to attend a special out-patient clinic. After explaining the study protocol in detail to the patient, an informed consent was obtained. A thorough history with particular stress on the prevalence of exertional chest pain, breathlessness, palpitations and syncope was obtained. Current drug therapy and the smoking status of the patient was documented. A thorough physical examination was then carried out including the height and weight of the patient. Appropriate blood investigations were done and finally signal-averaging of the electrocardiogram was performed. The patient was then fitted with an Oxford Medilog II frequency modulated recorder to wear around the waist for a period of 48 hours. During this period, all patients were fully ambulatory and none was receiving anti-arrhythmic medications. Hypokalaemia (serum K^+ ‹3.5 mmols/L) was not present in any patient. On the return appointment which was 48 hours later, detailed echocardiographic and doppler ultrasound examinations were performed. All data were analysed using the methodology previously described in Chapter 3.

Pre and post-operative clinical, echocardiographic, signal-averaged electrocardiographic and ambulatory electrocardiographic data were compared. In 21 patients who had ambulatory electrocardiographic monitoring performed during the pre-operative, early post-operative (5-7 days post AVR) and late post-operative (121 ± 24 days

post AVR) periods, a comparison in the prevalence of arrhythmias during these 3 periods was made.

8.3 Results

8.3.1. Clinical Characteristics of Patients

Table 8.2 presents the clinical characteristics of patients before and after surgery. Chest pain typical of angina pectoris was reported in only one patient post-operatively compared to 12 patients before surgery. This patient with post-operative angina had a normal coronary angiogram performed prior to operation. Palpitations were reported by 2 patients while none of the patients reported syncope post-operatively. There was a marked improvement in the functional status of the patients following surgery. Seventy percent of the patients were in NYHA functional Class I compared to only 20% prior to surgery. On the other hand, 13% of patients were in NYHA functional Class 3 before and none after surgery. Digoxin was prescribed more frequently after surgery and likewise atrial fibrillation was the basic rhythm in more patients post-operatively (9 Vs 7 patients). On the other hand, a slightly smaller number of patients continued to smoke cigarettes after operation and this may reflect an improvement in the awareness of the patients on the ill-effects of smoking.

Table 8.2

Clinical Characteristics of Patients Before and After Surgery

Characteristics	Pre-operative (n=30) number (%)	Post-operative (n=30) number (%)
Angina	12 (40)	1 (3)
Palpitations	18 (60)	2 (7)
Syncope	7 (23)	0 (0)
NYHA 1	6 (20)	21 (70)
NYHA 2	20 (67)	9 (30)
NYHA 3	4 (13)	0 (0)
Digoxin	8 (27)	14 (47)
Diuretics	11 (37)	8 (27)
AF	7 (23)	9 (30)
Smoking	14 (47)	8 (27)

NYHA = New York Heart Association functional Class

8.3.2. Echocardiography

Echocardiographic left ventricular hypertrophy (LVMI ›134 g/m^2 in males and ›110 g/m^2 in females) was present in 24 of the 30 patients (80%) post-operatively compared to 28 of the 30 patients (93%) pre-operatively. Table 8.3 depicts pre and post-operative echocardiographic data in the 30 patients distributed according to the predominant aortic valve lesion prior to operation. In patients with predominant AS, AVR was accompanied by a significant decrease in PWTd (1.29 ± 0.08 Vs 1.08 ± 0.05; p ‹0.004), LVMI (190 ± 12 Vs 154 ± 11; p ‹0.02) and as expected a marked reduction in the aortic gradient (81 ± 6 Vs 12 ± 2; p ‹0.0001) and LVSP (219 ± 7 Vs 156 ± 6; p ‹0.0001). Left ventricular systolic function was significantly reduced although still remaining within normal limits following AVR as assessed by both EF (66 ± 4 Vs 57 ± 3; p ‹0.04) and FS (37 ± 3 Vs 30 ± 2; p ‹0.03). Left ventricular diastolic function as assessed by E/A ratio showed some improvement following surgery, although this did not reach statistical significance. Marginal improvement in IVSTd (1.44 ± 0.10 Vs 1.20 ± 0.14; p ‹0.06), significant reduction in LVMI (235 ± 22 Vs 172 ± 20; p ‹0.02) and not surprisingly aortic gradient (61 ± 6 Vs 14 ± 3; p ‹0.0002) and LVSP (218 ± 14 Vs 160 ± 11; p ‹0.003) was noted in patients with combined AS and AR following AVR. Left atrial size on the other hand was significantly increased in these patients following surgery (3.75 ± 0.30 Vs 4.23 ± 0.15; p ‹0.03). Aortic vavle replacement did not result in any significant changes in echocardiographic variables in patients with predominant AR.

Table 8.3

Echocardiographic Data in Patients Studied Before and After Surgery - Data Presented According to the Predominant Aortic Valve Lesion

	AS (n=17)		AR (n=4)		AS + AR (n=9)	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
LVIDd (cm)	5.06 ± 0.70	5.09 ± 0.18	7.56 ± 0.51	6.40 ± 0.53	5.36 ± 0.18	4.99 ± 0.27
PWTd (cm)	1.29 ± 0.08*	1.08 ± 0.05	1.15 ± 0.06	1.10 ± 0.12	1.25 ± 0.10	1.16 ± 0.08
IVSTd (cm)	1.33 ± 0.09	1.17 ± 0.10	1.20 ± 0.08	1.35 ± 0.15	1.44 ± 0.10**	1.20 ± 0.14
LA (cm)	3.72 ± 0.24	3.87 ± 0.12	3.84 ± 0.16	4.93 ± 0.47	3.75 ± 0.30***	4.23 ± 0.15
EDV (cm^3)	125 ± 10	126 ± 11	299 ± 46	236 ± 53	140 ± 12	122 ± 17
LVMI (g/m^2)	190 ± 12+	154 ± 11	321 ± 36	265 ± 77	235 ± 22++	172 ± 20
EF (%)	66 ± 4+++	57 ± 3	48 ± 7	52 ± 3	63 ± 4	63 ± 5
FS	37 ± 3^	30 ± 2	26 ± 5	26 ± 1	33 ± 2	33 ± 3
E/A ratio	0.95 ± 0.07	1.08 ± 0.08	1.41 ± 0.68	1.18 ± 0.26	1.19 ± 0.25	1.05 ± 0.14
PSLVWS (dyn/cm^2)						
Reichek's method	83 ± 11	92 ± 10	166 ± 41	142 ± 9	96 ± 13	80 ± 15
Quinones' method	190 ± 16	193 ± 16	289 ± 53	264 ± 17	220 ± 23	175 ± 24
Aortic Gradient (mmHg)	81 ± 6^^	12 ± 2	13 ± 5	21 ± 4	61 ± 6^^^	14 ± 3
LVSP (mmHg)	219 ± 7V	156 ± 6	163 ± 7	183 ± 14	218 ± 14VV	160 ± 11

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Mean ± SD
LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LA = left atrium. EDV = end diastolic volume. LVMI = left ventricular mass index. EF = ejection fraction. FS = fractional shortening. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity. PSLVWS = peak systolic left ventricular wall stress. LVSP = left ventricular systolic pressure.

*	p <0.004	difference between pre and post-operative PWTd in patients with AS
**	p <0.06	difference between pre and post-operative IVSTd in patients with AS + AR
***	p <0.03	difference between pre and post-operative LA size in patients with AS + AR
+	p <0.02	difference between pre and post-operative LVMI in patients with AS
++	p <0.02	difference between pre and post-operative LVMI in patients with AS + AR
+++	p <0.04	difference between pre and post-operative EF in patients with AS
^	p <0.03	difference between pre and post-operative FS in patients with AS
^^	p <0.0001	difference between pre and post-operative aortic gradient in patients with AS
^^^	p <0.0002	difference between pre and post-operative aortic gradient in patients with AS + AR
v	p <0.0001	difference between pre and post-operative LVSP in patients with AS
vv	p <0.003	difference between pre and post-operative LVSP in patients with AS + AR

8.3.3. Ambulatory Monitoring

Technical problems with the recordings were encountered in 7 patients. Two of these 7 patients had repeat recordings and hence the data of 25 patients are presented in this part of the study.

8.3.4. Prevalence of Ventricular Arrhythmias (VA) (Table 8.4)

Twenty patients (80%) had infrequent ventricular extrasystoles (VES) (<10 VES/h). Of these 20 patients, 3 (12%) had no VES detected during the entire 48 hour period. Two (8%) patients had 10-30 VES/h while frequent VA (>30 VES/h) occurred in only 3 (12%) patients. Frequent couplets (>10 couplets/24hrs) were recorded in only one patient (4%) while infrequent couplets (<10 couplets/24hrs) occurred in 4 patients (16%). Four patients (16%) had nonsustained ventricular tachycardia (NSVT). The total number of VES per 24 hours was correlated with echocardiographic variables in the 25 patients (Table 8.5). No correlation was observed between frequency of VES and any echocardiographic variable.

Nonsustained Ventricular Tachycardia (Table 8.6)

There were a total of five episodes of NSVT occurring in 4 patients, one patient (patient 23) having 2 episodes of 3 VES and 4 VES recorded during the ambulatory period. The longest episode comprising 9 VES occurred in patient number 14 (Figure 8.1). Two episodes of NSVT were

Table 8.4

Prevalence of Ventricular Arrhythmias in the Late Post-operative Period

	Number of Patients (n=25)	%
<10 VES/hr	20	80
10-30 VES/hr	2	8
>30 VES/hr	3	12
Frequent couplets (>10/24 hrs)	1	4
Infrequent couplets (<10/24 hrs)	4	16
NSVT	4	16

VES = ventricular extrasystoles
NSVT = nonsustained ventricular tachycardia

Table 8.5

Relationship Between Number of VES per 24 Hours and Echocardiographic Data of the patients

	r - value	p - value
LVIDd	-0.051	NS
PWTd	0.104	NS
IVSTd	-0.091	NS
LVMI	-0.036	NS
LA	-0.358	NS
EDV	0.016	NS
EF	0.094	NS
FS	0.007	NS
PSLVWS: Reichek's method	-0.086	NS
Quinones' method	-0.139	NS
E/A ratio	0.134	NS

LVIDd = left ventricular internal dimension in diastole. PWTd = posterior left ventricular wall thickness in diastole. IVSTd = interventricular septal thickness in diastole. LVMI = left ventricular mass index. LA = left atrium. EDV = end diastolic volume. EF = ejection fraction. FS = fractional shortening. PSLVWS = peak systolic left ventricular wall stress. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity.

Table 8.6

Episodes of Nonsustained Ventricular Tachycardia and their Relationship to Other Forms of Ventricular Arrhythmias

Patient I.D.	No. of episodes	No. of VES* in each episode	Period of occurrence	Couplets in 24 hrs	No. of VES /24 hrs
14	1	9	1st 24 hrs	2	114
23	2	3	2nd 24 hrs	0	89
		4	2nd 24 hrs		
40	1	3	1st 24 hrs	12	837
49	1	3	2nd 24 hrs	0	9

* VES = ventricular extrasystoles

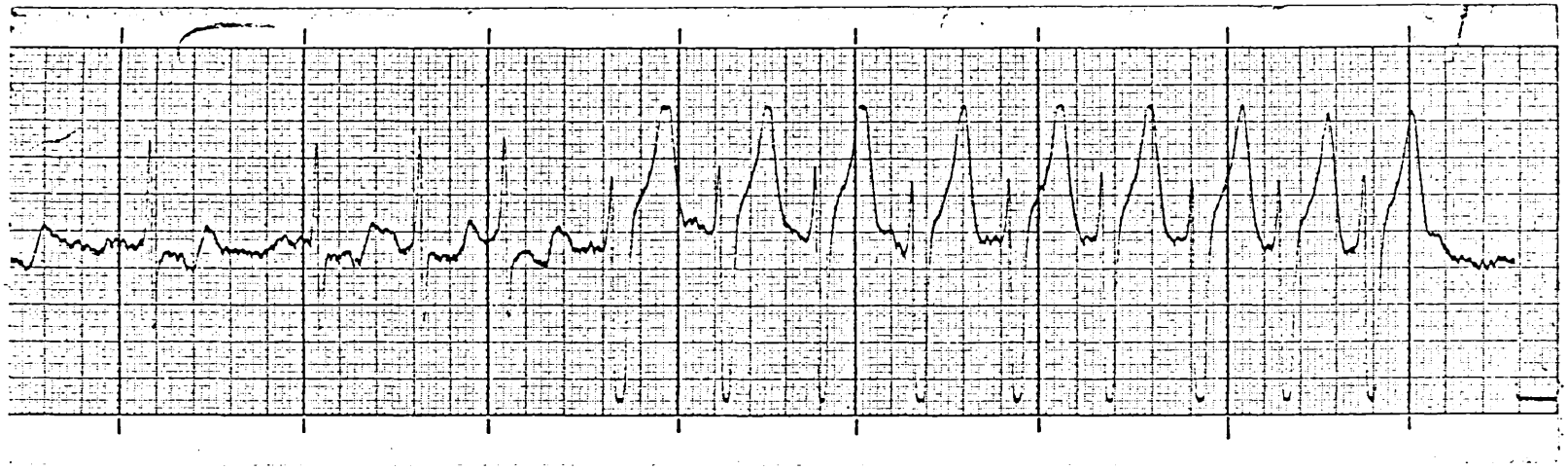

Figure 8.1: An episode of NSVT comprising 9 VES at a rate of approximately 120 beats per minute recorded in a 59 year old woman during the late post-operative period.

recorded in the first 24 hours while 3 episodes were recorded in the second 24 hour period. All these 5 episodes were asymptomatic. There was only one patient (patient 40) with NSVT who also had frequent couplets as well as frequent VES.

Table 8.7 summarises the operative data and echocardiographic findings in the 4 patients with NSVT. Two of these 4 patients were in atrial fibrillation and had mitral valve replacement in addition to aortic valve replacement. Left ventricular mass index was normal in only one patient (patient 49).

Table 8.8 presents the distribution of VA according to their maximum Lown Grade. Three (12%) patients were in Grade 0, 4 (16%) in Grade 1, one (4%) in Grade 4A and 17 (68%) in Grade 5. Thus, 72% of the patients had complex ventricular arrhythmias (Grades 3 to 5).

8.3.5. Frequency of Arrhythmias in the 3 Study Periods

Twenty-one of the total 100 patients in the study had ambulatory electrocardiographic recordings before, immediately after and late following aortic valve replacement. Table 8.9 and 8.10 show the prevalence of arrhythmias in these 21 patients during the 3 study periods. Ventricular extrasystoles per 24 hours tended to have occurred more frequently in the early post-AVR study (328 $\pm$ 460, range 0 to 1519) compared to the other 2 study periods (74 $\pm$ 174, range 0 to 726 before AVR and 134 $\pm$ 251, range 0 to 837 late post-AVR). These differences did

Table 8.7

Summary of Operative Data and Echocardiographic Findings in 4 Patients with Nonsustained Ventricular Tachycardia

Patient ID	Sex	Age	NYHA	AF	Native aortic valve	Type of Surgery	Type of Prothesis	EF	PSLVWS Reich	PSLVWS Quin	EDV	LVMI	E/A
14	F	61	2	+	Biscupid	AVR + MVR	BS + BS	55	125	245	149	150	-
23	M	69	2	+	Tricuspid	AVR + MVR	CE + CE	41	90	199	145	211	-
40	M	67	1	-	Tricuspid	AVR	CE	59	140	288	224	197	0.91
49	M	56	2	-	Biscupid	AVR	BS	45	131	300	157	98	0.91

NYHA = New York Heart Association functional Class. AF = atrial fibrillation. EF = ejection fraction. PSLWVS = peak systolic left ventricular wall stress. EDV = left ventricular end diastolic volume. LVMI = left ventricular mass index. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity. AVR = aortic valve replacement. MVR = mitral valve replacement. BS = Bjork-Shiley. CE = Carpentier-Edwards.

Table 8.8

Distribution of Ventricular Arrhythmias According to the Lown Grading[x]

	No. of Patients (n=25)	%
Grade 0	3	12
Grade 1	4	16
Grade 2	0	0
Grade 3	0	0
Grade 4A	1	4
Grade 4B	0	0
Grade 5	17	68

[x] Lown grades:
0 = no ventricular extrasystoles
1 = infrequent ventricular extrasystoles (‹30/h)
2 = frequent ventricular extrasystoles (›30/h)
3 = multifocal ventricular extrasystoles
4A = ventricular couplets
4B = nonsustained ventricular tachycardia
5 = R on T phenomenon

Table 8.9

Prevalence of Arrhythmias During the 3 Study periods in 21 Patients

	Ventricular ectopics/24 hr + couplets + NSVT			Supraventricular ectopics/24 hr		
Case	Pre-operative	Early post-operative	Late post-operative	Pre-operative	Early post-operative	Late post-operative
11	9	737 4C	800	1691	1118	1509
20	7 1C	6	0	88	8850	1720
21	12	10	45	1378	116	165
23	60	793	89 2V	1104	656	779
25	3	3	2	14	252	5
27	24	485 2C 1V	3 1C	18	362	107
29	80	6	62	12	5	22
31	408	8	11	2037	1468	2257
32	1	1127 3C	17	242	373	631
33	1 1V	1	1	13	23	29
36	11	4	27	80	23	26
38	16	0	39	2	850	12

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	Ventricular ectopics/24 hr + couplets + NSVT			Supraventricular ectopics/24 hr		
Case	Pre-operative	Early post-operative	Late post-operative	Pre-operative	Early post-operative	Late post-operative
39	1	444 4C	9	12	22	8
40	726 7C	1053 2C 1V	837 12C 1V	2446	476	1571
41	89	239 2C 1V	278 3C	33	10	2631
48	7	1	0	22	4	2
49	74	421	9 1V	21	1322	133
51	6 2C	38 1V	159	57	964	4612
55	27	1519 72C 9V	423	467	1227	81
57	0	18	0	17	13	91
67	0	0	2	48	857	13

NSVT = nonsustained ventricular tachycardia.
C = couplets
V = episodes of nonsustained ventricular tachycardia

Table 8.10

Prevalence of Arrhythmias in the 21 Patients Studied
Before, Early and Late After Aortic Valve Replacement

	Before AVR	Early post-AVR	Late post-AVR
VES/24 hr	74 ± 174 (0 - 726)	328 ± 460 (0 - 1519)	134 ± 251 (0 - 837)
Early VES/24 hr	2 ± 6* (0 - 30)	67 ± 170 (0 - 688)	30 ± 110 (0 - 509)
Atrial ectopics	467 + 769 (2 - 2446)	904 + 1887 (4 - 8850)	781 + 1209 (2 - 4612)
NSVT	1 patient	5 patients	3 patients

Mean ± SD (range)
AVR = aortic valve replacement. VES = ventricular extrasystoles. NSVT = nonsustained ventricular tachycardia

* p = 0.025 difference in Early VES/24hr between pre-AVR and Early post-AVR

not reach statistical significance. On the other hand, early VES per 24 hours (R on T phenomenon) were significantly more frequent in the early post-AVR period (67 ± 170) compared to the pre-operative period (2 ± 6, p = 0.025). There was no significant difference between the groups in the frequency of atrial ectopics. Nonsustained ventricular tachycardia was more common in the early post-AVR period, occurring in 5 patients (24%) compared to pre-operative (1 patient, 5%) and late post-operative (3 patients, 14%) periods.

Complex VES (Grades 3 to 5) were present in 16 patients before, in 17 patients early after, and in 15 patients late after aortic valve replacement (Figure 8.2). Twelve patients had Complex VES while only 2 had simple VES (Grades 1 and 2) in all the 3 recordings.

8.3.6. Signal-Averaged Electrocardiography (SAECG)

Signal-averaged electrocardiograms were technically satisfactory in 29 of the 30 patients, one patient being excluded due to an unacceptably high noise level (1.4 uV). Table 8.11 depicts the prevalence of abnormal SAECGS. QRS duration was prolonged in 5 patients (17%), low amplitude signals under 40 microvolts (LAS40) were prolonged in 2 (7%) patients and root mean square voltage of the signals in the terminal 40 milliseconds (RMSV40) was abnormally decreased in 2 (7%) patients. Late potentials were present (i.e. $\geq$2 abnormal criteria) in only 2 (7%) patients, one of whom had all the 3 criteria positive on the SAECG.

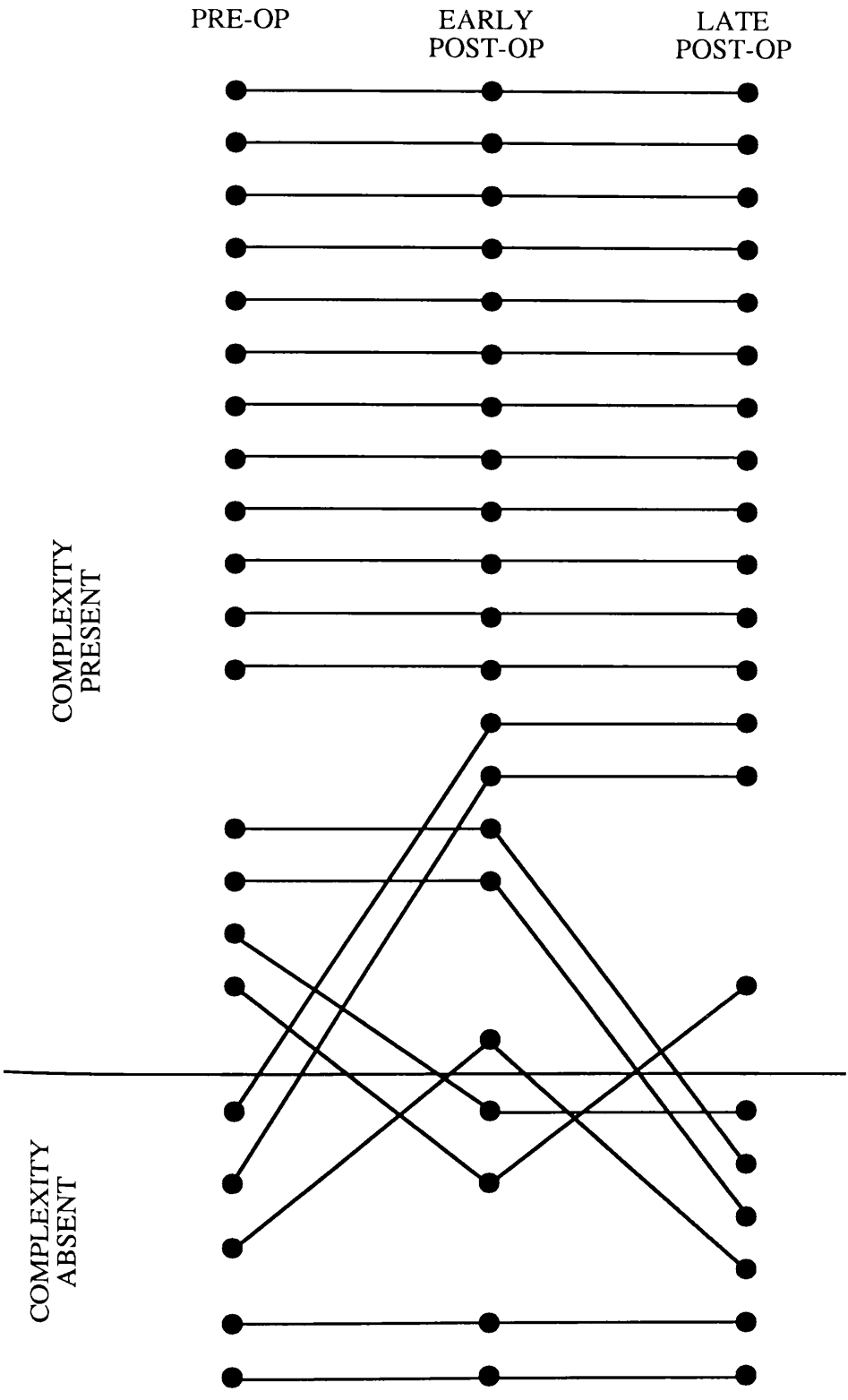

Figure 8.2 Presence of Complex Ventricular Extrasystoles Before, Early After And Late After Aortic Valve Replacement

Table 8.11

Prevalence of Abnormal Signal-Averaged Electrocardiograms in the Late Post-Operative Period

	No. of patients (n=29)	%
QRS (≥120 msec)	5	17
LAS 40 (≥38 msec)	2	7
RMSV 40 (≤25 uV)	2	7
Abnormality by 2 criteria	1	3
Abnormality by 3 criteria	1	3

QRS = filtered QRS duration. LAS40 = low amplitude signals under 40 uV. RMSV40 = root mean square voltage of the signals in the terminal 40 milliseconds.

Table 8.12 presents operative, echocardiographic and ambulatory electrocardiographic data in the 2 patients with abnormal SAECGS. Patient 47 also had an abnormal SAECG before surgery. Left ventricular systolic function assessed by echocardiographic ejection fraction was satisfactory while diastolic function (E/A ratio) was markedly abnormal in both the patients. Substantial left ventricular hypertrophy was present in patient 47 while LVMI was at the upper limit of normal in patient 58. Ambulatory electrocardiographic monitoring showed infrequent VES and absence of couplets in both. Neither of the two patients had episodes of nonsustained ventricular tachycardia (NSVT) throughout the 48 hours of ambulatory monitoring. Thus, in the 4 patients with episodes of NSVT (Table 8.6), none had late potentials on the SAECG.

8.3.7. SAECGS Before and Late After AVR

Table 8.13 depicts SAECG results in 29 patients studied before and late after AVR. Although there was a prolongation in the LAS40 post-operatively, the difference did not reach statistical significance. Root mean square voltage of the signals in the terminal 40 milliseconds on the other hand was significantly reduced post-operatively (119.7 ± 69.4 uV Vs 87.7 ± 65.4 uV; $p = 0.04$).

8.4 Discussion

As a result of improvement in intra-operative and post-operative management, aortic valve replacement (AVR) can

Table 8.12

Summary of Operative, Echocardiographic and Ambulatory Electrocardiographic Data in 2 Patients with Abnormal SAECGS

Patient ID	Sex	NYHA	Type of Surgery	Type of Prosthesis	EF	PSLVWS Reich	PSLVWS Quin	EDV	LVMI	E/A	No of VES/24hrs	Couplets per 24hrs	Episodes of VT
47	M	1	AVR+CABG	CE	73	70	162	131	195	0.67	54	0	0
58	F	1	AVR	CE	79	36	112	89	109	0.64	3	0	0

SAECG = signal averaged electrocardiogram. NYHA = New York Heart Association functional Class. EF = ejection fraction. PSLWS = peak systolic left ventricular wall stress. EDV = left ventricular end-diastolic volume. LVMI = left ventricular mass index. E/A = ratio between early (E) and late (A) left ventricular diastolic filling velocity. VES = ventricular extrasystoles. AVR = aortic valve replacement. CABG = coronary artery bypass graft surgery. CE = Carpentier-Edwards.

Table 8.13

SAECGS in 29 Patients Studied Before and Late After Aortic Valve Replacement

	Before AVR	After AVR	p - value
QRS duration	104 ± 16	104 ± 19	0.77
LAS 40	16.6 ± 8.5	20.5 ± 10.7	0.10
RMSV 40	119.7 ± 69.4	87.7 ± 65.4	0.04
Noise level	0.34 ± 0.12	0.34 ± 0.12	1.0

Mean + SD
LAS40 = low amplitude signals under 40 uV. RMSV40 = root mean square voltage of the signals in the terminal 40 milliseconds.

now be accomplished with an operative risk of 5% or less (Mullany et al, 1987; Jones et al, 1989; Lytle et al, 1989). However, late sudden death following AVR remains an important and unfortunately unresolved problem (Isom et al, 1977). These sudden deaths have been reported to account for 17 to 45 percent of all late deaths after AVR (Hirshfeld et al, 1974; Rubin et al, 1977; Barratt-Boyes, Roche and Whitlock, 1977; Samuels et al, 1979). Malignant ventricular tachyarrhythmias are thought by most workers to be the most likely underlying mechanism in these sudden deaths (Rubin et al, 1977; Samuels et al, 1979; Santinga et al, 1980). Santinga and co-workers (1980) compared pre-operative and post-operative data of 16 patients who died unexpectedly at least 2 years following AVR, with the data of 52 age-matched late survivors who had received the same type of aortic valve prosthesis. Post-operative ventricular arrhythmias were significantly more prevalent in the patients who had died suddenly compared with the survivors. In addition to this, fewer patients in the sudden death group were in NYHA functional Class 1 and significantly more were in congestive heart failure post-operatively compared with the control group.

In the present study 30 patients were investigated by echocardiography and doppler ultrasound and in 25 patients, 48 hour ambulatory electrocardiographic monitoring was performed at an average of 121 $\pm$ 24 days after AVR. Substantial symptomatic improvement was noted following AVR, angina being present in only one patient, palpitations in 2 while syncope was not reported in any. Of more clinical significance was the dramatic improvement

in the NYHA functional Class post-operatively. All patients were in NYHA Classes 1 and 2 post-operatively compared to 87% before surgery (Table 8.2). This is in agreement with previously reported improvement in NYHA functional Class of patients with aortic valve disease following AVR (Von Olshausen et al, 1984; Galloway et al, 1990). In a recent follow-up study reported by Galloway et al (1990), AVR was also shown to result in marked symptomatic improvement. Pre-operatively 9% of patients were in NYHA Class 2, 32% were in NYHA Class 3 and 59% were in NYHA Class 4, compared to 76% in NYHA Class 1 and 2, 22% in NYHA Class 3 and only 2% in NYHA Class 4 post-operatively. It must however be noted that the extent to which clinical improvement is associated with regression of left ventricular hypertrophy and abnormalities of ventricular function is not known (Gaasch, Andrias and Levine, 1978). Hence the finding of an impairment in left ventricular systolic function in the present study in patients with predominant AS was not entirely unexpected (Table 8.3).

8.4.1. Regression of Left Ventricular Hypertrophy

Left ventricular hypertrophy in significant aortic valve disease, whether stenotic or insufficient, occurs as a result of substantial haemodynamic stress on the left ventricle in the form of pressure or volume overload, thus enabling the heart to maintain systolic wall stress at or near normal levels (Grossman, Jones and McLaurin, 1975). This response to volume and pressure overload develops over many years as the disease progresses. Thus

regression of left ventricular hypertrophy following successful correction of volume or pressure overload by AVR would be expected to be a slow and continuous process, probably taking many years to reach a steady state.

In the present study AVR was accompanied with a significant reduction in LVMI in patients with AS and combined AS and AR (Table 8.3). Although patients with predominant AR also showed a noticeable decrease in LVMI, this did not reach statistical significance probably due to the very small number of patients belonging to this group. Previous clinical studies have reported similar results (Kennedy, Doces and Stewart, 1977; Gaasch, Andrias and Levine, 1978; Pantely, Morton and Rahimtoola, 1978). Kennedy and his colleagues (1977) studied 24 patients with aortic valve disease, 9 with pure AS, 10 with combined AS and AR and 5 with AR. They demonstrated a marked reduction in LVMI 19 $\pm$ 12 months after AVR. However, despite the impressive reduction in hypertrophy, LVMI did not return to within 2 standard deviations of normal. Contrary to these findings, Gaasch and his co-workers (1978) reported significant changes in left ventricular muscle mass in 19 patients with AR who had serial echocardiographic studies following AVR. Between 9 and 24 months after AVR, left ventricular muscle mass was within 2 standard deviations of the average for their normal controls. Furthermore, in a recent study reported by Monrad et al (1988), regression of left ventricular hypertrophy continued to take place to as late as 8.1 $\pm$ 2.9 years after AVR.

The present study has demonstrated a substantial reduction in LVMI following AVR, but regression of left ventricular hypertrophy was nevertheless incomplete. This was not unexpected given the fact that regression of left ventricular hypertrophy after AVR is a slow and continuous process which may take years before LVMI returns to normal. It is therefore possible that further reduction in hypertrophy will occur in these patients if they continue to have good prosthetic valve function over a longer period of time.

8.4.2. Prevalence of Ventricular Arrhythmias (VA)

In the present study ventricular ectopic activity was present in 22 of the 25 patients (88%) studied by ambulatory electrocardiographic monitoring. The majority (80%) of patients had infrequent VA (<10 VES/h) while frequent VA (>30 VES/h) occurred in only 3 (12%) patients. Frequent couplets were recorded in only one (4%) patient while episodes of NSVT occurred in 4 (16%) patients (Table 8.4).

Gradman et al (1981) monitored 45 patients for 48 hours at a mean interval of 3.3 years after aortic valve replacement. Eighty-nine percent of their patients had complex VA. In close agreement with their findings, complex VA occurred in 72% of patients in the present study (Table 8.8) However, their incidence of NSVT was higher, occurring in 36% of their patients compared to 16% in the present study. The main reason for the high incidence of NSVT in the study of Gradman et al was the considerable

impairment in left ventricular function seen in some of their patients. In fact, 70% of episodes of NSVT occurred in the patients with impaired left ventricular function. Von Olshausen et al (1984) studied 45 patients with aortic valve disease 14 ± 7 months after AVR. They reported a low incidence of complex VA in their patients. In contrast to their findings, Kostis et al (1984) reported a higher prevalence of complex VA in 13 patients with aortic valve disease studied 3 months following AVR.

These differing incidences in the frequency and complexity of VA reported by different studies may be explained by several factors. Firstly, these studies were performed at different periods following AVR. Secondly, patients were not comparable in terms of their age, type of aortic valve disease, prevalence of concomitant coronary artery disease, the degree of impairment of left ventricular function and most importantly the surgical procedure and the type of aortic valve prostheses. Thirdly, the methods used for arrhythmia detection and quantification were not uniform. Finally, there was a marked variability in the size of the study populations in the different studies. Furthermore, a spontaneous and marked variability in the frequency and complexity of VA of individual patients has been well documented (Morganroth et al, 1978; Michelson and Morganroth, 1980).

The present study has also shown the importance of longer periods of ambulatory electrocardiographic monitoring. Five episodes of NSVT occurred in 4 patients and of these 5 episodes, only 2 were recorded in the first 24 hour

period (Table 8.6) Thus, if only 24 hours of ambulatory monitoring had been performed, 60% of episodes of NSVT would have been missed. Obviously, longer recording periods (>48 hours) would have picked up more complex arrhythmias but the patients' tolerance and convenience have to be taken into consideration.

8.4.3. Significance of NSVT

Five episodes of NSVT occurred in 4 patients (16%) in the present study. However, none of these 4 patients had late potentials on their SAECG (Table 8.12). Signal-averaged electrocardiography has been shown by several workers to be the most accurate predictor for the induction of sustained ventricular tachycardia by programmed ventricular stimulation in patients with NSVT recorded on ambulatory electrocardiographic monitoring (Buxton et al, 1987; Turitto et al, 1988). Furthermore, the prognostic significance of late potentials has been studied prospectively by Breithardt, Martinez-Rubio and Borggrefe (1990). In patients with ischaemic heart disease and previous myocardial infarction, they showed a higher risk of major arrhythmic complications including sudden cardiac deaths in patients with late potentials on SAECG. Thus, the absence of late potentials in the 4 patients with NSVT in the present study would suggest a low risk for serious future arrhythmic events in these patients. Further follow-up of these patients would be needed in order to verify this prospectively.

8.4.4. Effect of AVR on VA and SAECG

Twenty-one of the total 100 study patients had ambulatory electrocardiographic monitoring performed before AVR, immediately after and late after AVR (Table 8.9 and 8.10). There were no significant differences in VES frequency in the 3 study periods. This is in agreement with Kostis et al's findings in 13 patients studied before and 3 months after AVR (Kostis et al, 1984). They showed no difference in pre and post-operative VES frequency (1073 ± 66 Vs 621 ± 355 VES/24 hrs). In another study Von Olshausen and co-workers reported a significant reduction in VES frequency only in a subgroup of their patients in whom AVR was accompanied with improvement in left ventricular function (Von Olshausen et al, 1984).

Signal-averaged electrocardiographic results in 29 patients studied before and late after AVR were compared (Table 8.13). Aortic valve replacement was accompanied by a significant reduction in RMSV40 (119.7 ± 69.4 uV before and 87.7 ± 65.4 uV after AVR; $p < 0.05$). This finding has not been previously reported in patients with aortic valve disease.

8.5 Summary

This part of the study has shown that infrequent, but complex VA occur in patients with aortic valve disease late after AVR. Nonsustained ventricular tachycardia occurred in 16% of the patients. However, there is little evidence to suggest the presence of an arrhythmogenic

substrate in these patients in view of the absence of late potentials on the SAECG. Aortic valve replacement was accompanied by a significant regression in LVH in patients with predominant AS and those with combined AS and AR, but this was however not associated with a decrease in VES frequency. Thus, the reported high incidence of late sudden deaths following AVR cannot entirely be explained on the basis of ventricular tachyarrhythmias.

CHAPTER NINE

IMPAIRED CARDIOVASCULAR AUTONOMIC FUNCTION IN AORTIC VALVE DISEASE

9.1 Introduction

Cardiovascular autonomic failure was first detected by Bradbury and Eggleston (1925) but it was in 1955 that one of the first large studies on cardiovascular autonomic disturbances was reported by Sharpey-Schafer. He demonstrated a conspicuous difference in continuous arterial pressure records between patients with heart failure and normal subjects during Valsalva manoeuvre. In the early sixties reports on abnormal circulatory reflexes in diabetic patients began to appear in the literature. Sharpey-Schafer and Taylor (1960) demonstrated an abnormal response to Valsalva manoeuvre in 20% of a total of 337 patients attending a diabetic clinic. In another study, Ewing et al (1973) reported a higher incidence (62%) of an abnormal heart-rate and blood pressure response to Valsalva manoeuvre in 37 diabetics with symptoms or signs of autonomic neuropathy. Two years later Murray and his colleagues showed for the first time the presence of abnormal autonomic cardiovascular reflexes in diabetics without any clinical features of autonomic neuropathy (Murray et al, 1975). Their findings were supported by subsequent reports (Bennett et al, 1976; Rubler, Chu and Bruzzone, 1985). In a recent and elegant study, Hornung and his co-workers by performing 24 hour ambulatory heartrate monitoring, demonstrated a decrease in diurnal heart-rate variation in patients with diabetes mellitus (Hornung, Mahler and Raftery, 1989). The mere presence of abnormal autonomic reflexes in patients with diabetes mellitus has been shown by several workers to be accompanied by a significant increase in both morbidity

and mortality (Ewing, Campbell and Clarke, 1976; Clarke, Ewing and Campbell, 1979; Ewing, Campbell and Clarke, 1980; Niakan et al, 1986; Burgos et al, 1989).

Several studies have demonstrated signs of autonomic disturbances in patients following acute myocardial infarction (Webb, Adgey and Pantridge, 1972; Kirby 1977; Bigger et al, 1988 and McAreavey et al, 1989). Correction of these disturbances by pharmacologic means was followed by a noticeable reduction in the in-hospital mortality (Webb, Adgey and Pantridge, 1972) and improvement in autonomic function occurred when the tests were repeated in the late convalescent period (Imaizumi et al, 1984). Furthermore, the prognostic importance of cardiac autonomic dysfunction in these patients has been assessed by several follow-up studies (Kleiger et al, 1987; Martin et al, 1987 and La Rovere et al., 1988). These workers have reported an increased mortality including sudden death in those patients with impaired autonomic function.

In a recent study, patients with aortic stenosis have been shown to have significantly impaired vagal heart-rate control when compared to age-matched healthy volunteers (Airaksinen et al, 1988). This impairment in vagal heart-rate control did not improve following aortic valve replacement (AVR).

The aim of this part of the study was therefore to assess the prevalence of impaired cardiovascular autonomic function in patients with aortic valve disease using non-invasive bedside tests and to relate the findings to

clinical and haemodynamic features. The effect of AVR on autonomic function was also evaluated in 10 patients 3 months following operation.

9.2 Study Population

Forty-seven of the original 100 patients were included in this part of the study. The predominant lesion was AS in 23, AR in 8 and combined AS and AR in 16 patients. Twenty-eight of the patients were males, 19 were females, their ages averaging 56 ± 12 years (range 32 - 78 years). Ewing et al (1985) reported no sex differences in normal values for autonomic function. None of the patients had hypertension, diabetes mellitus or uraemia. All patients were in sinus rhythm and none was receiving anti-arrhythmic medication, beta blockers or medication known to have anticholinergic activity. Three patients were taking digoxin and 14 were on diuretics. In 10 patients the tests were repeated after AVR.

The control group consisted of 20 male healthy volunteers of a mean age of 46 ± 6 years (range 40 - 61 years). They were considered to be healthy as confirmed by patient history, physical examination, echocardiographic and doppler examinations and exercise electrocardiography.

9.3 Methods

Bedside cardiovascular autonomic function tests were performed. These included heart-rate response to Valsalva manoeuvre (Valsalva ratio), heart-rate (R-R interval)

variation during deep breathing, immediate heart-rate response to standing (30:15 ratio) and blood pressure response to standing (fall in systolic blood pressure). These methods were described in detail in Chapter 3.

9.4 Results

Table 9.1 presents the results of autonomic function tests according to the predominant aortic valve lesion of the patients. Although heart-rate response to Valsalva manoeuvre, heart-rate variation during deep breathing, immediate heart-rate response to standing and blood pressure response to standing were marginally less abnormal in patients with predominant AS than in the other 2 groups, these differences were far from achieving any statistical significance. In view of this, it was felt unnecessary to divide the patients into the 3 subgroups in subsequent analysis of the results.

Generally accepted values were used (Ewing and Clarke, 1982) and accordingly heart-rate response to Valsalva manoeuvre, heart-rate variation during deep breathing, immediate heart-rate response to standing and blood pressure response to standing were abnormal in 4.3%, 38%, 4% and 4% respectively, while borderline impairment occurred in 28.3%, 36%, 13% and 32% respectively (Table 9.2).

Table 9.3 depicts autonomic function test results in 20 healthy controls. Immediate heart-rate response to stand-

Table 9.1

Cardiovascular Autonomic Function Test Results in the Study Patients According to the Predominant Aortic Valve Lesion

	AS (n=23)	AR (n=8)	AS+AR (n=16)
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.47 ± 0.41 (1.07 - 2.79)	1.24 ± 0.17 (1.12 - 1.64)	1.30 ± 0.12 (1.08 - 1.48)
Heart-rate (R-R interval) variation during deep breathing	14 ± 6 (4 - 26)	10 ± 5 (1 - 18)	2 ± 6 (4 - 24)
Immediate heart-rate response to standing (30:15 ratio)	1.13 ± 0.10 (1.03 - 1.41)	1.05 ± 0.04 (1.00 - 1.13)	1.10 ± 0.06 (1.00 - 1.21)
Blood pressure response to standing (fall in systolic blood pressure)	8.5 ± 9.3 (0 - 28)	12.3 ± 12.3 (0 - 32)	11.4 ± 7.9 (0 - 28)

Mean ± SD (range)
AS = aortic stenosis
AR = aortic regurgitation

Table 9.2

Cardiovascular Autonomic Function Test Results in the Study Patients n (%)

	Normal	Borderline	Abnormal
Heart-rate response to Valsalva manoeuvre (Valsalva ratio) (n=46)	≥1.21 31 (67.4)	1.11-1.20 13 (28.3)	≤1.10 2 (4.3)
Heart-rate (R-R interval) variation during deep breathing (n=47)	≥15 beats/min 12 (26)	11-14 beats/min 17 (36)	≤10 beats/min 18 (38)
Immediate heart-rate response to standing (30:15 ratio) (n=47)	≥1.04 39 (83)	1.01-1.03 6 (13)	≤1.00 2 (4)
Blood pressure response to standing (fall in systolic blood pressure) (n=47)	≤10 mmHg 30 (64)	11-29 mmHg 15 (32)	≥30 mmHg 2 (4)

Table 9.3

Cardiovascular Autonomic Function Test Results in 20 Normal Controls n(%)

	Normal	Borderline	Abnormal
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	≥1.21 19 (95)	1.11-1.20 1 (5)	≤1.10 0 (0)
Heart-rate (R-R interval) variation during deep breathing	≥15 beats/min 15 (75)	11-14 beats/min 5 (25)	≤10 beats/min 0 (0)
Immediate heart-rate response to standing (30:15 ratio)	≥1.04 18 (90)	1.01-1.03 1 (5)	≤1.00 1 (5)
Blood pressure response to standing (fall in systolic blood pressure)	≤10 mmHg 18 (90)	11-29 mmHg 2 (10)	≥30 mmHg 0 (0)

ing was the only variable that was abnormal, occurring in only one subject (5%).

Heart-rate response to Valsalva manoeuvre was markedly reduced in patients compared to controls (1.37 ± 0.31 Vs 1.90 ± 0.40; p=0.00005). The same was the case with heart-rate variation during deep breathing (12.6 ± 5.9 beats/minute Vs 22.3 ± 8.2 beats/minute; p=0.0003) (Figures 9.1 and 9.2). The 2 groups did not differ in respect to immediate heart-rate response to standing as well as blood pressure response to standing (Table 9.4). In view of the differences in age between patients and controls, comparisons between the 2 groups were made after correcting for age. This was done by regression of the response variables on age separately for the 2 groups and subsequently by comparison of these regression equations (Pocock, 1989).

Figures 9.3 and 9.4 illustrate examples of normal and abnormal heart-rate response to Valsalva manoeuvre respectively. Figure 9.5 shows normal (upper sample) and abnormal (lower sample) heart-rate variation during deep breathing. Examples of normal and abnormal immediate heart-rate response to standing (30:15 ratio) are illustrated in Figures 9.6 and 9.7 respectively.

Table 9.5 shows results of patients according to the presence (12 patients) or absence (35 patients) of syncope. Surprisingly, all the 4 variables were marginally less abnormal in patients with syncope, but the differences were statistically insignificant.

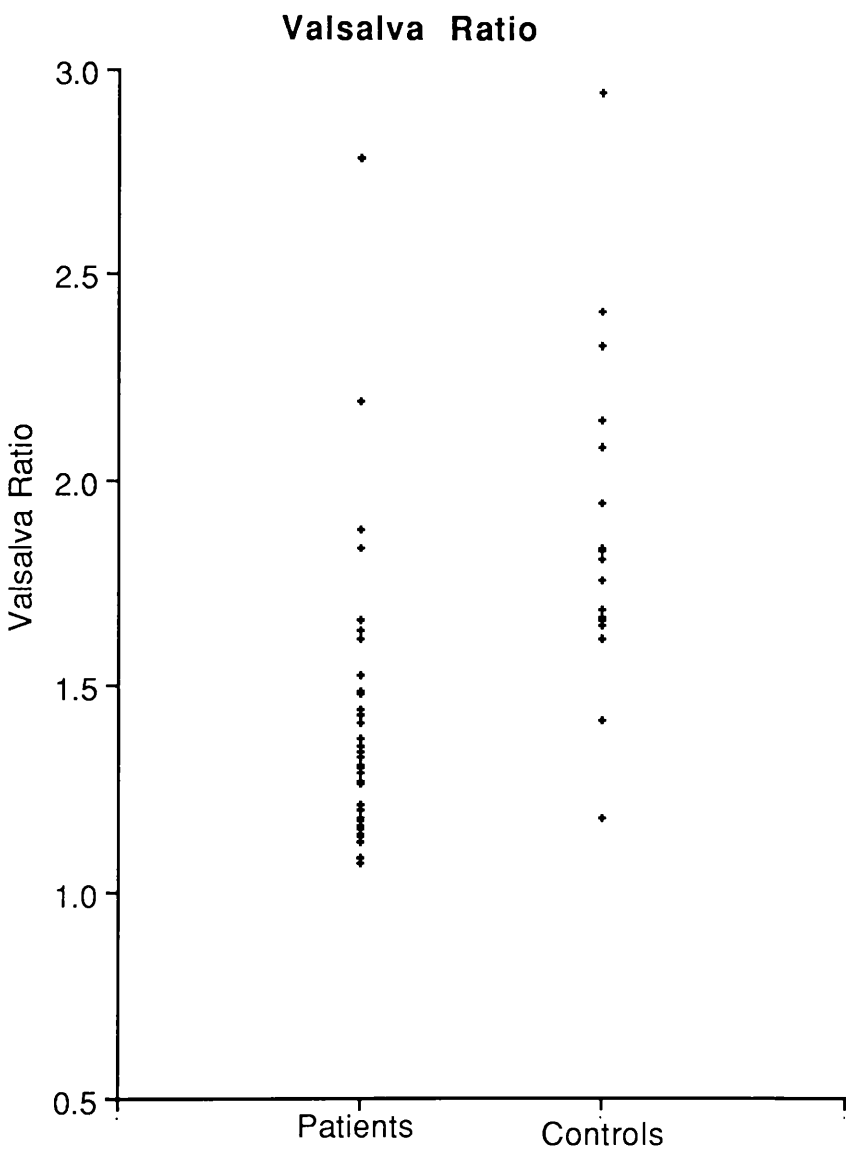

Figure 9.1: Heart-rate response to Valsalva manoeuvre in 46 patients with aortic valve disease and 20 healthy controls.

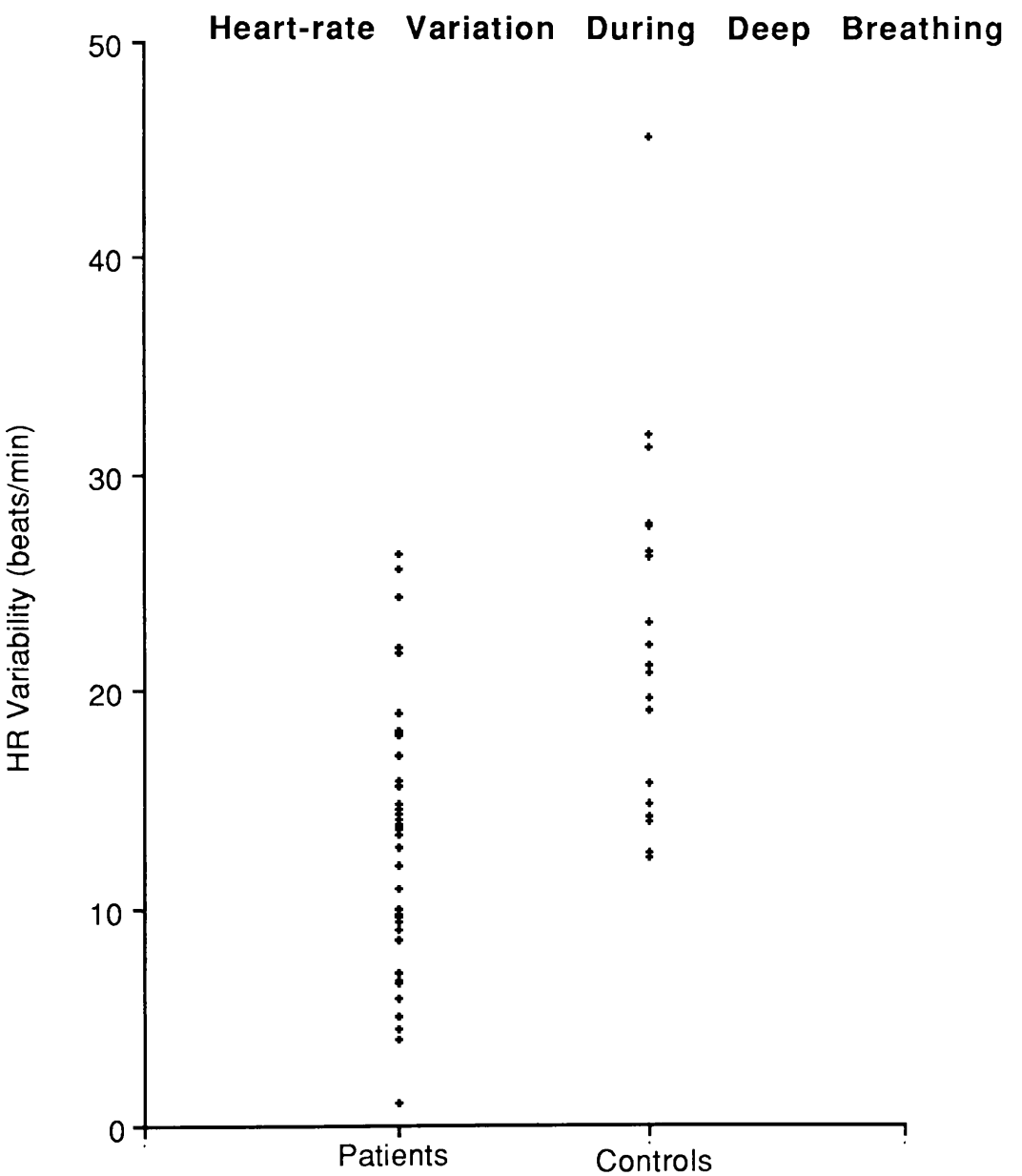

Figure 9.2: Heart-rate variation during deep breathing in 47 patients with aortic valve disease and 20 healthy controls.

Table 9.4

Cardiovascular Autonomic Function Test Data in Healthy Controls and Patients with Aortic Valve Disease

	Controls (n=20)	Patients (n=47)	p - value*
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.90 ± 0.40 (1.18 - 2.95)	1.37 ± 0.31 (1.07 - 2.79)	0.00005
Heart-rate (R-R interval) variation during deep breathing	22.3 ± 8.2 (12.3 - 45.7)	12.6 ± 5.9 (1.0 - 26.3)	0.0003
Immediate heart-rate response to standing (30:15 ratio)	1.19 ± 0.15 (0.99 - 1.54)	1.10 ± 0.08 (1.00 - 1.41)	NS
Blood pressure response to standing (fall in systolic blood pressure)	4.20 ± 4.3 (0 - 14)	10.13 ± 9.34 (0 - 32)	NS

Mean ± SD (range)

* this was done by regression of the response variables on age separately for the two groups and subsequently by comparison of these regression equations (Pocock, 1989)

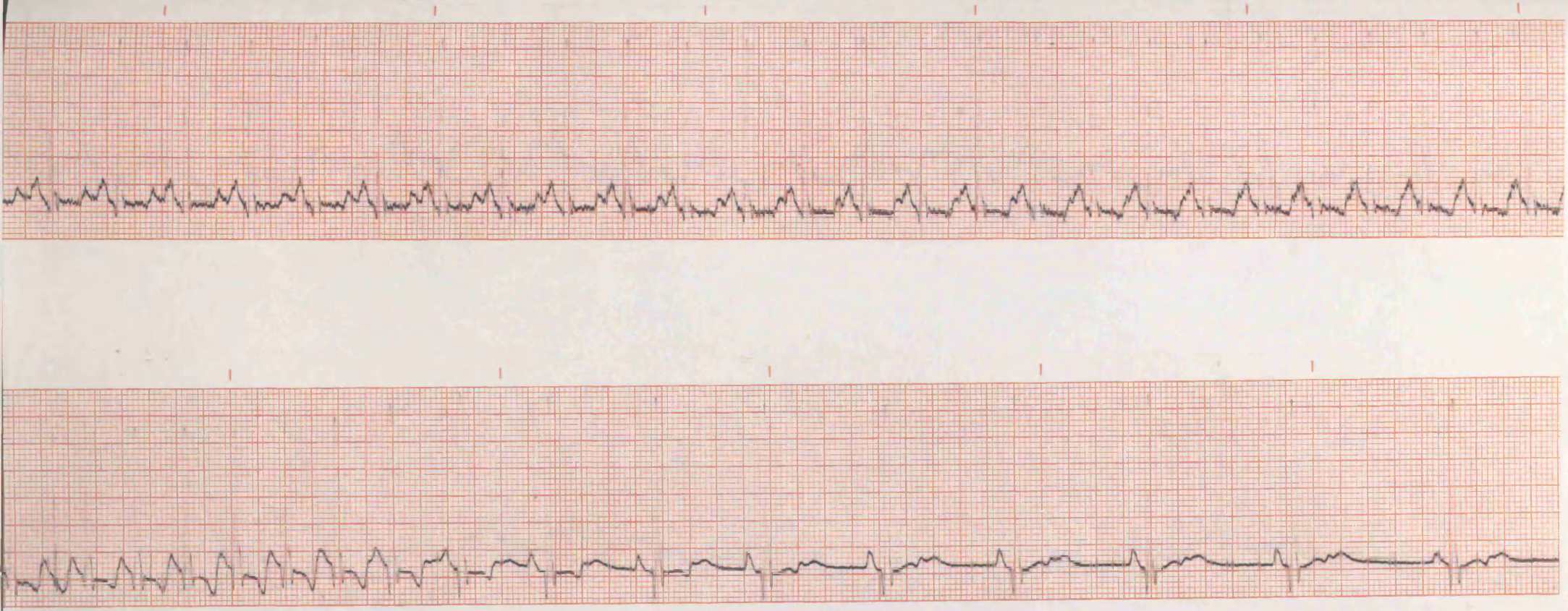

Figure 9.3: Electrocardiographic strips showing a normal heart-rate response to Valsalva manoeuvre (Valsalva ratio = 2.95) in a 42 year old healthy control. Upper panel shows tachycardia that occurs during strain followed after release (lower panel) by bradycardia.

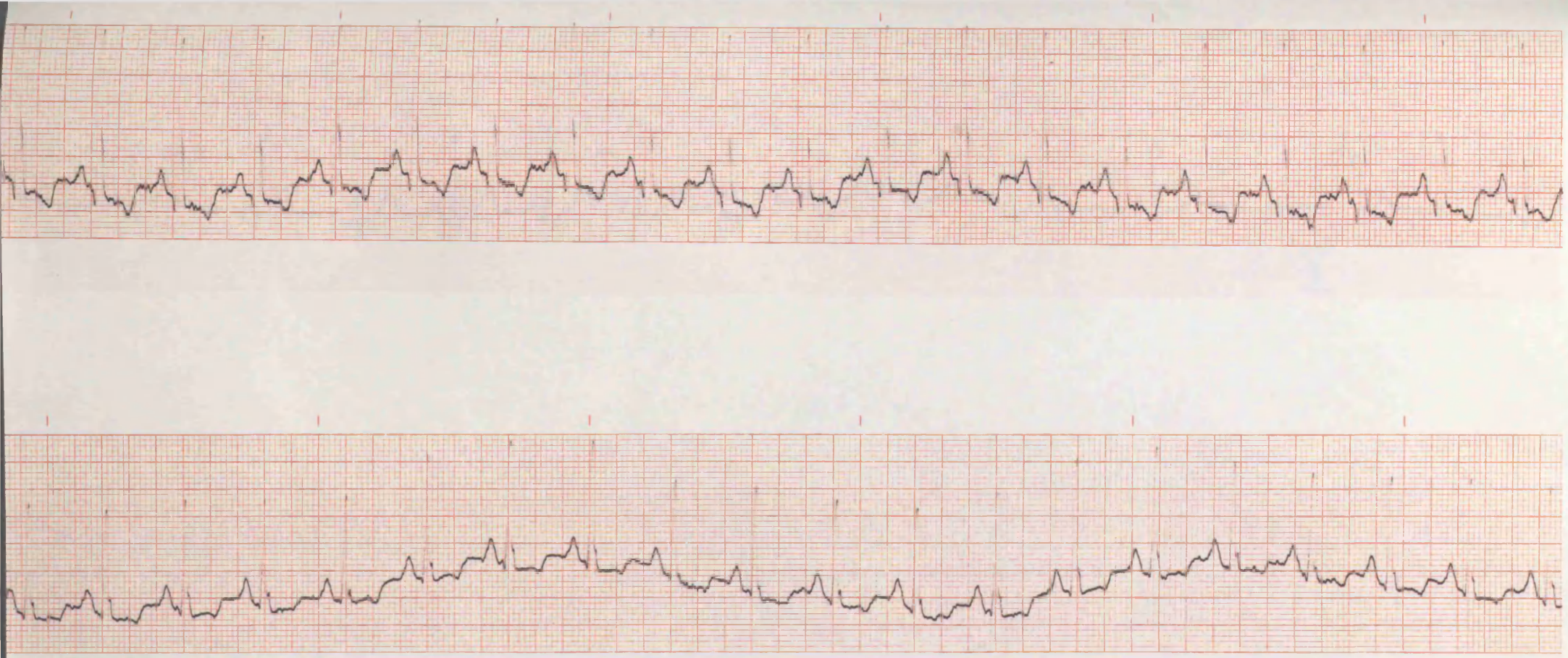

Figure 9.4: Electrocardiographic strips showing an abnormal heart-rate response to Valsalva manoeuvre (Valsalva ratio = 1.07) in a 38 year old man with predominant aortic stenosis. There is almost no difference in the heart-rate recorded during strain (upper panel) and following release (lower panel)

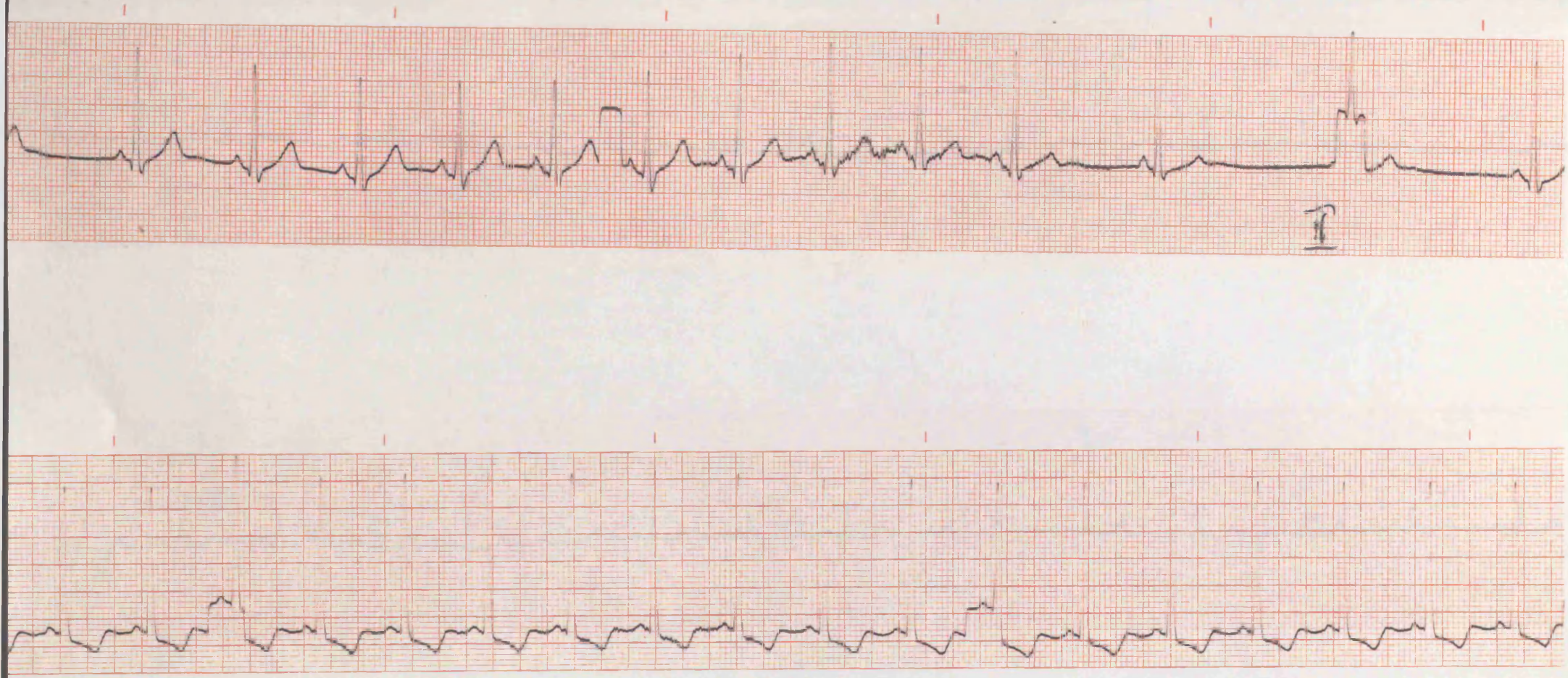

Figure 9.5: Electrocardiographic strips showing normal (upper panel) and abnormal (lower panel) heart-rate response to deep breathing.

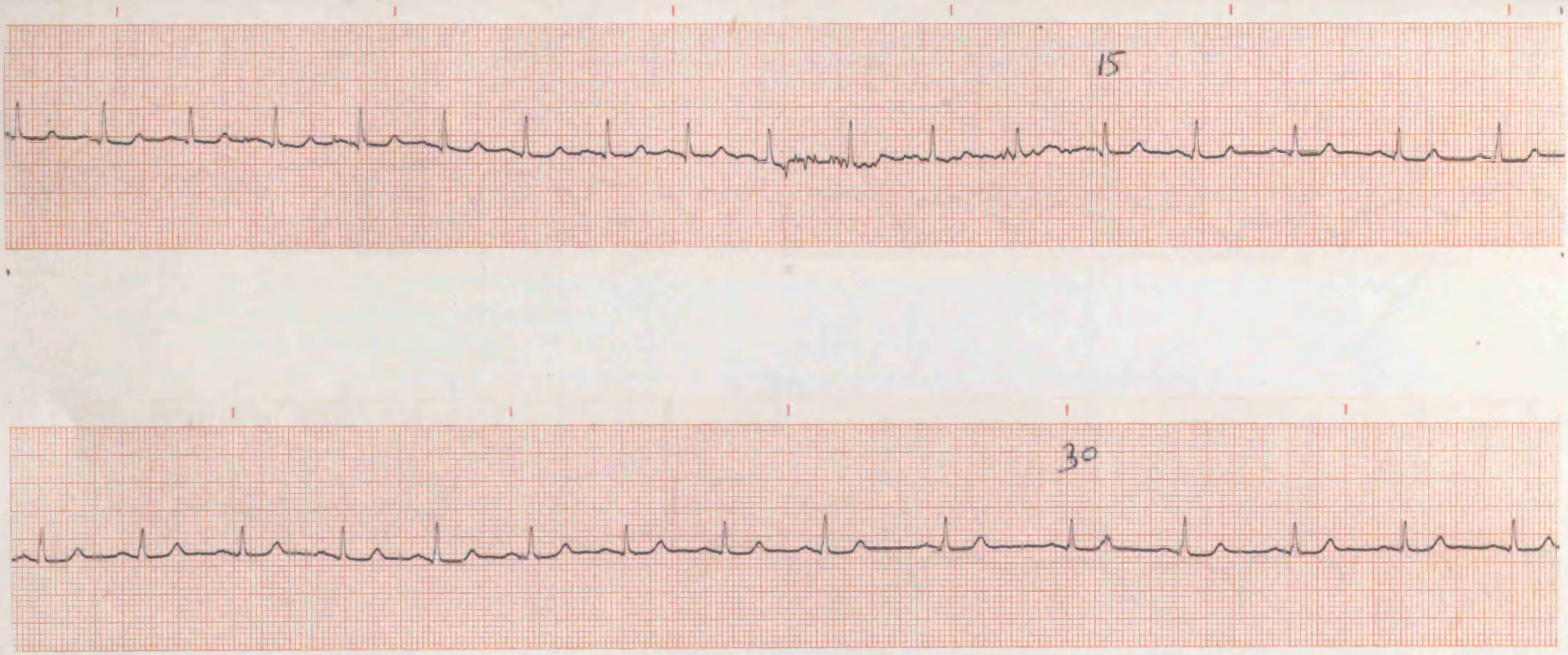

Figure 9.6: Electrocardiographic strips showing a normal immediate heart-rate response to standing (30:15 ratio = 1.41) in a 44 year old man with predominant aortic stenosis.

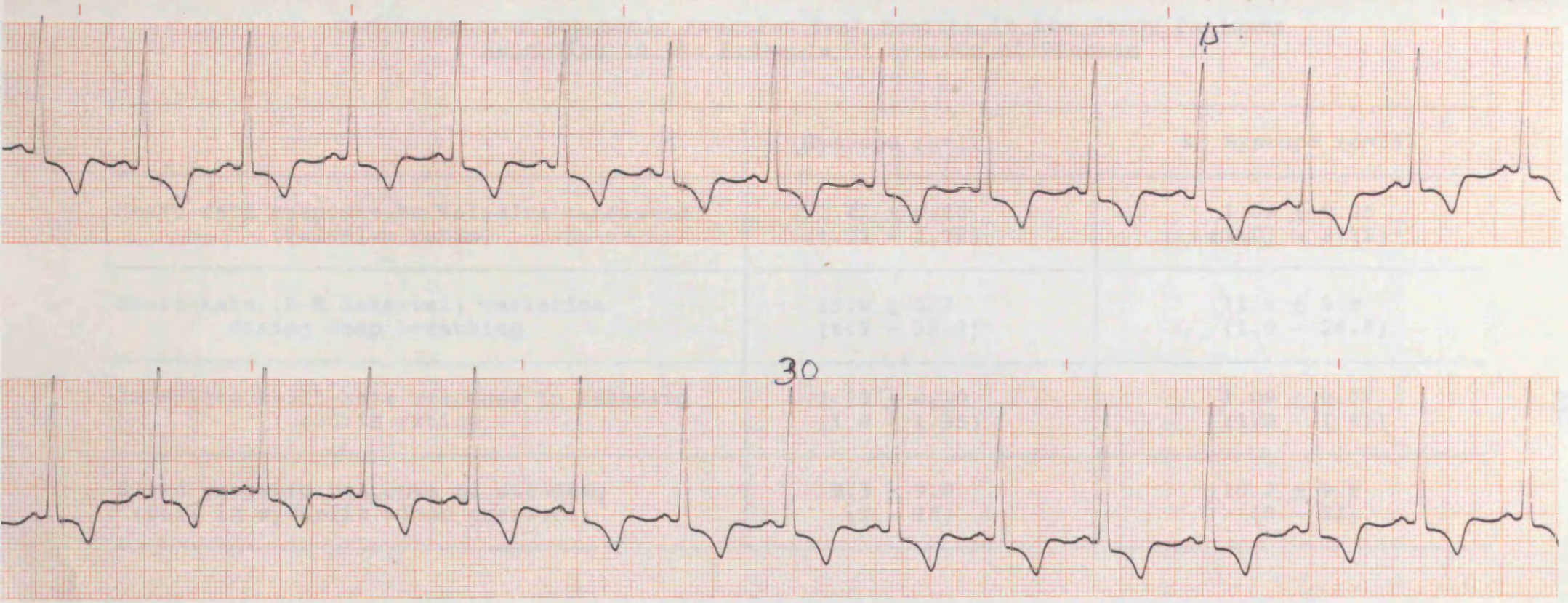

Figure 9.7: Electrocardiographic strips showing an abnormal immediate heart-rate response to standing (30:15 ratio = 1.00) in a 67 year old woman with combined aortic stenosis and aortic regurgitation.

Table 9.5

Cardiovascular Autonomic Function Test Results in the Study Patients According to the Presence or Absence of Syncope

	Syncope (n=12)	No Syncope (n=35)
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.42 ± 0.46 (1.12 - 2.79)	1.36 ± 0.25 (1.07 - 2.19)
Heart-rate (R-R interval) variation during deep breathing	15.0 ± 5.7 (6.7 - 25.7)	11.7 ± 5.8 (1.0 - 26.3)
Immediate heart-rate response to standing (30:15 ratio)	1.13 ± 0.10 (1.0 - 1.35)	1.09 ± 0.07 (1.0 - 1.41)
Blood pressure response to standing (fall in systolic blood pressure)	8.3 ± 9.0 (0 - 28)	10.7 ± 9.5 (0 - 32)

Mean ± SD (range)

Palpitations were present in 25 and absent in 22 patients. There were no significant differences in autonomic function test results between the 2 groups (Table 9.6).

Angina was present in 28 and absent in 19 patients. The groups did not differ in respect to all the 4 autonomic function tests (Table 9.7). The same was true when comparing patients with (8 patients) to those without (34 patients) significant coronary artery disease (Table 9.8).

The effect of age on autonomic function tests was assessed. Heart-rate variation during deep breathing was the only variable that showed a weak, but significant inverse relation to age occurring only in patients with predominant AS ($r = -0.579$; $p < 0.01$) (Figure 9.8). In patients with predominant AS, heart-rate variation during deep breathing also showed a weak, but significant inverse relation to PWTd ($r = -0.483$; $p < 0.02$) (Figure 9.9), IVSTd ($r = -0.491$; $p < 0.02$) (Figure 9.10), LVMI ($r = -0.463$; $p < 0.05$), systolic blood pressure ($r = -0.475$; $p < 0.05$) (Figure 9.11) as well as LVSP ($r = -0.510$; $p < 0.02$) (Figure 9.12).

In patients with predominant AR, heart-rate response to Valsalva manoeuvre was directly related to PSLVWS (Reichek's method) ($r = 0.746$; $p < 0.05$) (Figure 9.13) while heart-rate variation during deep breathing showed an inverse relation to E/A ratio ($r = -0.735$; $p < 0.05$) (Figure 9.14). However, there was no relationship between heart-rate variation during deep breathing and ejection fraction ($r = 0.289$). Immediate heart-rate response to

Table 9.6

Cardiovascular Autonomic Function Test Results in the Study Patients According to the Presence or Absence of Palpitations

	Palpitations (n=25)	No Palpitations (n=22)
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.37 ± 0.26 (1.07 - 2.19)	1.38 ± 0.36 (1.12 - 2.79)
Heart-rate (R-R interval) variation during deep breathing	11.7 ± 6.0 (1.0 - 26.3)	13.6 ± 5.7 (4.0 - 25.7)
Immediate heart-rate response to standing (30:15 ratio)	1.10 ± 0.09 (1.02 - 1.41)	1.11 ± 0.08 (1.0 - 1.35)
Blood pressure response to standing (fall in systolic blood pressure)	10.1 ± 9.9 (0 - 32)	10.2 ± 8.9 (0 -28)

Mean ± SD (range)

Table 9.7

Cardiovascular Autonomic Function Test Results in the Study Patients According to the Presence or Absence of Angina

	Angina (n=28)	No Angina (n=19)
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.39 ± 0.37 (1.13 - 2.79)	1.34 ± 0.21 (1.07 - 1.84)
Heart-rate (R-R interval) variation during deep breathing	12.7 ± 6.2 (1 - 26)	12.5 ± 5.5 (4 - 24)
Immediate heart-rate response to standing (30:15 ratio)	1.10 ± 0.06 (1.00 - 1.23)	1.12 ± 0.11 (1.00 - 1.41)
Blood pressure response to standing (fall in systolic blood pressure)	11.1 ± 10.3 (0 - 32)	8.7 ± 7.8 (0 - 30)

Mean ± SD (range)

Table 9.8

Cardiovascular Autonomic Function Test Results in the Study Patients According to the Presence or Absence of CAD*

	CAD (n=8)	No CAD (n=34)
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.30 ± 0.25 (1.13 - 1.88)	1.40 ± 0.33 (1.07 - 2.79)
Heart-rate (R-R interval) variation during deep breathing	15.5 ± 5.3 (9.6 - 24.4)	12.2 ± 6.1 (1 - 26.3)
Immediate heart-rate response to standing (30:15 ratio)	1.08 ± 0.07 (1.00 - 1.21)	1.11 ± 0.09 (1 - 1.41)
Blood pressure response to standing (fall in systolic blood pressure)	9.0 ± 10.4 (0 - 28)	10.1 ± 9.0 (0 - 30)

Mean ± SD (range)
* CAD = coronary artery disease
N.B. only 42 of the 47 patients had undergone coronary angiography

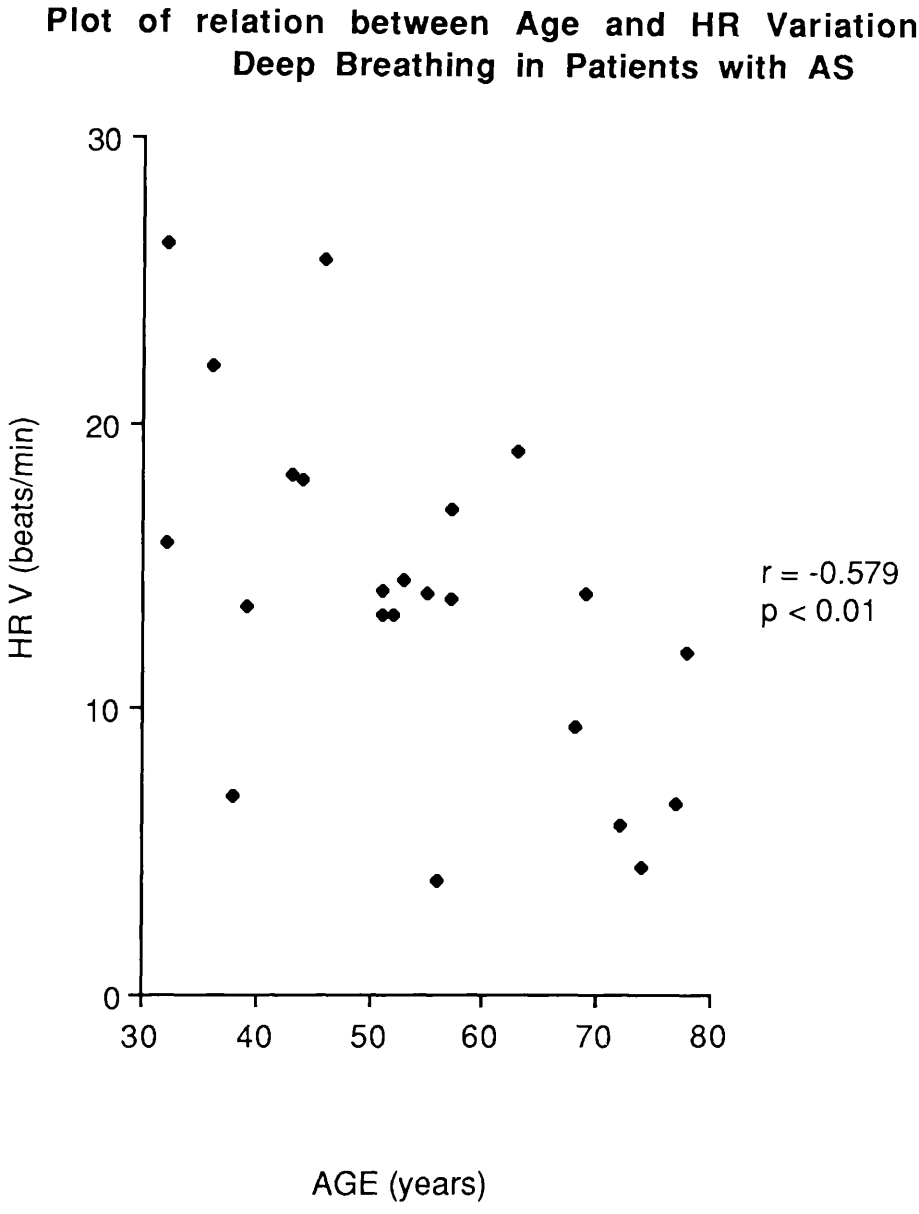

Figure 9.8: Correlation of age and heart-rate variation during deep breathing (beats/min) in patients with predominant AS. A weak but significant inverse relation was obtained ($r = -0.579$; $p < 0.01$).

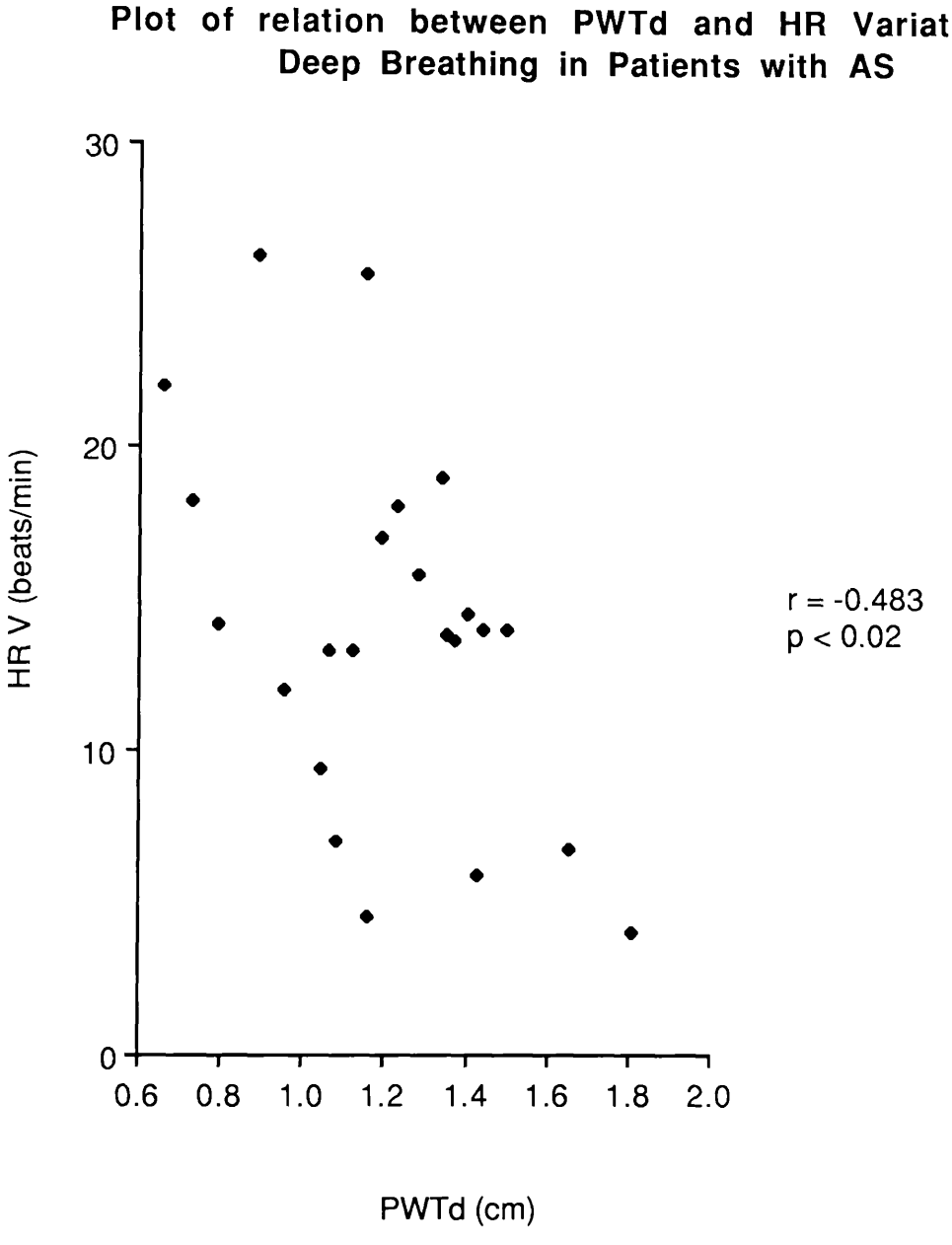

Figure 9.9: Correlation of PWTd (cm) and heart-rate variation during deep breathing (beats/min) in patients with predominant AS. A weak but significant inverse relation was obtained ($r = {}^{-}0.483$; $p < 0.02$).

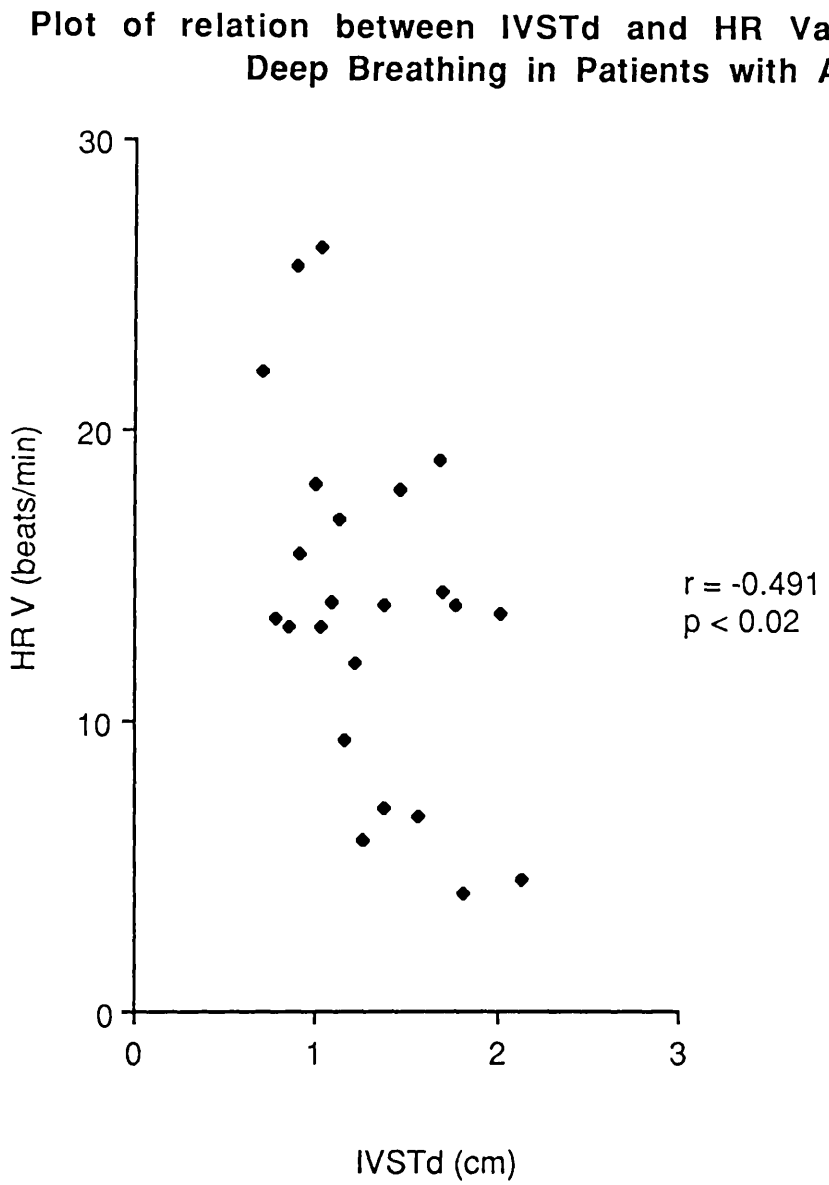

Figure 9.10: Correlation of IVSTd (cm) and heart-rate variation during deep breathing (beats/min) in patients with predominant AS. A weak but significant inverse relation was obtained ($r = {}^{-}0.491$; $p < 0.02$).

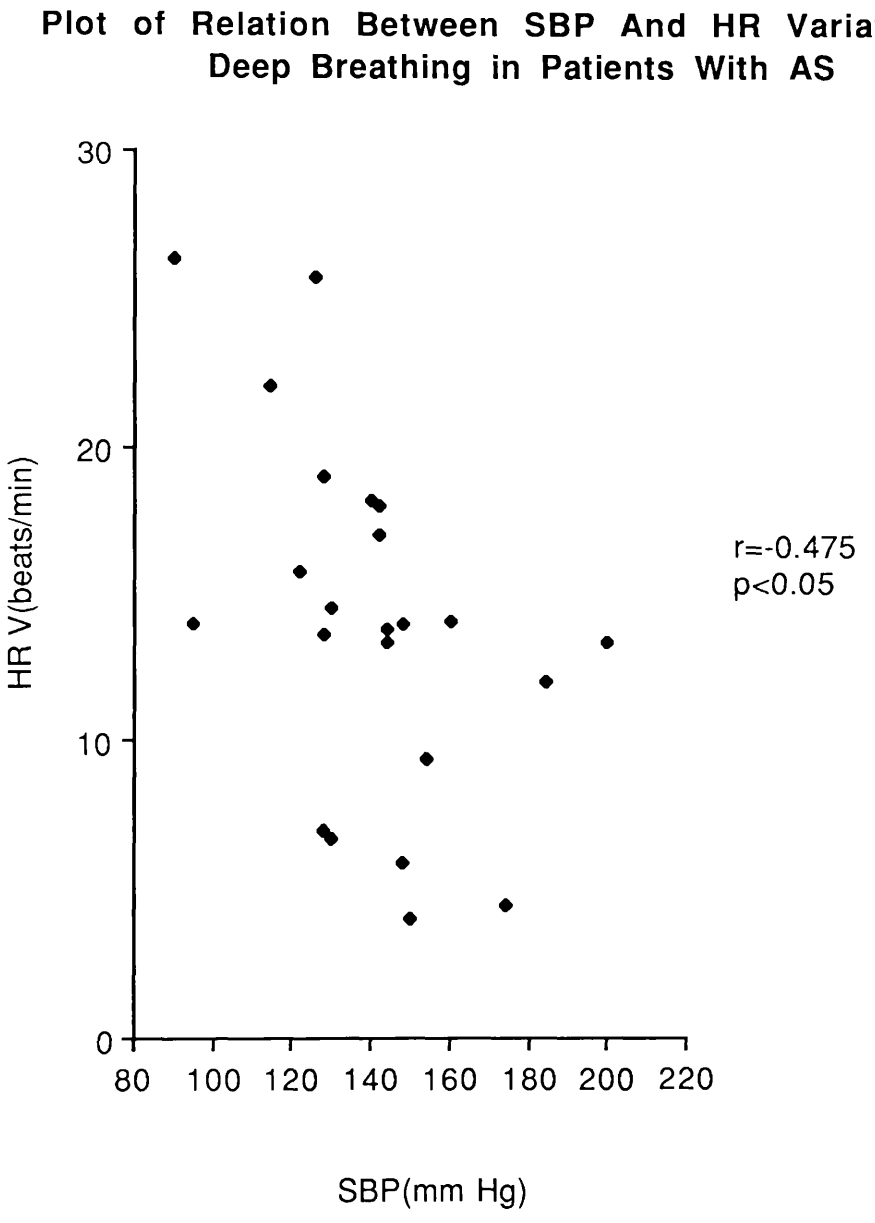

Figure 9.11: Correlation of systolic blood pressure (mm Hg) and heart-rate variation during deep breathing (beats/min) in patients with predominant AS. A weak but significant inverse relation was obtained ($r = -0.475$; $p < 0.05$).

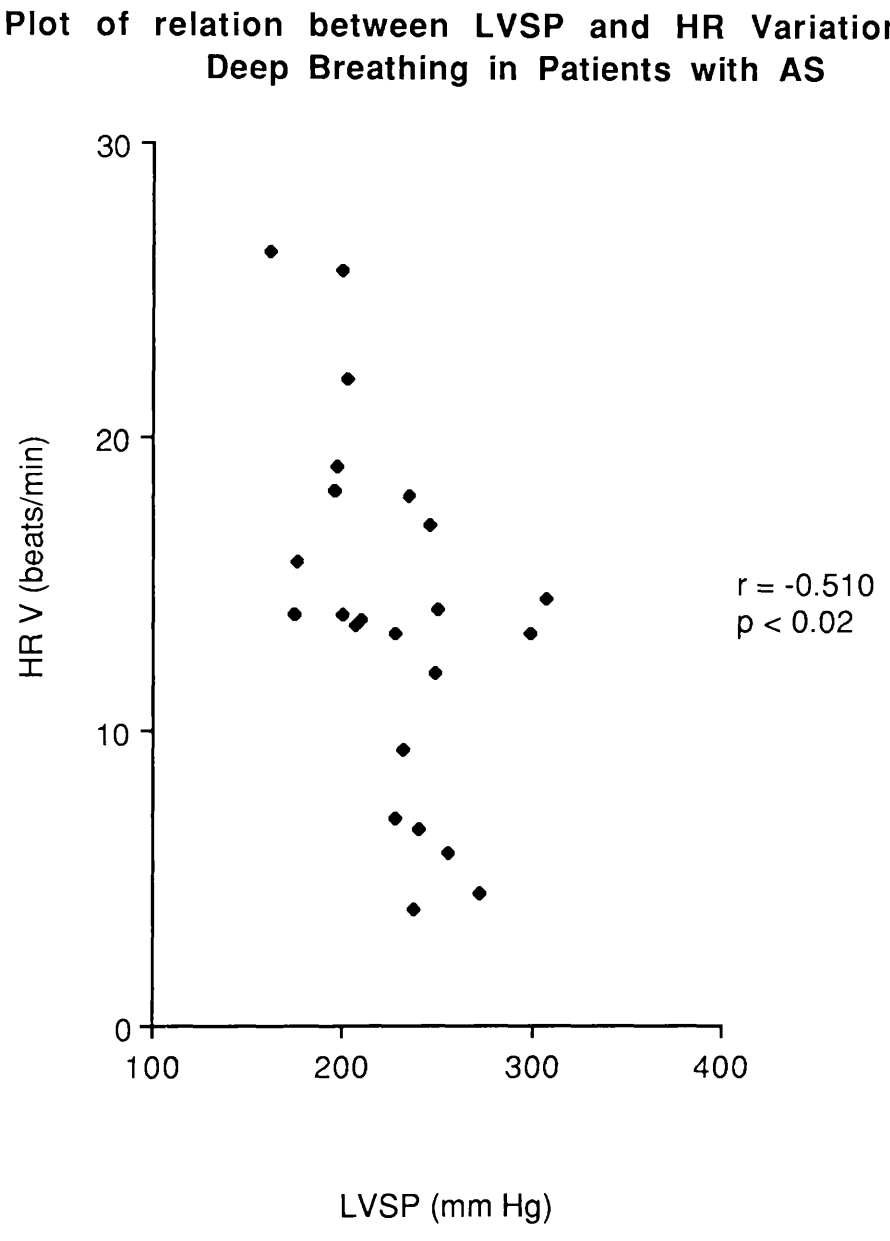

Figure 9.12: Correlation of left ventricular systolic pressure (mm Hg) and heart-rate variation during deep breathing (beats/min) in patients with predominant AS. A weak but significant inverse relation was obtained ($r = -0.510$; $p < 0.02$).

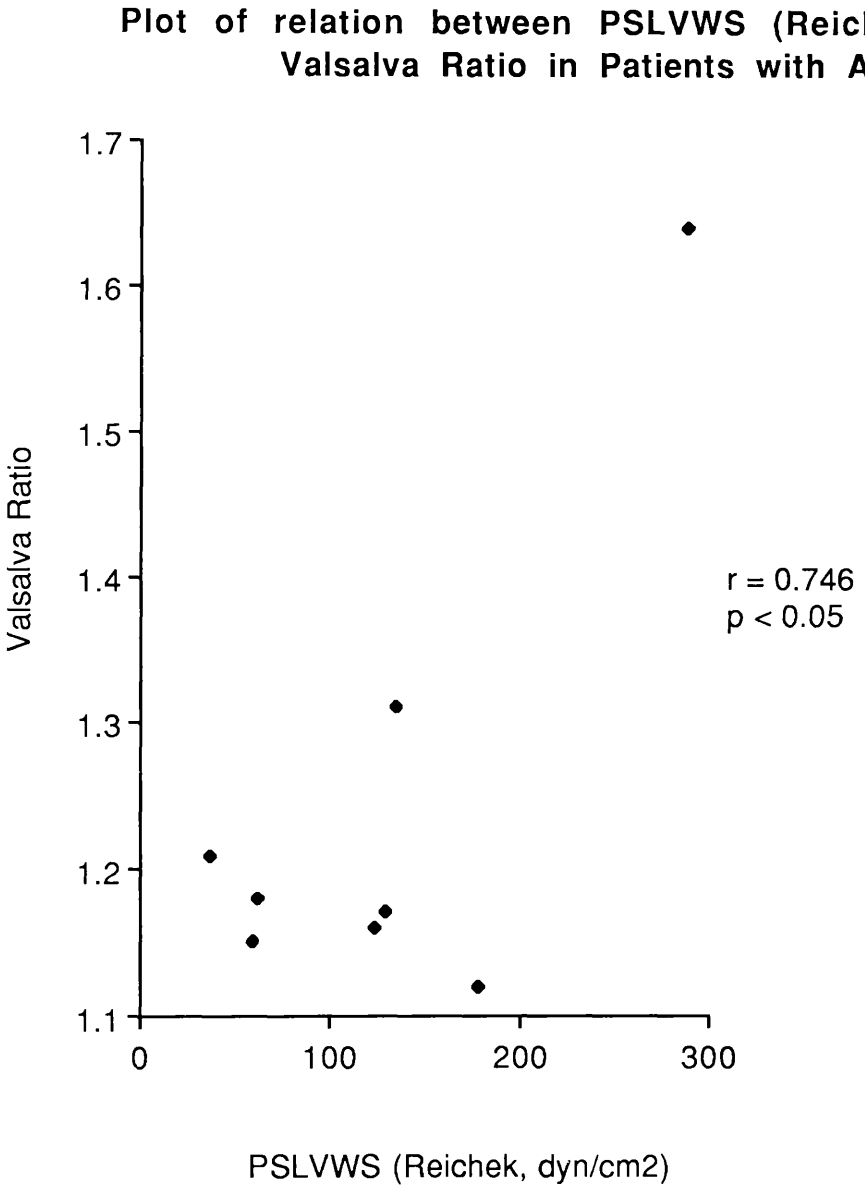

Figure 9.13: Correlation of peak systolic left ventricular wall stress by Reichek's method (dyne/cm^2) and heart-rate response to Valsalva manoeuvre (Valsalva ratio) in patients with predominant AR. A moderate but significant direct relation was obtained ($r = 0.746$; $p < 0.05$).

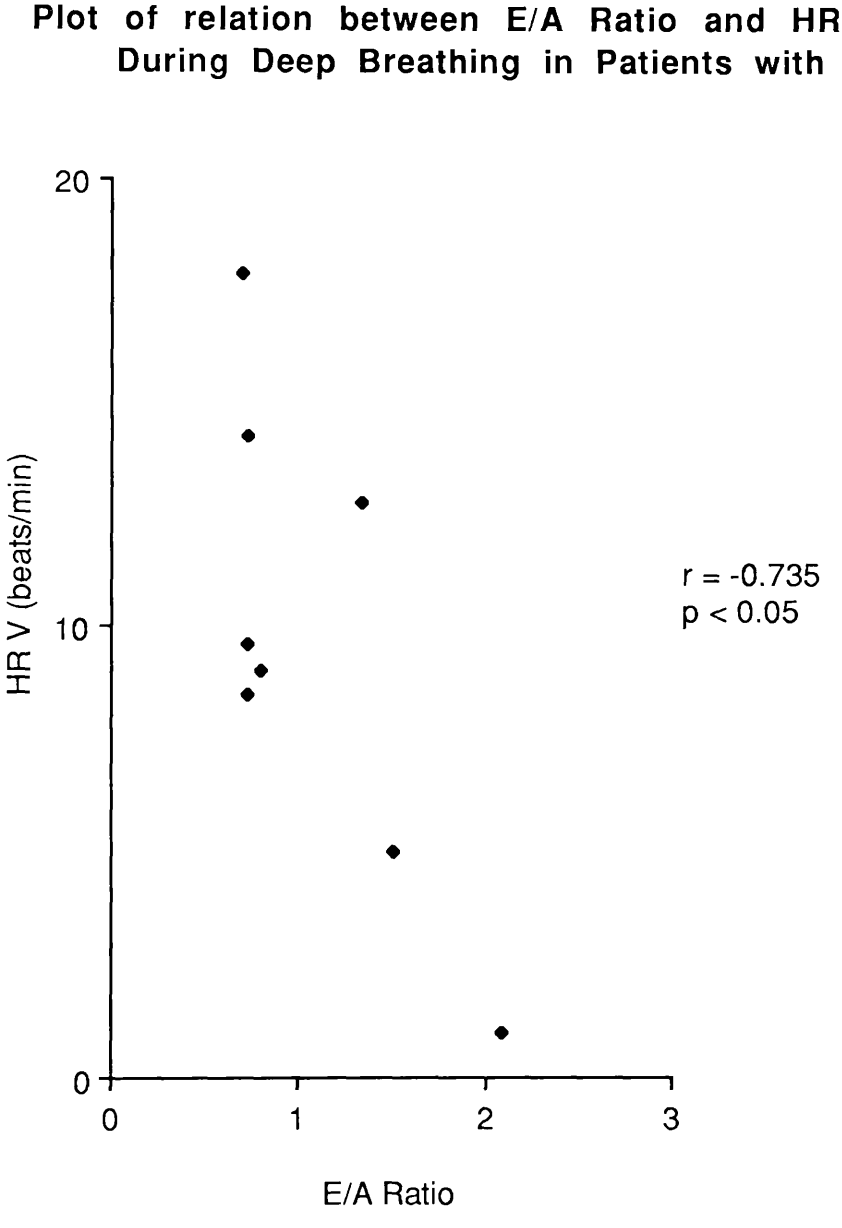

Figure 9.14: Correlation of the ratio between early (E) and late (A) left ventricular diastolic filling velocity (E/A ratio) and heart-rate variation during deep breathing (beats/min) in patients with predominant AR. A moderate but significant inverse relation was obtained ($r = -0.735$; $p < 0.05$).

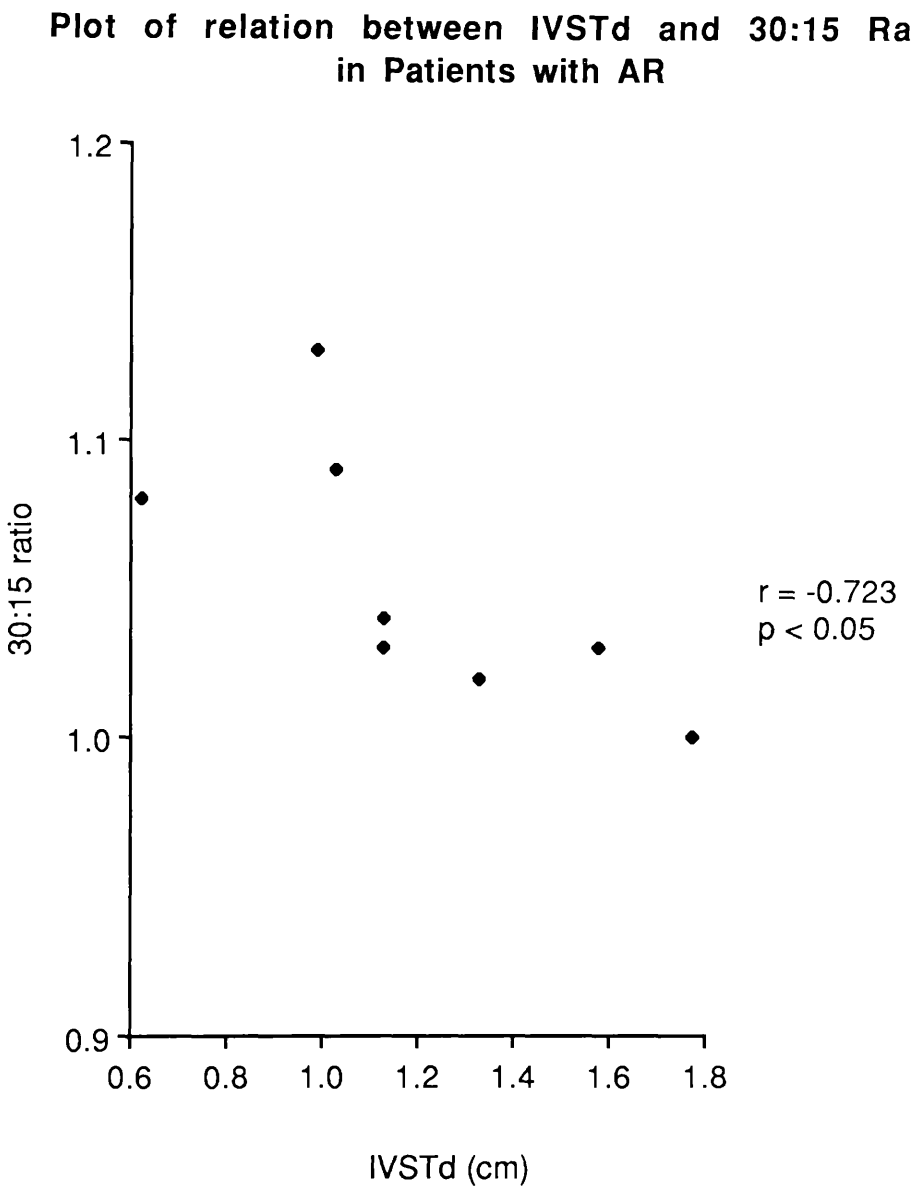

Figure 9.15: Correlation of IVSTd (cm) and immediate heart-rate response to standing (30:15 ratio) in patients with predominant AR. A moderate but significant inverse relation was obtained ($r = {}^{-}0.723$; $p < 0.05$).

standing on the other hand, was inversely related to IVSTd ($r = -0.723$; $p < 0.05$) (Figure 9.15), systolic blood pressure ($r = -0.809$; $p < 0.02$) (Figure 9.16) and LVSP ($r = -0.72$; $p < 0.05$) Figure 9.17).

In patients with combined AS and AR, heart-rate variation during deep breathing showed a direct relation to PSLVWS by both Reichek's ($r = 0.591$; $p < 0.02$) (Figure 9.18) and Quinones' ($r = 0.652$; $p < 0.01$) (Figure 9.19) methods.
To assess the effect of valve replacement on cardiovascular autonomic function, the tests were repeated in 10 patients 3 months after AVR. There were no significant differences in the autonomic function test results before and after AVR (Table 9.9)

9.5 Discussion

In the present study 19 (40%) patients had abnormality in at least one autonomic function test. Of these 19 patients, 18 (38%) had abnormal heart-rate variation during deep breathing (Table 9.2). This is not surprising given the fact that heart-rate variation during deep breathing is a sensitive, reproducible and specific test for one of the earliest defects of autonomic dysfunction i.e. cardiac vagal denervation (Watkins, 1990). Our results are in close agreement with the findings reported in the only study I am aware of that looked at cardiac autonomic function in aortic valve patients (Airaksinen et al, 1988). They reported a 46% incidence of abnormal heart-rate variation during deep breathing in 24 patients with AS. Furthermore, as is the case in the present

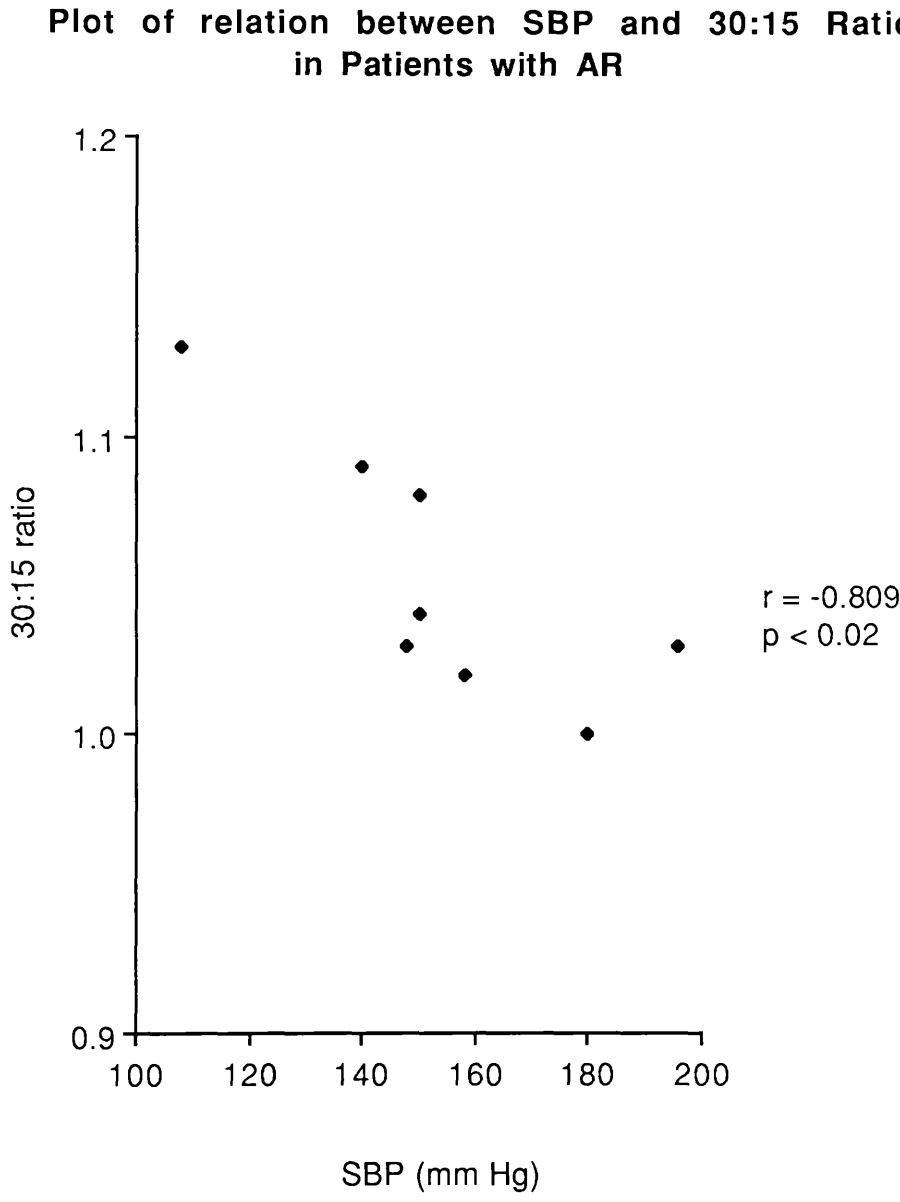

Figure 9.16: Correlation of systolic blood pressure (mm Hg) and immediate heart-rate response to standing (30:15 ratio) in patients with predominant AR. A fairly strong and significant inverse relation was obtained ($r = -0.809$; $p < 0.02$).

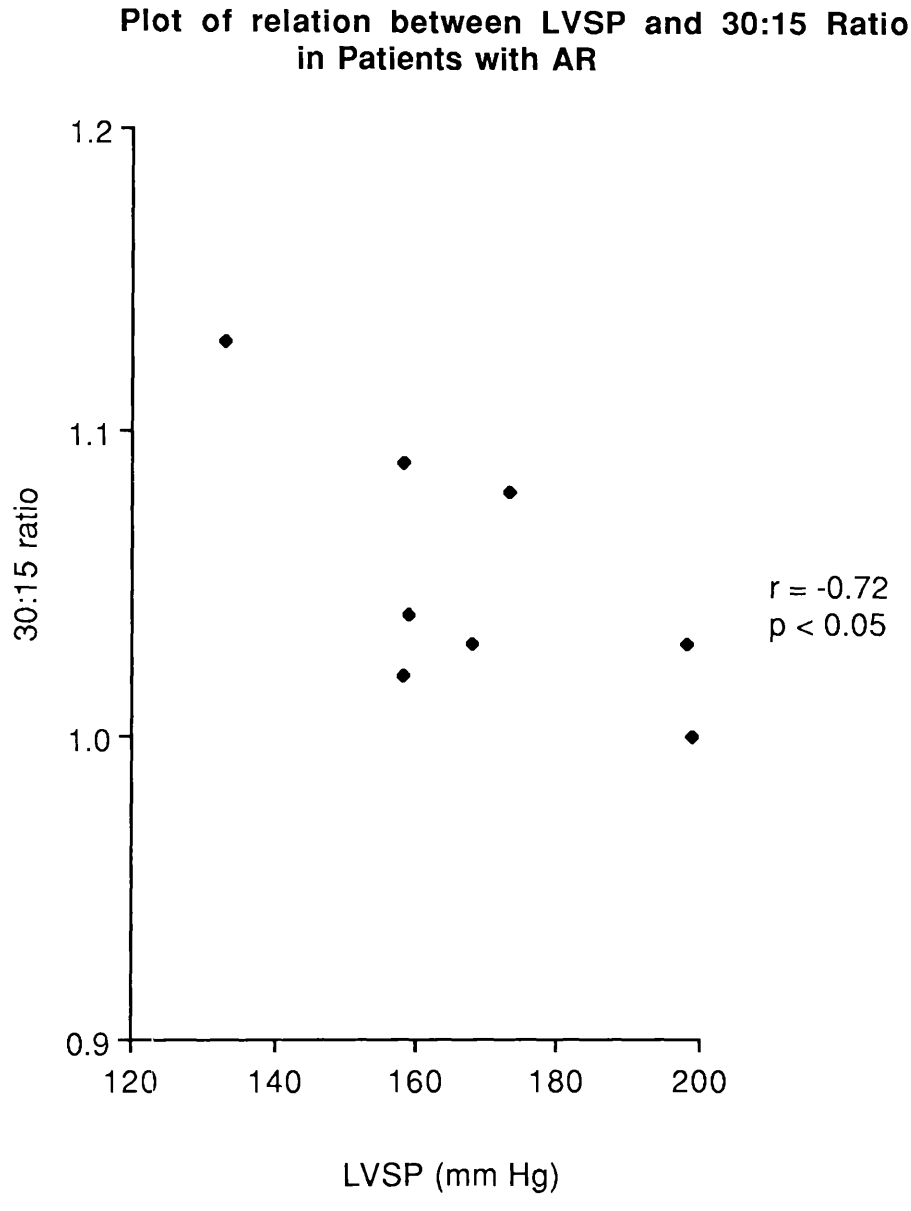

Figure 9.17: Correlation of left ventricular systolic pressure (mm Hg) and immediate heart-rate response to standing (30:15 ratio) in patients with predominant AR. A moderate but significant inverse relation was obtained ($r = -0.72$; $p < 0.05$).

Plot of relation between PSLVWS (Reichek) and HR Variation During Deep Breathing in Patients with Combined AS and AR

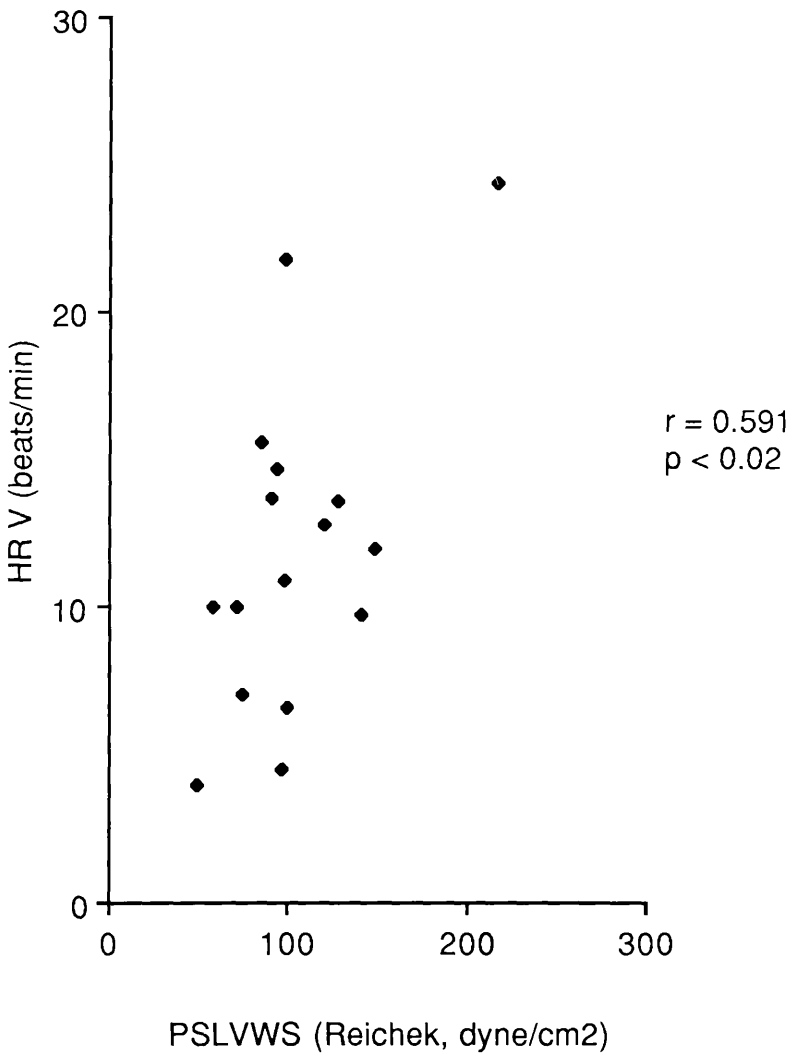

Figure 9.18: Correlation of peak systolic left ventricular wall stress by Reichek's method (dyne/cm^2) and heart-rate variation during deep breathing (beats/min) in patients with combined AS and AR. A weak but significant direct relation was obtained ($r = 0.591$; $p < 0.02$).

Plot of relation between PSLVWS (Quinones) and HR Variatio During Deep Breathing in Patients with Combined AS and AR

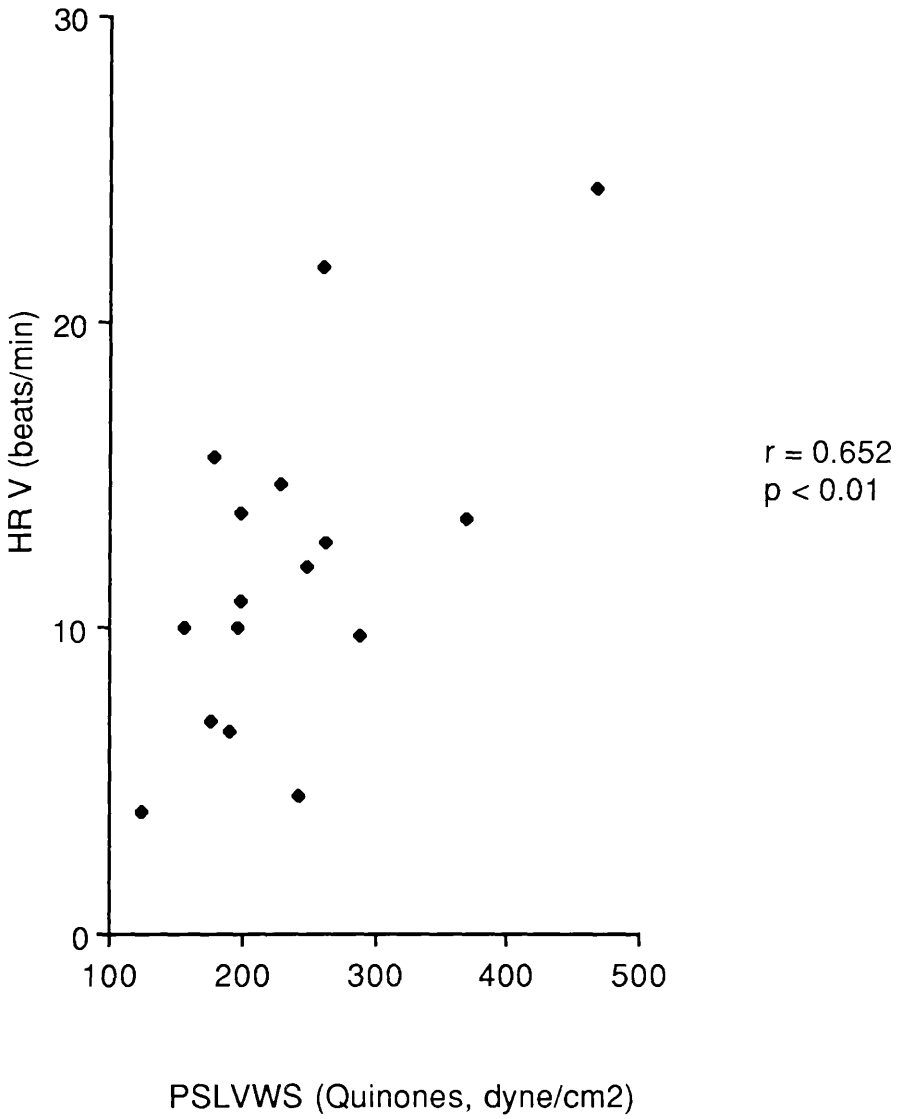

Figure 9.19: Correlation of peak systolic left ventricular wall stress by Quinones' method (dyne/cm^2) and heart-rate variation during deep breathing (beats/min) in patients with combined AS and AR. A weak but significant direct relation was obtained ($r = 0.652$; $p < 0.01$).

Table 9.9

Cardiovascular Autonomic Function Test Results in 10 Patients Before and After Aortic Valve Replacement (AVR)

	Before AVR	After AVR	p - value
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	1.45 ± 0.49 (1.13 - 2.79)	1.39 ± 0.25 (1.05 - 1.83)	0.79
Heart-rate (R-R interval) variation during deep breathing	14.3 ± 7.14 (1.0 - 25.7)	14.3 ± 5.7 (5.0 - 23.3)	0.91
Immediate heart-rate response to standing (30:15 ratio)	1.14 ± 0.12 (1.02 - 1.41)	1.12 ± 0.10 (0.99 - 1.29)	0.76
Blood pressure response to standing (fall in systolic blood pressure)	5.4 ± 7.7 (0 - 22)	9.6 ± 12.9 (0 - 38)	0.46

Mean ± SD (range)

study, they also reported a significant difference in the heart-rate variation during deep breathing between their patients and healthy controls while on the other hand, the 2 groups did not differ in respect to the immediate heart-rate response to standing (30:15 ratio).

There are several possible explanations for the impairment in cardiac autonomic function in patients with aortic valve disease. The reduced level of physical activity in these patients may contribute to the diminished para-sympathetic tone and reflex heart-rate control. This observation was made by Billman and his colleagues who showed a significant alteration of autonomic control of the heart by exercise in dogs possibly by decreasing sympathetic and/or increasing parasympathetic tone (Billman, Schwartz and Stone, 1984). Concomitant coronary artery disease could also contribute to the impairment in cardiac autonomic function (Airaksinen et al, 1987). However, only 8 of the 47 patients in the present study had significant coronary artery disease. Of these 8 patients, only 2 had an abnormality in one or more autonomic function tests. Moreover, there were no differences in the autonomic function test results between patients with compared to those without significant coronary artery disease (Table 9.8).

Heart-rate variation during deep breathing in patients with predominant AS and immediate heart-rate response to standing in patients with predominant AR showed an inverse relation to both systolic blood pressure and LVSP. This finding may suggest that the chronically increased left

ventricular pressures in these patients may blunt the baroreceptors within the left ventricle in the same way as increased aortic pressure causes aortic baroreceptor dysfunction in hypertension and so interfere with the vagal heart-rate regulation (Johnston, 1980. Johnson, 1971). If this is true, AVR which should normalise left ventricular pressures to a certain extent would be expected to result in an improvement in cardiovascular autonomic function. However, this was not the case in both the present study and the findings of Airaksinen et al (1988) who repeated the tests 6 weeks after AVR. It is however possible that functional recovery of left ventricular baroreceptors requires a longer period and therefore in order to explore this possibility further follow-up with repeat evaluation of cardiac autonomic function in these patients may be needed.

The significance of impaired cardiovascular autonomic function in aortic valve disease is still speculative. Previous studies on diabetic patients and in patients following acute myocardial infarction have reported an increased morbidity and mortality including sudden cardiac death in those patients with impaired cardiovascular autonomic function (Niakan et al, 1986, Burgos et al, 1989; Ewing, Campbell and Clarke, 1976; Ewing, Campbell and Clarke, 1980; Kleiger et al, 1987; Bigger et al, 1988; La Rovere et al, 1988). Kleiger et al (1987) investigated 808 patients who survived acute myocardial infarction and followed them up for a mean period of 31 months. They showed risk of mortality to be 5.3 times higher in patients with decreased heart-rate variability. Decreased

heart-rate variability increased the risk of death irrespective of average heart-rate, variables reflecting left ventricular function, those measuring left ventricular ectopic activity, clinical or demographic variables or drug treatment particularly digitalis and beta-adrenergic blocking drugs.

An increased risk of sudden cardiac death has been shown to be associated with impaired autonomic function (Billman, Schwartz and Stone, 1982; Schwartz, Billman and Stone, 1984; Kleiger et al, 1987; Martin et al, 1987; La Rovere et al, 1988). Given this fact, in addition to the known association of aortic valve disease and the occurrence of sudden death (Ross and Braunwald, 1968; Chizner, Pearle and de Leon, 1980; Lombard and Selzer, 1987), it would be tempting to speculate about the mechanism of sudden death in aortic valve disease on the basis of impairment in cardiovascular autonomic function. In most instances of sudden death, ventricular fibrillation is regarded as the underlying mechanism (Lown and Wolf, 1971). Decreased vagal tone decreases heart-rate variability and predisposes to ventricular fibrillation in animals with experimental myocardial infarction (Lown and Verrier, 1976; Magid, Eckberg and Sprenkle, 1983). Increased sympathetic activity during experimental ischaemia or infarction promotes ventricular fibrillation (Lown and Verrier, 1976; Corr, Witkowski and Sobel, 1978) while increased vagal or decreased sympathetic activity decreases vulnerability to ventricular fibrillation (Magid, Eckberg, and Sprenkle, 1983; Lown and Verrier, 1976). Furthermore, beta-

adrenergic blocking drugs have been shown to reduce ventricular fibrillation threshold in experimental myocardial ischaemia or infarction (Sharma and Corr, 1983; Anderson, Rodier and Green, 1983; Gang, Bigger and Uhl, 1984). Very low doses of atropine have been shown to increase cardiac vagal efferent activity in dogs. Thus increased vagal tone and heart-rate variability by small doses of atropine resulted in reduced ventricular fibrillation threshold both in normal dogs and dogs with experimental myocardial ischaemia (Magid, Eckberg and Sprenkle, 1983). Thus, the results of previous studies suggest that patients with decreased heart-rate variability have decreased vagal tone, increased sympathetic activity or both and hence are at a higher risk of developing ventricular fibrillation and sudden death. This speculation may have therapeutic implications as it may be assumed that the risk of sudden cardiac death could be lowered by instituting agents that blunt sympathetic activity e.g. beta-adrenergic blocking drugs or agents that promote vagal tone e.g. transdermal scopolamine (Dibner-Dunlap et al, 1985) particularly in patients with decreased heart-rate variability. Beta-adrenergic blockade in patients following an acute myocardial infarction has been shown to cause a significant reduction in sudden cardiac death (Wilhelmsson et al, 1974; The Norwegian Multicenter Study Group, 1981).

9.6 Summary

This part of the study has shown that impairment in cardiac autonomic function in patients with aortic valve

disease is quite common. Aortic valve replacement was not accompanied by any improvement in autonomic function at least in the short-term. The mechanism of sudden death in aortic valve disease could be speculated on the basis of impaired cardiac autonomic function and the issue of therapeutic manipulation of cardiac autonomic control particularly in those patients with marked impairment in heart-rate variability is a possibility worth pursuing in future studies. Beta-blocking drugs by blunting sympathetic influences on the heart reduce the risk of mortality after myocardial infarction and hence could be one of the potential therapeutic options. However, the myocardial depressant effect of these drugs would preclude their use in patients with significant aortic valve disease at least pre-operatively.

CHAPTER TEN

SUMMARY OF THE MAIN FINDINGS AND CONCLUSIONS

Electrocardiographic and echocardiographic left ventricular hypertrophy were present in 90% and 91% of patients respectively. The mean echocardiographic left ventricular mass index was 210 ± 72 g/m^2. Left ventricular systolic and diastolic function were normal in 94% and 61% of patients respectively.

Significant coronary artery disease was present in 21 out of a total of 89 patients who had coronary angiography. Angina pectoris could predict the presence of significant coronary artery disease with 95% sensitivity and 54% specificity.

In agreement with most previous workers, complex ventricular arrhythmias were present in the majority of patients (74%). Nonsustained ventricular tachycardia was uncommon, occurring in only 9 (9%) patients. There was no relationship between ventricular arrhythmia frequency and the degree of echocardiographic left ventricular hypertrophy or the severity of aortic valve disease. Left ventricular function did not have any effect on ventricular arrhythmias. This may have resulted from the fact that the majority of patients had normal left ventricular function. Of the 9 patients with nonsustained ventricular tachycardia, only 2 had significant coronary artery disease.

The effect of AVR on left ventricular hypertrophy and ventricular arrhythmias was assessed. Aortic valve replacement was accompanied by a significant regression in echocardiographic left ventricular hypertrophy in

patients with predominant AS and those with combined AS and AR. However AVR did not result in a reduction in ventricular ectopy. There were no differences in VES frequency between pre-operative, early post-operative (5 to 7 days post AVR) and late post-operative (121 ± 24 days post AVR) periods.

Nonsustained ventricular tachycardia occurred in 9 (9%) patients pre-operatively and 4 (16%) patients 121 ± 24 days post AVR. Ventricular late potentials on SAECG were present in only one patient pre-operatively and in none of the 4 patients post-operatively. There was therefore little to suggest an underlying arrhythmogenic substrate in these patients.

Twenty-nine patients had a SAECG performed before and late after AVR. Aortic valve replacement was accompanied by a significant reduction in RMSV40. The significance of this finding which has not been reported previously is unclear.

Of a total of 7 deaths in the study, 3 occurred suddenly in patients awaiting surgery. Sudden death could not be predicted by either ambulatory electrocardiographic monitoring or SAECG.

Several studies have shown an association between an increased risk of sudden cardiac death and impairment in cardiovascular autonomic function. Given this fact, in addition to the known association of aortic valve disease and the occurrence of sudden cardiac death, it was tempting to speculate about the mechanism of sudden death

in aortic valve disease on the basis of impairment in cardiovascular autonomic function. Of the 47 patients assessed, 19 (40%) had abnormality in at least one autonomic function test. Of these 19 patients, 18 (38%) had abnormal heart-rate variation during deep breathing. Follow-up studies on diabetic patients and patients following acute myocardial infarction have reported a marked increase in the risk of mortality in patients with decreased heart-rate variability. Thus long-term follow-up of patients in this study will be needed to verify the prognostic significance of impaired cardiovascular autonomic function. In 10 patients re-studied 3 months after operation, AVR was not accompanied by an improvement in cardiovascular autonomic function at least in the short-term.

Although the significance of impaired parasympathetic heart-rate control in aortic valve disease patients is still speculative, its presence could be regarded as one of the potential predictors of sudden death as reduced parasympathetic nervous activity has been shown in previous experimental work to reduce ventricular fibrillation threshold. Long-term follow-up in larger numbers of patients will be needed in future to verify this.

REFERENCES

Adams D.F., Fraser, D.B. & Abrams, H.L. (1973) The complications of coronary arteriography. Circulation, 48, 609 - 618.

Airaksinen, K.E.J., Ikaheimo, N.J., Linnaluoto, M.K., Niemela, M. & Takkunen, J.T. (1987) Impaired vagal heart rate control in coronary artery disease. British Heart Journal, 58, 592 - 597.

Airaksinen, K.E.J., Ikaheimo, N.J., Koistinen, M.J. & Takkunen, J.T. (1988) Impaired vagal heart rate control in aortic valve stenosis. European Heart Journal, 9, 1126 - 1130.

Anderson, J.L., Rodier, H.E. & Green, L.S. (1983) Comparative effects of B-adrenergic blocking drugs on experimental ventricular fibrillation threshold. American Journal of Cardiology, 51, 1196 - 1202.

Anderson, K.P., De Camilla, J. & Moss, A.J. (1978) Clinical significance of ventricular tachycardia (3 beats or longer) detected during ambulatory monitoring after myocardial infarction. Circulation, 57, 890 - 897.

Angelini, P., Feldman, M.I., Lufschanowski, R. & Leachman, R.D. (1974) Cardiac arrhythmias during and after heart surgery: diagnosis and management. Progress in Cardiovascular Diseases, 16, 469 - 495.

Aronow, W.S., Epstein, S., Schwartz, K.S. & Koenigsberg, M. (1987) Correlation of complex ventricular arrhythmias detected by ambulatory electrocardiographic monitoring with echocardiographic left ventricular hypertrophy in persons older that 62 years in a long-term health care facility. American Journal of Cardiology, 60, 730 - 732.

Baldwa, V.S. & Ewing, D.J. (1977) Heart-rate response to valsalva manoeuvre. Reproducibility in normals and relation to variation in resting heart rates in diabetics. British Heart Journal, 39, 641 - 644.

Barratt-Boyes, B.G., Roche, A.H.G. & Whitlock, R.M.L. (1977) Six year review of the results of freehand aortic valve replacement using an antibiotic sterilized homograft valve. Circulation, 55, 353 - 361.

Basta, L.L., Raines, D., Najjar, S. & Kioschos, J.M. (1975) Clinical, haemodynamic and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. British Heart Journal, 37, 150 - 157.

Bennett, T., Riggott, P.A., Hosking, D.J. & Hamptom, J.R. (1976) Twenty-four hour monitoring of heart rate and activity in patients with diabetes mellitus: a comparison with clinical investigations. British Medical Journal, I, 1250 - 1251.

Berbari, E.J., Scherlag, B.J., Hope, R.R. & Lazzara, R. (1978) Recording from the body surface of arrhythmogenic ventricular activity during the ST segment. American Journal of Cardiology, 41, 671 - 702.

Bergeron, J., Abelmann, W.H., Vasquez-Milan, H. & Ellis, L.B. (1954) Aortic stenosis - clinical manifestations and course of the disease - review of 100 proved cases. Archives of Internal Medicine, 94, 911 - 924.

Beyer, R.W., Ramirez, M., Josephson, M.A. & Shah, P.M. (1987) Correlation of continuous-wave Doppler assessment of chronic aortic regurgitation with haemodynamics and angiography. American Journal of Cardiology, 60, 852 - 856.

Bhatnagar, S.K., Al-Yusuf, A. & Al-Asfoor, A. (1987) Abnormal autonomic function in diabetic and non-diabetic patients after first acute myocardial infarction. Chest, 92, 849 - 852.

Bigger, J.T., Fleiss, J.L., Kleiger, R., Miller, J.P., Rolmitzky, L.M. & The Multicenter Post-infarction Research Group. (1984) The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation, 69, 250 - 258.

Bigger, J.T., Kleiger, R.E., Fleiss, J.L., Rolmitzky, L.M., Steinman, R.C., Miller, P. & The Multicenter Post-Infarction Research Group. (1988) Component of heart rate variability measured during healing of acute myocardial infarction. American Journal of Cardiology, 61, 208 - 215.

Billman, G.E., Schwartz, P.J. & Stone, H.L. (1982) Baroreceptor reflex control of heart rate: A predictor of sudden cardiac death. Circulation, 66, 874 - 880.

Billman, G.E., Schwartz, P.J. & Stone, H.L. (1984) The effects of daily exercise on susceptibility to sudden cardiac death. Circulation, 69, 1182 - 1189.

Bland, E.F. & Wheeler, E.O. (1957) Severe aortic regurgitation in young people. A long-term perspective with reference to prognosis and prosthesis. New England Journal of Medicine, 256, 667 - 671.

Bleich, H.L. & Boro, E.S. (1976) The effect of vagus nerve stimulation upon excitability of the canine ventricle: role of sympathetic-parasympathetic interactions. American Journal of Cardiology, 37, 1041 - 1045.

Borbola, J, Ezri, M.D., & Denes, P. (1988) Correlation between the signal-averaged electrocardiogram and electrophysiologic study findings in patients with coronary artery disease and sustained ventricular tachycardia. American Heart Journal, 115, 816 - 824.

Borbola, J., Serry, C., Goldin, M. & Denes, P. (1988) Short-term effect of coronary artery bypass grafting on the signal-averaged electrocardiogram. American Journal of Cardiology, 61, 1001 - 1005.

Borhani, N.O. (1987) Left ventricular hypertrophy, arrhythmias and sudden death in systemic hypertension. American Journal of Cardiology, 60, 131 - 181.

Bradbury, S. & Eggleston, C. (1925) Postural hypotension: a report on three cases. American Heart Journal, I, 73 - 86.

Braunwald, E. (1988) Textbook of Cardiovascular Medicine (3rd edition).

Breithardt, G. & Borggrefe, M. (1986) Pathophysiological mechanisms and clinical significance of ventricular late potentials. European Heart Journal, 7, 364 - 385.

Breithardt, G., Becker, R. & Seipel, L. (1980) Non-invasive recording of late ventricular activitation in man. Circulation, 62 (Supplement III), III - 320.

Breithardt, G., Borggrefe, M., Karbenn, U., Abendroth, R., Yeh, H. & Seipal, L. (1982) Prevalence of late potentials in patients with and without ventricular tachycardia; correlation with angiographic findings. American Journal of Cardiology, 49, 1932 - 1937.

Breithardt, G., Martinez-Rubio, A. & Borggrefe, M. (1990) Correlation between programmed ventricular stimulation and signal-averaged electrocardiograms in the identification of patients at high risk for serious ventricular arrhythmias. Pace, 13, 685 - 691.

Bristow, J.D., McCord, C.W., Starr, A., Ritzman, L.W. & Griswold, H.D. (1964) Clinical and haemodynamic results of aortic valvular replacement with a ball valve prosthesis. Circulation, 30 (Supplement 1), 36 - 46.

Brown, A.M. (1967) Excitation of afferent cardiac sympathetic nerve fibres during myocardial ischaemia. Journal of Physiology, 190, 35 - 53.

Brown, K.W., MacMillan, R.L., Forbath, N., Mel'Grano, F. & Scott, J.W. (1963) An intensive-care centre for acute myocardial infarction. Lancet, 2, 349 - 352.

Burgos, L.G., Ebert, T.J., Asiddao, C., Turner, L.A., Pattison, C.Z., Wang-Cheng, R & Kampine, J.P. (1989) Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. Anaesthesiology, 70, 591 - 597.

Buxton, A.E., Marchlinski, F.E., Waxman, H.L., Flores, B.T., Cassidy, D.M. & Josephson, M.E. (1984) Prognostic factors in nonsustained ventricular tachycardia. American Journal of Cardiology, 53, 1275 - 1279.

Buxton, A.E., Simson, M.B., Falcone, R.A., Marchlinski, F.E., Doherty, J.U. & Josephson, M.E. (1987) Results of signal-averaged electrocardiography and electrophysiologic study in patients with nonsustained ventricular tachycardia after healing of acute myocardial infarction. American Journal of Cardiology, 60, 80 - 85.

Cabot, R.C. (1926) Facts on the heart. Saunders, Philadelphia.

Califf, R.M., Burks, J.M., Behar, V.S., Margolis. J.R. & Wagner, G.S. (1978) Relationships among ventricular arrhythmias, coronary artery disease, and angiographic and electrocardiographic indicators of myocardial fibrosis. Circulation, 57, 725 - 732.

Calvert, A., Lown, B. & Gorlin, R. (1977) Ventricular premature beats and anatomically defined coronary heart disease. American Journal of Cardiology, 39, 627 - 634.

Canedo, M.I., Frank, M.J. & Abdulla, A.M. (1980) Rhythm disturbances in hypertrophic cardiomyopathy: prevalence, relation to symptoms and management. American Journal of Cardiology, 45, 848 - 855.

Chakko, C.S. & Gheorghiade, M. (1985) Ventricular arrhythmias in severe heart failure: Incidence, significance, and effectiveness of anti-arrhythmic therapy. American Heart Journal, 109, 497 - 504.

Chizner, M.A., Pearle, D.L. & de Leon, A.C. (1980) The natural history of aortic stenosis in adults. American Heart Journal, 99, 419 - 424.

Chobadi, R., Wurzel, M., Teplitsky, I., Menkes, H. & Tamari, I. (1989) Coronary artery disease in patients 35 years of age or older with valvular aortic stenosis. American Journal of Cardiology, 64, 811 - 812.

Clarke, B.F., Ewing, D.J. & Campbell, I.W. (1979) Diabetic autonomic neuropathy. Diabetologia, 17, 195 - 212.

Contratto, A.W. & Levine, S.A. (1937) Aortic stenosis with special reference to angina pectoris and syncope. Annals of Internal Medicine, 10, 1636 - 1653.

Corr, P.B., Witkowski, F.X. & Sobel, B.E. (1978) Mechanisms contributing to malignant dysrhythmias induced by ischaemia in the cat. Journal of Clinical Investigation, 61, 109 - 119.

Coumel, P., Leclercq, J.F. & Leenhardt, A. (1987) Arrhythmias as predictors of sudden death. American Heart Journal, 114, 929 - 937.

Cripps, T., Bennett, E.D., Camm, A.J. & Ward, D.E. (1988) High gain signal-averaged electrocardiogram combined with 24 hour monitoring in patients early after myocardial infarction for bedside prediction of arrhythmic events. British Heart Journal, 60, 181 -187.

Currie, P.J., Seward, J.B., Reeder. G.S., Vlietstra, R.E., Bresnahan, D.R., Bresnahan, J.F., Smith, H.C., Hagler, D.J. & Tajik, J. (1985) Continuous-wave Doppler echo-cardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-Catheter correlative study in 100 patients. Circulation, 71, 1162 - 1169.

Denes, P., Santarelli, P., Hauser, R.G. & Uretz, E.F. (1983) Quantitative analysis of the high-frequency components of the terminal portion of the body surface QRS in normal subjects and in patients with ventricular tachy-cardia. Circulation, 67, 1129 - 1138.

Denes, P., Uretz, E.F. & Santarelli, P. (1984) Determinants of arrhythmogenic ventricular activity detected on the body surface QRS in patients with coronary artery disease. American Journal of Cardiology, 53, 1519 - 1523.

Denniss, A.R., Cody, D.V. & Fenton, S.M. et al. (1983) Significance of delayed activation potentials in survivors of myocardial infarction. Journal of the American College of Cardiology, 68, (Abstract), I - 582.

Denniss, A.R., Richards, D.A., Cody, D.V., Russell, P.A., Young, A.A., Ross, D.L. & Uther, J.B. (1987) Correlation between signal-averaged and programmed stimulation in patients with and without spontaneous ventricular tachyarrhythmias. American Journal of Cardiology, 59, 568 - 590.

Devereux, R.B., Lutas, E.M., Casale, P.N., Kligfield, P., Eisenberg, R.R., Hammond, I.W., Miller, D.H., Reis, G., Alderman, M.H. & Laragh, J.H. (1984) Standardization of M-Mode echocardiographic left ventricular anatomic measurements. Journal of the American College of Cardiolgoy, 4, 1222 - 1230.

Devereux, R.B. & Reichek, N. (1977) Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation, 55, 613 - 618.

Diamond, G.A. & Forrester, J.S. (1979) Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. New England Journal of Medicine, 300, 1350 - 1358.

Dibner-Dunlap, M.E., Eckberg, D.L., Magid, N.M. & Cintron-Trevino, N.M. (1985) The long-term increase of baseline and reflexly augmented levels of human vagal-cardiac nervous activity induced by scopolamine. Circulation, 71, 797 - 804.

Dodge, E.T., Sandler, H., Ballew, D.W. & Lord, J.D. (1960) The use of biplane cine-angiography for the measurement of left ventricular volume in man. American Heart Journal, 60, 762 - 766.

Dry, T.J. & Willius, F.A. (1939) Calcareous disease of the aortic valve. A study of 228 cases. American Heart Journal, 17, 138.

Dubois, D. & Dubois, E.F. (1916) A formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine, 17, 863 - 871.

Dunn, F.G., Chandraratna, P., De Carvalho, J.G., Basta, L.L. & Frohlich, E.D. (1977) Pathophysiologic assessment of hypertensive heart disease with echocardiography. American Journal of Cardiology, 39, 789 - 795.

Duvoisin, G.E., Wallace, R.B., Ellis, F.H. Jr., Anderson, M.W. & McGoon, D.C. (1968) Late results of cardiac replacement. Circulation, 38 (Supplement 2), 75 - 85.

Eckberg, D.L., Drabinsky, M & Braunwald E. (1971) Defective cardiac parasympathetic control in patients with heart disease. New England Journal of Medicine, 285, 877 - 883.

El-Sherif, N., Lazzara, R., Hope, R.R. & Scherlag, B.J. (1977) Reentrant ventricular arrhythmias in the late myocardial infarction period. III. Manifest and concealed extra-systolic grouping. Circulation, 56, 225 - 234.

El-Sherif, N., Scherlag, B.J., Lazzara, R. & Hope, R.R. (1977) Reentrant ventricular arrhythmias in the late myocardial infarction period. I. Conduction characteristics in the infarction zone. Circulation, 55, 686 - 702.

El-Sherif, N., Scherlag, B.J., Lazzara, R. & Hope, R.R. (1977) Reentrant ventricular arrhythmias in the late myocardial infarction period. II. Patterns of initiation and termination of reentry. Circulation, 55, 702 - 719.

Ellenbogen, K.A., Mohanty, P.K., Szentpetery, S. & Thames, M.D. (1989) Arterial baroreflex abnormalities in heart failure. Reversal after orthotopic cardiac transplantation. Circulation, 79, 51 - 58.

Ewing, D.J. (1978) Cardiovascular reflexes and autonomic neuropathy. Clinical Science and Mollecular Medicine, 55, 321 - 327.

Ewing, D.J., Borsey, D. Q., Bellavere, F. & Clarke, B.F. (1981) Cardiac autonomic neuropathy in diabetes - comparison of measures of R-R interval variation. Diabetologia, 21, 18 - 24.

Ewing, D.J., Campbell, I.W. & Clarke, B.F. (1976) Mortality in diabetic autonomic neuropathy. Lancet, I, 601 - 605.

Ewing, D.J., Campbell, I.W. & Clarke, B.F. (1980) The natural history of diabetic autonomic neuropathy. Quarterly Journal of Medicine, 193, 95 - 108.

Ewing, D.J., Campbell, I.W., Burt, A.A. & Clarke, B.F. (1973) Vascular reflexes in diabetic autonomic neuropathy. Lancet, 2, 1354 - 1356.

Ewing, D.J., Campbell, I.W., Murray, A., Neilson, J.M.M. & Clarke, B.F. (1978) Immediate heart rate response to standing: simple test for autonomic neuropathy in diabetes. British Medical Journal, 1, 145 - 147.

Ewing, D.J. & Clarke, B.F. (1982) Diagnosis and management of diabetic autonomic neuropathy. British Medical Journal, 285, 916 - 918.

Ewing, D.J., Martyn, C.N., Young, R.J. & Clarke, B.F. (1985) The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care, 8, 491 - 498.

Ewing, D.J., Neilson, J.M.M. & Travis, P. (1984) New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. British Heart Journal, 52, 396 - 402.

Exadactylos, N., Sugrue, D.D. & Oakley, C.M. (1984) Prevalence of coronary artery disease in patients with isolated aortic valve stenosis. British Heart Journal, 51, 121 - 124.

Frank, M.J., Watkins, L.D., Prisant, L.M., Stefadouros, N.H. & Abdulla, A.M. (1984) Potentially lethal arrhythmias and their management in hypertrophic cardio-myopathy. American Journal of Cardiology, 53, 1608 - 1613.

Frank, S., Johnson, A. & Ross, J., Jr. (1973) Natural history of valvular aortic stenosis. British Heart Journal, 35, 41 - 46.

Freedman, R.A., Gillis, A.M., Keren, A., Soderholm-Difatte, V. & Mason, J.W. (1985) Signal-averaged electrocardiographic late potentials in patients with ventricular fibrillation or ventricular tachycardia: correlation with clinical arrhythmia and electrophysiologic study. American Journal of Cardiology, 55, 1350 - 1353.

Gaasch, W.H., Andrias, C.W. & Levine, H.J. (1978) Chronic aortic regurgitation: The effect of aortic valve replacement on left ventricular volume, mass and function. Circulation, 58, 825 - 836.

Galloway, A.C., Colvin, S.B., Grossi, E.A., Baumann, F.G., Sabban, Y.P., Esposito, R., Ribakove, G.H., Culliford, A.T., Slater, J.N., Glassman, E., Harty, S. & Spencer, F.C. (1990) Ten-year experience with aortic valve replacement in 482 patients 70 years of age or older: Operative risks and long-term results. Annals of Thoracic Surgery, 49, 84 - 93.

Gang, E.S., Bigger, J.T. Jr. & Uhl, E.W. (1984) Effects of timolol and propranolol on inducible sustained ventricular tachyarrhythmias in dogs with subacute myocardial infarction. American Journal of Cardiology, 53, 275 - 281.

Gang, E.S., Lew, A.S., Hong, W., Wang, F.Z., Siebert, C.A. & Peter, T. (1989) Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. New England Journal of Medicine, 321, 712 - 716.

Gang, E.S., Peter, T., Rosenthal, M.E., Mandel, W.J. & Lass, Y. (1986) Detection of late potentials on the surface electrocardiogram in unexplained syncope. American Journal of Cardiology, 58, 1014 - 1020.

Glew, R.H., Varghese, P.J., Krovertz, L.J., Durst, J.P. & Rowe, R.D. (1969) Sudden death in congenital aortic stenosis. A review of eight cases with an evaluation of premonitory clinical features. American Heart Journal, 78, 615 - 625.

Glover, D.R. & Littler, W.A. (1987) Factors influencing survival and mode of death in severe chronic ischaemic cardiac failure. British Heart Journal, 57, 125 - 132.

Goldschlager, N., Pfeifer, J., Cohn, K., Popper, R. & Seltzer, A. (1973) The natural history of aortic regurgitation. American Journal of Medicine, 54, 577 - 588.

Gomes, J.A.C., Hariman, R.I., Kang, R.S., El-Sherif, N., Chowdhry, I. & Lyons, J. (1984) Programmed electrical stimulation in patients with high-grade ventricular ectopy: electrophysiologic findings and prognosis for survival. Circulation, 70, 43 - 51.

Graboys, T.B. & Cohn, P.F. (1977) The prevalence of angina pectoris and abnormal coronary arteriograms in severe aortic valve disease. American Heart Journal, 93, 683 - 686.

Gradman, A.H., Bell, P.A. & De Busk, R.F. (1977). Sudden death during ambulatory monitoring. Circulation, 55, 210 - 211.

Gradman, A.H., Harbison, M.A., Berger, H.J., Geha, A.S., Shaw, R.K., Cynthia, J.C., Suzanne, S., Linda, P. & Barry, L.Z. (1981) Ventricular arrhythmias late after aortic valve replacement and their relation to left ventricular performance. American Journal of Cardiology, 48, 824 - 831.

Grayburn, P.A., Handshoe, R., Smith, M.D., Harrison, M.R. & De Maria, A.N. (1987) Quantitative assessment of the haemodynamic consequences of aortic regurgitation by means of continuous-wave Doppler recordings. Journal of the American College of Cardiology, 10, 135 - 141.

Green, G.S., McKinnon, C.M. & Rosch, J. (1972) Complications of selective percutaneous transfemoral coronary arteriography and their prevention: a review of 445 consecutive examinations. Circulation, 45, 552 - 557.

Grossman, W., Jones D. & McLaurin, L.P. (1975) Wall stress and patterns of hypertrophy in the human left ventricle. Journal of Clinical Investigation, 56, 56 - 64.

Hakki, A.H., Kimbiris, D., Iskandrian, A.S., Segal, B.L., Mintz, G.S. & Bemis, C.E. (1980) Angina pectoris and coronary artery disease in patients with severe aortic valvular disease. American Heart Journal, 100, 441 - 449.

Hamilton, W.F., Woodbury R.A. & Harper, H.T. (1936) Physiologic relationships between intrathoracic, intraspinal and arterial pressures. Journal of American Medical Association, 107, 853 - 856.

Hancock, W. (1977) Aortic stenosis, angina pectoris and coronary artery disease. American Heart Journal, 93, 382 - 393.

Hatle L., Angelsen, B.A. & Tramsdal, A. (1980) Non-invasive assessment of aortic stenosis by Doppler ultrasound. British Heart Journal, 43, 284 - 292.

Hatle, L. (1981) Non-invasive assessment and differentiation of left ventricular outflow obstruction with Doppler ultrasound. Circulation, 64, 381 - 387.

Hatle, L., Angelson, B. & Tramsdal, A. (1979) Non-invasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation, 60, 1096 - 1104.

Hilden, T., Raaschan, F., Iversen, K. & Schwartz, M. (1961) Anticoagulants in acute myocardial infarction. Lancet, 2, 327 - 331.

Hilsted, J. & Jensen, S.B. (1979) A simple test for autonomic neuropathy in Juvenile diabetics. Acta Medica Scandinavica, 205, 385 - 387.

Hirshfeld, J.W., Epstein, S.E., Roberts, A.J., Glancy, D.L. & Morrow, A.G. (1974) Indices predicting long-term survival after valve replacement in patients with aortic regurgitation and patients with aortic stenosis. Circulation, 50, 1190 - 1199.

Hochreiter, C., Borer, J.S., Kligfield P., Deveraux, R., Jacobstein, J. & Kase, M. (1982) Complex ventricular arrhythmias in patients with valvular regurgitation: a potentially important, clinically overlooked phenomenon? American Journal of Cardiology, 49 (Abstract), 910.

Holmes, J., Kubo, S.H., Cody, R.J. & Kligfield, P. (1985) Arrhythmias in ischaemic and non-ishaemic dilated cardiomyopathy: Prediction of mortality by ambulatory electrocardiography. American Journal of Cardiology, 55, 146 - 151.

Hornung, R.S., Mahler, R.F. & Raftery, E.B. (1989) Ambulatory blood pressure and heart rate in diabetic patients: an assessment of autonomic function. Diabetic Medicine, 6, 579 - 585.

Huang, S.K., Messer, J.V. & Denes., P. (1983) Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. American Journal of Cardiology, 51, 507 - 512.

Imaizumi, T., Takeshita, A., Makino, N., Ashihara, T., Yamamoto, K. & Nakamura, M. (1984) Impaired baroreflex control of vascular resistance and heart rate in acute myocardial infarction. British Heart Journal, 52, 418 - 421.

Isom, O.W., Spencer, F.C., Glassman, E., Teiko, P., Boyd, A.D., Cunningham, J.N. & Reed, G.E. (1977) Long-term results in 1375 patients undergoing valve replacement with the Starr-Edwards cloth-covered steel ball prothesis. Annals of Surgery , 186, 310 - 323.

Johnson, A.M. (1971) Aortic stenosis, sudden death and the left ventricular baroreceptors. British Heart Journal, 33, 1 - 5.

Johnston, L.C. (1980) The abnormal heart-rate response to a deep breath in borderline labile hypertension: a sign of autonomic nervous dysfunction. American Heart Journal, 99, 487 - 493.

Jones, M., Schofield, P.M., Brooks, N.H., Dark, J.F., Moussalli, H., Deiraniya, A.K., Lawson, R.A.M. & Rahman, A.N. (1989) Aortic valve replacement with combined myocardial revascularisation. British Heart Journal, 62, 9 - 15.

Kalbfleisch, J.H., Stowe, D.F. & Smith, J.J. (1978) Evaluation of the heart rate response to the valsalva manoeuvre. American Heart Journal, 95, 705 - 715.

Kannel, W.B. (1983) Prevalence and natural history of electrocardiographic left ventricular hypertrophy. American Journal of Medicine, 75 (Supplement 3A), 4 - 11.

Kannel, W.B., Gordon, T. & Offutt, D. (1969) Left ventricular hypertrophy by ECG. Prevalence, incidence and mortality in the Framingham Study. Annals of Internal Medicine, 71, 89 - 105.

Kelly, T.A., Rothbart, R.M., Cooper, C.M., Kaiser, D.L., Smucker, M.L. & Gibson, R.S. (1988) Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. American Journal of Cardiology, 61, 123 - 130.

Kennedy, H.L., Underhill, S.J., Poblete, R.F. & Weiss, J.L. (1975) Ventricular ectopic beats in patients with aortic valve disease. Circulation 52 (Abstract), Supplement II, 202.

Kennedy, H.L., Whitlock, J.A., Sprague, M.K., Kennedy, L.J., Buckingham, T.A. & Goldberg, R.J. (1985) Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. New England Journal of Medicine, 312, 193 - 197.

Kennedy, J.W., Doces, J. & Stewart, D.K. (1977) Left ventricular function before and following aortic valve replacement. Circulation, 56, 944 - 950.

Kent, K.M., Smith, E.R., Redwood, D.R. & Epstein, S.E. (1973) Electrical stability of acutely ischaemic myocardium. Influences of heart rate and vagal stimulation. Circulation, 47, 291 - 298.

Khurmi, N.S. & Raftery, E.B. (1987) Reproducibility and validity of ambulatory ST segment monitoring in patients with chronic stable angina pectoris. American Heart Journal, 113, 1091 - 1096.

Kienzle, M.G., Falcone, R.A. & Simson, M.B. (1988) Alterations in the initial portion of the signal-averaged QRS complex in acute myocardial infarction with ventricular tachycardia. American Journal of Cardiology, 61, 99 - 103.

Kirby, B.J. (1977) Circulatory reflexes in myocardial infarction. British Heart Journal, 39, 168 - 172.

Kleiger, R.E., Miller, J.P., Bigger, J.T., Moss, A.J. & The Multicenter Post-Infarction Research Group. (1987) Decrease heart-rate variability and its association with increased mortality after acute myocardial infarction. American Journal of Cardiology, 59, 256 - 262.

Klein, R.C. (1984) Ventricular arrhythmias in aortic valve disease: analysis of 102 patients. American Journal of Cardiology, 53, 1079 - 1083.

Kolman, B.S., Verrier, R.L. & Lown, B. (1975) The effect of vagus nerve stimulation upon vulnerability of the canine ventricle. Role of sympathetic-parasympathetic interactions. Circulation, 52, 578 - 585.

Kostis, J.B., Tupper, B., Moneyra, A.E., Hosler, M., Cosgrove, N. & Terregino, C. (1984) Aortic valve replacement in patients with aortic stenosis. Chest, 85, 211 - 214.

Kotler, M.N., Tabatznik, B., Mower, M.M. & Tominaga, S. (1973) Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post-infarction period. Circulation, 47, 959 - 966.

Kowly, P.R., Eisenberg, R. & Engel, T.R. (1984) Sustained arrhythmias in hypertrophic obstructive cardiomyopathy. New England Journal of Medicine, 310, 1566 - 1569.

Kremers, M.S., Black, W.H. & Wells, P.J. (1989) Cardiac death: etiologies, pathogenesis and management. Disease A Month, 35 (6), 381 - 445.

Kuchar, D.L., Thorburn, C.W. & Sammel, N.L. (1986) Signal-averaged electrocardiogram for evaluation of recurrent syncope. American Journal of Cardiology, 58, 949 - 953.

Kuchar, D.L., Thorburn, M.B. & Sammel, N.L. (1986) Late potentials detected after myocardial infarction: natural history and prognostic significance. Circulation, 74, 1280 - 1289.

La Rovere, M.T., Specchia, G., Mortara, A. & Schwartz, P.J. (1988) Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospecitve study. Circulation, 78, 816 - 824.

Lahiri, A., Balasubramanian, V. & Raftery, E.B. (1979) Sudden death during ambulatory monitoring. British Medical Journal, I, 1676.

Lee, S.J.K., Barr, C., Callaghan, J.C. & Rossall, R.E. (1975) Long-term survival after aortic valve replacement using Smeloff-Cutter prosthesis. Circulation, 52, 1132 - 1137.

Levin, A.B. (1966) A simple test of cardiac function based upon the heart rate changes induced by the valsalva manoeuvre. American Journal of Cardiology, 18, 90 - 99.

Levy, D., Anderson, K.M., Savage, D.D., Balkus, S.A., Kannel, W.B. & Castelli, W.P. (1987) Risk of ventricular arrhythmias in left ventricular hypertrophy. Framingham Heart Study. American Journal of Cardiology, 60, 560 - 565.

Levy, D., Garrison, R.J., Savage, D.D., Kannel, W.B. & Castelli, W.P. (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. New England Journal of Medicine, 322, 1561 - 1566.

Lindsay, B.D., Amboz, H.D., Schectman, K.B. & Cain, M.E. (1986) Improved selection of patients for programmed ventricular stimulation by frequency analysis of signal-averaged electrocardiograms. Circulation, 73, 675 - 683.

Lombard, J.T. & Selzer, A. (1987) Valvular aortic stenosis. A clinical and haemodynamic profile of patients. Annals of Internal Medicine, 106, 292 - 298.

Lown, B. & Wolf, M.A. (1971) Approaches to sudden death from coronary heart disease. Circulation, 44, 130 - 142.

Lown, B. & Verrier, R.L. (1976) Neural activity and ventricular fibrillation. New England Journal of Medicine, 294, 1165 - 1170.

Lown, B., Fakhro, A.M., Hood, W.B. & Thorn, G.W. (1967) The Coronary Care Unit: New perspectives and directions. Journal of the American College of Medicine, 199, 188 - 198.

Luu, M., Stevenson, W.G., Stevenson, L.W., Baron, K. & Walden, J. (1989) Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation, 80, 1675 - 1680.

Lytle, B.W., Cosgrove, D.M., Loop, F.D., Taylor, P.C., Gill, C.C., Golding, L.A.R., Goormastic, M. & Groves, L.K. (1983) Replacement of aortic valve combined with myocardial revascularisation: determinants of early and late risk for 500 patients, 1967 - 1981. Circulation, 68, 1149 - 1162.

Lytle, B.W., Cosgrove, D.M., Taylor, P.C., Goormastic, M., Stewart, R.W., Golding, L.A.R., Gill, C.C. & Loop, F.D. (1989) Primary isolated aortic valve replacement: early and late results. Journal of Thoracic and Cardiovascular Surgery, 97, 675 - 694.

Magid, N.B., Eckberg, D.L. & Sprenkle, J.M. (1983) Low dose atropine reduces ventricular vulnerability in normal and ischaemic hearts. Clinical Research, 31 (Abstract), 461A.

Malliani, A., Schwartz, P.J. & Zanchetti, A. (1969) A sympathetic reflex elicited by experimental coronary occlusion. American Journal of Physiology, 217, 703 - 709.

Martin, G.J., Magid, N.M., Myers, G., Barnett, P.S., Schaad, J.W., Weiss, J.S., Lesch, M. & Singer, D.H. (1987) Heart-rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. American Journal of Cardiology, 60, 86 - 89.

Martin, H.M. & Sullivan, A.G. (1935) Clinical observations upon syncope and sudden death in relation to aortic stenosis. American Heart Journal, 10, 705 - 735.

Massell B.F., Amezcua, F.J. & Czoniczer, G. (1966) Prognosis of patients with pure or predominant aortic regurgitation in the absence of surgery. Circulation, 34 (Supplement III), III - 164 (Abstract).

Masuyama, T., Kodama, K., Kitabatake, A., Nanto, S., Sato, H., Uematsu, M., Inoue, M. & Kamada, T. (1986) Non-invasive evaluation of aortic regurgitation by continuous-wave Doppler echocardiography. Circulation, 73, 460 - 466.

Meinertz, T., Hofmann, T., Kasper, W., Treese, N., Bechtold, H., Stienen, U., Pop, T., Leitner, E.V., Andresen, D. & Meyer, J. (1984) Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. American Journal of Cardiology, 53, 902 - 907.

Meinertz, T., Kasper, W., Bodecker, W., Hofmann, T., Zehender, M., Geibel, A., Treese, N. & Just, H. (1987) Relation between haemodynamics and ventricular arrhythmias in patients with heart diseases. Zeitschrift for Kardiologie, 76 (Abstract in English), 421 - 427

Messerli, F.H., Ventura, H.D., Elizardi, D.J., Dunn, F.G. & Frohlich, E.D. (1984) Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. American Journal of Medicine, 77, 18 - 22.

Michelson, E.L. & Morganroth, J. (1980) Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. Circulation, 61, 690 - 695.

Michelson, E.L., Morganroth, J. & McVaugh, H. III. (1979) Postoperative arrhythmias after coronary artery and cardiac valvular surgery detected by long-term electrocardiographic monitoring. American Heart Journal, 97, 442 - 448.

Mitchell, A.R., Sackett, C.H., Hunzickein, W.J. & Levine, S.A. (1954) The clinical features of aortic stenosis. American Heart Journal, 48, 684 - 720.

Monrad, E.S., Hess, O.M., Mukarami, T., Nonogi, H., Corin, W.J. & Krayenbuehl, H.P. (1988) Time course of regression of left ventricular hypertrophy after aortic valve replacement. Circulation, 77, 1345 - 1355.

Morganroth, J., Michelson, E.L., Horowitz., L.N., Josephson, M.E., Pearlman, A.S. & Dunkman, W.B. (1978) Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation, 58, 408 - 414.

Moss, A.J., Davis, H.T., De Camilla, J. & Bayer, L.W. (1979) Ventricular ectopic beats and their relation to sudden death after myocardial infarction. Circulation, 60, 998 - 1003.

Mukharji, J., Rude, R.E., Poole, K., Gustafson, N., Thomas L.J., Strauss, W., Jaffe, A.S., Muller, J.E., Roberts, R., Raabe, D.S., Croft, C.H., Passamani, E., Braunwald, E., Willerson, J.T. & the MILIS STUDY GROUP. (1984) Risk factors for sudden death after acute myocardial infarction: Two year follow-up. American Journal of Cardiology, 54, 31 - 36.

Mullany, C.J., Elveback, L.R., Frye, R.L., Pluth, J.R., Edwards, W.D., Orszulak, T.A., Nassef, L.A., Riner, R.E. & Danielson, G.K. (1987) Coronary artery disease and its management: Influence on survival in patients undergoing aortic valve replacement. Journal of the American College of Cardiology, 10, 66 - 72.

Multicenter Post-infarction Research Study Group, (1983) Risk stratification and survival after myocardial infarction. New England Journal of Medicine, 309, 331 - 336.

Murray, A., Ewing, D.J., Campbell, I.W., Neilson, J.M.M. & Clarke, B.F. (1975) RR interval variations in young male diabetics. British Heart Journal, 37, 882 - 885.

McAreavey, D., Neilson, J.M.M., Ewing, D.J. & Russell, D.C. (1989) Cardiac parasympathetic activity during the early hours of acute myocardial infarction. British Heart Journal, 62, 165 - 170.

McDonald, I.G, Feigenbaum, H. & Chang, S. (1972) Analysis of left ventricular wall motion by reflected ultrasound. Application to assessment of myocardial function. Circulation, 46, 14 - 25.

Macfarlane, P.W. (1979) Computer assisted analysis of dynamic (24 hour) electrocardiograms. Progress in Electrocardiology, 123 - 126.

McGuire, M., Kuchar, D., Ganis, J., Sammel, N. & Thorburn, C. (1988) Natural history of late potentials in the first ten days after acute myocardial infarction and relation to early ventricular arrhythmias. American Journal of Cardiology, 61, 1187 - 1190.

Mackay, J.D., Page, M.M., Cambridge, J. & Watkins, P.J. (1980) Diabetic autonomic neuropathy. The diagnostic value of heart rate monitoring. Diabetologia, 18, 471 - 478.

McKenna, W.J., Chetty, S., Oakley, C.M. & Goodwin, J.P. (1980) Arrhythmias in hypertrophic cardiomyopathy: exercise and 48 hour ambulatory electrocardiographic assessment with and without beta adrenergic blocking therapy. American Journal of Cardiology, 45, 1 - 5.

McKenna, W.J., England, D., Doi, Y.L., Deanfield, J.E., Oakley, C. & Goodwin, J.F. (1981) Arrhythmias in hypertrophic cardiomyopathy. British Heart Journal, 46, 168 - 172.

McLenachan, J.M., Henderson, E., Morris, K.I. & Dargie, H.J. (1987) Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. New England Journal of Medicine, 317, 787 -792.

Nalos, P.C., Gang, E.S., Mandel, W.J., Myers, M.R., Oseran, D.S., Lass, Y. & Peter, T. (1988) Utility of the signal-averaged electrocardiogram in patients presenting with sustained ventricular tachycardia or fibrillation while on an anti-arrhythmic drug. American Heart Journal, 115, 108 - 114.

Niakan, E., Harati, Y., Rolak, L.A., Comstock, J.P. & Rokey, R. (1986) Silent myocardial infarction and diabetic cardiovascular automonomic neuropathy. Archives of Internal Medicine, 146, 2229 - 2230.

Nikolic, G., Bishop, R.L. & Singh, J.B. (1982) Sudden death recorded during Holter monitoring. Circulation, 66, 218.

Norwegian Multicenter Study Group. (1981) Timolol induced reduction in mortality and re-infarction in patients surviving acute myocardial infarction. New England Journal of Medicine, 304, 801 - 807.

Pantely, G., Morton, M. & Rahimtoola, S.H. (1978) Effects of successful, uncomplicated valve replacement on ventricular hypertrophy, volume and performance in aortic stenosis and in aortic incompetence. Journal of Thoracic and Cardiovascular Surgery, 75, 383 - 391.

Paquay, P.A., Anderson, G., Diefenthal, H., Nordstrom, L., Richman, H.G., & Gobel, F.L. (1976) Chest pain as predictor of coronary artery disease in patients with obstructive aortic valve disease. American Journal of Cardiology, 38, 863 - 869.

Pocock, S.J. (1989) Clinical Trials, Page 216.

Poll, D.S., Marchlinski, F.E., Falcone, R.A., Josephson, M.E. & Simson, M.B. (1985) Abnormal signal-averaged electrocardiograms in patients with non-ischaemic congestive cardiomyopathy: relationship to sustained ventricular tachyarrhythmias. Circulation, 72, 1308 - 1313.

Pool, I., Kurst, K. & Van Wermeskerken, J.L. (1978) Two monitored cases of sudden death outside hospital. British Heart Journal, 40, 627 - 629.

Pratt, C.M., Eaton, T., Francis, M., Woolbert, S., Mahmarian, J., Roberts, R. & Yound, J.B. (1989) The inverse relationship between baseline left ventricular ejection fraction and outcome of anti-arrhythmic therapy: A dangerous imbalance in the risk-benefit ratio. American Heart Journal, 118, 433 - 440.

Pratt, C.M., Francis, M.J., Luck, J.R., Wyndham, C.R., Miller, R.R. & Quinones, M.A. (1983) Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. Journal of the American College of Cardiology, 2, 789 - 797.

Pringle, S.D., Dunn, F.G., McKillop, J.G., Macfarlane, P.W. & Lorimer, A.R. (1987) Hypertensive left ventricular hypertrophy: identification of a high risk subgroup. British Heart Journal, 57 (Abstract), 99.

Pringle, S.D., Macfarlane, P.W., McKillop, J.H., Lorimer, A.R., Dunn, F.G., Dunn, F.G. & Cobbe, S.M. (1989) The pathophysiological significance of ventricular arrhythmias in hypertensive left ventricular hypertrophy. Journal of the American College of Cardiology, 15, (Abstract), 110A.

Quinones, M.A., Mokotoff, D.M., Nouri, S., Winters, W.L. & Miller, R.R. (1980) Non-invasive quantification of left ventricular wall stress. Validation of method and application to assessment of chronic pressure overload. American Journal of Cardiology, 45, 782 - 790.

Quyyumi, A.A., Crake, T., Wright, C., Mockus, L., Levy, R.D. & Fox, K.M. (1986) The incidence and morphology of ischaemic ventricular tachycardia. American Heart Journal, 7, 1037 - 1044.

Rackley, C.E. (1976) Quantitative evaluation of left ventricular function by radiographic techniques. Circulation , 54(b), 862 - 879.

Reichek, N., Wilson, J., Sutton, M.S.J., Plappert, T.A., Goldberg, S. & Hirshfeld, J.W. (1982) Non-invasive determination of left ventricular end-systolic stress: Validation of the method and initial application. Circulation 65, 99 - 108.

Reynolds, J.L., Nadas, A.S., Rudolph, A.M. & Gross, R.E. (1960) Critical congenital aortic stenosis with minimal electrocardiographic changes. A report on two siblings. New England Journal of Medicine, 262, 276 - 282.

Ross, J. & Braunwald, E. (1968) Aortic stenosis. Circulation, 38 (Supplement V), 61 - 67.

Rozanski, J.J., Martara, D., Myerburg, R.J. & Casteuanoz, A. (1981) Body surface detection of delayed depolarisations in patients with recurrent ventricular tachycardia and left ventricular aneurysm. Circulation, 63, 1171 - 1178.

Ruberman, W., Weinblatt, E., Goldberg, J.D., Frank, C.W. & Shapiro, S. (1977) Ventricular premature beats and mortality after myocardial infarction. New England Journal of Medicine, 297, 750 - 757.

Rubin, J.W., Moore, H.V., Hillson, R.F. & Ellison, R.G. (1977) Thirteen year experience with aortic valve replacement. American Journal of Cardiology, 40, 345 - 354.

Rubler, S., Chu, D.A., & Bruzzone, C.L. (1985) Blood pressure and heart rate responses during 24 hour ambulatory monitoring and exercise in men with diabetes mellitus. American Journal of Cardiology, 55, 801 - 806.

Rundles, R.W. (1945) Diabetic neuropathy: a general review with a report of 125 cases. Medicine, Baltimore, 24, 111 - 160.

Ryan, M., Lown, B. & Horn, H. (1975) Comparison of ventricular ectopic activity during 24-hour monitoring and exercise testing in patients with coronary heart disease. New England Journal of Medicine, 292, 224 - 229.

Salerno, D., Hodges, M., Graham, E., Asinger, R.W. & Mikell, F.L. (1981) Fatal cardiac arrest during continuous ambulatory monitoring. New England Journal of Medicine, 305, 700.

Samuels, D.A., Curfinan, G.D., Friedlich, A.L., Buckley, M.J. & Austen, W.G. (1979) Valve replacement for aortic regurgitation: long-term follow-up with factors influencing the results. Circulation, 60, 647 - 654.

Santinga, J.T., Kirsh, M.M., Flora, J.D. & Brymer, J.F. (1980) Factors relating to late sudden death in patients having aortic valve replacement. Annals of Thoracic Surgery, 29, 249 - 253.

Savage, D.D., Drayer, J.I.M., Henry, W.L., Matthews, E.C.J., Ware, J.H., Gardin, J.M., Cohen, E.R., Epstein, S.E. & Laragh, J.H. (1979) Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. Circulation, 59, 623 - 631.

Savage, D.D., Seides, S.F., Moran, B.J., Myers, D.J. & Epstein, S.B. (1979) Prevalence of arrhythmias during 24 hour electrocardiographic monitoring and exercise testing in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. Circulation, 59, 866 - 875.

Schilling, G., Finkbeiner, T., Elberskirch, P., Kirchhoff, P.G. and Simon, H. (1982) Incidence of ventricular arrhythmias in patients with aortic valve replacement. American Journal of Cardiology, 49 (Abstract), 894.

Schulze, R.A. Jr., Strauss, H.W. & Pitt, B. (1977) Sudden death in the year following myocardial infarction: relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. American Journal of Medicine, 62, 192 - 199.

Schwartz, L.S., Goldfischer, J., Sprague, G.J. & Schwartz, S.P. (1969) Syncope and sudden death in aortic stenosis. American Journal of Cardiology, 23, 647 -658.

Schwartz, P.J., Billman, G.E. & Stone, H.L. (1984) Autonomic mechanisms in ventricular fibrillation induced by myocardial ischaemia during exercise in dogs with healed myocardial infarction: An experimental preparation for sudden cardiac death. Circulation, 69, 790 - 800.

Schwartz, P.J., Varoli, E., Stromba-Badiale, M., De Ferrari, G.M., Billman, G.E. & Foreman, R.D. (1988) Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation, 78, 969 - 979.

Selzer, A. & Lombard, J.T. (1988) Clinical findings in adult aortic stenosis - then and now. European Heart Journal, 9 (Supplement E), 53 - 55.

Sharma, A.D. & Corr, P.B. (1983) Adrenergic factors in arrhythmogenesis in the ischaemic and reperfused myocardium. European Heart Journal, 4 (Supplement D), 79 - 90.

Sharpey-Schafer, E.P. (1955) Effects of Valsalva's manoeuvre on the normal and failing circulation. British Medical Journal, 693 - 695.

Sharpey-Schafer, E.P. & Taylor, P.J. (1960) Absent circulatory reflexes in diabetic neuritis. Lancet, 2, 1354 - 1356.

Shean, F.C., Austen, W.G., Buckley, M.J., Mundth, E.D., Scannel, J.G. & Dagget, W.M. (1971) Survival after Starr-Edwards aortic valve replacement. Circulation, 44, 1 - 18.

Siegel, D., Cheitlin, M.D., Black, D.M., Seeley, D., Hearst, N. & Hulley, S.B. (1990) Risk of ventricular arrhythmias in hypertensive men with left ventricular hypertrophy. American Journal of Cardiology, 65, 742 - 747.

Simson, M., Horowitz, L., Josephson, M., Moore, E.N. & Kastor, J. (1980) A marker for ventricular tachycardia after myocardial infarction. Circulation, 62 (Supplement III), III - 262.

Simson, M.B., Falcone, R. Dresden, C., Buxton, A., Marchlinski, F., Waxman, H. & Josephson M. (1983) The signal-averaged ECG and electrophysiological studies in patients with ventricular tachycardia and fibrillation. Circulation, 68 (Abstract), III - 173.

Simson. M.B. (1981) Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation, 64, 235 - 242.

Siostrzonek, P., Gossinger, H., Schmoliner, R., Kronik, G. & Mosslacher, H. (1987) Sudden cardiac death during long-term ECG monitoring of a patient with aortic stenosis. Dtsch-Med-Warchenschr, Sep 4, Vol: 112 (36) (Abstract in English)., 1374 - 1376

Smith, H.J., Neutze, J.M., Roche, A.H.G., Agnew, T.M. & Barratt-Boyes, B.G. (1976) The natural history of rheumatic aortic regurgitation and the indications for surgery. British Heart Journal, 38, 147 - 154.

Smith, R., Grossman, W., Johnson, L., Segal, H., Collins, J. & Dalen, J. (1972) Arrhythmias following cardiac valve replacement. Circulation, 45, 1018 - 1023.

Sokolow, M. & Lyon, T.P. (1949) The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. American Heart Journal, 67, 161 - 186.

Spagnuolo, M., Kloth, H., Taranta, A., Doyle, E. & Pasternack, B. (1971) Natural history of rheumatic aortic regurgitation. Criteria predictive of death, congestive heart failure and angina in young patients. Circulation, 44, 368 - 380.

Sprito, P., Walson, R.M. & Maron, B.J. (1987) Relation between extent of left ventricular hypertrophy and occurrence of ventricular tachycardia in hypertrophic cardiomyopathy. American Journal of Cardiology, 60, 1137 - 1142.

Stamm, R.B. & Martin, R.P. (1983) Quantification of pressure gradients across stenotic valves by Doppler ultrasound. Journal of the American College of Cardiology, 2, 707 - 718.

The Criteria Committee of the New York Heart Association. (1979) Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 8th ed., 290. Boston. Little, Brow.

Torstkotte, D & Loogen, F. (1988) The natural history of aortic valve stenosis. European Heart Journal, 9 (Supplement E), 57 - 64.

Turina, J., Hess, O., Sepulcri, F. & Krayenbuehl, H.P. (1987) Spontaneous course of aortic valve disease. European Heart Journal, 8, 471 - 483.

Turitto, G., Fontaine, J.M., Ursell, S.N., Caref, E.B., Henkin, R. & El-Sherif, N. (1988) Value of the signal-averaged electrocardiogram as a predictor of the results of programmed stimulation in nonsustained ventricular tachycardia. American Journal of Cardiology, 61, 1272 - 1278.

Verrier, R.L., Thompson, P.L. & Lown, B. (1974) Ventricular vulnerability during sympathetic stimulation: role of heart rate and blood pressure. Cardiovascular Research, 8, 602 - 610.

Von Olshausen, K.V., Amann, E., Hofmann, M., Schwarz, F., Mehmel, H.C. & Kubler, W. (1984) Ventricular arrhythmias before and late after aortic valve replacement. American Journal of Cardiology, 53, 142 - 146.

Von Olshausen, K.V., Schafer, A., Mehmel, H.C., Schwarz, F., Serges, J. & Kubler, W. (1984) Ventricular arrhythmias in idiopathic dilated cardiomyopathy. British Heart Journal, 51, 195 - 201.

Von Olshausen, K.V., Schwarz, F., Apfelbach, J., Rohrig, N., Kramer, B. & Kubler, W. (1983) Determinants of the incidence and severity of ventricular arrhythmias in aortic valve disease. American Journal of Cardiology, 51, 1103 - 1109.

Von Olshausen, K.V., Schwarz, F., Kaden, F. & Kubler, W. (1982) Sudden cardiac death in aortic stenosis. Zeitschrift for Kardiologie, 71 (II), 784 - 785.

Von Olshausen, K.V., Witt, T., Schmidt, G. & Meyer, J. (1987) Ventricular tachycardia as a cause of sudden death in patients with aortic valve disease. American Journal of Cardiology, 59, 1214 - 1215.

Wagner, H.R., Ellison, R.C., Keane, J.F., Humphries, J.O. & Nadas, A.S. (1977) Clinical course in aortic stenosis. Circulation, 56 (Supplement I), 47 - 56.

Watkins, P.J. (1990) Diabetic autonomic neuropathy. New England Journal of Medicine, 322, 1078 - 1079.

Weaver, W.D., Lorch, G.S., Alvarez, H.A. & Cobb, L.A. (1976) Angiographic findings and prognostic indicators in patients resuscitated from sudden cardiac death. Circulation, 54, 895 - 900.

Webb, S.W., Adgey, A.A.J. & Pantridge, J.F. (1972) Auotonomic disturbances at onset of acute myocardial infarction. British Medical Journal, 3, 89 - 92.

Wheeler, T. & Watkins, P.J. (1973) Cardiac denervation in diabetes. British Medical Journal, 4, 584 - 586.

Wilhelmsson, C., Vedin, J.A., Wilhelmsson, L., Tibblin, G. & Werko, L. (1974) Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet, ii, 1157 -1160.

Williams, D.O., Scherlag, B.J., Hope, R.R., El-Sherif, N. & Lazzara, R. (1974) The pathophysiology of malignant ventricular arrhythmias during acute myocardial ischaemia. Circulation, 1164 - 1172.

Winkle, R.A., Peters, F. & Hall, R. (1981) Characterization of ventricular tachyarrhythmias on ambulatory ECG recordings in post-myocardial infarction patients: Arrhythmia detection and duration of recording, relationship between arrhythmia frequency and complexity, and day-to-day reproducibility. American Heart Journal, 102, 162 - 169.

Winters, S.L., Stewart, D. & Gomes, A. (1987) Signal-averaging of the surface QRS complex predicts inducibility of ventricular tachycardia in patients with syncope of unknown origin. A prospective study. Journal of the American College of Cardiology, 10, 775 - 781.

Winters, S.L., Stewart, D., Targonski, A. & Gomes, J.A. (1988) Role of signal-averaging of the surface QRS complex in selecting patients with nonsustained ventricular tachycardia and high grade ventricular arrhythmias for programmed ventricular stimulation. Journal of the American College of Cardiology, 12, 1481 - 1487.

Wood, P. (1958) Aortic stenosis. American Journal of Cardiology, 1, 553 - 571.

Zheutlin, T.A., Roth, H., Chua, W., Steinman, R., Summers, C., Lesch, M. & Kehoe, R.F. (1986) Programmed electrical stimulation to determine the need for antiarrhythmic therapy in patients with complex ventricular ectopic activity. American Heart Journal, 111, 860 - 867.

Zimmermann, M., Adamec, R., Simonin, P. & Richez, J. (1985) Prognostic significance of ventricular late potentials in coronary artery disease. American Heart Journal, 109, 725 - 732.

Zipes, D.P. (1975) Electyrophysiological mechanisms involved in ventricular fibrillation. Circulation, 52 (Supplement III), 120 - 130.