VENTRICULAR ARRHYTHMIAS IN HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

A thesis presented to the University of Glasgow, Faculty of Medicine, for the degree of Doctor of Medicine by

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Note: all data expressed as x ± y refer to mean ± S.E.M. unless otherwise stated.

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Declaration

Chapter 4 of this thesis includes data derived from the Glasgow Blood Pressure Clinic; this information has been collected by many individuals over a period of almost twenty years.

Using these data, analysis of the mortality risk associated with electrocardiographic evidence of left ventricular hypertrophy in the Glasgow Blood Pressure Clinic was carried out over a period of eighteen months by a group of individuals including Dr. C. Isles, Dr. F.G. Dunn, Dr. A.R. Lorimer, Dr A.F. Lever, Dr H.J. Dargie, Dr. G. Murray, Dr. J.W.K. Robertson and myself. In my thesis, I have have included part of this analysis from the Glasgow Blood Pressure Clinic because it was the stimulus to my further studies. Only that part of the data analysis with which I was closely involved has been included.

All of the studies described in chapters 5,6,7,8,9,10 and 11 were performed entirely by me with the technical assistance of Miss E. Henderson and Miss K.I. Morris and under the supervision of Dr. H.J. Dargie.

The thesis was composed by me and typed by me using a "BBC B" word processor and "Canon LBP-8A1" printer.

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SUMMARY

Introduction

Electrocardiographic evidence of left ventricular hypertrophy (LVH) in hypertensive patients is associated with increased mortality, and in particular with an increased incidence of sudden death.
Multivariate analysis of the Glasgow Blood Pressure Clinic mortality data has shown that the risk associated with this electrocardiographic abnormality is in excess of that attributable to the associated hypertension, suggesting an independent contribution of left ventricular hypertrophy to mortality. The mechanism of this increased risk is unknown although sudden death in such patients is frequently attributed to myocardial infarction.
Other forms of cardiac hypertrophy, in particular hypertrophic cardiomyopathy, are also associated with sudden death; in hypertrophic cardiomyopathy, ambulatory electrocardiographic monitoring has revealed a high prevalence of ventricular arrhythmias including episodes of non-sustained ventricular tachycardia; furthermore, follow-up studies have demonstrated that such arrhythmias are predictive of subsequent sudden death.
Thus it was postulated that a tendency to ventricular arrhythmia, rather than a predisposition to myocardial

infarction, might explain the excess mortality associated with left ventricular hypertrophy in hypertensive patients.

Studies

1. Validation of the diagnosis of left ventricular hypertrophy in the Glasgow Blood Pressure Clinic.

Before interpreting the Glasgow Blood Pressure Clinic mortality data too widely, some form of validation of the electrocardiographic diagnosis of left ventricular hypertrophy was required.
Detection of left ventricular hypertrophy in the clinic was based on the reports of many clinicians over a period of fifteen years without standardised criteria. Using echocardiography as the "gold standard" for detection of LVH in vivo, the sensitivity of the ECG reporting system was 62% with a specificity of 77%. The sensitivity compares favourably with other series, although the specificity is low.
In an attempt to improve the ECG diagnosis of left ventricular hypertrophy, four different sets of electrocardiographic criteria were examined. Overall, the criteria of Sokolow-Lyon and Romhilt-Estes were the most sensitive and specific. However, when patients were subdivided into "obese" and "non-obese," it was demonstrated that body build had different effects on

different criteria. The clinical significance of this is that stratification of patients by body build might improve the electrocardiographic diagnosis of left ventricular hypertrophy.

2. Prevalence of ventricular arrhythmias in hypertensive patients with and without electrocardiographic left ventricular hypertrophy.

To determine whether ventricular arrhythmias occur commonly in hypertensive patients with left ventricular hypertrophy, forty-eight hour ambulatory ECG monitoring was carried out in fifty normotensive control subjects and in one hundred hypertensive patients comprising fifty with electrocardiographic left ventricular hypertrophy (Sokolow-Lyon criteria) and fifty without. To control for any possible effect of hypertension itself on arrhythmia frequency, the two hypertensive groups were matched with each other for initial and achieved blood pressure; in addition, all three groups were matched for age, sex and smoking habit. Ventricular arrhythmias were uncommon in the control group; all grades of arrhythmia occurred more commonly in the hypertensives, particularly in those with left ventricular hypertrophy, of whom 28% had at least one episode of ventricular tachycardia (three or more consecutive ventricular complexes) compared with 8% of those hypertensives without left ventricular

hypertrophy. Among those with left ventricular hypertrophy and ST-T changes (the so-called LVH and "strain" pattern), over 50% had at least one episode of ventricular tachycardia.

3. Influence of diuretic therapy on arrhythmia frequency.

In view of the suggestion from several studies that diuretic-induced hypokalaemia may predispose to ventricular arrhythmias and sudden death, the distribution of ventricular arrhythmias was examined separately in those patients whose antihypertensive treatment included a diuretic. Although diuretic therapy was clearly associated with a lower serum potassium concentration, there was no suggestion that this degree of hypokalaemia increased arrhythmia frequency in patients with or without left ventricular hypertrophy.

4. Relationship of ventricular arrhythmia to coronary artery disease and to myocardial histology.

Further investigations, including coronary arteriography and left ventricular endomyocardial biopsy, were undertaken in those patients thought to be at increased risk of sudden death. Of seventeen patients with hypertension, left ventricular

hypertrophy and ventricular tachycardia during ambulatory monitoring, nine (53%) were free of significant coronary artery disease (stenosis of 70% or greater in a major epicardial vessel) and none had triple vessel disease; this suggests that occult coronary disease is not the cause of the high prevalence of ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy.
To examine the importance of myocardial factors in the pathophysiology of ventricular arrhythmias, left ventricular biopsies from eleven patients with left ventricular hypertrophy and ventricular tachycardia were analysed for fibrous tissue content by a point counting technique and compared with biopsies from sixteen patients also with left ventricular hypertrophy, but without ventricular tachycardia during ambulatory monitoring. Percentage fibrosis was significantly greater in those patients with ventricular tachycardia than in those without ($13\pm3\%$ vs. $2\pm1\%$, $p<0.001$) suggesting that the state of the myocardium, rather than the state of the coronary arteries, is important in the pathogenesis of ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy.

5. Ventricular compliance in hypertensive LVH.

Finally, an echocardiographic study of the

hypertrophied ventricle was undertaken. This demonstrated that diastolic compliance of the left ventricle declines as left ventricular mass rises. Filling of the ventricle will then become more dependent on atrial contraction. Thus the hypertrophied left ventricle may be more sensitive, on account of its abnormal filling pattern, to any arrhythmia involving loss of atrial transport function.

Conclusion

Thus high grade ventricular arrhythmias occur commonly in hypertensive left ventricular hypertrophy. Their prevalence is not attributable to occult coronary artery disease, nor to hypokalaemia, but is related to the presence of subendocardial fibrosis. This tendency to ventricular arrhythmia might explain why left ventricular hypertrophy is associated with a high mortality rate in excess of that attributable to the associated hypertension. It may be, therefore, that forms of therapy other than those aimed at reduction of blood pressure, perhaps including anti-arrhythmic drug therapy, will be required to reduce mortality in this high risk group.

CHAPTER 1

A CASE HISTORY

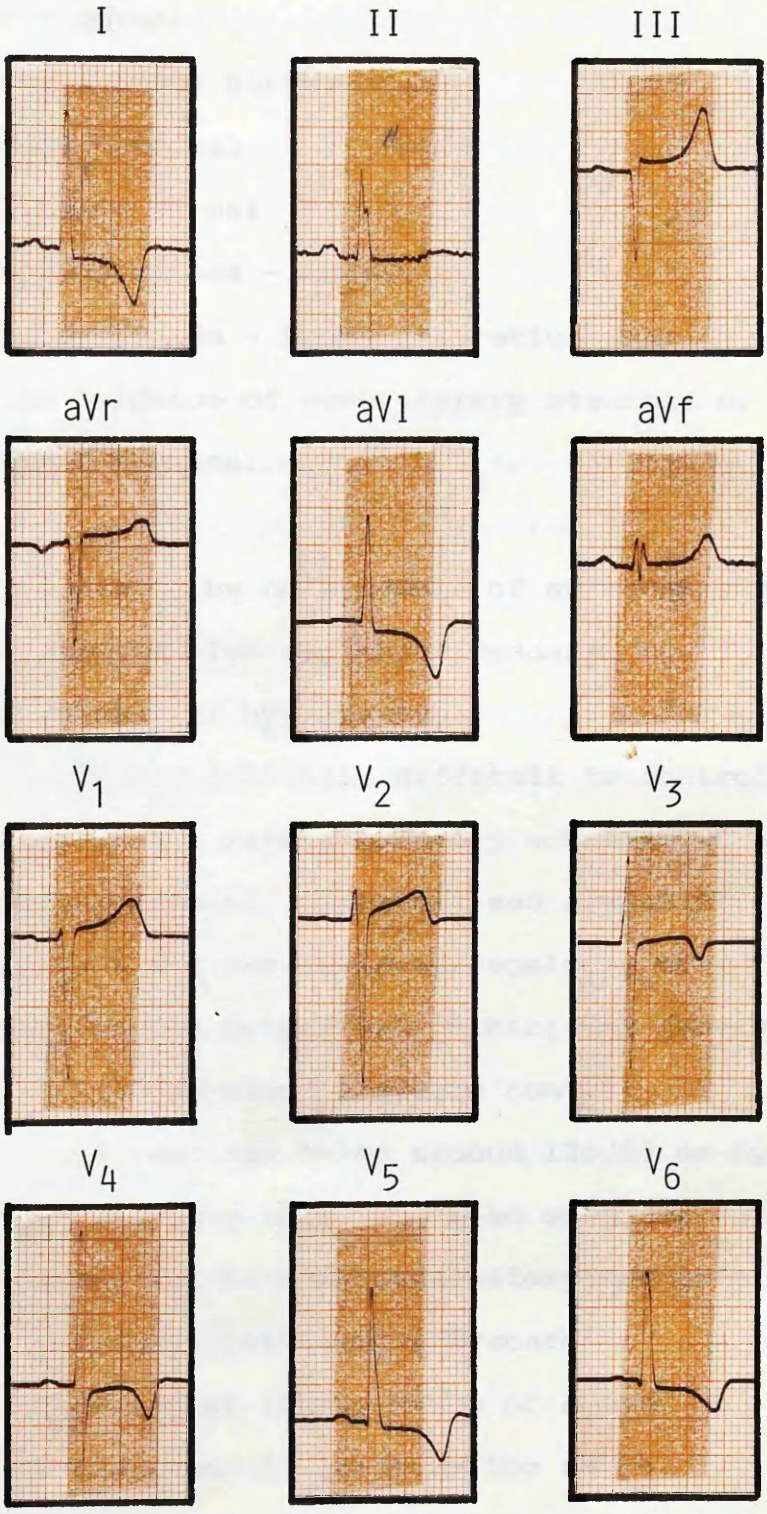
A fifty-four year old gentleman was referred by his general practitioner to a medical outpatient clinic for investigation and treatment of hypertension. The patient was entirely asymptomatic, the elevated blood pressure having been found at a routine clinical examination. Apart from a cholecystectomy, there was no past history of serious illness and he was a non-smoker.

Clinical examination at the outpatient clinic revealed a blood pressure of 212/127 mm Hg recumbent and a thrusting but non-displaced cardiac apex beat; the optic fundi showed arteriolar narrowing but no haemorrhages or exudates. The remainder of the clinical examination was normal. In view of the high pressure, he was admitted to hospital for a period of inpatient assessment.

The following investigations were carried out:

1. **chest X-ray** - heart size at the upper limit of normal with a left ventricular configuration.
2. **electrocardiogram** - left ventricular hypertrophy by chest lead criteria with lateral ST-T changes ("LVH and strain"). The ECG is illustrated in figure 1.

Figure 1
ECG at presentation (BP212/127mmHg)



3. **full blood count** - normal

4. **blood urea** - normal

5. **serum electrolytes** - normal

6. **blood glucose** - normal

7. **fasting lipids** - normal

8. **urinary catecholamines** - normal

9. **intravenous pyelogram** - Prompt excretion seen bilaterally. No evidence of renal artery stenosis or parenchymal renal disease.

Thus there appeared to be no evidence of an underlying cause for his hypertension and the diagnosis, by exclusion, was essential hypertension.
His blood pressure was initially difficult to control but satisfactory levels were eventually achieved on a combination of propranolol, minoxidil and frusemide. He was discharged home and was reviewed regularly over the next eight years at the outpatient clinic; his general health was good and his blood pressure control excellent, average readings being around 130/85 mm Hg. Then, at the age of sixty-three, he died suddenly and unexpectedly. There had been no premonitory symptoms. His general practioner, believing a myocardial infarction to be the most likely cause of death, entered this as the cause of death on the death certificate, although the patient had never experienced chest pain. A post-mortem examination was not performed.

In summary, this gentleman's only risk factor for ischaemic heart disease was hypertension. Despite impeccable control of blood pressure, he had died suddenly and prematurely and his death had been attributed to a myocardial infarction.

Discussion

This case history was the stimulus to the studies to be described in this thesis. At about the time of this man's death, the first analysis of mortality from the Glasgow Blood Pressure Clinic was being discussed; this demonstrated that mortality was particularly high in hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy (1). A review of the literature revealed that left ventricular hypertrophy was a major, although often neglected risk factor for cardiovascular mortality. The pathogenesis of LVH was not entirely clear and it appeared that factors other than blood pressure may influence its development. Furthermore, data from the Framingham study had suggested that the risk associated with ECG LVH was in excess of that attributable to hypertension alone, suggesting an independent contribution of left ventricular hypertrophy to mortality (2). The mechanism of this excess risk was not clear.

Also around this time, it had been shown that in other forms of cardiac hypertrophy, notably hypertrophic

cardiomyopathy, ventricular arrhythmias occur commonly during ambulatory electrocardiographic monitoring and are predictive of subsequent sudden death (3).
Thus it was postulated that a primary ventricular arrhythmia, rather than a myocardial infarction, might have been the cause of this patient's sudden death.
The studies to be described investigate the relationships between left ventricular hypertrophy and ventricular arrhythmias and suggest a possible explanation for the high mortality associated with left ventricular hypertrophy in hypertensive patients.

CHAPTER 2

A REVIEW OF THE LITERATURE

2.1 INTRODUCTION

In this section, the development of left ventricular hypertrophy and its relationship to arterial pressure is discussed. Since the studies to be described in this thesis are essentially clinical, the literature on experimental left ventricular hypertrophy is dealt with briefly, with reference mainly to major reviews. There then follows a review of the incidence, prevalence, and diagnosis of left ventricular hypertrophy in man together with an analysis of the associated risk. The structural and functional adaptations of the hypertrophied ventricle are then reviewed, again with brief reference to experimental animal models. The complex relationships between hypertension, left ventricular hypertrophy, coronary artery disease and myocardial ischaemia are then examined. The evidence for recent changes in attitudes towards sudden cardiac death is presented with particular reference to left ventricular hypertrophy.

Finally, hypertrophic cardiomyopathy is described and similarities between this and hypertensive heart disease outlined.

2.2 DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION.

Primitive cardiac muscle cells can be identified early in embryonic life and the mammalian heart begins to contract at about eleven days gestation (4). At first the myofibrils are randomly arranged but soon align themselves parallel to the direction of maximum force development. Hyperplasia (increase in cell number) and hypertrophy (increase in cell size) continue throughout foetal life (5). The rate of division of myocytes slows markedly at birth and stops at about four weeks in experimental models (5). Any increase in muscle cell mass after this period is, therefore, usually attributed to cellular enlargement rather than to cell division.

The major determinant of left ventricular hypertrophy (LVH) is the "afterload" i.e. the load against which the left ventricle must pump. The true afterload is determined not only by the arterial pressure but by other factors including the left ventricular wall thickness and left ventricular internal diameter and is more accurately reflected by the left ventricular wall tension or stress which effectively represents the amount of force generated per unit of myocardium. After heart rate, left ventricular wall stress is the next most important determinant of myocardial oxygen

consumption and it has been suggested that the ultimate aim of cardiac hypertrophy is to maintain the wall tension within normal limits (6). The wall stress, or tension, can be calculated from the Law of Laplace which states that the wall tension (T) of a thin-walled sphere is related to the radius (r) of the sphere and to the pressure within it (P) (7):

$$T = P \times r/2$$

This expression is modified as follows if the sphere has a significant wall thickness (WT):

$$T = P \times r/2WT$$

or $$P = T \times 2WT/r$$

or P varies as 2WT/r

Thus, if the pressure increases and the left ventricular internal radius remains constant, left ventricular wall thickness must increase in order to prevent the wall tension from rising. Indeed, if the wall stress is to remain constant, then we would expect that the pressure (P) would be directly proportional to the ratio of left ventricular wall thickness (WT) to left ventricular radius (r).

In man, Grossman et al have studied this relatioship by comparing patients with chronic pressure overload and

patients with chronic volume overload with normal control subjects (8). Compared to the controls, both patient groups had markedly increased left ventricular mass. Left ventricular systolic pressure was greatly increased in the presence of pressure, but not volume, overload and wall thickness was increased in both groups. However, the ratio of wall thickness to cavity radius was increased only in the pressure overload group. Using a modification of the Law of Laplace, calculated values for systolic wall stress were normal for both the pressure and volume overload groups. Thus the cardiac hypertrophy prevents an increase in systolic wall stress (force per unit myocardium) which would otherwise occur in the presence of raised pressure. Furthermore, other studies in man have shown that the ratio of left ventricular radius to wall thickness bears a constant relationship to systolic blood pressure which holds for both physiological and pathological forms of hypertrophy (9).

There is some evidence that this "normalisation" of wall stress allows the contractile machinery to operate at its most efficient length. Using electron microscopy to measure the length of individual sarcomeres, it has been shown that the sarcomere length in the hypertrophied ventricle corresponds to a point on the steep slope of the Frank-Starling curve in both chronically dilated (10) and hypertrophied hearts (11). It is evident that hypertrophy cannot occur

instantaneously and that the relationship between wall stress, cavity radius and wall thickness will vary with time. If the pressure load is introduced acutely, as by banding of the aorta in dogs, then an initial increase in wall stress occurs followed by an increase in wall thickness so that the wall stress has returned to normal within three months (12).

Thus increased wall stress is probably the stimulus to hypertrophy of the myocardial cells although the mechanism at a cellular level has not been fully elucidated. Certainly increased manufacture of contractile proteins is detectable soon after wall stress is increased in experimental left ventricular hypertrophy. Schreiber et al have detected increased RNA activity (13) and increased production of myosin, mitochondria and microsomes (14) within hours of aortic banding in dogs. While the muscle stretch itself may be directly responsible for increased RNA transcription (15), cellular deficiency of ATP, the ultimate energy source within the cell, and accumulation of cyclic AMP in the face of increased workload (16,17) have been suggested as an alternative mechanism.

Whatever the cellular processes involved, it has been shown that the distribution of hypertrophy in experimental LVH is such that those areas subjected to the greatest stress show the greatest hypertrophy (18); this observation is in keeping with the concept that wall stress is the principal determinant of cardiac

hypertrophy.

2.3 NON-PRESSURE MODULATORS OF LEFT VENTRICULAR HYPERTROPHY

If arterial pressure is the sole determinant of left ventricular hypertrophy, we might expect a close correlation between arterial pressure and left ventricular mass. Early studies suggested that this was so. Animal studies of experimental renovascular hypertension in rats demonstrated this with respect not only to the development, but also the reversal, of cardiac hypertrophy (19). Early studies of left ventricular hypertrophy in man also suggested a close relationship between systolic blood pressure and the presence of left ventricular hypertrophy (20). However, this has been challenged by a more recent clinical study in which only a weak correlation between left ventricular mass and the level or duration of hypertension was found (21). In other forms of experimental hypertension, for example the spontaneously hypertensive rat (SHR), Sen has drawn attention to the poor relationship between arterial blood pressure and degree of left ventricular hypertrophy (22). There are several possible explanations for this.

First, casual blood pressure recordings may not reflect mean blood pressure over the course of the day. When blood pressure is measured continuously over 24 hours using an intra-arterial canula, a closer relationship

does emerge between blood pressure and left ventricular mass (23). This finding has been confirmed by Rowlands (24) who showed a significant correlation between left ventricular mass index (LVMI) assessed echocardiographically and mean intra-arterial systolic blood presure over 24 hours but no significant correlation between LVMI and casual systolic blood pressure. Second, arterial pressure is not the only determinant of the pressure load against which the heart must work; better, although less easily measured determinants of this load are the aortic impedance and the left ventricular myocardial wall stress which is dependent on the diameter of the left ventricular cavity and the left ventricular wall thickness as well as the blood pressure.

Even when these factors are taken into account, the coorrelation between blood pressure and LVH remains relatively poor, suggesting that factors other than the level and duration of blood pressure might modify the development and regression of LVH.

The following factors are believed to influence the development of LVH independently of blood pressure:

A. Age

The effects of ageing on cardiac structure in both experimental animals and in man have been extensively reviewed (25,26). It appears that progressive

hypertrophy of the ventricular wall occurs with increasing age even in the absence of significant hypertension (25). It is well established, however, that arterial pressure does rise progressively with age even though it may not exceed some arbitrary upper limit of normal, and it is thus difficult to separate this effect from the rise in left ventricular mass. With ageing, the arterial tree also becomes "stiff" or non-compliant, causing a rise in aortic input impedance which could, conceivably, stimulate left ventricular hypertrophy even in the absence of a detectable rise in blood pressure. In practice, it is likely that both mechanisms contribute to the increase in left ventricular wall thickness with age which is of the order of 25% over a period of fifty years (27).

B. Race

Racial differences in the pathophysiology of hypertension have been reviewed by Gillum (28). Several studies, including the Hypertension Detection and Follow-Up Program (HDFP) (29) and the Evans County Georgia Study (30) have demonstrated that black hypertensive patients develop more electrocardiographic evidence of cardiac involvement for a given elevation of blood pressure than do white hypertensives. In addition, Dunn has shown that mean left ventricular mass measured by echocardiography is higher in black

than in white hypertensives even when the two groups are matched for age, sex and mean arterial pressure (31). This finding has recently been confirmed by Hammond in an echocardiographic study which demonstrated that increased left ventricular mass was twice as prevalent in black as in white hypertensives (32). In contrast, enlargement of the left ventricular chamber was more common in white hypertensives suggesting that volume overload was more common in whites. The same authors also noted differences in the prevalence of LVH between men and women; however, most studies define separate sex-specific normal ranges for left ventricular mass and thus sex is not usually regarded as a determinant of LVH.

C. Physical Exercise

Athletes who perform repeated isometric exercise, such as weight-lifters or shot-putters, require brief increases in cardiac output against a high systolic aortic pressure that can reach 300 mm Hg; consequently, they develop left ventricular hypertrophy with only slight chamber enlargement (33). The hypertrophy may be quite marked and an echocardiographic study has demonstrated that there is often disproportionate thickening of the septum mimicking hypertrophic cardiomyopathy (33). Although this is often regarded as "physiological" hypertrophy, there have been no

long-term studies on the fate of such individuals. Athletes engaging in endurance exercise such as long-distance running or swimming also develop some thickening of the left ventricular wall and thus raise their left ventricular mass; however, the principal cardiac adaptation in this case is an increase in left ventricular volume and thus in stroke volume to allow development of a greater cardiac output during exercise (34,35). Similar changes have been documented in experimental animals. Carew and Covell have shown that both wall thickness and left ventricular cavity size are increased by exercise in greyhounds (36) while Pfeffer et al have shown that an intensive swimming programme increases left ventricular cavity size and left ventricular mass in rats (37).

D. The sympathetic nervous system

The role of catecholamines in left ventricular hypertrophy has been reviewed recently (38). Most of the work has been in experimental models of hypertension and centres around four main areas of research.

First, LVH can be induced by the chronic infusion of catecholamines. Isoprenaline was first used in 1959 (39) and noradrenaline in 1970 (40) to induce LVH in dogs. Laks and Marady induced left ventricular hypertrophy in rats by infusing subpressor doses of

noradrenaline (41), and suggested that noradrenaline might be the "myocardial hypertrophy hormone" (42). Yamori et al also produced left ventricular hypertrophy in rats by infusion of noradrenaline despite concurrent administration of an alpha adrenergic blocker which prevented any rise in blood pressure (43). The same group noted that beta adrenergic receptor blockade significantly reduced the degree of hypertrophy that resulted from noradrenaline infusion (43).

Second, several investigators have measured both total myocardial catecholamines and catecholamine concentration in experimental LVH. These investigations have yielded different results in different experimental models. Myocardial hypertrophy secondary to a pure pressure load, such as constriction of the aorta appears to reduce myocardial noradrenaline concentration (44) although total content of noradrenaline is normal until a late stage when cardiac failure supervenes. In other animal models of hypertension, similar changes were noted in renovascular hypertension in rats (38) but not in spontaneously hypertensive rats (SHR) in which total ventricular catecholamine content was increased (38). These results are difficult to interpret; it has been suggested that left ventricular hypertrophy occurring in the SHR could be a form of primary cardiomyopathy (45) since it occurs early and may precede the hypertension. This is a difficult point to establish

experimentally and, if correct, it could explain the difference between SHR and other experimental models of LVH since primary hypertrophic cardiomyopathy in man may also be associated with excess catecholamines (46).

The third area of research concerns the contractile response of isolated hypertrophied myocardium to inotropic stimulation. It has been demonstrated that the response to beta adrenergic stimulation is reduced in both SHR (47) and experimental renovascular hypertension (48). Initially this was thought to be due to a reduction in cardiac beta adrenergic receptors in the hypertrophied myocardium but a number of intracellular alterations have now been identified in the chain of events leading from the beta receptor to to activation of adenylate cyclase (49). These hearts, however, remain capable of responding to different types of stress. Saragoca and Tarazi (48) have suggested that the reduction in inotropic responsiveness represents a shift in the heart's reserve mechanisms, with less dependence on beta adrenergic stimulation as a means of increasing cardiac output during stress and more dependence on the Frank-Starling mechanism.

Finally, experimental work has been directed at the regression of LVH. In spontaneously hypertensive rats, drugs that reduce circulating catecholamines, such as methyldopa, cause regression of LVH while those that

activate the sympathetic system, such as thiazides, do not, despite the fact that both drugs control blood pressure (38). Indeed, in this animal model, reversal of hypertrophy was found to be related to ventricular catecholamine levels but not to degree of blood pressure control, although as noted earlier, the pathogenesis of hypertrophy may be different in the SHR when compared with other experimental models.

In man, evidence for the importance of the sympathetic system has centred on the effects of different anti-hypertensive agents on the reversal of LVH. Devereux has shown that blood pressure control with diuretics, which activate the sympathetic nervous system, did not produce regression of LVH while treatment with beta-blockers, either alone or in combination with captopril, did reduce LVH for the same degree of blood pressure control (50). Others, however, have found that reduction of blood pressure does regress LVH regardless of the effects on the sympathetic nervous system; for example, the Hypertension Detection and Follow-Up Program (HDFP) demonstrated that aggressive treatment of blood pressure, usually with diuretics, both reduced the rate of development of electrocardiographic LVH and produced some regression of ECG LVH when this was present at entry (51). Echocardiographic analysis of a subgroup of the HDFP study also demonstrated significant regression of LVH (52) and this has been confirmed in at least one

other study where diuretics were used as the sole anti-hypertensive agent (53).

E. Renin angiotensin system

A direct stimulating action of angiotensin II on protein synthesis in myocardial cells has been suggested (54). In experimental hypertension, changes in plasma renin activity have been shown to correlate with changes in left ventricular mass during drug treatment of hypertension in spontaneously hypertensive rats (55). Sen et al have demonstrated that treatment with minoxidil controls blood pressure but increases plasma renin activity and left ventricular mass while treatment with propranolol reduces plasma renin activity and left ventricular mass without significantly reducing blood pressure (55). In a later study, the same authors demonstrated that an angiotensin converting enzyme inhibitor effectively prevented and, if already present, reversed left ventricular hypertrophy in spontaneously hypertensive rats (56).

In human studies, however, the marked haemodynamic effects of angiotensin make it difficult to dissociate pressure-induced changes in left ventricular mass from possible direct myocardial effects.

F. Expansion of intravascular volume

Conditions associated with volume overload such as chronic anaemia (57), renal failure (58) and obesity (59) increase the preload rather than the afterload with respect to the left ventricle. The initial response to increased preload is an increase in the diameter of the ventricle. However, according to the Law of Laplace, the wall stress increases as the diameter increases and this in itself is a stimulus to hypertrophy. However, the ratio of left ventricular wall thickness to chamber diameter is said to remain constant in obese hypertensives in contrast to the situation in the non-obese hypertensive in whom thickening of the ventricular wall occurs without any increase in chamber size (59).

G. Other humoral factors

Many other hormones, including thyroxine (60), growth hormone (60) and parathormone (61) have been invoked as inducers of cardiac hypertrophy because, in each case, excess circulating hormone is associated with increased left ventricular mass. As with other vaso-active hormones, however, it is difficult to separate their effects on blood pressure from any possible direct effect on the myocardium.

Summary

In summary, the mechanism of cardiac hypertrophy is not fully understood. While arterial pressure is the prime stimulus to the development of hypertrophy, it is clear that this can be modified by various genetic and neuro-endocrine factors. In some experimental situations, such neuro-endocrine factors can produce cardiac hypertrophy in the absence of measurable hypertension. Whether this occurs in man is not known although it is possible that hypertrophic cardiomyopathy, which can be difficult to distinguish from hypertensive heart disease, represents one end of a spectrum in the relationship between blood pressure and cardiac hypertrophy.

2.4 DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY IN MAN

Left ventricular hypertrophy can often be detected on clinical examination when palpation of the praecordium reveals a "heaving" or "thrusting" cardiac apex often accompanied by a soft fourth heart sound. However, clinical examination is highly subjective and is thus not used for the diagnosis of LVH in epidemiological studies.

The two most commonly used investigations for detection of left ventricular hypertrophy are electrocardiography and echocardiography. Chest radiography was also used previously but cannot differentiate cardiac enlargement secondary to ventricular hypertrophy from that secondary to chamber dilatation and will not be discussed further. At this point, however, it is worthwhile defining three terms, two of which are derived from the use of radiography to identify LVH, which are commonly confused:

1. Concentric LVH

This is the normal response of the ventricle to a pressure load such as hypertension or aortic stenosis. It implies thickening of the left ventricular wall without dilation of the left ventricular cavity; the wall thickness to cavity ratio, therefore, is increased.

2. Eccentric LVH

This is the normal response to a volume load and implies hypertrophy with dilation of the cavity such that the wall thickness to cavity ratio remains constant. This occurs pathologically in mitral and aortic incompetence and also physiologically in endurance athletes.
This state was defined as "eccentric" during the Framingham study because the dilated heart becomes "eccentric" with respect to the thorax on chest X-ray.

3. Asymmetrical hypertrophy

This implies disproportionate thickening of the interventricular septum such that the ratio of septal thickness to left ventricular posterior wall thickness exceeds an arbitrary value of 1.3:1. It is typical, but not diagnostic, of hypertrophic cardiomyopathy and may also occur in young hypertensives and in some athletes.

Diagnosis of left ventricular hypertrophy by electrocardiography.

Even in the earliest days of electrocardiography, Einthoven (62) and Lewis (63) recognised that specific

electrocardiographic patterns occurred in association with hypertrophy of the cardiac chambers. However, it was not until 1942 when, to allow prognosis in hypertension to be estimated for insurance purposes, Gubner and Ungerleider defined specific criteria for left ventricular hypertrophy (64). Their criteria were based not on any post-mortem verification of left ventricular hypertrophy but on a comparison of ECG patterns in groups of patients with and without hypertension. At that time, only the standard limb leads were available; they considered left ventricular hypertrophy to be present when the sum of the R wave in lead I and the S wave in lead III exceeded 25mm, the ECG being standardised at 10mm=1mV. In addition, the presence of ST segment depression was noted and they suggested that the combination of increased voltages and ST segment depression, labelled "strain", was associated with marked hypertrophy. Furthermore Gubner and Ungerleider suggested that the increased amplitude of the QRS complex was most likely to be directly attributable to increased left ventricular mass and that changes in the ST segment and T wave were a manifestation of subendocardial ischaemia. Although their criteria are less commonly used, the principles behind them persist. In 1949, Sokolow and Lyon published a study comparing the ECG characteristics of 147 patients with abnormal ECGs and a clinical diagnosis of hypertension, aortic valvular disease or

coarctation of the aorta with 151 normal subjects (65). The amplitude of each P,Q,R,S and T wave from all twelve leads of each tracing was calculated. Their main conclusions involved the use of unipolar chest leads for the diagnosis of left ventricular hypertrophy. They found the characteristic and diagnostic changes, in order of frequency, to be:

a) a depressed ST segment and asymmetric inversion of the T wave in lead V5 or V6. In early cases, the T wave could be low, biphasic or flat in association with a depressed ST segment.

b) increase in voltage of the QRS complex with the R wave in V5 or V6 exceeding 26mm and/or the the sum of the R wave in V5 and the S wave in V1 exceeding 35mm.

c) the onset of intrinsic deflection (i.e. the ventricular activation time) exceeding 0.05 seconds in lead V5 or V6.

These criteria are far from ideal but remain the most commonly used criteria for the detection of left ventricular hypertrophy in the clinical setting although over thirty different sets of criteria have since been derived. In 1960, Allenstein and Mori evaluated eight sets of ECG criteria for left ventricular hypertrophy in a post-mortem study (66).

Left ventricular hypertrophy was considered to be present if the left ventricular wall thickness exceeded 10 mm. Most of the ECG criteria examined had low sensitivity; that is, they were unable reliably to detect left ventricular hypertrophy. However, the criteria of Sokolow and Lyon had acceptably high sensitivity but low specificity i.e. they produced a large number of "false positives". It was then noted that most of the false positives were related to the presence of ST segment and T wave abnormalities; if these were ignored, and reliance placed only on the QRS voltage criteria, then the specificity of the Sokolow-Lyon criteria was significantly increased. In another post-mortem study of 100 cases, Scott found that the Sokolow-Lyon criteria were the most reliable for the detection of left ventricular hypertrophy although specificity was not measured (67). In 1964, Carter and Estes (68) re-established the importance of ST-T changes in the diagnosis of left ventricular hypertrophy when they demonstrated that post-mortem heart weight correlated not only with QRS amplitude but also with QRS duration, left ventricular activation time, ST segment depression and left axis deviation. These findings were developed into a point scoring system for diagnosis of LVH by Romhilt and Estes in 1967 (69).

By the 1970s, it was apparent that there were major limitations to the ECG diagnosis of left ventricular

hypertrophy. First, many of the criteria had been derived from populations in which the prevalence and severity of LVH were high and they performed poorly when applied to other groups including normal populations. Second, factors other than left ventricular mass were shown to affect the sensitivity and specificity of different ECG criteria. Murphy (70) showed that the type of cardiac disease was important, praecordial voltage criteria being sensitive for left ventricular hypertrophy secondary to hypertension or valvular heart disease but insensitive for hypertrophy in patients with ischaemic heart disease. Geometric considerations also were seen to be important since left ventricular hypertrophy accompanied by chamber enlargement produced greater praecordial voltages than hypertrophy without chamber enlargement (71,72).

In an attempt to improve the ECG diagnosis of LVH, more complex methods of analysis including multiple logistic linear regression equations were used to derive new criteria which could then be prospectively validated. Using such methods, Casale et al derived ECG criteria that have greater predictive accuracy than the more commonly used Sokolow-Lyon criteria and Romhilt-Estes point scoring system (73). They point out, however, that further improvement in ECG performance for detection of LVH could be achieved if patients are stratified for age and sex and different criteria applied to different groups.

Diagnosis of left ventricular hypertrophy by echocardiography.

The application of echocardiography to the measurement of left ventricular wall thickness in man was first described in 1972 (74). The method was initially validated against angiographic measurements made in the same patients, but in 1977 Devereux and Reichek published results of a comparison of antemortem echocardiographic measurements and post-mortem left ventricular weight in thirty-four subjects, all of whom had undergone echocardiography within 120 days of death (75). Using a simple formula which assumes the ventricle to be a cube, they obtained a correlation co-efficient between echocardiographic ventricular mass obtained from M-mode tracings and anatomic left ventricular weight of 0.96. Other studies have confirmed that estimation of left ventricular mass is a more sensitive index of LVH than simple measurement of wall thickness (76). Methods using different geometric equations for estimation of left ventricular mass have been described but are no more accurate (77). Recently, two dimensional echocardiography has become widely available and methods of estimating mass from the two-dimensional image described (78,79). Although these have theoretical advantages over M-mode estimates, in which the ventricle is assumed to be

regular in shape, studies in hypertensive patients have not shown any differences between the two techniques. Not surprisingly, the two dimensional method is more accurate in the small proportion of patients who have left ventricular aneurysms or other major causes of geometric distortion of the ventricle.

Overall, the principal advantages of the echocardiogram over the electrocardiogram are its superior sensitivity, allowing detection of milder degrees of cardiac hypertrophy, and its ability to quantify left ventricular mass and thus detect sequential changes in response to treatment. In their post-mortem study, Devereux and Reichek found the sensitivity of the echocardiogram for detection of LVH to be 93%; ECG criteria performed less well with a sensitivity of 50% for the Romhilt-Estes point scoring system and 21% for the Sokolow-Lyon voltage criteria. The specificity of both sets of ECG criteria and of echocardiography was 95% (75). The disadvantages of echocardiography are that it is less widely available than electrocardiography, more time-consuming and more expensive. In addition, it is not possible to obtain high quality tracings in all subjects; patients who are obese, are cigarette smokers or have chronic lung disease are often technically difficult subjects and as many as 10-20% of patients may be unsuitable for detailed echocardiographic examination.

In summary, the electrocardiogram and echocardiogram

are both commonly used for the detection of left ventricular hypertrophy. For epidemiological purposes, ECG criteria utilising multiple logistic linear regression equations and stratification of patients by age and sex holds promise for increased sensitivity. In the clinical setting, however, the praecordial voltage criteria of Sokolow-Lyon and the point scoring system of Romhilt-Estes remain in common use. Both have reasonable specificity (approximately 90%) but low sensitivity, varying from 20% to 70% in different series. The echocardiogram has practical disadvantages, especially in large-scale studies, but is quantitative rather than qualitative and is more sensitive for detection of mild degrees of hypertrophy than the ECG.

2.5 INCIDENCE AND PREVALENCE OF LEFT VENTRICULAR HYPERTROPHY

Both the ECG and the echocardiogram have been used to study the prevalence of LVH.

Assessed by electrocardiography.

Electrocardiography is the most widely used technique for the diagnosis of LVH. Most of our knowledge concerning the prevalence and incidence of electrocardiographic LVH has been derived from the Framingham study (2,80,81,82) which is unique in general population surveys in terms of the number of subjects, duration of follow-up and completeness of data. The Framingham study is a longitudinal study of 5209 men and women aged 30-62 from a representative general population sample with a follow-up period exceeding twenty years. As well as routine examination, blood pressure measurement and chest X-ray, a thirteen lead electrocardiograph was taken at entry and then at each biennial return visit. Information relating to all major medical events was obtained from hospital records and from attending physicians; in addition, death certificates and medical examiners reports were reviewed. The drop-out rate from the study was low; of the initial cohort of 5209 persons, 4678 were still alive sixteen years later and of these, 86% attended

for the examination. Even those who failed to attend were not entirely lost to follow-up since local hospital admissions were monitored and relatives interviewed. Thus the authors' claim that loss to examination is unlikely to have led to any substantial loss of information relating to the appearance of new cardiovascular disease seems to be justified. Electrocardiographic left ventricular hypertrophy was divided into "definite" and "possible," the former being the presence of voltage amplitude criteria with ST-T abnormalities and the latter being voltage amplitude criteria alone. The voltage criteria fulfilled could be any one of the following:

RI + SIII	$\geq$ 25mm
RaVl	$\geq$ 11mm
RaVf + SaVf	$\geq$ 20mm
SV1 + RV5	$\geq$ 35mm
any single praecordial deflection	$\geq$ 20mm

The overall prevalence of "definite" ECG LVH (i.e. LVH with repolarisation changes) was 1.5%. Prevalence rose sharply with age; LVH with repolarisation changes was uncommon at age 35 but affected 10% of subjects by the age of seventy and was slightly more common in men than in women. The prevalence of "possible" LVH (i.e. voltage criteria without repolarisation changes) was similar to that of "definite" LVH and also increased

with age.

The longitudinal nature of the study also allows us to estimate an incidence rate. Over a period of twelve years, 3% of the original cohort developed definite ECG LVH and 4.5% of those without any evidence of LVH at entry developed voltage criteria. Thus ECG evidence of LVH was either present at entry, or developed during twelve years of follow-up, in 10% of this normal population group. Those with "possible" LVH were twenty times more likely to develop "definite" LVH than those without any LVH at entry. This is to be expected since voltage criteria with ST-T changes simply indicate greater hypertrophy than voltage changes alone (83,84). Thus the "possible" group from Framingham can be regarded as having moderate left ventricular hypertrophy while the "definite" group have more advanced hypertrophy. As Kannel points out, the development of ECG LVH occurs at a rate greater than that suggested by the prevalence data because of the high mortality associated with this ECG finding (81). As expected, the Framingham study demonstrated a strong association between blood pressure and ECG LVH. The higher the blood pressure, the more likely was the patient to have, or to develop, ECG LVH. Over 50% of those with systolic blood pressure readings exceeding 200 mm Hg had ECG LVH and the relationship was in general more striking with respect to systolic than to diastolic blood pressure. Abnormalities of

repolarisation, including ST segment depression and T wave inversion were also more common as pressure rose. A further analysis, derived from the original Framingham study, is of relevance here. In 1982, Savage et al reported on the prevalence of LVH in a "second generation" Framingham cohort comprising offspring and spouses of the initial subjects (mean age 44, range 17-77 years) (85). The prevalence of LVH with repolarisation changes was only 0.2% compared with 1.5% in the original cohort; although the two groups were not ideally matched, this result has been widely interpreted as signifying a considerable reduction in the prevalence of left ventricular hypertrophy over a period of twenty years and has been attributed to the use of effective anti-hypertensive therapy (85).

Assessed by echocardiography

The Framingham data have also been used to define the prevalence of echocardiographic left ventricular hypertrophy (85,86). Using previously derived sex-specific upper limits of normal for left ventricular mass, the overall prevalence of echocardiographic left ventricular hypertrophy was 10% reflecting the greater sensitivity of the echocardiogram for detection of left ventricular hypertrophy when compared with the ECG. As with ECG LVH, the prevalence of echocardiographic LVH rose

sharply with age, being present in 6% of those under the age of fifty compared with 33% of men and 50% of women over the age of eighty. Prevalence also rose sharply with blood pressure.

In a recent review, Devereux noted that between 26% and 48% of all hypertensive patients had echocardiographic LVH (87). Hammond et al have also recently reported on the prevalence of echocardiographic LVH among patients with uncomplicated hypertension (32). Again using sex-specific values for left ventricular mass, they identified LVH in 12% of patients with borderline hypertension (140-159 mm Hg systolic or 90-94 mm Hg diastolic after being recumbent for twenty minutes) and 20% of patients with sustained hypertension ($\geqslant$160 systolic or $\geqslant$95 diastolic).

In summary, the prevalence of left ventricular hypertrophy rises with age as well as with blood pressure. On average, between one-quarter and one-half of all hypertensive patients have echocardiographic LVH and approximately half of those will have ECG LVH.

2.6 LEFT VENTRICULAR HYPERTROPHY AND RISK

As with incidence and prevalence of left ventricular hypertrophy, the Framingham study is the major source of data relating left ventricular hypertrophy to mortality and morbidity (2,80,81,82). The first paper relating specifically to left ventricular hypertrophy and risk was published in 1969 (80); this demonstrated that LVH with and without ST-T changes was associated with increased mortality in both men and women. For example, 60% of men and 41% of women with LVH and ST-T changes died during the first fourteen years of the study compared with 25% and 12% of age-matched groups without LVH. A similar pattern was seen in all age groups. Although the absolute risk of death was greatest in in the oldest age group, the relative risk of dying (risk in those with LVH divided by the risk in those without) was greatest in the youngest age group. As expected, the increase in mortality was confined to cardiovascular causes of death.

The initial findings have been confirmed in a more recent publication based on a twenty year follow-up period (2). Calculation of age-adjusted mortality rates demonstrates that LVH with repolarisation changes is associated with an increase in total mortality by a factor of 5.0 in men and 4.7 in women compared with a normal ECG, and increased cardiovascular mortality by a factor of 8.5 in men and 9.6 in women (2). LVH without

ST-T changes is associated with approximately a two-fold increase in total mortality and a three-fold increase in cardiovascular mortality. In all groups, most of the excess mortality is attributed to coronary heart disease and sudden death.

A criticism of the Framingham study, and of other epidemiological studies, is that sudden death has in the past been considered to be almost synonomous with acute myocardial infarction. An example of this in the Framingham analysis is seen in the relationship between ECG LVH and the "risk of clinical manifestations of coronary disease" which include angina, myocardial infarction and sudden death (2). There is, however, some evidence from the data of a particularly strong association between left ventricular hypertrophy and sudden death. Compared to a normal ECG, LVH in men is associated with a two-fold increase in angina, a three-fold increase in myocardial infarction and an almost six-fold increase in sudden death. This suggests either that the case fatality rate for myocardial infarction is increased by the presence of LVH or that not all of the sudden deaths in LVH patients are attributable to myocardial infarction. This is discussed further in chapter 2.9.

The Framingham data demonstrate also that cardiovascular morbidity is substantially increased by the presence of LVH. In addition to an increase in myocardial infarction and cardiac failure, there is an

increased incidence of stroke and occlusive peripheral vascular disease (2).

Since left ventricular hypertrophy is related both to the duration and to the severity of hypertension, it is not surprising that it should be associated with increased cardiovascular morbidity and mortality. However, the Framingham data suggest that LVH is an independent risk factor for mortality since the presence of LVH, for a given level of blood pressure, carries three times the risk of hypertension without LVH. Furthermore, multivariate analysis demonstrates a significant net effect of ECG LVH with ST-T changes on mortality that is independent of associated risk factors including blood pressure, smoking habit, plasma glucose, and serum cholesterol (81). In contrast, the authors suggest that the increased risk of LVH without ST-T changes is entirely attributable to the associated hypertension.

In summary, ECG LVH is a major risk factor for cardiovascular morbidity and mortality. The Framingham data demonstrate that the risk associated with LVH in the presence of ST-T changes is not wholly attributable to associated risk factors, suggesting an independent contribution of LVH, at least when accompanied by ST-T changes, to mortality.

2.7 STRUCTURE AND FUNCTION OF THE HYPERTROPHIED VENTRICLE

Changes in both the structure and function of the left ventricle occur with the development of hypertrophy.

A. Structural changes

Since division of myocytes ceases at the age of three months in man (87), any increase in left ventricular muscle mass implies hypertrophy of the individual myocytes. It should be noted, however, that the myocytes may become polyploid and thus increased chromosomal material has been reported in hypertrophy (88).

Although there is no division of myocytes, hyperplasia of the connective tissue cells and increase in collagen content do occur with cardiac hypertrophy (89). Whether this increase in collagen is appropriate to, or in excess of, the accompanying hypertrophy is controversial and depends partly on the method used to estimate collagen production. Sasaki measured hydroxyproline content as an index of collagen systhesis in hypertrophied human myocardium and found this to be increased (90). Caspari measured collagen concentration in normal and hypertrophied hearts with and without aortic valve disease (91) and reported that, in the absence of valve disease, collagen content

was increased in hypertrophied hearts while collagen concentration (expressed as mg. collagen per g. dry weight) was normal. In the presence of aortic stenosis, however, both content and concentration of collagen were increased. Although the authors suggest that collagen concentration is affected by the nature of the stimulus to hypertrophy, the individual heart weights are not recorded. Thus an alternative explanation would be that the degree of hypertrophy was greater in the hearts with aortic stenosis, and that there is a "critical weight" above which increased collagen production occurs.

When volume fraction of collagen was measured by point counting, this was found to be raised (92). Increase in collagen occurs particularly in the subendocardial area (92) and it has been suggested that tissue hypoxia is the stimulus to collagen production, since in vitro studies have shown that hypoxia stimulates collagen synthesis by fibroblasts (93). An alternative explanation is that increased collagen content in the subendocardium reflects an increase in, or altered distribution of, left ventricular wall stress (8). Whatever the mechanism, it appears that hyperplasia of fibroblasts and increased collagen synthesis, particularly in the subendocardium, both occur with the development of myocardial hypertrophy.

B. Functional changes

Systolic function of the hypertrophied ventricle

The contractile properties of hypertrophied myocardium have been studied in the intact heart in both man and experimental animals and at a cellular level in experimental hypertrophy.

The "end stage" of hypertensive heart disease involves dilatation of the previously hypertrophied left ventricle with clinical development of heart failure. Clearly, myocardial contractility is reduced at this stage; there is much debate, however, as to whether contractility is reduced at an earlier stage when the ventricle is hypertrophied but not dilated.

In experimental hypertension, several studies have demonstrated normal or even elevated indices of systolic function in the intact hypertrophied, but not dilated, ventricle (94,95,96). The indices measured in these studies include the the maximum tension developed (94), the ventricular stroke work and minute work (95) and the pressure developed by the ventricle (96). In adddition, several studies of isolated papillary muscle have been reported (97,98,99,100). Tension developed per unit weight was significantly greater than normal in hypertrophied rat muscle (98) and non-significantly greater than normal in hypertrophied cat papillary muscle (97). Two other studies have reported depressed

function in isolated papillary muscle preparations (99,100). Possible explanations for these apparently contradictory results include the use of different indices of contractility, differences in the time relationship between application of the pressure load and measurement of systolic function, and the abruptness of onset of the pressure load. The importance of differences in experimental design has been shown by Williams and Potter who demonstrated that the contractile function of cat papillary muscle was reduced 6 weeks after banding of the pulmonary artery but had returned to normal by twenty-four weeks (101) and by Bishop and Melsen who showed that acute volume loading of the right ventricle in cats leads to local necrosis and fibrosis and subsequently to impaired systolic function (102).

Thus a gradually increasing pressure load, as in systemic hypertension, may be associated with normal or even increased contractility during the early stages. In man, assessment of systolic function is difficult because all commonly used indices of systolic function are dependent on the loading conditions of the heart. In other words, there is no measure of myocardial contractility that is independent of preload and afterload. As Grossman points out in a review of the subject (103), the studies that have reported impaired myocardial contractility in ventricles subjected to pressure overload have utilised indices of systolic

function that are themselves affected by alterations in loading conditions. To investigate an index of systolic function that would be independent of preload, Fifer examined the rate of stress development, as opposed to total sress, in patients with severe aortic stenosis and found no evidence of reduced myocardial contractility (104). Several other experiments appear to support this view. Gunther and Grossman (105) studied fourteen patients with pressure overload hypertrophy and found a close inverse correlation between systolic wall stress and ejection fraction suggesting that the apparent reduction in ejection fraction was related to increased afterload. When ejection fraction was plotted against wall stress for normal subjects, it was found that the points fell along the same line as for patients with aortic stenosis while those for patients with congestive cardiomyopathy fell below this line. The authors held that this was consistent with the absence of an intrinsic contractile abnormality in patients with left ventricular hypertrophy secondary to aortic stenosis. They further cite the well documented "normalisation" of left ventricular function after aortic valve replacement as further evidence that there is no intrinsic reduction of contractility in hypertrophied myocardium (105).

Much of the debate as to whether ventricular hypertrophy in hypertension is a physiological response

to increased afterload or a pathological process centres on biochemical changes that have been detected in experimental LVH. Schwartz et al have shown that the rate of hydrolysis of ATP, an index of energy utilisation, is reduced in hypertrophied hearts from hypertensive rats (106); this contrasted with the increased rate of ATP hydrolysis found in the "physiological" hypertrophy in the thyroxine treated rat (107). Changes have also been noted in the structure and properties as well as the quantity of myosin produced with appearance of new iso-enzymes in experimental LVH (106,107). However, the relevance of these results to human cardiac hypertrophy is not known. As with assessment of structural changes, factors such as the nature and duration of the pressure load applied may affect the results. Indeed, in a recent study using a gradually increasing pressure load in the pig (108), chosen as an experimental model specifically because its myosin iso-enzyme pattern most closely resembles that of man, no changes were seen in myosin iso-enzyme pattern nor in myosin ATPase activity despite an increase in left ventricular mass to almost 170% of the control value.

Thus most of the recent evidence suggests that there is no intrinsic disorder of contractility in left ventricular hypertrophy secondary to hypertension; earlier reports of impaired contractile function may in part reflect the lack of suitable techniques for

assessing contractility independently of loading conditions.

2. Diastolic function of the hypertrophied ventricle

Until recently, interest in cardiac function focused mainly on the pumping ability of the heart, and little attention was paid to the function of the heart during diastole. Realisation that abnormalities of diastolic function can significantly influence pumping ability has led to increased interest in diastolic function.

Normal diastolic function

Diastolic function of the left ventricle is dependent on many factors of which two of the most important are the completeness of ventricular relaxation and the passive elastic properties of the ventricular wall (109). Relaxation of ventricular muscle is not a passive process; the active uptake of calcium ions by the sarcoplasmic reticulum is necessary to lower the calcium concentration around the myofibrils and thus allow the cleavage of actin-myosin crossbridges leading to relaxation (110). The uptake of calcium by the sarcoplasmic reticulum requires ATP as an energy source and it has been suggested that as much as 15% of the total energy expenditure of the heart may be used in the process of "active" relaxation (111). Following

this period of ventricular relaxation, there is a period of passive ventricular filling, the rate and degree of which are determined not only by the filling pressure (i.e. the pressure gradient between left atrium and left ventricle during diastole) but also by the passive elastic properties of the ventricle.

Abnormalities of diastolic function

Abnormalities of either the process of active ventricular relaxation or the passive elastic properties of the ventricle may adversely affect diastolic function.

If the ventricle becomes ischaemic, then there may be insufficient energy available for resorption of calcium by the sarcoplasmic reticulum and thus ventricular relaxation will be slowed and may be incomplete (112,113). It has been suggested that this "impaired relaxation" rather than depressed contractility may account, at least in part, for the high filling pressures found in acute myocardial ischaemia (114,115).

The passive elastic properties of the ventricle may be influenced by several factors including the thickness and composition of the ventricular wall. Increased ventricular wall thickness is associated with increased stiffness of the ventricle, as is the deposition of abnormal material such as scar tissue or amyloid (109).

All of these mechanisms may be operating in the hypertrophied ventricle of a hypertenive patient in which the ventricular wall thickness is increased, diffuse myocardial fibrosis is present and subendocardial ischaemia can occur even in the absence of coronary artery disease.

The functional importance of these diastolic abnormalities is that the pattern of ventricular filling changes. In a heart of normal compliance, approximately 80% of ventricular filling occurs during the "passive" phase of ventricular filling before the onset of atrial systole. There is then a period of reduced flow across the mitral valve followed by the final "kick" as the left atrium contracts shortly before the onset of ventricular systole. In the hypertrophied ventricle with reduced diastolic compliance, the flow across the mitral valve during the early period of diastole is reduced; as a result, atrial systole becomes increasingly important for the maintainance of normal ventricular filling.

Several studies have specifically investigated diastolic filling properties of the ventricle in hypertension using a variety of relatively noninvasive techniques including apex cardiography, echocardiography and radionuclide ventriculography. Dreslinski et al used the echocardiographic left atrial emptying index (LAEI) to compare hypertensives with and without LVH and normotensive controls (116). The LAEI

is a measure of the amount of ventricular filling that occurs during the first one third of diastole divided by the total amount of ventricular filling. Thus a high value (approximately 0.75-1.00) indicates normal compliance of the ventricle and a low value indicates reduced compliance. As expected, they found compliance was reduced in those hypertensives with LVH although compliance was also reduced in those hypertensives without LVH and in whom echocardiographic indices of systolic function were normal (116). The technique of radionuclide ventriculography has also been used to assess diastolic function. Here the red blood cells are "labelled" using radioactive technetium and the radioactive counts are detected using a gamma camera placed over the chest. Commonly used indices of ventricular diastolic function derived from this technique are the peak filling rate (of the ventricle) and the time to peak filling (measured from the beginning of diastole). Studies in hypertension have shown that the peak filling rate is reduced and the time to peak filling prolonged in hypertensives when compared with normal subjects (117); again, these abnormalities were present even when systolic function was completely normal in the hypertensive group.

Summary

In summary, while there is debate as to whether

systolic function is normal or impaired in the hypertrophied but undilated left ventricle, the recent evidence suggests that systolic function may well be normal. In contrast, the available evidence suggests that diastolic function of the ventricle is abnormal at an early stage in hypertensive heart disease and deteriorates further as hypertrophy progresses. The practical significance of this is that filling of the ventricle becomes increasingly dependent on effective atrial contraction as left ventricular mass rises. Sudden loss of effective atrial contraction in a hypertrophied heart, caused for example by the onset of atrial fibrillation or a ventricular arrhythmia, will be accompanied by a marked reduction in ventricular filling and presumably in cardiac output. Thus impaired diastolic filling might render the heart more vulnerable to an arrhythmia that involves loss of atrial transport function.

2.8 LEFT VENTRICULAR HYPERTROPHY, MYOCARDIAL ISCHAEMIA AND CORONARY ARTERY DISEASE

Introduction

The terms "coronary artery disease" and "myocardial ischaemia" are sometimes wrongly used synonomously. In left ventricular hypertrophy, there is evidence that myocardial ischaemia can occur for reasons other than coronary artery disease. In this section, the relationships between left ventricular hypertrophy, cardiac ischaemia and coronary artery disease are discussed.

1. Left ventricular hypertrophy and myocardial ischaemia.

It has been known for many years that patients with left ventricular hypertrophy as a result of either hypertension or aortic valve disease can develop typical exercise-induced angina pectoris accompanied by electrocardiographic changes of ischaemia even when the major coronary vessels are widely patent (118,119). In addition, post mortem histological examination in such patients often reveals patchy myocardial necrosis, particularly in the subendocardium (120), and an intracoronary collateral circulation (121), the stimulus for which has presumably been ischaemia. There

is convincing evidence, therefore that myocardial ischaemia can and does occur in hypertrophied ventricles in the absence of coronary artery disease, implying an imbalance of oxygen supply and demand. Initial studies of myocardial blood flow in patients with left ventricular hypertrophy suggested that coronary blood flow and myocardial oxygen consumption (corrected for ventricular mass) were normal (122,123) although Malik et al suggested that coronary flow was reduced in the hypertrophied ventricle but that oxygen consumption was unchanged due to increased oxygen extraction (124).

The available techniques, however, had two major limitations; they could only be performed at rest and were therefore unable to detect exercise-induced ischaemia and they measured only total myocardial blood flow and could not detect localised ischaemia due to regional differences in perfusion. Recent studies using animal models to investigate total and regional perfusion both at rest and after different types of stress have demonstrated significant abnormalities in the hypertrophied ventricle. Rembert et al (125) used radioactive microspheres to assess transmural variations in perfusion in dogs with left ventricular hypertrophy after aortic banding. They found resting subendocardial blood flow to be reduced in the hypertrophied hearts, the ratio of subendocardial to subepicardial blood flow being 1.10 ± 0.08 compared to

1.25±0.07 in control animals. These findings have been confirmed by another group who reported an inverse correlation between left ventricular mass and the subendocardial to subepicardial blood flow ratio (126). One group failed to show reduced subendocardial flow at rest but the degree of cardiac hypertrophy in this study (127) was less than in Rembert's study in which left ventricular mass was increased by 80-100% (125). Other investigators have studied the ability of myocardial blood flow to increase in response to various vasodilator stimuli including pharmacologial agents such as adenosine (128) or dipyridamole infusions both at resting heart rates and at higher heart rates induced either by exercise (129) or rapid atrial pacing (128). In general, these studies have shown that the vasodilator capacity, or "vascular reserve" of the coronary circulation, is reduced in experimental left ventricular hypertrophy (127,128). In studies that have measured regional perfusion using microspheres or similar techniques, redistribution of perfusion away from the subendocardium with reduction in the ratio of subendocardial to subepicardial flow has been observed particularly at rapid heart rates (129).

Why is the subendocardium particularly vulnerable to ischaemia? Several mechanisms have been suggested all of which may combine to ensure that the subendocardial area is the first to be affected when myocardial oxygen

demand exceeds supply. First, subendocardial muscle uses approximately 20% more oxygen per unit mass than the remaining myocardium (130). Since coronary autoregulation regulates myocardial blood flow in response to local metabolic needs, the high subendocardial flow presumably represents increased energy requirements as a result of the greater systolic stress in the deeper layers of the ventricular wall. Thus the high energy requirement of the subendocardial zone immediately renders it susceptible to ischaemia. A second factor involves the coronary vascular reserve, i.e. the ability to increase coronary blood flow by vasodilatation. It has been shown that when a progressive imbalance develops between myocardial supply and demand, maximum vasodilatation occurs earliest in the left ventricular subendocardial area (131,132); thereafter subendocardial flow becomes pressure dependent. Thus coronary vascular reserve is lost in the subendocardial but not the subepicardial layer; any further increase in oxygen requirement will then result in subendocardial ischaemia.
Third, physical factors may be important in determining subendocardial susceptibility to ischaemia. This subject has been reviewed by Hoffman (133); if blood vessels were rigid, then the flow rate would be determined only by the arteriovenous pressure difference and by the properties of the fluid and vessel. However, blood vessels are compressible and

tissue pressure can affect their diameter and thus influence flow. For some years, high tissue pressure during systole has been invoked as a contributing factor to subendocardial ischaemia. Several investigators had shown that tissue pressure in the subendocardial zone during systole was high and approximated to intracavitary systolic pressure but decreased centrifugally to low values in the subepicardial area (133). Thus it was suggested that myocardial flow to the subendocardium occurred only in diastole while subepicardial flow could occur during at least part of systole. Recent evidence, however, suggests that most of the myocardium receives no flow during systole (134,135) and thus systolic tissue pressures may not be relevant to myocardial perfusion. However, diastolic tissue pressure also displays a gradient from the subendocardial area outwards and it is possible that the high tissue pressures found in the deeper layers of the hypertrophied ventricle may restrict subendocardial flow during diastole (133). How far can these observations be applied to man? Coronary vascular reserve has been studied in man by measuring the hyperaemic reaction to intra-coronary injection of contrast medium in patients with and without left ventricular hypertrophy (136). As in the animal models, coronary vascular reserve was markedly reduced in those patients with left ventricular hypertrophy. Assessment of transmural differences in

myocardial flow in man has proved more difficult and there are no suitable in vivo techniques available. However, the occurrence of typical angina pectoris with accompanying ST segment depression in patients with cardiac hypertrophy and normal coronary arteries, when taken with the experimental evidence, strongly suggests that subendocardial ischaemia does occur during exercise and measurement of coronary sinus lactate concentration has provided biochemical confirmation of ischaemia (83). While this technique cannot pinpoint the site of ischaemia, the distribution of myocardial fibrosis at post mortem suggests that ischaemia is predominantly subendocardial. It remains to be seen whether newer imaging techniqes, such as Positron Emission Tomography and Magnetic Resonance Imaging will be able to demonstrate regional differences in perfusion in vivo.

As in the various experimental models, the factors that are likely to be responsible for the susceptibility of the subendocardium to ischaemia include a high metabolic demand, early loss of vasodilator capacity during stress and high tissue diastolic pressures which impede myocardial perfusion.

2. Left ventricular hypertrophy and coronary artery disease.

An association between hypertension and myocardial

infarction was first noted by Sir Thomas Lewis when he observed that thrombosis of a coronary artery occurred most commonly in men over the age of fifty with signs of arterial disease *"and as often as not high blood pressure"* (137). It is now well established that hypertension is a major risk factor for myocardial infarction (138); the higher the arterial pressure, the greater the risk (2). Hypertension appears to accelerate the process of atherosclerosis and a greater percentage of the surface area of the coronary arteries, and other major arteries, is affected by atherosclerosis in hypertensive when compared to normotensive individuals (139).

There is some evidence that pressure itself is the mediator of vascular damage since atherosclerosis of the pulmonary arteries is usually only seen in pulmonary hypertension (140). In the presence of other risk factors, such as elevated serum cholesterol concentration, the severity of atherosclerosis is increased in experimental animal models (141) and there is evidence in man that the potential for atherosclerosis in hypertension is reduced if the serum cholesterol level is low (142).

Thus there is a strong association between hypertension and coronary artery disease. However, does an association exist between left ventricular hypertrophy and coronary artery disease? Since there is a correlation, albeit a poor one, between blood pressure

and left ventricular mass, we would expect some relationship between LVH and coronary disease. Is there any evidence, however, that LVH, which is an independent risk factor for cardiovascular mortality, is also an independent risk factor for coronary artery disease? This is of considerable practical importance because the excess mortality that is associated with LVH is frequently attributed to coronary artery disease.

Several post-mortem studies have examined the relationship between coronary artery disease and left ventricular hypertrophy (143,144); without exception, cardiac hypertrophy has been a common finding in patients dying from ischaemic heart disease. Buja and Willerson (143) reported that 85% of hearts from subjects dying of ischaemic heart disease weighed over 400g (normal range 300-350g). This hypertrophy, however, need not be due to associated hypertension; any factor that increases afterload or preload, such as congestive cardiac failure or valvular disease, will lead to cardiac hypertrophy. Even in the absence of frank cardiac failure, previous infarction will lead to compensatory hypertrophy of the remaining myocardium and ischaemia itself may be the stimulus to myocardial hypertrophy either by increasing wall stress or by the direct action of intracellular ischaemia to reduce ATP concentration and stimulate myosin synthesis (16,17). Dean and Gallacher (144) have examined the relationship

between cardiac hypertrophy and coronary artery disease in a series of fifty post-mortem hearts. Overall, there was a weak correlation between the extent of coronary artery disease and total heart weight although in the subgroup of ten patients with left ventricular hypertrophy secondary to either hypertension or valvular disease, there was no correlation. Gould et al studied eighty-five patients including a group with congestive cardiomyopathy and normal coronary arteries and a group with triple vessel disease but with a similar degree of left ventricular dysfunction, and found that left ventricular mass was similarly increased in both groups suggesting that the left ventricular dysfunction rather than the coronary artery disease was the cause of the cardiac hypertrophy (145). They concluded that left ventricular mass rose in proportion to the left ventricular end-diastolic volume.

Summary

Thus there is considerable evidence that myocardial ischaemia occurs in left ventricular hypertrophy even when the coronary arteries are free of significant disease; there is also evidence that myocardial ischaemia from any cause, including coronary artery disease, may stimulate left ventricular hypertrophy. There is, however, little to suggest that left

ventricular hypertrophy per se predisposes to coronary artery disease. This is important because, as noted previously, left ventricular hypertrophy is an independent risk factor for cardiovascular mortality, and particularly for sudden death. One possible explanation is that the case fatality rate for myocardial infarction is greater in patients with pre-existing left ventricular hypertrophy either because of an increased tendency to ventricular arrhythmia or because of greater infarct size as a result of reduced coronary reserve. An alternative explanation is that left ventricular hypertrophy predisposes to sudden death by a mechanism other than coronary artery disease.

2.9 RELATIONSHIP BETWEEN SUDDEN DEATH, CORONARY ARTERY DISEASE AND LEFT VENTRICULAR HYPERTROPHY.

A. The definition of sudden cardiac death.

Investigators have subdivided sudden death into categories according to whether the death was instantaneous or whether the patient experienced a change in symptoms within two hours or one hour of death. A recent World Health Organisation Scientific Group declined to define the word "sudden" but instead recommended that data surrounding the terminal event should be collected including the presence of prior pain or myocardial infarction, time of onset of symptoms, whether death was witnessed etc (146). Accurate registration of sudden death is difficult not only because of difficulties in definition but because "sudden death" is not recognised as a "cause" of death by the Registrar General for the purpose of death certification. Since most sudden deaths occur in the community, the death certificate is usually completed by the general practitioner. Faced with the problem of a sudden death in a patient whom he has been attending, the general practitioner can either decline to certify on the grounds that the cause of death is not known, or he can put forward a "best guess" regarding the cause of death, such as myocardial infarction or cerebrovascular accident. Estimates suggest that sudden

cardiac death accounts for approximately 75,000 deaths per annum in the United Kingdom, the rate in industrialised countries being 30 per million population per week (146).

B. Mechanism of sudden death.

It is now widely accepted that ventricular tachyarrhythmias are responsible for most cases of sudden cardiac death. In a study of four hundred and twenty-six "would be" victims of sudden death, Liberthson reported that the initial cardiac rhythm recorded was ventricular fibrillation in 72% of cases (147). Two other studies confirmed that ventricular firbrillation was present in approximately two-thirds of sudden death victims at the time of attempted resuscitation (148,149).

However, the increased availability over the last five years of twenty-four hour Holter monitoring has demonstrated that ventricular fibrillation is not invariably the initial arrhythmia in cases of sudden cardiac death. In 1982, Nikolic documented six cases of sudden death that occurred during ambulatory monitoring. The terminal arrhythmia was ventricular fibrillation in five but this had been immediately preceded by either ventricular tachycardia or other complex ventricular ectopic activity in five (150). This finding has been confirmed by at least two other

studies (151,152).

If there is a delay of several minutes from the time of cardiac arrest, it is likely that the rhythm will have degenerated from ventricular tachycardia to ventricular fibrillation thus making the latter the most commonly detected arrhythmia in out-of-hospital cardiac arrest.

C. Sudden death and coronary artery disease.

In 1974, WB Kannel, author of many of the Framingham papers, wrote:

> *"Sudden death is a common and possibly incidental expression of lethal coronary heart disease..... The inescapable conclusion is that the prevention of sudden death requires the prevention of coronary attacks." (82)*

This statement reflected a widely held belief that sudden death was almost invariably a result of acute myocardial infarction. Subsequent post-mortem studies of the coronary arteries of sudden death victims tended to confirm this viewpoint. Liberthson, reporting on a series of two hundred and twenty sudden cardiac deaths, found at least one coronary artery stenosis in 94% of victims, and 60% had three or four vessel disease (147). In a series of fifty-nine, Friedman found only four that were free of any coronary artery stenosis and

again triple vessel disease was the norm (153).
In view of the known association between myocardial infarction and ventricular fibrillation, it was generally assumed that the fatal arrhythmia resulted from an ischaemic insult to the myocardium. However, several observations suggested that this relationship was not as straightforward as it at first appeared. First, it was noted that survivors of out-of-hospital cardiac arrest did not invariably develop signs of myocardial infarction. In Liberthson's series, only 39% of defibrillated survivors developed electrocardiographic evidence of myocardial infarction (147). In a series of three hundred and fifty-two cardiac arrests, Myerburg found that only 36% of the survivors had evidence of definite myocardial infarction although 79% had coronary artery disease (148). In a study by Baum, transmural infarction was confirmed in only 17% of one hundred and forty-six patients resuscitated from ventricular fibrillation (154) and the authors point out that sudden cardiac death should not be equated with myocardial infarction. The second unexpected finding was the low incidence of acute coronary thrombosis found at post mortem in victims of sudden cardiac death. This has varied from 4% to 59% in different studies, but on average only 22-30% of cases of sudden cardiac death have an acute coronary thrombosis (155). In contrast, acute coronary thrombosis is almost invariably present in patients

with acute myocardial infarction. The recent increase in the use of thrombolytic therapy early in the course of myocardial infarction has necessitated early coronary arteriography which has demonstrated acute coronary thrombosis in the vast majority of patients with acute myocardial infarction (156); thus it has been suggested that sudden cardiac death and acute myocardial infarction should be regarded as different diseases (157). The third unexpected finding was the high prevalence of old healed myocardial infarction in those patients dying suddenly. Most studies demonstrated that at least 50% of sudden death victims had an old myocardial infarction (153). Thus there is a stronger association between sudden death and old myocardial injury than between sudden death and acute myocardial infarction. As Reichebach points out (158), the observations suggest that acute coronary thrombosis and recent myocardial infarction do not occur with sufficient frequency to be considered causally related to the sudden collapse. It is now generally accepted that sudden cardiac death is more commonly the result of pre-existing myocardial disease than of acute myocardial infarction, and that the ventricular "scar" somehow predisposes to ventricular arrhythmia.

D. Sudden death and left ventricular hypertrophy.

Electrocardiographic evidence of left ventricular

hypertrophy is strongly associated with sudden death. In the Framingham study, 36% of sudden deaths were preceded by ECG LVH compared with 19% of non-sudden deaths and 6% of cancer deaths (81). ECG LVH was associated with a five-fold increase in sudden death and, indeed, the association between ECG LVH and sudden death was more striking than the association between hypertension and sudden death. Post mortem evidence confirms that left ventricular hypertrophy is common in victims of sudden cardiac death (82). Although it could be argued that ischaemia secondary to coronary artery disease may be a stimulus to cardiac hypertrophy, Perper found no correlation between heart weight and the degree of coronary artery disease in victims of sudden death (159) suggesting that the hypertrophy itself is not simply a reflection of more severe coronary artery disease and may itself predispose to sudden death. In a post-mortem study of one hundred and fifty-one sudden death victims, Rissanen identified a subgroup of eighteen patients without coronary artery thrombosis in whom death had been instantaneous and was presumed to be due to primary ventricular arrhythmia (160). Cardiac hypertrophy and a history of hypertension were more common in this "primary arrhythmia" group than in those with evidence of myocardial infarction and coronary atherosclerosis was less common. Of the eighteen, seven (5%) had no coronary artery disease whatsoever;

two had aortic stenosis and two had hypertension and left ventricular hypertrophy with no other abnormal findings.

In summary therefore, there appears to be an association between left ventricular hypertrophy and sudden death that is independent of coronary artery disease.

2.10 HYPERTROPHIC CARDIOMYOPATHY - A MODEL FOR HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY?

Introduction

Hypertrophic cardiomyopathy was first described by Donald Teare in 1958, as a condition characterised by striking myocardial hypertrophy, particularly involving the interventricular septum, in the absence of left ventricular dilatation (161). Early interest in the condition focused on the presence of a pressure gradient within the left ventricle (162) with development of a high pressure apical region and a low pressure outflow region. As a result, names such as idiopathic hypertrophic subaortic stenosis (IHSS) and Teare's original term, hypertrophic obstructive cardiomyopathy (HOCM), came into common use.
Since it is now clear that the majority of patients do not in fact have an intraventricular pressure gradient, the term hypertrophic cardiomyopathy is preferred for the condition of left ventricular hypertrophy in the absence of any other cause, such as aortic stenosis or hypertension (163). Following the early interest in systolic pressure gradients, it is now generally accepted that systolic function in hypertrophic cardiomyopathy is excellent. Systolic outflow from the ventricle is unusually rapid and ejection fraction, a commonly used index of systolic function, is often

high. Diastolic function, however, is impaired (163). The ventricle is abnormally stiff leading to impaired ventricular filling and a high left ventricular end diastolic pressure. This in turn leads to elevated left atrial, pulmonary venous and pulmonary capillary wedge pressures. As in left ventricular hypertrophy secondary to hypertension, both echocardiography and radionuclide ventriculography have been used to demonstrate the impairment of diastolic ventricular filling. One study suggested that ventricular compliance in hypertrophic cardiomyopathy was a dynamic process, possibly related to chronic subendocardial ischaemia, since diastolic function appears to improve acutely after administration of the calcium antagonist nifedipine (164).

The condition is inherited, usually as an autosomal dominant trait with a high degree of penetrance. Thus examination of the relatives of a patient with hypertrophic cardiomyopathy will often reveal hypertrophic cardiomyopathy, although the condition may be mild and detectable only by echocardiography (165).

Aetiology of hypertrophic cardiomyopathy.

The aetiology of this condition is unknown. The various suggestions include increased responsiveness of the heart to circulating catecholamines (46), an intrinsic abnormality of collagen (166), abnormal

intramural coronary arteries leading to myocardial ischaemia and secondary fibrosis in the absence of epicardial coronary disease (166) and abnormally rapid conduction through the atrioventricular node leading to asynchronous ventricular contraction and resultant cardiac hypertrophy (166).

Pathology of hypertrophic cardiomyopathy.

The major pathological findings of hypertrophic cardiomyopathy have been reviewed by Maron and Epstein (163) and by Wynne and Braunwald (167). Marked hypertrophy of the ventricles in the absence of dilatation is characteristic. Commonly, there is disproportionate thickening of the interventricular septum when compared with the free wall of the left ventricle (163). If the ratio of interventricular septal thickness to free wall thickness exceeds 1.3, this is termed asymmetrical septal hypertrophy (ASH). ASH was previously regarded as being pathognomonic of hypertrophic cardiomyopathy. However, it is now recognised that hypertrophy secondary to hypertension may sometimes preferentially affect the septum and that some patients with inherited hypertrophic cardiomyopathy may have symmetrical hypertrophy (168); the diagnosis, therefore, of hypertrophic cardiomyopathy cannot be made on the basis of asymmetric septal hypertrophy alone.

Histologically the condition is characterised by hypertrophied, bizarrely-shaped and abnormally arranged myocytes and attempts have been made to quantify the degree of cellular disorganisation (169). Electron microscopy has demonstrated that this disorganisation and disarray is not restricted to the cellular level but also involves the myofibrils and myofilaments within the myocardial cells (170).

There is some debate as to the distribution of these changes within the ventricle. Maron stated that these abnormalities were common in the septum and rare in the free wall of the left ventricle (170), although this has been questioned in a review of the subject by Olsen (171). In affected areas, foci of disorganised cells are found interspersed in areas of hypertrophied, but otherwise normal, muscle. Such changes were previously thought to be specific for hypertrophic cardiomyopathy. However, it is now recognised that they can occur in other forms of cardiac hypertrophy, including hypertrophy secondary to hypertension or aortic valve disease, although there does appear to be a quantitative relationship between the degree of cellular disorganisation and the underlying disease process, the degree of disorganisation being far greater in hypertrophic cardiomyopathy than in secondary cardiac hypertrophy (169).

Prognosis in hypertrophic cardiomyopathy.

Patients with hypertrophic cardiomyopathy are prediposed to sudden death; indeed this is a common presentation of the condition, the annual rate of sudden death being approximately 3% in adults and 5% in children (172). Post-mortem examination confirms the diagnosis of hypertrophic cardiomyopathy but rarely identifies the cause of death. Various possible mechanisms of sudden death have been suggested including haemodynamic causes, such as dynamic obstruction of the outflow tract in response to a sudden change in preload or afterload and diseases of the conducting system involving either accessory atrio-ventricular bypass pathways, intermittant heart block or sinus arrest (172).

However, it is generally believed that the most likely mechanism of sudden death is the development of ventricular tachycardia followed by ventricular fibrillation. This mechanism was first suggested by Goodwin and Krikler in 1976 (173). Since then, several studies have demonstrated a high prevalence of complex ventricular arrhythmias in patients with hypertrophic cardiomyopathy (3,174). McKenna (3) reported that 28% of patients with hypertrophic cardiomyopathy had at least one episode of ventricular tachycardia during a 72 hour period of ambulatory ECG monitoring. Savage (174) reported a figure of 19% although the lower

prevalence may be because monitoring was for twenty-four rather than forty-eight hours.

The mechanism of ventricular arrhythmia in hypertrophic cardiomyopathy is unknown. The presence of cellular disorganisation itself does not appear to be important since this histological finding is rare in children who die suddenly (172). Histological evidence of myocardial ischaemia, due to inadequate myocardial blood flow, is common even in the absence of coronary disease (175) and may provide a focus for ventricular arrhythmias. James et al suggested that septal clefts might provide a "re-entry" circuit for ventricular arrhythmias (166). Thus there are possible explanations for initiation and propagation of ventricular tachycardia although the precise mechanisms remain to be elucidated.

Whatever the mechanism, two studies have demonstrated a significant link between ventricular tachycardia detected during ambulatory monitoring and subsequent sudden death. This is in contrast to studies of haemodynamic and ECG parameters which were unable to discriminate between survivors and decedents (167). McKenna et al carried out ambulatory ECG monitoring in eighty-six unselected patients with hypertrophic cardiomyopathy, of whom twenty-four had at least one episode of ventricular tachycardia (3). During a mean follow-up period of 2.6 years, seven patients died suddenly of whom five had VT. Thus 21% of the patients

with VT died suddenly compared with 3% of the patients without VT. Maron et al found very similar results in a study of ninety-nine patients (176); sudden death occurred in 24% of patients with and 3% of those without VT. In this study, only VT was associated with sudden death whereas McKenna et al also reported an association, although less strong, between sudden death and both multiform ventricular extrasystoles and ventricular couplets.

Influence of treatment on mortality.

If ventricular arrhythmias are the cause of sudden death in hypertrophic cardiomyopathy, and not merely markers of the condition, then effective anti-arrhythmic therapy should improve prognosis in hypertrophic cardiomyopathy.
Trials involving beta blockers and the calcium antagonist verapamil have failed to show any reduction in the incidence of ventricular arrhythmia.
Furthermore, conventional anti-arrhythmic agents, including quinidine, disopyramide and mexilitene, have been found to be poorly tolerated and unsuccessful in reducing complex ventricular arrhythmias (172).
However, the Class III anti-arrhythmic agent amiodarone has successfully reduced ventricular arrhythmia frequency and early evidence suggests that it does improve prognosis (177).

Hypertrophic cardiomyopathy and hypertensive left ventricular hypertrophy.

There are some similarities between hypertrophic cardiomyopathy and hypertensive left ventricular hypertrophy. Both are characterised by myocardial hypertrophy, subendocardial ischaemia and ultimately myocardial fibrosis; both are associated with sudden death. In hypertrophic cardiomyopathy, there is persuasive evidence to suggest that the mechanism of sudden death is primary ventricular arrhythmia, usually ventricular tachycardia which then degenerates to ventricular fibrillation. Furthermore there is some evidence, although less conclusive, that effective anti-arrhythmic therapy may reduce mortality. In hypertensive left ventricular hypertrophy, there is evidence that left ventricular hypertrophy defined by standard ECG criteria is an independent risk factor for cardiovascular mortality and in particular for sudden death. In other words, LVH is associated with an increased risk that cannot be explained by the presence of hypertension or other associated risk factors.
It is possible, therefore, that the excess risk associated with left ventricular hypertrophy in essential hypertension may be related to ventricular arrhythmia and that, as in hypertrophic cardiomyopathy, such arrhythmias may be related to metabolic and

structural abnormalities associated with hypertrophy itself rather than to co-existent atherosclerotic disease of the major coronary arteries.

CHAPTER 3

AIMS OF THIS THESIS

Broadly, the aim was to investigate a possible mechanism which might explain the high mortality in hypertensive patients with left ventricular hypertrophy.
Since the high mortality associated with this ECG finding in the Glasgow Blood Pressure Clinic was a major stimulus to my studies, I have included a description of the clinic and an analysis of the relationship between electrocardiographic left ventricular hypertrophy, associated risk factors and cardiovascular mortality. During the past eighteen months, I have been one member of a group investigating this relationship with the statistical assistance of Dr. G Murray. Other members of the group include Dr C Isles, Dr FG Dunn, Dr AF Lever, Dr AR Lorimer and Dr HJ Dargie. In this thesis, I have included only those parts of the analysis with which I was closely involved (chapter 4).

The aims of the subsequent studies were as follows:

1. To validate the reporting of LVH in the Glasgow Blood Pressure Clinic. Since mortality data from the Glasgow Blood Pressure Clinic are based on an ECG

reporting system without "standardised" criteria, some form of validation of the electrocardiographic diagnosis of LVH in the Glasgow Blood Pressure Clinic was required; this I have done by calculating the sensitivity and specificity of the ECG reporting system using echocardiography as a "gold standard" for the assessment of hypertrophy (chapter 5).
Having completed this, two further analyses of the ECG and echocardiographic data have been undertaken to attempt to both standardise and improve the ECG diagnosis of LVH (chapter 6):

a) a comparison of the sensitivities and specificities of four commonly used sets of ECG criteria for LVH.

b) analysis of the influence of body build on various ECG criteria for LVH to determine whether knowledge of a patient's height and weight could perhaps be used to improve the ECG diagnosis of LVH.

2. To determine the prevalence of ventricular arrhythmias in hypertensive patients with LVH and to compare this with both a hypertensive control group without ECG LVH and a normotensive control group. If, as in hypertrophic cardiomyopathy, a tendency to ventricular arrhythmia is important in the high mortality associated with LVH, then ventricular arrhythmias might occur more commonly in hypertensives

with ECG LVH than in those without (chapter 7).

3. To examine the influence of diuretic therapy and serum potassium concentration on ventricular arrhythmias in hypertensives with and without left ventricular hypertrophy (chapter 8).

4. To examine the relationship between ventricular arrhythmias and coronary artery disease in hypertensive patients with left ventricular hypertrophy and thus determine whether such arrhythmias are a manifestation of coronary artery disease (chapter 9).

5. To examine the relationship between ventricular arrhythmias and myocardial histology in patients with left ventricular hypertrophy and thus determine whether factors other than coronary artery disease might be important in the genesis of ventricular arrhthmia (chapter 10).

6. To examine the function of the hypertrophied left ventricle with particular reference to ventricular filling; since loss of diastolic compliance is believed to be the major functional abnormality in hypertrophic cardiomyopathy, this may also occur in hypertensive heart disease and may "sensitise" the heart to the effects of an arrhythmia that leads to loss of atrial contraction (chapter 11).

CHAPTER 4

LEFT VENTRICULAR HYPERTROPHY AND MORTALITY IN THE GLASGOW BLOOD PRESSURE CLINIC

Introduction

While the level of blood pressure is an important risk factor for cardiovascular mortality in hypertensive patients, other variables, including cigarette smoking, a history of angina, myocardial infarction or stroke, impaired renal function and ECG evidence of left ventricular hypertrophy, may influence outcome (1,2,178,179). Data from the Framingham study have suggested that ECG LVH with ST-T changes is an independent predictor of outcome while the risk associated with ECG LVH without ST-T changes can be wholly attributed to the associated hypertension (81). The purpose of this study was to examine the relationship between ECG LVH with and without ST-T changes and mortality in the Glasgow Blood Pressure Clinic. The clinic provides an unusual opportunity for an analysis of this type because of the high prevalence of LVH, the high mortality, the long duration of follow-up and the completeness of the mortality data.

Materials and methods

1. Patients

The Glasgow Blood Pressure Clinic was set up in 1968 to record standardised information on hypertensive patients attending four Glasgow hospitals (the Western Infirmary, Glasgow Royal Infirmary, Stobhill Hospital and the Southern General Hospital). Patients are referred either from their general practitioner, other hospitals or other departments within the four main hospitals. Although patients with all grades of hypertension are referred, there is a bias towards those whose hypertension is complicated or is difficult to control. The system of recording information in he clinic has been described previously (1,180) as has the high mortality in clinic patients when compared with other hypertensive groups (1).

Between 1968 and January 1983, 4283 patients were referred to the clinic of whom 3783 had non-malignant hypertension and a diastolic blood presssure greater than 90 mm Hg before treatment. 85% of this group (3216 patients) had an ECG within three months of initial attendance at the clinic. These patients have been followed for a mean of 6.5 years and it is on this group that calculations of risk are based.

2. Blood pressure

Blood pressure was measured using a standard sphygmomanometer in either the lying or seated position. Phase V was taken as diastolic pressure. Average blood pressure for men at entry to the clinic was 181/111 mm Hg falling to 158/96 mm Hg during treatment. Corresponding values for women were 185/109 mm Hg and 161/96 mm Hg.

3. ECG analysis

Standard twelve lead electrocardiograms were recorded at a paper speed of 25 mm/sec. These were then reported by physicians in each of the four hospitals and the presence of left ventricular hypertrophy with or without ST-T changes, myocardial ischaemia and myocardial infarction noted using "conventional" criteria. The criteria, however, were not standardised among the reporting clinicians. (This is discussed in chapter five).

4. Record linkage and mortality data.

To ensure completeness of mortality data, all patients were flagged with the Registrar General for Scotland. Provided that death occurred in the United Kingdom, copies of all relevant death certificates with the

cause of death coded according to the International Classification of Diseases were returned to the clinic. Causes of death were then analysed in five groups using the 9th revision of this classification (181): ischaemic heart disease (codes 410-414), cerebrovascular disease (codes 430-438), other vascular disease (codes 390-456 excluding the above), cancer (codes 140-208 and 235-239) and all other causes (any other code).

5. Statistical methods

Age-specific mortality rates were calculated as deaths/1000 patient years of observation, based on the age at death and on years spent by each patient in each decile (182). Comparison between groups was made using Chi-squared analysis. The relation between LVH and survival was also determined by stepwise multiple regression using the Cox proportional hazards model (183) to control for the possible influence of age, sex, smoking habit, initial blood pressure, past history of vascular disease, raised blood urea, retinal arteriovenous nipping and referral to the clinic before 1976.

Results

1. Prevalence of LVH and relation to blood pressure.

LVH was present in 34.5% of men and 21.5% of women at presentation (table 1). In addition to voltage evidence of LVH, 12.9% of men and 8.9% of women had ST-T changes (the "strain" pattern). While ECG LVH was more common in men, ST-T changes alone were seen more commonly in women. Evidence of myocardial infarction was seen in 6.0% of men and 3.4% of women.

In an analysis confined to patients who were untreated at the time of presentation (n=2664), the prevalence of LVH increased with the height of the initial diastolic blood pressure in both sexes (figure 2) although men had more ECG LVH than women at every level of initial blood pressure. Table 2 shows the mean reduction in diastolic blood pressure between the initial and the final clinic visit for the different ECG categories. Absolute reduction was similar for those with and without LVH, those with LVH having slightly higher final blood pressures than those without.

2. Risk of LVH

The mortality rate and relative risk associated with ECG LVH and other major ECG abnormalities are shown in table 3 (for men) and table 4 (for women). Thus LVH by

TABLE 1

FREQUENCY AND TYPE OF MAJOR ECG ABNORMALITIES

	MEN (n=1609)	WOMEN (n=1609)
NORMAL ECG	34.1%	44.4%
LVH WITHOUT ST-T CHANGES	21.6%	12.6%
LVH WITH ST-T CHANGES	12.9%	8.9%
ST-T CHANGES ONLY	13.2%	17.1%
MYOCARDIAL INFARCTION	6.0%	3.4%

TABLE 2

LEVEL OF INITIAL AND ACHIEVED DIASTOLIC BP IN RELATION TO ECG AT PRESENTATION

ECG ABNORMALITY	INITIAL DBP (mmHg)	ACHIEVED DBP (mmHg)	CHANGE IN DBP (mmHg)
NORMAL	108	94	14
LVH ONLY	114	98	16
LVH AND ST-T CHANGES	116	100	16
ST-T CHANGES ONLY	113	98	15
MYOCARDIAL INFARCTION	114	98	16

Figure 2
Prevalence of ECG LVH in relation to blood pressure at presentation.

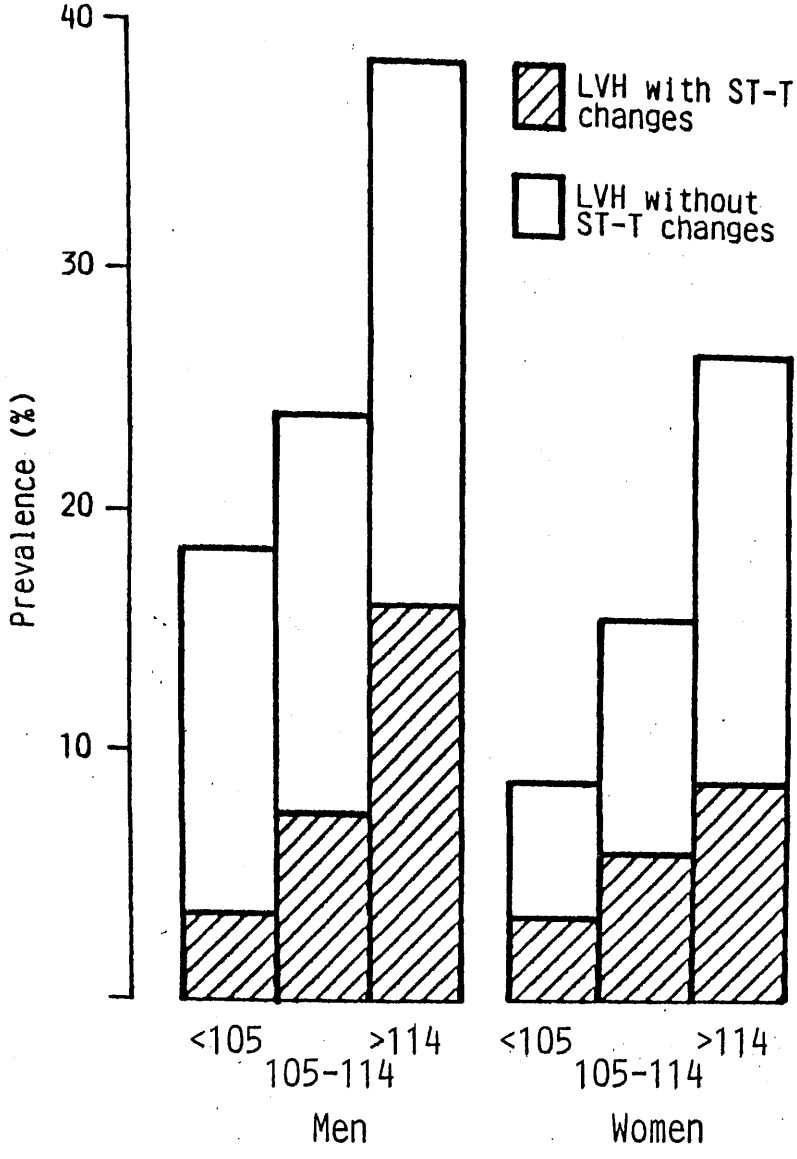


TABLE 3

MORTALITY AND RELATIVE RISK OF LVH AND OTHER ECG ABNORMALITIES IN MEN

	ALL CAUSE				IHD				CVA			
	n	MR	RR	p	n	MR	RR	p	n	MR	RR	p
NORMAL ECG	73	27.6	1.0		19	6.0	1.0		15	7.2	1.0	
LVH WITHOUT ST-T CHANGES	92	43.2	1.6	***	35	16.2	2.7	***	19	13.3	1.8	**
LVH WITH ST-T CHANGES	80	56.9	2.1	***	33	23.8	4.0	***	18	12.5	1.7	*
ST-T CHANGES ONLY	74	46.7	1.7	***	42	27.2	4.5	***	6	3.7	0.5	**
MYOCARDIAL INFARCTION	44	73.1	2.6	***	21	31.9	5.3	***	11	23.5	3.2	**

n = number of deaths
MR = age-adjusted mortality rate (deaths/1000 patient years)
RR = relative risk i.e. mortality rate for a given ECG abnormality divided by mortality rate for a normal ECG

* = $p<0.05$ -
** = $p<0.01$ - compared with a normal ECG
*** = $p<0.001$ -

TABLE 4

MORTALITY AND RELATIVE RISK OF LVH AND OTHER ECG ABNORMALITIES IN WOMEN

	ALL CAUSE				IHD				CVA			
	n	MR	RR	p	n	MR	RR	p	n	MR	RR	p
NORMAL ECG	65	13.7	1.0		24	4.9	1.0		15	3.1	1.0	
LVH WITHOUT ST-T CHANGES	49	33.1	2.4	***	15	9.6	2.0	*	17	12.3	4.0	***
LVH WITH ST-T CHANGES	39	36.2	2.6	**	12	11.5	2.3	*	11	10.1	3.3	**
ST-T CHANGES ONLY	56	22.9	1.6	***	23	9.9	2.0	*	10	4.2	1.4	
MYOCARDIAL INFARCTION	18	39.9	2.9	***	7	19.4	4.0	*	4	6.1	2.0	

n = number of deaths
MR = age-adjusted mortality rate (deaths/1000 patient years)
RR = relative risk i.e. mortality rate for a given ECG abnormality divided by mortality rate for a normal ECG

* = $p<0.05$ -
** = $p<0.01$ - compared with a normal ECG
*** = $p<0.001$ -

voltage alone was associated with a 57% increase in mortality in men (27.6 vs 43.2 deaths per thousand patient years, $p<0.001$) and a 142% increase in women (13.7 vs 33.1 deaths per thousand patient years, $p<0.001$). LVH with ST-T changes was associated with an even greater increase in mortality, the rate being 56.9 per thousand patient years for men and 36.2 per thousand patient years for women. The highest mortality rates for both sexes were seen in patients with ECG evidence of myocardial infarction (73.1 and 39.9 per thousand patient years respectively) but the contribution of LVH to total mortality in the clinic was greater than that of myocardial infarction because it was more common. As expected, the increased risk was largely confined to vascular causes of death.

The "independence" of LVH as a risk factor was then tested by regression analysis using the Cox proportional hazards model. Initially, the following covariates were tested by univariate analysis for their relation to mortality: age, smoking habit, past history of vascular disease, referral to the clinic before 1976, initial mean arterial blood pressure, retinal arteriovenous nipping, raised blood urea and ECG LVH with and without ST-T changes. Retinal arteriovenous nipping and referral to the clinic before 1976 were included because both had emerged as risk factors in a previous analysis from the Glasgow Blood Pressure Clinic (1). In univariate analyses, all were

significantly related to outcome in both sexes ($p<0.001$).

Controlling for mean arterial blood pressure at presentation, the relative risk associated with ECG LVH (compared to patients with a normal ECG) was 1.80 for men and 1.97 for women; relative risk for those with LVH and ST-T changes was 2.87 for men and 2.09 for women. Furthermore, 95% confidence limits drawn around these values did not cross unity in any of the four groups analysed (figure 3). When multivariate analysis was repeated controlling simultaneously for age, mean arterial blood pressure at presentation, smoking habit, previous vascular disease and raised blood pressure, LVH, both with or without ST-T changes, again emerged as a strong and independent risk factor for mortality (figure 4).

Discussion

The first main finding was that LVH with or without ST-T changes was common among patients referred to the clinic, being present in no fewer than one-third of the men and one-fifth of the women. The high prevalence contrasts with the much lower rates found in general population surveys such as Framingham (2) and in large groups of patients with mild to moderate hypertension (184,185). This presumably reflects referral to the clinic of patients with more severe, more resistant, or

more complicated forms of hypertension. In this study, the prevalence of LVH was related to the height of the initial blood pressure as was the case in the Framingham and HDFP studies (2,184). LVH was more common in men but higher blood pressure was not the explanation. Men must develop more ECG LVH than women for some other reason, therefore. Differences in body build affect ECG voltages, particularly when praecordial leads are used. In general, women have more centrally distributed fat than than men and this may reduce the sensitivity of the ECG for detection of LVH in women. In support of this, the sex difference in LVH prevalence is much less marked when LVH is assessed echocardiographically (85).

The second main finding relates to the risk associated with LVH. Mortality in the clinic has previously been noted to be high (1), but patients with ECG LVH when first seen were twice as likely to die as those without LVH. This was true for men and women separately (tables 3 and 4) and although absolute mortality was greater in men, relative risk was the same for both sexes. LVH with ST-T changes was associated with a high mortality risk almost comparable to that of a previous myocardial infarction. Multivariate analysis confirmed that LVH with or without ST-T changes was a highly significant and independent predictor of outcome. This is in contrast to the Framingham data which showed that while "definite" LVH (LVH with ST-T changes) was an

Figure 3

Relative hazard with 95% confidence limits of ECG LVH with and without ST-T changes compared with a normal ECG controlling for initial blood pressure.

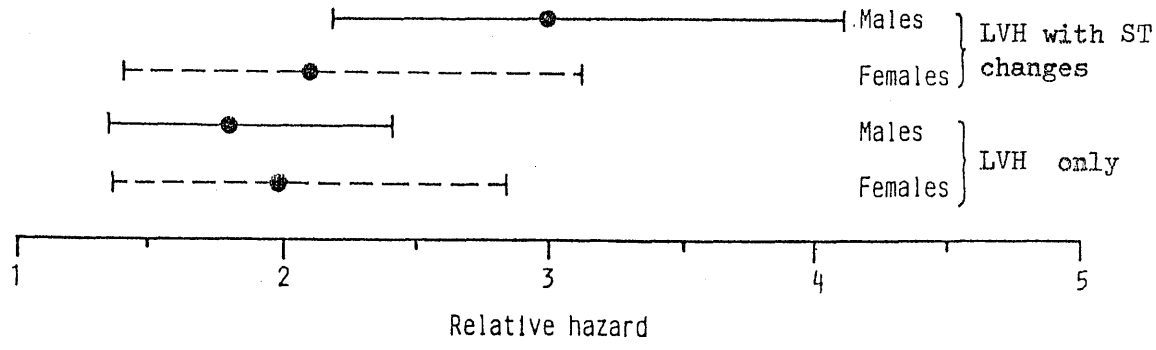
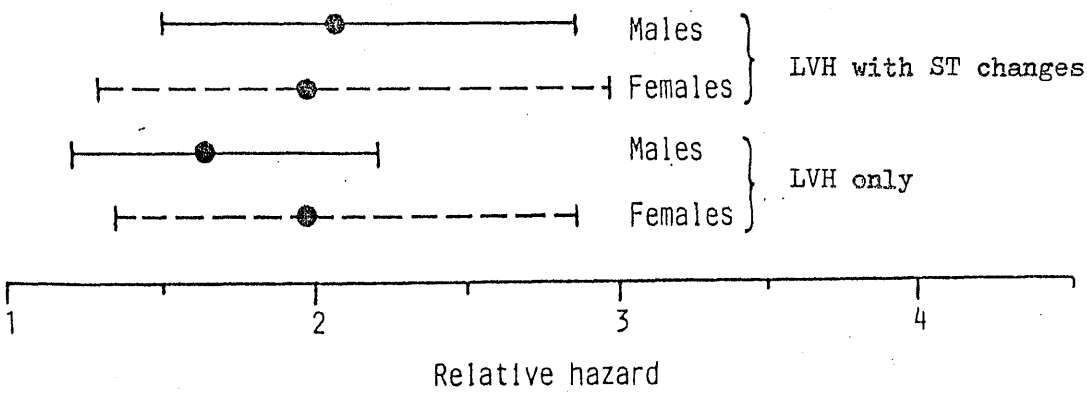


FIGURE 4

Relative hazard with 95% confidence limits of ECG LVH with and without ST-T changes compared with a normal ECG controlling for initial blood pressure and other risk factors (see text for details).



more complicated forms of hypertension. In this study, the prevalence of LVH was related to the height of the initial blood pressure as was the case in the Framingham and HDFP studies (2,184). LVH was more common in men but higher blood pressure was not the explanation. Men must develop more ECG LVH than women for some other reason, therefore. Differences in body build affect ECG voltages, particularly when praecordial leads are used. In general, women have more centrally distributed fat than than men and this may reduce the sensitivity of the ECG for detection of LVH in women. In support of this, the sex difference in LVH prevalence is much less marked when LVH is assessed echocardiographically (85).

The second main finding relates to the risk associated with LVH. Mortality in the clinic has previously been noted to be high (1), but patients with ECG LVH when first seen were twice as likely to die as those without LVH. This was true for men and women separately (tables 3 and 4) and although absolute mortality was greater in men, relative risk was the same for both sexes. LVH with ST-T changes was associated with a high mortality risk almost comparable to that of a previous myocardial infarction. Multivariate analysis confirmed that LVH with or without ST-T changes was a highly significant and independent predictor of outcome. This is in contrast to the Framingham data which showed that while "definite" LVH (LVH with ST-T changes) was an

independent risk factor for mortality, "possible" LVH (LVH without ST-T changes) was not associated with a risk in excess of that attributable to hypertension alone (81). A limitation of the multivariate analysis is that it controls for initial rather than achieved arterial pressure. However, as table 2 demonstrates, the mean absolute reduction in blood pressure was similar for those with and without LVH and thus it seems likely that the relative risk of LVH would be unaffected had it been possible to control for achieved, as well as initial, blood pressure.

Why LVH should be an independent risk factor for mortality is not known. Since it is independent of the major risk factors for coronary artery disease, namely cigarette smoking, high blood pressure and cholesterol, we must postulate either that LVH itself accelerates the process of coronary atherosclerosis or that LVH is contributing to mortality through a mechanism other than coronary artery disease and myocardial infarction.

In conclusion, ECG LVH is common in patients from the Glasgow Blood Pressure Clinic and is associated with a high mortality that is in excess of that attributable to other co-existent risk factors. The mechanism of this excess risk is unknown.

CHAPTER 5

ECHOCARDIOGRAPHIC VALIDATION OF ECG REPORTING IN THE GLASGOW BLOOD PRESSURE CLINIC.

Introduction

The analysis of mortality in the Glasgow Blood Pressure Clinic with respect to ECG LVH was based on the original ECG reports made by a number of junior and senior physicians over a period of almost twenty years using "conventional" but not standardised criteria for left ventricular hypertrophy. It was necessary, therefore, that some form of validation of this reporting system be carried out before firmly accepting the findings. Echocardiography is now regarded as the "gold standard" for assessment of left ventricular hypertrophy in vivo and thus it was used to calculate the sensitivity and specificity of the "routine" ECG reporting service for the diagnosis of LVH.

Materials and methods

Before examining the hypertensive subjects, it was necessary first to define a normal range for left ventricular mass based on a normotensive control population. Since myocardial mass is generally greater in men than in women and also varies with body build,

the normal range was defined in terms of left ventricular mass index (expressed as g/m2 body surface area) for men and women separately.
In total, one hundred and fifty subjects, comprising fifty normal controls and one hundred hypertensive patients were studied. The subjects were derived from "screening" of fifty-nine normal controls and one hundred and twenty-one hypertensives, the remainder being excluded usually because of inability to obtain an echocardiogram of sufficient quality for analysis.

Study groups

1. Control group

This comprised fifty normal subjects, the majority being either employees of the hospital or ambulance service or friends or relatives of members of the cardiac department. None had a history of current cardiac symptoms or of previous cardiac disease. None had a history of hypertension or were taking antihypertensive medication. In view of the wide range of blood pressures found in any "normal" population, it was decided that individuals should be excluded only if their supine blood pressure, after resting for at least ten minutes, exceeded 160 mm Hg systolic or 105 mm Hg diastolic; this did not apply to any of the fifty controls. However, subjects were excluded if the

resting electrocardiogram showed evidence of left ventricular hypertrophy; four of the fifty-nine subjects screened were excluded for this reason. Baseline data, relating to age, sex and blood pressure levels for the fifty controls are given in table 5.

2. Hypertensive group

One hundred hypertensive patients were studied. For the purposes of the study on arrhythmia frequency (to be described in chapter 7), two matched groups of hypertensives were studied. Thus fifty patients had ECG evidence of left ventricular hypertrophy by the criteria of Sokolow and Lyon ($SV1+RV5 \geq 35mm$)(65) and fifty did not. The majority (seventy-eight patients) attended the Glasgow Blood Pressure Clinic at the Western Infirmary and the remaining twenty-two attended the cardiology outpatient clinic also at the Western Infirmary. All one hundred had essential hypertension; none had a history or electrocardiographic changes of myocardial infarction or bundle branch block and none had clinical evidence of valvular heart disease. Baseline data relating to age, sex and blood pressure levels for the two hypertensive groups are shown in tables 6 and 7. An important feature of the study of arrhythmia prevalence was that the hypertensive groups with and without ECG LVH should be matched for both initial and achieved blood pressure. Initial (i.e.

pre-treatment) blood pressure readings were obtained from the Glasgow Blood Pressure Clinic records and from the clinic referral letters for those patients attending the cardiac clinic. Each patient in the group with ECG LVH was matched with a hypertensive without LVH for age (within five year age bands), smoking habit (current smoker or non-smoker), initial systolic blood pressure (within 10 mm Hg) and achieved systolic blood pressure (within 5 mm Hg). In addition, the two hypertensive groups were matched in the same way with the control group for age, sex and smoking habit. All of the hypertensives were receiving regular antihypertensive medication which included one or more of beta blocker, diuretic and vasodilator; treatment was continued throughout the period of investigation. The baseline data for the hypertensive and control groups are summarised in table 8. There were no significant differences in age, sex distribution or smoking habit between the groups. Blood pressure levels, despite treatment, were higher in the hypertensive groups than in the controls.

Methods

1. Blood Pressure

Systolic and diastolic blood pressure was measured in all one hundred and fifty subjects after ten minutes

TABLE 5

BASELINE DATA - NORMAL CONTROLS

SUBJECT NUMBER	AGE (years)	SEX	SBP (mm Hg)	DBP (mm Hg)
1	55	F	120	73
2	26	F	116	89
3	64	F	122	76
4	48	F	128	87
5	43	F	134	90
6	54	F	136	76
7	45	F	110	70
8	32	M	106	77
9	52	F	110	80
10	41	M	116	86
11	32	M	118	86
12	67	M	132	82
13	33	M	92	64
14	61	M	144	88
15	76	M	156	92
16	65	M	124	78
17	64	M	128	84
18	62	M	110	76
19	50	M	132	98
20	63	M	134	76
21	44	M	158	84
22	68	M	98	82
23	53	M	120	76
24	45	M	126	94
25	67	F	136	94
26	51	M	124	80
27	69	F	102	68
28	76	M	132	76
29	52	M	157	84
30	42	M	118	80
31	50	M	159	94
32	56	M	132	88
33	53	M	160	98
34	57	M	158	98
35	57	M	156	92
36	54	F	134	78
37	73	M	135	88
38	59	M	122	86
39	58	F	112	65
40	30	F	110	74
41	76	M	134	84
42	68	M	128	79
43	73	M	138	90
44	71	M	139	82
45	69	F	122	78
46	69	F	118	74
47	68	M	130	84
48	67	F	137	94
49	74	M	140	102
50	66	M	136	84

SBP = SYS. BLOOD PRESSURE (mmHg)
DBP = DIA. BLOOD PRESSURE (mmHg)

TABLE 6

BASELINE DATA - HYPERTENSIVES WITHOUT ECG LVH

NO.	SEX	AGE	INITIAL BP (mm Hg) SBP	INITIAL BP (mm Hg) DBP	ACHIEVED BP (mm Hg) SBP	ACHIEVED BP (mm Hg) DBP	DURATION OF THERAPY (YEARS)
51	F	67	201	70	138	94	3
52	M	67	200	130	156	82	6
53	M	58	152	98	132	94	11
54	M	64	166	98	150	88	4
55	F	54	204	107	158	92	10
56	M	61	154	86	128	94	4
57	M	69	200	115	164	90	10
58	M	68	208	108	164	70	3
59	M	29	146	90	145	103	4
60	M	71	152	88	134	88	11
61	F	62	260	114	154	92	4
62	M	59	187	110	168	84	2
63	F	36	195	116	165	88	6
64	M	62	210	108	136	90	6
65	M	58	180	88	148	86	10
66	M	48	182	92	192	92	3
67	M	64	190	80	188	80	5
68	F	58	200	110	126	82	2
69	F	63	190	118	128	86	3
70	F	77	170	96	176	81	11
71	F	76	164	92	212	92	4
72	F	42	194	90	161	65	11
73	M	32	164	104	162	104	11
74	M	59	156	103	132	78	5
75	F	44	162	108	126	68	8
76	M	39	170	104	128	92	9
77	M	32	174	117	140	80	7
78	M	79	210	100	164	92	10
79	M	71	190	140	176	82	4
80	M	58	149	81	158	85	10
81	F	60	150	95	158	88	2
82	M	57	172	108	136	74	2
83	F	65	179	87	172	92	5
84	M	65	212	110	168	86	11
85	F	50	150	86	128	82	6
86	M	43	210	136	154	82	2
87	M	47	184	112	160	94	2
88	F	46	182	108	168	94	12
89	F	67	210	130	146	94	3
90	M	55	178	106	142	94	10
91	M	57	186	108	148	98	8
92	M	74	185	100	150	92	1
93	M	77	173	108	154	96	3
94	M	55	196	86	170	98	7
95	M	59	150	100	156	104	6
96	F	62	160	106	140	92	10
97	M	64	158	107	170	100	6
98	F	66	200	110	145	90	5
99	F	54	220	144	190	85	10
100	F	58	185	116	165	92	1

TABLE 7

BASELINE DATA - HYPERTENSIVES WITH ECG LVH

NUMBER	SEX	AGE (YEARS)	INITIAL BP (mm Hg) SBP	INITIAL BP (mm Hg) DBP	ACHIEVED BP (mm Hg) SBP	ACHIEVED BP (mm Hg) DBP	DURATION OF THERAPY (YEARS)
101	M	68	223	111	210	104	12
102	M	62	165	95	142	90	1
103	M	55	155	100	150	78	6
104	F	65	175	105	130	77	1
105	M	66	210	120	177	86	9
106	F	77	182	100	166	100	9
107	M	54	168	106	170	95	2
108	M	65	184	110	174	90	4
109	M	55	176	104	152	100	4
110	M	55	150	90	174	94	2
111	F	70	154	102	240	105	10
112	M	65	167	108	135	80	1
113	M	36	164	82	144	82	9
114	M	54	210	106	164	84	3
115	M	62	160	95	160	82	11
116	M	62	183	92	178	100	10
117	M	31	150	92	136	90	10
118	M	59	150	92	160	92	8
119	M	30	174	70	136	84	2
120	M	58	190	104	190	94	12
121	F	57	238	84	192	95	4
122	M	58	192	114	180	76	11
123	M	29	166	116	154	108	8
124	M	71	202	108	192	104	1
125	M	65	192	99	164	88	5
126	F	67	236	110	206	102	5
127	M	70	200	110	168	107	3
128	M	71	172	108	172	92	5
129	M	60	170	110	134	92	12
130	F	73	182	115	165	96	4
131	F	61	158	98	136	92	1
132	M	67	180	92	160	86	9
132	M	67	200	100	144	72	6
134	M	60	194	102	138	92	5
135	M	57	174	113	132	90	7
136	M	68	166	106	134	82	3
137	F	74	190	110	190	90	10
138	M	72	175	81	170	90	3
139	F	71	210	95	175	110	1
140	F	66	210	100	206	106	6
141	M	59	180	98	154	98	2
142	F	62	167	108	150	80	11
143	M	51	160	106	130	110	7
144	M	52	170	103	168	94	12
145	M	41	170	92	160	94	2
146	M	50	174	90	140	78	7
147	F	74	160	110	165	90	10
148	M	61	152	84	120	90	8
149	M	62	155	85	155	80	4
150	M	29	188	116	145	74	4

TABLE 8

CHARACTERISTICS OF CONTROL SUBJECTS AND HYPERTENSIVE PATIENTS

	NORMOTENSIVE CONTROLS	HYPERTENSIVES WITHOUT ECG LVH	HYPERTENSIVES WITH ECG LVH
	(n=50)	(n=50)	(n=50)
AGE (YEARS)	57±2	58±2	59±2
M:F RATIO	34:16	31:19	34:16
INITIAL SYS BP (mm Hg)	-	182±4	179±4
INITIAL DIA BP (mm Hg)	-	104±2 **	101±2 **
ACHIEVED SYS BP (mm Hg)	129±2	155±3 **	162±3 **
ACHIEVED DIA BP (mm Hg)	83±2	88±2	91±3
DURATION OF THERAPY (years)	-	6.2±0.5	6.0±0.5
SMOKERS	58%	52%	42%
HEIGHT (cm)	168±1	167±2	168±2
WEIGHT (kg)	71±2	73±2	72±1

** $p<0.01$ - difference from controls

recumbency using a "Hawksley" random zero sphygmomanometer.

2. Electrocardiograms

Standard 12 lead electrocardiograms were recorded with a paper speed of 25 mm/sec and standardisation of 1mV/cm. The ECGs were sent for reporting in the routine non-standardized manner and the report coded as in the Glasgow Blood Pressure Clinic office. Since the purpose of this analysis was to examine the validity of ECG reporting of LVH, the coding system described here has been simplified as follows to exclude other diagnoses:

1 = no ECG LVH

2 = ECG LVH without ST-T changes

3 = ECG LVH with ST-T changes

3. Echocardiograms

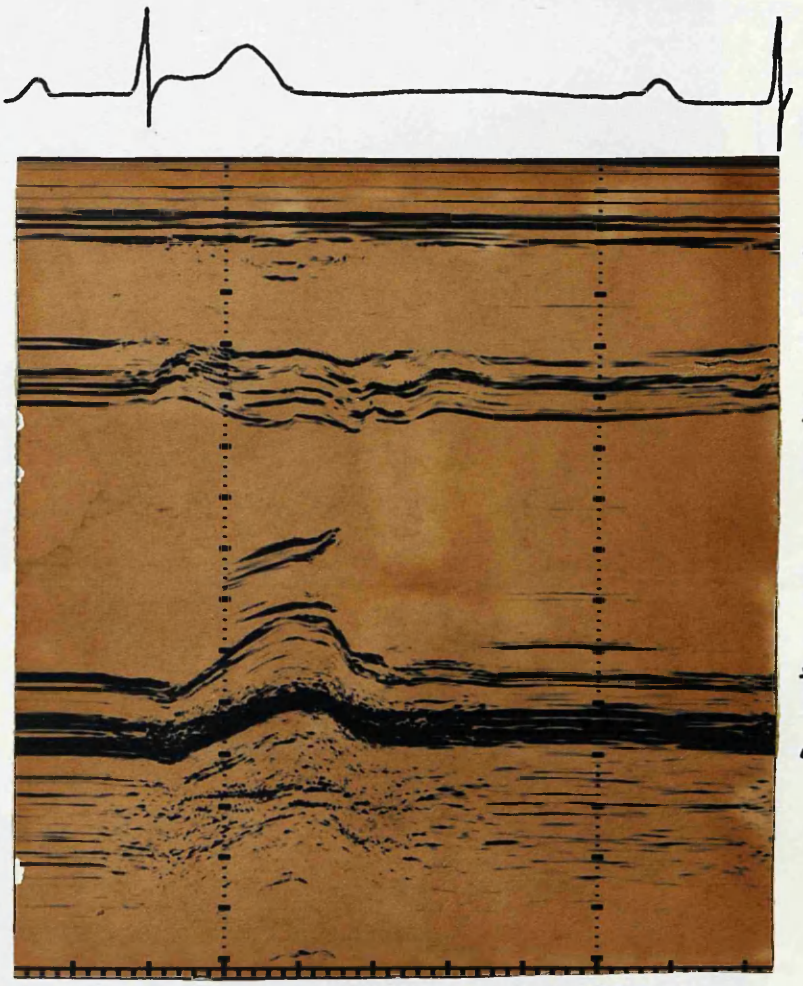
Echocardiography was carried out using an "IREX SYSTEM III" phased array ultrasound unit with a 2.5 MHz transducer and an aperture size of 16 mm. All echocardiograms were recorded by myself. M-mode recordings were made on six inch light-sensitive paper with a paper speed of 50 mm/sec. The ECG was recorded simultaneously. The two dimensional echocardiogram

image was used to position the M-mode cursor appropriately. The recordings were coded for later analysis so that the electrocardiographic characteristics of the subject were not known to me at the time of analysis. Analysis was performed using a digitising tablet (KONTRON Ltd) and a micro-computer. In addition, the reproducibility of echocardiographic measurements was assessed and both intra- and inter-observer variability in the calculation of left ventricular mass were estimated.
The measurements taken and calculations made were as follows:

(a) Left ventricular dimensions

Left ventricular posterior wall thickness (LVPW), interventricular septal thickness (IVS) and left ventricular cavity diameter (LVCD) were all measured distal to the tips of the mitral valve leaflets. All measurements were made at end-diastole which was taken to be the peak of the 'R' wave on the ECG. The measured septal thickness included contributions from both right and left ventricular endocardium while the measured left ventricular wall thickness included left ventricular endocardium. Measurements were made over three consecutive cardiac cycles and mean values calculated. Figure 5 shows an M-mode recording from a normal subject illustrating the interventricular

Figure 5
M-mode echocardiogram through the left ventricle distal to the tips of the mitral valve leaflets



septum, the left ventricular cavity and the left ventricular posterior wall.

(b) Left ventricular mass

As discussed earlier, several methods have been described for the calculation of left ventricular mass. In this analysis, the method used was the cube formula incorporating the Penn convention as described by Devereux (75). This method is currently the most widely used for estimation of left ventricular mass and has been validated against actual left ventricular weight in a post-mortem study (75).
The formula is as follows:

$$\text{LV mass (g)} = 1.04((\text{IVSD}+\text{LVPWD}+\text{LVEDD})^3 - (\text{LVEDD})^3)$$

where 1.04 = density of myocardium
IVSD = interventricular septal thickness
LVPWD = left ventricular posterior wall thickness
LVEDD = left ventricular internal diameter

These measurements are not the same as in (a) but are made using the "Penn" convention in which endocardial echoes are excluded from the wall thickness measurements; calculations using this convention have been shown to correlate well with left ventricular weight at post-mortem (75).

Thus,

IVSD = septal thickness excluding right and left ventricular endocardial echoes

LVPWD = posterior wall thickness excluding endocardial and epicardial echoes

LVEDD = left ventricular internal diameter including the septal and posterior wall endocardial echoes

Examples of M-mode echocardiograms from normal and hypertensive subjects are illustrated in figure 6. Measurements were again made over three consecutive cardiac cycles and mean values calculated. The left ventricular mass index was used to define echocardiographic LVH. This was obtained by dividing the left ventricular mass by the body surface area, estimated from height and weight using standard reference tables (186). Baseline data including left ventricular mass and left ventricular mass index values for the three groups are shown in tables 9, 10 and 11. Using the data from table 9, upper limits of normal, equivalent to the mean plus two standard deviations, of 145 g/m2 for men and 110 g/m2 for women were derived. These are close to the values reported in other series (32).

TABLE 9

LEFT VENTRICULAR MASS AND MASS INDEX - NORMAL CONTROLS

NUMBER	HEIGHT (cm)	WEIGHT (kg)	BODY SURFACE AREA (m2)	LV MASS (g)	LVMI (g/m2)
1	158	71.2	1.81	139	76.9
2	160	53.7	1.55	102	65.6
3	155	58.0	1.61	145	90.3
4	153	40.8	1.32	113	85.8
5	156	71.7	1.81	138	76.3
6	164	63.0	1.71	127	74.3
7	160	61.0	1.67	132	79.2
8	178	79.5	1.99	214	107.6
9	157	57.1	1.60	139	87.4
10	170	72.7	1.87	196	104.9
11	182	71.9	1.90	214	112.9
12	171	60.2	1.69	66	39.1
13	170	72.7	1.87	125	66.9
14	179	78.4	1.98	206	104.2
15	166	72.0	1.85	194	105.1
16	180	78.2	1.98	138	69.8
17	152	75.2	1.84	214	116.3
18	172	74.0	1.89	188	99.3
19	173	87.4	2.08	187	90.0
20	182	78.0	1.98	244	123.1
21	178	74.4	1.92	201	104.7
22	180	75.8	1.95	130	66.8
23	180	76.2	1.95	207	106.1
24	184	76.2	1.96	147	75.1
25	164	77.2	1.62	133	82.0
26	176	74.6	1.92	186	97.2
27	179	65.8	1.80	177	98.5
28	162	64.0	1.72	205	119.6
29	163	59.0	1.65	212	128.8
30	170	69.0	1.82	186	102.4
31	182	99.3	2.26	160	70.9
32	166	71.6	1.84	189	102.7
33	165	67.1	1.77	110	62.2
34	187	88.4	2.14	210	98.1
35	170	53.5	1.58	234	148.0
36	152	79.0	1.61	187	116.0
37	179	65.8	1.80	102	56.8
38	173	91.6	2.13	213	99.9
39	142	86.0	1.53	92	59.9
40	144	43.8	1.35	111	82.9
41	174	76.2	1.93	256	132.8
42	176	76.3	1.94	209	108.4
43	168	69.1	1.81	220	121.6
44	168	70.9	1.84	173	94.1
45	155	61.1	1.65	165	69.1
46	159	55.8	1.59	214	94.8
47	171	75.5	1.90	165	86.6
48	155	71.3	1.65	117	70.8
49	167	68.6	1.64	165	100.4
50	168	70.9	1.84	154	83.9

TABLE 10

PERCENTAGE IDEAL WEIGHT AND LEFT VENTRICULAR MASS INDEX

HYPERTENSIVES WITHOUT ECG LVH

NUMBER	HEIGHT (cm)	WEIGHT (kg)	% IDEAL WEIGHT	LV MASS (g)	LVMI (g/m2)
51	149	88.2	172	240	120
52	168	88.4	172	332	160
53	167	65.3	107	227	130
54	168	73.5	115	325	174
55	166	73.4	124	183	98
56	177	75.8	106	150	78
57	173	71.0	106	118	64
58	177	68.0	96	180	99
59	168	61.6	96	160	94
60	174	82.2	123	202	100
61	139	86.2	164	317	159
62	175	74.3	106	392	205
63	157	55.4	104	164	104
64	180	96.2	133	384	173
65	174	72.2	108	165	88
66	177	89.8	126	292	137
67	173	92.5	139	271	127
68	160	63.8	116	137	80
69	167	61.4	103	93	55
70	158	74.0	138	241	131
71	147	54.0	112	122	80
72	157	64.4	119	148	87
73	177	88.2	124	196	93
74	181	90.6	125	217	101
75	160	54.0	96	137	88
76	187	95.6	120	128	57
77	161	53.8	91	89	57
78	166	61.2	96	299	177
79	175	77.6	110	243	124
80	165	70.2	110	277	152
81	167	75.0	125	110	58
82	162	77.0	129	280	147
83	167	76.8	130	129	67
84	184	85.3	115	209	100
85	159	60.6	110	203	123
86	164	85.5	143	132	65
87	166	92.0	145	291	137
88	165	80.0	136	143	73
89	157	79.4	148	229	119
90	170	85.6	136	183	90
91	179	85.4	128	219	106
92	178	75.2	144	268	146
93	166	98.0	170	113	52
94	169	63.4	100	176	102
95	152	64.0	122	310	184
96	155	63.0	120	193	115
97	167	81.6	126	321	162
98	161	75.4	137	184	98
99	152	74.5	143	438	239
100	167	64.2	107	172	99

TABLE 11

LEFT VENTRICULAR MASS AND MASS INDEX

HYPERTENSIVES WITH ECG LVH

NO.	HEIGHT (cm)	WEIGHT (kg)	% IDEAL WEIGHT	LV MASS (g)	LVMI (g/m2)
101	171	72.4	109	401	215
102	173	75.6	111	446	232
103	161	68.5	116	450	253
104	154	52.7	101	330	217
105	172	89.4	134	386	184
106	180	89.4	134	226	106
107	180	87.2	121	206	98
108	149	58.0	126	332	156
109	168	71.4	112	260	141
110	171	75.6	116	438	229
111	165	71.0	120	353	193
112	152	60.0	109	302	186
113	181	64.0	88	235	132
114	161	73.0	124	181	98
115	189	88.0	136	476	199
116	165	81.2	133	330	168
117	167	51.4	79	231	150
118	181	85.6	118	269	129
119	157	54.6	95	99	129
120	178	74.2	104	308	161
121	158	75.0	139	494	266
122	160	47.6	79	200	137
123	172	55.6	85	598	370
124	176	70.8	101	361	194
125	178	88.3	124	511	243
126	155	91.2	173	489	238
127	161	64.0	108	362	211
128	172	86.0	128	367	179
129	187	86.4	109	506	240
130	153	69.5	133	191	108
131	158	67.6	126	248	141
132	157	71.3	123	245	136
133	167	66.4	104	369	209
134	182	74.0	101	337	175
135	167	61.8	95	292	164
136	175	75.6	108	500	260
137	161	67.8	120	387	219
138	177	72.0	100	469	249
139	151	56.0	109	232	148
140	162	73.8	128	199	107
141	189	102.0	146	465	194
142	159	57.1	104	324	115
143	176	71.6	102	367	154
144	166	85.6	140	500	247
145	169	77.0	120	391	203
146	168	89.0	139	355	171
147	156	66.4	126	206	119
148	172	80.2	120	812	410
149	165	63.0	103	375	219
150	176	69.8	100	563	305

(c) Validation of echocardiographic measurements

In this study, it was not possible to calculate the precision of echocardiographic estimation of left ventricular mass since this would require knowledge of actual left ventricular weight.

However, we did assess the reproducibility of the technique. First, the reproducibility of acquiring the echocardiographic tracing was assessed by recording M-mode images across the left ventricle in the left parasternal view from a single subject on ten separate occasions over a period of three days. All tracings were recorded by one observer (JMM) and analysed by a second observer (AD) for septal thickness, posterior wall thickness, left ventricular cavity diameter and left ventricular mass as described above.

The results are shown in table 12. Thus the coefficient of variation (standard deviation divided by the mean and expressed as a percentage) was approximatly 6% for estimation of septal thickness, 3% for left ventricular end-diastolic diameter, 8% for posterior wall thickness and 3% for calculated left ventricular mass. On reviewing the tracings in the light of these results, it appeared that variation in the placement of the M-mode cursor with respect to the tips of the mitral valve leaflets accounted for much of the variability in the measured septal and posterior wall thickness.

We then assessed the intra- and inter-observer

TABLE 12

REPRODUCIBILITY OF ECHOCARDIOGRAPHIC MEASUREMENTS IN A SINGLE SUBJECT

NO.	IVS (cm)	LVEDD (cm)	LVPW (cm)	LV MASS (g)
1	1.47	4.58	0.69	175.4
2	1.51	4.48	0.61	171.0
3	1.31	4.44	0.76	164.3
4	1.42	4.51	0.69	165.6
5	1.54	4.52	0.66	171.8
6	1.60	4.13	0.77	163.6
7	1.41	4.54	0.60	160.7
8	1.51	4.42	0.66	169.5
9	1.53	4.39	0.65	168.3
10	1.33	4.68	0.72	175.1
MEAN	1.463	4.469	0.681	168.5
S.D.	0.094	0.146	0.057	4.95
COEFFICIENT OF VARIATION	6.4%	3.3%	8.3%	2.9%

IVS = INTERVENTRICULAR SEPTUM
LVEDD = LEFT VENTRICULAR END-DIASTOLIC DIAMETER
LVPW = LEFT VENTRICULAR POSTERIOR WALL THICKNESS

TABLE 13

CALCULATION OF LEFT VENTRICULAR MASS

ESTIMATION OF INTRA-OBSERVER VARIABILITY

NUMBER	OBSERVER A (FIRST)	OBSERVER A (SECOND)	FIRST - SECOND	DIFFERENCE SQUARED
1	139	128	11	121
2	102	94	8	64
3	145	107	38	1444
4	113	115	-2	4
5	138	153	-15	225
6	127	126	1	1
7	132	149	-17	289
8	214	203	11	121
9	139	137	2	4
10	196	175	21	441
11	240	224	16	256
12	332	341	-9	81
13	227	251	-24	576
14	325	302	23	529
15	183	194	-11	121
16	150	153	-3	9
17	118	116	2	4
18	180	164	16	256
19	160	153	7	49
20	202	228	-26	676
21	410	383	27	729
22	446	453	-7	49
23	450	438	12	144
24	330	358	-28	784
25	386	390	-4	16
26	226	243	-17	289
27	206	218	-12	144
28	232	230	2	4
29	260	253	7	49
30	438	407	31	961
TOTAL	13832		60	8440
MEAN	231		1	

's' SQUARED (DIFFERENCE SQUARED/2n) = 8440/(2x30) = 140.7

's' = 11.9

COEFFICIENT OF VARIATION (SD/MEAN) = (11.9/231) X 100% = 5.2%

TABLE 14

CALCULATION OF LEFT VENTRICULAR MASS

ESTIMATION OF INTER-OBSERVER VARIABILITY

NUMBER	OBSERVER A	OBSERVER B	FIRST - SECOND	DIFFERENCE SQUARED
1	139	110	29	841
2	102	88	14	196
3	145	167	-22	484
4	113	135	-22	484
5	138	136	2	4
6	127	147	-20	400
7	132	146	-14	196
8	214	193	21	441
9	139	144	-5	25
10	196	220	-24	576
11	240	159	81	6561
12	332	307	25	625
13	227	249	-22	484
14	325	313	12	144
15	183	188	-5	25
16	150	141	9	81
17	118	98	20	400
18	180	163	17	289
19	160	154	6	36
20	202	186	16	256
21	410	435	-25	625
22	446	407	39	1521
23	450	482	-32	1024
24	330	347	-17	289
25	386	371	15	225
26	226	245	-19	361
27	206	267	-61	3721
28	232	208	24	576
29	260	241	19	361
30	438	454	-16	256
TOTAL	13847		45	21507
MEAN	231		0.75	

's' SQUARED (DIFFERENCE SQUARED/2n) = 21507/(2x30) = 358.5

's' = 18.9

COEFFICIENT OF VARIATION (SD/MEAN) = (18.9/231) X 100% = 8.2%

variability for calculation of left ventricular mass in a sample of thirty of the original one hundred and fifty tracings comprising ten from normal controls, ten from hypertensives without ECG LVH and ten from patients with ECG LVH. Each subgroup of ten patients was selected at random from the original cohorts of fifty normal controls, fifty hypertensives without ECG LVH and fifty hypertensives with ECG LVH. The thirty tracings were then analysed on two further occasions, once by the original observer (JMM) and once by a second observer who was unaware of the results of previous analyses. The results are shown in tables 13 (intra-observer variability) and 14 (inter-observer variability). Thus the coefficient of variation was 5.2% for a second analysis of the tracing by the same observer and 8.2% for analysis by a second observer. We concluded that our echocardiographic measurements were sufficiently reproducible to be employed for the validation of the electrocardiographic diagnosis of left ventricular hypertrophy.

4. Calculation of sensitivity and specificity

The sensitivity and specificity values for the ECG reporting system were then calculated as follows:

$$\text{sensitivity (\%)} = \frac{TP}{TP + FN} \times 100$$

$$\text{specificity (\%)} = \frac{TN}{TN + FP} \times 100$$

where:

TP = true positive = ECG +ve, ECHO +ve

FP = false positive = ECG +ve, ECHO -ve

TN = true negative = ECG -ve, ECHO -ve

FN = false negative = ECG -ve, ECHO +ve

Thus, for example, patients were considered to be "true positives" if they had an elevated left ventricular mass index (> 145g/sq. metre for males and >110g/sq. metre for females) and fulfilled the appropriate ECG criteria.

Results

All parametric data (age, blood pressure, echocardiographic measurements etc.) are expressed as mean + S.E.M. and differences between groups calculated using a two-tailed t-test for unpaired data. Differences in non-parametric data (sex ratio, smoking habit, etc.) are calculated using a Chi-squared test. The echocardiographic dimensions of the two

hypertensive groups and the normal control subjects are summarised in table 15. Mean left ventricular mass was significantly greater in those hypertensives without ECG LVH than in the controls. For those hypertensives with ECG LVH, mean LV mass was higher still, being approximately 50% greater than in those hypertensives without ECG LVH and double that of the normotensive controls.

Table 16 shows the ECG codes and echocardiographic findings in the study group of one hundred hypertensives. Sixty-nine patients had echocardiographic LVH of whom forty-three also had ECG LVH (true positives). This gives a sensitivity for the ECG reporting system of 43/69 = 62%. Specificity (true negatives / true negatives + false positives) was 24/31 = 77%.

Those patients with ECG and echo evidence of LVH (true positives) had significantly more hypertrophy than those with echo LVH only (false negatives) (206±10 vs. 151±6 g/m2, $p<0.01$)(table 17).

In twenty-six patients, the echo, but not ECG, criteria for LVH were fulfilled (false negatives). Compared to those patients with both ECG and echo evidence of LVH, left ventricular mass index was lower, thus confirming that the echocardiogram can detect milder degrees of LVH than the ECG. This group also differed from the three other groups in being more obese, their mean weight being 130+4% of their predicted ideal weight

TABLE 15

ECHOCARDIOGRAPHIC DIMENSIONS FOR THE THREE GROUPS

	CONTROLS (n=50)	HYPERTENSIVES WITHOUT ECG LVH (n=50)	HYPERTENSIVES WITH ECG LVH (n=50)
INTRAVENTRICULAR SEPTUM (cm)	1.04±0.04	1.33±0.09 **	1.63±0.06 *** ++
LEFT VENTRICULAR POSTERIOR WALL (cm)	0.93±0.03	1.13±0.06 **	1.38±0.07 ** +
LEFT VENTRICULAR CAVITY (cm)	4.71±0.08	4.59±0.13	4.83±0.12
LEFT VENTRICULAR MASS (g)	169±6	215±12 *	359±20 *** +++

* p<0.02 -
** p<0.01 - difference from controls
*** p<0.001 -

\+ p<0.02 -
++ p<0.01 - difference between hypertensive groups
+++ p<0.001 -

Note: significance assumed at level of p<0.02 (i.e. 0.05 divided by 3) to take account of multiple comparisons (Bonferroni correction)

TABLE 16

EVIDENCE OF LVH BY ECG AND BY ECHO IN 100 HYPERTENSIVES

PATIENT NO.	ECG CODE	ECHO LVH	PATIENT NO.	ECG CODE	ECHO LVH
51	1	2	101	3	2
52	1	2	102	3	2
53	1	2	103	2	2
54	1	2	104	2	2
55	1	2	105	2	2
56	1	1	106	2	2
57	1	1	107	2	1
58	1	1	108	2	2
59	1	1	109	2	2
60	1	1	110	2	2
61	1	2	111	2	2
62	1	2	112	3	2
63	1	1	113	2	1
64	1	2	114	2	1
65	1	1	115	2	2
66	1	2	116	3	2
67	1	2	117	3	2
68	1	1	118	2	1
69	1	1	119	2	1
70	1	2	120	2	2
71	1	1	121	3	2
72	1	1	122	2	1
73	1	1	123	3	2
74	1	1	124	2	2
75	1	1	125	2	2
76	1	1	126	3	2
77	1	1	127	2	2
78	1	2	128	3	2
79	1	2	129	2	2
80	1	2	130	2	2
81	1	1	131	2	2
82	1	2	132	2	1
83	1	1	133	2	2
84	1	1	134	3	2
85	1	2	135	3	2
86	1	1	136	2	2
87	1	2	137	3	2
88	1	1	138	3	2
89	1	2	139	2	2
90	1	1	140	2	2
91	1	2	141	2	2
92	1	2	142	2	2
93	1	1	143	3	2
94	1	1	144	3	2
95	1	2	145	3	2
96	1	2	146	3	2
97	1	2	147	2	2
98	1	2	148	3	2
99	1	2	149	3	2
100	1	2	150	3	2

ECG : 1 = NO LVH
2 = LVH (VOLTAGE ONLY)
3 = LVH AND ST-T CHANGES

ECHO : 1 = NO LVH
2 = LVH

TABLE 17

CHARACTERISTICS OF FALSE NEGATIVES AND FALSE POSITIVES

	TRUE NEGATIVES	FALSE NEGATIVES	FALSE POSITIVES	TRUE POSITIVES
n	24	26	7	43
M:F	15:9	16:10	7:0	27:16
% IDEAL WEIGHT	117±4	130±4 *	108±6	117±3
LVMI (g/m2)	81±4	151±6	125±6	206±10

* P<0.05 vs. TRUE NEGATIVES
P<0.05 vs. TRUE POSITIVES
P<0.01 vs. FALSE POSITIVES

(table 17).

Discussion

There are several potential sources of error in the existing reporting system. First, standardised ECG criteria are not used. While it is likely that most reporters will have used the chest lead criteria of Sokolow and Lyon, there are several variations of these criteria in common usage such as SV1 + RV5 $\geq$ 35mm and SV1 or 2 + RV5 or 6 $\geq$ 40mm although only the former is included in the original paper (65). Furthermore, some reporters may also have used criteria based on limb lead voltages.

Second, the ECGs were not reported "blind"; that is, the reporter was aware that the patient attended the blood pressure clinic and this may have introduced some bias towards the reporting of "borderline" LVH.

Third, the low sensitivity of the ECG for diagnosis of LVH is well known (187,188,189). Indeed, the value of 62% obtained in this analysis is one of the highest sensitivities recorded; this is reflected by the specificity being lower than in most recorded series (188,189). The population studied, however, is not a random group of hypertensives and it is possible that the high sensitivity and low specificity are related to the high prevalence of left ventricular hypertrophy in the study group. Had left ventricular hypertrophy been

less common in this group, then the sensitivity of ECG diagnosis might have been lower. In addition, the high sensitivity and low specificity reflect the use of 35 mm as an arbitrary cut-off point. Had we defined LVH as RV5 + SV1 $\geq$ 37mm or even RV5 + SV1 $\geq$ 40mm, sensitivity would have been lower and specificity higher.

In general, however, the sensitivity of the ECG is poor and almost 40% of patients with echocardiographic LVH are not detected by the electrocardiogram. ECG LVH is, however, a relatively specific finding (small number of false positives) and it did allow us to identify a subgroup of hypertensive patients at increased risk of cardiovascular mortality.

CHAPTER 6

POSSIBLE IMPROVEMENT IN THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY

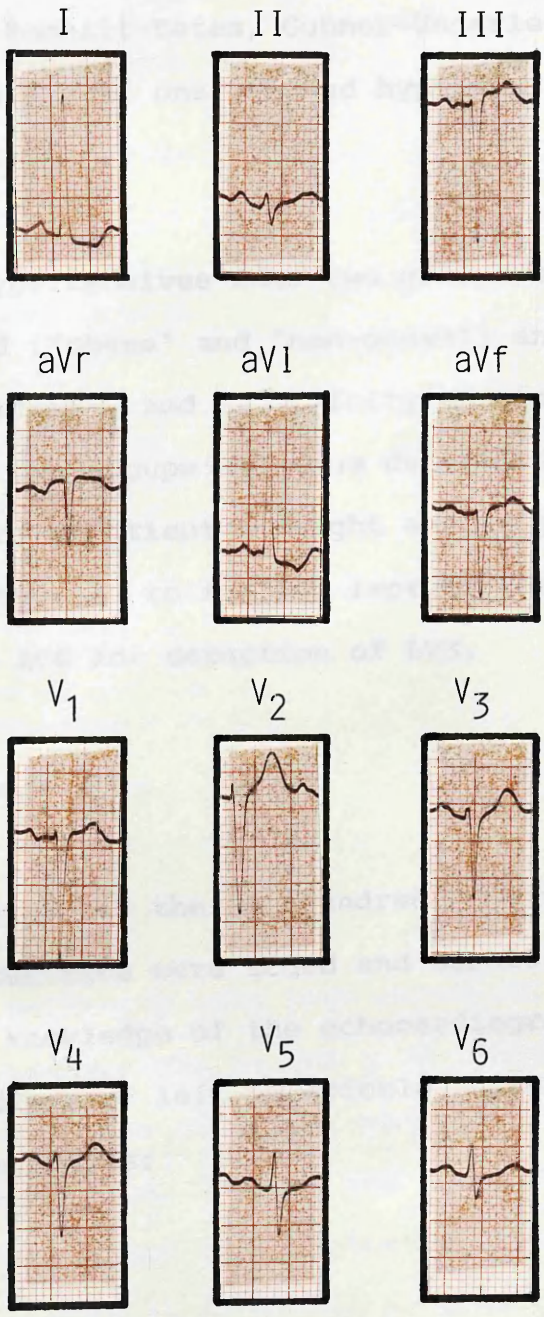
Introduction

Many studies have shown that the ECG is an insensitive indicator of LVH (187,188,189). In attempts to improve this sensitivity, over thirty different sets of ECG criteria now exist (87). However, it seems unlikely that any single set of electrocardiographic criteria will reliably detect LVH in a heterogeneous population. Thus stratification of patients has been suggested, with different criteria being applied to different groups; for example, Casale et al recently suggested that stratification by age and sex can improve the diagnostic performance of the ECG for detection of LVH (73).

We have previously observed a number patients with marked echocardiographic left ventricular hypertrophy in whom the limb lead, but not chest lead, criteria were fulfilled. These patients were more often than not female, elderly and obese. An ECG from such a patient is shown in figure 7.

In this chapter, a further analysis of ECG criteria for LVH is described. The aims of this analysis were as

Figure 7
ECG showing LVH by limb lead, but not chest lead, criteria in an obese patient (weight 91kg, height 152cm).



follows:

1. to compare the sensitivity and specificity of four commonly used sets of electrocardiographic criteria for LVH (Sokolow-Lyon, Romhilt-Estes, Gubner-Ungerleider and RaVl), in the group of one hundred hypertensives described in chapter 5.

2. to divide the hypertensives into two groups on the basis of body build ("obese" and "non-obese") and to calculate the sensitivity and specificity of each set of criteria in the two groups and thus determine whether knowledge of a patient's height and weight could potentially be used to further improve the sensitivity of the ECG for detection of LVH.

Materials and methods

The electrocardiograms of the one hundred hypertensives described in chapter five were coded and carefully analysed, without knowledge of the echocardiographic findings, for evidence of left ventricular hypertrophy by the following criteria:

1. Sokolow-Lyon (65)

RV5 + SV1 $\geq$ 35 mm

2. Romhilt-Estes point scoring system (69)

		POINTS
a) Voltage		
largest R or S wave in limb leads	$\geq$20mm	3
or S wave in V1 or V2	$\geq$30mm	
or R wave in V5 or V6	$\geq$30mm	
b) ST-T depression		
without digitalis		3
with digitalis		1
c) left atrial "strain" i.e. terminal negativity of 'P' wave in V1 $\geq$1mm in depth with duration of $\geq$0.04 second		3
d) left axis deviation (mean axis of -30 degrees or less)		2
e) QRS duration $\geq$0.09 second		1
f) Intrinsicoid deflection in V5/V6 $\geq$0.05second		1
	TOTAL SCORE =	------

4 POINTS = PROBABLE LVH
5 POINTS = DEFINITE LVH

3. Gubner-Ungerleider (64)

RI + SIII $\geq$25mm

4. RaVl $\geq$ 12mm

Sensitivity and specificity were then calculated as before using echocardiography as the gold standard. For the second part of the analysis, patients were subdivided into two groups, "obese" and "non-obese" according to whether or not their actual weight exceeded their predicted ideal weight by more than 20%. Predicted weight for age, sex and height was derived from standard reference tables (186) and is given in

tables 10 and 11. Sensitivity and specificity values were then calculated separately for the obese and non-obese subgroups for all four sets of criteria.

Results

Sensitivities and specificities for the four different sets of electrocardiographic criteria are shown in table 18. The criteria of Sokolow-Lyon and Romhilt-Estes have similar values for sensitivity (57% and 54% respectively) and identical specificity (94%); the criteria based on limb lead voltages (RaVl and Gubner-Ungerleider) are reasonably specific (both 87%) but less sensitive (35% and 42% respectively) than either Sokolow or Romhilt-Estes.

For the obese hypertensives (n=49), the criteria of Gubner and Ungerleider were able to correctly detect LVH in 69% of those obese hypertensives with echocardiographic LVH (table 19) while the Sokolow criteria detected only 41%. Thus, in obese patients, the criteria of Gubner and Ungerleider are more sensitive for detection of LVH than the criteria of Sokolow and Lyon (69% vs 41%); this just achieves statistical significance at the 0.05 level when tested by Chi-squared analysis. The height of the 'R' wave in aVl also appeared more sensitive than the Sokolow criteria for detection of LVH in the obese although this difference was not significant (p=0.2).

Furthermore, this increase in sensitivity in obese patients was not achieved at the cost of a marked reduction in specificity, there being no significant differences in specificity between the four sets of criteria.

In the non-obese hypertensives, the situation was reversed (table 20). Here, sensitivity of the Sokolow criteria was three times greater than that of Gubner and Ungerleider (70% vs 19%, $p<0.001$). RaVl was slightly less sensitive than the criteria of Gubner and Ungerleider in both groups of hypertensives but followed a similar pattern, being significantly more sensitive (19/32 vs 5/37 $p<0.002$) in obese than in non-obese hypertensives. Estes criteria, which include contributions from both chest lead and standard lead voltages, showed intermediate sensitivity in both groups, being more sensitive than Sokolow in obese hypertensives and more sensitive than either Gubner and Ungerleider or RaVl in the non-obese.

Finally, table 21 shows what would happen if we divided the patients into "obese" and "non-obese" and then applied the most sensitive criteria to the two groups (Gubner and Ungerleider in the obese, Sokolow and Lyon in the non-obese). Thus the overall sensitivity of the ECG for detection of LVH could be increased from 57% (table 18) to 70% (table 21) ($p=0.055$) with only a small fall in specificity (94% to 90%) (NS).

TABLE 18

SENSITIVITY AND SPECIFICITY OF VARIOUS ECG CRITERIA FOR LVH

ALL HYPERTENSIVES (n=100)

	SOKOLOW	ESTES	RaVl	GUBNER
TRUE POSITIVES	39	38	24	29
FALSE POSITIVES	2	2	4	4
FALSE NEGATIVES	30	31	45	40
TRUE NEGATIVES	29	29	27	27
SENSITIVITY	57%	55%	35%	42%
SPECIFICITY	94%	94%	87%	87%

TABLE 19

SENSITIVITY AND SPECIFICITY OF VARIOUS ECG CRITERIA FOR LVH

OBESE HYPERTENSIVES (n=49)

	SOKOLOW	ESTES	RaVl	GUBNER
TRUE POSITIVES	13	15	19	22
FALSE POSITIVES	1	1	2	2
FALSE NEGATIVES	19	17	13	10
TRUE NEGATIVES	16	16	15	15
SENSITIVITY	41%	47%	60%	69%
SPECIFICITY	94%	94%	88%	88%

TABLE 20

SENSITIVITY AND SPECIFICITY OF VARIOUS ECG CRITERIA FOR LVH

LEAN HYPERTENSIVES (n=51)

	SOKOLOW	ESTES	RaVl	GUBNER
TRUE POSITIVES	26	23	5	7
FALSE POSITIVES	1	1	2	2
FALSE NEGATIVES	11	14	32	30
TRUE NEGATIVES	13	13	12	12
SENSITIVITY	70%	62%	14%	19%
SPECIFICITY	94%	93%	86%	86%

TABLE 21

EFFECT OF SELECTING CRITERIA ACCORDING TO BODY BUILD

	OBESE (Gubner and Ungerleider)		LEAN (Sokolow)		TOTAL
TRUE POSITIVES	22	+	26	=	48
FALSE POSITIVES	2	+	1	=	3
FALSE NEGATIVES	10	+	11	=	21
TRUE NEGATIVES	15	+	13	=	28
		SENSITIVITY		=	70%
		SPECIFICITY		=	90%

Discussion

In accordance with other studies, (187,188,189), this analysis has shown that current electrocardiographic criteria are insensitive and fail to detect almost 50% of those patients who fulfill echocardiographic criteria for left ventricular hypertrophy. Also in agreement with other studies (189), it has demonstratred that the criteria of Romhilt-Estes and Sokolow-Lyon are more sensitive than criteria based on standard limb lead voltages (RaVl and Gubner and Ungerleider). However, it has not previously been reported that criteria based on limb lead voltages are more sensitive than chest lead criteria for detection of LVH in obese hypertensives.

The likely explanation relates to the orientation of the heart within the thorax and indeed the relationship between body build and QRS voltage has previously been studied in normal individuals. Kilty and Lepeschkin correlated QRS voltages against ponderal index (as a measure of obesity) in 300 individuals free from cardiorespiratory disease (190). The ponderal index was derived by dividing height by the cube root of body weight; a low value, therefore, indicated obesity and a high value indicated lean build. They found a significant positive correlation between the sum of SV1 and RV5 or 6 and ponderal index and a significant negative correlation between the sum of RI and SIII and

ponderal index. The authors suggested that the fall in the SV1+RV5/6 sum and rise in the RI + SIII sum with increasing obesity was:

> *"most likely caused by a more transverse position of the heart resulting from a higher diaphragm position with increasing accumulation of adipose tissue in the abdomen."*

This association between cardiac *position* and QRS voltages was noted by Sokolow and Lyon in their original paper (65). Although no mention is made of body build, it was noted that "conventional" criteria for LVH (i.e. those based on limb lead voltages) detected LVH in "horizontal" hearts while their newly devised criteria, based on chest lead voltages, detected LVH in "vertical" hearts.

The clinical importance of these observations is that it may be possible to improve the diagnostic ability of the ECG to detect LVH if the patient's body build is taken into account.

Other variables, such as chest wall thickness (71) and the size and shape of the left ventricular cavity (72) have been shown to influence ECG voltages, and could be used to improve the ECG detection of LVH; however, unlike height and weight, such data are not routinely available in the outpatient clinic and criteria based on these variables are unlikely to pass into clinical

use.

There are several limitations to this analysis. First, there is a complex relationship between obesity, hypertension and left ventricular hypertrophy (59). Obesity and hypertension are believed to have disparate cardiovascular effects; while essential hypertension is associated with increased afterload, obesity is associated with an expanded intravascular volume and increased preload (59). As far as is possible, these factors have been taken into account. Thus ventricular hypertrophy has been defined in terms of left ventricular mass index (g/m2) which makes allowance for dilatation of the left ventricular cavity when calculating left ventricular mass and also corrects for increased cardiac size in "big" people.

Second, the number of patients studied is too small to allow simultaneous stratification of patients according to age, sex and body build.

However, this analysis has demonstrated that criteria based on chest lead voltages, such as Sokolow-Lyon, are more sensitive for detection of LVH in patients of "average" weight than criteria based on limb lead voltages and that the reverse is true in obese patients. Casale has recently shown that stratification of patients by age and sex can improve ECG diagnosis of LVH (73) and it may be that stratification by age, sex and body build will lead to further improvement.

Clearly a prospective echocardiographic study of a

large number of patients would be required to establish such criteria.

Interestingly, there is a suggestion that the clinicians reporting ECGs from the Glasgow Blood Pressure Clinic may have been using several sets of criteria since the sensitivity for detection of LVH was greater for the non-standardised system that for any of the four sets of criteria examined in this analysis. The likely explanation is that LVH would be reported as being present by some observers if either chest lead or limb lead voltage criteria were fulfilled.

For the future documentation of LVH in the Glasgow Blood Pressure Clinic, a new form has been devised using standardised criteria in which limb lead, as well as chest lead, voltages are recorded.

CHAPTER 7

VENTRICULAR ARRHYTHMIAS IN HYPERTENSIVE PATIENTS WITH AND WITHOUT ECG LVH

Introduction

Both the Glasgow Blood Pressure Clinic data (1) and the Framingham study (80) have demonstrated that electrocardiographic left ventricular hypertrophy is associated with an increased cardiovascular mortality; in particular, it appears to be associated with an increased risk of sudden death (155) that is in excess of the risk attributable to hypertension or other associated cardiovascular risk factors (2).
One cause of this excess mortality could be a predisposition to ventricular arrhythmia and indeed increased ventricular ectopic activity has been found in hypertensive patients with LVH (191). However, in other conditions, the relationship between single ventricular extrasystoles and subsequent mortality is unclear while the relationship between complex ventricular arrhythmias, particularly ventricular tachycardia, appears more clear-cut. No data have been reported relating specifically to more complex ventricular arrhythmias in hypertensive patients with LVH.

Aim

The aim of this analysis was to determine the frequency of both simple and complex ventricular arrhythmias in hypertensive patients with and without left ventricular hypertrophy, and to compare this with a control group. Since previous studies have made no allowance for a possible effect of hypertension itself on arrhythmia frequency, an important feature of this study was that the two hypertensive groups were matched with each other for both initial and achieved blood pressure as well as for other cardiovascular risk factors including age, sex and smoking habit.

Materials and methods

Patients

The one hundred hypertensive patients and fifty normotensive control subjects described in chapter 5 were investigated for arrhythmia frequency. As mentioned in chapter 5, the one hundred hypertensives comprised two groups of fifty patients each, one with ECG LVH and one without. ECG LVH for this purpose was defined by chest lead voltage criteria according to Sokolow-Lyon (SV1+RV5 $\geq$35mm) (65). Baseline data relating to the two hypertensive groups and the normal controls have been summarised previously (tables 5-11

and table 15). Those with electrocardiographic LVH were further subdivided according to whether the ECG also demonstrated major ST-T wave changes, defined as horizontal or down-sloping ST segment depression of 1mm or greater in leads V5 and V6 or T wave inversion in the same leads (n=21).
As noted earlier, the two hypertensive groups were matched with each other for both initial and achieved blood pressure.

Methods

Ambulatory ECG monitoring

Ambulatory ECG recordings were made over two consecutive twenty-four hour periods using "TRACKER TR1" ambulatory tape recorders (Reynolds Medical Limited). The complete forty-eight hour record was printed using a "REYNOLDS TP1" full disclosure unit. After coding, the printouts were analysed manually. For analysis of ventricular extrasystoles, the tapes were subdivided into the following categories:
a) <10 extrasystoles per hour over 48 hours
b) 10-30 extrasystoles per hour over 48 hours
c) >30 extrasystoles per hour over 48 hours.

For analysis of complex ventricular arrhythmias, ventricular couplets were considered to be present if

there were two or more couplets per 48 hours and ventricular tachycardia was defined as one or more episode of at least 3 consecutive ventricular beats at a heart rate greater than 120 beats per minute. Examples of the arrhythmias detected are shown in figure 8.

All one hundred and fifty printouts were analysed by two observers (myself and K.I.M.). Although there were minor differences in the total ectopic count between the two observers, there were no differences in the classification of printouts into the different categories:

i.e. a) <10, 10-30, >30 VEs per hour

b) couplets / no couplets

c) VT / no VT

RESULTS

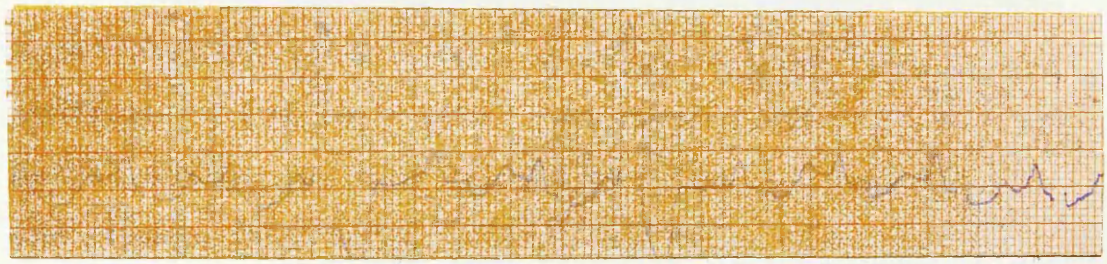
Differences in non-parametric data (arrhythmia frequency, prevalence of ECG LVH etc.) are calculated using a Chi-squared test; differences in parametric data (age, left ventricular mass etc.) are expressed as mean $\pm$ S.E.M. and differences between groups expressed using a two-tailed t-test for paired data.

1. Frequency of ventricular arrhythmias

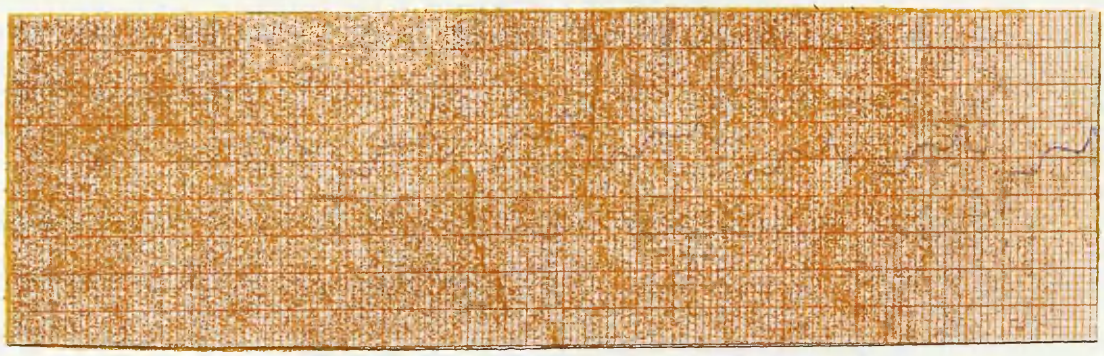
The frequency of ventricular arrhythmias is shown in

Figure 8
Ventricular arrhythmias detected

(a) Frequent ventricular extrasystoles (>30/hour)



(b) Ventricular couplets



(c) Ventricular tachycardia

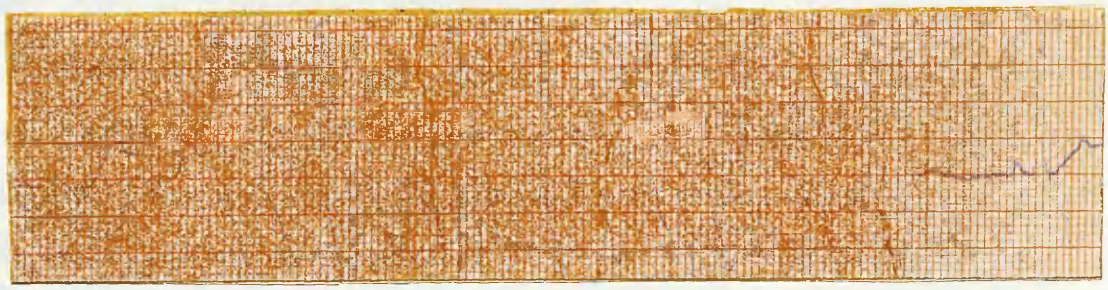


TABLE 22

PREVALENCE OF VENTRICULAR ARRHYTHMIA DURING 48 HOUR ECG MONITORING
(EXPRESSED PER 24 HOURS)
NORMAL CONTROL SUBJECTS

SUBJECT NUMBER	NUMBER OF VENTRICULAR EXTRASYSTOLES	NUMBER OF VENTRICULAR COUPLETS	EPISODES OF VENTRICULAR TACHYCARDIA
1	0	0	0
2	3	0	0
3	0	0	0
4	0	0	0
5	35	0	0
6	0	0	0
7	0	0	0
8	7	0	0
9	0	0	0
10	0	0	0
11	48	0	0
12	0	0	0
13	55	0	0
14	7	0	0
15	4	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	3	0	0
20	1	0	0
21	0	0	0
22	0	0	0
23	0	0	0
24	31	0	0
25	0	0	0
26	0	0	0
27	2	0	0
28	3	0	0
29	8	0	0
30	0	0	0
31	706	3	0
32	0	0	0
33	0	0	0
34	0	0	0
35	0	0	0
36	0	0	0
37	0	0	0
38	0	0	0
39	6	0	0
40	0	0	0
41	87	2	1
42	0	0	0
43	5	0	0
44	0	0	0
45	14	0	0
46	0	0	0
47	0	0	0
48	3	0	0
49	0	0	0
50	0	0	0

TABLE 23

PREVALENCE OF VENTRICULAR ARRHYTHMIA DURING 48 HOUR ECG MONITORING
(EXPRESSED PER 24 HOURS)
HYPERTENSIVES WITHOUT ECG LVH

SUBJECT NUMBER	NUMBER OF VENTRICULAR EXTRASYSTOLES	NUMBER OF VENTRICULAR COUPLETS	EPISIDES OF VENTRICULAR TACHYCARDIA
51	120	0	0
52	76	0	0
53	62	0	0
54	104	0	0
55	0	0	0
56	0	0	0
57	2	0	0
58	0	0	0
59	0	0	0
60	532	0	0
61	0	0	0
62	1318	5	3
63	0	0	0
64	1	0	0
65	112	0	0
66	8	0	0
67	240	0	1
68	4	0	0
69	0	0	0
70	4	0	0
71	0	0	0
72	0	0	0
73	0	0	0
74	0	0	0
75	0	0	0
76	0	0	0
77	0	0	0
78	3	0	0
79	62	0	0
80	0	0	0
81	0	0	0
82	1199	0	0
83	371	3	0
84	1	0	0
85	161	4	0
86	2	2	0
87	0	0	0
88	19	0	0
89	39	0	0
90	8	0	0
91	61	0	0
92	212	0	0
93	7086	2	0
94	0	0	0
95	0	0	0
96	262	7	0
97	54000	546	19
98	25	0	0
99	1	2	3
100	43	0	0

TABLE 24

PREVALENCE OF VENTRICULAR ARRHYTHMIA DURING 48 HOUR ECG MONITORING
(EXPRESSED PER 24 HOURS)
HYPERTENSIVES WITH ECG LVH

NUMBER	NUMBER OF VENTRICULAR EXTRASYSTOLES	NUMBER OF VENTRICULAR COUPLETS	EPISODES OF VENTRICULAR TACHYCARDIA
101	2748	1	2
102	14920	1271	14
103	2	2	0
104	4164	67	11
105	24	0	0
106	0	0	0
107	56	0	0
108	580	0	0
109	2	0	0
110	0	0	0
111	10	0	0
112	1027	1	0
113	2	0	0
114	74	1	0
115	16	2	0
116	4384	42	1
117	0	0	0
118	2	0	0
119	10	0	0
120	48	0	0
121	80	5	17
122	676	1	0
123	0	0	1
124	612	3	0
125	54	2	0
126	608	4	3
127	2	0	0
128	10	0	2
129	0	0	0
130	2	0	0
131	0	0	0
132	4	0	0
133	0	0	0
134	0	0	0
135	24	2	1
136	1104	0	0
137	21721	8653	22
138	2	0	0
139	6	0	0
140	540	0	0
141	42	4	1
142	1653	1	0
143	0	0	0
144	8	0	0
145	614	0	1
146	2	0	0
147	0	0	0
148	0	0	0
149	802	0	1
150	701	2	3

TABLE 25

PREVALENCE OF SIMPLE AND COMPLEX VENTRICULAR ARRHYTHMIAS

	CONTROLS (n=50)	HYPERTENSIVES WITHOUT ECG LVH (n=50)		HYPERTENSIVES WITH ECG LVH (n=50)	
<10 VPCs/hr	49	45	]	34	]
10-30 VPCs/hr	1	3	] *	10	] ***
>30 VPCs/hr	0	2	]	6	] +
VENTRICULAR COUPLETS	2	8		18	***
VENTRICULAR TACHYCARDIA	1	4		14	*** +

* P<0.05 -
\- DIFFERENCE FROM CONTROLS
*** P<0.001 -

\+ P<0.05 - DIFFERENCE BETWEEN GROUPS WITH AND WITHOUT ECG LVH

had marked left ventricular hypertrophy by echocardiography (LV mass values of 271, 321 and 438g).

2. Relation of ventricular tachycardia to repolarisation abnormalities.

In table 26, the LVH group has been subdivided into those with and without ST-T changes. Twenty-one patients had LVH with ST-T changes of whom eleven (52%) had ventricular tachycardia, twelve (57%) had ventricular couplets (57%) and five (24%) had more than thirty ventricular extrasystoles per hour. Both ventricular tachycardia and ventricular couplets were significantly more common in those with than in those without ST-T changes. This is confirmed in table 27 which demonstrates the principal differences between hypertensives with and without VT. There were no significant differences between the two groups in terms of age, sex ratio and smoking habit. Blood pressure levels were, on average, 10 mm Hg higher in those with VT although this achieved statistical significance for diastolic pressure only. The most striking differences between the two groups, however, relate to the presence of ECG LVH and to the degree of hypertrophy as assessed by echocardiography.

TABLE 26

PREVALENCE OF ARRHYTHMIAS IN HYPERTENSIVES WITH AND WITHOUT ST-T CHANGES

	HYPERTENSIVES WITH ECG LVH (VOLTAGE ONLY) (n=29)	HYPERTENSIVES WITH ECG LVH AND ST-T CHANGES (n=21)
>30 VPCs/hr	1	5
VENTRICULAR COUPLETS	6	12 *
VENTRICULAR TACHYCARDIA	4	14 *

* $P < 0.05$

TABLE 27

CHARACTERISTICS OF HYPERTENSIVES WITH VENTRICULAR TACHYCARDIA

	HYPERTENSIVES WITH V.T. (n=18)	HYPERTENSIVES WITHOUT V.T. (n=82)	"p" VALUE
AGE (YEARS)	59±3	58±1	NS
M:F RATIO	12:6	53:29	NS
ACHIEVED SYS. BP (mm Hg)	162±6	152±2	NS
ACHIEVED DIA. BP (mm Hg)	98±5	88±2	$p<0.05$
SMOKERS	6 (33%)	38 (48%)	NS
ECG LVH - VOLTAGE ONLY	14 (78%)	36 (43%)	$p<0.001$
ECG LVH WITH ST-T CHANGES	11 (61%)	10 (12%)	$P<0.001$
LEFT VENTRICULAR MASS (g)	390±29	261±15	$P<0.001$

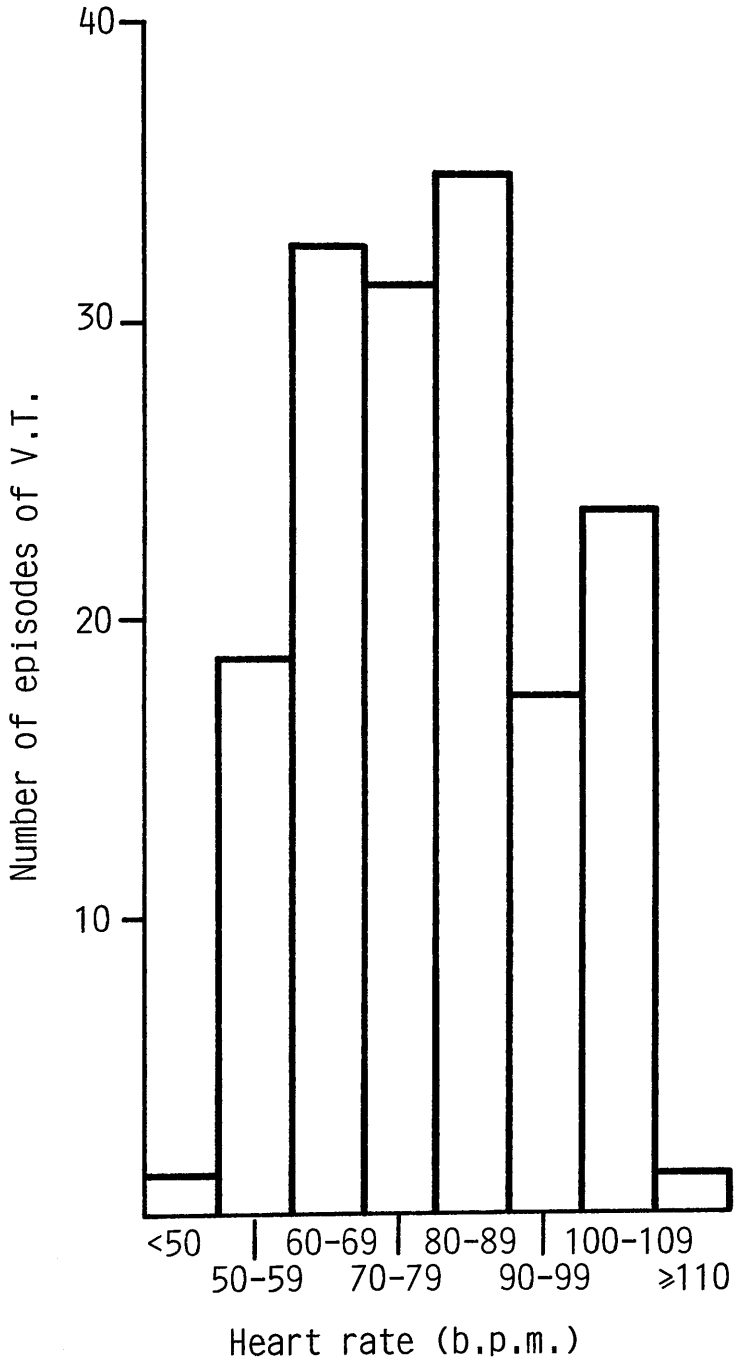
3. Relation of ventricular tachycardia to heart rate.

Since the episodes of ventricular tachycardia were asymptomatic, it was not possible to determine the subject's activity at the time of the arrhythmia. It was possible, however, to determine mean heart rate during the thirty second period immediately prior to onset of the arrhythmia. As shown in figure 9, over 80% of episodes occurred when mean heart rate was less than one hundred beats per minute. This suggests that myocardial ischaemia secondary to increased cardiac workload was unlikely to be a major factor in the initiation of ventricular arrhythmia.

DISCUSSION

Ventricular arrhythmias do occur in individuals free of overt heart disease; this, together with the known spontaneous variability in ventricular ectopic frequency in short-term studies (192) and variability in simple and complex arrhythmias in long-term studies (193), has led to difficulties in the interpretation of studies of ventricular arrhythmia frequency.
In this study, we have attempted to control for some of these problems by including an age and sex matched control group. The prevalence of arrhythmia in the control group was of a similar order to that reported in asymptomatic individuals (194). Although spontaneous

Figure 9
Heart rate immediately before the onset of ventricular tachycardia



variability in arrhythmia frequency is a problem in longitudinal studies when trying to assess changes in ectopic frequency in response to an intervention, this should not introduce a systematic bias in a cross-sectional study such as this.

Thus the present study confirms the increased ventricular ectopic activity in hypertensive left ventricular hypertrophy described by Messerli (191) but demonstrates for the first time that ventricular tachycardia occurs significantly more often in hypertensive patients with LVH than in those without. Ventricular tachycardia occurred most commonly in those patients in whom overall mortality risk, as discussed in chapter 4, is highest, namely those with left ventricular hypertrophy and accompanying ST-T abnormalities on the resting ECG.

Experimentally, left ventricular hypertrophy predisposes to ventricular arrhythmia. It has been shown that spontaneously hypertensive rats have a lower threshold for ventricular fibrillation than controls (195) and that afterpotentials, which may predispose to arrhythmia, can be induced in hypertrophied rat myocardium but not in normal rat myocardium (196). In man, programmed electrical stimulation at the time of cardiac surgery has been used to determine vulnerability to ventricular tachyarrhythmias in patients with primary left ventricular hypertrophy (hypertrophic cardiomyopathy) and left ventricular

hypertrophy secondary to aortic stenosis (197). Ventricular tachycardia could be induced in 82% of those patients with hypertrophic cardiomyopathy, 57% of those with aortic stenosis but in none of a "control" group with severe coronary artery disease but normal left ventricular function and no previous myocardial infarction.

In summary, this study has demonstrated that ventricular arrhythmias occur commonly in hypertensive left ventricular hypertrophy; their prevalence is not attributable to differences in age, sex, smoking habit or blood pressure but is related to the degree of cardiac hypertrophy. It is possible that this tendency to arrhythmia might be an important factor in the high mortality, and in particular, the high incidence of sudden death, in hypertensive patients with LVH.

CHAPTER 8

INFLUENCE OF DIURETIC THERAPY AND HYPOKALAEMIA ON THE FREQUENCY OF VENTRICULAR ARRHYTHMIAS

Introduction

In chapter seven, an increased frequency of ventricular arrhythmia was demonstrated in hypertensive patients with LVH and it was suggested that such arrhythmias might explain why LVH is an independent risk factor for mortality as described in chapter four.

Hypokalaemia is an alternative cause of ventricular arrhythmia and several studies have reported an association between diuretic-induced hypokalaemia and ventricular arrhythmia in treated hypertensive patients (198,199). Furthermore, a subgroup analysis of the Multiple Risk Factor Intervention Trial (MRFIT) suggested that mortality from coronary heart disease was increased in a group of patients with resting electrocardiographic abnormalities, including LVH, in whom "active" treatment included thiazide therapy for hypertension (200,201). This has been interpreted as suggesting that thiazide diuretics increase the incidence of fatal arrhythmias in hypertensive patients with abnormal ECGs.

In view of the importance of the MRFIT analysis, we have examined the prevalence of ventricular arrhythmias

in those patients taking a diuretic as part of their antihypertensive regime and compared this to arrhythmia frequency in patients not taking a diuretic.

Materials and methods

The one hundred patients were as described in chapter five. The group was then subdivided according to whether or not the patients were taking a regular diuretic. Patients were initially included in the diuretic group whether or not they were taking oral potassium supplementation or a potassium sparing diuretic and the analysis was then repeated with these patients excluded.

A ten millilitre sample of venous blood was taken from a peripheral vein from each of the one hundred hypertensive subjects described in chapter five after at least ten minutes' recumbency in a quiet room for estimation of serum potassium concentration.

Differences in arrhythmia prevalence between groups were calculated using a Chi-squared test and differences in serum potassium concentration calculated using a two-tailed t-test for unpaired data.

Results

Fifty-six hypertensives were taking a diuretic as part of their treatment regimen at the time of assessment; four were taking oral potassium supplementation and three a potassium sparing diuretic. Forty-two were taking a thiazide diuretic (usually bendrofluazide) and fourteen were taking a loop diuretic (usually frusemide). Serum potassium concentration for this group was 3.5 $\pm$ 0.3 mmol/l compared to 4.2 $\pm$0.3 mmol/l for those not taking a diuretic ($p<0.01$). There were, however, no significant differences in the frequency of ventricular extrasystoles, couplets or tachycardia between the diuretic treated and non-diuretic treated groups (table 28).

To determine whether potassium supplements might "dilute" any difference in arrhythmia frequency between diuretic and non-diuretic treated patients, this analysis was repeated excluding those patients taking either potassium supplements or potassium sparing diuretics; again there were no differences in arrhythmia frequency between the two groups (table 29).

The effect of diuretics on arrhythmia was then examined separately in those patients with and without LVH. Although all grades of ventricular arrhythmia were more common in those with LVH, there was no evidence that diuretic therapy, although clearly associated with a reduction in serum potassium concentration, was

TABLE 28

DIURETIC TREATMENT AND ARRHYTHMIA FREQUENCY

ALL HYPERTENSIVES

	DIURETIC (n=56)	NO DIURETIC (n=44)	"p" VALUE
SERUM K+ (mmol/l)	3.5±0.3	4.2±0.3	<0.01
VENTRICULAR EXTRASYSTOLES (>30 PER HOUR)	5 (9%)	3 (7%)	NS
VENTRICULAR COUPLETS	10 (18%)	9 (20%)	NS
VENTRICULAR TACHYCARDIA	11 (20%)	7 (16%)	NS

TABLE 29

DIURETIC TREATMENT AND ARRHYTHMIA FREQUENCY

ALL HYPERTENSIVES EXCLUDING THOSE ON TAKING K+ SUPPLEMENTATION

	DIURETIC (n=49)	NO DIURETIC (n=44)	"p" VALUE
SERUM K+ (mmol/l)	3.4±0.3	4.2±0.3	<0.01
VENTRICULAR EXTRASYSTOLES (>30 PER HOUR)	4 (8%)	3 (7%)	NS
VENTRICULAR COUPLETS	8 (16%)	9 (20%)	NS
VENTRICULAR TACHYCARDIA	10 (20%)	7 (16%)	NS

TABLE 30

DIURETIC TREATMENT AND ARRHYTHMIA FREQUENCY

HYPERTENSIVES WITH LEFT VENTRICULAR HYPERTROPHY

	DIURETIC (n=29)	NO DIURETIC (n=21)	"p" VALUE
SERUM K+ (mmol/l)	3.6±0.4	4.1±0.3	<0.05
VENTRICULAR EXTRASYSTOLES (>30 PER HOUR)	3 (10%)	2 (10%)	NS
VENTRICULAR COUPLETS	7 (24%)	5 (24%)	NS
VENTRICULAR TACHYCARDIA	8 (24%)	6 (29%)	NS

TABLE 31

DIURETIC TREATMENT AND ARRHYTHMIA FREQUENCY
HYPERTENSIVES WITHOUT LEFT VENTRICULAR HYPERTROPHY

	DIURETIC (n=27)	NO DIURETIC (n=23)	"p" VALUE
SERUM K+ (mmol/l)	3.3±0.3	4.3±0.3	<0.01
VENTRICULAR EXTRASYSTOLES (>30 PER HOUR)	2 (7%)	1 (4%)	NS
VENTRICULAR COUPLETS	3 (11%)	4 (17%)	NS
VENTRICULAR TACHYCARDIA	3 (11%)	1 (4%)	NS

TABLE 32

DIFFERENCES IN THERAPY BETWEEN HYPERTENSIVES WITH AND WITHOUT VT

	HYPERTENSIVES WITH VT (n=18)	HYPERTENSIVES WITHOUT VT (n=82)	"p" VALUE
DIURETIC TREATED	11 (61%)	45 (55%)	NS
BETA BLOCKER TREATED	14 (78%)	58 (70%)	NS
SERUM K+ (mmol/l)	3.9±0.1	3.9±0.1	NS

associated with increased ventricular arrhythmic activity in either group (tables 30 and 31). Finally, the treatment details of the patients with and without ventricular tachycardia are compared in table 32. There were no significant differences in the proportion of patients treated with diuretics, or in the serum potassium concentration, between the two groups. Interestingly, there was also no significant difference in the proportion of patients taking regular beta blocker therapy and thus, indirectly, no suggestion that beta blockade protected against ventricular tachycardia in this group of patients.

Discussion

Thus we found no evidence that diuretics increase ventricular arrhythmias in hypertensives with or without left ventricular hypertrophy. This is in keeping with the results of Papademetriou et al (202) who demonstrated in a controlled prospective study that thiazide diuretic therapy did not increase ventricular ectopic activity in hypertensive patients with and without LVH. Leif et al also demonstrated in a study of thirteen hypertensives that hydrochlorothiazide 100 mg once daily for one to six months does not increase either ventricular ectopic rate or the prevalence of complex ventricular arrhythmias (203); similar findings have been reported by Madias in a placebo controlled

crossover study (204).

Other studies, however, have produced conflicting results. Holland et al (198) carried out twenty-four hour ambulatory ECG monitoring before and after hydrochlorothiazide 100 mg once daily and reported an increase in both simple and complex ventricular arrhythmias. However, the study design excluded patients with either multifocal extrasystoles or complex ventricluar arrhythmias during the initial assessment. Since ventricular ectopic activity varies markedly from day to day (192), this exclusion would increase the chance of finding greater ectopic activity during the second assessment whether or not there had been any change in therapy. Although the authors argue that subsequent potassium repletion reduced ectopic activity, this third period of assessment was carried out only on a group of seven patients (21% of the original group) who had demonstrated the highest grades of ventricular ectopy while on thiazides. By selecting those with the highest rate of ectopic activity, we might again expect some reduction in ectopic frequency by chance alone. Hollifield and Slaton (199) also reported that hydrochlorothiazide 50-100 mg once daily increased arrhythmia frequency; however, ECG monitoring in this study was carried out over very short time periods (five minutes only) before and during exercise testing and the study was not placebo-controlled.

The MRC Mild Hypertension Trial included two substudies

of the effects of thiazide diuretics on ventricular ectopic activity which also produced conflicting results (205). In the first, one hundred and ten patients were randomly allocated to either placebo or bendrofluazide with or without potassium supplementation and were studied by twenty-four hour ambulatory ECG monitoring at baseline and again at ten weeks; none of the groups showed a significant change in ectopic activity. In the second, longer-term study, ventricular extrasystoles occurred more commonly in those taking thiazides than in the placebo group but no baseline assessment was carried out and there was no significant association between the number of ventricular extrasystoles and serum potassium concentration within the thiazide treated group. Interest in the relationship between thiazide diuretics and ventricular arrhythmia has been stimulated by the sub-group analysis from MRFIT suggesting that diuretic therapy may predispose to ventricular arrhythmia and thus increase mortality in hypertensives with abnormal ECGs (201). This form of analysis, however, has been much criticised and other major studies have failed to provide confirmatory evidence. Data have recently been published from the Glasgow Blood Pressure Clinic demonstrating that diuretic-induced hypokalaemia is not a risk factor for mortality either in the clinic as a whole or in a subgroup of patients with left ventricular hypertrophy (206). In addition, the

Hypertension Detection and Follow-up Program (HDFP), which included one thousand, nine hundred and sixty-three patients with mild hypertension and minor ECG abnormalities, found that diuretic therapy (usually chlorthalidone 50 mg once daily) reduced cardiovascular mortality (207). In other studies, including the Veterans Administration Study (208) and the Australian Mild Hypertension Study (209), there was again no evidence that thiazides predisposed to sudden death, the incidence of both fatal myocardial infarction and sudden death being lower in thiazide treated groups than in controls.

In summary, we found that although left ventricular hypertrophy was associated with an increased prevalence of simple and complex ventricular arrhythmias, arrhythmia frequency was not increased by diuretic-induced hypokalaemia.

CHAPTER 9

RELATIONSHIP OF VENTRICULAR ARRHYTHMIAS TO CORONARY ARTERY DISEASE.

Introduction

In chapter four, ECG LVH was shown to be associated with a risk of cardiovascular mortality that was in excess of that attributable to associated risk factors such as cigarette smoking and hypertension. It was suggested that this excess risk might be explained by the high prevalence of ventricular arrhythmias in hypertensive patients with LVH. It is possible, however, that the risk is associated with, but not directly attributable to, arrhythmia and that ambulatory ECG monitoring was simply detecting those patients with coronary artery disease who were already at increased risk.

It was considered important, therefore, to determine whether high grade ventricular arrhythmias occurring in this group of patients are simply a manifestation of asymptomatic coronary artery disease. The question has therapeutic implications; if severe and extensive coronary artery disease was prevalent in a group of middle aged individuals known to have a five year mortality rate in excess of 35%, there may be a case for more intensive investigation and treatment of the

coronary disease either by aorto-coronary bypass grafting or other techniques. If, however, the arrhythmias were related to the process of hypertrophy itself, or to other myocardial (as opposed to coronary) abnormalities, treatment should be aimed at either preventing hypertrophy and its complications or perhaps treating the arrhythmia.

Thus the aim of this analysis was to determine the prevalence and severity of coronary artery disease in those patients with LVH and ventricular tachycardia.

Materials and methods

Study group

Seventeen hypertensive patients with both electrocardiographic and echocardiographic evidence of LVH underwent cardiac catheterisation and coronary arteriography. Two patients had definite Q wave evidence of previous infarction but were asymptomatic at the time of catheterisation. None had experienced chest pain within one year of cardiac catheterisation. The indication for coronary arteriography was that all seventeen had shown at least one episode of ventricular tachycardia during 48 hour ambulatory ECG monitoring. The baseline characteristics of the study group are summarised in table 33.

TABLE 33

BASELINE CHARACTERISTICS OF PATIENTS UNDERGOING CORONARY ARTERIOGRAPHY

INITIALS	SEX	AGE (YRS)	SMOKER
JC	M	58	NO
MO	F	68	NO
JK	M	61	NO
CP	M	66	NO
WH	M	63	YES
AM	M	30	YES
JM	M	52	YES
JB	M	69	YES
MP	F	46	NO
TC	M	61	NO
MM	F	67	NO
RS	M	44	YES
AN	M	56	NO
LM	M	43	YES
DD	M	48	NO
TD	M	61	NO
WJ	M	61	NO

Methods

Written informed consent was obtained from all patients. Standard left heart catheterisation was then carried out under local anaesthetic via the right femoral artery using a modified Seldinger technique. A long J-shaped guide wire was passed into the femoral artery and a 7F pigtail catheter was threaded over the guide wire and into the aorta. Heparin 5000 International Units was given as an intra-arterial bolus. A left ventricular angiogram was then performed using 40-50 ml contrast medium (NIOPAM) injected mechanically over 1-2 seconds, the angiogram being recorded onto 35 mm film at a film speed of 50 frames per second. The pigtail catheter was then replaced by appropriate coronary catheters, usually size 7 shape 4 Judkins left and right coronary catheters, but variable according to local anatomy. Four views of the left coronary artery (30 degrees right anterior oblique, 60 degrees left anterior oblique, craniocaudal and 90 degrees left lateral) and two views of the right coronary artery (60 degrees left anterior oblique and 30 degrees right anterior oblique) were recorded. At the end of the procedure, heparinisation was reversed by a slow intravenous injection of protamine sulphate (5 millilitres).

The coronary arteriograms were then reviewed independently by myself and by a consultant

cardiologist (HJD); any discrepancies in reporting were settled by discussion. The arteriograms were classified according to whether or not they demonstrated occlusion or stenosis, the latter defined as a reduction of the luminal diameter by <30%, 30-50%, 50-70% or >70% in one or more of the major epicardial coronary vessels.

Results

The results of coronary arteriography in those patients with left ventricular hypertrophy and ventricular tachycardia are shown in table 34. Of the seventeen patients, seven (41%) had no significant coronary artery disease. When the two patients with both history and ECG evidence of previous infarction are excluded (JK and WH), only five of the fifteen remaining (33%) had either an occluded vessel or a stenosis of greter than 70% and none had triple vessel disease.

Discussion

A limitation of this analysis was the lack of a suitable control group. Nonetheless, the high prevalence of ventricular arrhythmia in hypertensive left ventricular hypertrophy cannot be attributed solely to "conventional" epicardial coronary artery disease since almost one half of the study group were free of severe stenoses. This does not necessarily

TABLE 34

FINDINGS AT CORONARY ARTERIOGRAPHY IN PATIENTS WITH V.T.

INITIALS	L.M.	L.A.D.	CX	R.C.A.
JC	N	>70%	N	<30%
MO	N	OCC	<30%	>70%
JK	N	<30%	N	OCC
CP	N	N	N	N
WH	N	OCC	<30%	OCC
AM	N	N	N	N
JM	N	N	N	N
JB	N	>70%	>70%	N
MP	N	N	N	N
TC	N	N	N	N
MM	N	>70%	>70%	<30%
RS	N	N	N	N
AN	N	N	N	30-50%
LM	N	30-50%	N	>70%
DD	N	N	N	N
TD	N	N	30-50%	N
WJ	N	>70%	<30%	OCC

L.M. = LEFT MAINSTEM
L.A.D. = LEFT ANTERIOR DESCENDING
CX = CIRCUMFLEX
R.C.A. = RIGHT CORONARY ARTERY

N = NORMAL
<30% = <30% STENOSIS
30-50% = 30-50% STENOSIS
50-70% = 50-70% STENOSIS
>70% = >70% STENOSIS
OCC = OCCLUDED

imply, however, that ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy are unrelated to myocardial ischaemia. As discussed in chapter 2.8, it is clear that patients with left ventricular hypertrophy can develop typical exercise-induced angina pectoris and electrocardiographic evidence of myocardial ischaemia even when the major coronary vessels are patent (118,119). This presumably reflects the inability of the coronary supply to keep pace with the increased demand of the hypertrophied left ventricle and at least one clinical study has demonstrated a reduced coronary vascular reserve in patients with left ventricular hypertrophy secondary to hypertension (136).

It is possible, therefore, that coronary stenoses less severe than those considered "critical" in an otherwise normal heart may result in ischaemia in the presence of an already reduced coronary reserve. We have, however, not investigated this further, partly because of the lack of suitable "in vivo" techniques for assessing the functional significance of coronary stenoses in patients with left ventricular hypertrophy.

The relationship between hypertrophy, coronary artery disease and ventricular arrhythmia has not previously been studied in hypertension but there has been some corroborative evidence from other forms of left ventricular hypertrophy. Klein recently reported on the prevalence of ventricular arrhythmias in one hundred

and twelve patients with aortic valve disease and the relationship of arrhythmia to the presence or absence of associated coronary artery disease (210). Complex ventricular arrhythmias occurred in 40 of 102 patients (39%) but the presence of arrhythmia bore no relationship to the presence of coronary artery disease.

In summary, therefore, the occurrence of ventricular tachycardia during ambulatory monitoring was not simply an indicator of severe but otherwise "silent" coronary disease. This would be in keeping with the suggestion that a tendency to ventricular arrhythmia might explain the "excess" mortality associated with LVH over and above that attributable to associated risk factors such as cigarette smoking and hypertension. As noted in chapter seven, the occurrence of such arrhythmias is related to the degree of cardiac hypertrophy assessed by echocardiography and to the presence of repolarisation changes on the ECG; it does not appear to be closely related to the presence of coronary disease.

CHAPTER 10

HISTOLOGY OF HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

Introduction

Having shown that high grade ventricular arhythmias occur with increased frequency in those hypertensives with left ventricular hypertrophy, and that this tendency to arrhythmia is not wholly explained by coronary artery disease, we next investigated myocardial factors that might be related to ventricular arrhythmia. It has been shown previously that marked cardiac hypertrophy is associated with subendocardial ischaemia (125) and myocardial fibrosis (92).
The aim of this analysis was to quantify, using a point counting system, the ischaemic myocardial changes present in the left ventricular subendocardium of hypertensive patients with LVH and ventricular tachycardia and to compare this with a control group.
A further aim was to investigate the association between myocardial changes seen on biopsy and left ventricular mass, as determined by echocardiography, and left ventricular function, as determined by estimation of the left ventricular ejection fraction from the cineangiogram.

Materials and Methods

Patients

Over a two year period, we carried out left ventricular endomyocardial biopsy as an extension of the cardiac catheterisation investigation if catheterisation, angiography and coronary arteriography had not provided an explanation for the patient's symptoms or for the results of non-invasive investigations.
During this period, forty-eight hour ambulatory ECG monitoring was performed on all patients with left ventricular hypertrophy undergoing cardiac catheterisation. Thirty-seven patients were investigated but satisfactory biopsies were achieved in only twenty-seven. In the remainder, either the bioptome could not be manouvred into a suitable position, or the biopsy obtained was too small for quantitative analysis.
The twenty-seven patients comprised two groups:

1. A study group of eleven patients in whom forty-eight hour ambulatory ECG monitoring had demonstrated at least one episode of ventricular tachycardia. Six of the eleven came from the original group of one hundred hypertensives described in chapter five. The remainder were detected after we had completed the study of arrhythmia prevalence. In addition to ventricular

tachycardia during ambulatory monitoring, all had left ventricular hypertrophy by both ECG and echocardiographic criteria.

2. A control group of sixteen patients. As in the study group, all had ECG and echo evidence of left ventricular hypertrophy. The principal difference between the two groups was that none of the control group had demonstrated either ventricular tachycardia or ventricular couplets during forty-eight hour ambulatory ECG monitoring. Left ventricular biopsy was only carried out if the catheterisation procedure had not provided an explanation for the patient's symptoms. Thus nine patients who were investigated because of chest pain and an abnormal non-invasive test (either treadmill exercise test or exercise radionuclide ventriculogram) were found to have no significant coronary artery disease and underwent left ventricular biopsy. In addition, seven patients with hypertension and a systolic aortic valve murmur were found to have a non-significant aortic valve gradient at catheterisation; left ventricular biopsy was also carried out on these patients.

Methods

1. Left ventricular mass was calculated in all patients from the M-mode echocardiogram using the cube formula

and the "Penn" convention as described in chapter 5.

2. Left ventricular ejection fraction was estimated from the left ventricular cineangiogram taken in the 30 degree right anterior oblique projection. The angiogram was recorded onto 35 mm film as described in chapter 9. The image was then projected onto a screen and the outline of the ventricle at both end-systole and end-diastole traced onto transparent paper. Left ventricular volumes at end-systole and end-diastole were then calculated according to the method described by Greene et al (211):

$$V = \frac{3.14}{6} LM2$$

where,

V = volume

L = long axis of the ventricle

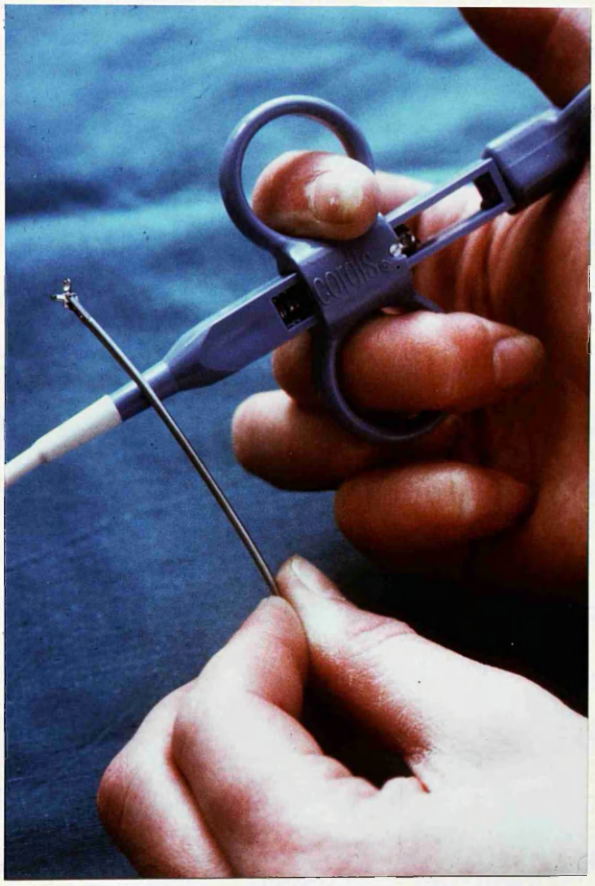
M = short axis taken at right angles to the midpoint of L

Ejection fraction was then calculated as follows:

percutaneously for biopsy of the right or left ventricle. The tissue obtained can then be analysed by histological, immunochemical, virological or enzymatic techniques.

In our routine practice, biopsy is carried out at the end of cardiac catheterisation. Since formation of mural thrombus with subsequent embolism seems potentially a greater hazard than perforation of an already thick left ventricular wall, all biopsies are carried out with the patient heparinised, and the heparin effect reversed with protamine sulphate at the end of the procedure. Using the Seldinger technique, the coronary catheter and short sheath are replaced by a size 7F "pigtail" catheter and long sheath with a valve at the proximal end. The guide wire is removed and the catheter flushed and connected to the pressure transducer. The catheter tip is manipulated into the left ventricle using both the pressure recordings and the X-ray screening unit to determine its position. The catheter is then withdrawn, leaving the distal end of the sheath in the ventricle. The lumen of the sheath is then flushed with saline via a side-port. Finally, the biopsy forceps (shown in figure 10) are advanced and the jaws opened as soon as the forceps project out of the sheath. The open forceps are then advanced against the ventricular wall, closed and withdrawn. The procedure is repeated from three to five times, the angulation of the sheath being adjusted after each

Figure 10
Biopsy forceps as used for left ventricular biopsy.
(shown with jaws open)



biopsy so that samples are taken from different areas of the ventricle. The biopsy samples are then prepared for light microscopy in the standard way.

B. Risk of biopsy

At the Western Infirmary, over one hundred patients have now undergone cardiac biopsy. There have been no deaths, and, among the twenty-seven patients described in this analysis, no side-effects with the exception of short-lived ventricular arrhythmias (usually five to ten complexes) as the biopsies are taken. In other patients undergoing endomyocardial biopsy, the most serious complication has been haemopericardium which has occurred twice following attempted right ventricular biopsy and once during left ventricular biopsy on a patient with a dilated ventricle and active myocarditis. In all three cases, the haemopericardium was confirmed by echocardiography; surgical intervention has not been required. In addition, one patient developed a transient ischaemic episode approximately twelve hours after biopsy, presumably as a result of embolism from a mural thrombus; fortunately this resolved completely.

In 1980, Richardson reviewed the published world-wide complications of endomyocardial biopsy (213). Of a total of 2337 biopsies, haemopericardium occurred in nine patients (0.38%) requiring surgery in six (0.26%).

Dysrhythmia occurred in 0.81% and other complications were rare. No deaths were reported.
Thus left ventricular biopsy appears to be a relatively safe procedure which adds little to the risk of standard cardiac catheterisation.

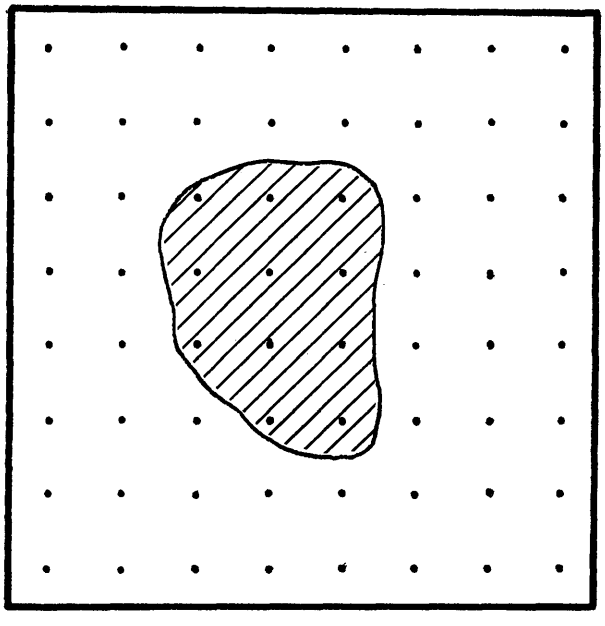
C. Biopsy analysis - theory and practice

1. Theory

The principle of point counting is as follows: if we superimpose a grid containing a number of dots or points on a transected area, we can count the number of points overlying a given "area of interest" and divide this by the total number of points to derive the "area fraction" occupied by our region of interest. This is illustrated in figure 11. Having calculated the area fraction in two dimensions in this way, it has been shown that this approximates to the volume fraction in three dimensions (214).
The major problem with this technique is in deciding how many points to count and this has been the subject of some controversy. There are two issues to consider:

1. The greater the number of points counted, the greater will be the accuracy of the technique.
2. The smaller the area fraction of the substance or tissue being measured, the greater will be the total

Figure 11
Principle of point counting



The square grid contains 64 points, each one at the centre of a square. We can estimate the "volume fraction" of the area of interest (shaded area) by expressing the number of points inside this area as a fraction of the total number of points.
i.e. volume fraction of shaded area = 11/64 = 0.172.

number of points required for a given degree of accuracy.

The optimum number of points to count can be expressed using binomial statistics as follows:

$$RSE = \frac{1-Vv}{\sqrt{n}}$$

where RSE = relative standard error

Vv = volume fraction of interest

n = number of points falling on an area of interest (number of "hits")

If the area fraction under investigation does not vary greatly from one specimen to another, then the recommended technique is to calculate the number of "hits" required for a given error that is considered acceptable, say 5%, and then to continue counting until this number of "hits" is achieved. All measurements will then have a similar error. However, analysis of the first myocardial biopsies revealed that the area fraction occupied by fibrous tissue could vary between 0% and 30%. Clearly, if there was no evidence of fibrous tissue in a specimen, then there would be no "hits" and the optimum number of points to count would

be infinite. Thus some compromise in the methodology was required. Preliminary analysis of the first ten biopsies suggested that the mean percentage area staining positively with either Masson's connective tissue stain or Elastica van Gieson stain might be around 5%. If we then consider an error of 5% to be acceptable, we can calculate the number of points to be counted as follows:

$$\text{relative standard error} = \frac{1-Vv}{\sqrt{n}}$$

$$0.05 = \frac{1-0.05}{\sqrt{n}}$$

$$\sqrt{n} = \frac{0.95}{0.05}$$

$$n = 361$$

However, n represents the number of hits required; since Vv = 0.05, the total number of points to be counted (N) to achieve a relative standard error of 5% is equal to 361 x 20 = 7220. Thus it was decided to count 8000 points in each biopsy although we have to

accept that the relative error increases as the area fraction occupied by our area of interest (i.e. the percentage fibrosis) falls. Table 35 illustrates the relative standard error for different values of Vv ranging from 40% to 0.1%. Thus when Vv equals 5%, the error of the method is just under 5%; when Vv equals 1%, the error rises to 11%. When viewed in the context of the results section to follow, errors of this magnitude appear to be acceptable although clearly it would be wrong to discriminate between groups with low values for Vv since the error within each measurement at this level is large.

2. Practice

Having decided on the number of points to be counted, endomyocardial biopsies from 27 patients were analysed. Full documentation of left ventricular function (ejection fraction measured at angiography), left ventricular structure (left ventricular mass estimated echocardiographically), coronary anatomy and the presence or absence of ventricular arrhythmia during ambulatory monitoring was available in all patients. To eliminate any bias, biopsies were identified by their specimen number only and thus the identity of the patient was unknown at the time of microscopy. A standard binocular microscope (ERNST LEITZ WETZLAR) with 10X eyepiece lenses and a 40X objective lens was

TABLE 35

CALCULATION OF STANDARD ERROR FOR DIFFERENT VALUES OF "n"

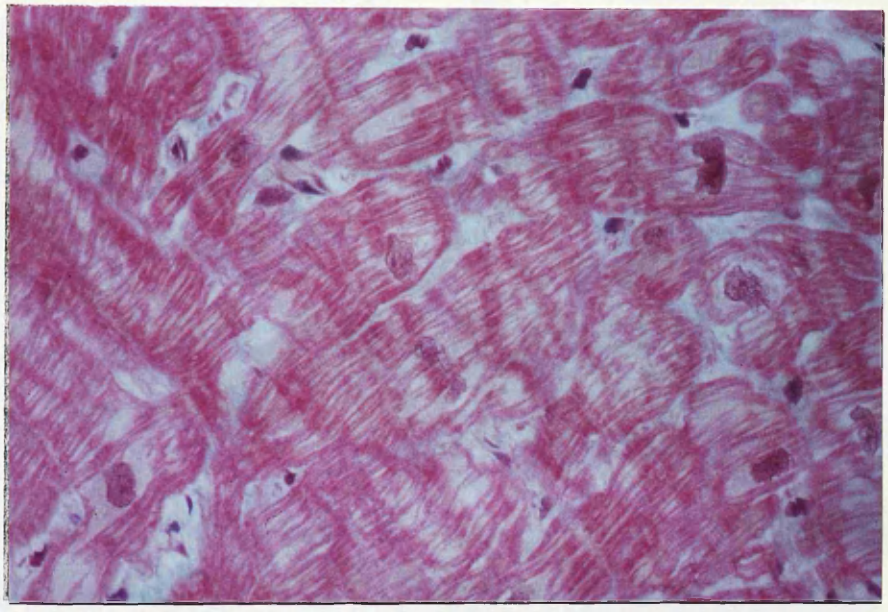
PERCENTAGE HITS	1-Vv	n	$\sqrt{n}$	RELATIVE STANDARD ERROR
40	0.6	3200	56.6	0.011
20	0.8	1600	40.0	0.020
10	0.9	800	28.3	0.032
5	0.95	400	20.0	0.048
1	0.99	80	8.94	0.110
0.5	0.995	40	6.32	0.157
0.1	0.999	8	2.83	0.353

used. A "Chalkey" graticule with 25 points randomly distributed was inserted into the right eyepiece. Sections stained with Masson's connective tissue stain and Elastica van Gieson stain were then examined separately. The former stains collagen and other extracellular protein green while the latter stains collagen purple. For each stain, eighty high power fields were examined. From each patient, there were between two and five biopsies and a variable number of slices had been taken serially through each biopsy. To count eighty high power fields, I started at a preselected corner of the first section of the first biopsy and worked diagonally towards the opposite corner. The process was repeated on all available sections from each biopsy from that patient. If this did not result in eighty fields, as might occur if few biopsies had been obtained or if the biopsies themselves were particularly small, the process was repeated starting at a different corner of the same sections until eighty fields had been counted. The only requirements of a "field" were that it had to be completely filled by tissue and that it did not include the endocardium since the aim was to measure subendocardial connective tissue and thus the normal endocardial collagen was excluded. At times, the endocardial surface had been cut tangentially causing the endocardial connective tissue to appear to lie in the deeper subendocardium; fields showing this

Figure 12

Examples of myocardial histology
Masson's trichrome connective tissue stain

(a) Normal myocardium (x400)



(b) Myocardium showing increased fibrous tissue (Green staining) - (x400)

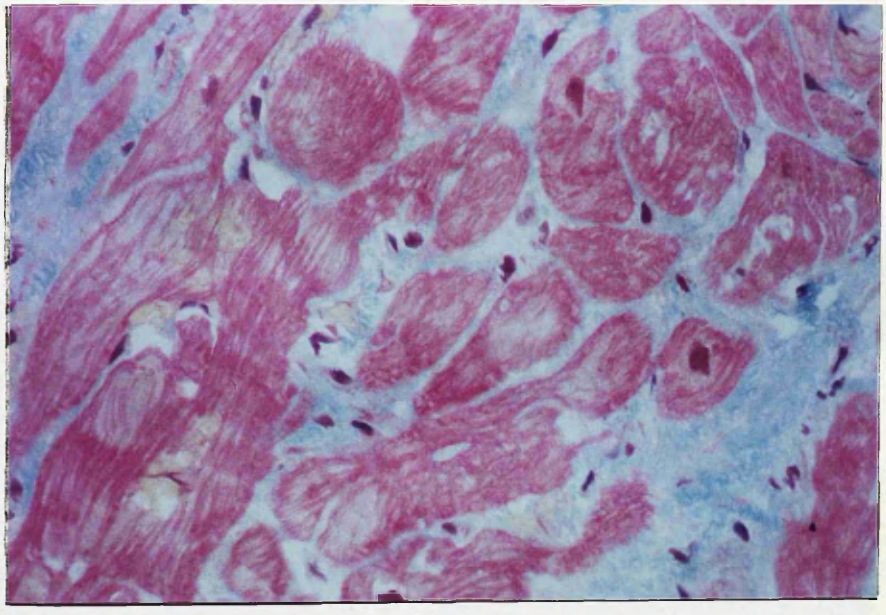
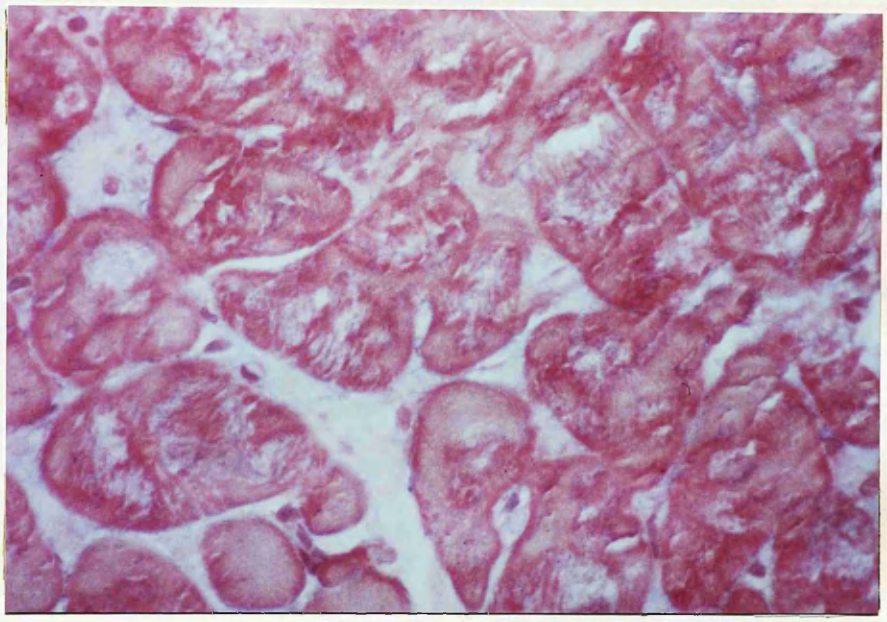


Figure 13

Examples of myocardial histology
Elastica/Van Gieson stain

(a) Normal myocardium (x400)



(b) Myocardium showing increased fibrous tissue (Purple staining) - (x400)

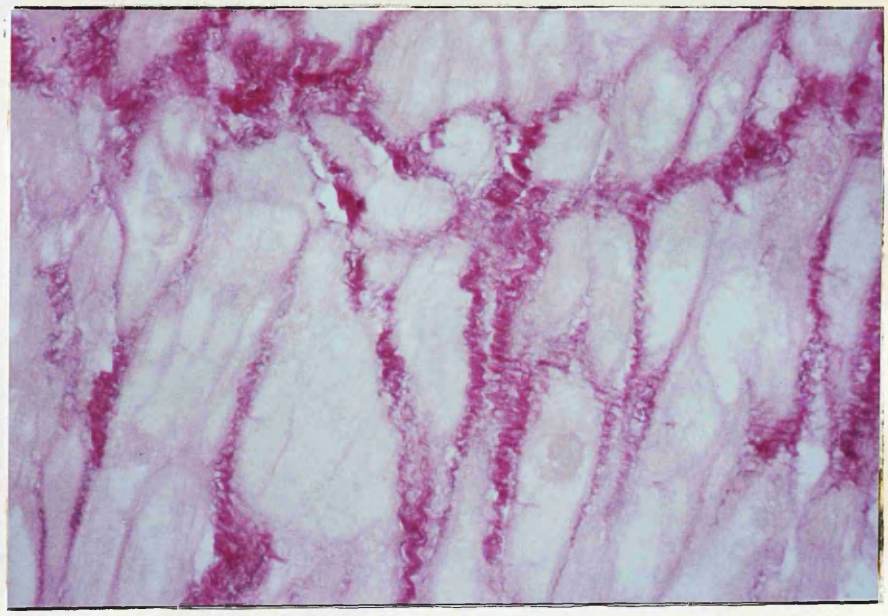
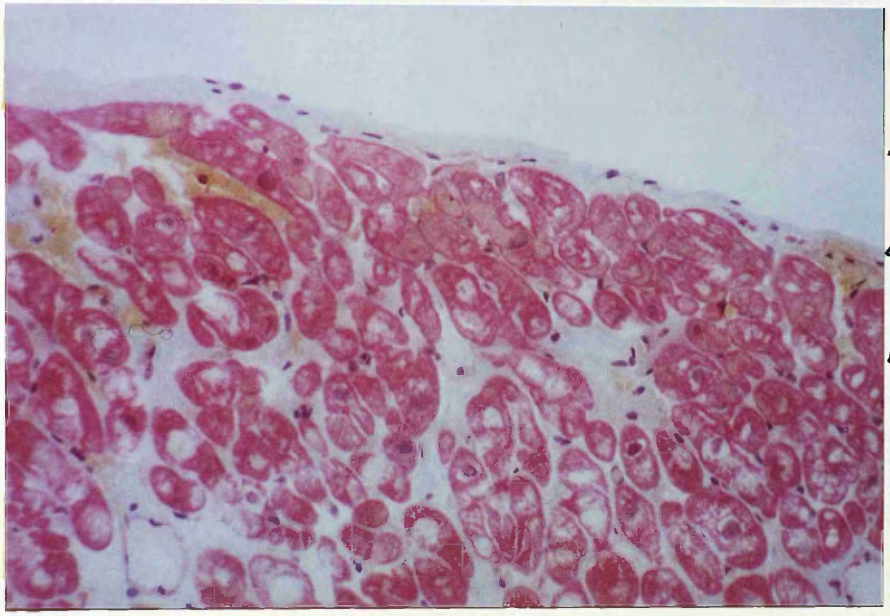


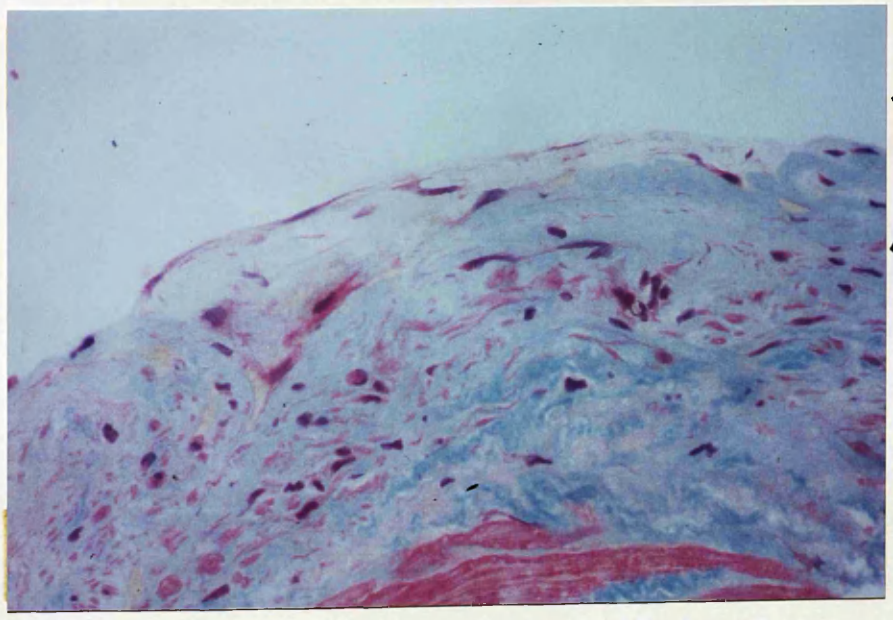
Figure 14

Illustration of Endocardial Thickening

(a) Normal endocardium (x200) -Masson's Stain



(b) Abnormally thickened endocardium (x200) - Masson's Stain



appearance were also excluded.

For each field, a total of 100 counts were made by rotating the 25 point eyepiece lens through 90 degrees three times thus yielding a total of 8000 points counted per patient. The number of "hits" was then divided by eighty to obtain the percentage fibrosis (EVG stain) and the percentage interstitium (Masson). Examples of the two stains are shown in figures 12 and 13. Although no quantitative assessment of endocardial thickness was made, it was noted that those patients with marked fibrosis also tended to have thickening of the endocardium. This is illustrated in figure 14.

Results

Data relating to age, sex, degree of left ventricular hypertrophy, and left ventricular function for the two groups are shown in tables 36 and 37 and the results summarised in table 38. The two groups were of course not matched for symptoms or indication for cardiac catheterisation, but in other respects they were similar. Mean age for those with VT was 56$\pm$4 years (range 30-69 years) compared to 54$\pm$2 (range 30-68 years) for those without VT (NS). Sex distibution was also similar in the two groups. Ejection fraction measured at cardiac catheterisation is plotted for both groups in figure 15. The group with VT shows a wider range of ejection fractions (from 15% to 80%) and has a

mean ejection fraction that is lower, although not significantly so, than the group without VT. Values for left ventricular mass for the two groups are shown in figure 16. Taking 200 g as an approximate upper limit of normal for left ventricular mass, all of those with VT and 13/17 of those without had LVH. However, the degree of left ventricular hypertrophy was more marked in those with VT (442±28 g vs 339±34g, p=0.037).

The results of the histological analysis are shown in table 39 and demonstrated graphically in figures 17 and 18. The biopsy results for the two groups were compared using a two-tailed t-test for unpaired data. The area fraction, and thus volume fraction, occupied by both interstitium (figure 17) and fibrous tissue (figure 18) was significantly greater in those with ventricular tachycardia than in those without (19±4% vs. 3±1% for interstitium, ($p<0.001$), and 13±3% vs. 2±1% for fibrosis, ($p<0.001$)).

The relationships between myocardial fibrosis and hypertrophy, and between myocardial fibrosis and left ventricular function, are examined in figures 19 and 20 respectively. Although most patients with more than 10% fibrosis did have marked hypertrophy, the reverse was not true and overall there was no significant correlation between the two variables (figure 19). There was, however, a significant correlation between ejection fraction and percent fibrosis. Four patients had ejection fractions less than 30% (normal range

TABLE 36

CHARACTERISTICS OF PATIENTS WITH LVH AND VT IN WHOM SUCCESSFUL BIOPSY ACHIEVED:

INITIALS	AGE (years)	SEX	LV MASS (g)	LVEDP (mmHg)	EJECTION FRACTION (%)
JC	58	M	362	9	73
MO	68	F	387	12	70
AM	30	F	598	11	54
JB	69	M	401	16	29
MP	46	F	296	12	73
TC	61	M	475	15	70
MM	67	F	417	4	80
RS	44	M	387	20	23
AN	56	M	540	18	15
DD	48	M	442	9	77
MA	66	F	561	20	24

TABLE 37

CHARACTERISTICS OF PATIENTS WITH LVH BUT WITHOUT VT ON 48 HOUR AMBULATORY MONITORING IN WHOM SUCCESSFUL BIOPSY ACHIEVED:

INITIALS	AGE (years)	SEX	LV MASS (g)	LVEDP (mmHg)	EJECTION FRACTION (%)
IR	42	M	302	8	74
JD	59	M	189	20	50
JW	62	M	612	11	74
JM	61	M	196	9	68
JM	30	M	563	14	64
IM	44	F	261	7	64
RD	60	M	485	12	69
HM	63	M	294	16	66
CM	58	F	175	8	74
JS	68	F	274	7	57
NG	50	M	286	20	40
EO	55	F	170	16	64
JH	59	M	327	11	65
LM	43	M	497	9	65
WM	62	M	375	10	65
EK	43	F	476	9	43
PL	52	M	278	11	59

TABLE 38

HAEMODYNAMICS AND OTHER VARIABLES IN PATIENTS WITH AND WITHOUT VT

	HYPERTENSIVES WITH VT (n=11)	HYPERTENSIVES WITHOUT VT (n=17)
AGE (YEARS)	58±4	54±2
M:F	8:3	13:4
LV MASS (g)	442±28	339±34 *
LVEF (%)	53±8	62±2
LVEDP (mm Hg)	13±2	12±1

* $p<0.05$

TABLE 39

BIOPSY FINDINGS - ALL PATIENTS

INITIALS	% INTERSTITIAL PROTEIN	% FIBROSIS
JC	11.5	12.8
MO	16.2	8.8
AM	11.8	9.0
JB	18.0	9.4
MP	23.0	12.4
TC	5.7	3.4
MM	4.2	5.0
RS	18.6	29.8
AN	43.9	16.4
DD	14.2	6.8
MA	41.4	31.2
IR	15.3	9.6
JD	4.3	3.6
JW	0.2	1.4
JM	8.0	5.4
JM	2.2	1.6
IM	2.2	2.0
RD	3.9	2.2
HM	0.0	0.0
CM	0.6	2.0
JS	1.2	2.4
NG	0.0	0.0
EO	6.2	7.6
JH	0.2	0.4
LM	2.6	1.0
WM	0.5	0.4
EK	0.3	1.6
PL	2.4	1.6

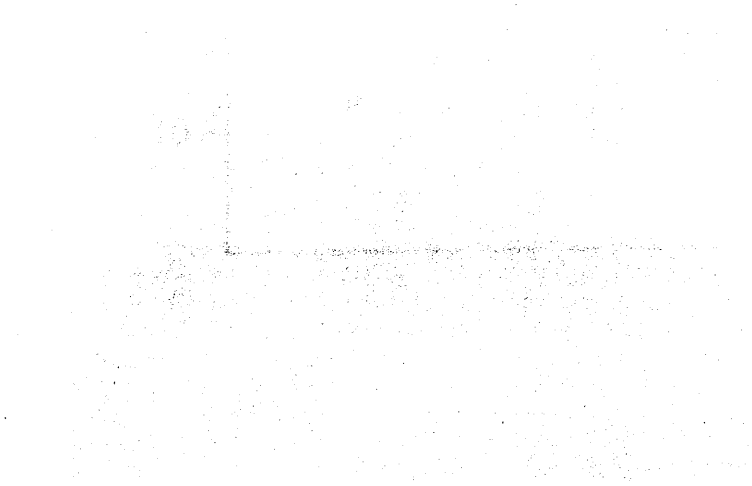


Figure 15
Ejection fraction values for patients with and without ventricular tachycardia

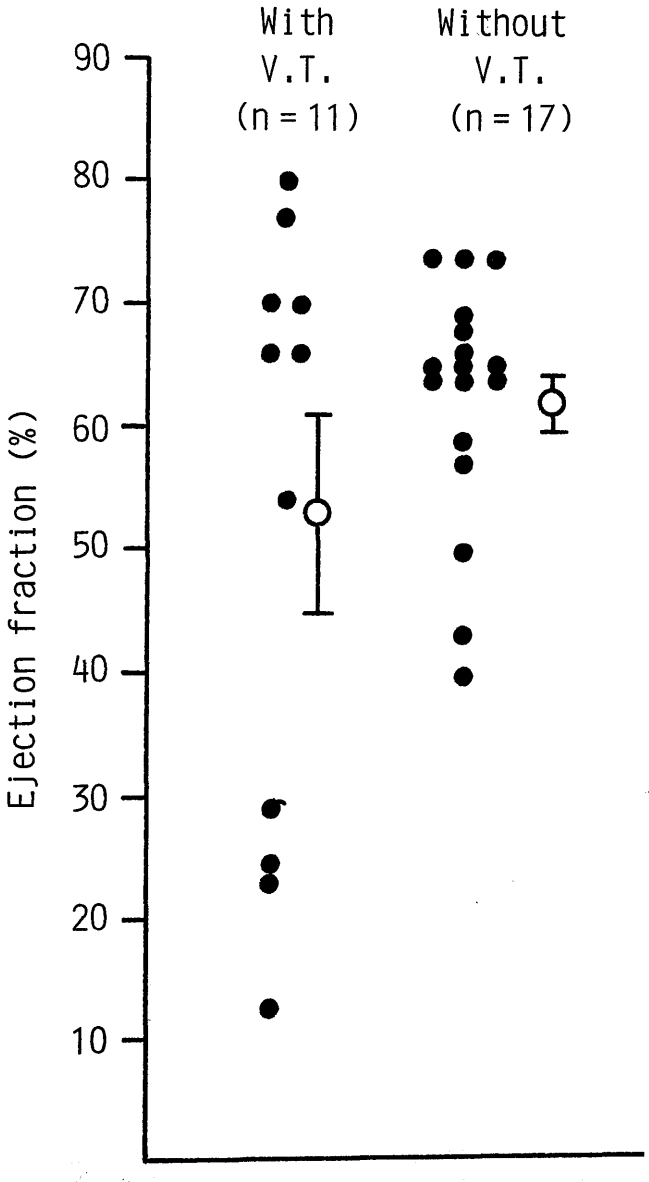


Figure 16
Left ventricular mass for patients with and without ventricular tachycardia

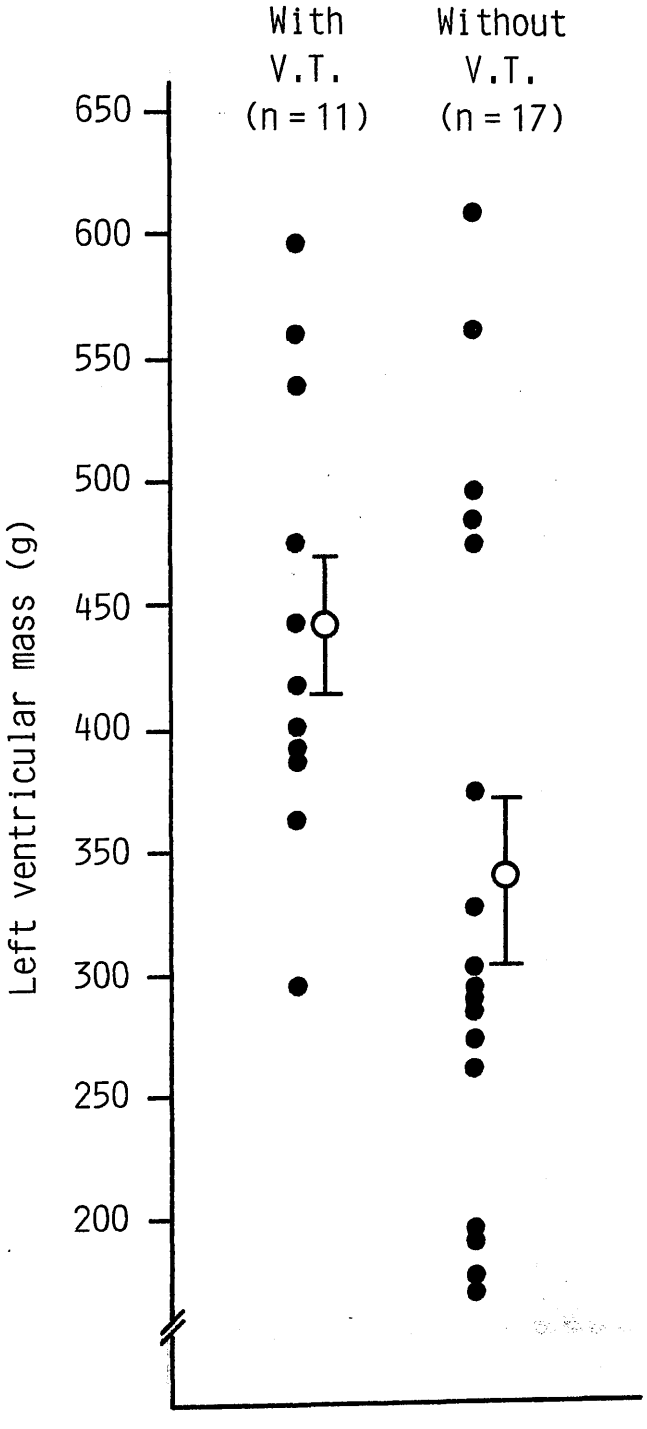


Figure 17
% interstitial volume in patients with and without ventricular tachycardia

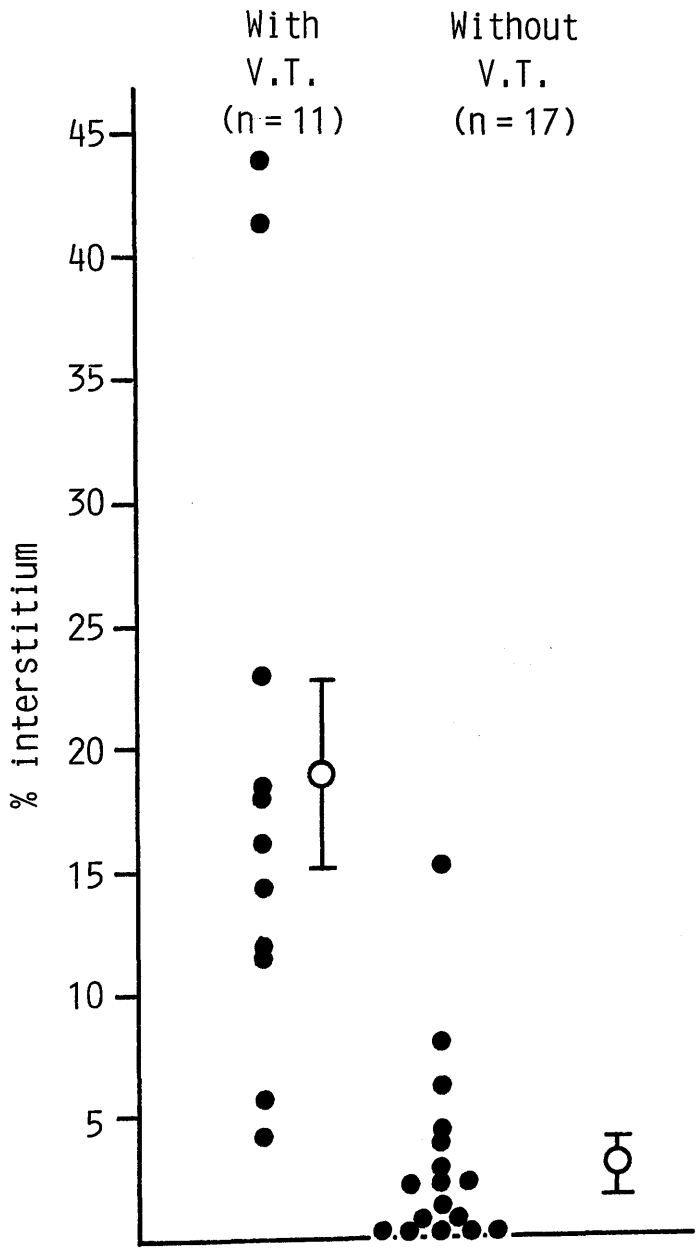


Figure 18
% volume of fibrosis in patients with and without ventricular tachycardia

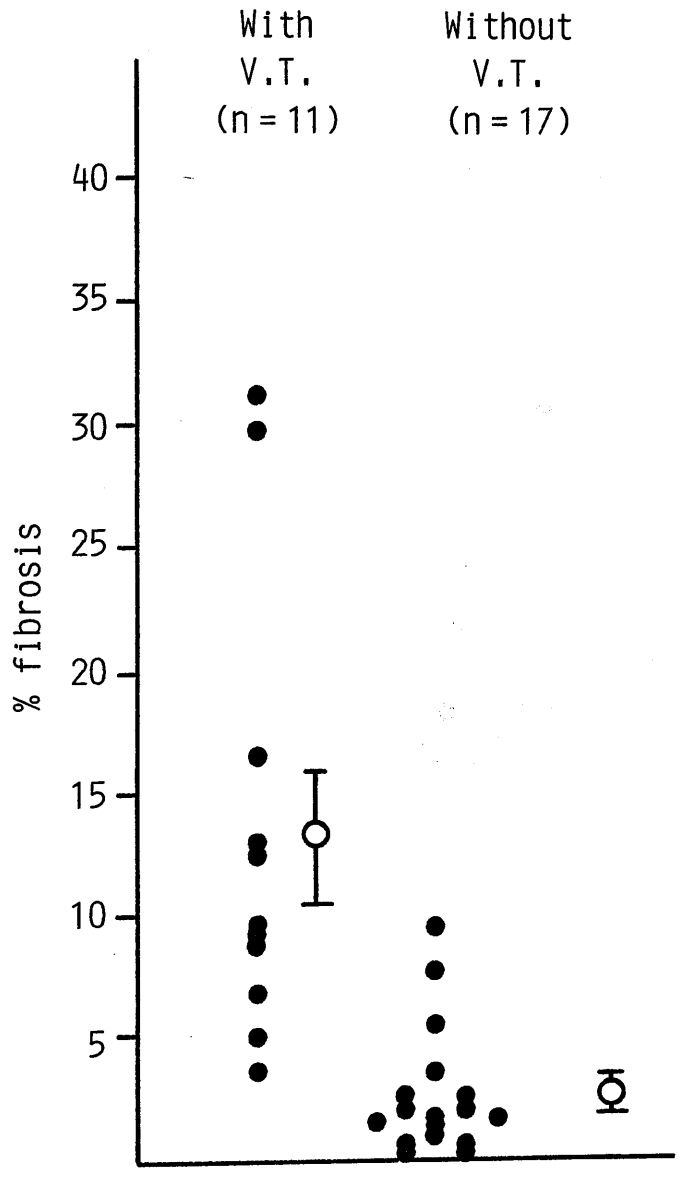


Figure 19
Relationship between left ventricular mass and fibrosis

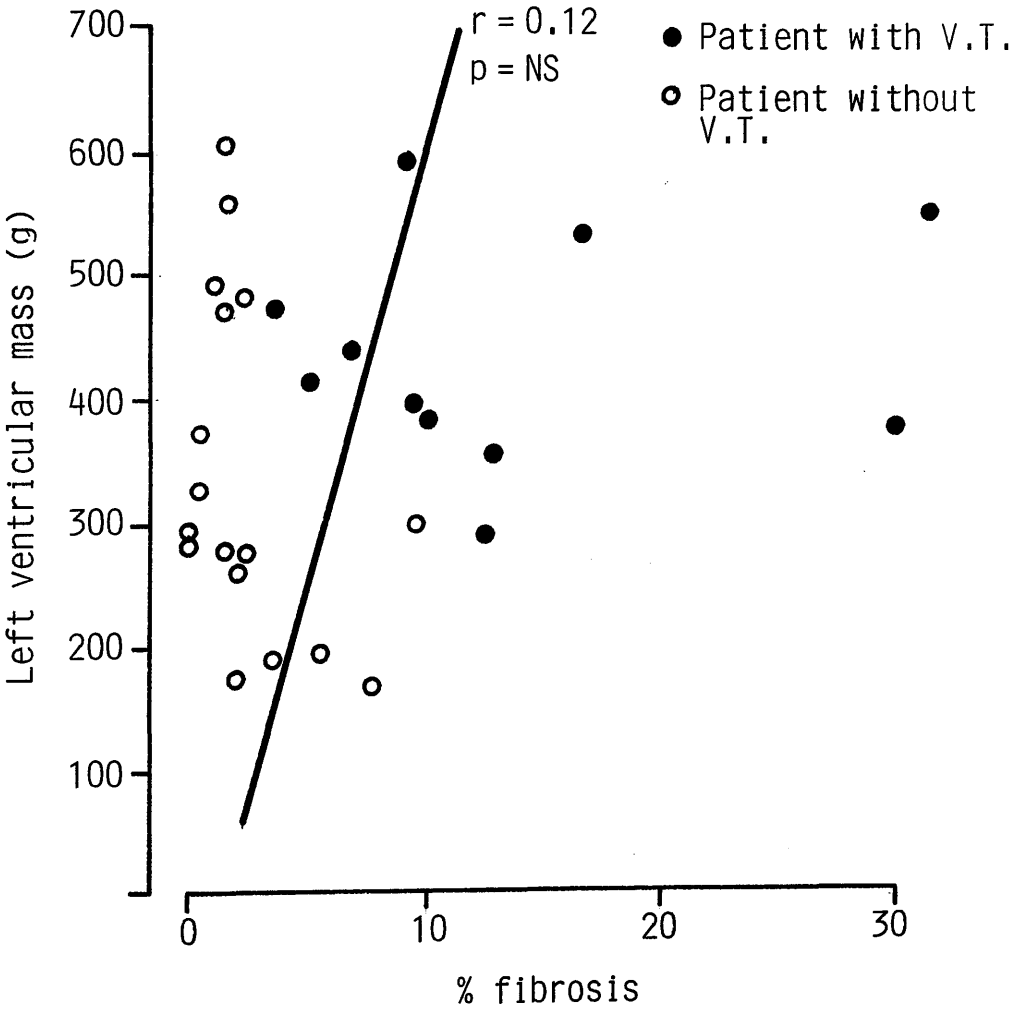
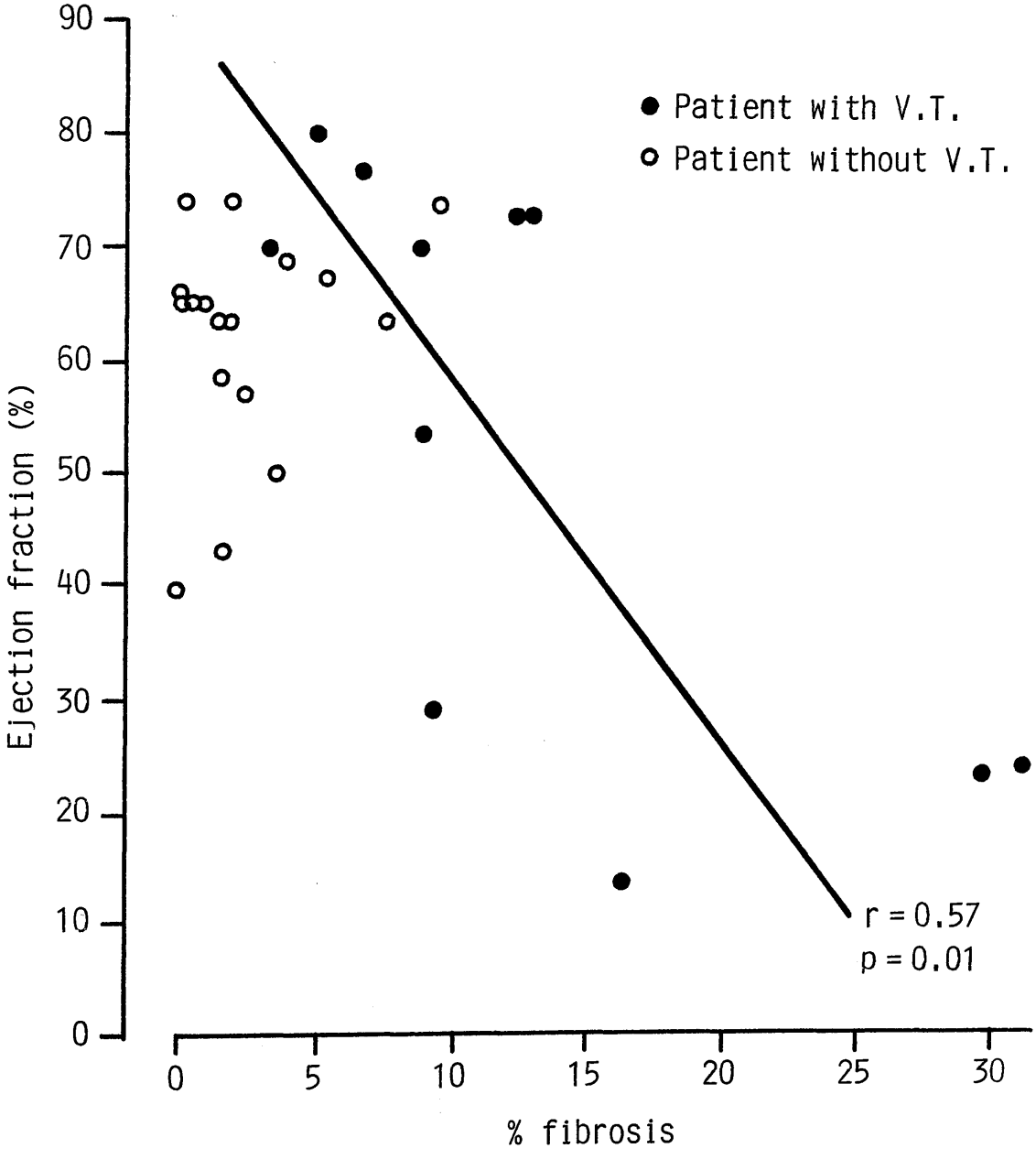


Figure 20
Relationship between left ventricular function and fibrosis



45-70%); all four had significant amounts of myocardial fibrosis and two had approximately 30% fibrous tissue by volume. Overall, there was a weak inverse correlation between ejection fraction and % fibrosis (figure 20) although several patients with up to 12% fibrous tissue by volume still had a normal ejection fraction.

Discussion

These results demonstrate a relationship between the occurrence of ventricular arrhythmias and the amount of interstitial and fibrous tissue present on endomyocardial biopsy. In addition, there is a positive inverse relationship between ejection fraction and fibrous tissue content but no significant relationship between degree of hypertrophy and fibrous tissue content, suggesting that factors other than hypertrophy contribute to the development of fibrosis.

No other study has been reported relating quantitative histological features with arrhythmias in hypertensive patients. Other studies, however, have attempted to quantify the amount of fibrous tissue in hypertrophied hearts. Oldershaw et al used a similar point counting technique on myocardial biopsies taken from ninety-seven patients with aortic valve disease (215). In fifty-five patients with aortic stenosis, they found a distribution of values for percentage volume fibrosis

that was similar to our series, the range being from 0% to 30%. They found a positive relationship between fibrosis and aortic valve gradient and a negative relationship between fibrosis and left ventricular ejection fraction. They found no relationship between fibrosis and the presence of co-existent coronary artery disease. Follow-up analysis showed that percentage fibrous tissue was correlated with mortality. Hess et al have assessed the fibrous tissue content in patients with primary left ventricular hypertrophy (hypertrophic cardiomyopathy and congestive cardiomyopathy) and hypertrophy secondary to aortic valve disease, and related this to cardiac function (216). They found morphological alterations to be most marked in those with hypertrophic cardiomyopathy and least marked in those with aortic valve disease, although the latter group still had approximately 20% myocardial fibrosis. In both of these groups, systolic function remained normal despite fibrosis. In those with congestive cardiomyopathy, systolic function was impaired, this being attributed to "inadequate hypertrophy" by the authors. Diastolic function, however, was abnormal in the majority of patients and the degree of impairment was related to the extent of myocardial fibrosis. Baandrup et al have also quantitatively assessed endomyocardial biopsies but found no significant relationship between the amount of collagen present and either haemodynamic variables or

symptomatic status (217). Their study group, however, comprised a heterogeneous group of patients suspected of cardiomyopathy, small vessel disease and myocarditis.

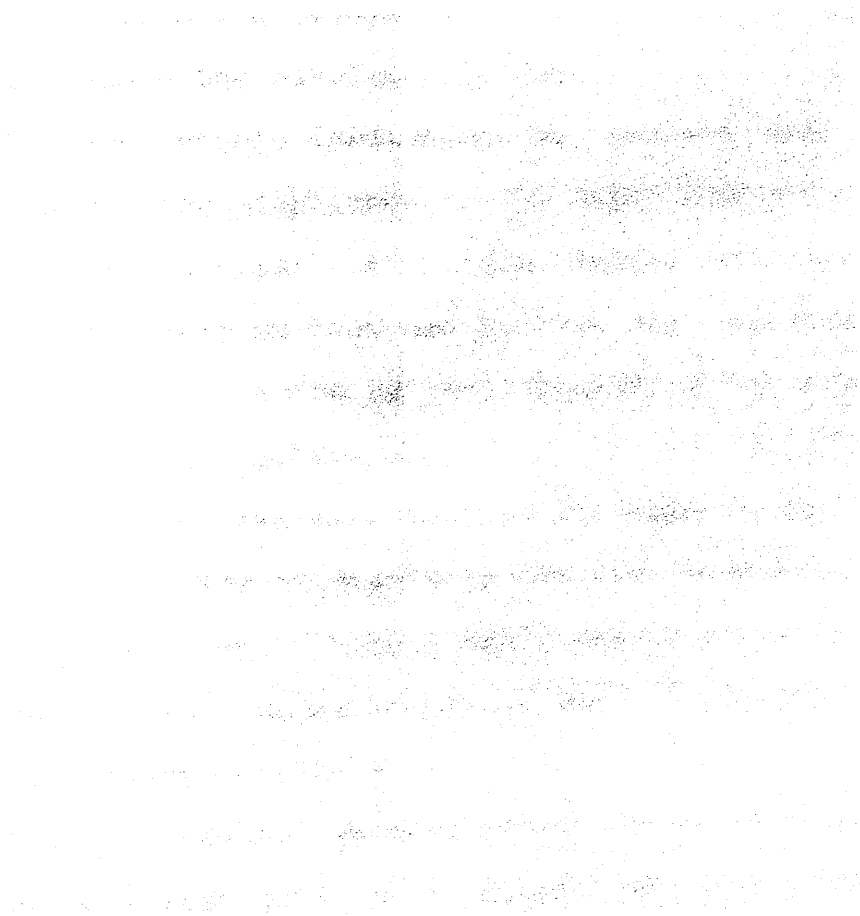
In all studies of quantitative histology, reference is made to the limitations inherent in the technique. First, the pathological process under investigation may be patchy and may be missed by the biopsy; this is particularly likely to occur in inflammatory or infiltrative disorders such as myocarditis or sarcoidosis. Even if the process is diffuse, there may be considerable variation from one part of the ventricle to another. Baantrup et al have studied the regional variation in cell diameter, volume fraction of interstitium and of collagen in biopsies from twenty-three hearts; they found the coefficients of variance for these three varibles to be 18.6%, 28.9% and 80.5% respectively and suggested that at least five biopsies should be obtained before attempting to correlate structural changes with the functional state of the heart (217,218). A further problem in trying to correlate structural changes seen on biopsy with cardiac function is in knowing to what extent subendocardial changes are representative of changes throughout the thickness of the left ventricular wall. This relationship between the site and extent of fibrosis and left ventricular hypertrophy has recently been examined in a post-mortem study by a Japanese

group (219). They carried out quantitative analysis of the entire left ventricular wall in twenty normal hearts, ten hearts from patients with hypertrophic cardiomyopathy and ten from hypertensive patients. In those with hypertrophic cardiomyopathy, they found significantly more fibrosis in the septum than in the free wall of the ventricle. In the hypertensive hearts, the distribution of fibrosis was more uniform, there being no significant difference between the septum and the free wall. There was, however, a marked transmural difference, the surface area of fibrosis being almost four times greater in the inner third (subendocardium) than in the outer third (subepicardium).

Thus there are good reasons for caution when attempting to correlate subendocardial histological changes with alterations in global left ventricular function. However, these arguments do not invalidate the data relating to arrhythmias since the aim of this analysis was to identify any structural changes, focal or diffuse, that might be associated with ventricular arrhythmia and because any abnormalities present were likely to be most marked in the subendocardium.

In summary, we found an association between myocardial fibrosis and ventricular arrhythmia; ten of eleven patients with ventricular tachycardia had >5% fibrosis by volume (figure 19) compared with only three of seventeen of those without VT ($p<0.01$). There were differences in left ventricular mass between the two

groups but these were less marked; while all of those with VT had left ventricular mass values greater than 250g, thirteen of seventeen of those without VT also had high left ventricular mass. Thus it appears that hypertrophy with fibrosis rather than hypertrophy alone is important in the pathogenesis of ventricular arrhythmia in hypertensive patients.



CHAPTER 11

VENTRICULAR COMPLIANCE IN HYPERTENSIVE LEFT VENTRICLUAR HYPERTROPHY

Introduction

We have demonstrated that ventricular arrhythmias occur commonly in hypertensive patients with left ventricular hypertrophy and have suggested that the frequency of arrhythmia may contribute to the high mortality associated with this ECG abnormality. However, factors other than the origin and rate of a tachyarrhythmia can influence the cardiac response.

In hypertrophic cardiomyopathy, reduced left ventricular compliance is the major abnormality of cardiac function (167); this becomes important particularly at high heart rates and when effective atrial contraction is lost, both of which occur during ventricular tachycardia.

In hypertensive left ventricular hypertrophy, similar abnormalities of diastolic function have been reported (220) and, as in hypertrophic cardiomyopathy, they may be important determinants of the haemodynamic response to a tachyarrhythmia.

For this reason, we have investigated the relationship between left ventricular hypertrophy and diastolic function in three groups of hypertensive patients

matched with each other for age and sex but with varying degrees of left ventricular hypertrophy. Diastolic function was assessed by measurement of the left atrial emptying index (LAEI) which has previously been shown to be a simple and sensitive assessment of diastolic function (116).

Materials and methods

Subjects

Ten normal control subjects and thirty hypertensives comprising ten without ECG LVH, ten with ECG LVH and ten with LVH and ST-T changes, were studied. All forty had been part of the original cohort of fifty normal controls and one hundred hypertensives. They were selected on the basis of having a high quality M-mode echocardiogram of the aortic root and left atrium and further selected to allow the four groups to be approximately matched for age and sex; in addition, to control for any possible effect of high blood pressure itself on diastolic function, the three hypertensive groups were matched with each other for achieved systolic blood pressure.

Left atrial emptying index

As described by Dreslinski (116), the left atrial

emptying index (LAEI) is estimated from the M-mode echocardiogram recorded through the aortic root and left atrium. This is illustrated in diagramatic form in figure 21. The LAEI is a measure of the proportion of total atrial emptying, and thus ventricular filling, that occurs during the first one-third of diastole. The first third is the rapid "passive" phase of ventricular filling before the onset of atrial contraction. A high value (0.75-1.0) indicates normal ventricular compliance and a low value indicates reduced compliance. As with earlier calculations, measurements were taken over three consecutive cardiac cycles and mean values calculated.

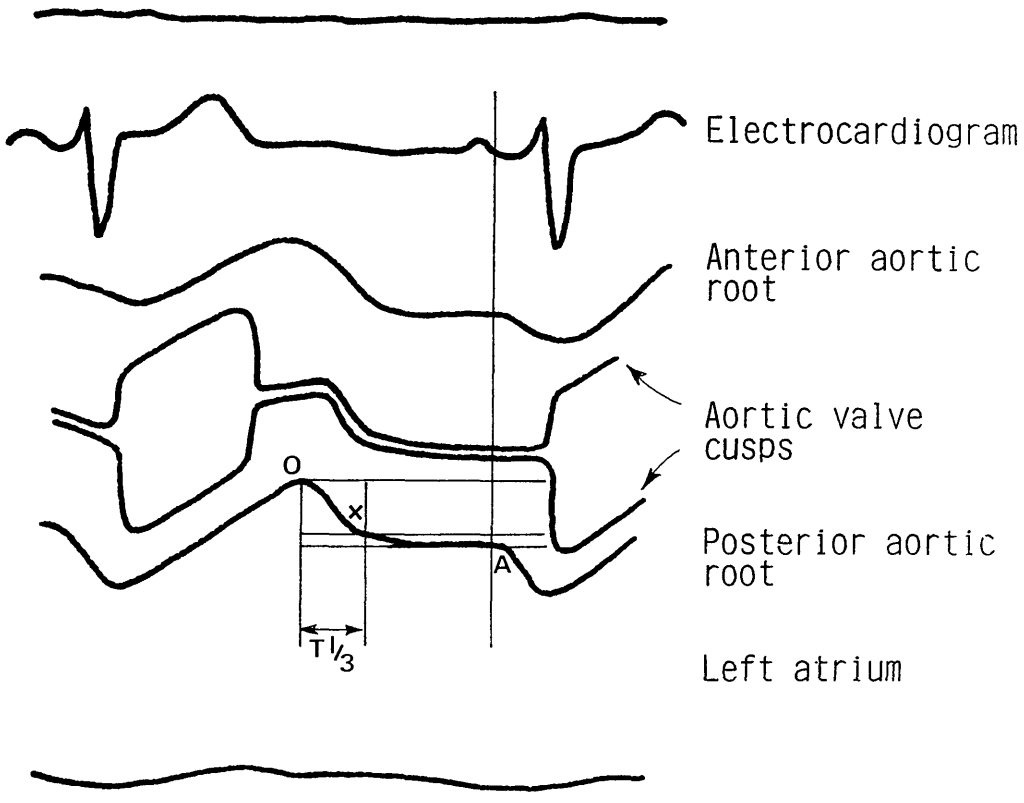
To illustrate the method, two examples are shown in figure 22, one from a normotensive subject with normal diastolic function (figure 22a) and one from a hypertensive patient with marked left ventricular hypertrophy and abnormal diastolic function (figure 22b).

Results

Table 40 shows the blood pressure, left ventricular mass index and atrial emptying index for the thirty hypertensive patients and ten normal control subjects studied; mean values for the four groups are shown in table 41. As before, differences between groups were calculated using a two-tailed t-test for unpaired data

Figure 21

Calculation of left atrial emptying index - Diagram



O = Initial posterior motion of aortic root

A = Aortic root motion after total atrial emptying (end of 'P' wave on ECG)

X = Aortic root displacement after 1/3 total atrial emptying

Then:- Parallel lines are drawn through O,A and X

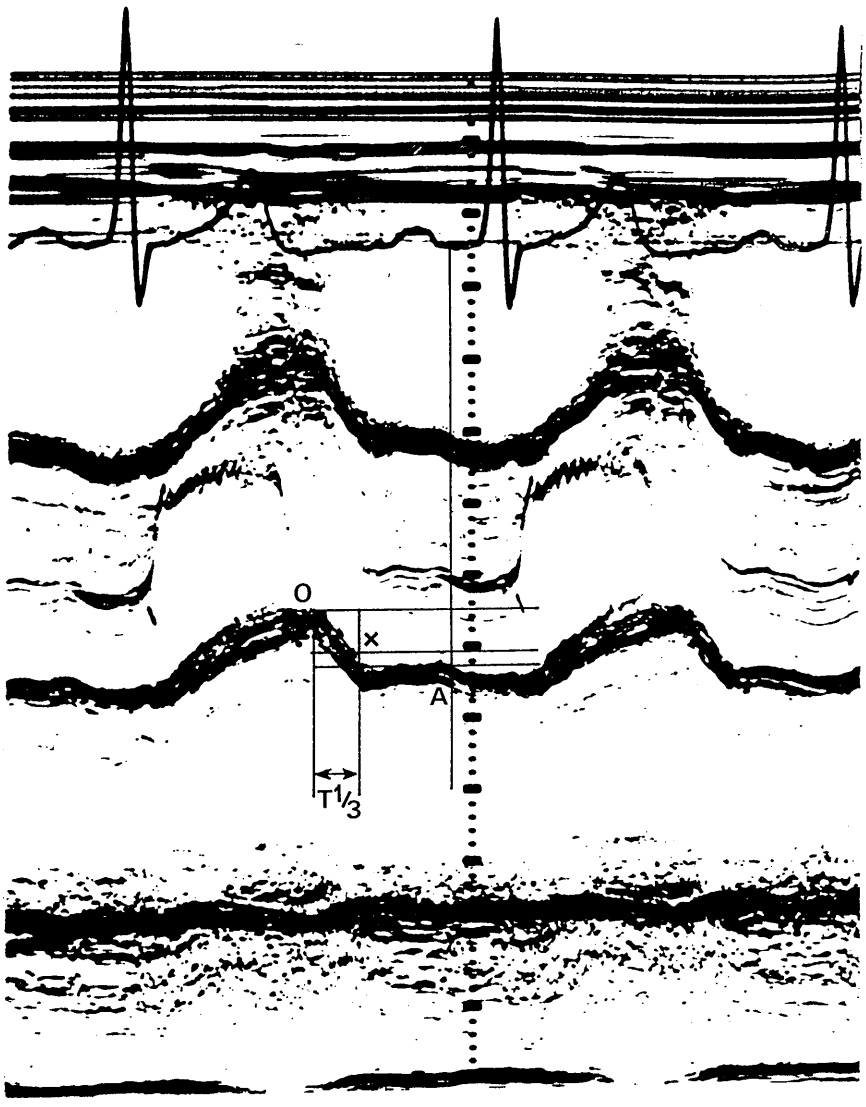
Then:- Atrial emptying index = $\frac{\text{vertical distance O-X}}{\text{vertical distance O-A}} = \frac{6.3}{7.4}$

= **0.851**

Figure 22

Calculation of left atrial emptying index - Examples

(a) Normal control

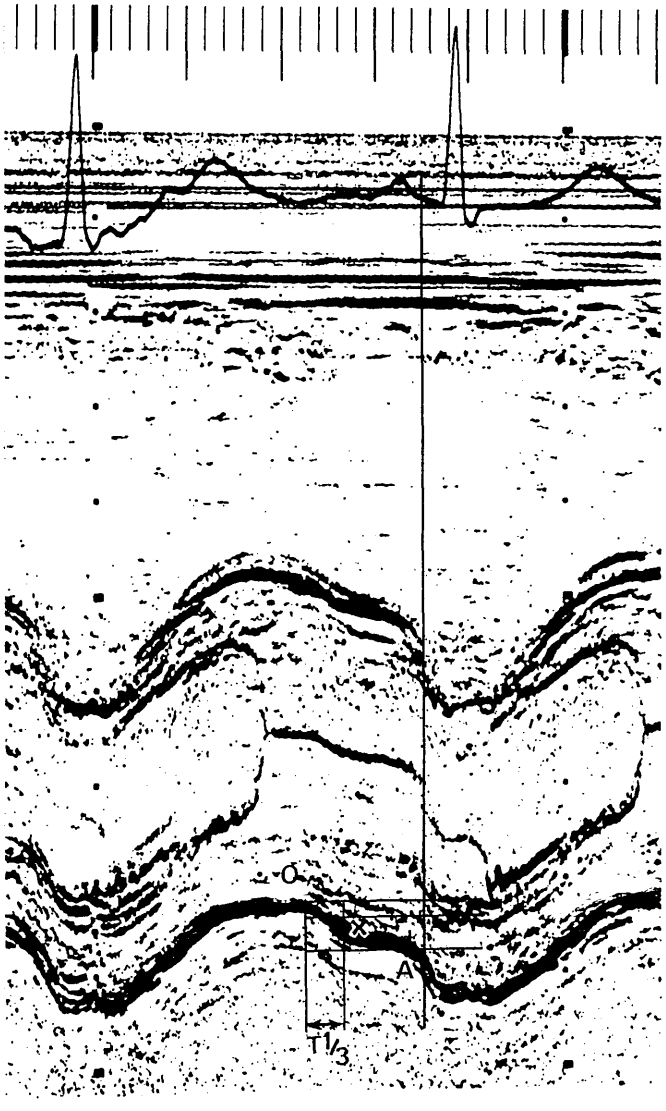


$$\text{Atrial emptying index} = \frac{\text{vertical distance O-X}}{\text{vertical distance O-A}} = 0.769$$

Figure 22 (continued)

Calculation of left atrial emptying index - Examples

(b) Hypertensive patient with left ventricular hypertrophy



$$\text{Atrial emptying index} = \frac{\text{vertical distance O-X}}{\text{vertical distance O-A}} = 0.277$$

TABLE 40

BASELINE AND ECHO DATA FROM THE FOUR GROUPS STUDIED

INITIALS	AGE (years)	SBP (mmHg)	DBP (mmHg)	LVMI (g/m2)	LAEI
a) NORMAL CONTROLS					
JA	56	132	88	102.7	0.839
AW	32	118	86	112.9	0.950
DM	51	124	80	97.2	0.798
AC	76	132	76	119.6	0.445
MH	67	136	64	82.0	0.847
MH	67	132	82	39.1	0.902
RH	54	134	78	116.0	0.781
JS	69	102	68	98.5	0.698
JP	52	157	84	128.8	0.823
DM	42	118	80	102.4	0.884
b) HYPERTENSIVES WITHOUT ECG LVH					
LS	58	165	92	99.0	0.639
MI	63	128	86	54.8	0.817
IM	65	168	86	100.1	0.693
MW	42	161	65	87.1	0.517
AP	60	158	88	58.2	0.746
AM	32	140	80	57.1	0.736
MM	76	212	92	80.3	0.357
DB	62	140	92	114.8	0.558
AM	39	128	92	57.3	0.751
MS	50	128	82	122.5	0.288
c) HYPERTENSIVES WITH ECG LVH					
WS	67	160	86	135.7	0.579
MY	71	175	110	148.4	0.581
SD	36	144	82	132.3	0.309
KB	59	160	92	129.2	0.584
AG	55	150	78	253.4	0.593
MM	30	136	84	129.1	0.733
MI	74	120	90	119.5	0.494
MV	77	166	100	105.7	0.628
AG	66	177	86	183.9	0.483
VM	65	174	90	156.2	0.558
d) HYPERTENSIVES WITH LVH AND STRAIN					
MK	60	138	92	174.5	0.379
JM	29	145	95	304.8	0.388
JB	68	210	104	214.7	0.138
AM	60	132	98	174.8	0.581
TD	71	172	92	178.6	0.584
DJ	62	155	85	218.8	0.306
ES	52	168	94	247.1	0.497
JL	50	140	78	170.8	0.707
MC	51	130	110	153.8	0.172
AM	29	154	108	369.6	0.402

TABLE 41

SUMMARY OF BASELINE DATA

	NORMALS CONTROLS (n=10)	HYPERTENSIVES WITHOUT LVH (n=10)	HYPERTENSIVES WITH LVH (n=10)	HYPERTENSIVES WITH LVH+STRAIN (n=10)
AGE (years)	57±4	55±4 *	60±5 **	53±5 **
SBP (mmHg)	129±5	153±8	156±6 **	154±8 ***
DBP (mmHg)	79±2	86±3 **	90±3 **	95±3 **
HEART RATE (bpm)	75±2	67±3	66±3 **	67±3 ***
LVMI (g/m2)	100±8	83±8	149±13	221±22

* p<0.02 -
** p<0.01 - COMPARED WITH NORMALS
*** p<0.001 -

Results corrected for multiple comparisons (normals vs. the three other groups) using Bonferroni correction factor.

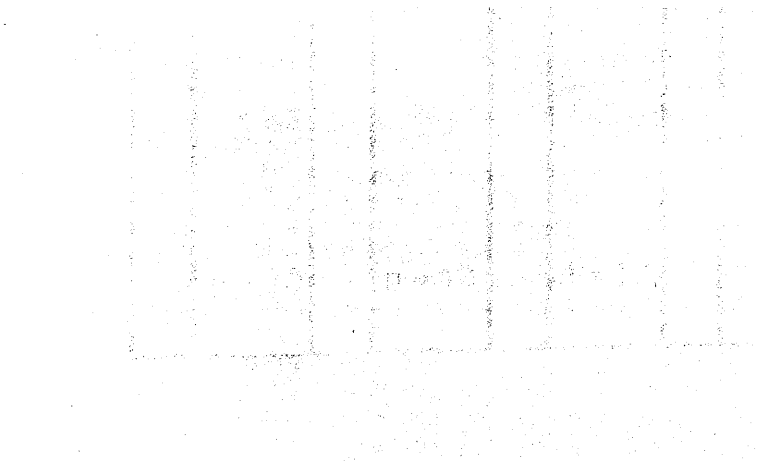
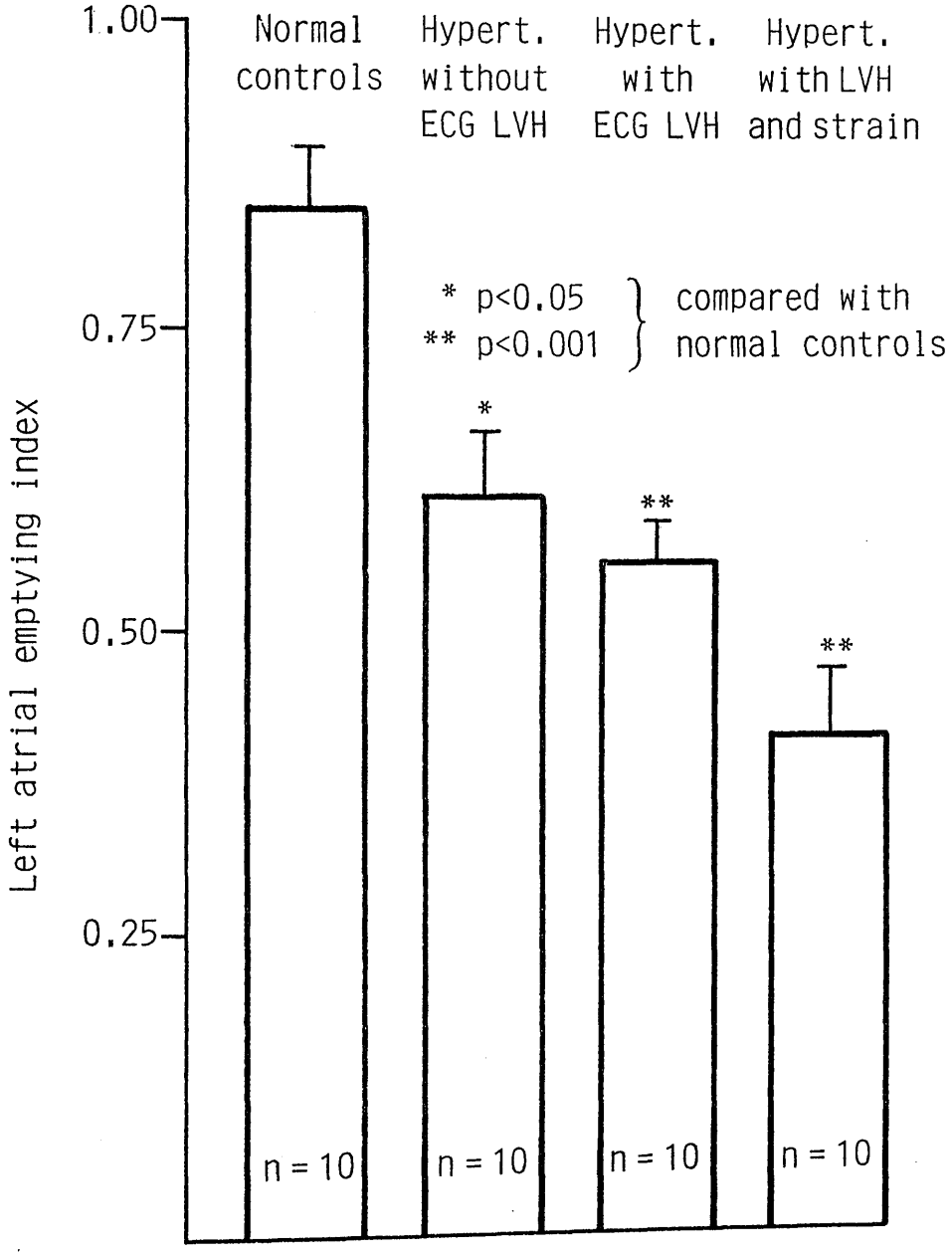


Figure 23
Relationship between left atrial emptying index and ECG LVH



possibility that high pressure itself, by increasing systolic wall tension and producing subendocardial ischaemia, may reduce diastolic compliance and thus atrial emptying index. There is a suggestion in our data that this does occur; figure 23 demonstrates that atrial emptying index is lower in those hypertensives without ECG LVH than in the control subjects despite similar left ventricular mass index values in the two groups. Thus it may be that high blood pressure itself reduces left ventricular compliance. In addition, the effects of heart rate and antihypertensive treatment on left atrial emptying index have not been studied; since all of the hypertensives were on treatment, including a beta blocker in over 50%, this may contribute to the difference between the controls and the hypertensives without left ventricular hypertrophy (figure 23). However, neither heart rate nor blood pressure is likely to explain the differences between the three hypertensive groups (figure 23) since both variables were similar for all three groups (table 41).
Thus the implication is that as left ventricular mass rises, so left ventricular compliance falls and passive left ventricular filling is reduced. The heart then becomes increasingly dependent on effective atrial contraction to maintain ventricular filling and ultimately there is hypertrophy of the atrium with the appearance of the so-called "left atrial strain pattern" on the ECG. The clinical significance is that

if effective atrial contraction is lost, by for example the development of atrial fibrillation or a ventricular arrhythmia, then left ventricular filling and thus cardiac output will be markedly reduced. It is for this reason that the onset of atrial fibrillation in a patient with either aortic stenosis or hypertrophic cardiomyopathy is an ominous prognostic sign, usually accompanied by the development of cardiac failure.

We have not induced ventricular arrhythmias in hypertensive patients with LVH, nor have we measured cardiac output during a spontaneous tachyarrhyhmia, but it is not difficult to imagine that the onset of a ventricular tachyarrhythmia in a patient with a hypertrophied, non-compliant ventricle will lead to a greater fall in cardiac output than would a similar arrhythmia in a normal ventricle.

In summary, we have confirmed the finding of Dreslinski et al (116) that ventricular compliance, assessed by calculation of the left atrial emptying index, is reduced in hypertensives with left ventricular hypertrophy. By matching the hypertensive groups for blood pressure, we have shown that this reduction in ventricular compliance is at least in part related to the process of hypertrophy rather than to the associated hypertension.

CHAPTER 12

GENERAL DISCUSSION

The first part of this thesis discusses left ventricular hypertrophy as a risk factor for cardiovascular mortality. Other known risk factors include cigarette smoking, high blood pressure, raised plasma cholesterol and obesity. However, risk factors are often inter-related; for example, there are known direct correlations between cholesterol and obesity, blood pressure and obesity, and blood pressure and cholesterol as well as an inverse correlation between cigarette smoking and obesity. Because of these complex inter-relationships, statistical techniques such as multivariate analysis are needed to determine the individual contribution of each risk factor to the total risk. Using this technique, it was shown in chapter 4 that electrocardiographic left ventricular hypertrophy is a risk factor for cardiovascular mortality and that the increased risk is not fully explained by its association with other known risk factors.

In the first part of the text it was also demonstrated that the commonly used ECG criteria for left ventricular hypertrophy have low sensitivity. Although increased risk in epidemiological studies has so far

only been demonstrated for ECG LVH, and not for echo LVH, it seems reasonable to strive to improve the ECG diagnosis of LVH. This should aid in the understanding of the natural history of cardiac hypertrophy and it may be that treatment will produce more effective regression if hypertrophy is detected at an early stage. Improved diagnosis could be achieved if echocardiography was universally available; however, this technique is more time-consuming and more expensive than electrocardiography and it is not possible to obtain technically satisfactory echocardiograms from as many as ten or even twenty per cent of patients. Thus an improvement in the ECG detection of LVH would be a desirable goal. As discussed in chapter 6, this could be achieved by some form of stratification of patients using readily available data, such as age, sex, height and weight. The second part of this thesis suggested a mechanism that might explain why ECG LVH is an independent risk factor for mortality. Although it is generally believed that the majority of deaths among hypertensives with LVH are due to coronary artery disease, the very "independence" of LVH as a risk factor argues against this since LVH is "independent" of the known risk factors for coronary artery disease including age, sex, cigarette smoking and blood pressure. This suggests either that LVH per se potentiates coronary artery disease or that LVH is increasing mortality via a

different mechanism. We investigated the prevalence of ventricular arrhythmia in hypertensive patients with and without LVH and found that complex arrhythmias occurred commonly in those with ECG LVH and that the prevalence of arrhythmia was related to the degree of cardiac hypertrophy.

The relationship between ventricular arrhythmias and subsequent sudden death, however, has been the subject of some controversy. In the Tecumseh Epidemiologic Study of 5,200 individuals, premature ventricular extrasystoles were associated with an increased incidence of sudden death (224). The Coronary Drug Project also reported an increased risk of sudden death in survivors of myocardial infarction who demonstrated ventricular extrasystoles on the resting electrocardiogram (225). However, Fisher et al suggested that extrasystoles were merely a marker of cardiac disease and were no more predictive of sudden death than other ECG abnormalities (226). There is, however, some consensus of opinion regarding the importance of ventricular tachycardia, which has been shown to be more closely associated with sudden death in patients following myocardial infarction (227), in patients with congestive cardiomyopathy (228) and in other forms of cardiac hypertrophy, notably hypertrophic cardiomyopathy. Some similarities exist between hypertensive left ventricular hypertrophy and hypertrophic cardiomyopathy and the two conditions may

be difficult to differentiate (229). Both are associated with sudden death and in hypertrophic cardiomyopathy, ventricular tachycardia detected by ambulatory monitoring is the most powerful single predictor of subsequent sudden death (3); furthermore, appropriate anti-arrhythmic therapy can reduce arrhythmia frequency and may prolong survival (172). No such trials of anti-arrhythmic therapy have been reported in patients with left ventricular hypertrophy secondary to essential hypertension.

It was possible that ambulatory monitoring was simply detecting those patients with otherwise silent coronary artery disease who were already at increased risk. However, further studies suggested that the frequency of these arrhythmias was not attributable to a high prevalence of coronary artery disease but was related to the extent of subendocardial fibrosis which is presumably a reflection of chronic subendocardial ischaemia. Clearly, an association between the amount of fibrosis and the occurrence of ventricular arrhythmia does not imply that fibrosis itself is the cause of the arrhythmia. However, when viewed in the context of the coronary arteriograms of those patients with ventricular tachycardia, it does suggest that myocardial factors, such as fibrosis or factors that correlate with the amount of fibrous tissue present, are more important in the pathogenesis of ventricular arrhythmia than is the presence of epicardial coronary

artery disease. In other conditions in which ventricular arrhythmias occur commonly, such as hypertrophic cardiomyopathy, myocardial fibrosis is common and often extensive; in patients with coronary artery disease and ventricular arrhythmias, and in the vast majority of victims of sudden cardiac death, fibrosis is almost always present, usually as a discrete "scar" which is thought to be involved in the fatal arrhythmia.

The mechanism of ventricular tachycardia has been a source of controversy since Mines first suggested that ventricular arrhythmias might be caused by a "re-entry" circuit (230). However, it is now generally accepted that most episodes of ventricular tachycardia, with the exception of those occurring within the first twenty-four hours of myocardial infarction, are sustained by some form form of "re-entrant" circuit (231) rather than by repetitive discharge from a single focus. Thus, for an episode of ventricular tachycardia to occur, there must be both an initiating arryhthmia and an abnormal circuit to sustain the arrhythmia. In patients with LVH, it is possible that relative myocardial ischaemia, due to increased myocardial requirements, may initiate such an arrhythmia and that myocardial fibrosis, by disrupting and disorganizing the myocardial cells, may result in a micro-reentry circuit. Certainly the association between myocardial fibrosis and ventricular arrhythmia in this analysis

appeared strong; ten of eleven patients with ventricular tachycardia had >5% fibrosis by volume (figure 18) compared with only three of seventeen of those without V.T. ($p<0.05$). Differences in left ventricular mass were less marked between those with and without VT; thus while all of those with VT had left ventricular mass values greater than 250g, thirteen of seventeen of those without VT also had high left ventricular mass suggesting that hypertrophy with fibrosis rather than hypertrophy alone is important in the genesis of ventricular arrhythmia in hypertensive patients.

Finally, it was demonstrated that increasing hypertrophy leads to reduced ventricular compliance and suggested that this might "sensitise" the heart to the effects of a ventricular arrhythmia which involved loss of effective atrial contraction.

To demonstrate that this postulated mechanism is the cause of the excess risk associated with ECG LVH, two pieces of evidence are required. First, we would need to demonstrate that the occurrence of ventricular arrhythmia on ambulatory monitoring was an independent predictor of outcome in patients with LVH. At the time of writing (May, 1987), three of the eighteen patients with ventricular tachycardia on ambulatory monitoring are known to have died compared with one of the eighty-two without ventricular tachycardia. Although this represents a statistically significant difference

when tested by Chi-squared analysis, (3/18 vs. 1/82, $p<0.02$), it has to be borne in mind that those with ventricular tachycardia were already at increased risk on account of their higher prevalence of left ventricular hypertrophy and slightly higher blood pressure readings. The numbers are clearly too small for multivariate analysis.

Ultimately, the only justification for instituting treatment that is designed to modify a risk factor is the demonstration that such risk factor reduction improves prognosis. Although such proof is not available for the treatment of ventricular arrhythmias in hypertensive left ventricular hypertrophy, there is some evidence that, in hypertrophic cardiomyopathy, effective anti-arrhythmic therapy with amiodarone can prolong survival (177).

In conclusion, a possible mechanism for the excess mortality associated with left ventricular hypertrophy has been suggested. It is known that hypertensive patients, particularly those with left ventricular hypertrophy, remain at increased risk of death even if blood pressure is apparently well controlled as was the case in the patient described in chapter one.

In the past, the aim of the clinician has been to control blood pressure in such patients and, if possible, to modify other risk factors such as cigarette smoking and cholesterol. However, it may be that this is not sufficient; other forms of therapy,

perhaps aimed specifically at regression of cardiac hypertrophy, or at suppression of ventricular arrhythmia, may be required to reduce mortality in this high risk group.

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