Echocardiographic wall-to-cavity ratios in hypertrophic cardiomyopathy and other types of cardiac hypertrophy.

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MD 2001
Statement of conjoint work

I hereby acknowledge that a proportion of the data presented in this thesis was collected jointly with Dr I Östman-Smith. I believe this statement to be a fair reflection of my personal contribution.

The contributions to the control data from 262 normal subjects were approximately equal as were the contributions to the disease population. Approximately 70% of the data from the first-degree family members, 85% of the data from the athletes and 100% of the data from the hypertensive group was contributed by the thesis author.

Wall thickness data from magnetic resonance imaging (MRI) studies was contributed by Dr N Moore and left ventricular mass measurements were collected jointly. The echocardiographic measurements used for comparison were made by the thesis author.

In the published material submitted in support of this thesis, the data presentation, the reasoning behind the results and conclusions and the statistical approaches were all jointly agreed.
ABSTRACT

Background - Left ventricular (LV) hypertrophy is diagnosed by increased LV wall thickness or increased LV mass. A single cut-off for echocardiographic wall thickness (>15mm in adults) is commonly used irrespective of gender. This approach has yielded an inexplicable excess in male prevalence of 2-3:1 for hypertrophic cardiomyopathy (HCM) in population based studies. Children's cardiac measurements are referenced to body surface area by nomograms or regression equations which take no account of LV cavity size. LV mass or mass index is a continuous variable in the normal population with no absolute diagnostic cut-off for hypertrophy, whilst published normal values can be seen in hypertrophic cardiomyopathy. Consequently, a need exists for a simpler echocardiographic method to diagnose and sequentially monitor LV hypertrophy at all ages irrespective of gender, which may also help to differentiate between aetiologies.

Objectives - To describe a new echocardiographic method for assessing LV hypertrophy which is applicable at all ages and is independent of gender.

Methods - 262 normal subjects, 41 patients with hypertrophic cardiomyopathy, 52 first degree relatives from families with familial hypertrophic cardiomyopathy, 26 athletes and 16 patients with hypertension underwent echocardiography. M-mode diastolic and systolic ratios of LV wall thickness to LV diameter were calculated. A subset of 10 patients with HCM had LV wall thickness and mass measurements performed using magnetic resonance imaging (MRI) for comparison with echocardiography.

Results - Diastolic and systolic wall-to-cavity ratios show little variation with age and are independent of gender. In adults diastolic ratios are independent of body surface area. A septum-to-cavity ratio of >0.26 identified all HCM patients (100% sensitivity) and no control subjects (0% false positives). A systolic LV wall-to-cavity ratio of >0.63 performed equally well in subjects >1 year. Septum-to-posterior wall thickness ratio >1.3 performed less well (90% sensitivity, 10% false positive rate). A septum-to-cavity ratio >0.26 identified all first-degree relatives with an abnormal phenotype suggestive of gene carriage with no obvious false positives. It was also more successful than traditional measures at dividing relatives in to affected and unaffected subjects in the proportions expected for autosomal dominant inheritance. Athletes with marked cardiac hypertrophy showed a 7.7% false positive rate for the diagnosis of HCM using diastolic septum-to-cavity ratio >0.26, but are recognised as showing physiological hypertrophy by the presence of normal systolic function (systolic LV wall-to-cavity ratios). Hypertensive cardiac hypertrophy is also identified by a septum-to-cavity ratio >0.26. Systolic LV wall-to-cavity ratios are significantly lower than in subjects with HCM as are other measures of systolic function. MRI and echocardiography show good agreement between LV wall thickness measurements, particularly of the anterior interventricular septum. The agreement between the assessments of LV mass was poor.

Conclusions - Septum-to-cavity ratio and systolic LV wall-to-cavity ratio can diagnose LV hypertrophy at all ages, are useful in the diagnosis of and screening for HCM and can help differentiate physiological from pathological hypertrophy. MRI and echocardiography are complimentary techniques in the assessment of LV hypertrophy and any positive treatment effects.
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1. INTRODUCTION

1.1 Hypertrophic Cardiomyopathy

1.1.1 History and nomenclature

It is thought that the first observation of myocardial disease, which can be interpreted as hypertrophic cardiomyopathy (HCM), was made in the middle of the 19th century in France (1, 2). A century later in the 1950s there remained no classification or framework for the cardiomyopathies, which were frequently considered alongside myocarditis even when the myocarditis was known to have a specific inflammatory aetiology (3). In 1957 Brigden published his St Cyres lecture on "Uncommon myocardial diseases; the non coronary cardiomyopathies" and was one of the first to employ the term "cardiomyopathy" (4). In the same year Brock published the first clinical account of hypertrophic cardiomyopathy (5) which was followed in 1958 by Teare's systematic description of the disease characterised by "asymmetrical hypertrophy of the heart" with a non-dilated ventricular cavity (6). Further characterisation of the disease was performed by Goodwin (7) who attempted a first descriptive title for the disorder of "obstructive cardiomyopathy" which was subsequently modified as follows: "Cardiomyopathy - an acute, subacute or chronic disorder of heart muscle of unknown or obscure aetiology, often with associated endocardial or sometimes with pericardial involvement but not atherosclerotic in origin" (8).

During the first 15 years following Teare's description of HCM (6), the obstructive features of the disease associated with massive ventricular hypertrophy and impaired diastolic function had been recognised (7, 9, 10) and this was reflected in the nomenclature. Terms such as idiopathic hypertrophic subaortic stenosis (11), hypertrophic obstructive cardiomyopathy (10, 12) and muscular or hypertrophic subaortic stenosis (9, 13) were employed. However, the idea of obstruction as an essential component of the disease was called in to question by Criley et al (13) when the outflow tract gradients in a series of patients with HCM were located in the ventricle itself, in areas which emptied early such as the apex and the trabecular spaces. In addition, Goodwin's group noted that as the disease became more severe the signs of obstruction tended to disappear which is unlike the picture in true obstructive outflow tract disease of the left ventricle (14). Furthermore, with the development of echocardiography large numbers of patients were subsequently identified in whom obstruction was absent (15). These observations led to the omission of the word obstructive from the definition.

The asymmetric nature of the hypertrophy seen in the disorder was then emphasised and was characterised by Henry et al (16) as the pathognomonic feature of the disease by the observation that the ratio of diastolic septal thickness of the left ventricle to the diastolic thickness of the left ventricular free wall was at least 1.3:1. Subsequently, this was shown to be present in approximately half of the first-degree
relatives of index cases, implying that HCM was a disease with autosomal dominant inheritance (15). This led to the term asymmetric septal hypertrophy or "ASH" being used to describe the disease entity of HCM.

In 1975 Goodwin called for agreement in nomenclature (17) the need for which was reinforced by Maron and Epstein (18) who listed no fewer than 58 terms by which hypertrophic cardiomyopathy had become known. This was partly because the disease was characterised simultaneously by many groups who assigned it a different name and partly because information about and concepts of the disease evolved over time and became incorporated in to the nomenclature. However, since the most consistent feature of the disease, that of a hypertrophied heart with an non-dilated left ventricular cavity in the absence of a systemic disease that could itself produce hypertrophy, there was a consensus to refer to the disease as Hypertrophic Cardiomyopathy (HCM) (18). This term had already been developed and employed by those in the United Kingdom for some years (19) and remains consistent with the current title endorsed by the joint task force of the World Health Organisation and International Society and Federation of Cardiology (20).

1.12 Pathology

The interventricular septum is formed from the apical in-folding of a unichamber structure. At that point the septum is approximately twice as thick as either the left or right ventricular free wall. Subsequent remodelling during cardiogenesis allows the septum to become a left ventricular structure in both configuration and dimension (21) except for the outer surface, which is formed by the right ventricular trabeculae. The hallmark of HCM is the finding of left ventricular hypertrophy (LVH), particularly of the interventricular septum, with a normal sized or small left ventricular cavity (22). In 1958 Teare emphasised the asymmetric nature of the left ventricular (LV) hypertrophy in his initial morphologic description of HCM (6). Menges and others added quantitation of ventricular septal thickness measurement to the necropsy diagnosis and found that the increased ratio of septal to free LV wall thickness separated those subjects with HCM from those with other cardiac diseases and normal hearts (23, 24). In addition to asymmetric ventricular hypertrophy without dilatation, morphological observations include endocardial thickening in the outflow portion of the ventricle caused by the impact of the anterior mitral valve leaflet (mirror image of the leaflet), enlargement of the atria, thickening of the mitral valve leaflets and areas of fibrosis in the ventricular wall (22, 25).

HCM is associated with the presence of mutations in the genes coding for contractile proteins and this is discussed in detail later (chapter 1.17). The resulting microscopic appearance of the cardiac muscle cells of the septum and elsewhere is one of greatly hypertrophied fibres with a characteristic disorganised arrangement in which adjacent cells are arranged obliquely and perpendicularly to one another. There is increased cellular branching with extensive side to side junctions with evidence of formation of new.
sarcomeres (6, 26, 27) which is seen irrespective of the presence of outflow tract obstruction in vivo (26-
28). The myocardial pathology of infants, children and adults with asymmetric septal hypertrophy (ASH)
has been compared to subjects of a similar age with normal hearts and those with other types of congenital
or acquired heart disease (29, 30). In the normal heart the cardiac muscle cells are rectangularly shaped
and arranged in parallel. Some small foci of disorganised cardiac cells were observed but occupy
approximately 2% of septal tissue sections (30). In the normal heart the cardiac muscle cells are rectangularly shaped
and arranged in parallel. Some small foci of disorganised cardiac cells were observed but occupy
approximately 2% of septal tissue sections (30). The transverse diameters of the muscle cells in the
ventricular septum and LV wall in one study (29) ranged from 5-15μ. Myocardium from the septum and
free wall of hearts with congenital defects other than ASH shows hypertrophied normally arranged cells
with transverse diameters of 6-27μ. In those with HCM extensive muscle cell disorganisation is seen
occupying a mean of 53% of septal tissue sections (30). The cells show abnormal size and arrangement
with diameters of 10-70μ (27, 29). The disorganisation assumes two patterns: 1) foci where adjacent cells
are arranged perpendicularly and obliquely and 2) small groups or bundles of cardiac muscle cells that are
interlaced in various directions among larger and more normally arranged groups of cells resulting in a
swirling appearance (27, 29). These regions of disorganised myocardial architecture are not confined to
greatly thickened portions of the left ventricular wall and were present in regions of normal or only mildly
increased thickness (31). These changes reflect the abnormalities seen in all age groups.

In the normal heart the collagen matrix consists of an orderly arrangement of thin "spring-like" perimysial
coils which run parallel to the long axis of the muscle cells. These coils are connected through transversely
oriented struts to a network of pericellular weaves encircling the sarcolemma of individual muscle cells
(30). In one study (30), total collagen volume in septal tissue sections of the normal heart was found to be
4% and was evenly distributed throughout all parts of the septum. Conversely in the hearts from subjects
with HCM there was a marked increase in number and thickness of all fibre components of the collagen
matrix (30). The perimysial fibres were thickened and had lost the coiled configuration and the pericellular
weave formed dense networks of thickened fibres which showed a disorganised pattern when compared to
normal hearts. Mean total collagen volume in the septal tissue sections was 16.7% and was sited in
interstitial rather than perivascular tissue. The expanded size of the collagen matrix bore no relation to any
morphologic or clinical variable nor was it related to the degree of myocyte disorganisation, suggesting
that it was an independent and primary abnormality in HCM (30). This is supported by the observation of
an increased collagen matrix even in infants dying at less than 5 months of age. Interestingly those with
hypertensive heart disease showed no areas of increased myocyte disorganisation, no change in
morphology of the perimysial coils although they were thicker and appeared more abundant. The total
collagen volume was increased above normal occupying 8.2% of the septal tissue sections but was still far
less than in the hearts with HCM (30).

As well as an increase in interstitial connective tissue elements (32) replacement fibrosis of variable
severity and distribution is described including scarring which may be extensive (32, 33) or transmural
(34). Abnormal intramural coronary arteries have also been reported in as many as 80% of patients with
HCM at post-mortem (33, 34). The walls of these vessels show increased smooth muscle, collagen, elastic fibres and mucoid deposits in the intima or media, which frequently narrow the lumen. Clusters of these abnormal vessels are seen within or at the margins of sizeable areas of fibrosis or collagen including large areas of transmural infarction (30, 33).

The extent to which myocardial fibre disarray and asymmetric septal hypertrophy were pathognomonic of HCM was called in to question by Bulkley et al (35) who studied 215 hearts including those of normal embryos, foetuses, children and adults, and those with congenital and acquired disease. Disproportionate septal thickening was present in all embryos and in some abnormal hearts particularly those with severe right ventricular hypertrophy. Small areas of myocardial fibre disarray were present in all hearts, including normal hearts, at the junction of interventricular septum and ventricular free wall. Extensive areas were found in hearts with semilunar valve atresia with intact ventricular septum and in the infundibulum of a proportion of those with tetralogy of Fallot. Disarray was also described at the borders of human myocardial infarcts (35) and in experimental myocardial infarction (36). It is noteworthy that abnormal myocardial fibre disarray was not present in the developing embryo or foetus despite the presence of disproportionate septal thickening and was not found in those hearts with mitral atresia with ventricular septal defect or in combined aortic and mitral atresia. It was also absent in the adult hearts with aortic stenosis. Therefore the presence of left ventricular outflow tract obstruction alone does not appear to provide the substrate for the development of the disorganised muscle fibre appearances. The substrate appears to be the presence of a hypertrophied ventricle with an extremely small cavity such as that found in outflow tract obstruction with intact septum. It was speculated therefore that the fibre disarray in HCM and aortic or pulmonary valve atresia with intact ventricular septum might result from the loss of direction-orientated wall stresses due to systolic cavity obliteration during cardiac development (37). Consideration was also given to whether this feature represented a primary genetic abnormality but this was difficult to argue as the various disorders in which it occurred demonstrated no other unifying features. Olsen (22) suggested that additional histological/histochemical features such as bizarre nuclei, perinuclear halos and perinuclear pools of glycogen were which helpful in distinguishing HCM from other forms of hypertrophy.

Primary structural abnormalities of the mitral valve are also well recognised in HCM and have been identified both pathologically (38) and echocardiographically (39). Examination of almost 100 valves removed at surgery or post-mortem showed alterations in size, shape and morphologic characteristics (38). The abnormalities included increased valve area of up to twice normal and was caused primarily by elongation of the leaflets or segments of the leaflets of either the anterior or posterior leaflet or both. Some patients with normal sized mitral valves may show anomalous insertion of papillary muscle directly in to the anterior mitral valve leaflet without interposition of chordae (39, 40).
1.13 Natural history

Prevalence
There have been many studies estimating the prevalence of HCM in a given population. One of the earlier investigations involved M-mode echocardiography of 3000 offspring of the original Framingham cohort (41) and found echocardiographic markers of HCM in 0.3%. A large cohort of 12841 Japanese workers (42) underwent electrocardiography in the first instance followed by echocardiography in a subset of 12%. The reported prevalence of HCM in this subset was 0.17%. The use of electrocardiography as the primary screening method could have resulted in an underestimation of the prevalence in that study. A more recent community-based population study of those referred for echocardiography because of a suspicion of cardiac disease demonstrated a prevalence of 0.5% (43) whereas a population based study in Olmsted County, Minnesota (44) described an age and sex adjusted prevalence of only 0.02% for HCM. However, the latter study was a disease surveillance analysis of patients who had come to medical attention for HCM rather than identification of subjects by population screening which could easily lead to an underestimate of the true prevalence.

A more recent assessment of the population prevalence of HCM was established in the CARDIA study of 4111 subjects age range 23-35 years (45) and was found to be 0.2%. This prevalence is supported by the figure of 0.29% from a very large study where 15 137 echocardiograms were performed in 64 rural communities at the request of the primary care physician for the purpose of excluding cardiovascular abnormalities (46). The CARDIA study showed that the recognition of HCM by morphological criteria yields up to 10 times the number of positive cases than those based on symptomatic presentation and substantiates that most young people identified with HCM have no symptoms. Interestingly, HCM was found to be 2.9 times more common in men than in women in this study (45) for which the cut-off for the diagnosis was a maximum absolute LV wall thickness measurement of ≥15mm irrespective of sex. An epidemiological study in children showed a similar male preponderance (47). Since there is no ready explanation for the skew in the sex-related prevalence in what has been shown to be an autosomal dominant disorder, it might be concluded that the diagnostic criteria employed were not of sufficient sensitivity to detect affected females.

Adult disease
McKenna et al (48) retrospectively reviewed the clinical, electrocardiographic and haemodynamic features of 254 patients of all ages diagnosed and followed-up at the Royal Postgraduate Medical School for 1-23 years with a mean of 6 years. 58 (23%) had died, 32 suddenly and 6 with heart failure. In those aged 15-45 years at diagnosis there was a 2.5% annual mortality rate. Discriminant analysis showed that young age (14 years or less), syncope at diagnosis, positive family history of sudden death from HCM and severe dyspnoea at last examination best predicted future sudden death. However, 38% of the patients who died were < 30 years at the time of death and 70% were in New York Heart Association (NYHA) class I.
high incidence of sudden death was seen in earlier studies, one from the same group which included 119 patients of which 30 died, 19 suddenly (49) and another multicentre study by Shah et al (50) of 190 patients with a left ventricular outflow tract gradient at rest or with provocation, of whom 49 died, 26 suddenly. All suggested that the annual mortality rate in adults was in the region of 2-4% (50, 51) and that HCM was thus, not a benign disease.

Over time however, it has come to be appreciated that most published studies have come from a small number of tertiary institutions expert in the study and management of the disease and therefore subject to biases in patient referral (52). Since patients with severe symptoms or those at high risk for sudden cardiac death have been preferentially referred to these centres, the outlook reported in the literature has perhaps been skewed towards the more dismal end of the spectrum (53). More recently, studies have been conducted in regional cohorts not referred for specialist care. They have shown that many patients can remain asymptomatic (54) and have an annual mortality rate as low as 0.6-1.3% (54-57) with a normal overall life expectancy (57).

The difficulty remains in the identification of those most at risk of sudden death. This is complicated by the phenotypic heterogeneity and by a prevalence which means that few centres have a disease population of sufficient size to ascertain risk factors in subgroups (58). These centres are subject to referral biases and tend to see the more severe cases. Almost half of the studies on HCM from a previous decade which were published in 3 American and 1 British journal came from only two centres and >90% of the patients reported to have severe symptoms also came from these institutions (59). Some have found that in certain groups the history and particularly changes in symptoms were better predictors of poor prognosis than any haemodynamic or electrocardiographic measurements (3). However, whilst the documentation of changes in symptomatology appeared to be quite specific in identifying a high-risk group it is insufficiently sensitive. This point was illustrated by Maron et al (60) who described a subgroup of families in whom early sudden death occurred with considerable frequency and referred to this as “malignant” hypertrophic cardiomyopathy. 18/31 subjects who died suddenly were <25 years old and in 15 subjects this was the first manifestation of cardiac disease (60).

Since then work has shown that a high risk group can be identified on the basis of electrophysiological factors (61), a family history of sudden death (60) and more recently guidelines on risk factors and risk stratification for sudden cardiac death in patients with hypertrophic cardiomyopathy have been published (58). Factors thought to suggest a high risk of sudden death are young age at diagnosis (48, 62, 63), history of aborted sudden death (58), strong family history of sudden death (60), syncope (62, 64) and the presence of arrhythmias including occult conduction disease (58, 65). More recent studies suggested that in addition, atrial fibrillation, a basal outflow tract gradient of ≥ 30mmHg and an LV wall thickness of >25mm were independent predictors of mortality in HCM (56, 57). All of these factors, apart from family
history, are largely helpful in those already known to have the disease. The challenge remains however, to identify subjects before their clinical presentation with cardiac symptoms such as sudden death.

**Childhood disease**

HCM was recognised as cause of morbidity and mortality in adults in the 1960s and 70s (6, 8, 19, 49, 51) but in children little clinical, haemodynamic, echocardiographic information or natural history was known before 1976 (28). HCM had been observed at the post-mortem studies of infants demonstrating that this disease may be present at birth or indeed in utero (29, 66). It had also been described in those less than 6 months of age where it was responsible for the death of 4 infants in the first five months of life (28, 29). This suggested that the abnormal cells are present at or near the time of birth and lent support to the idea that these morphological features are an expression of a genetic defect (29). Unfortunately, when overt clinical manifestations of the disease such as heart failure and marked ventricular hypertrophy are evident in infancy the prognosis is particularly unfavourable and such infants rarely survive beyond the first two years of life (66). In one study, 9/11 such infants died in the first year of life despite medical or surgical therapy (66).

The study by Maron et al (28) of children with HCM showed that of the children with clinical signs of cardiac disease, 60% (21/35) clinically deteriorated or died over a mean follow-up period of 7.4 years (1-16 years). Sudden death occurred in 31% (11/35) over the same period giving an annual mortality rate of 4%. 3 children who died were completely asymptomatic at the time of death and a further child had suffered a single syncopal episode 16 months prior to death. The occurrence of sudden death showed no relationship to age at onset of symptoms, functional status, electrocardiographic abnormalities or left ventricular ejection or upstroke time. Three other children, siblings of children in the study, who were known to but not formerly evaluated by the group, died without any overt evidence of cardiac disease but the diagnosis of HCM was confirmed at necropsy (28). The mortality in this study by Maron et al was in agreement with previous studies in adults (49, 50) but somewhat higher than that reported by other studies of children (49, 67). The most concerning feature of the study was the observation that sudden death in children and siblings of affected children occurred without prior warning and could not be linked to symptoms or functional status.

A later study by McKenna et al (48) confirmed the concerning nature of HCM in childhood compared to adult disease by showing an annual mortality rate of 5-6% which was higher than that described for adults (48-50). McKenna's study (48) found that patients diagnosed in childhood were usually asymptomatic and had an unfavourable family history. 41% of the patients diagnosed at ≤ 14 years old died over the mean follow-up period of 6 years compared to 12-14% of those diagnosed > 14 years old. 4/11 of those diagnosed in childhood had one or more first-degree relatives who died with HCM and 7/11 suffered syncope, which was the only symptom in the children in this study. These children may have represented
offspring from families with "malignant" HCM as described by Maron et al (60). Even in more recent studies describing a more benign natural history of HCM in adults, those individuals identified with disease in childhood showed significantly reduced survival compared with a similar non-diseased population cohort (57). The need to seek to identify children affected by HCM is therefore clear since they often fail to identify themselves before the occurrence of a catastrophic cardiac event. Therefore any methods which assist in the diagnosis of the disease in childhood may help to prevent such sudden deaths by allowing medical or surgical intervention such as the treatment of arrhythmias.

In 1986 Maron et al (68) undertook a study to determine whether the pattern of left ventricular hypertrophy in HCM is always established at or shortly after birth or if the process is an evolving one which develops and progresses during childhood. Serial echocardiograms of 39 children <15 years old with a family history or morphologic evidence of the disease were followed over a mean period of 4 years. The presence and progression of the disease in childhood was assessed by extrapolation from the nomograms for normal myocardial wall thickness corrected for age and BSA devised by Henry et al (69). The study produced further worrying results with regard to this disease in childhood and adolescence. 22/39 showed a substantial increase in left ventricular wall thickness. 17 had shown pre-existing hypertrophy which had increased and 5 previously normal subjects had become abnormal, to the extent of having wall thickness measurements of 18-28mm in three cases. In the 22 subjects with disease progression the maximal wall thickness at the start of the study was 8-27mm and at follow-up was 14-46mm, with increases of >10mm in 14 subjects. These changes occurred at different periods in childhood but most frequently in the adolescent years. 14/22 were asymptomatic throughout the period of follow-up and none who were asymptomatic at the start became symptomatic. Those with symptoms were affected by fatigue and dyspnoea on exertion, chest pain, light-headedness or syncope and had no noteworthy increase in these symptoms. Thus, marked increases in the magnitude and distribution of hypertrophy may occur in childhood and children with morphologically normal hearts may rapidly become abnormal without the development of symptoms. Serial evaluation of the growing child at risk of developing HCM is clearly necessary for which accurate methods for individualised, sequential assessment are essential.

Athletes

In 1992 the Hypertrophic Cardiomyopathy Association launched a campaign to raise awareness of HCM in association with the National Sports Medicine Institute following the death from the condition of the son of a well known footballer (70). Athletes are particularly vulnerable as HCM is the commonest cause of death in this group (71), which predominantly involves children and young adults (72). Liberthson (72) performed a combined analysis of 9 papers examining the causes of sudden death in those aged 1-30 years and found a rate of 1.3-8.5 per 100 000 patient years and in 2/3 a specific cardiac cause of death was identified. When extrapolated, this observation predicts that several thousand young Americans die suddenly from cardiac disorders every year. Analysis of sudden death associated with physical exertion
identified HCM as the commonest cause. In another study (62) 70% of patients with hypertrophic cardiomyopathy who died suddenly did so before the age of 30 years and 40% died during or after exertion. 54% of individuals were free of functional limitation and no clinical or morphologic variable could be shown to reliably identify patients at risk of sudden death. Once again, it would appear that the majority of these subjects require to be identified since they do not present with symptoms.

A study by Maron et al (71) examined the causes of sudden and unexpected death in 29 highly conditioned competitive athletes aged 13-30 years. Sudden death occurred during or just after severe exertion on the athletic field in 22/29 athletes and structural cardiovascular abnormalities were identified at necropsy in 28/29 athletes and in 22 were thought to be the cause of death. The abnormalities included anomalous origin of the left coronary artery, idiopathic concentric left ventricular hypertrophy, coronary heart disease and ruptured aorta. However, the most common underlying pathology was HCM, which was present in at least 14 subjects.

8/29 athletes had experienced transient symptoms including syncope in three, presyncope in one, chest pain in two, periodic mild fatigue in one and mild fatigue, presyncope and palpitations in one. In two of these subjects and five other asymptomatic athletes cardiovascular disease had been suspected by an examining physician during life. In the latter five cardiovascular disease had been suspected because of a heart murmur in two, a family history of heart disease in one, ventricular tachycardia on an exercise electrocardiogram (ECG) during a routine preparticipation athletic examination in one and during evaluation for the Marfan syndrome in one. 6/7 athletes suspected of having cardiovascular disease during life turned out to have HCM. One was correctly diagnosed following the sudden death of his brother from the disease. The diagnoses made in the other five athletes during life were "normal athlete heart" in three, ventricular septal defect in one and Wolff-Parkinson-White syndrome in one. All were permitted to continue participation in competitive athletics and tragically died subsequently in practice or during competition. These deaths must surely be considered as potentially preventable and subsequently guidelines have been produced concerning the eligibility for competition of athletes with cardiovascular abnormalities (73).

HCM was re-affirmed as the commonest cause of death during exercise in those less than 30 years in a recent study from France (74). This study illustrates that it is not only athletes who partake of regular training who are at risk but also those with HCM who happen to participate in occasional exercise. It also reinforces the need for forensic autopsy in these cases so that other members of the family might be alerted to potential dangers surrounding exercise. These studies demonstrate the importance of correctly differentiating between physiological hypertrophy or "normal athletes heart", other cardiac lesions and HCM and show the need for more accurate and reliable methods for this purpose than were available to the assessing clinicians of the six subjects who died in Maron's study.
1.14 Clinical features

Examination

Before the advancements in technology, which permitted such techniques as cardiac catheterisation, the clinician relied on the bedside examination to make the diagnosis of HCM. The diagnosis largely rested on the presence of three cardinal signs: the presence of a late onset ejection systolic murmur audible at the apex, the left sternal edge and occasionally the base, a jerky quality to the arterial pulse due to the rapid upstroke and rapid decline of the impulse and a palpable atrial beat caused by the strong contraction of the left atrium needed to fill the non-compliant left ventricle. However, it has been shown that HCM is not always associated with a loud heart murmur (2) and when a murmur is present the intensity bears no relation to the severity of the obstruction (50). In a study by Clark et al (15) the symptomatic history was negative in 60% and the physical examination in 65% of those with HCM. Likewise the CARDIA study of disease prevalence (45) showed that only 1/7 of those identified with the disease had suffered any previous cardiac symptomatology. Therefore the clinical history and the presence of abnormal clinical signs can not be relied upon to detect subjects with HCM.

Arrhythmias

Sudden death was initially assumed to be secondary to outflow tract obstruction but subsequent work pointed to arrhythmia as a potential cause (75) even in the absence of functional limitation (76). Serious ventricular arrhythmias have been documented in up to 50% of unselected subjects with HCM (77, 78) using ambulatory monitoring and exercise testing. However, no clinical or haemodynamic index could be found in these and other studies which could predict those patients who would suffer from ventricular tachycardia or sudden death (76, 78). A link between sudden death and ventricular arrhythmia was subsequently described by McKenna et al (65) when the incidence of ventricular tachycardia and subsequent sudden death was explored using 72-hour electrocardiographic (ECG) recordings from 86 patients. 24 patients experienced ventricular tachycardia, 10 having more than 3 episodes. The patients were followed for 1-4 years (mean 2.6). 7 died suddenly of whom 5 had shown either multiform paired premature ventricular contractions or episodes of ventricular tachycardia on the ambulatory recordings. The presence of ventricular tachycardia was also significantly associated with sudden death in older patients with symptoms (65). This and another study concluded that the finding of episodes of non-sustained ventricular tachycardia during ambulatory ECG monitoring was the best single identifying marker of the adult at high risk of sudden death (65, 79). However, a more recent study proposes that non-sustained ventricular tachycardia is of poor prognostic significance only when associated with impairment of consciousness (61) and others have questioned the prognostic value of non-sustained ventricular
tachycardia in asymptomatic populations free from the selection bias of the tertiary referral centre (80, 81).

The prognosis in infants and children with regard to arrhythmias was also investigated by McKenna et al (82). During the follow-up period of 1 week to 7 years there were 5 deaths and 2 successful resuscitations from out-of-hospital ventricular fibrillation. None of these subjects had shown ventricular arrhythmias during 2-7 days of previous ECG monitoring. Furthermore, neither of the two patients with ventricular fibrillation, none of the five subjects with ventricular tachycardia, none of the seven subjects with recurrent syncope or adverse family history or the subject with Wolff-Parkinson-White syndrome died. This suggests that in contrast to adults, the absence of ventricular arrhythmia during ambulatory ECG monitoring during childhood does not indicate a low risk for sudden death.

Attempts to identify morphological features of the disease that were associated with the presence of arrhythmia have yielded varying results. One M-mode echocardiographic study of 26 patients (83) showed that none of the classical features of HCM were predictive of the occurrence of arrhythmia. Features of obstruction i.e. systolic anterior motion of the mitral valve (SAM) and mid-systolic closure of the aortic valve were inversely correlated with the occurrence of ventricular tachycardia and the magnitude of septal thickness and septum-to-free wall ratio showed no correlation. However, patients with ventricular tachycardia showed the most severely impaired pattern of septal motion i.e. reduced amplitude of motion at chordal level and reduced septal systolic thickening. In contrast, a previous study (84) had shown that features of obstruction such as SAM were positively associated with ventricular arrhythmia and a later study by Spirito et al (85) found a strong association between magnitude of LV hypertrophy and occurrence of VT in patients with HCM. The presence of any association between arrhythmias and morphological features of HCM therefore remains unclear (86).

**Syncope**

Syncope is an important symptom in HCM and in the retrospective review of patients from the Hammersmith hospital, syncope in patients less than 45 years of age indicated a poor prognosis (48). Clearly, arrhythmias represent a well recognised cause of syncope but a further possible mechanism for syncope in HCM was postulated by McKenna et al (64). This followed an incident where a patient fainted and lost consciousness when walking to the X-ray department whilst attached to an ambulatory ECG monitor. The pulse disappeared for > 1 minute before she was successfully resuscitated. The early stages of the attack showed tachycardia and ischaemic ST segment changes. On recovery there was some atrioventricular dissociation and fusion beats but no bradycardia, asystole, ventricular tachycardia or fibrillation. The proposed mechanism was one of initial peripheral vasodilatation, which led to reduced ventricular volume, further aggravated by tachycardia, which led to further reduction in cardiac output and
so on in a descending spiral. This is interesting in the light of subsequent work on abnormalities of peripheral vascular responses in those with HCM (87).

The dismal outlook for those suffering from syncope was further underlined in a retrospective study of 37 patients diagnosed with HCM in childhood (63). Various clinical, electrocardiographic and haemodynamic features were compared between the group in which there were 11 sudden deaths and the group of 19 survivors over a follow-up period of 1-21 years, mean 9 years. Syncope and the presence of right ventricular hypertrophy on the ECG were the only factors associated with sudden death. Since syncope appears to be the only prelude to sudden death in this age group it might be prudent to consider the diagnosis of HCM in any young person who presents with a history of recurrent syncope.

Sudden death

In addition to arrhythmias as a cause of sudden death in HCM previous studies had suggested that subjects with HCM were unable to maintain stroke volume and thus unable to increase cardiac output during exercise or tachycardia. This was mainly thought to be due to the reduced filling time allowed for a poorly compliant ventricle (19). McKenna and Camm (88) suggested that subsequent investigation of the mechanisms surrounding sudden death in HCM should include haemodynamic factors in addition to the investigation of myocardial vulnerability to arrhythmias, especially since the latter did not identify children and adolescents at risk.

It was subsequently shown that hypotension during exercise is not uncommon in subjects with HCM and was seen in 1/3 of patients in one study (89) who experienced falls in blood pressure of 20-110mmHg. The same group used the measurement of forearm blood flow (87) to demonstrate that a sub-group of patients with HCM show an abnormal vascular response to supine exercise. These patients were younger and more of them had a family history of sudden death than did those without an abnormal vascular response. It was postulated that haemodynamic mechanisms might be important in sudden death in HCM. Such abnormal haemodynamic responses have also been shown following a meal in those with HCM, with failure of stroke volume to increase accompanied by an increase in left atrial pressure (90). Further study into the nature of abnormal haemodynamic mechanisms in the HCM population and the associated provoking factors will be interesting and may contribute to any risk stratification model.
1.15 Diagnostic investigations

**Angiography**

Obviously the diagnostic criteria for HCM have evolved along with the advances in technology but in the 1960s and early 1970s angiography appearances were the mainstay of the diagnosis (91) at a time when the obstructive component of the disease was to the fore. Angiographic studies showed complete elimination of the apex and body of the LV in systole with greatly reduced LV volume (3). Subsequent studies correlated echocardiographic with angiographic findings in HCM (92) and the good correlation between the techniques along with the rapid advancements in echocardiographic imaging, meant that echocardiography supervened as the main diagnostic imaging modality in HCM.

**ECG and electrophysiological studies**

Different ECG criteria for the diagnosis of hypertrophy have been employed in HCM, the most common of which are that employed by Romhilt and Estes using a point scoring system (93) and that employed by Sokolow and Lyon involving addition of the voltages of RV5 + SV1 (94). However, some of the earlier studies (15, 95) and several later studies (96-98) found that these criteria were insufficiently sensitive for disease detection when compared to echocardiography and did not bear any relation to wall thickness even in the normal heart.

The progression of hypertrophy in subjects with HCM has been assessed using electrocardiography (ECG) (99) but this technique was subsequently thought to be unsuitable for this purpose since it shows low sensitivity and specificity for the detection of hypertrophy in these patients (100). However, in 1989 it was suggested that in those < 20 years who are at risk of developing HCM, the ECG may become abnormal earlier than does the echocardiogram (101). It is noteworthy though, that the voltage measurements did not change even in those with evolving hypertrophy over a period of 3-8 years. Following this there has been renewed interest in the use of the ECG to identify the abnormal cardiac phenotype in HCM particularly in childhood.

Recent publications have shown that family members known to have inherited a disease mutation show ECG abnormalities in the absence of echocardiographic abnormalities (102-106). These abnormalities included the presence of left ventricular hypertrophy (LVH) with repolarisation changes, isolated repolarisation changes with moderate to severe T wave inversion, and deep Q waves. However, a subsequent study of 37 matched pairs of children with HCM and normal children revealed that the ECG did not differentiate between affected and normal children reliably enough to allow it to be used as a screening test in the general population (107). Further evidence that the ECG is not appropriate for population screening is provided by both the CARDIA study (45) where 5/7 of those identified as having...
HCM had normal ECGs and a later large population based study (46) in which only 10% of those identified with HCM showed left ventricular hypertrophy on ECG. Certainly when present ECG abnormalities appear highly significant but when absent are unhelpful.

The role of electrophysiological (EP) studies in the investigation of both symptomatic and asymptomatic patients with HCM remains controversial (108, 109). Some authors report that EP studies are useful for the identification of patients at high and low risk for subsequent cardiac events and advocate a study for all those patients with symptoms of impaired consciousness (108). However, it is thought by others that as many as 80% of the arrhythmias provoked by intensive stimulation of these patients are either polymorphic ventricular tachycardia or primary ventricular fibrillation, both of which are non-specific and may result from such intensive stimulation (58). Often the clinically relevant arrhythmia is not produced and the arrhythmias, which are produced, require resuscitation. It has thus been concluded that electrophysiological studies of this type probably have a very limited role and should not form part of standard management protocols (58, 109).

Echocardiography

Asymmetric septal hypertrophy

Following the pathological description of HCM (6) the disease was characterised by several authors in the 1970s using echocardiography. Disproportionate septal thickening of the ventricular septum with respect to the LV free wall was again described as it had been in the pathological studies (6, 7, 9, 16, 23, 110-112). Asymmetric septal hypertrophy (ASH) became known as the essential feature of the echocardiographic diagnosis (15, 16, 110, 112-116) and was well described by Maron's group in 1979 in the well known paper entitled "Hypertrophic cardiomyopathy: a discussion of nomenclature" (18).

However, some uncertainty surrounded the issue of which diastolic septum-to-free wall ratio should be used. The group at the National Institutes of Health, Maryland used a ratio of ≥1.3 as diagnostic for the condition (16) whereas other investigators preferred a ratio of ≥1.5 as this improved specificity (110, 111, 115, 117). However, it became apparent that neither value provided absolute sensitivity or specificity for the diagnosis of HCM (118) which supported the findings of Bulkley et al who had made a similar observation from pathological specimens (35, 37, 119).

Echocardiographic studies from a similar period confirmed the presence of ASH in conditions other than hypertrophic cardiomyopathy (120, 121). Larter et al (120) undertook a study to determine if the ratio of septum-to-left ventricular free wall of ≥1.3 was specific for the diagnosis of HCM in children. Increased ratios were found in infants and young children without heart disease and in those with a variety of cardiac
lesions not associated with cardiomyopathy. Other morphologic studies alone or in combination with echocardiography confirmed that ASH may be seen in those with congenital heart disease (122) hypertension (123) and in approximately 10% of those with coronary heart disease (124) and that it could be observed in weight lifters (125).

However, the limitations of direct comparisons between in vivo echocardiographic measurements and post-mortem measurements were demonstrated by Maron et al (126) when such measurements were compared in patients with and without disproportionate septal thickening. Of the 9 patients with an echocardiographically determined septum-to-free wall ratio of 1.3 or greater during life, 6 had a ratio of ≤ 1.3 at post-mortem. One explanation for the discrepancy between the two types of examination is that the echocardiographic measurements are made in diastole whereas many hearts are fixed in systole (126, 127). The left ventricular free wall thickens considerably more than the septum in systole which results in a smaller septum-to-free wall ratio in systole than in diastole. This explanation is supported by the observation that the post-mortem measurements of the septum, LV free wall and the ratio of the two concorded to a far greater degree with the echocardiographic measurements in systole than in diastole (126). In addition, Bulkley's group (127) showed further discrepancies in 9 subjects thought to have ASH during life. Only 2/9 had the diagnosis confirmed at post-mortem. The other 7 were thought to show no evidence of the disease of which two were thought to show symmetric concentric LVH, one showed coronary atherosclerosis, one showed amyloidosis and three were thought to show no cardiac disease at all. These studies demonstrate that asymmetric septal hypertrophy observed during life may not be confirmed at post-mortem examination and suggests therefore that this feature can not be used as the single defining morphological characteristic of HCM in comparative studies.

Further echocardiographic studies including one by Kansal et al (128) showed that a septum-to-free wall ratio of ≥ 1.3 was found in 12% of normal subjects, 39% of those with myocardial hypertrophy secondary to hypertension and valvular heart disease, and in 95% of subjects with HCM and suggested that a ratio of ≥ 1.5 may be more useful. However, the continued lack of specificity at the expense of necessary sensitivity afforded by this increased ratio was shown when a ratio of > 1.5 was described in 56% of those with HCM, 28% of those with hypertension, and 7% of athletes (129, 130) with 21% of athletes defined as abnormal in the same study with a ratio of ≥ 1.3. Roeske et al (131) found a septum-to-free wall ratio > 1.3 in 4/10 athletes and 5/10 control subjects and Gibson et al (132) described the finding in those with secondary LVH of various causes. Conversely, a sub-group of patients described by Lewis and Maron (133) with definite HCM were described where the diastolic septum-to-free wall ratio was ≤ 1.1 in all cases due predominant involvement of the posterior wall.

In many patients with HCM the septum-to-free wall ratio identified by M-mode echocardiography is abnormally large because the path of the M-mode beam is through the posterior LV free wall which is
preferentially spared from the hypertrophic process. Thus, when the ratio is increased it expresses only the
degree to which the septum is thickened in comparison to the LV wall and has limited value when both are
affected. This is one reason why the ratio is no longer adhered to as the sole criterion for the
morphological identification of HCM (134). Instead it was suggested by Maron that the disease could be
characterised by the appearance of a non-dilated hypertrophied left ventricle in the absence of another
cardiac or systemic disease that could produce LV hypertrophy (18).

**Absolute wall thickness measurement**

The new definition (18) inevitably focussed attention on the measurement of absolute LV wall thickness
as the way to detect hypertrophy and increased wall thickness is said to be the "sine qua non" of the
disease (30). Kansal et al (128) had shown that an absolute maximal wall thickness measurement of 15mm
distinguished normal subjects from subjects with HCM but that wall thickness measurements of >15mm
also occurred in 50% of the group with LVH due to hypertension or valvular heart disease in their study.
However, a thickness of ≥ 15mm in the septum or posterior LV wall continues to be used to diagnose
HCM in adult individuals and family members (45, 135, 136).

In studies using cross-sectional imaging, hypertrophy was considered to be present if septal wall thickness
was ≥ 15mm or if segments of the LV wall near to the lateral borders of the sector were ≥ 17mm thus
allowing for the limited lateral resolution of the technique (113, 137). Other authors have since used a cut­
off measurement of ≥13mm for the anterior septum and posterior wall and ≥15mm in the posterior septum
or free wall for the same reason (138). The 15mm cut-off between normal and abnormal left ventricular
wall thickness was accepted up to and including 1993 (136). Then Hengstenberg et al (139) proposed that
maximum left ventricular wall thickness of >13mm should be used to diagnose hypertrophic
cardiomyopathy in subjects <60 years, raising it to 15mm for those >60 years which was approved at an
international workshop. This cut-off value of 13mm was subsequently employed in various genotype
studies (104, 140). Despite this, one of the largest prevalence studies to date continued to employ the
diagnostic criterion for HCM for both men and women of a maximal diastolic LV wall thickness of ≥
15mm which was not associated with systemic hypertension (45). The mean value and standard deviation
of wall thickness for the study group was 8.7 +/-1.7mm so this cut-off was clearly a conservative one from
the point of view of making the diagnosis.

It is known that LV wall thickness measurements are greater in men than in women as are the left
ventricular internal dimensions (95, 141, 142). As such any chosen cut-off measurement which offers high
specificity for the detection of affected males is likely to lack sufficient sensitivity for the detection of
affected females. This may explain the skewed sex distribution in the CARDIA study (45). The alternative
of a single highly sensitive cut-off for both sexes would result in an unacceptable lack of specificity and
over diagnosis of a serious disorder. Interestingly, the idea of having a separate cut-off for men and women has not been pursued.

Other patterns of hypertrophy

The vast majority of patients with HCM show asymmetric and predominant thickening of the ventricular septum (16, 18, 68, 110, 113, 116, 134, 143, 144). The anterior ventricular septum alone or in combination with other parts of the ventricle has been shown to be hypertrophied in up to 82-96% of individuals using standard criteria (113, 145). However, the advent of cross-sectional two-dimensional echocardiography in the 1980s allowed a more comprehensive assessment of hypertrophy throughout the whole left ventricle. It also provided good localisation for the M-mode beam as this modality remained the most accurate way of measuring wall thickness in parts of the ventricle accessible to it (137).

Hypertrophy involving many areas of the left ventricle was then recognised and a study of >500 patients with HCM at one institution showed that there was a substantial degree of heterogeneity in the distribution of the hypertrophy (113, 135, 146) even within the same kindred (147). Hypertrophy could be localised and confined to discrete segments of the free wall leaving out the septum in some patients (113, 146). This resulted in a lumpy appearance since the process rarely involved all segments equally. Examples of such hearts have been described at necropsy (148). These studies suggested that septum-to-free wall ratio calculated from M-mode echocardiography gave an accurate description of overall LV hypertrophy in as few as 20% of subjects. In the remaining 80% the septum-to-free wall ratio could be misleading, as the area of maximal hypertrophy was not be accessible to the M-mode beam. No information was given regarding the LV cavity size in these subjects.

Some investigators have described a symmetrical pattern of hypertrophy in patients with HCM similar to that seen in valvular aortic stenosis and systemic hypertension (96, 126, 147, 149-151). But most of these are early single reports or small series and include isolated M-mode data, which may have missed asymmetrically thickened areas that would have been visible on cross-sectional imaging. Overall these patients are thought to be rare with an estimated prevalence of only 1-2% (113). However, another study from the Hammersmith Hospital using a septum-to-LV free wall ratio of <1.3 as the criterion for symmetry (117) described symmetric LV hypertrophy in about 34% of patients with HCM. The differences may be attributable to patient selection or differing approaches to the diagnosis on cross-sectional imaging. Coexistence of asymmetric and symmetric forms of hypertrophy has been described in one family with HCM (147). It has previously been speculated that one of the mechanisms for the development of symmetrical hypertrophy in HCM is that ASH could produce subvalvular obstruction and subsequent hypertrophy of the LV free wall occurs as a secondary phenomenon (116).
It was thought by some that sudden death was less common in subjects with unusual morphology (134). By inference one might assume that the same applied to the occurrence of morbidity. However, in 1991 Lewis and Maron (133) described a subgroup of 17 patients with marked thickening of the posterior left ventricular free wall and normal or only modestly increased septal thickness creating an "inverted" asymmetry pattern. This group was young (mean age 31, range 13-54) and 11/17 had severe functional limitation before the age of 40 years. In addition, Spirito has described a group with mild localised hypertrophy with severe functional limitation (152) which suggests that the substrate involved in the production of symptoms and functional limitation is complex and not merely related to site of hypertrophy and the presence of obstruction due to a grossly hypertrophied septum.

**Left ventricular mass**

Left ventricular mass is significantly increased in HCM with weights of up to 970g (30). Estimating left ventricular mass using echocardiography has been well described and anatomically validated in the normal population (153-155). However, the methodology involves geometric formulae in to which LV measurements are entered. When the LV hypertrophy is localised to the anterior ventricular septum in HCM, the M-mode measurements of the LV lead to an overestimate of LV mass. In other subjects with more diffuse hypertrophy, up to 55% of some populations examined, LV mass will be under estimated (134). Furthermore, although an increased left ventricular mass usually accompanies the presence of left ventricular hypertrophy it is clear that the presence of increased myocardial mass is not sufficient to diagnose some patients with HCM. One report by McKenna et al (156) showed that hypertrophic cardiomyopathy with myocardial disarray could occur in families without an increase in LV mass and another report by Maron et al (157) described sudden death due to HCM in the absence of increased LV mass. Therefore the usefulness of this parameter to diagnose HCM is very limited. Firstly, it need not be present and secondly, as will be discussed, it is non-specific and will not discriminate between hypertrophy of different aetiologies.

**Diagnosis in children**

Establishing the diagnosis of HCM in childhood has always posed more difficulty than in adults since the absolute wall thickness measurements used in adults are clearly inappropriate and increased septum-to-free wall ratios have been described in normal children and those with other cardiac defects (120, 122). One study of infants with other congenital heart diseases revealed septum-to-free wall thickness ratios from 1-1.7 and the authors conceded that this criteria alone could not be used as the sole criteria for the diagnosis of HCM and had to be supported by appropriate histology (29). Four infants in this study died at < 5/12 of age suggesting that HCM in this age group was not as rare as had been previously thought. Perhaps the paucity of reported cases was, in part, due to the difficulties in making the diagnosis in this
age group and the diagnosis was not made clinically in any of the infants in that particular study prior to death.

Despite the lack of specificity of an elevated septum-to-free wall ratio for the diagnosis of HCM in childhood, this continued to be used in one of the first and most informative studies of HCM in this age group (28). Significant progression of hypertrophy, symptoms, and the incidence of sudden death was described using the diagnostic criterion of echocardiographic or necropsy documentation of a septum-to-free wall ratio of ≥ 1.3 (28). McKenna's group in 1997 mention that fulfilment of the diagnostic criteria for HCM in children < 10 years would require a body surface area corrected left ventricular wall thickness of >10mm but then go on to say that the absence of this feature does not exclude the disease (138). Other studies have defined children as having excessive hypertrophy if the body surface area corrected maximum left ventricular wall thickness is greater than the 95% prediction limits for body surface area described by Henry (135, 158, 159) or greater than that expected for weight or height (139). Clearly a single measure, which could be used to diagnose hypertrophy in the growing heart, would be extremely valuable and would permit more consistency in the approach to the echocardiographic diagnosis and sequential assessment of this disease in childhood.

Other echocardiographic features of HCM

Outflow tract obstruction

Several other echocardiographic features such as the presence of outflow tract obstruction, systolic anterior motion of the mitral valve and impaired diastolic performance have all been described in HCM. The presence of pressure gradients across the left ventricular outflow tract in systole has been widely described (91) but this is not invariable and when present does not appear to constitute the fixed haemodynamic obstruction seen in aortic stenosis (3). The differences include the variability of the gradient and the lack of correlation of magnitude of the gradient with prognosis, symptoms and disease progression. Ejection of all of the LV volume in the first half of the cardiac cycle and the tendency for obstruction to diminish with increasing disease severity are also contrary to the findings in fixed obstruction (3).

Criley et al (13) showed that left ventricular catheter gradients could be produced in patients with HCM when the catheter became lodged in areas of the ventricle which emptied quickly such as the trabeculae and reproduced such gradients of 72-146mmHg in dogs using isoproterenol. However, Wigle et al (91) went on to show that in the presence of true muscular subaortic stenosis there was a direct relationship between the magnitude of the gradient and the left ventricular ejection time whereas with catheter entrapment there was an inverse relationship between the measured gradient and the left ventricular ejection time. The same group also noted that there was an invariable reduction in left ventricular ejection
time following left ventricular myectomy/myotomy providing important evidence of the pre-existence of true obstruction in those patients.

Others noted that gradients could be produced in normal hearts by powerful inotropic stimulation (160) or acute ventricular hypovolaemia (161) suggesting that the presence of a gradient does not imply obstruction per se. Murgo et al (162) measured high velocity flow and pressure in the left ventricle and aorta and were unable to show any evidence of true obstruction to outflow from the left ventricle in HCM. They therefore concluded that hypertrophy and abnormal ventricular compliance played a more dominant role in the generation of symptoms in hypertrophic cardiomyopathy.

Gradients " though variable, transient and fickle in many cases " (75) were thought to be diagnostically valuable however, in warning against the use of powerful inotropic agents or manoeuvres which reduce ventricular volume. Persistent gradients can also alert the clinician to the presence of a fixed obstruction which may require surgical intervention to improve symptoms but not necessarily prognosis (3). The implications of the presence of a LV outflow tract obstruction for survival were examined by McKenna et al (48) in a large retrospective study. The haemodynamic features of those surviving were compared with the features of those who died. 66% of the patients who died and 63% of the patients who survived had a resting or provable left ventricular outflow tract gradient and neither the presence nor absence of a gradient predicted subsequent mortality. This issue was investigated by another group in 1990 (163) and again the presence of a gradient was not shown to be of adverse prognostic significance.

Echocardiography appears to be an adequate technique to demonstrate an outflow tract gradient as a good correlation has been shown between Doppler-estimated and catheter-measured gradients in HCM (164, 165). However, care is needed to avoid confusion between the Doppler jet of LV outflow tract obstruction and the jet of mitral incompetence which may co-exist in those with obstructive disease (136). A recent review concluded that in many patients an outflow tract gradient is compatible with normal longevity in the absence of significant symptoms (53). The significance of LV outflow tract with respect to outcome and risk stratification therefore remains unclear.

**Systolic anterior motion of the mitral valve (SAM)**

Systolic anterior movement of the mitral valve apparatus (SAM) and mid-systolic closure of the aortic valve were also described when gradients were found (166). Romeo et al (163) noted that 92% of their patients with a gradient at catheterisation exhibited SAM on M-mode echocardiography. The contribution made to the gradient by apposition of the mitral valve leaflets or papillary muscles with the hypertrophied septum has been discussed by many authors (167-171). Various theories were proposed to explain the mechanism of SAM and left ventricular outflow obstruction. Pridie and Oakley (172) suggested that an abnormally directed and dissynchronous papillary muscle contraction could pull the anterior mitral valve
leaflet into the left ventricular outflow tract during systole and cause both outflow tract obstruction and mitral regurgitation but later Henry et al (173) showed that contraction of miss-aligned papillary muscles was not the cause of the abnormal mitral valve motion since forward displacement of the mitral valve occurred at the onset of systole and not in diastole.

Since patients with obstructive HCM had narrower left ventricular outflow tracts than those with non-obstructive HCM, another factor thought to contribute to the forward positioning of the mitral valve leaflet included distortion of the left ventricular cavity caused by extreme septal hypertrophy. In this situation abnormal hydrodynamic forces would be generated as blood was ejected through the narrowed tract during a short left ventricular ejection period, creating a Venturi effect. As a result the mitral valve would be sucked into the outflow tract producing the obstruction and the gradient (1).

A early study by Rossen et al (149) showed that SAM may be present in patients with HCM without the co-existence of a left ventricular outflow tract gradient, and that the "obstruction index" and calculated gradients from echocardiography did not correlate with actual gradients at catheterisation. The obstruction index was calculated by dividing the duration of left ventricular outflow narrowing by the mean distance between the anterior mitral leaflet and the septum during systole as described by Henry (170). The predicted gradient was calculated from a regression equation. Interestingly, Henry's group also described patients in whom SAM was present in the absence of a pressure gradient (170). These discrepancies may not be that surprising in that the same degree of SAM visualised in two dimensions may not be representative of the three-dimensional orifice formed in different patients. However, a quantitative relationship between the onset and duration of SAM and the magnitude of the LVOT gradient was described in later studies (114, 174). Gilbert et al (114) using M-mode echocardiography and cardiac catheterisation showed that those with a definite gradient did exhibit SAM but that this occurred when SAM was severe (anterior leaflet-septal contact >30% of echocardiographic systole).

A further division of SAM into "true SAM" and "pseudo-SAM" was suggested by some authors. True SAM is defined as an abrupt systolic anterior motion of the mitral valve out of proportion to the motion of the left ventricular posterior wall at or before the end of systole or before the aortic component of the second heart sound. Pseudo-SAM is said to be an exaggeration of the normal anterior motion of the mitral valve during systole that parallels the motion of the left ventricular posterior wall motion during systole and in to diastole (175). Pseudo-SAM may be seen in many disease states including pericardial effusion (176), atrial septal defect and anomalous pulmonary venous drainage (177), mitral valve prolapse (178), and ventricular aneurysm (179). True SAM may occur in hypovolaemia and anaemia (180), dextroposition of the great vessels (181) and membranous subaortic stenosis (182). In addition, true SAM has been described in the absence of ASH (175, 183) and Mintz et al (175) showed that SAM, systolic septal-mitral valve apposition and left ventricular outflow tract obstruction could exist in the absence of a
thickened septum. In their study four of the patients with SAM and no septal thickening had resting or provokable gradients at cardiac catheterisation and prolonged LV ejection time with amyl nitrite. Thus, it was concluded that asymmetric septal hypertrophy may not be the cause of SAM or LVOT obstruction and these features may have more to do with abnormal ventricular ejection dynamics.

Thus the presence or absence of LV outflow tract gradients or SAM on echocardiography in HCM whilst interesting do not offer the necessary sensitivity or specificity to be useful as major diagnostic or screening criteria for the disorder.

**Diastolic function**

The impaired diastolic properties of the abnormally hypertrophied ventricle in HCM have been described (2, 10, 11). Angiographic studies revealed greatly reduced LV volumes in diastole (3). Subsequent studies using angiography (184) and echocardiography (185) showed delayed opening of the mitral valve indicating abnormal relaxation which was inversely related to the peak filling rate of the LV, which was prolonged. Prolonged isovolumic relaxation time was also shown and thought to be a primary abnormality in HCM. The abnormal filling pattern was thought to be due both to impaired relaxation and to the abnormal shape of the LV cavity. The work of Webb-Peploe (186) and Swanton (187) showed that beta-adrenergic blocking agents administered acutely to patients with HCM produced an increase in LV volume and a fall in left ventricular end diastolic pressure suggesting an improvement in diastolic function. Alvares et al (188) used phonocardiography, apex cardiography, and M-mode echocardiography to show that the sequence of events in diastole is completely disrupted in hypertrophic cardiomyopathy. Aortic valve closure occurred after the minimum dimension of the LV cavity, and the isovolumic relaxation time (from aortic valve closure to mitral valve opening) though often prolonged tended to be shorter in those with gradients. The effects of chronic beta blockade in that study were reported as variable. In the majority the "active sucking" period was prolonged thus aiding ventricular filling but in the minority was shortened. Transmitral Doppler flow characteristics have also been studied in the HCM population (189) and have shown prolongation of the early diastolic peak, reduced maximal flow velocity in early diastole with slow deceleration and a reduced E wave to A wave ratio which are all indicative of impaired diastolic function.

These varied results demonstrate the complexity of ventricular diastolic function in HCM and the difficulties of predicting any benefit from medication. This is perhaps not surprising since the increased and abnormal collagen matrix described recently in the pathological specimens from those with HCM is thought to play a major part in diastolic dysfunction and may not respond to pharmacological agents (30).

**Systolic function**

Left ventricular systolic hypercontractility (2, 110, 190) or a hyperdynamic left ventricle (144) is a recognised feature of the disease. However, it has been suggested that the angiographic studies of HCM
and control patients use complicated wall stress equations which make assumptions about circumferential wall stress which have not been validated in HCM and may not be valid in a situation with marked myocardial fibre disarray. Pouleur et al (191) examined force-velocity-length relations in HCM and suggested that hypertrophy led to a reduction in wall stress, which resulted in a reduced end systolic afterload and the hypercontractile appearance. However, they suggested that the mechanics were not truly hypercontractile and were normal or depressed. More recently others have again suggested that cardiac contractility is reduced in HCM and that the hypertrophy is likely to be an attempt to compensate for impaired rather than exaggerated LV systolic function (192). However, this was contested in a letter to the Lancet by Östman-Smith and Wettrell (193) who compared wall thickness and ejection fraction data from normal infants with that from infants of diabetic mothers and infants with HCM. The group with primary HCM showed increased ejection fractions compared with normal infants. This could not be attributed to the hypertrophy alone since the infants of diabetic mothers with comparable hypertrophy to those with primary HCM, showed ejection fractions lower than the normal group. These infants would appear to provide a good in vivo model of the trophic effects of insulin and insulin-like growth factor 1 on the heart and do not exhibit the enhanced contractility seen in the HCM infants. They also compare data from normal pre-pubertal children with data from those with HCM and aortic stenosis which shows that the HCM group have similar contractility to those with a fixed obstruction. The suggested alternative hypothesis therefore is that increased cardiac sympathetic nervous activity is the final common pathway in the induction of most adaptive cardiac hypertrophy. This is supported by the reduction in hypertrophy (194) and morbidity and mortality (195) associated with high dose β-blocker treatment.

**Cavity dimension**

The presence of a small left ventricular cavity (129, 144, 166) has also been recognised as a feature of the disease. A recent prevalence study of HCM (45) used M-mode echocardiographic measurements of maximal left ventricular wall thickness to make the diagnosis but recognised a left ventricular end diastolic diameter (LVEDD) < 45mm and systolic hypercontractility with fractional shortening of >25% as features of the disease although these were not included in the diagnostic criteria (45). The presence of a small left ventricular cavity in HCM though recognised was likewise not employed in the diagnostic criteria in other studies (127, 166). Recently it has been suggested that a small LV cavity size is associated with functional limitation and a history of syncope in HCM, irrespective of obstruction or hypertrophy (196). It has also been associated with the presence of a hypotensive response to exercise in those with HCM (89). This suggests that this feature is a separate morphological marker for the disease, which is associated with the presence and severity of symptoms, and as such, it would seem logical to incorporate this measure in to the diagnostic criteria for the disorder.
1.16 Treatment

Much of the pessimism surrounding the diagnosis of HCM and the reluctance to devise better ways of screening for the disorder have centred around the opinion that there are no effective treatments. However, there is increasing evidence that there are effective medical and surgical treatments for this disease.

**Acute treatment**

When acutely ill there should be prompt treatment of arrhythmias or cardiac failure as decompensation may be rapid. For example, immediate cardioversion is recommended for rapid atrial fibrillation followed by long term treatment with an appropriate anti-arrhythmic agent (3). Such prompt treatment may be life saving. Congestive cardiac failure implies advanced disease which can be treated cautiously with diuretics but vasodilator treatment of heart failure is contraindicated in this disorder and may worsen the acute on chronic presentation.

**Medical therapies**

Accepted treatment goals should include reducing symptoms, preventing sudden death and retarding the advance of the disease (3).

**Beta-adrenoceptor blockade**

Beta-adrenergic blocking agents have been shown to produce increased LV volume, a fall in left ventricular end diastolic pressure and thus improved diastolic function with prolongation of the isovolumic relaxation time (IVRT) (187, 188, 197). However, the effects of chronic beta blockade have been variable and although the IVRT was increased in the majority there was a proportion of patients for whom this was not the case (188). Flamm et al (198) reported a reduction in outflow tract gradient at rest, post exercise and with isoproterenol in those with HCM using propranolol and the disappearance of SAM has also been reported in some patients treated with beta-blockers (168).

The failure of beta blockade to reduce supraventricular arrhythmias, ventricular ectopics and ventricular tachycardia and consequently to prevent sudden death has been reported by some authors (50, 78) who compared 48hr ECG monitoring in those with and without beta-adrenergic blockade. However, only a dose range and mean dose are quoted for the group as a whole and not for affected individuals. Another study however, showed that arrhythmias were controlled by larger doses of propranolol alone in 30% of cases whilst the remainder needed a second agent (199) and noted that between 1975-1980 none of the patients on high dose propranolol died. A study in children and young adults (age 5 months-20 years)
reported no deaths in 7 patients treated with propranolol compared with 7/13 deaths in the no treatment group (200). However, these earlier studies suffered from small numbers of patients which were not matched for age or symptoms. In the studies from Goodwin's group about 50% of patients who died were on beta-blockers (3) and in a multicentre study (50) the appearance of supraventricular arrhythmias was not prevented by the use of propranolol. Because of this Goodwin advocated 48-72 hour ECG monitoring before starting any treatment and that if ventricular tachycardia was present, treatment should be with amiodarone. If no arrhythmia was identified but symptoms were present treatment with propranolol was advised as the sole therapy (3).

Interestingly, an earlier study by Frank et al (201) and a more recent study by Östman-Smith et al (195) with an appropriate control group, have reported a reduction in the incidence of sudden death on long-term treatment with very large doses of propranolol. This may result from beneficial effects on cardiac performance and thus haemodynamics and may be beneficial to aspects of the abnormal haemodynamic and vascular responses implicated in the causation of sudden death. Additional benefits such as reduction in rate of progression of hypertrophy and increased capillary perfusion of the myocardium are suggested by animal work using long-term beta-adrenoceptor blockade (202). Regression of hypertrophy has been reported in a study which showed a reduction in ECG indices of hypertrophy in two patients with HCM on long-term high dose therapy (99) and subsequent echocardiographic studies in childhood HCM also demonstrated echocardiographic regression in hypertrophy (194, 203).

**Calcium antagonists**

Verapamil has been shown to improve symptoms, haemodynamics including diastolic function, and exercise capacity in some patients with HCM (204-206) and one author described a reduction in left ventricular mass in HCM (207). However, lengthening of the PR interval and hypotension may occur with intravenous administration (204, 205) and in one study (204) one patient suffered hypotension and sinus arrest after one dose of 80mg of oral verapamil, and another developed second degree atrioventricular block. Two further patients died; one experienced severe chest pain and had no recordable blood pressure after 4 doses of oral verapamil, was resuscitated but died one week later and the other died during septal myectomy having suffered pulmonary oedema following 13 doses of verapamil treatment at a dose of 120mg six hourly (204). Following the identification of arrhythmias in one group of patients with HCM treatment with verapamil was attempted but further ambulatory ECG recordings revealed no reduction in the frequency of arrhythmias for those patients (208). However, one long term study of medical versus surgical treatment by Seiler et al (209) showed that the 10 year survival rate was similar in the verapamil treated compared to the surgically treated group.
A very short (4 weeks each), small, double-blind, placebo-controlled crossover trial of nadolol and verapamil was reported (210) in which neither treatment appeared to improve maximal oxygen consumption but in which many patients appeared to derive symptomatic benefit from both therapies, an accepted treatment goal. Treatment with nifedipine has also been attempted with some success but again liability to vasodilatation and hypotension make caution imperative (211).

**Amiodarone**

Amiodarone was shown to successfully reduce ventricular arrhythmias and abolished ventricular tachycardia in 10/13 patients in one study (208). Furthermore, it was reported to reduce the number of extrasystoles and restored sinus rhythm to 3/5 patients with longstanding atrial fibrillation. Following this McKenna et al went on to show an indication of improved outcome in adults (212) and children (82) when treated with amiodarone. However, this has subsequently been questioned by another group who demonstrated increased sudden death in symptomatic patients during therapy with amiodarone (213). More recently a population based study prescribed amiodarone to those suffering frequent non-sustained ventricular tachycardia and found that this group showed no increase in mortality when compared to the untreated group (81). Whilst this does not establish that amiodarone is truly protective, there was no excess of adverse features associated with its use. The need for further larger prospective treatment trials is clear.

**Disopyramide**

Disopyramide a type la anti-arrhythmic agent has been shown to exert a favourable influence on the haemodynamic abnormalities seen in HCM when administered intravenously (214) and has been shown by others to afford clinical improvement and reduction in left ventricular outflow tract gradient and SAM when used on a long-term basis (215).

These studies show that there are many medical treatment options for patients with HCM, some of which have shown very encouraging results (195, 201, 209, 212). At the very least this evidence makes a case for the establishment of large collaborative prospective randomised controlled trials to better define which patient groups obtain benefit from which treatments.

**Pacing**

In the early 1990s dual chamber pacing was proposed as an alternative to surgical treatment for the relief of symptoms in patients with obstructive HCM. Reports of significant reduction in outflow gradients and symptoms along with improvements in effort tolerance have been made (216-219). The proposed
mechanism for the reduction in outflow tract gradient is the abnormal septal motion produced by right ventricular pacing. However, opinions vary on the usefulness of this treatment since some well designed studies have shown that a strong placebo effect is the predominant mechanism for perceived short-term symptomatic improvement (109, 220). Furthermore, objective evidence of improved functional capacity is unconvincing (53, 218, 220) and the gradient was unchanged or increased in 43% of subjects (220). Understandably, there is more reservation still about the placement of dual chamber pacemakers in children in an attempt to attenuate the future course of the disease (53, 221). Therefore uncertainty still surrounds the role of pacing in the treatment of obstructive HCM.

**Implantable defibrillators**

If medical therapy fails to control life-threatening arrhythmias consideration can be given to the insertion of an implantable defibrillator. Some studies have suggested that defibrillator implantation should be considered in patients who have survived cardiac arrest, patients with non-obstructive HCM with syncope/presyncope and inducible sustained ventricular tachycardia (VT) at EP study, asymptomatic patients in whom sustained VT is easily induced at EP study and young patients with recurrent syncope despite medical therapy (108, 222). A recent retrospective study by Maron et al (223) examined the efficacy of implantable defibrillators in 128 patients with HCM. Current sophisticated devices allow the documentation of the rhythm which has triggered the defibrillation shock and in all 21 patients in whom this data was available, the shock was triggered by ventricular tachycardia or fibrillation suggesting this as the predominant mechanism of sudden death in HCM. One third of the patients had a device placed as a secondary prevention measure having had a previous episode of cardiac arrest or sustained ventricular tachycardia. The activation rate of the defibrillator in this group was 11% per year. In the group in whom it was used as primary prevention because of high risk, the rate was lower at 5% per year. Further investigation of the activation patterns of these devices in cohorts with different risk factors, phenotypes and genetic mutations will contribute valuable information to risk assessment and stratification.

**Percutaneous septal ablation**

This procedure is an alternative to surgery and is under-going further research. It involves infusion of ethanol in to one or more septal perforator branches of the left anterior descending coronary artery leading to infarction and thinning of the proximal interventricular septum which is implicated in the causation of left ventricular outflow tract obstruction (108). Early studies have reported a 70% reduction in LV pressure gradients and significant symptomatic improvement but heart block necessitating pacing, ventricular arrhythmias and death have all been recognised as complications (108). A recent study quotes a 4% procedure related mortality with a further 4% requiring resuscitation from ventricular fibrillation within 48 hours of the procedure and 38% required an atroventricular sequential pacemaker system for persistent high grade atroventricular block (224). The long-term effects are as yet unknown but may
include arrhythmias or sudden death attributable to the myocardial scar resulting from the procedure (225). The enthusiasm for this type of intervention is considerable and a large number these procedures and pacemaker insertions have been performed at selected centres in the last 3-4 years for seemingly milder indications (53). Therefore, the use of this procedure must continue to be subjected to a healthy degree of scrutiny, particularly in the light of recent studies in which the natural history of the disorder appears to be more benign than was previously thought.

Surgery

Surgery in HCM is performed to relieve sub-aortic obstruction and thereby reduce intraventricular pressure (226-229). It is reserved for severely symptomatic individuals with gradients of ≥50mmHg (basal or with provocation) who have not benefited from medical therapy and despite newer developments, remains the gold standard for treatment of this small sub-group of patients (<5% of overall HCM population) (1, 3, 53). The "Morrow operation" where a small amount of muscle is resected from the basal part of the ventricular septum is the procedure of choice (226). However, mitral valve replacement has been used in those with a relatively thin septum (≤18mm) (230), those with atypical distribution of hypertrophy or mid-cavity muscular obstruction (40) or in cases with significant valve calcification, turbulence or infection (3). Resection of the papillary muscles as part of this procedure assists in the abolition of systolic LV gradients (3). A combination of myotomy-myectomy and suture plication of the anterior mitral valve leaflet is sometimes suggested to reduce the chance of SAM persisting after surgery (231).

Studies have reported excellent symptomatic and haemodynamic results from myotomy-myectomy (226-231). Approximately 70% patients have marked improvement in symptoms, functional capacity, and quality of life over an average follow-up period of 5 years and outflow gradient is reduced or abolished in >90% (53, 227, 232, 233). Operative mortality has improved from up to 7% (226, 234) to ≤1-2% in more recent reports which include paediatric patients as young as 2 months (2, 232, 235, 236) and there are few reports of late congestive heart failure after surgery.

Some studies have compared treatments such as surgery with beta blockade (237). One study showed progression of hypertrophy in 4 adult patients treated with propranolol (80-160mg/day) (137) but in contrast, no clinical or echo progression was seen in 11 patients following septal myotomy/myectomy. A recent non-randomised study compared dual-chamber pacing with septal myotomy for the treatment of patients with obstructive disease (233). 90% of the surgical group experienced symptomatic improvement compared with 47% of the group who underwent pacing. There were also significant improvements in exercise duration and maximum oxygen consumption in the surgical group whereas these did not reach statistical significance in the pacing group.
Transplantation

Transplantation can be considered for the few very severely affected patients who are at high risk of sudden death and whose disease has proven refractory to other treatment or for those who have entered the preterminal dilated phase of the disease and who are cardiac invalids. Early diagnosis has greatly improved the prognosis of dilated cardiomyopathy (238) as have a better understanding of the disease, more sensitive diagnostic tools, better treatments and greater awareness of the indications for cardiac transplantation and the optimal timing of this procedure. The four year survival following the diagnosis of dilated cardiomyopathy increased from 54% in patients diagnosed during 1978-82 to 83% in those diagnosed during 1988-92 and is even better if transplanted patients are included (239). Selection of the correct group for transplantation at the correct time is crucial to the outcome and studies of those undergoing transplantation for HCM are necessary to better define those for whom transplantation would be of benefit and the optimal timing for the procedure in this disease.

1.17 Inheritance and genetics

Pathology

One of the first large pedigrees was reported in 1960 by Hollman et al (240) and during the 1960s both familial and sporadic forms of HCM were described based on history, clinical features and post-mortem studies (11, 24, 240-244). In these studies, genetic transmission appeared to occur in approximately one third of families (244) with an autosomal dominant pattern of transmission (11, 24, 240-244).

Echocardiography

The advent of echocardiography allowed the identification of many subjects with HCM who would otherwise have remained undetected clinically (16, 110). Family studies using M-mode echocardiography followed which used asymmetric septal hypertrophy as the marker for the disease and suggested that HCM was secondary to a genetic defect which was transmitted in an autosomal dominant manor with a high degree of penetrance (15, 112, 245, 246). But even in these early echocardiographic family studies it was noted that echocardiographic findings in relatives of patients with HCM were heterogeneous (246).

Maron et al (135) undertook a large study of 367 relatives from 70 families using M-mode and two-dimensional echocardiography. Abnormal hypertrophy was identified as a thickness of ≥ 15mm in the septum or posterior LV wall in adults and >95% confidence intervals for children quoted by Henry (158). However, asymptomatic adults with septal thickness of 13 and 14mm were not considered normal or
abnormal but were classified as having a "borderline morphologic abnormality" which in all cases was confined to the anterior ventricular septum (135). 39/70 (56%) kindreds appeared to have familial HCM and in total 22% of first degree relatives were affected. In 30 kindreds the inheritance was consistent with an autosomal dominant trait. In the other 9, two or more affected relatives were identified in only one 1 generation and the precise mode of inheritance could not be definitively categorized. In as many as 31 pedigrees (44%) the proband was thought to be the only affected family member and this was therefore considered to be a sporadic occurrence. This study was in contrast to the study by Clark et al (15) in which "idiopathic hypertrophic subaortic stenosis" (HCM) was described as an autosomal dominant genetically transmitted disease with a segregation ratio as high as 0.46.

A later but virtually identical study by Greaves et al (159) examined a large group of 50 probands and 193 first-degree relatives. Diagnostic criteria were the same as in Maron's study. In 15 kindreds the mode of inheritance was autosomal dominant and in 13 the affected members were identified in a single generation and therefore the inheritance could not be determined. This resulted in an overall figure of 20% of first degree relatives being classified as affected with HCM and as in Maron's study the frequency in offspring (8%) was significantly less than in siblings (25%) or parents (37%) and male first degree relatives were more commonly affected than females. The apparent shortfall in affected first degree relatives in an disorder now known to be transmitted in an autosomal dominant manner may have several explanations. There could have been inadequate in vivo or post-mortem data from those who had died to acknowledge or refute the diagnosis. Relatives who lived far out with the geographical area of the study may not have participated and of those close enough to participate there may have been some who were unwilling to participate. It may also be explained by the increased morphologic expression of HCM with increasing age (68) such that the application of the full echocardiographic diagnostic criteria for HCM in family members of all ages will inevitably lead to an underestimation of the number of affected relatives. However, in a sufficiently large group of first degree relatives one might still expect better separation in to the proportions expected for an autosomal dominant disorder than appears to be the case in either of these two studies particularly since the incidence of true sporadic HCM is considered to be rare (247).

In 1988 an Italian group described equivocal and borderline hypertrophy in relatives of patients with hypertrophic cardiomyopathy (248). They acknowledged that minor abnormalities of left ventricular geometry might be important subtle indicators of the expression of a disease mutation. As such an increased ratio of diastolic mean wall thickness-to-cavity radius was assessed in a control population and then used to detect an abnormal phenotype. When the generally accepted complement of diagnostic criteria were used to identify affected family members (maximal wall thickness ≥15mm in adults or >95% confidence limits Henry) only 11/74 family members were found to be affected. However, when relatives with increased LV wall thickness to cavity radius ratios were included as "affected", along with those with a positive family history of sudden death and those with borderline septal thickness measurements of 13-14mm, the familial occurrence of the disease rose to 90%. In the studies of Maron et al (135) and Greaves
et al (159) offspring were consistently less affected than parents or siblings. In this study fully affected relatives had a mean age of 51 +/-17 years and those who were "unaffected" but had increased LV wall/LV radius ratios had a mean age of 28 +/- 9 years. This suggests that a more subtle morphological indicator may be required to identify potential, latent or occult disease especially in the younger population who have yet to or may never develop the full blown diagnostic criteria.

Genetic mutations

Recent years have seen the discovery of mutations coding for the genes of contractile proteins in subjects and families with HCM which are transmitted in an autosomal dominant manner (190, 249-251). Sporadic disease is thought to constitute less than 10% of cases (247) however, haplotype analysis within groups of families sharing identical mutations has shown instances of independent origin of the mutations rather than a founder effect (252, 253). This indicates that there is a relatively high new mutation rate and that the sporadic occurrence may be higher than first anticipated. This implies that any genetic screening programme would require systematic screening for both known and novel mutations.

Seven disease genes have been identified (247) in which > 100 mutations are described which produce this disease of the sarcomere (108, 249, 250, 254). These mutations occur in the genes which code for contractile proteins. This includes the thick filament components such as β-cardiac myosin heavy chains (104, 105, 255), essential and regulatory myosin light chains (247, 256) and cardiac myosin binding protein C (257, 258), in addition to the thin filament components such as cardiac troponins T and I and α-tropomysin (102, 259). Despite this, mutations are identified in <50% of kindreds with the disease (108, 260) and only one of the known mutations was found in a search of 96 unrelated subjects with HCM studied by Nishi (261, 262).

Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the beta-myosin heavy chain gene have been reported. Thus, the presence of mutations does not appear to govern the presence or the severity of the phenotype per se (104). However, various phenotype-genotype associations have been noted. The 403Thr→Gln β-MHC gene mutation is associated with a 100% disease penetrance in adults and three of four affected children in the kindred were symptomatic (104). The disease in the kindred in this study was severe resulting in 6/15 premature sudden deaths and syncope or presyncope in the remaining 7/9. Conversely, the 908Leu→Val and the 256Cys→Gln β-MHC gene mutations are associated with a markedly reduced disease penetrance of 47-61% (104, 263) and in the former, no family members <16 years were affected and there was a low incidence of cardiac events. Troponin T mutations typically appear to display the disconcerting combination of mild often clinically borderline hypertrophy with a high incidence of sudden death (102, 264). Those with myosin binding protein C mutations typically display late-onset HCM with clinically detectable abnormalities in mid to later life (258). They are most likely to be labelled as sporadic cases as parents have often died before the diagnosis
is made and offspring do not exhibit the abnormal phenotype until later. Overall, they appear to have a
good prognosis with few cases of sudden death before the onset of hypertrophy (247).

Nevertheless, the clinical presentation of the disease varies significantly in affected patients within the
same kindred. For example the risk of sudden cardiac death may differ within the family on the basis of
whether individuals have ventricular arrhythmias, atrial tachycardia, bradyarrhythmias, myocardial
ischaemia or severe left ventricular outflow tract obstruction (265). Therefore it has been suggested that
genetic stratification is best used in combination with, not in place of, other risk stratification parameters
(247). Recently, it has been postulated that the increased and abnormal collagen matrix observed in the
hearts from those with HCM may significantly influence the phenotypic expression of the disease.
Therefore, the observed phenotype is likely to be the result of a combination of many factors rather than
simply a reflection of the genetic defect responsible for the abnormalities of sarcomeric structure (30).

Screening

In general any screening test for a given condition should fulfil certain criteria: the disease which it
identifies should be common or important in its effects; there must be a reliable screening procedure to
detect disease early; there should be treatment to modify the outcome (266). HCM with a prevalence of
1/500 (45) is more common than many congenital conditions routinely screened for such as
hypothyroidism 1/4000 and phenylketonuria 1/10 000. It is important in its effects in that there is a
significant annual mortality associated with the condition especially in children and adolescents (48) and it
is the commonest cause of death in young athletes (71). Potential treatments associated with reduction in
morbidity and mortality have been described above and in 1997 Goodwin (267) and subsequently others
(247) have argued in favour of screening for the disorder on the grounds that there are treatments for the
condition which improve symptoms and may prevent sudden death. The difficulty lies in fulfilling the
final criterion for a screening test, which is the existence of a reliable screening procedure that identifies
those at risk.

In 1993 Clark and Coats (266) concluded that screening for HCM could not be justified because of the
"low sensitivity and specificity of the available screening tests". With the discovery of the first gene locus
in 1989 (268) and the first disease gene in 1990 (255) it was hoped that these difficulties could be
overcome using genetic screening tests particularly since the true sporadic occurrence is probably rare
(269). The pre-clinical diagnosis of familial hypertrophic cardiomyopathy was subsequently described by
the analysis of blood lymphocytes (270) and has been performed in a new-born infant (271). This family
exhibited a known mutation and testing was requested by the father who was affected. However,
unexpected genetic heterogeneity was subsequently found with several loci and many disease mutations
(102, 247, 250, 254). This has revealed that genetic screening does not differentiate between those
genetically susceptible individuals who express the disease and those who do not. The baby identified by
genetic screening mentioned above was found to have inherited the disease mutation but appeared to be phenotypically normal.

With some β-myosin heavy chain mutations (e.g. Arg403Trp, Arg249Glu, Leu908Val, Gly 256Glu) 39-77% of adult carriers have a wall thickness of <13mm (104, 106, 140, 262). The use of molecular markers has demonstrated the marked phenotypic variability of HCM even within the same family. Features such as arrhythmias, myocardial ischaemia and diastolic dysfunction may be present in patients in the absence of conventionally diagnosed left ventricular hypertrophy (≥13mm)(104, 263) and in some families it has been reported that the expected LVH can skip a generation altogether (272). Most families are not large enough or of a suitable structure for the necessary linkage studies required to identify new disease mutations. But this is further hindered by such phenotypic heterogeneity especially if the pedigrees include equivocal or apparently unaffected cases by standard wall thickness criteria (106). A more sensitive phenotypic marker than the ones currently available would be desirable to assist in further genotypic characterisation of such kindreds.

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<th>Major criteria</th>
<th>Minor criteria</th>
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<td><strong>Echocardiographic</strong></td>
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<tr>
<td>LV wall thickness ≥ 13mm in the anterior septum and posterior wall or ≥15mm in the posterior septum or free wall</td>
<td>LV wall thickness of 12mm in the anterior septum or posterior wall or 14mm in the posterior septum or free wall.</td>
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<td>Severe SAM (septal-leaflet contact)</td>
<td>Moderate SAM (no leaflet-septal contact)</td>
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<td>Redundant mitral valve leaflets</td>
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<td><strong>Electrocardiographic</strong></td>
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<td>LVH + repolarisation changes (Romhilt and Estes).</td>
<td>Complete BBB or (minor) interventricular conduction defect (in LV leads)</td>
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<td>T wave inversion in leads I and aVL (≥3mm, with QRS-T wave axis difference ≥30°), V3-V6 (≥3mm) or II and III and aVF (≥5mm).</td>
<td>Deep S V2 (&gt;25mm)</td>
</tr>
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<td>Abnormal Q (&gt;40ms or &gt;25% of R wave) in at least two leads from II, III, aVF (in absence of left anterior hemiblock), V1-V4; or I, aVL, V5-V6.</td>
<td>Unexplained chest pain, dyspnoea or syncope</td>
</tr>
</tbody>
</table>

*From McKenna et al 1997 (138).*

Many have therefore concluded that in families without a known gene defect other means such as electrocardiography and echocardiography remain the only practicable screening method (138, 266).
Furthermore, the identification of these individuals is important because sudden death, supraventricular and ventricular tachycardias and embolic cerebrovascular accidents have occurred in those showing only mild echocardiographic and/or electrocardiographic abnormalities (102, 103, 156, 157). There is also a need to identify these individuals for the purposes of pedigree analysis and genetic counselling despite the absence of a mutation. The case for a more sensitive phenotypic marker than those currently available appears clear and based on these factors McKenna et al (138) introduced new diagnostic criteria for use in adult members of affected families (table above). The diagnosis is fulfilled by the presence of one major criterion or, two minor echocardiographic criteria or, one minor echocardiographic and two minor electrocardiographic criteria. It is emphasised in their manuscript that the diagnosis of HCM in the presence of other conditions which may result in LV hypertrophy such as athletic training is troublesome and out with the scope of their article as are children and adolescents. This is unfortunate, as these are the two target groups who perhaps stand to benefit most from early identification.
1.2 The normal heart

1.21 Post-mortem studies

Post-mortem measurements of left ventricular wall thickness and cavity dimensions will be influenced by
the place and obliquity of the cut, the inclusion of trabeculae or papillary muscles and the state of
myocardial tone. Many hearts are fixed in systole (127) so the effect of diastolic filling on the thickness of
the LV wall or the magnitude of the LV dimension is not seen. There have been many studies quoting
different limits of normality for left ventricular wall thickness in adults. Latimer (273) described up to
15mm as allowable and Allenstein and Mori (274) put 10mm as the upper limit of normal. One might
conclude from these data that >15mm is definitely abnormal and might allow for any systolic tone in an
otherwise normal wall.

1.22 Angiography

Several series were published of angiographic estimations of LV wall thickness in diastole and these too
offer widely differing normal ranges with Kennedy et al (275) describing the normal range in males to be
9.8-15mm and that in females to be 6.6-11mm whereas Levine et al (276) described a range of 5-9.5mm
per m² BSA irrespective of sex. It can be seen that the establishment of normal ranges for LV wall
thickness measurements has always posed difficulty.

1.23 Echocardiography

History
Echocardiography made its debut in 1954 when Edler and Hertz (277) described the use of the ultrasonic
reflectoscope for the continuous recordings of movements of the heart. In the late 60s and early 70s
echocardiographic studies were published which employed a combination of A-mode and M-mode slow
sweep techniques in acquired (278-280) and congenital lesions in adults (281, 282). The studies in adults
demonstrated an excellent correlation between cardiac measurements made by echocardiography and
those made by angiography (283, 284) and the technique was rapidly extended to infants and children with
congenital heart disease (285-287).

Echocardiography offers several advantages over angiography: it is non-invasive, allows measurement of
the LV posterior wall, can identify pericardial effusions such that they are not included in the estimate of
wall thickness, can discern what contribution any right ventricular hypertrophy is making to the AP
projection of LV lateral wall thickness and can note the presence of any mural thrombus or aneurysm in the LV. The concept of measuring function was explored early and it was noted for example that a LV wall thickening during systole of 60% or greater was associated with an ejection fraction > 0.5 (284).

Two-dimensional phased array echocardiography became available in the mid-1970s and allowed images to be produced at a rate of 20 per second or more while maintaining a resolution of 2-4mm throughout the field of view (288). The advantages of the technique in the diagnosis of congenital and acquired lesions became apparent (289). The combination of M-mode and two-dimensional techniques provides important information about left ventricular function, which may help with patient management in a variety of clinical situations. In ischaemic heart disease echocardiography may help to differentiate between left ventricular aneurysm (290) and globally poor left ventricular function as the cause of cardiac failure following myocardial infarction. In patients with valvular heart disease it may supply sufficient information to proceed to surgery without cardiac catheterisation. It may also be useful for repeated monitoring following an intervention such as the effect of exercise on left ventricular function in patients with ischaemic heart disease (291). Since the use of the technique was quickly becoming more widespread it was important that accuracy and reproducibility were examined.

Resolution

Edler and Hertz (277) showed that echo signals were best obtained from the deeper structures of the adult thorax using a transducer with a middle frequency of 2.5 MHz and the 2.25 MHz M-mode transducer became commercially available. A 5 MHz transducer was shown to produce good results in thin adults and children. Solinger et al (292) commissioned a spectrum and real-time analysis on the transducer used in their study in normal neonates and found that the centre frequency was 9MHz which was capable of resolving two structures 0.5mm apart. In general, higher frequencies result in less beam spread and greater resolution but offer less tissue penetrance than lower resolution transducers. The use of standard transducers is reported to allow a resolution in the order of 1mm using M-mode (153). This is superior to the resolution offered by two-dimensional echocardiography which is of the order of 2-4mm especially for structures in the lateral parts of the sector and those which are perpendicular to the chest wall (113, 137, 293).

Roelandt et al (293) described the poor lateral resolution of echoes due to echoes generated and received from structures located away from the main axis. "Dropout", overlapping of echoes and errors in the interpretation of mitral valve motion in systole are also described in the study, along with the advantages of M-mode echocardiography over cross-sectional echocardiography in the identification of endocardial echoes. This advantage is because the "true" endocardial echo has the greatest intensity on M-mode recordings and is the last to disappear when gain settings are gradually decreased thus allowing it to be identified. However, the problems with oblique ultrasound beam angle along with the varying contour of
the septal and intraventricular echoes and endocardial dropout continued to be recognised as sources of error in M-mode estimates of septal thickness (294).

**Reproducibility**

Martin (295) reviewed the work written on the reproducibility of M-mode echocardiography and concluded that the reproducibility of the measurement of left ventricular end diastolic diameter was anywhere between 1.8-4mm and was similar to the measurement of the end systolic dimension. His recommendation was that leading edge to leading edge measurements from the M-mode print could be made to the nearest millimetre. However, Sahn et al (296) showed that end-diastolic dimension and wall thickness measurements were more reproducible than end systolic ones and issued guidance on how M-mode prints should be measured. These were endorsed both by the American Society of Echocardiography (296) and by European guidelines issued by Roelandt and Gibson (297). A later study utilising digitised M-mode echocardiographic images were similar to earlier studies and found that the 95% confidence limits of the measurements were +/-3mm for the LVEDD and +/-2mm in LV wall thickness (298).

The use of two-dimensional (2D) echocardiographic guidance of M-mode measurements has been shown to improve the accuracy of the measurements of septal thickness and septal: posterior wall thickness ratios (299). In addition, the improvement in positioning of the M-mode beam on repeated examinations has undoubtedly helped to limit the variability of unguided M-mode measurements previously described (300-303). To improve things further, Devereux et al (304) published guidance on the standardisation of M-mode echocardiographic left ventricular anatomic measurements. This degree of standardisation and repeatability of measurements was needed as echocardiographic assessment of LV hypertrophy and mass had become widespread and was utilised by many groups to assess cardiovascular risks (305-308) and to describe the natural history of hypertrophy along response or resistance to treatments (209).

One of the difficulties with 2D echocardiography is that the precise position and orientation of the real time image are unknown due to the inability to visualise any anatomical landmarks orthogonal to the 2D real-time image. Three-dimensional (3D) echocardiography registers transducer position using a 3D spatial co-ordinate system and creates a "line of intersection" display. King et al described this technique and went on to look at the variability of measurements taken by experienced echocardiographers (309). They studied the positioning of standard two-dimensional images by experienced technicians using 3D echocardiography and found that the short axis image plane was consistently angulated across the ventricle lengthening the LV dimension to a variable degree. In the study of 85 examinations and 340 images the long axis, short axis, apical two and four chamber images were compared with optimal image positioning. Images were considered optimal if within +/-5mm of displacement and +/- 15 degrees of rotation/angulation. Only 24% of images were optimally positioned relative to both displacement and
angulation/rotation. The parasternal long axis view was optimal two-thirds of the time and 2/3 of the optimal images were achieved from parasternal long axis views. The parasternal short axis view however, was displaced or angulated in 93% of examinations. A further study (310) concluded that 3D echocardiography does improve accuracy and hence reproducibility of LV measurements. However, when only 2D echocardiography is available, which is largely the case, the parasternal long axis view is more robust in terms of displacement, angulation and rotation than the parasternal short axis view and should therefore be used to measure the wall thickness and cavity dimensions accessible by this view (309).

No single figure can be quoted to describe the reproducibility of echocardiographic measurements as it is dependent upon random variables even where these are strictly minimised and will vary with study conditions. However, it is important to be aware of the limitations in resolution and reproducibility that exist in any imaging technique so that it is used appropriately. Echocardiography is a valuable, widely applied technique and ultimately it has to be accepted that it is the best technique that can be offered currently for the purpose of sequential non-invasive cardiac imaging.

**Left ventricular measurements**

*Adults*

Normal echocardiographic values for left ventricular measurements in adults have been published by several authors (95, 303). The paper by Sjögren (95) described that left ventricular wall thickness in diastole was greater in males than in females and that the thickness of the left ventricular walls in both systole and diastole increased with age. There was also no correlation between wall thickness and weight and a very weak relationship with height in women only. Irrespective of sex and age the quoted upper limit of normal for the left ventricular wall thickness was taken to be 12mm which is in keeping with the figure used to this day (311). Gerstenblith et al (312) also found that in adults increasing age was associated with increased left ventricular thickness in the absence of hypertension or cardiovascular disease.

Although relationships between cardiac dimensions and weight and BSA had been described in children and adolescents in whom they might reasonably be expected to occur, they had not been described for adults. This was addressed by Reneman et al (141) who found that in healthy adults who were not regularly participating in sports, the dimensions of the aorta and the heart were larger in males than in females. Most of the differences between the sexes disappeared when the dimensions were adjusted for either BSA or body weight which was in agreement with another group (313). However, Reneman and colleagues questioned whether this adjustment was permissible because the correlation co-efficients for the dimensions of the aorta and the heart related to BSA or body weight were poor. This would suggest that in adults the dimensions are not dependent on BSA or weight. They suggested that the disappearance of most of the differences between the sexes after adjustment for BSA or weight simply reflected the
difference in these parameters between the two groups and concluded that differences between men and women should be taken into account in studies of echocardiographic dimensions. However, this idea has not really been pursued and a subsequent study of adults by Henry et al (158) concluded that the maximum left ventricular wall thickness allowable for normal adults irrespective of gender was 12mm.

**Children**

Some studies in infants and children report growth-related changes in echocardiographic measurements as a function of BSA, (69, 314), height (315), weight (286) or weight and sex (316). Lundstrom (286) found that left ventricular end diastolic diameter (LVEDD) varied as a cubed root function of weight whereas the thickness of the interventricular septum varied with weight alone and no differences between males and females were described.

Perhaps the most frequently quoted study is the one by Henry et al (69). 105 subjects aged 1 day-23 years were examined. LVEDD was found to vary in a linear fashion with the cubed root of BSA as did left ventricular end systolic diameter (LVESD), aortic root, left atrial dimension and mitral EF slope (on M-mode). Wall thickness in systole and diastole were best related to the square root of the BSA and LV mass (Troy method) to BSA alone. Nomograms were produced to which the clinician could refer in order to ascertain normality or abnormality. Ejection fraction, fractional shortening and % thickening of the septum and free LV wall in systole were independent of the BSA although scatter of +/- 13%, +/-.23% and +/- 48% was seen (69). Rogé et al (317) however, found that in infants and children height, weight, BSA and cubed root of weight were so correlated with one another that for practical purposes the regressions were equivalent and they used BSA alone against which to plot the measurements.

Henry et al (158) re-analysed their data on normal subjects following the introduction of the American Society of Echocardiography standards (296) and in that paper normal data are derived and nomograms shown based on weight as well as BSA. This eliminates the intermediate step of calculating BSA. The study included both adults and children and an independent effect of age was acknowledged and was incorporated in to the regression analysis. However, the normal ranges given by the new nomograms are still wide with the allowable range of septal thickness in a 20kg 6 year old boy (5.3-7.8mm) overlapping with that allowed for a 70kg man (7.5-11.2mm). Interestingly, the paper from Epstein et al (314) also looked at the ratio of septum-to-free wall in normal children and found this to range from 0.67-1.33, the value previously used to diagnose HCM.

More recently, Huwzez et al (318) published normal data on 127 subjects aged 7 months to 19.5 years and made a case for the development of age related norms as well as norms related to BSA. In this study age and BSA were, not surprisingly, highly correlated but separate equations were calculated for each. In order to assess normality of cardiac dimensions or mass, age or BSA have to be entered in to up to 11 complex
equations; one for each of the cardiac dimensions and the system is not validated for infants less than 7 months.

**Neonates**

Several studies have described wall thickness and cavity dimensions in neonates as a sub-group (292, 319-322) and these are quoted collectively in Feigenbaum's text book as the normal ranges in this age-group (311). Echocardiographic measurements have shown a good correlation with those made on neonatal human hearts at autopsy (323, 324). Solinger et al (292) divided the neonatal population into small groups depending on weight and found that the mean septal thickness increased with increasing weight although no defining relationship or correction is given. In contrast, Hagan et al (320) searched for a relationship between all of the cardiac measurements and weight and body surface area and did not find one.

The assessment of normality or otherwise of cardiac dimensions is therefore quite complicated. In adults the normal ranges quoted for wall thickness and cavity dimensions appear unaffected by body surface area and although these measurements are known to be larger in men than in women no allowance or separate normal range is usually quoted for women. The assessment of children requires reference to a separate range of values for neonates which are unrelated to BSA (320) and which are possibly unrelated to weight. Conversely, the assessment of older children requires reference to nomograms or complex equations that relate cardiac measurements to BSA or various transformations of it. If a simpler measure could be found which took account of body size without the need to measure it and remained consistent over all age groups, it would be very helpful to the busy clinician.

**Left ventricular mass**

Pathological papers and books describe the range of cardiac weights in the population of normal adults and children (30, 323, 325) and in those with hypertrophy (30, 325, 326). Some have employed a straightforward cut-off for normal of <350g in women and <400g in men (30).

Initially unguided M-mode (153) and subsequently two-dimensional echocardiographic guided M-mode measurements (142, 155, 304) of the LV were used in geometric formulas to provide a reproducible and non-invasive quantification of LV mass. These methods were anatomically validated with comparison to post-mortem weights (153-155). It is an interesting observation that an increase in wall thickness of 1mm would result in an increase of 8g in myocardial mass employing the technique of Devereux (304). A two-dimensional echocardiographic method of estimating LV mass (LVM) was developed by Feigenbaum's group (327) but is thought by some not to have come in to general use because it offers insufficient improvement to justify the technical difficulty (328).
One study looked at the echocardiographically determined LVM in normal children, adolescents and young adults (329) and generated BSA related normal ranges. Another study (330) suggested that LV mass was independently influenced by age however the genders were not separated and thus the gender specific influence of age was not explored. A much earlier study had failed to find a significant effect of age (304) whilst the Framingham study initially reported an independent influence of age on LV mass which was not significant when the healthy cohort was analysed in isolation (331). Thus the interpretation was that in previous studies the increased frequency of hypertension and other conditions with age had caused these age related effects in adults.

In general, subsequent studies found that LV mass determined echocardiographically was related to gender, blood pressure, body size (height) and mass (obesity) and physical activity (304, 332, 333). Many had noted that left ventricular volume and mass were larger in men than in women and remained so even after correction for body surface area suggesting a separate influence of gender on LV mass (334). Subsequently, separate gender specific BSA indexed norms have been produced (142, 329).

Shub et al (142) in their two-dimensional guided M-mode study in a healthy population found that as before gender, blood pressure, and body size independently influenced LV mass but in addition that LV mass was influenced by age but only in women. In females there was also an age-related increase in body mass index which was maximal in the fifth decade whereas the increase in LV mass occurred in the sixth decade. This either means that LV mass changes very slowly with increased body mass or there is another contributory factor. In the study from Lauer et al (332) obesity lead to an increase in LV internal dimension and wall thickness but in Shub's study the increase in LV mass with age appeared to be solely due to increased wall thickness (142). It might be speculated that these results may be attributable to sex hormone effects and may represent an example of the loss of oestrogenic cardioprotective factors as observed in some animal models (335).

Three dimensional (3D) echocardiography offers an alternative method of estimating LV mass using 3D ventricular surface reconstruction. The endocardial and epicardial surfaces of the LV are reconstructed by a series of triangular shapes whose volume is then calculated by subdividing it in to a series of polyhedra (336). This method was validated in vitro (336) and in vivo (337). The myocardial volume is calculated from the epicardial volume minus the endocardial volume and the mass is determined by multiplying the volume by the density of myocardium. This method has been validated by comparison with in vitro specimens and direct comparison with MRI showed no significant difference. Conversely, the two-dimensional cross-sectional determination of LV mass using the truncated ellipsoid formula (Penn convention) showed standard errors of up to 25.6g when compared to MRI which was 2-3 times those with 3D echocardiography (338). However, three-dimensional echocardiography is not yet widely available and technology in the field of magnetic resonance imaging is rapidly advancing such that this investigation is likely to be more readily available in most tertiary centres than 3D echocardiography.
1.3 Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an independent risk factor for sudden death (339), ventricular dysrhythmias (340) and myocardial ischaemia (341). The prevalence of LVH correlates strongly and independently with age, obesity and systolic blood pressure. In the Framingham study LVH on the electrocardiogram (ECG) conferred a 6-8 fold excess risk of cardiovascular death (342) and based on echocardiographic estimation of left ventricular mass (LVM) the risk factor adjusted relative risk of cardiovascular disease was 1.5-2 for each increment of 50g per metre in height (308). In the New York (306) and Framingham studies (305), LVH correlated more closely with outcome than blood pressure, cigarette smoking or total blood cholesterol concentrations. Furthermore, LVH was not only a predictor of cardiac events but also of stroke. The difficulty is that the association of increasing LVM with adverse cardiovascular events is a continuous one with no apparent threshold value above which intervention is desirable.

LVH is usually considered to be a beneficial myocardial adaptation but this evidence shows it to be a promoter of cardiovascular morbidity and mortality. It may be that LVH integrates the influence of many factors such as blood pressure, obesity, blood viscosity, salt and alcohol intake. Or it could be that the benefits of LVH in the reduction of LV wall stress outweigh the disadvantages of limiting both the coronary reserve and ease of LV filling up to a point beyond which the opposite is true. But no such "critical" mass has been identified in any of the studies thus far (343). Some postulate that in some individuals the hypertrophy could be pathological from the beginning since abnormalities in left ventricular filling do not correlate well with LVM and may be found in young hypertensive subjects before any detectable LVH (344). Proliferation of interstitial tissue and collagen in the myocardium as a consequence of pressure overload and hypertension could explain most of the functional disturbances described in hypertensive LVH (345) and may be controlled by different mechanisms than those leading to myocyte hypertrophy. The further investigation of these potential mechanisms is clearly needed as each has different implications for therapeutic intervention.

1.31 Electrocardiography

Initially ECG was the primary methodology used to detect LVH and in the Framingham study (342) the risk of morbid and mortal events was 6-8 fold higher in middle-aged adults with definite ECG LVH compared with similarly aged normal adults. The limitations of the ECG in detecting LVH was shown in a later report from The Framingham Study frequency when LVH was detected in less than 3% of adults aged 40 years or more, in a later using ECG (308) compared to 15-20% using echocardiography. The overall sensitivity of the ECG for the detection of LVH in that study was estimated to be only 6.9% with a specificity of 98.8%.
It has been shown previously that ECG criteria identifies only 20-50% of instances of LVH revealed at post-mortem or using echocardiographic reference standards (155, 346). But this may be an overestimate due to the selection of patients in these studies with advanced disease. In the general population (347) the sensitivity of standard ECG criteria was far less at <10% for the detection of increased LVM on echocardiography. Newer ECG methods have improved upon this, particularly the regression criteria produced at Cornell, which improved the sensitivity to 51% for a specificity of 90% in echocardiographically determined LVH (348). The limitations of the technique for identifying LVH included factors such as reduced ECG recognition of LVH in obesity (347), smokers (347), increasing age and increased chest wall thickness (349). This led to the production of formulae which adjust the Cornell criteria for age and obesity and improved the sensitivity of the ECG for the detection of hypertrophy from 10-17% in men and from 12-22% in women for a specificity of 98%. In the detection of severe hypertrophy (LV mass > 3sds above the gender specific mean) the sensitivity increased from 23-38% for men and from 22-55% in women for a specificity of 95% (350).

1.32 Echocardiography

This is the most easily accessible and sensitive method for the detection of LVH in a given population and can be used to assess both anatomy and function. In the fields of longitudinal population based studies such as the Framingham study and in the evaluation of hypertensive heart disease the assessment of LVH has been made by the estimation of LV mass and calculation of relative wall thickness (343, 351, 352). Devereux et al (153, 154) have validated the use of echocardiographic measurements to determine the LV mass in humans. Relative wall thickness (RWT) measurement is described as (septal thickness + PWT)/LVEDD by some (343) and (2xPWT)/LVEDD by others (353). Increases in RWT are reported to be the hallmark of concentric LVH (351) if the LVM is increased whilst concentric remodelling is said to have occurred if LVM is normal (352). Based on the Framingham study of overwhelmingly white subjects (354) and the studies from New York of a more mixed race cohort (304, 355) normal upper limits for gender specific LVM indexed to body surface area were established (100g/m² for women, 131g/m² for men and 110g/m² for women and 134g/m² respectively) although an average value of 125g/m² is used by some studies irrespective of gender (306, 352). In obese patients no prognostic power was lost by indexing LVM to height instead of BSA (354). The need remains however, to identify those subjects at increased cardiovascular risk such that risk stratification studies and therapeutic interventions can be assessed.
**1.4 Physiological cardiac hypertrophy**

Since the turn of the century it has been recognised that athletes may develop cardiac chamber enlargement, left ventricular hypertrophy (LVH) and bradycardia which for many years was given the term "harmonious hypertrophy". Sometime later, some believed that the cardiac enlargement was a consequence of pre-existing congenital or rheumatic heart disease and this became standard teaching in some textbooks (129). Subsequently, the changes mentioned above became recognised as a normal physiological response to training that did not represent any sort of disease process. However, the examining clinician might find himself disconcerted by the presence of intermittent systolic murmurs, third and fourth heart sounds and increased cardiothoracic ratio which have all been described in athletes (131).

**1.41 Electrocardiogram (ECG)**

In addition to unusual findings on examination, athletes may exhibit abnormal findings on the ECG. With increased levels of training, increased conduction times including periods of Wenkebach block, decreased heart rates, nodal and coronary sinus rhythm, left and right ventricular hypertrophy and repolarisation abnormalities have all been reported (129, 131, 356). In one study of 42 professional male basketball players 25% met Romhilt-Estes ECG voltage criteria for left ventricular hypertrophy (131). Whilst a normal exercise test may be reassuring, up to 10% of athletes may have a false positive exercise stress tests (357).

**1.42 Echocardiography**

Following the development of echocardiography it was noted that athletes showed increased left ventricular cavity dimensions and mass (131, 356-360) and that mass was elevated to a similar degree to that found in patients with hypertension, aortic stenosis and hypertrophic cardiomyopathy. It has been shown that mass is increased even following correction for BSA (356, 361-364).

The process of increased physical activity increases left ventricular mass (LVM) by as much as 45-50% (356, 362). In one study (365) it was calculated that an energy expenditure of 2 kcal/kg/day (1000 kcal/wk in a 70kg person) would lead to an increase in LVM in both sexes of 17-20g. In the Framingham study a similar activity level explained only a 2.5-4.6g change in LVM in young men with no association in women or older men (333). Another study (366) demonstrated that increase in LV mass was related to physical activity both in healthy subjects and those with spinal injury and that 1000kcal/week of exercise
resulted in an increase in LV mass of 3g/m^2. These varying results may reflect difference in the study groups or the assessment of physical activity as the latter two studies relied on either retrospective leisure time activity assessments over the preceding year or self-reported levels of exercise. Bjornstad et al (356) showed that the increase in left ventricular end diastolic volume per m^2 was 14.3% in athletic students and 28% in top class athletes compared with controls. The corresponding increases in LVM were 23 and 47.3% and presented difficulty in the identification of those with physiological as opposed to pathological hypertrophy.

Training induced hypertrophy can be detected within 7 days of starting a sports programme and increases of 5-10% in diastolic and systolic dimensions and 15-20% increases in wall thickness occur quite quickly (362, 367, 368) accompanied by a bradycardia. After sustained training, athletes may develop much larger systolic and diastolic cavity dimensions which are out with the 95% confidence limits of normal (129). There seems to be a relationship between the amount and type of exercise and the increase in left ventricular size with the elite athletes showing the largest cavity dimensions (369). It has been noted by some authors (361, 369) that runners and swimmers showed a significantly enlarged left ventricular cavity and these athletes were called aerobic as they performed mainly endurance training. Shot-putters and weight-lifters have been called "anaerobic" because of the isometric nature of their exercise and in contrast to the "aerobic" athletes showed wall thickness measurements which can be normal when corrected for body mass and whose left ventricular cavity is smaller than normal or normal (361, 364, 369). The mechanisms for this are not clear and have been the subject of much debate. Arterial blood pressures as high as 480/350mmHg have been recorded in power lifters during peak exercise (370). Some have postulated that afterload of this magnitude in the absence of a sustained increase in cardiac output promotes the changes which are akin to those seen in pressure-overload cardiac diseases such as hypertension and aortic stenosis (361).

Gaasch (371) discussed the left ventricular cavity radius-to-wall thickness ratio in the presence of physiological hypertrophy seen in trained athletes. He pointed out that in this situation and in the situation of compensated aortic regurgitation both left ventricular wall thickness and cavity dimension were increased so that the ratio remained normal. Wall thickness-to-cavity radius ratios have also been used to study physiological hypertrophy in various types of athletes (130, 372). These studies have shown that some athletes may increase LV wall thickness disproportionately to cavity size and that the wall thickness to cavity radius as a measure of this (359). Various groups were studied but in one study cyclists exhibited an increased ratio of wall thickness to cavity radius when compared to a matched group of runners and it was postulated that this might be due to the isometric effect of gripping the handlebars (372). The same mechanism was held responsible for the increased relative wall thickness seen in weight-lifters (364). However, others have reported that the relation between mean wall thickness and cavity radius was similar in all groups of athletes and that in addition there were no differences in ejection fraction or isovolumic relaxation time (IVRT) (356). Indeed the normality of LV systolic performance in athletes as expressed by
ejection fraction and fractional shortening has been confirmed by many authors (131, 356, 360, 362-364, 372).

Using conventional wall thickness diagnostic criteria for HCM (45), it can be difficult to distinguish between this disease and the physiological hypertrophy of the athlete, particularly since the HCM phenotype may be relatively subtle in young adults and children (68, 144, 159, 373). This difficulty has been acknowledged and described previously (129, 373, 374). Those athletes with diastolic maximal wall thickness measurements of 13-15mm are referred to by some as being in the "gray zone" (362, 373) since they fall beyond the 12mm upper limit for normal (311), but fall short of the 15mm cut-off for the diagnosis of HCM (45). Clearly, it is desirable to be able to differentiate these two morphologies as accurately as possible since HCM is the commonest cause of sudden death in this group (71), which can be provoked by exertion (50). However, the implications are far-reaching for an athlete who may be advised to avoid further strenuous exercise in the light of this diagnosis (373).

In a study of the causes of sudden death in a cohort of 29 athletes (71) the diagnosis of HCM was substantiated by the presence of a hypertrophied non-dilated left ventricle as defined by a maximum LV wall thickness of ≥ 15mm in the absence of another disease which could produce these changes (18). Each subject in addition had to show a septum-to-free wall thickness ratio ≥ 1.3, or marked disorganisation of muscle cells in the ventricular septum involving at least 5% of the relevant areas of the tissue section (375), or clinical or echocardiographic evidence of HCM in one or more closely related family members. Interestingly, asymmetric septal hypertrophy as defined by a septal-to-free wall ratio of ≥ 1.3 was absent in 6/14 of the athletes known to have died of HCM suggesting that this measure is not sufficiently sensitive to detect these individuals. Conversely, echocardiographic septum-to-free wall ratios > 1.5 have also been described in the athletic group (129).

Pelliccia et al (374) presented data from the pre-Olympic selection medical examinations which have been mandatory in Italy since 1984 and includes echocardiography. The examinations of a large group of 947 elite athletes who participated in a wide variety of sports were reviewed in an attempt to clarify the diagnostic ambiguities between the physiological changes seen in athletes and pathological hypertrophy. Hypertrophy compatible with the diagnosis of HCM (≥ 13mm) was present in 16/947 or 1.7%. These were predominantly Caucasian but in a similar study by Lewis and Maron (376) in which 262/265 subjects were black, 29/265 or 11% showed septal thickness measurements of ≥ 13mm. In 26/29 the septum measured 13 or 14mm but in three subjects it was 16 or 18mm. Most of the recent published work concentrates on a definition of an absolute maximal wall thickness cut-off value for the differentiation of athletes from those with pathological hypertrophy and it is acknowledged that there is a marked paucity of equivalent work in athletic children (362). There are a few studies however, which confirm that similar physiological changes as those seen in adults may be seen in children. Wall thickness measurements are reported to increase but
diastolic cavity dimension may not even when indexed against BSA (377, 378). This implies the existence of a slightly different training effect in children than in adults and merits further study.

The hypertrophy seen in the athletic heart is not associated with the diastolic dysfunction or ventricular arrhythmias (356, 379) seen in hypertension related hypertrophy and HCM (380, 381). In one study ventricular arrhythmias were seen more frequently in the hypertensive athletic population than in the normotensive athletic population (382) from which it might be inferred that it is the component of the hypertrophy due to hypertension that provides the arrhythmogenic substrate and is thus pathological. Clearly, athletes may exhibit ECG abnormalities, increased left ventricular wall thickness measurements and increased left ventricular mass (362) which is not associated with the ominous prognosis described by the Framingham study in the non-athletic population (308). It is important therefore to be able to differentiate these athletes from those with HCM and other forms of undesirable hypertrophy. Previous strategies have been discussed and a different echocardiographic strategy will be explored in this thesis.
1.5 Hypertensive cardiac hypertrophy

Hypertensive heart disease can be defined as the response of the heart to the afterload imposed on the left ventricle by the progressively increasing arterial pressure and total peripheral resistance produced by hypertensive vascular disease (381). Left ventricular hypertrophy (LVH) is an independent risk factor for myocardial infarction and death in men and women with hypertension (352, 383) and the prevalence of LVH in hypertension ranges from 20-80% depending on the criteria used (343). Some have suggested a relation between the height of the arterial blood pressure and the severity of left ventricular hypertrophy (307). Others have proposed a synergistic interaction between dietary salt and blood pressure such that high sodium may in some way sensitise the heart to the hypertrophic stimulus of pressure load (365). Consequently, there is much interest in the potential to reverse this process with anti-hypertensive medication and diet.

1.51 Electrocardiography (ECG)

ECG was the primary methodology used to detect LVH prior to the advent of echocardiography and was successful in identifying a population at risk for cardiovascular events (342). However, when applied to a population with hypertension, results are disappointing. In a study of subjects with hypertension who ultimately came to post-mortem (384), established ECG methods showed a sensitivity of 30-57% for the detection of severe and a sensitivity of 10-38% for the detection of moderate left ventricular hypertrophy. Echocardiographic LVM index criteria showed a sensitivity of 98% for severe and 57% for mild LVH. Another study of those with mild/moderate hypertension (385) revealed that 61% had echocardiographic LVH as defined by increased echocardiographic wall thickness measurements compared with less than 10% identified as showing LVH on ECG or chest X-ray. Since LVH is an independent risk factor for cardiovascular morbid events in this group (306, 341, 352, 386) it is useful to identify it so that treatment may be escalated until regression of such changes can be seen (387).

1.52 Echocardiography

The echocardiogram has been shown to be 5-10 times more sensitive than the electrocardiogram for the detection of LVH both in the general population (308) and in those with hypertension (385). If present LVH increases the risk of myocardial infarction or death by up to three times that of hypertensive subjects without LVH (306, 352, 383). LVM is the usual way of quantifying LVH in this population as it has been shown by some authors that LVM is a more sensitive indicator for post-mortem proven LVH in those with hypertension than wall thickness or relative wall thickness measurements (388). However, the distribution
of LVM indexed to height in a population with hypertension is not bimodal for those with and without increased LVM but is a continuous variable and approximated a Gaussian distribution as it does in the normal population (343). Since LVM in the normal population shows such variation the need to characterise hypertrophy with reference to the wall thickness and geometry of the left ventricle has been appreciated.

Some authors have used relative wall thickness measurements (RWT) calculated by \((\text{septum + LV posterior wall})/\text{LVEDD}\) for this purpose and "concentric" and "eccentric" geometric patterns have been described (343). Concentric hypertrophy is described as increased LVM with elevated RWT which would result in the reduction of systolic wall stress, and eccentric hypertrophy as that with an increased LVM but with a normal or reduced RWT. The prevalence of eccentric hypertrophy varies depending on the criteria used (usually RWT < 0.45) (343) and the data presented by Gosse and Dallocchio (343) suggest that those with normal or low RWT tend to be younger and have smaller left atria than those with the concentric type of hypertrophy. Magnitude of blood pressure or obesity was the same in the two types. This is consistent with other studies (388-390) which suggest that eccentric hypertrophy in hypertensive patients may represent an earlier stage of LVH or may represent a response to volume overload in some types of hypertension. In addition, some have found RWT measurements are more sensitive at separating those with hypertension from normal subjects than either LV mass or LV mass index measurements (390).

A further geometric classification involves the description of symmetric or asymmetric LVH. Asymmetric septal hypertrophy (ASH) is well documented in hypertension and was present in 16% of subjects in one study (343). Previous studies had also shown that an increased septum-to-free wall ratio could be seen in other forms of secondary hypertrophy (117, 128, 132). In one study (128) up to 39% of subjects with secondary LVH including those with hypertension exhibited an increased ratio. Absolute wall thickness measurements were of little help with septal thickness of \(\geq 15\text{mm}\) seen in 50% of the same group. A comparative study (117) of those with HCM and hypertension showed that a septum-to-free wall ratio of \(>1.5\) was seen in 18% of those with hypertensive cardiac hypertrophy. In addition although symmetrical LVH occurs much more commonly in secondary left ventricular hypertrophy than in HCM there was no significant differences in the distribution of the hypertrophy of the two groups.

The title of one paper "Asymmetrical septal hypertrophy in patients with hypertension: a type of hypertensive left ventricular hypertrophy or hypertrophic cardiomyopathy combined with hypertension?" (391) summarises the difficulty in the differentiation of the two conditions. In that study the interventricular septal thickness and left ventricular (LV) posterior wall thickness were not significantly different between the group with HCM and the group with hypertension. Ejection fraction, end systolic volume and LV peak ejection rate was similar in both groups indicating comparable systolic properties of the LV. There was one significant difference in diastolic function between the two groups, which was in the rapid filling volume index that was derived from gated blood pool scintigraphy. Other diastolic indices
were similar in the hypertensive subjects and those with HCM. Since there was no difference in LV wall thickness between the two groups it is postulated that the difference lay in the myocardial properties. Maron et al (375) found increased interstitial fibrosis and myocardial fibre disarray in the hearts of those with HCM but not in the 2/33 patients with asymmetric septal hypertrophy and hypertension (123).

The difficulty in separating the two conditions using echocardiography was shown in the recent CARDIA study (45) in which 5/4111 subjects were excluded from having the diagnosis of HCM because of hypertension. These subjects showed septal thickness measurements of 15-21mm, the same range of values found in those with HCM. Discrimination between these two diagnoses is usually achieved by the documentation of the presence or absence of raised blood pressure. However, co-existence of the two conditions in one subject continues to present diagnostic difficulty.

Dunn et al (386) reviewed the issue of left ventricular hypertrophy in hypertension and the associated major cause of death in this group which is coronary artery disease. The need to identify LVH accurately using echocardiography was underlined, as was the insufficient sensitivity of the ECG for this purpose. The success of various treatments including nicardipine, angiotensin converting enzyme inhibitors and β-adrenergic blockade in reducing the magnitude of the LVH and the benefits of these treatments to myocardial perfusion was also reported. Therefore, continued effort is required to find better ways of identifying pathological left ventricular hypertrophy using echocardiography.
1.6 Magnetic resonance imaging in hypertrophic cardiomyopathy

As previously described, hypertrophic cardiomyopathy (HCM) is a genetically inherited disease with a significant prevalence (45) and mortality (48, 71). Since known genetic mutations can only be identified in as few as 50% of kindreds with the disease (260) imaging of the heart remains an essential modality in the screening for and diagnosis of the disease. The extent of left ventricular hypertrophy in this disease and in hypertension is an independent and adverse cardiovascular risk factor (85, 383, 392). Therefore, techniques, which accurately measure left ventricular wall thickness and left ventricular mass, will be necessary to evaluate the effectiveness of treatment strategies in attenuating this feature of these diseases (387).

Echocardiography is a relatively cheap, rapid and reproducible technique (295) that measures left ventricular wall thickness and cavity dimensions for both screening and diagnostic purposes (126, 136, 139). Previous studies have shown good agreement between echocardiographic estimations of left ventricular mass and post mortem findings in normal hearts (154). However, the potential limitations of these geometric assumptions in the morphologically abnormal heart have been alluded to (134).

Magnetic resonance imaging (MRI) is a reproducible technique and provides accurate measurements of left ventricular mass in ex vivo cadaver hearts (393, 394), hypertrophied canine hearts (395), and morphologically abnormal human left ventricles (396). Previous studies have successfully employed MRI in the study of patients with HCM (397, 398). However, the MRI methodology and the nature of the comparisons made with echocardiography are different in these papers to those explored in this work. One of the benefits of MRI is that serial images can be acquired in the short axis plane from which a summated estimate of LV mass can be made. In addition, measurements of wall thickness made in this plane are directly comparable to those obtained by echocardiography.
1.7 Aims of the thesis

1. To assess the value of echocardiographic left ventricular wall-to-cavity ratios in the diagnosis of and screening for hypertrophic cardiomyopathy (HCM) at all ages by:

   a) Describing the distribution of these parameters in the normal population including infants and children.

   b) Describing the diagnostic performance of these measurements in those with an established diagnosis of HCM.

   c) Describing the distribution of these ratios in a population of first-degree relatives of patients with established HCM.

2. To assess the usefulness of echocardiographic wall-to-cavity ratios in the differentiation of physiological from pathological cardiac hypertrophy by comparing values in athletes to those from the normal population and those with HCM.

3. To describe the distribution of the wall-to-cavity ratios in those with hypertension and compare this with the values obtained from the normal population and those with established HCM.

4. To compare echocardiography and magnetic resonance imaging as imaging modalities in subjects with HCM.
2. SUBJECTS AND METHODS

2.1 Echocardiography

2.11 Subjects

262 normal subjects consisting of normal neonates, healthy siblings of children attending the Paediatric Cardiology out-patient clinics, children and adolescents assessed for innocent heart murmurs with structurally normal hearts and adult normotensive volunteers. 200 subjects were children (age range 1 day-15 years, mean 5.5 years and median 4.7 years) and 62 subjects were adults (age range 15-60 years, mean and median 27 years, 31 males and 31 females).

41 patients with HCM diagnosed on conventional echocardiographic criteria i.e. diastolic septal or left ventricular (LV) wall thickness of greater than 15mm in adults (45, 136) and substantially greater than two standard deviations above the mean for weight in children (139). There were 4 infants, 12 children (aged 1-15 years) and 25 adults (>15 years) with 23 females and 18 males. All were normotensive with other causes of cardiac hypertrophy excluded.

52 first degree relatives from 14 kindreds with HCM (age range 1.5-72 years, mean and median 30 years equal proportions of males and females). There were 13 children (aged ≤15 years) and 39 adults (aged >15 years).

26 competitive athletes with significant physiological hypertrophy including 16 rowers, 4 runners, 3 pentathletes and 3 weight-lifters/throwers, all training at least three times per week in addition to competitions (age range 12-39 years, mean and median 24 years, 6 females and 20 males). There were 3 subjects <15 years and 23 subjects >15 years of age.

16 subjects with significant hypertension as defined by a mean blood pressure > 140/90mmHg ascertained by 24 hour ambulatory recording with > 20 readings (399) (age range 33-60 years, mean and median 48 years, 6 females and 10 males). Subjects were recruited following attendance at the ambulatory blood pressure recording service at the John Radcliffe Hospital.
2.12 Methods

Echocardiography was performed with the subject in the supine position in infants and young children, and in the left lateral position in adolescents and adults during quiet respiration. The left ventricle was imaged in a long axis parasternal view from the 3rd-5th intercostal space. The M-mode cursor was positioned on the real time image such that it transected the septum, cavity and posterior left ventricular wall at right angles at, or just distal to, the tips of the mitral valve leaflets. When the subject was sufficiently co-operative, ECG electrodes were applied and diastolic measurements were made at the onset of the QRS complex. In less co-operative younger subjects diastolic measurements were taken just before the pre-systolic thinning of the posterior left ventricular wall or at the closure of the anterior mitral valve leaflet if that could be seen. Systolic measurements were taken at the point of maximum excursion of the left ventricular posterior wall. Many cycles were recorded and where possible measurements from 3 cycles were averaged. Measurements were made manually from large prints using a magnification spot lamp, fine point callipers and a metallic ruler stable in size at 20°C on a solid flat surface and according to the leading edge to leading edge convention recommended by both European and American Echocardiography groups (296, 297). Ratios were calculated from these measurements as follows:

- Diastolic septal thickness / LV end diastolic diameter (septum-to-cavity ratio)
- Diastolic LV posterior wall thickness / LV end diastolic diameter (LV wall-to-cavity ratio)
- Systolic LV posterior wall thickness / LV end systolic diameter (systolic LV wall-to-cavity ratio)
- Diastolic septal thickness / diastolic LV posterior wall thickness (septum-to-LV wall ratio).

Cross-sectional short axis images were also obtained using standard transducer positions (113) and were measured with electronic callipers in order to comprehensively describe cases of HCM, particularly those with hypertrophy in areas out with the M-mode plane.

Statistical analyses
Standard t-test and Mann-Whitney U tests were used to assess differences in the mean/median values of a variable from two populations. For comparison of more than two groups, standard one way analysis of variance (ANOVA) or the equivalent non-parametric test (Kruskal-Wallis) were used. Summary statistics, linear regression analysis, confidence limits and the prediction limits were calculated with statistical software packages (Statgraphics Plus and Prism). Optimal diagnostic cut-off points for particular variables were ascertained using receiver-operator characteristic (ROC) curves.

Inter-observer variability
Inter-observer variability was assessed by comparing the independent and blinded measurements of two observers from the M-mode prints of 25 control subjects. The mean and standard deviation of the differences was calculated as recommended by Bland and Altman (400).

62
2.2 Magnetic Resonance imaging

2.21 Subjects

10 patients with hypertrophic cardiomyopathy diagnosed by standard echocardiographic criteria (45, 136) formed the study group. All subjects were normotensive. There were 6 males (mean age 29.3 years, range 14-46 years) and 4 females (mean age 33, range 17-47 years). Informed consent was obtained in all cases. Four patients were symptomatic and six patients had been identified through family screening.

2.22 Methods

MRI methods

Examinations were performed on a superconducting MRI machine (Signa, International General Electric, Slough, England) operating at 1.5 Tesla. T1 weighted coronal and long axis oblique images (TR = R-R interval, TE = 12ms) with respiratory artefact suppression techniques and electrocardiographic gating were acquired initially. Short axis double oblique gradient recalled acquisition in the steady state (GRASS, TR = 66ms, TE = 17ms, 30 degree flip angle) images were obtained as described by Semelka et al (401). The entire left ventricle was encompassed with 1cm contiguous sections from apex to the mitral valve annulus. The images were transferred to the remote workstation for subsequent off-line analysis. The depiction of endocardial and epicardial borders was optimised on end-diastolic and end-systolic images for each section using window levels and window widths in accordance with the calculations published by Semelka. The borders were traced manually by outlining the endocardial and epicardial margins with the electronic cursor.

Each diastolic short axis image of the left ventricle was split into four quadrants; anterior interventricular septum (AIVS), posterior interventricular septum (PIVS), posterior left ventricular free wall (PLVFW) and anterior left ventricular free wall (ALVFW). The wall thickness was measured at the thickest part of each quadrant. A line was constructed which transected the left ventricle from the left of the sternum, through the anterior ventricular septum, left ventricular cavity and left ventricular posterior wall. The left ventricular end-diastolic diameter was measured here for comparison with M-mode and cross-sectional echocardiographic measurements. Anatomical landmarks such as the mitral valve, chordae and papillary muscles were noted for each section so that the anatomically appropriate one could be compared with the echocardiographic measurements. The observer performing the MRI wall thickness measurements was blinded to the measurements already obtained by echocardiography.

Left ventricular myocardial volumes were produced by regions of interest placed within the epicardial and endocardial margins respectively. The left ventricular mass was calculated using the sum of the myocardial regions of interest in both systole and diastole multiplied by 1.05g/ml, the density of
myocardial tissue. This was performed by two observers independently of one another and the results are compared; observer 1 is a consultant radiologist and observer 2 is myself.

**Echocardiography methods for the MRI study**

These were performed by a single observer using an ATL Ultramark 9 with a separate Mitsubishi printer. Standard M-mode and cross-sectional echocardiographic views were obtained at the level of the tips of the mitral valve or chordae. M-mode images were printed along with the cross-sectional reference image. Short axis cross-sectional views were also printed. Printed images were analysed by one observer using fine point callipers giving anterior interventricular septal thickness (AIVS), left ventricular end-diastolic dimension (LVEDD) and posterior left ventricular free wall thickness (PLVFW) measurements from the M-mode prints. Short axis images were divided into four quadrants as for the MRI images, and the thickest part of each quadrant was measured allowing direct comparison of AIVS, PIVS, PLVFW and ALVFW measurements.

An estimate of left ventricular mass was calculated from the M-mode echocardiographic measurements using an equation published by Devereux et al (154).

**Statistical analysis**

Statistical examination of the differences between the measurements from these two techniques was performed according to the methods of Bland and Altman (400).
3. RESULTS

3.1 The Control Population

The results from the control population of 262 normal subjects, age range 0-59 years are shown below.

3.11 Left ventricular measurements

Figure 1A-E shows left ventricular wall thickness and cavity dimension measurements plotted against age for the control population of 262 adults and children. Various lines or quadratic curves could be fitted to the data in these plots which resemble those described by other authors in relation to body surface area (69, 158). However, the purpose of this thesis was not to derive formulae to describe left ventricular measurements as a function of age although reference to these curves is helpful when considering the wall-to-cavity ratios.

3.12 Left ventricular wall-to-cavity ratios

Septum-to-cavity ratio (SEPCAVR)

Figure 2A shows the distribution of septum-to-cavity ratios (diastolic septal thickness/left ventricular end diastolic diameter) with respect to age in the control population. The mean value of the ratio appears higher in the first year of life than it is at 3 years of age following which there is a steady but small increase in value until the age of 15 after which values show no further increase. There is a significant negative linear slope (p < 0.00002) from birth to 3 years and a significant positive slope (p = 0.01) between age 3 to 15 years after which no significant slope is observed. The values of intercepts and slopes, correlation coefficients and the significance values of the slopes are shown in Table 1. Both negative and positive slopes are of low numerical value allowing all data to fall within a relatively narrow range with no normal individuals having a septum-to-cavity ratio greater than 0.26 or less than 0.12 and with only neonates showing values above 0.25.

The average septum-to-cavity ratio is 0.23 at birth, falls to 0.17 at 3-5 years of age and is 0.18 in adults. The average for the whole group regardless of age is also 0.18 (standard deviation 0.03). A one way analysis of variance (ANOVA) shows that the mean values from three age groups (0-3 years, 3-15 years, >15 years) are significantly different (p < 0.0001) from one another with no significant skewness in the distribution of values such that the mean equals the median in each group. The mean, median, range along with 95% and 99% prediction limits derived from the regression analysis are shown in table 2 for selected age groups commonly referred for cardiac assessment.
FIGURE 1 A-E. LEFT VENTRICULAR MEASUREMENTS IN THE NORMAL POPULATION

A

![Graph A](image1)

B

![Graph B](image2)

C

![Graph C](image3)

66
FIGURE 1.
A. Diastolic septal thickness (IVSD) plotted against age in years.
B. Diastolic LV wall thickness (LVPWD) plotted against age in years.
C. LV end diastolic diameter (LVEDD) plotted against age in years.
D. Systolic LV wall thickness (LVPWS) plotted against age in years.
E. LV end systolic diameter (LVESD) plotted against age in years.
Diastolic LV wall-to-cavity ratio (LVCAVR)

Figure 2B and Table 1 show that the LV wall-to-cavity ratio (diastolic left ventricular wall thickness/left ventricular end diastolic diameter) has a similar relationship with age as the septum-to-cavity ratio. The initial negative regression from birth to 3 years is less steep but still significant (p = 0.00002) and the positive regression between 3 and 15 years is more obvious with a highly significant slope (p = 0.00001). In subjects above 15 years of age there is no further change with increasing age. All observed data again fall within a relatively narrow range with no normal individuals having a LV wall-to-cavity ratio greater than 0.25 or less than 0.12. The mean ratio is 0.18 in both neonates and adults with the lowest mean value (0.16) observed in the 3-5 years olds. Again there is no significant skewness in the distribution of values in specific age groups. These values along with the range, 95% and 99% prediction limits derived from the regression equations are shown in Table 2.

**TABLE 1. RELATIONSHIP BETWEEN AGE AND WALL-TO-CAVITY RATIOS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Intercept</th>
<th>S.E.</th>
<th>Slope</th>
<th>S.E.</th>
<th>Correl.Coeff.</th>
<th>P value slope t-test</th>
<th>P value ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &lt; 3yrs</td>
<td>0.218</td>
<td>0.004</td>
<td>-0.0225</td>
<td>0.0027</td>
<td>-0.70</td>
<td>0.000011</td>
<td></td>
</tr>
<tr>
<td>age 3-15 yrs</td>
<td>0.16</td>
<td>0.006</td>
<td>0.0018</td>
<td>0.0007</td>
<td>0.23</td>
<td>0.010</td>
<td>&lt;0.0001</td>
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<tr>
<td>age &gt; 15 yrs</td>
<td>0.192</td>
<td>0.012</td>
<td>-0.0003</td>
<td>0.0004</td>
<td>-0.1</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>LVCAVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &lt; 3 yrs</td>
<td>0.177</td>
<td>0.004</td>
<td>-0.0121</td>
<td>0.0027</td>
<td>-0.46</td>
<td>0.00002</td>
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<tr>
<td>age 3-15 yrs</td>
<td>0.143</td>
<td>0.005</td>
<td>0.0029</td>
<td>0.0004</td>
<td>0.39</td>
<td>0.00001</td>
<td>0.0017</td>
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<td>age &gt; 15 yrs</td>
<td>0.188</td>
<td>0.011</td>
<td>-0.0004</td>
<td>0.0004</td>
<td>-0.11</td>
<td>n.s.</td>
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</tr>
<tr>
<td>SYSCAVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age&lt; 2.5 yrs</td>
<td>0.51</td>
<td>0.018</td>
<td>-0.0337</td>
<td>0.0118</td>
<td>-0.24</td>
<td>0.07 (n.s.)</td>
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</tr>
<tr>
<td>age 2.5-15 y</td>
<td>0.399</td>
<td>0.014</td>
<td>0.0072</td>
<td>0.0017</td>
<td>0.35</td>
<td>0.00003</td>
<td>0.0263</td>
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<tr>
<td>age &gt; 15 yrs</td>
<td>0.453</td>
<td>0.034</td>
<td>0.0008</td>
<td>0.0012</td>
<td>0.08</td>
<td>n.s.</td>
<td></td>
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FIGURE 2.
A. Septum-to-cavity ratio (SEPCAVR) versus age in years. Age 3 and 15 years are marked in dashed lines.

B. Diastolic LV wall-to-cavity ratio (LVCAVR) versus age in years. Age 3 and 15 years are marked in a dashed line.

C. Systolic LV wall-to-cavity ratio (SYSCAVR) versus age in years. Age 2.5 and 15 years are marked in a dashed line.
### TABLE 2. REFERENCE RANGES FOR WALL-TO-CAVITY RATIOS IN SELECTED AGE GROUPS

<table>
<thead>
<tr>
<th>Age group</th>
<th>Mean</th>
<th>Median</th>
<th>Standard deviation</th>
<th>95% C.I. mean</th>
<th>Range</th>
<th>95% Prediction limits</th>
<th>99% Prediction limits</th>
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<tr>
<td>&lt;1 month</td>
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<td></td>
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</tr>
<tr>
<td>SEPCAVR</td>
<td>0.23</td>
<td>0.23</td>
<td>0.02</td>
<td>0.22-0.24</td>
<td>0.19-0.26</td>
<td>0.19-0.27</td>
<td>0.18-0.28</td>
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<tr>
<td>LVCAVR</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.17-0.19</td>
<td>0.15-0.21</td>
<td>0.15-0.21</td>
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<td>SYSSEPCAVR</td>
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<td>0.44</td>
<td>0.06</td>
<td>0.41-0.48</td>
<td>0.36-0.54</td>
<td>0.33-0.55</td>
<td>0.30-0.58</td>
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<tr>
<td>6-12 months</td>
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<td>0.21</td>
<td>0.02</td>
<td>0.19-0.22</td>
<td>0.17-0.24</td>
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<td>0.15-0.27</td>
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<td>LVCAVR</td>
<td>0.17</td>
<td>0.17</td>
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<td>0.16-0.18</td>
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<td>1-2 years</td>
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<tr>
<td>SEPCAVR</td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
<td>0.16-0.18</td>
<td>0.13-0.22</td>
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<tr>
<td>SEPCAVR</td>
<td>0.17</td>
<td>0.16</td>
<td>0.03</td>
<td>0.16-0.17</td>
<td>0.12-0.24</td>
<td>0.12-0.22</td>
<td>0.12-0.24</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.16</td>
<td>0.15</td>
<td>0.02</td>
<td>0.15-0.16</td>
<td>0.12-0.21</td>
<td>0.12-0.20</td>
<td>0.12-0.21</td>
</tr>
<tr>
<td>SYSSEPCAVR</td>
<td>0.43</td>
<td>0.42</td>
<td>0.07</td>
<td>0.41-0.45</td>
<td>0.30-0.57</td>
<td>0.33-0.56</td>
<td>0.30-0.57</td>
</tr>
<tr>
<td>6-10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEPCAVR</td>
<td>0.17</td>
<td>0.17</td>
<td>0.03</td>
<td>0.17-0.18</td>
<td>0.12-0.21</td>
<td>0.12-0.21</td>
<td>0.12-0.24</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
<td>0.16-0.17</td>
<td>0.13-0.21</td>
<td>0.13-0.20</td>
<td>0.13-0.21</td>
</tr>
<tr>
<td>SYSSEPCAVR</td>
<td>0.46</td>
<td>0.46</td>
<td>0.07</td>
<td>0.43-0.48</td>
<td>0.30-0.59</td>
<td>0.34-0.58</td>
<td>0.30-0.59</td>
</tr>
<tr>
<td>11-15 years</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(n=33)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEPCAVR</td>
<td>0.18</td>
<td>0.18</td>
<td>0.03</td>
<td>0.17-0.19</td>
<td>0.12-0.25</td>
<td>0.13-0.23</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.18</td>
<td>0.18</td>
<td>0.03</td>
<td>0.17-0.19</td>
<td>0.11-0.24</td>
<td>0.13-0.23</td>
<td>0.11-0.24</td>
</tr>
<tr>
<td>SYSSEPCAVR</td>
<td>0.48</td>
<td>0.47</td>
<td>0.07</td>
<td>0.46-0.50</td>
<td>0.32-0.62</td>
<td>0.36-0.61</td>
<td>0.32-0.62</td>
</tr>
<tr>
<td>&gt;15 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEPCAVR</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.18-0.19</td>
<td>0.13-0.23</td>
<td>0.14-0.23</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.17-0.19</td>
<td>0.13-0.23</td>
<td>0.13-0.22</td>
<td>0.12-0.24</td>
</tr>
<tr>
<td>SYSSEPCAVR</td>
<td>0.47</td>
<td>0.47</td>
<td>0.07</td>
<td>0.46-0.49</td>
<td>0.30-0.63</td>
<td>0.34-0.61</td>
<td>0.30-0.65</td>
</tr>
</tbody>
</table>
Systolic LV wall-to-cavity ratio (SYSCAVR)

Figure 2C and Table 1 show that there appears to be a decrease in the average systolic wall-to-cavity ratio (systolic LV wall thickness/left ventricular end systolic diameter) in early life although the slope does not quite reach statistical significance ($p = 0.07$). The decrease stops at around 2.5 years followed by a significant slow rise until 15 years ($p = 0.00003$). After 15 years of age there is no further age related change. After the age of 1 year, no values greater than 0.61 or less than 0.30 were observed in normal individuals. In adults the mean systolic LV wall-to-cavity ratio is 0.47 with the lowest mean value observed once again in the 3-5 year old age group (0.43).
3.13 Gender comparisons

There were no significant differences in diastolic septal thickness, diastolic LV wall thickness, left ventricular end diastolic diameter, systolic LV wall thickness and left ventricular end systolic diameter between males and females aged < 15 years. By adulthood males showed significantly larger diastolic septal thickness (IVSD), left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) measurements compared to females (Table 3). In contrast there was no influence of gender at any age on septum-to-cavity ratio, diastolic LV wall-to-cavity ratio and systolic LV wall-to-cavity ratio (p >0.1). The significant gender differences in the absolute measurements are illustrated alongside the ratios for adults in Figure 3.

**TABLE 3. GENDER DIFFERENCES IN CARDIAC MEASUREMENTS IN ADULTS**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adult females (n=31)</th>
<th>Adult males (n=31)</th>
<th>Unpaired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic septal thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cm)</td>
<td>Mean</td>
<td>Median</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td></td>
<td>0.86</td>
<td>0.86</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>P = 0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LV end diastolic diameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cm)</td>
<td>Mean</td>
<td>Median</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td></td>
<td>4.73</td>
<td>4.76</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>P = 0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LV end systolic diameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cm)</td>
<td>Mean</td>
<td>Median</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td></td>
<td>3.03</td>
<td>2.93</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>P = 0.0031</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 3. GENDER COMPARISONS OF CONVENTIONAL MEASUREMENTS AND WALL-TO-CAVITY RATIOS IN ADULTS

Diastolic septal thickness

Diastolic septum-to-cavity ratio

LV end diastolic diameter

Diastolic LV wall-to-cavity ratio

LV end systolic diameter

Systolic LV wall-to-cavity ratio

F = females
M = males
### 3.14 Influence of body surface area

Previous studies have shown significant relationships between LV wall thickness and cavity measurements with body surface area (BSA m²) and have derived complex equations for deriving one from the other (69, 158, 314). BSA measurements were available in 38 adult subjects and 34 children. The ratios for adults are plotted against BSA in Figure 4 and details of the linear regression are shown in Table 4. There is no significant relationship between septum-to-cavity ratio or LV wall-to-cavity ratio and BSA in adults. All children were not analysed together since the ratios show some age variation suggesting that variation with BSA may also exist. However, when considered in the age bands represented in Table 2 there is no significant relationship between septum-to-cavity ratio or LV wall-to-cavity ratio and BSA, albeit that the numbers in each subgroup are small. This shows that in contrast to absolute wall thickness and cavity dimension measurements, the diastolic wall-to-cavity ratios are independent of BSA. There is however, a significant inverse relationship between the systolic LV wall-to-cavity ratio and increasing BSA in adults. This could be accounted for by the lack of any significant relationship between systolic LV wall thickness and BSA (p=0.22) and the presence of a significant relationship between LV end systolic diameter and BSA (slope 1.36, p<0.0001).

#### TABLE 4. WALL-TO-CAVITY RATIOS AND BODY SURFACE AREA IN ADULTS

<table>
<thead>
<tr>
<th>Wall-to-cavity ratio</th>
<th>Slope of regression line of the ratio plotted against BSA m² (n=38)</th>
<th>Significance level of slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td>-0.0038</td>
<td>P = 0.88</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>-0.021</td>
<td>P = 0.35</td>
</tr>
<tr>
<td>SYSCAVR</td>
<td>-0.14</td>
<td>P = 0.009</td>
</tr>
</tbody>
</table>

#### Inter-observer variability

Inter-observer variability of measurements was assessed by blind measurements of two observers from the M-mode prints of 25 subjects. The mean (and standard deviation) of the difference between the measurements made by the two observers were 0.002 (0.016) for diastolic septum-to-cavity ratio, 0.000 (0.014) for diastolic left ventricular wall-to-cavity ratio and 0.011 (0.005) for systolic left ventricular wall-to-cavity ratio. Thus there was good agreement between the two observers.
FIGURE 4. BODY SURFACE AREA (BSA) AND WALL-TO-CAVITY RATIOS IN ADULTS

Diastolic septum-to-cavity ratio

Diastolic LV wall-to-cavity ratio

Systolic LV wall-to-cavity ratio
3.2 Patients with hypertrophic cardiomyopathy (HCM)

The results from 41 patients with HCM (age 0.2-75 years) are presented below and are compared with those from the control group.

3.21 Left ventricular measurements

Measurements from 25 patients with HCM >15 years old were compared with those from 62 control subjects of the same age with equal proportions of males and females in each group. Diastolic septal thickness (IVSD), diastolic LV wall thickness (LVPWD) and cubed ejection fraction (EF) were, as expected, significantly larger in the HCM group. These differences are illustrated in Figure 5 and in Table 5. All except one HCM patient showed a diastolic septal thickness measurements > 15 mm. The subject with a value of 14.7mm was aged between 15-16 years and has a measurement >2sds above that permissible for weight. This group are therefore representative of an unambiguous disease group. By using the standard deviations of the measurements from the HCM group, it can be seen that the mean value for LV end diastolic diameter in the control group (4.8 cm) was 2 standard deviations larger than that in the HCM group (3.8 cm) whilst the mean value of diastolic septal thickness in the control group was 2.4 standard deviations smaller than that in the HCM group. This suggests that a small LV end diastolic diameter and an increased diastolic septal thickness are of comparable importance as disease characteristics. A measure which combines both elements (wall-to-cavity ratio) is therefore likely to provide increased diagnostic sensitivity compared to the sensitivity of each measurement used separately.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control subjects (n=62)</th>
<th>HCM patients (n=25)</th>
<th>Mann-Whitney-U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic septal thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.89</td>
<td>2.31</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>2.27</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.6 - 1.21</td>
<td>1.47 - 3.81</td>
<td></td>
</tr>
<tr>
<td>Diastolic LV wall thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.87</td>
<td>1.24</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.64 - 1.21</td>
<td>0.87 - 2.28</td>
<td></td>
</tr>
<tr>
<td>LV end diastolic diameter (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.85</td>
<td>3.79</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>4.88</td>
<td>3.75</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.38</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.19 - 5.88</td>
<td>2.71 - 4.93</td>
<td></td>
</tr>
<tr>
<td>Cubed Ejection Fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.72</td>
<td>0.85</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.72</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.06</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.58 - 0.85</td>
<td>0.63 - 1.0</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 5. LEFT VENTRICULAR MEASUREMENTS IN ADULT HCM PATIENTS COMPARED WITH THE CONTROL GROUP

Diastolic septal thickness

LV end diastolic diameter

Diastolic LV wall thickness

Cubed ejection fraction

FIGURE 5.
O Control subjects
● HCM patients
3.22 Left ventricular wall-to-cavity ratios

The range of wall-to-cavity ratios in healthy controls and HCM patients at all ages are shown in Table 6 and are illustrated by frequency distribution histograms in Figure 6 A-D. The diastolic septum-to-cavity ratio (SEPCAVR) is the only variable that completely separates the two groups of subjects (Fig. 6A). With the systolic LV wall-to-cavity ratio (Fig. 6B), diastolic LV wall-to-cavity ratio (Fig. 6C) and septum-to-LV wall ratio (Fig. 6D) progressively more overlap between the two populations is seen. The septum-to-LV wall ratio conventionally used for screening showed a substantial overlap between the populations.

### TABLE 6. WALL-TO-CAVITY RATIOS IN CONTROL SUBJECTS AND HCM PATIENTS

<table>
<thead>
<tr>
<th>RATIO</th>
<th>Controls (n=262)</th>
<th>HCM subjects (n=41)</th>
<th>Mann-Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td>0.49</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.03</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.12 - 0.26</td>
<td>0.32 - 1.26</td>
<td></td>
</tr>
<tr>
<td>SYSCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.46</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.46</td>
<td>0.97</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.08</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.3 - 0.71</td>
<td>0.43 - 3.35</td>
<td></td>
</tr>
<tr>
<td>LVCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.17</td>
<td>0.31</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.17</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.03</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.11 - 0.24</td>
<td>0.13 - 0.7</td>
<td></td>
</tr>
<tr>
<td>SEPLVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.1</td>
<td>1.93</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
<td>1.80</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.17</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.69 - 1.71</td>
<td>0.96 - 3.82</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 6 A-D. FREQUENCY DISTRIBUTION OF WALL-TO-CAVITY RATIOS IN THE HCM GROUP COMPARED TO THE CONTROL GROUP

A. Septum-to-cavity ratio

B. Systolic LV wall-to-cavity ratio
C. Diastolic LV wall-to-cavity ratio

Relative frequency

Controls

HCM subjects

D. Septum-to-LV wall ratio

Relative frequency

Controls

HCM subjects
Although it is relatively easy to select a value for septum-to-cavity ratio which would separate the disease group from the control group, this is less clear with the other ratios because of the degree of overlap. Therefore, in order to select a cut-off point for each ratio which would optimally separate the disease from the control population, receiver operator characteristic (ROC) curves were constructed and are shown in Figure 7 A-D. The optimal cut-off value for each ratio is that value which produces the point of the curve closest to the upper left-hand corner of the plot area. The performance of the derived cut-off points with the associated sensitivities and false positive rates are shown in Table 7. The cut-off of septum-to-LV wall ratio suggested by the ROC curve is 1.3 but the performance of a value of 1.5 is also shown for comparison as it has been used as a diagnostic criterion by some authors.

**TABLE 7. RESULTS OF THE APPLICATION OF THE DERIVED CUT-OFF VALUES IN THE DISEASE AND CONTROL POPULATIONS**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Cut-off value</th>
<th>Number of positive cases out of 41 HCM patients</th>
<th>Detection rate (%)</th>
<th>False positives out of 262 controls</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td>&gt;0.26</td>
<td>41</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SYSCAVR (all)</td>
<td>&gt;0.63</td>
<td>40</td>
<td>97.6</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>SYSCAVR (≥1yr)</td>
<td>&gt;0.63</td>
<td>37/37</td>
<td>100</td>
<td>0/239</td>
<td>0</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>&gt;0.23</td>
<td>32</td>
<td>78</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt;1.3</td>
<td>37</td>
<td>90.2</td>
<td>27</td>
<td>11.3</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt;1.5</td>
<td>31</td>
<td>75.6</td>
<td>5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

A cut-off value of 0.26 for septum-to-cavity ratio (SEPCAVR) produces a 100% disease detection rate with a 0% false positive rate. Referring back to the control data in section 3.1 it can be seen that the value of 0.26 is also above the 99% prediction limits for any subject > 1 year of age.

The systolic LV wall-to-cavity ratio (SYSCAVR) showed a slightly lower detection rate (97.6%) and a higher false positive rate (1.9%) than the septum-to-cavity ratio. However, all of the false positive results occurred in subjects <1 year of age in whom the upper 99% prediction limit is 0.77. When subjects >1 year are considered separately the false positive rate reduces to zero.
FIGURE 7 A-D. RECEIVER OPERATOR CHARACTERISTIC (ROC) CURVES FOR WALL-TO-CAVITY RATIOS

A. Septum-to-cavity ratio ROC curve

B. Systolic LV wall-to-cavity ratio ROC curve
C. LV wall-to-cavity ratio ROC curve

D. Septum-to-LV wall ratio ROC curve

Cut-off value

0.23

1.3
The cut-off value for the LV wall-to-cavity ratio suggested by the ROC curve was 0.22. However, the sensitivity of this value for diagnosing HCM was limited (83%) so specificity was optimised by adopting a value of 0.23 which offered a sensitivity of 78% with a false positive rate of 0.8%.

For comparison the detection rates and false positive rates for the traditional diastolic septum-to-LV wall (SEPLVR) ratios using cut-off values of 1.3 and 1.5 are shown (Table 7). It can be seen that a septum-to-cavity ratio of >0.26 and a systolic LV wall-to-cavity ratio of >0.64 show superior diagnostic sensitivity for HCM compared to the traditionally used ratios with improved false positive rates.
3.3 First degree relatives from kindreds with hypertrophic cardiomyopathy

Mutations for hypertrophic cardiomyopathy are transmitted in an autosomal dominant manner. Therefore, in a sufficiently large population of first degree relatives 50% of the subjects would be expected to have inherited the mutation whether or not it is expressed as overt disease. 52 first-degree relatives from 14 kindreds with familial HCM were examined.

3.3.1 Septum-to-cavity ratio

Bimodal distribution

The frequency distribution histogram for the septum-to-cavity ratio in this population compared to normal subjects is shown in Figure 8. The frequency distribution in the first-degree relatives appears bimodal. The first peak mirrors that of normal subjects and the second broader peak resembles that seen in the HCM patients. Using the cut-off point of 0.26 the two populations are separated with 27 relatives having a ratio equal to or less than 0.26 and 25 having a ratio greater than 0.26. Thus this ratio divides first degree relatives into two discrete populations.

Specificity and estimated false positive rate

Of the 25 relatives with septum-to-cavity ratios above 0.26, 10 adult subjects fulfil classical diagnostic criteria for HCM with diastolic septal thickness measurements greater than 15mm (45, 136). A further 13 subjects fulfil the criteria for "affected" by having a diastolic septal thickness measurement of ≥ 13mm in adults, a cut-off agreed at an international workshop (139), or by having a septal thickness > 2SD above the mean for age, weight and sex (316, 402). Thus 23/25 subjects with a septum-to-cavity ratio >0.26 could justifiably be classed as affected on diastolic septal wall thickness measurements alone. In addition, 19/25 showed either asymmetrical septal hypertrophy with a septum-to-LV wall ratio >1.3 or cubed ejection fractions > 95% prediction limits for the control population or both.

It is of particular interest to study more closely the two remaining subjects not identified by diastolic wall thickness criteria alone but who were identified as abnormal by the septum-to-cavity ratio. They were both adult normotensive females with M-mode diastolic septal thickness measurements of 12 and 11 mm respectively. Both had an abnormally small diastolic left ventricular dimension of 3.8cm which is > 2SDs below the mean for adult females both from this thesis (4.7cm) and from a previous study (4.9cm) (141)
FIGURE 8. SEPTUM-TO-CAVITY RATIOS IN FIRST-DEGREE RELATIVES OF SUBJECTS WITH HCM COMPARED WITH THE CONTROL POPULATION

![Graph showing septum-to-cavity ratios in first-degree relatives of subjects with HCM compared with the control population.]
and would be average for a 22kg or approximately 6 year old child (316). Chapter 3.2 demonstrates the importance of an abnormally small LV cavity as a disease characteristic in HCM and in these women the small LV cavity size also resulted in abnormal values for the other wall-to-cavity ratios. The systolic LV wall-to-cavity ratio was >0.63 in both cases which was shown previously (chapter 3.2) to provide 100% specificity for the diagnosis of HCM in those > 1 year of age. In addition, the diastolic LV wall-to-cavity ratio was >0.23 in both cases, a measure which had limited sensitivity (78%) but a specificity of 99.2% for the diagnosis in the disease population. Furthermore, one subject had a cubed ejection fraction > 99% prediction limits for adults (see chapter 3.2) and the other showed a septum-to-LV wall ratio >1.3. Therefore both subjects had five M-mode echocardiographic measurements which were not only outside the normal range but were in keeping with the echocardiographic disease characteristics of HCM discussed in chapter 3.2. This supports the concept that these two subjects are, in fact, phenotypically abnormal despite not showing a diastolic septal thickness above the accepted normal range. Short axis cross-sectional echocardiography showed that the anterior most septal wall thickness in both subjects was 13mm and as such both subjects may be classified as "borderline" by some authors (139). These measurements are in keeping with the M-mode measurements as cross-sectional imaging has a lower resolution than M-mode echocardiography with poorer definition of the LV wall edges (chapter 1). It is noteworthy that subjects exhibiting predominantly apical HCM were still correctly identified by an elevated septum-to-cavity ratio even though the M-mode beam did not transect the apical septum.

By closely examining those subjects identified by an elevated septum-to-cavity ratio >0.26, no obvious false positive subjects can be identified.

**Sensitivity and estimated false negative rate**

All 27 subjects with a septum-to-cavity ratio <0.26 showed diastolic septal thickness measurements of < 13mm and within 2SDs for age, sex and weight with normal left ventricular end diastolic dimensions. No subjects showed a systolic LV wall-to-cavity ratio >0.63 (100% detection rate for those >1 year) or a diastolic LV wall-to-cavity ratio >0.23 (specificity 99.2%) and none had a cubed ejection fraction >95% prediction limits for normal.

Three adult subjects (2 male and 1 female) showed a septum-to-LV wall ratio of >1.3 but <1.5 as did 27 of the control subjects. In particular, all 3 showed normal LV end diastolic dimensions and none exhibited systolic hypercontractility. Therefore, on best echocardiographic criteria, none of the 27 subjects could be classed as phenotypically abnormal implying that septum-to-cavity ratio has an estimated detection rate of 100% for the abnormal cardiac phenotype suggestive of HCM.

It would therefore appear that the septum-to-cavity ratio has separated the first-degree relatives into two phenotypically separate populations: those with phenotypic qualities which have been shown to be disease
characteristics in HCM and those who are completely normal. It appears to be equally as successful in children as in adults and therefore offers great practical advantages over and above existing measurements. Both adult first-degree relatives (n=42) and those in childhood (n=10) appear to be separated in the expected proportions for a disorder with autosomal dominant inheritance with 48% of adults and 50% of children classified as affected.

3.32 Other wall-to-cavity ratios

Table 8 shows the results from all three wall-to-cavity ratios and for comparison the results using absolute septal thickness measurements and septum-to-LV wall ratios. The assumption made in calculating these estimates is that the septum-to-cavity ratio has correctly produced two phenotypically separate populations, one with characteristics consistent with the HCM phenotype and the other completely normal. As such it is used as a measurement against which others are judged. The performance of each ratio is more closely examined below.

**Systolic LV wall-to-cavity ratio**

No apparent false positive subjects are identified by a cut-off of >0.63 for this ratio, however two subjects with an elevated septum-to-cavity ratio were not identified by the systolic LV wall-to-cavity ratio. These were two male subjects the first of whom showed a diastolic septal thickness measurement of 13mm, an LV end diastolic dimension on the 5% prediction limit for normal subjects and asymmetric septal hypertrophy with a septum-to-LV wall ratio of 1.86. The second subject was a child with a septal thickness > 2SD above the mean for age, weight and with an LV end diastolic diameter <2SD below the mean for age, sex and weight (data from this thesis) (316, 402). Thus both appear to be phenotypically abnormal and are classified as false negative subjects using this ratio.

**Diastolic LV wall-to-cavity ratio**

Again, no false positive subjects appear to have been identified by a cut-off of >0.23 for this ratio. However, 7 subjects with an elevated septum-to-cavity ratio are not identified. 3 subjects were children who all showed diastolic septal thickness measurements >2SDs above the mean for age, weight and sex (316, 402), systolic hypercontractility as evidenced by a systolic LV wall-to-cavity ratio of >0.63 (100% sensitivity and specificity in the disease population) and septum-to-LV wall ratios were >1.3 in one subject and >1.5 in two. 4 unidentified subjects were adults who showed diastolic septal thickness measurements of 13-16.4mm, systolic LV wall-to-cavity ratio >0.63 in 3 out of 4, a septum-to-LV wall ratio >1.5 in 3 out of 4 with the remaining subject showing a ratio >1.3. Thus these subjects appear to have
an abnormal phenotype by other echocardiographic criteria and are considered to be false negative subjects using this ratio.

**TABLE 8. WALL-TO-CAVITY RATIOS IN FIRST DEGREE RELATIVES OF SUBJECTS WITH HCM WITH ESTIMATED SENSITIVITY AND FALSE POSITIVE RATES**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut-off value</th>
<th>Positive cases in 25 relatives with abnormal phenotype</th>
<th>Estimated sensitivity (%)</th>
<th>Positive cases in 27 relatives with normal phenotype</th>
<th>Estimated false positive rate (%)</th>
<th>Proportion of test positive 1st degree relatives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td>&gt;0.26</td>
<td>25</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>SYSCAVR</td>
<td>&gt;0.63</td>
<td>22/24</td>
<td>92</td>
<td>0</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>&gt;0.23</td>
<td>18</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt;1.3</td>
<td>17</td>
<td>71</td>
<td>3</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt;1.5</td>
<td>11</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Septal thickness (adults n=42)</td>
<td>≥ 13mm</td>
<td>17/20</td>
<td>85</td>
<td>0/22</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Septal thickness (adults n=42)</td>
<td>≥ 15mm</td>
<td>10/20</td>
<td>50</td>
<td>0/22</td>
<td>0</td>
<td>24</td>
</tr>
</tbody>
</table>

**Septum-to-LV wall ratio**

No false positive subjects appear to be identified by a ratio of >1.5. However, 3 false positive adult subjects are identified by a cut-off of 1.3, as were 27 control subjects. All 3 subjects showed a diastolic septal thickness of < 13mm and all had normal LV end diastolic dimensions along with no evidence of systolic hypercontractility. In this respect they appear to have a normal phenotype using other echocardiographic measurements and are therefore considered to be false positive subjects using this ratio.

A ratio of >1.5 fails to identify 13 subjects with an elevated septum-to-cavity ratio and a ratio of >1.3 fails to identify 7 subjects. Of the 7 subjects, 2 were children with diastolic septal thickness measurements >2SDs above the mean for age, weight and sex (this thesis) (316, 402), one of whom showed systolic hypercontractility with systolic LV wall-to-cavity ratios >0.63, and both of whom showed diastolic LV wall-to-cavity ratios >0.23 (99.6% specificity in the disease population). A further 5 unidentified subjects were adults, 3 of whom showed diastolic septal thickness measurements of >13mm and 4/5 of whom showed LV end diastolic dimension < 1% prediction limits for gender with the fifth showing a
measurement < 5% prediction limit. Furthermore all 5 subjects showed systolic hypercontractility with systolic LV wall-to-cavity ratios >0.63 and all 5 subjects showed diastolic LV wall-to-cavity ratios >0.23. Thus, all subjects had other echocardiographic measurements suggestive of an abnormal phenotype and are considered to be false negative subjects.

Having examined in detail, both groups of first degree relatives (potentially affected and potentially unaffected) created by each ratio in turn, it would appear that the septum-to-cavity ratio is the only one in which there is an absence of both false positive and false negative subjects as judged by several other echocardiographic criteria.
3.4 The athletic population

3.41 Left ventricular measurements

The athletes showed significant cardiac hypertrophy when compared to the control population. As expected diastolic septal thickness, diastolic left ventricular posterior wall thickness, left ventricular end diastolic dimension and left ventricular mass and mass index are all significantly larger in the athletes than in the control group and this is illustrated in Figure 9 and in Table 9.

**TABLE 9. LEFT VENTRICULAR MEASUREMENTS IN ATHLETES AND CONTROL SUBJECTS**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adult control subjects (n=62)</th>
<th>Adult athletes (n=23)</th>
<th>Mann-Whitney-U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic septal thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.89</td>
<td>1.2</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.6 - 1.21</td>
<td>0.95 - 1.67</td>
<td></td>
</tr>
<tr>
<td>Diastolic LV wall thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.87</td>
<td>1.1</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.64 - 1.21</td>
<td>0.90 - 1.41</td>
<td></td>
</tr>
<tr>
<td>LV end diastolic diameter (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.85</td>
<td>5.26</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>4.88</td>
<td>5.16</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.38</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.19 - 5.88</td>
<td>4.39 - 6.1</td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>147</td>
<td>252</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>144</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>36</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>84 - 254</td>
<td>149 - 388</td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m² BSA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>82</td>
<td>136</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>82</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>54 - 132</td>
<td>102 - 178</td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>38</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 9. LEFT VENTRICULAR MEASUREMENTS IN ADULT ATHLETES AND CONTROL SUBJECTS

Diastolic septal thickness

LV end diastolic diameter

LV mass

LV mass index

FIGURE 9.

Control subjects

Athletes
3.42 Left ventricular wall-to-cavity ratios

The wall-to-cavity ratio measurements from the athletes includes those from three subjects > 12 years but <15 years. The values of these ratios are compared with those from the control population > 12 years of age in Table 10 and in Figure 10 where the cut-off values used to diagnose HCM are shown as a dashed line.

**TABLE 10. WALL-TO-CAVITY RATIOS IN ATHLETES AND CONTROL SUBJECTS**

<table>
<thead>
<tr>
<th>RATIO</th>
<th>Control subjects (n=86)</th>
<th>Athletes (n=26)</th>
<th>Mann-Whitney U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.23</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.12 - 0.25</td>
<td>0.15 - 0.29</td>
<td></td>
</tr>
<tr>
<td>SYSCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.48</td>
<td>0.47</td>
<td>P = 0.48</td>
</tr>
<tr>
<td>Median</td>
<td>0.48</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.07</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.3 - 0.63</td>
<td>0.38 - 0.59</td>
<td></td>
</tr>
<tr>
<td>LVCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.21</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.11 - 0.24</td>
<td>0.15 - 0.28</td>
<td></td>
</tr>
<tr>
<td>SEPLVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1</td>
<td>1.1</td>
<td>P = 0.15</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.14</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.72 - 1.6</td>
<td>0.83 - 1.31</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 10. SEPTUM-TO-CAVITY RATIOS AND SYSTOLIC LV WALL-TO-CAVITY RATIOS IN ATHLETES AND CONTROL SUBJECTS

Septum-to-cavity ratio

Systolic LV wall-to-cavity ratio
None of the athletes in this study were thought to have HCM despite values of septum-to-cavity ratio and LV wall-to-cavity ratio which were higher than in the control group (Table 10). This is because few fell outside the upper limits for normal with only two subjects showing a septum-to-cavity ratio >0.26. Furthermore, neither of these two subjects and indeed none of the athletes showed systolic hypercontractility with no values of systolic LV wall-to-cavity > 0.63 (100% sensitivity and specificity for HCM disease detection > 1 year of age) and values were not significantly different to those in the control population (Table 10). Cubed ejection fraction was also not elevated in the two athletes with an elevated septum-to-cavity ratio and EF in the athletic group as a whole was not significantly different to the control population (p = 0.68). One of the athletes showed asymmetric septal hypertrophy with a value of septum-to-LV wall ratio of 1.31 (Table 11) but none showed an abnormally small LV end diastolic diameter, in fact values were significantly larger than in the control group (Figure 9). The results of the application of the echocardiographic criteria used to diagnose HCM are shown in Table 11.

**TABLE 11. DIAGNOSTIC CRITERIA FOR HCM APPLIED TO THE ATHLETIC POPULATION**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut-off value</th>
<th>False positives of 26 athletes</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td>&gt; 0.26</td>
<td>2</td>
<td>7.7</td>
</tr>
<tr>
<td>SYSCAVR</td>
<td>&gt; 0.63</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>&gt; 0.23</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt; 1.3</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Diastolic septal thickness (adults n=23)</td>
<td>&gt; 13mm</td>
<td>5</td>
<td>22</td>
</tr>
</tbody>
</table>

It would appear that those with particularly marked physiological hypertrophy may show a septum-to-cavity ratio >0.26. The two subjects with elevated ratios in this study were male national standard rowers with diastolic septal thickness measurements of 16.7 and 14.2mm and LV end diastolic diameter measurements of 5.75 and 5.13 cm giving ratios of 0.29 and 0.28. However, in contrast to HCM systolic hypercontractility (systolic LV wall-to-cavity ratio >0.63) does not appear to be a feature of physiological hypertrophy with a frequency distribution which mirrors that of the control population. Thus, by using these two ratios in combination true physiological hypertrophy is discernible from the pathological hypertrophy of HCM. It is noteworthy that a cut-off value of 13mm for diastolic septal thickness yields a false positive rate of 22%.
3.5 Subjects with hypertension

3.51 The group with hypertension and the control group

The group with hypertension showed significant cardiac hypertrophy when compared to the adult control group. Diastolic septal thickness (IVSD), diastolic LV wall thickness (LVPWD), left ventricular mass (LVM) and mass index (LVMI) are all significantly larger in the group with hypertension. But unlike the athletic group and resembling the group with HCM, the LV end diastolic dimension is smaller than in the control population. Left ventricular measurements in those with hypertension compared with those in the control group are shown in Table 12 and Figure 11.

**TABLE 12. LEFT VENTRICULAR MEASUREMENTS IN HYPERTENSIVE SUBJECTS AND CONTROL SUBJECTS**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adult control subjects (n=62)</th>
<th>Hypertensive subjects (n=16)</th>
<th>Mann-Whitney-U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic septal thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.89</td>
<td>1.60</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.6 - 1.21</td>
<td>1.20 - 1.94</td>
<td></td>
</tr>
<tr>
<td>Diastolic LV wall thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.87</td>
<td>1.16</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.12</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.64 - 1.21</td>
<td>1.01 - 1.41</td>
<td></td>
</tr>
<tr>
<td>LV end diastolic diameter (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.85</td>
<td>4.43</td>
<td>P = 0.0078</td>
</tr>
<tr>
<td>Median</td>
<td>4.88</td>
<td>4.45</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.38</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.19 - 5.88</td>
<td>3.53 - 5.42</td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td></td>
<td></td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Mean</td>
<td>147</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>144</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>36</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>84 - 254</td>
<td>165 - 368</td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td></td>
<td></td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Mean</td>
<td>82</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>82</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>19</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>54 - 132</td>
<td>93 - 198</td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>38</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 11. LEFT VENTRICULAR MEASUREMENTS IN HYPERTENSIVE SUBJECTS AND CONTROL SUBJECTS

Diastolic septal thickness

LV end diastolic diameter

LV mass

LV mass index

FIGURE 11.
- ○ Control subjects
- ■ Hypertensive subjects
15/16 of the hypertensive patients showed a diastolic septal thickness > 13mm and all showed values ≥ 99% prediction limits for adult normal subjects (12mm). In addition, 11/16 had a sex specific LV mass index which would define them as showing LV hypertrophy according to the Framingham criteria (354) (100g/m² females, 130g/m² males). Therefore using simple wall thickness criteria and LV mass index most subjects represent a group with significant cardiac hypertrophy secondary to hypertension.

Table 13 shows the comparison between the wall-to-cavity ratios in hypertensive subjects and control subjects. It can be seen that values of all ratios are significantly higher in the hypertensive group.

**TABLE 13. WALL-TO-CAVITY RATIOS IN HYPERTENSIVE SUBJECTS AND ADULT CONTROL SUBJECTS**

<table>
<thead>
<tr>
<th>RATIO</th>
<th>Control subjects (n=62)</th>
<th>Hypertensive subjects (n=16)</th>
<th>Mann-Whitney-U</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.37</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.02</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.13 - 0.23</td>
<td>0.22 - 0.55</td>
<td></td>
</tr>
<tr>
<td>SYSCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.47</td>
<td>0.62</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.47</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.07</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.3 - 0.63</td>
<td>0.42 - 0.9</td>
<td></td>
</tr>
<tr>
<td>LVCAVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.27</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.02</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.13 - 0.23</td>
<td>0.19 - 0.4</td>
<td></td>
</tr>
<tr>
<td>SEPLVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.04</td>
<td>1.4</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>1.00</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.15</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.72 - 1.6</td>
<td>1.18 - 1.79</td>
<td></td>
</tr>
</tbody>
</table>

The various echocardiographic criteria used to diagnose HCM might also be expected to identify pathological hypertrophy of other causes. The results of the application of these cut-off values are shown in Table 14.
### TABLE 14. DIAGNOSTIC CRITERIA FOR HCM APPLIED TO THE HYPERTENSIVE POPULATION

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut-off value</th>
<th>Positive results in 16 hypertensive patients</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td>&gt; 0.26</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>SYSACAVR</td>
<td>&gt; 0.63</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>&gt; 0.23</td>
<td>13</td>
<td>81</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt; 1.3</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt; 1.5</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Diastolic septal thickness</td>
<td>&gt; 13mm</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>Diastolic septal thickness</td>
<td>&gt; 15mm</td>
<td>10</td>
<td>62.5</td>
</tr>
</tbody>
</table>

The only subject with a septum-to-cavity ratio <0.26 had a diastolic septal thickness of 12 mm (99% prediction limit for control population) and as such might be considered to have a wall thickness at the upper limit of normal. Values of all other wall-to-cavity ratios were within normal limits (diastolic LV wall-to-cavity ratio 0.19, systolic LV wall-to-cavity ratio 0.5, septum-to-LV wall ratio 1.2). In addition, he showed the largest left ventricular end diastolic diameter (5.42 cm approx 90% prediction limit of control group) of the subjects with hypertension (all of the others had an LVEDD < 1 standard deviation above mean for control group) and a LV mass index of 117 g/m². Interestingly, this subject also exhibited borderline hypertension with a mean of 140/93 (> 20 readings). It might therefore be concluded that he did not exhibit significant cardiac hypertrophy and was correctly categorised as such by the septum-to-cavity ratio.

All of the other subjects showed a diastolic septal thickness of > 13 mm and would be considered by many to have cardiac hypertrophy on that basis alone. It is probable therefore that 15/16 subjects did show significant left ventricular hypertrophy.

Interestingly there was only one significant correlation between an LV measurement and blood pressure in the hypertensive subjects. This occurred between diastolic septal thickness and mean systolic pressure and the correlation co-efficient was 0.59 (R² = 0.34, p=0.017). None of the other wall thickness or cavity...
dimension measurements, LVM, LVMI, calculated ejection fraction and none of the wall-to-cavity ratios showed any correlation with mean systolic or mean diastolic blood pressure readings.

3.52 Subjects with hypertension and those with HCM

The frequency distribution of the wall-to-cavity ratios in the hypertensive subjects and the HCM group are shown in Figure 12 along with the cut-off values derived from normal subjects and subjects with HCM marked in a dashed line. It can be seen that none of the chosen echocardiographic diagnostic criteria used to separate control subjects from HCM subjects can adequately separate those with hypertension from those with HCM. Therefore the wall-to-cavity ratios appear to provide an excellent tool for differentiating normal subjects and those with physiological hypertrophy from those with pathological hypertrophy but will not discriminate between pathological hypertrophy of different aetiologies.

Intuitively, one would expect that any differences in myocardial performance between those with hypertension and those with HCM would occur in systole. It can be seen from Table 14 and Figure 12 that the systolic LV wall-to-cavity ratio is greater than normal in only 44% of the hypertensive group, far fewer than in the population with HCM. In order to explore this further, results from the group with hypertension and the group with HCM are compared further with regard to other measures of systolic function such as cubed ejection fraction, fractional LV wall thickening in systole (LVPWS/LVPWD) and the ratio of the systolic LV wall-to-cavity ratio: diastolic LV wall-to-cavity ratio referred to as the contractility index. Values of these parameters were significantly higher in the HCM group when compared with the hypertensive group (LVPWS/LVPWD p=0.0016, cubed ejection fraction p<0.0001, contractility index p<0.0001). Receiver-operator characteristic curves were used in order to ascertain the optimum cut-off points between the two populations for each measure. The results of the application of these cut-offs to both populations is shown in Table 15 and are illustrated in Figure 13 (cut-off values are shown with a dashed line).

The cut-off values shown above were designed to ascertain whether a subject had HCM or not and the best measure for this purpose would appear to be the contractility index with the highest detection rate for the lowest false positive rate. Caution is necessary to avoid over-interpretation of these results with the small sample sizes in this study but nevertheless a separation of the populations was seen.
FIGURE 12 A-D. WALL-TO-CAVITY RATIOS IN HYPERTENSIVE SUBJECTS AND THOSE WITH HCM

A. Septum-to-cavity ratio

B. Systolic LV wall-to-cavity ratio
C. LV wall-to-cavity ratio

D. Septum-to-LV wall ratio
TABLE 15. MEASURES OF SYSTOLIC FUNCTION IN HYPERTENSIVE SUBJECTS AND SUBJECTS WITH HCM

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut-off value</th>
<th>Positive results in HCM (n=24)</th>
<th>Detection rate (%)</th>
<th>Positive results in hypertension (n=16)</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic wall thickening (LVPWS/LWPWD)</td>
<td>&gt; 1.66</td>
<td>16/22</td>
<td>73</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Cubed ejection fraction (%)</td>
<td>&gt; 0.78</td>
<td>20</td>
<td>83</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Contractility index (SYSCAVR/LVCAVR)</td>
<td>&gt; 2.73</td>
<td>20/23</td>
<td>87</td>
<td>1</td>
<td>6.25</td>
</tr>
</tbody>
</table>

However, since systolic function may be linked with degree of hypertrophy the process has been repeated in 8 HCM subjects with diastolic septal thickness measurements equivalent to those of the hypertensive group (15-20mm). The values remained significantly higher in the HCM group when compared to the subjects with hypertension (LVPWS/LVPWD p=0.0049, cubed ejection fraction p=0.0037, contractility index p<0.0008). The results of the cut-off points applied to the hypertensive group and the modified HCM group are shown in Table 16. These results suggest that the differences in systolic function between the groups can not be accounted for by the degree of cardiac hypertrophy alone and, not surprisingly, suggests that the aetiology of the cardiac hypertrophy has an important influence on performance characteristics.

It might be anticipated that medication could influence systolic performance, especially beta-adrenergic blocking agents. 6/24 of the adult HCM group were on medication which included conventional doses of a beta-adrenergic blocker when their measurements were taken, whereas 9/16 of the hypertensive subjects were on medication at the time of the echocardiogram. Only two of the hypertensive subjects were on beta-adrenergic blocking agents, two subjects were on calcium antagonists, 7 subjects were on an angiotensin converting enzyme inhibitor and 4 subjects were on a diuretic. The hypertensive subject with a contractility index > 2.73 was in fact on treatment with a beta-adrenergic blocking drug, an angiotensin converting enzyme (ACE) inhibitor and a diuretic. The same patient also showed an ejection fraction > 0.78 along with another subject treated with an ACE inhibitor. The same patient again also showed a
FIGURE 13 A-C. MEASURES OF SYSTOLIC FUNCTION IN HYPERTENSIVE SUBJECTS AND THOSE WITH HCM

A. LV systolic wall thickening (LVPWS/LVPWD)

B. Cubed ejection fraction
fractional systolic LV wall thickening of > 1.66 along with the other patient receiving a beta-adrenergic blocking drug. In this sample population none of the 7 untreated subjects with hypertension fell above the cut-off points for any of the measures of systolic function. Since more subjects with HCM were on beta-adrenergic blocking agents in any case, this would also suggest that there is a genuine difference in systolic function between these two groups which cannot be explained on the basis of treatment alone. However, it must be remembered that the single hypertensive patient with a contractility index > 2.73 exhibited a value of 3.21 which is just below the mean for HCM subjects and on the 99% prediction limit for hypertensive subjects. This suggests that in a bigger sample size there may be a substantial overlap in the values of the contractility index such that the mean values of the two populations may still be significantly different but that any chosen cut-off point would offer insufficient sensitivity or specificity to be clinically helpful. Since it is possible to exclude hypertension clinically, the best approach may be to
make several blood pressure recordings prior to any treatment in subjects thought to have HCM followed by 24 hour ambulatory monitoring for those in whom high random readings have occurred.

**TABLE 16. MEASURES OF SYSTOLIC FUNCTION IN SUBJECTS WITH HYPERTENSION AND HCM PATIENTS WITH SEPTAL THICKNESS MEASUREMENTS OF 15-20 mm**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut-off value</th>
<th>Number positive in HCM population (n=8)</th>
<th>Detection rate (%)</th>
<th>Number positive in hypertensive population (n=16)</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic wall thickening (LVPWS/LWPWD)</td>
<td>&gt; 1.66</td>
<td>4/7</td>
<td>57</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Cubed ejection fraction (%)</td>
<td>&gt; 0.78</td>
<td>7</td>
<td>88</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Contractility index (SYSCAVR/LVCAVR)</td>
<td>&gt; 2.73</td>
<td>6/7</td>
<td>86</td>
<td>1</td>
<td>6.25</td>
</tr>
</tbody>
</table>
3.6 Magnetic resonance imaging (MRI) and echocardiography as imaging modalities in hypertrophic cardiomyopathy

3.6.1 Wall thickness measurements

Comparisons of MRI and echocardiographic measurements of the left ventricular wall thickness at the level of the tips of the mitral valve/chordae are shown in Figure 14; the closer of the two echocardiographic estimates to the MRI measurement (M-mode or cross-sectional) is individually illustrated in figures 14A-D. The differences between the techniques were calculated by subtracting the echocardiographic measurement from the MRI measurement in each case. From this the mean difference (d), standard deviation of the differences (s) and 95% limits of agreement (d±2s) were calculated. Only 9 patients are compared with regard to the anterior left ventricular free wall measurements due to unsatisfactory echocardiographic prints from this area in one patient. Other results are shown in Table 17.

Anterior interventricular septum

The excellent agreement between the M-mode echocardiographic and MRI measurements of the AIVS is shown in Figure 14A. There was no significant bias between the techniques with a mean difference of 0mm and the narrowest 95% limits of agreement (-1.5 to +1.5mm) obtained for any comparison of wall thickness. This represents a variation of -6 to +6% around the mean measurements. The comparison of MRI with cross-sectional echocardiography is shown in Table 16. The 95% limits of agreement (-2.4 to +1.7mm or -4 to +10% variation around the mean measurements) are slightly wider than with M-mode echocardiography.

Posterior interventricular septum

The comparison between MRI and cross-sectional echocardiography measurements is shown in Figure 14B. Again, there is no significant bias between the two techniques with a mean difference of 0.27mm. The 95% limits of agreement are wider than with the AIVS -2.4 to +2.9mm (-9 to +14% variation around the mean measurements).

Posterior left ventricular free wall

M-mode and cross-sectional echocardiographic measurements compared virtually equally with MRI in this case. The comparison between wall thickness estimates from cross-sectional echocardiography and
FIGURE 14 A-D. BLAND-ALTMAN PLOTS COMPARING WALL THICKNESS MEASUREMENTS MADE BY MRI AND ECHOCARDIOGRAPHY

A. Anterior interventricular septal thickness

B. Posterior interventricular septal thickness
C. Posterior left ventricular free wall

D. Anterior left ventricular free wall
MRIs shown in Figure 14 C as it has slightly narrower 95% limits of agreement than the comparison with M-mode echocardiography. There is no significant bias between the two techniques with a mean difference of -0.44mm with 95% limits of agreement of -3.4 to +2.5mm. However, there is a slight suggestion from this graph and the one comparing M-mode echocardiography with MRI (not shown), that echocardiography tended to give higher estimates of the thickness of thinner walls and lower estimates of the thickness of thicker walls when compared to the MRI values.

**Anterior left ventricular free wall**

Figure 14 D shows the comparison between cross-sectional echocardiographic and MRI measurements of the ALVFW. There was no significant bias between the two techniques with a mean difference of -0.4mm and 95% limits of agreement of -2.4 to +1.7mm (-13 to +5% variation around the mean measurements).

**Left ventricular end-diastolic dimension**

The comparisons of M-mode and cross-sectional echocardiography with MRI are very similar (table 16). There is a small positive bias in the comparison of both types of echocardiography with MRI and similar 95% limits of agreement.

**TABLE 17. DEGREES OF BIAS AND LIMITS OF AGREEMENT BETWEEN MEASUREMENTS MADE BY MRI AND ECHOCARDIOGRAPHY**

<table>
<thead>
<tr>
<th>Type of Echocardiography</th>
<th>Site of measurement</th>
<th>Bias between MRI and Echo</th>
<th>95% limits of agreement of the differences</th>
<th>% variation around the mean measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M-mode</strong></td>
<td>Posterior left ventricular free wall</td>
<td>0.22 mm</td>
<td>-3.3 to +2.9 mm</td>
<td>-26 to +12%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular end-diastolic dimension</td>
<td>1.2 mm</td>
<td>-5 to +8 mm</td>
<td>-8 to +15%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular mass</td>
<td>-117.7 g</td>
<td>-291 to +56 g</td>
<td>-66 to -5%</td>
</tr>
<tr>
<td><strong>Cross-sectional</strong></td>
<td>Anterior interventricular septum</td>
<td>-0.36 mm</td>
<td>-2.4 to +1.7 mm</td>
<td>-3 to +9.4%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular end-diastolic dimension</td>
<td>1.9 mm</td>
<td>4.1 to +8 mm</td>
<td>-8 to +17%</td>
</tr>
</tbody>
</table>
3.62 Left ventricular mass (LVM)

The range of LVM estimates using MRI was 119g to 261g in systole and 118g to 260g in diastole (observer 1). The range using M-mode echocardiographic estimates from the Devereux formula was 189g to 599g. Results in the table show that in HCM extrapolation of M-mode measurements using the Devereux formula greatly overestimates the LVM when compared to MRI measurements with a mean difference of -117g and 95% limits of agreement -291 to +55.5g (a variation of -66% to +6% from the mean measurements). There was no significant difference between the MRI estimates of LVM in systole or diastole with a mean difference of -1.6g and 95% limits of agreement of -20 to +17g (a variation of -12 to +6% around the mean measurements; observer 1).

**FIGURE 15. BLAND-ALTMAN PLOT SHOWING THE INTEROBSERVER VARIABILITY OF THE MEASUREMENT OF LV MASS USING MRI**

In addition, there was no significant difference between the measurements by observer 1 and observer 2 of LVM in either systole or diastole. The differences obtained with the diastolic measurements are shown in Figure 15. There was a mean difference of -2.3g with 95% limits of agreement of -9 to +5g (a variation of -5 to +1% around the mean measurements). In comparison, the mean difference in systole was 2.7g with 95% limits of agreement of -7 to +12g (a variation of -3 to +6% around the mean measurements).
4. DISCUSSION

4.1 The normal population

4.11 M-mode echocardiography

The limitations in resolution of two-dimensional cross-sectional (2D) echocardiography particularly towards the lateral borders of the scanning sector has been described by several authors (113, 137, 293). A range resolution of 2mm with an azimuthal resolution of 2-5mm has been quoted (113) which will clearly affect wall thickness measurements and will produce a larger error in children whose walls are much thinner. M-mode echocardiography offers the advantage of a 1mm (153) image resolution with a beam which can now be accurately placed using two-dimensional image guidance. In addition, two-dimensional cross-sectional images are often analysed on screen in freeze frame mode with the use of electronic callipers. The quality of these images is unavoidably degraded optically compared with the real-time display (403) and they do not offer the clarity of M-mode prints. Indeed it is thought that 50% of the video information drops out in the video freeze frame mode. However, two-dimensional echocardiography does offer invaluable information on the distribution of the hypertrophy in individual patients and is relied upon to assess the magnitude of hypertrophy in those areas inaccessible to the M-mode beam. But for those areas such as the anterior ventricular septum, posterior left ventricular wall and left ventricular end diastolic diameter (LVEDD), which are both highly accessible to the M-mode beam, the two-dimensionally guided M-mode technique offers advantages. Three dimensional (3D) echocardiographic techniques have shown the parasternal long axis view to be more robust in terms of probe placement and optimal imaging compared with the parasternal short axis view (309). The wall-to-cavity ratios in this study were therefore acquired using M-mode echocardiography from this view and not from the parasternal short axis view.

4.12 Normal ranges

It was initially hoped that the wall-to-cavity ratios would be independent of age. However, there appears to be a biphasic relationship although the numerical differences are small. This justifies a slightly higher normal reference ranges particularly for infants < 1 year. The reasons for this may, in part, be understood by looking at the variation of the individual components of the ratio with age.

Figure 1 shows that the left ventricular end-diastolic diameter (LVEDD) rises more steeply in early life than subsequently and that it rises more steeply than does diastolic septal thickness particularly in the first
year. In fact, the linear regression of the diastolic septal and LV wall thickness versus age is not significantly different to zero in the first six months of life. This may be because the right ventricular contribution to total septal thickness is high at birth and reduces in response to the postnatal fall in right ventricular pressure. This results in little apparent growth in this structure in the first six months providing a relatively constant numerator for the septum-to-cavity ratio. Conversely, the relationship of LVEDD to age in the first six months of life is not significantly non-linear (p=0.8 runs test) but shows a slope of 1.5 which is significantly different to zero (p=0.0005). This suggests that the small but rapidly increasing left ventricular end diastolic diameter in early life results in high initial values of the septum-to-cavity and diastolic LV wall-to-cavity ratios which subsequently fall. By the age of approximately 3 years the rate of rise of the LVEDD slows (Figure 1C) and that of the septal and diastolic LV wall thickness is relatively steady (Figures 1A+C) resulting in smaller changes in the septum-to-cavity ratio and LV wall-to-cavity ratio thereafter. The subsequent slow rise in both diastolic ratios from 3-5 years onwards may be related to the slow increase in systemic blood pressure that occurs throughout childhood, as it appears to cease at about the same time as adult blood pressure levels are reached.

The relatively small size of the LVEDD in early life and the rapid subsequent growth may, in part, be explained physiologically as the adaptation of the left ventricle (LV) to the additional volume of the systemic circulation following birth. Henry et al (69), using their derived formulae for BSA related cardiac measurements, also noted that some myocardial properties were different in early life compared with subsequently. Neonates showed clustering of values at or around the lower 95% prediction limit for measurements of LVEDD, LV wall thickness in systole and diastole, % systolic thickening of LV wall and ejection fraction. They postulated that this could be due to bypassing of the left atrium (LA) and LV during foetal life which would result in failure of the myocardial properties to concord with the relationship to body surface area in the first month of life (69). Both these observations and those made in this thesis concerning the change in absolute left ventricular measurements in the first 6 months of life suggest that the formulae derived by Huwez et al (318) are not valid for those subjects less than 6 months old.

Systole appears more complicated. Initially in the first 3 months of life the systolic LV wall thickness rises sharply in a linear fashion with a slope of 1.32 (p=0.0023) whilst the values of LV end systolic diameter (LVESD) have no significant slope (p=0.30). This means that at a time when the LVEDD is rapidly growing the LVESD remains more or less the same. This can only be achieved by an enhanced systolic performance and it is therefore not surprising that values of relative LV systolic wall thickness also grow rapidly in early life. The enhanced systolic performance seen in early life may be because these subjects are more likely to be anxious and unsettled during the examination resulting in increased sympathetic nervous activity. By the age of 2.5 years the slope of both the LVPWS and the LVESD lessens providing a relatively narrow range of normal values for systolic LV wall-to-cavity ratio at older ages.
There is a clinical need for a simple but reliable way of representing single or sequential age related cardiac measurements, which are valid in children, where continual cardiac growth makes assessment difficult. In studies where LV dimensions and wall thickness measurements were related to body surface area (BSA) (314, 317) or the square and cubed roots of BSA or weight (69, 286) the BSA has to be calculated followed by the squared or cubed root, followed by reference to complicated nomograms with wide normal ranges. Most of these data were also compiled using stand-alone M-mode transducers. For example, a 6 year old child with an average body surface area of 0.8m$^2$ is permitted a measurement of diastolic septal thickness of 5.7-8.2mm and an average man of 70 kg and 1.75m tall with a BSA of 1.9m$^2$ may have a measurement of 7.9-11.6mm (69). Despite the significant difference in size there is still some overlap in the permitted wall thickness measurements, which are considered in isolation from cavity diameter. Disproportionate septal or left ventricular wall thickening may be missed in these circumstances. For the same subjects ranges for the LVEDD are 3.18-4 cm in the 6 year old child versus 4.41-5.41cm in the adult male. It might be concluded that LVEDD is a better discriminator of age and size related cardiac growth than septal thickness since there is less overlap of the normal ranges at different subject sizes. This suggests that it should be included in any assessment of normal or abnormal cardiac growth at all ages.

Henry et al re-analysed their data on normal subjects (158) following the introduction of the American Society of Echocardiography standards (296) and produced nomograms based on weight as well as BSA. In addition, an independent effect of age was acknowledged and was incorporated in to the regression analysis. However, the normal ranges given by the new nomograms were still wide with the range for septal thickness in a 20kg (6 yr. old boy) of 5.3-7.8mm overlapping with that allowed for a 70kg man (7.5-11.2mm). A more recent study by Huwez et al (318) published data on 127 normal subjects from the age of 7 months to 19.5 years and derived formulae to derive wall thickness and cavity size dimensions from age or body surface area. But this still requires cumbersome calculations for each individual measurement and may not be valid for infants < 7 months old. Indeed it has already been discussed (above) that data from this thesis and from others (69) suggest that the relationship between cardiac measurements and age or BSA is different in early life.

The expression of wall thickness and cavity size as a ratio has been explored previously when the law of Laplace has been the rationale for the cultivation of formulae to predict LV pressure from wall thickness and cavity radius measurement. Ford (404) described that the normal inverse relation between end-diastolic radius/thickness ratio (R/Th) and systolic pressure is approximated by the equation R/Th = 1/0.0027P where P is left ventricular systolic pressure and that in normotensive subjects this ratio averaged $3 \pm 0.7$ (mean $\pm 2$ sds). Expressed in terms of septum-to-cavity ratio this would give a normal range of 0.14 - 0.22 which is similar to the normal adult ranges quoted in our study.
Bennett et al (405) and Aziz et al (406) also made careful studies of the relationship between LV systolic pressure and the ratios of systolic and diastolic wall thickness measurements to systolic diameter or diastolic radius measurements. The application of such measurements to the assessment of aortic stenosis was described. However, these observations were also made without two-dimensional echocardiographic localisation of the M-mode beam and without two-dimensional visualisation of the aortic valve and no normal values for the ratios in childhood were published. Moreover, this approach to the assessment of aortic stenosis has largely been superseded by two-dimensional image guidance of direct Doppler measurements. However, the principle of considering the thickness of the left ventricle in the context of a particular cavity dimension both in normal subjects and in those with aortic stenosis was found to be of value.

The wall-to-cavity ratios in this thesis take account both of left ventricular wall thickness and cavity diameter in the assessment of age related cardiac growth. The importance of LV diastolic diameter in the discrimination between pathological and non-pathological LV hypertrophy has been clearly shown. These ratios offer a simpler and quicker approach to the assessment of normal age related cardiac growth compared with previous methods which is extremely useful to the busy clinician and as such represent an advance.

4.13 Gender variation

The wall thickness and cavity dimension data from adult males and females in this thesis show that values are significantly larger in males than females which is in keeping with previously published normal data (95, 141, 142). However, many subsequent studies have employed a single wall thickness measurement as the cut-off of for normality irrespective of gender (158, 311) and echocardiographic studies of individuals and kindreds with hypertrophic cardiomyopathy (HCM) give single diagnostic wall thickness measurements in adults (45, 113, 135-137, 139). The advantage of wall-to-cavity ratios is that there are no significant differences in values between males and females at any age. This is illustrated for adults in figure 3. This means that a single value for the upper limit of normal, valid for both sexes, is possible along with a single diagnostic cut-off value for the diagnosis of hypertrophy. This offers much to the busy practising echocardiographer and cardiologist and as such also represents an advance.

4.14 Body surface area (BSA) variation

Previous studies have described ways of deriving wall thickness and cavity dimension size from body surface area as described above (69, 158, 314). But some authors have reported that in adults the relationship of cardiac dimensions with BSA is very weak and other authors have reported that in neonates
there is a trend for the cardiac wall thickness and diameter measurements to increase with weight (292) whilst others reported no relationship with weight or BSA in this sub-group (320). The wide normal ranges allowable for a given surface area has already been alluded to above. Thus normal ranges related to BSA are not straightforward. Wall-to-cavity ratios are examined in relation to body surface area in adults and children aged between 0.15-39 years in this thesis. There is no significant relationship between BSA and septum-to-cavity ratio or diastolic LV wall-to-cavity ratio in any of the age bands quoted in Table 2. There is a significant slope to the regression line of systolic LV wall-to-cavity ratio against BSA in adults but this is small as can be seen in figure 4 and table 4 and is not easy to explain. The absence of any relationship of the diastolic ratios to BSA offers significant advantages since it completely avoids the task of computing BSA followed by either reference to nomograms or further computation using complex equations. Instead a simple reference table with the normal ranges such as that shown in Table 2 can be displayed and easily referred to on the basis of age alone. Indeed, certain important diagnostic values such as a septum-to-cavity ratio >0.26 for HCM can be committed to memory.
4.2 The diagnosis of hypertrophic cardiomyopathy (HCM).

Until now the diagnosis of HCM has been made in two ways. The first revolved around the presence of asymmetric septal hypertrophy with a septum-to-posterior LV wall ratio of $\geq 1.3$ (15, 16, 18) or $\geq 1.5$ (110, 111) but the lack of sensitivity and specificity of this approach has been discussed in chapter 1.1. The second was dependent upon the presence of increased diastolic wall thickness measurements of $\geq 15\text{mm}$ (45, 113, 136-138) or $\geq 13\text{mm}$ (139) both of which are inapplicable to children.

The upper limit of normal given for diastolic LV wall thickness in adults is either 11mm (311) or 12mm (95, 158) irrespective of gender. In this thesis the upper 99% prediction limit for diastolic septal thickness is 11.1mm for females and 12.4mm for males. Since large normal populations have been studied in order to define these normal ranges, which are consistent to within 1mm between authors, it would be incorrect to bridge the gap between normality (12mm) and HCM (15mm) by allowing a greater wall thickness measurement in the normal population. It is more likely that the diagnostic value of $15\text{mm}$ for HCM should be lowered, perhaps more so for women than for men. Support for this approach is provided by data from the CARDIA study (45). In this study the prevalence of HCM was found to be 0.17% using a diastolic LV wall thickness of $\geq 15\text{mm}$ as the diagnostic test. However, the disease was found in 2.9 times as many males as females. This is not readily explained for a disease with autosomal dominant inheritance and suggests that this diagnostic test is insufficiently sensitive particularly in the female population.

Doi et al (166) compared echocardiographic features from 70 patients with HCM aged 12-70 years with 36 normal subjects aged 14-61 years. Some of the results from the study from Doi are shown in Table 17 along side those from a study by Maron et al and those from this thesis. Doi et al showed that an absolute septal thickness measurement of $< 13\text{mm}$ was still compatible with the diagnosis of HCM, but despite this diagnostic strategies have continued to focus on this or a higher value of absolute wall thickness as the diagnostic cut-off (45, 46) irrespective of age and gender (113).

Initially, in order to assess the performance of the wall-to-cavity ratios as diagnostic tests for HCM, an unambiguous population was chosen in whom the diagnosis of HCM would not be in dispute since all subjects showed maximal LV wall thickness measurements of $\geq 15\text{mm}$ in adults and substantially $> 2\text{sds}$ above weight for children. By comparing the values of cardiac dimensions and cubed ejection fraction in adults from the control and disease populations the importance of a small left ventricular diameter as a characteristic of the disease phenotype is shown (figure 5). This has been the subject of comment from previous authors (45, 129, 166) but none have then proceeded to incorporate this feature in to a diagnostic test. Since an increased wall thickness and a small left ventricular cavity are both important phenotypic features of the disease, it was anticipated and has been confirmed that the incorporation of both measures
in to a single parameter provides improved diagnostic sensitivity when compared to the use of either measurement separately.

**TABLE 18. COMPARISON OF ECHOCARDIOGRAPHIC MEASUREMENTS USED TO DIAGNOSE HCM**

<table>
<thead>
<tr>
<th>Echocardiographic features</th>
<th>Doi et al (166)</th>
<th>Maron et al (113)</th>
<th>Devlin and Ostman-Smith</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td>Sensitivity %</td>
</tr>
<tr>
<td>Septal thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 13mm</td>
<td>83</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>≥ 15mm</td>
<td>70</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>IVS/LVPW ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1.3</td>
<td>91</td>
<td>56</td>
<td>78</td>
</tr>
<tr>
<td>≥ 1.5</td>
<td>79</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>LVESD &lt;25mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEPCAVR &gt;0.26</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SYSCAVR &gt;0.63</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LVCAVR &gt;0.23</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Moreover, a recent study which examined the influence of left ventricular cavity size on the clinical presentation in HCM (196) showed that the LV cavity size was significantly smaller in those with functional limitation irrespective of obstruction or hypertrophy and was the only independent predictor of syncope. Therefore, the inclusion of cavity size as a component of the phenotypic assessment of the disease would seem advisable both on structural and functional grounds.

Likewise, systolic hypercontractility as measured by cubed ejection fraction is also shown to be a functional characteristic of the disease phenotype (figure 5) and has been recognised by other authors (2, 45, 110, 190). The concept of measuring the degree to which the left ventricular wall thickens during systole has previously been explored angiographically in animals using an intracardiac stainless steel transducer (407) and in humans using triple layered colour coded photographic material (408). These methods showed a good correlation to subsequent angiographic determination of ejection fraction (284) in valvular and myocardial disease. The systolic LV wall-to-cavity ratio described in this thesis combines
one element of systolic wall thickening (the LV wall thickness in systole) with one element of the ejection fraction (LV end systolic dimension) to produce a single measure which reflects both the hypercontractile nature of the myocardium in HCM and the diminutive size of the contracted chamber.

A septum-to-cavity ratio >0.26 provides a single diagnostic test for HCM for subjects > 1 year of age which incorporates both diastolic wall thickness and cavity size measurements. It is not surprising therefore that it provides 100% diagnostic sensitivity when applied to a population defined by increased wall thickness alone. It also provides 0% false positive rate in the normal population. A systolic LV wall-to-cavity >0.63 also provides 100% diagnostic sensitivity for the diagnosis of HCM in subjects > 1 year of age with a 0% false positive rate. Both ratios represent a new approach to the diagnosis of HCM which is shown to provide diagnostic sensitivity at least equal to accepted wall thickness criteria and superior diagnostic sensitivity to a septum to LV wall ratio of 1.3 or 1.5 (Table 7) in a population with undisputed HCM.

4.21 Diagnosis in childhood

In 1997 new diagnostic criteria for HCM were proposed (138) which included a new diagnostic measure for HCM in children < 10 years old. This measure was a body surface area corrected left ventricular wall thickness of >10mm. However, it was then emphasised in the paper that the absence of this feature does not exclude the disease. Consequently, the diagnosis in children continues to be made on the basis that an individual child has a maximum diastolic wall thickness > 2sds larger than that described for BSA, weight or age (158, 316, 318). Septum-to-cavity ratio and systolic LV wall-to-cavity ratio have been shown to provide at least equal diagnostic sensitivity and specificity compared to these accepted criteria in the population of children with HCM in this study. The ratios are far less cumbersome to use which should appeal to the busy practising clinician.
4.3 Screening for hypertrophic cardiomyopathy

There is an ever-increasing array of treatments available to those with HCM, from simple medical treatments which have been shown to improve morbidity and mortality (195) to electrophysiological approaches such as pacing (216-219) and implantable defibrillators (108, 222, 223), to even more invasive treatments such as septal myotomy-myectomy (232, 235, 236) and percutaneous septal ablation (224). Therefore, it can no longer be argued that the identification of subjects with this disease is futile due to the paucity of effective treatments (247, 267). Sudden death may be the presenting event in HCM particularly in children and Goodwin has argued a strong case for screening children in affected families where the potential for reducing sudden death is greatest (267). Indeed, there is emerging evidence that identification of affected subjects may lead to the prevention of sudden death particularly for those who engage in sports (409). Accordingly, efforts continue to be concentrated on the search for new tests and measures which identify affected individuals.

4.31 Echocardiographic screening

Clark et al (15) were among the first to use echocardiography to screen families for HCM and used a septum-to-posterior LV wall ratio of > 1.3 as the cut-off to identify affected members. In that particular study 46% of the first degree relatives studied were considered to be affected and thus the population was divided in the expected proportions for a disorder with autosomal dominant inheritance. However, a septum-to-LV wall ratio > 1.3 gave only a 55% probability of being affected in a study of known gene carriers (410) and asymmetric septal hypertrophy has been found in normal individuals (128, 166), athletic hearts (129), and different types of heart disease (18) as discussed in chapter 1. Conversely, symmetrical forms of HCM also exist, particularly in the athletic population where up to 43% of athletes suffering sudden death from HCM exhibited normal septum-to-LV wall ratios (71). These observations, together with the results in this thesis and previous papers (Table 17, chapter 4.2) show that this traditional wall thickness ratio is unreliable as a diagnostic or screening tool.

Two subsequent echocardiographic studies which screened kindreds with the disorder used maximal diastolic wall thickness ≥ 15mm as the diagnostic and screening test in adults and wall thickness measurements greater than those in the BSA related nomograms by Henry (158) as the screening test for children (135, 159). In the earlier study (135) the disease was thought to be familial in only 56% of the kindreds and sporadic in 44% and in the later, almost identical study (159), only 54% of disease was thought to be familial. Those with wall thickness measurements of 13-14mm were not considered to be normal or abnormal therefore there was obviously concern that the cut-off of 15mm may have been too
high to identify all affected subjects. This is supported by the observation that 10% of the subjects classified as unaffected had abnormalities in the electrocardiogram (135). Interestingly, in both studies male relatives, particularly fathers of the probands, were more often affected than females and this was consistent when parents, siblings and offspring were analysed separately. The inexplicable excess male prevalence when using these diagnostic criteria in population based studies has already been discussed and is also observed in these earlier kindred studies. The subsequent identification of disease mutations means that it is now known that sporadic occurrence of the disease is rare (269) and in addition, the use of diastolic septal wall thickness measurements \( \geq 15 \text{mm} \) for screening, fails to identify known gene carriers (104, 262). This suggests therefore, that these earlier echocardiographic studies failed to identify some subjects who had inherited a disease mutation and that an absolute wall thickness measurement of this magnitude is insufficiently sensitive for this purpose.

Later, it was agreed at an international workshop (139) that a maximal wall thickness of \( > 13 \text{mm} \) should be used in the screening of adults under 60 years of age for the disorder. But the estimated disease penetrance using these criteria averages only 80% (139) and this lower cut off value of 13mm also fails to identify known gene carriers (104, 106, 140, 262). Yet since the mutations causing HCM clearly affect all myocardial cells, one might expect that there should be some phenotypic characteristic which identifies these hearts even in the absence of overt disease.

Our results suggest that, apart from septal hypertrophy and systolic hypercontractility, a small left ventricular end diastolic diameter is an important part of the phenotypic expression of the mutation, as it is clearly present in subjects with only very mild left ventricular hypertrophy. This view is supported by the finding that the mean left ventricular end-diastolic diameter of most patients with hypertrophic cardiomyopathy is below the 95% prediction limits for normal subjects even in childhood (Devlin and Östman-Smith, unpublished observation). It has been shown in this thesis that by using values of septum-to-cavity ratio \( > 0.26 \) and systolic LV wall-to-cavity ratios \( > 0.63 \), all adult family members with absolute wall thickness measurements \( \geq 13 \text{mm} \) are identified. But in addition, two female subjects with wall thickness measurements \(< 13 \text{mm} \) are also identified as having phenotypic characteristics consistent with HCM (chapter 3.3). Since the upper 99% prediction limits for diastolic septal thickness in females in this study was 11.1mm it is perhaps not surprising that some affected females might have wall thickness measurements between 11 and 13 mm. Furthermore, it is significant that in addition to identifying two individuals who would not have been identified using accepted criteria, a septum-to-cavity ratio of \( > 0.26 \) better separates first degree relatives into the expected proportions for an autosomal dominant disorder (46% affected of whom 42% were female) when compared to previous studies. Therefore wall-to-cavity ratios and in particular the combination of septum-to-cavity ratio and systolic LV wall-to-cavity ratio appear to offer a new and more sensitive approach to screening in kindreds known to have HCM.
New screening parameters for the detection of abnormal cardiac phenotype in adult members of families with HCM were proposed in 1997 (138). These involved numerous combinations of major and minor criteria, which were only applicable to adults (see chapter 1). No control group was described therefore the prevalence of the various subtle echocardiographic and electrocardiographic criteria in the normal population is unknown. This makes estimations of sensitivity and specificity impossible and surely by definition invalidates its use as a screening test. This thesis describes the distribution of values of all the wall-to-cavity ratios in infants, children and adults from the normal population before applying it in both a diagnostic and screening context in HCM. Thus some estimation of likely sensitivity and specificity can be made. In addition, the quoted paper acknowledged that minor echocardiographic abnormalities in first degree relatives of subjects with HCM were more likely to represent an abnormal phenotype. Implicit in this acknowledgement is the acceptance that a more sensitive phenotypic marker than those currently available would be desirable. Indeed, included within the proposed new minor criteria for abnormal phenotype is an anterior septal thickness measurement of 12mm which is below any previously accepted absolute wall thickness measurement for the diagnosis. However, if this feature combined with for example "redundant mitral valve leaflets" qualifies as "affected", the false-positive rate would be likely to be high in athletes and significant in the general population. These criteria are also inapplicable in children.

However, the importance of considering cavity size alongside wall thickness is alluded to in the paper by McKenna et al (138) when it is stated that a left ventricular wall thickness measurement of 12mm would have a higher "diagnostic power" in a woman 160cm in height and with a left ventricular end diastolic diameter (LVEDD) of < 45mm than in a man 180cm in height with a cavity of 55mm. However, normal values or guidance on how to interpret this observation for use in ones own practice are not given. Furthermore, the methodology and results which justify the claim of increased "diagnostic power" are unclear since the diagnostic power resulting from application of these criteria to a population with HCM or to family members is not given. The data in this thesis has however, validated the assumptions made by those authors regarding the increased diagnostic power offered by considering wall thickness measurements in the context of cavity size measurements, and goes on to include LVEDD as an integral part of the screening test. The two female family members in this thesis with diastolic septal thickness measurements < 13mm but with more than five other echocardiographic abnormalities, personify the hypothetical description of the female with a borderline septal thickness but small cavity (above) (138) and were labelled as abnormal using the ratios. This suggests that the septum-to-cavity ratio and systolic LV wall-to-cavity ratio may provide the instruments for obtaining the increased diagnostic power that they were seeking. In addition, the ratios offer a methodology along with normal ranges which are accessible for use by other practitioners.
Screening in childhood

In view of the rapid increase in hypertrophy that can occur in children with HCM (28) and the significant annual mortality which can result from HCM in this age group (48, 57, 195) there is a consensus that children at risk of developing HCM should be clinically screened every two years in childhood and annually through adolescence. Currently this is performed by measuring wall thickness alone followed by reference to cumbersome nomograms (158) or equations (318) as discussed previously (chapter 4.1 and 4.2). These methods yield wide normal ranges for a given BSA or age as illustrated in chapter 4.1 where it is discussed that the permissible wall thickness of an average sized 6 year old may overlap with that of an adult. Furthermore, a child is examined after intervals during which the heart will have grown and the challenge is to decide whether the heart has grown normally or abnormally.

Using BSA or age related nomograms provide separate snapshots of wall thickness measurements at each examination, which are considered in the context of a wide normal range. Since wall-to-cavity ratios show no variation with BSA and very little variation with age, the measurements from any single child can serve as a benchmark for subsequent examinations in that individual. In this respect, the septum-to-cavity ratio and systolic LV wall-to-cavity ratio not only offer a new diagnostic measure for HCM but also represent a new and useful tool for the sequential assessment of left ventricular hypertrophy in children. This should again be of considerable practical help to the busy clinician as well as correctly alerting them to the development of left ventricular hypertrophy at an early stage. These ratios have already been used successfully for this purpose to follow children with HCM and to assess regression of hypertrophy with treatment (194, 203).

Previous echocardiographic studies (135, 159) noted that consistently fewer offspring were considered to be affected when compared to either siblings or parents. This may in part be due to the disease becoming more evident with increasing age. However, it may also arise for the same reasons that were discussed in chapter 4.2. Wide normal ranges for wall thickness measurements are given by BSA derived nomograms with no reference to the size of the left ventricular cavity. This may miss some affected children with normal or only borderline hypertrophy. However, a cut-off value for septum-to-cavity ratio of >0.26 in first-degree relatives succeeded in separating both adults and children in to two groups in the expected proportions for a disease with autosomal dominant inheritance. This suggests that the septum-to-cavity ratio is able to identify an abnormal cardiac phenotype even in childhood.

The cut-off for septum-to-cavity ratio of >0.26 does, however, leave a grey area where subjects may be above the 99% prediction limit for age but still below the cut-off. This occurs primarily in the 3-5 year old age group who demonstrate the lowest values of septum-to-cavity ratio with an upper 99% prediction limit
of 0.22 (Table 2). Although this has not presented a problem in the families studied thus far, it is possible that mildly affected children may fail to be detected by septum-to-cavity ratio alone. In this group, as with the athletes, the combination of this ratio with systolic LV wall-to-cavity ratio will be valuable, as this offers increased specificity for the diagnosis of HCM. The data in this work suggests that carriage of a HCM-mutation should be suspected if the systolic wall-to-cavity ratio is >0.63 in any subject more than 1 year old and sequential echocardiographic monitoring advised. Likewise a diastolic LV wall-to-cavity ratio >0.23 makes further monitoring advisable. Using the ratios in combination will thus ensure that in children the evolution of an abnormal phenotype will not be missed.

In summary, wall-to-cavity ratios in general and septum-to-cavity ratio and systolic LV wall-to-cavity ratio in particular, provide an accurate echocardiographic diagnostic and screening tool for HCM which takes account of reduced LV cavity size and is readily available at District Hospital level. Furthermore, they can be used sequentially from childhood to adulthood since a value of >0.26 for septum-to-cavity ratio is above the 99% prediction limits for all normal subjects >1 year of age. Thus, they represent a new and valuable contribution to the echocardiographic screening for HCM at all ages, and appear to combine the highest detection rate and lowest false positive rate of any echocardiographic screening method described so far.

4.32 The electrocardiogram

Electrocardiographic (ECG) abnormalities have been shown to be present in known mutation carriers with echocardiograms judged to be normal by absolute wall thickness criteria (102, 104, 106, 140, 156). These abnormalities include left ventricular hypertrophy with repolarisation changes, isolated repolarisation changes with moderate to severe T wave inversion, and deep Q waves. These criteria were therefore all adopted as "major" criteria in the recently proposed screening criteria for first degree relatives (138). However, these features can all be seen in the context of other cardiac disease and in some cases in physiological hypertrophy. Moreover in other studies, one by the same author, the limited correlation between positive echocardiograms and ECG in HCM is discussed (97, 98) along with the failure of the ECG to show progression of the disease (99, 137). These studies led others to conclude that ECG alone was not suitable for making the diagnosis of HCM or for studying disease progression because of the low sensitivity and specificity of the technique (100).

Epstein et al (104) described minor ECG abnormalities in 5 out of 12 carriers of disease alleles whilst no abnormalities were apparent in the remaining 7. Clearly, knowledge of genotypic status of the subject permits more confidence in the interpretation of such minor and non-specific changes. This would not be the case in kindreds without known mutations in which minor abnormalities might appear with increasing
age. The electrocardiogram is also reported to be particularly valuable in detecting abnormal cardiac phenotype in children with evolving HCM (101) or in those known to have a mutation (139). However, in studies by Epstein et al (104) and Posen et al (140) 1/11 and 0/2 children respectively had ECG abnormalities in the presence of a mutant allele. This suggests that the electrocardiogram and the echocardiogram should be used side by side and not in isolation in the assessment of kindreds with HCM, as practised in most cardiac units already.

### 4.33 Genetic screening

The assessment of the wall-to-cavity ratios as screening tests is handicapped by the absence of any firm "gold standard" for in vivo diagnosis of HCM. The discovery of disease causing mutations has allowed some correlation between genotype and phenotype which has proved revealing and has not necessarily provided a "gold standard" for the in vivo diagnosis in the relevant kindreds as will be discussed.

In a review of kindreds known to have various mutations in the β-myosin heavy chain gene (403Arg>Glu, 949Glu→Lys, 453Arg→Cys, 584Gly→Arg, 606Val→Met, 924Glu→Lys) Solomon et al (410) compared echocardiographic features in those who had inherited the disease mutation and compared them to family members who had not inherited the mutation. A septum-to-free wall ratio of > 1.3 had a sensitivity of 77%, specificity of 93% for the identification of gene carriers which is similar to the assessments of sensitivity and specificity for the same ratio in our study and therefore suggests that we had correctly identified affected family members. Systolic anterior motion of the mitral valve and reversed septal curvature were highly specific with predictive values of 100% but had sensitivities of 62% and 79% respectively. Maximal wall thickness of 15mm or a septal-to-free wall ratio of 1.5 was associated with only a 75% probability of being affected and a septal-to-free wall ratio of ≥ 1.3 conferred a 55% probability of being affected (410). It appears therefore that these measures are weak phenotypic markers of mutation carriage and conversely that gene carriers do not necessarily show asymmetric septal hypertrophy.

Certain mutations such as 908Leu→Val, 256Gly→Glu and 403Arg→Tp are said to be associated with markedly reduced penetrance (104, 140, 262). But incomplete penetrance was said to have occurred if the maximum left ventricular wall thickness was <15mm (262) in some studies and <13mm in others (104, 106, 140) and the criteria by which children were evaluated were not stated. 39-77% of adult carriers with the same mutations are reported to have maximal diastolic wall thickness measurements of < 13mm (104, 104, 140, 262). It might therefore be concluded that this cut-off value is not sufficiently sensitive to detect the phenotype indicative of gene carriage and conversely that all gene carriers do not exhibit phenotypic features consistent with the disease.
This conclusion is supported in an editorial by Fananapazir and Epstein (262) in which it is suggested that left ventricular hypertrophy should not be assessed by reference to an arbitrary value of diastolic wall thickness, but should be assessed in the context of the wall thickness measurements of family members without the disease allele. The upper limit of normal for left ventricular wall thickness in the family with the 908Leu-Val β-MHC gene mutations was 12mm and that in the family with 256Ser-Oh β-MHC mutation was 14mm. It is noteworthy that some members of the latter family may have been assigned an incorrect disease label using traditional wall thickness criteria alone. The echocardiographic measurements for the 12 members of the kindred who had inherited the 908Leu-Val β-MHC gene mutation but whose maximum wall thickness measurements were less than 13mm are quoted (104). However, only two-dimensional echocardiographic methods are described in this paper and the use of this without M-mode echocardiography may explain some of the strange results. For example, in three subjects the left ventricular end systolic diameter was larger than or the same size as the left ventricular end diastolic diameter. One must be guarded therefore about the interpretation and validity of the other measurements.

Furthermore, absolute wall thickness measurements based on the upper limit of normal in a particular kindred offers nothing to families where not all of the family members can be examined and takes no account of the size and gender of the individual. The lower cut-off of >13 mm will also yield false positive examinations in some athletes (129, 374). The principle underlying the use of wall-to-cavity ratios is that the wall thickness is not considered in isolation or in direct comparison with other individuals but in the context of the cavity size of the same individual. This will control both for the size and sex of the individual and allow an individualised assessment to be made.

As recently discussed by McKenna et al (138), the great genetic heterogeneity in HCM and the varying degree of penetrance of some mutations, means that in some instances the presence of a specific mutation merely reflects increased susceptibility to the disease necessitating close echocardiographic monitoring. Furthermore, 50% of families with HCM do not have an identified mutation and are therefore offered nothing by these molecular techniques, leaving them with echocardiography as the essential diagnostic and screening tool. Accordingly, the presence of a mutation per se cannot be considered the gold standard for the diagnosis of overt HCM. Moreover, the laboratory techniques for screening for an unknown mutation are only available in selected research laboratories, and it remains technically demanding, unless the family is big enough for linkage analysis (3 or 4 affected members) (247). Since relatives of individuals with this disorder have a one in two chance of being affected it is felt, by some investigators experienced in the identification of disease mutations, to easily justify clinical screening but only in some circumstances to justify genetic screening for a mutation (247). The technically demanding work involved in attempting to identify a known mutation in a single affected individual is not thought to be justified by its clinical usefulness (247). The screening of specific populations such as athletes for the presence of mutations responsible for HCM is therefore also not a feasible option and any investigation of such
populations would be undertaken using echocardiography. It is not surprising therefore that attention has returned to the search for more sensitive echocardiographic and electrocardiographic markers for the disease (138) since it is obvious that both techniques are not only necessary but are complimentary to the further molecular investigation of this disease.

4.34 Benefits of screening

Sudden death in a previously asymptomatic individual is a common presentation of HCM in children and in athletes (60, 71) therefore these groups would be most likely to benefit from any screening and preventative strategies. Where genetic testing is possible, the pre-clinical identification of subjects with mutations known to cause HCM will permit accurate prospective observation of disease progress thereby providing greater understanding of the natural history. A window of opportunity for the investigation of the effects of potentially preventative treatments would also be provided. Animal studies suggest that certain medical therapies may prevent or delay the development of left ventricular hypertrophy (202). Medical treatment with high dose propranolol (194, 195, 201), amiodarone (212) and verapamil (209) have all been reported to be associated with a low annual mortality in retrospective studies and regression of hypertrophy has been observed in some children with HCM (194, 203). The natural history of HCM caused by specific disease mutations and further description of genotype-phenotype correlation would also yield information about presenting clinical features, tendency to sudden death and response to treatments associated with particular mutations and would thus add another tier to the risk stratification model (58).

It has been shown using echocardiography that HCM can be rapidly progressive during childhood and adolescence in those whose echocardiograms were previously judged as normal on standard criteria (68). Therefore, suitable subjects for any intervention or treatment studies have and will continue to be identified without the use of genetic techniques. A recent retrospective study identified such subjects during childhood using echocardiography and showed a statistically significant improvement in survival in those treated with high-dose propranolol compared with either no treatment, or other treatment regimes, in patients matched for risk factors (195). The data in this thesis suggests that the echocardiographic measurement of septum-to-cavity ratio provides a powerful tool to identify candidates of all ages for preventative and treatment purposes, including susceptible family members in families where a genetic mutation has not been found. Furthermore, once treatment regimens had commenced, the severity, progression or regression of the disease at all ages could be monitored, as indicated by the successful use of the ratio to monitor children with HCM (194).

In addition, more accurate echocardiographic means of identifying phenotypic characteristics of HCM are crucial to progress in the identification of further disease mutations. This is because the process of linkage analysis requires a kindred in whom echocardiography has identified a minimum of 3 or 4 affected family
members. Potential disease loci are then explored and the appearance at these sites in affected individuals is compared with the appearance in unaffected individuals. Septum-to-cavity ratio and systolic LV wall-to-cavity ratio appear to offer a more sensitive echocardiographic tool for this purpose at all ages. This is shown by the separation of the first degree relatives in to more equal proportions of "affected" and "unaffected" compared to previous echocardiographic studies (135, 159) and by the inclusion of two subjects who fail to meet the diagnostic criteria based on absolute wall thickness measurements alone. The importance of identifying "mildly" affected individuals is that an individual with borderline left ventricular hypertrophy who has inherited a genetic mutation associated with a high incidence of sudden death (102, 264) may have a worse prognosis than an individual with a 32mm septum identified by all criteria as being abnormal but in whom the inherited mutation is associated with a benign prognosis (104, 263).

Early diagnosis has other advantages. If diagnosed in childhood, a child can grow up without competitive sporting ambitions rather than having these thwarted in adolescence when considerable success or expertise may have developed along with related career aspirations. It is reasonable to counsel against vigorous exertion since up to 40% of those < 30 years with HCM who die suddenly, do so during or after exertion (62) and therefore these individuals may be a group in whom death might have been prevented. In addition, regular medical assessment could be offered allowing symptoms to be identified and treated instead of ignored (271).

However, in any screening strategy the disadvantages of positive identification also have to be considered. The main disadvantage of early detection of the disorder are the subsequent restrictions, limitations and fear experienced by the individual who may never overtly express the condition and whose prognosis is uncertain. As discussed above the presence of a mutation may merely be a predisposing factor to hypertrophy in the presence of other factors and so its presence alone does not allow accurate prediction of phenotype or prognosis. Employment, life insurance and loans may all be affected by the knowledge, gleaned either by genetic or echocardiographic techniques, that an individual has or is susceptible to the development of HCM. However, most companies involved in the fields of life insurance and income protection ask for a detailed family history. The policy will become null and void if details of this are not revealed and therefore any history of a sudden death in the family due to HCM or any details of an affected family member will alert the companies to the 1 in 2 chance of the applicant being affected. These agencies are likely therefore, to make the necessary adjustments in risks and cost or reject the application altogether based on the family history alone. In the case of a particular employment such as that of an airline pilot, the candidate would be subjected to the most rigorous testing available with such a family history in any case. It may be therefore that the unaffected subjects (half of the first-degree family members) may achieve much benefit in these areas from knowing that they are not affected. In the case of the affected family members, it is likely that more knowledge regarding the natural history associated with
particular mutations, particularly the more benign ones, will assist them in these areas. For those with less benign mutations or with unidentified mutations, the development of accurate risk stratification profiles, access to detailed sequential phenotypic evaluation and the implementation of successful treatments will all help to modify the prejudice experienced by these individuals and may provide the necessary reassurance to the relevant institutions.

Despite these potential disadvantages, a very moving and honest account about the decision of one set of parents to have their new-born baby genetically screened for HCM (411) provides significant justification for offering screening of whatever type to families. The father of the baby in the article had himself been diagnosed with HCM at the age of 24 years following the illness of his sister. He had, since his teenage years, experienced difficulty with exercise and believed that earlier identification of the disease would have allowed him to better adapt his lifestyle. His wife wrote, "knowledge itself can be a kind of cure". They were in no doubt about having their daughter screened for the mutation since they perceived that this knowledge could bring only benefit to themselves and the baby. At the age of 4 weeks the baby was identified as a carrier of the disease mutation. The parents thought that this knowledge would enable them to have their daughter carefully assessed throughout life such that any problems or symptoms could be identified and treated early and that in the event of illness experts with full knowledge of her condition would be available quickly. They are aware that they may lose their daughter through the condition but feel that knowing about it from the start enables them to do the "very best for her" and that through knowledge and research the risks for her might be reduced. Not all families will feel the same, nor would they have made the same decision as the parents in the article but surely families and individuals should at least be offered screening of whatever type; it can be rejected if it is not wanted.
4.4 Physiological left ventricular hypertrophy

The difficulty in the differentiation of physiological from pathological hypertrophy has long been acknowledged (129, 362) and more recently McKenna et al (138) emphasised that the diagnosis of HCM in the presence of other conditions which may result in LV hypertrophy such as athletic training remains difficult and was outwith the scope of their article on new screening parameters for HCM. However, this differentiation is extremely important as HCM remains a common cause of sudden death in athletes (71, 72) and also the commonest cause of death during exercise in those < 30 years (74). The impact of excluding those with HCM from vigorous competitive sports was shown in a recent paper by Corrado et al (409) in which pre-participation screening of athletes resulted in a reduction of deaths from HCM.

The confusion surrounding the echocardiographic differentiation of physiological hypertrophy from HCM is well illustrated in a study by Maron et al (71) investigating the causes of sudden death in athletes. 6 of those identified as having hypertrophic cardiomyopathy showed symmetric LVH with septal-free wall ratio <1.3. 3/6 showed septal disorganisation and three did not, and in 4/6 echocardiographic evidence of HCM was shown in the relatives. Clearly neither the septum-to-free wall ratio nor histological evaluation seemed adequate to diagnose all 6 cases which had been identified by increased wall thickness measurements. Conversely, five subjects in the same study showed concentric LV hypertrophy with wall thickness measurements of 16-23mm and increased cardiac weights 420-530g. These subjects however, were considered not to have HCM by virtue of the absence of asymmetric septal hypertrophy, absence of disorganisation of muscle cells in the septum and absence of clinical or echocardiographic features of HCM in closely related family members. All of these features can be absent in HCM. Explanations for the "idiopathic concentric LVH" in these individuals included subtle features suggestive of mild mitral valve prolapse associated with fibromuscular hyperplasia of the artery to the atrioventricular node in one patient, isolated fibromuscular hyperplasia of the same artery in another patient and reduced coronary arterial distribution to the posterior wall of both ventricles. None of these features refute the diagnosis of HCM.

It was subsequently acknowledged that the use of the left ventricular septum-to-free wall ratio was insufficient to separate those individuals with HCM from athletes with significant physiological hypertrophy as a ratio of ≥1.5 occurred in 56% of those with hypertrophic cardiomyopathy, 18% of those with hypertension and 22% of athletes (117). In the same study it was noted that athletes showed normal systolic and diastolic function of the left ventricle and it was inferred that the presence of normal or exaggerated left ventricular systolic or diastolic function in a sportsman with LVH is useful evidence of non-pathological hypertrophy, even in the presence of ECG abnormalities, (129). An earlier study of subjects pre-and post an 11 week jogging programme noticed a reduced LV end systolic diameter and increased fractional shortening following training (358). However, the data presented in this thesis and in other studies (125, 131, 356, 364, 379) using other measures as well as ejection fraction, show that
exaggerated systolic contractility is not a regular feature of physiological hypertrophy but is a consistent feature in HCM. It is therefore anything but reassuring in the athletic group.

There is therefore, a need for a simpler and more accurate way of discriminating between physiological and pathological left ventricular hypertrophy than the presence of asymmetric septal hypertrophy or the presence of increased absolute wall thickness. The short-comings of the latter approach in the diagnosis of HCM have already been discussed and the same shortcomings such as there being no gender separation and no correction for body size also apply in the diagnosis of physiological left ventricular hypertrophy. The same difficulties are also encountered in childhood where a child may have a left ventricular wall thickness > 95th percentile for BSA, weight or age but may be exhibiting physiological hypertrophy and not HCM whilst a child with a lesser wall thickness in the presence of a diminutive LV cavity diameter may be exhibiting the HCM phenotype. The ECG can not be relied upon to differentiate between HCM and the physiologically hypertrophied heart as in the athletic heart voltage criteria for LVH may be met, slowed conduction and nodal or coronary sinus rhythm may be seen, there is an increased prevalence of incomplete RBBB as well as ST elevation and negative T waves in the lateral chest leads (356).

Previous studies including one by Fagard et al (372) noted increased wall thickness measurements and increased left ventricular end diastolic diameter (LVEDD) in athletes compared with age, sex, height and weight matched controls and considered these measurements in the form of ratios. The mean wall thickness-to-cavity radius ratio was the same for runners as in their control group but was elevated at a mean of 0.45 in the cyclists compared with their control group at 0.39. Since only 1 of the athletes in this thesis showed a septum-to-posterior wall thickness ratio of > 1.3 the septum-to-cavity ratio could be considered to be approximately half of the value of the mean wall thickness-to-cavity radius ratio. Therefore, the cyclists from the study by Fagard et al (372) would have a mean value of 0.45/2 = 0.225 which is not above the cut-off of normal suggested by this thesis and is virtually equal to the mean and median value of septum-to-cavity ratio of athletes in this thesis of 0.23 (see chapter 3.4). Unfortunately no standard deviation is quoted in the paper by Fagard et al. In fact in a more recent review article by the same author (412) converted values of mean wall thickness-to-cavity radius ratios to mean left ventricular wall thickness-to-cavity diameter ratios in long distance runners and swimmers from 3 other studies (1980 - 1987) range from 0.165 - 0.23. Such mean values in 3 studies of cyclists and triathletes (1984-1989) were 0.19 - 0.24, and in weight lifters and throwers (1980-1988) were 0.12 - 0.20, all within the normal ranges quoted in this thesis. In a more recent study involving weight-lifters (364) wall thickness-to-cavity radius ratios showed a mean of 0.42 (0.21 converted to mean wall thickness-to-cavity diameter ratio) and was above that of normal controls 0.36 (0.18) and endurance runners 0.39 (0.195). Septum-to-free wall ratios were again <1.3 in this study enabling the approximate comparison with wall-to-cavity diameter ratio to be made.
In Shapiro's study (130) the ratio of wall thickness-to-cavity radius (2PWT/LVEDD) was greater in athletes than in normal controls and increased with the standard of the athlete. The range of values was 0.27-0.57, which equates to values of 0.14-0.29 for wall thickness-to-cavity diameter ratios. This is remarkably similar to the range of values of 0.15-0.29 for the septum-to-cavity ratio for athletes in this thesis. Furthermore, 5/154 athletes in the study by Shapiro showed a wall thickness-to-cavity diameter ratio of >0.26, the cut-off for HCM in this thesis. All such athletes were of a national or international standard. Therefore, using septum-to-cavity ratio alone a 3.2% false positive rate for the diagnosis of HCM was seen in this athletic group which is better than the 7.7% false positive rate in the subjects in this thesis.

Comparison with more recent studies also demonstrates the validity both of the athletic group and the control group described in this study. The LV mass and LV mass index in the control group are not significantly different (p > 0.1) to that quoted in the healthy control group of 854 subjects from the Framingham study (354) and the measurements in the athletic group are not significantly different (p > 0.10) to those reported from a group of top athletes by Bjornstad et al (356). Indeed close comparisons can be made with the study from Bjornstad et al (356) who also examined a cohort of top athletes with a mean septal thickness 9.7mm (SD 1), mean LVEDD 5.21cm (SD 0.37), mean LVM of 244.4 g (SD 53.9) and mean LVM/BSA 138.2 gm^2 (SD 25.6). The equivalent data in the current thesis is; mean septal thickness 12 mm (SD 1.7), mean LVEDD 5.26 cm (SD 0.37), mean LVM 252 g (SD 58) and mean LVM/BSA 136 gm^2 (SD 21). Mean left ventricular wall thickness-to-cavity radius ratios were also calculated from Bjornstad's paper and were found to show a mean of 0.39 (SD 0.09). This equates to a mean wall-to-cavity diameter ratio of 0.195 but with an upper 95% prediction limit of 0.28 and compares well with such values from this work.

The athletes in the current work consist of a high proportion of top class rowers (62%), a group which are likely to have a higher false-positive rate for the diagnosis of HCM than any other sport. In a large study by Pelliccia et al (374) of 947 elite athletes, only 16 subjects had a wall thickness of 13mm or above, and 15/16 were rowers or canoeists. It was proposed in that study that pathological hypertrophy should be diagnosed by a diastolic left ventricular wall thickness >16mm in any sport, whilst lowering this to ≥13mm in athletes who were not rowers, canoeists or cyclists. However, this provides a very conservative cut-off based on values from a large proportion of males with large BSA. No separate cut-off is suggested for females who may exhibit pathological hypertrophy with a lesser wall thickness and no guidance is suggested for the evaluation of children. Furthermore, no strategy is described which will enable subjects with HCM with wall thickness measurements ≥13mm - 16mm to be differentiated from the athletes.
The average diastolic septum-to-cavity ratios calculated from the published measurements (374) were 0.18 for swimmers, cross-country skiers and pentathletes (the same as the average in the adult controls in this work), 0.19 for track event athletes and cyclists, and 0.20 for rowers and weight lifters (374). Interestingly though the LVM and LVMI in the athletic subjects in this study are significantly larger (p < 0.01) than those in the study by Pelliccia. Of the 16 elite athletes with maximum wall thickness >13mm in that study, only 3 had a wall-to-cavity ratio >0.26 giving a false-positive rate for the diagnosis of HCM of 0.32% from 947 athletes. As in our group, none of these subjects had systolic hypercontractility as defined by normal fractional shortening in their group (374) and by systolic LV wall-to-cavity ratios <0.63 in the group in this work. In contrast, the absolute septal thickness measurement of ≥ 13mm for the diagnosis of HCM would yield a 1.7% false positive rate in Pelliccia's study (374) and a yields a 22% false positive result in the adult athlete cohort in this thesis. This confirms that septum-to-cavity ratio and systolic LV-to-cavity ratio used in combination represent a new and improved echocardiographic method for the differentiation of physiological from pathological hypertrophy.

The 16 athletes identified by Pelliccia (374) were further examined by Maron et al (413) following a reduction in training for 6-34 weeks after Olympic competition. The maximum LV wall thickness reduced by 2-5mm (15-33%) in each case such that the measurements were all 11mm or less and thus fell within the normal range. LV mass decreased by 8-37% and LVEDD was unchanged. This confirms that in cases where the distinction between HCM and the athletic heart is difficult, reassessment following a period of de-conditioning is diagnostic. This is however, very disruptive to the training programme and fitness of the athlete who may be preparing for a major competition. The use of septum-to-cavity ratio and systolic LV wall-to-cavity ratio in combination will reduce the number of athletes for whom reassessment after a period of reconditioning is necessary.

This comparison and the comparison with the mean values from all of the studies quoted above suggests that the cohort of athletes in this thesis may be representative of the more severe end of the spectrum of physiological hypertrophy. This is useful in the evaluation of a new measure designed to discriminate between physiological and pathological hypertrophy since the sensitivity and specificity is unlikely to be over-estimated.
4.5 Cardiac hypertrophy secondary to hypertension

4.51 Hypertensive subjects and normal subjects

There is now extensive literature describing the increased risk of cardiovascular morbidity and mortality associated with the presence of left ventricular hypertrophy (340-343, 352). The presence of this feature is an independent cardiovascular risk factor, more closely correlated with outcome than blood pressure, cigarette smoking or total blood cholesterol (305, 306). Therefore, much time has been given to investigating the optimal way to define this feature. The electrocardiogram was the initial tool used for this purpose in studies such as the Framingham study (342) but this technique offers limited sensitivity (155, 348).

Attention therefore turned to echocardiography as a means for detecting cardiac hypertrophy. Left ventricular mass estimates using echocardiography were initially used. However, the relationship between LVM and age, obesity and systolic blood pressure is a continuous one (343). The use of LVM as the diagnostic criteria for LVH can underestimate the true prevalence of LVH because of the marked variation of LVM in the normal population. In addition, LV mass will not differentiate between physiological and pathological causes of hypertrophy (129). The data in this thesis would support this since five of the male hypertensive subjects showed values of both LVM/BSA gm$^{-2}$ and LVM/Ht gm$^{-1}$ below the upper limit of normal as defined in the Framingham study (131g/m$^2$ in males, 100g/m$^2$ in females) (354) whereas one male and three female control subjects and 8/12 male and 3/4 female athletes showed values above this. The greatest values of LVM/BSA m$^2$ in normal adult subjects in this thesis (n=38) were remarkably similar to the upper limits for normal obtained in the Framingham cohort at 110g/m$^2$ in females and 132 g/m$^2$ in males. Since there was no significant gender difference when compared (MWU p= 0.33) the group was considered as a whole for comparison with athletes and hypertensive subjects. Again 9/16 athletes on whom BSA data were available had values greater than 132g/m$^2$ as did only 6/16 of the hypertensive subjects. When the values of LVM/BSA m$^2$ from athletes were compared with those from hypertensive subjects there was no significant difference (MWU p=0.44). This was also noted in a study by Savage et al (351) when substantial overlap was noted in the values of septal thickness measurements among subjects with and without LVH defined on the basis of LVM. Septal thickness measurements were as high as 16-17mm in men, which is likely to represent significant LVH although they showed LVM values in the normal range.

Interestingly, in another study some of those with systemic hypertension classified as having a normal LVM went on to demonstrate a reduction in LVM on treatment (343). This is important since those with an LVM below the cut-off for LVH in whom concentric LVH is shown by an increased relative wall thickness are still at increased risk of cardiac events. Therefore, LV mass alone is an inadequate tool for
identifying those with significant left ventricular hypertrophy and subsequent efforts have concentrated on
the use of relative wall thickness ratios and LV mass in combination to define this feature (343, 352).

However, normal relative wall thickness measurements have been shown to occur in up to 50% of those
with hypertension defined as mean wall thickness-to-cavity radius ratio of < 0.45 (<0.225 if wall
thickness-to-cavity diameter ratio is used) and is said to represent an "eccentric" pattern of LVH (343,
351, 355, 388, 390). No such pattern was seen in the subjects with significant hypertension in this study
who all showed a concentric pattern of left ventricular hypertrophy. Of course, much depends on the way
in which the presence of hypertension is defined. The subjects in this thesis, although a small group, were
defined by ambulatory cuff recording away from the hospital setting and with a mean of 20 readings over
a 24 hour period. Continuous intra-arterial ambulatory monitoring has been shown to be better correlated
with LVM than casual systolic or diastolic readings (414). The technique employed in this thesis is also
known to correlate more closely with surrogate markers of morbidity such as left ventricular hypertrophy,
subclinical cerebrovascular disease, hypertensive retinopathy, microalbuminuria and to cardiovascular
outcome (399) as well as excluding cases of "white coat" hypertension.

15/16 subjects in the current work showed increased septum-to-cavity ratio, a measure of relative wall
thickness and the single subject who did not clearly had borderline hypertension with a mean reading of
140/93 and a septal thickness of 12mm. One study (343) which showed a high proportion of subjects with
normal relative wall thickness used a blood pressure of > 140/90mmHg on two separate occasions to
define their group of newly diagnosed previously untreated subjects. It is possible therefore that this study
included a large proportion of those with "white coat" hypertension. However, in common with the study
by Gosse et al (343) the magnitude of the blood pressure readings from the subjects in this thesis did not
show any relationship to any measure of relative wall thickness suggesting that the adaptive cardiac
response to a given blood pressure differs between individuals and is likely to be related to a number of
other factors.

Asymmetric septal hypertrophy is a recognised pattern of LV hypertrophy in chronic disorders such as
renal failure (415, 416), LV outflow tract obstruction (417) as well as in those with hypertension
suggesting that this may also represent a particular type of adaptive cardiac response. Asymmetric septal
hypertrophy with a septal-to-posterior LV wall > 1.3 occurred in 75% of the hypertensive subjects in this
thesis compared to 10% in the control population. Another population based study showed a rate of
asymmetric septal hypertrophy of 5% (351) and other studies of those with hypertension have shown rates
of 16-50% (132, 343). Previous studies have noted asymmetric hypertrophy to be a feature of either older
(351) or younger (418) patients with hypertension and others have found no age variation at all (343). In
addition, Safar et al (418) reported asymmetric septal hypertrophy in those with borderline hypertension
and symmetric hypertrophy in those with sustained hypertension. This, added to the report of Devereux et
al (419) who showed that LVH in hypertensive patients is correlated with blood pressure at work rather than with resting blood pressure suggests that asymmetric septal hypertrophy in borderline hypertension may result from abnormalities of the sympathetic nervous system. This may have implications for the choice of treatment in these patients with β adrenergic blockade being high on the list of possible approaches. These diverse findings suggest that the cardiac adaptive response to hypertension may not only differ between individuals for the same given blood pressure but that the type of ventricular remodelling may also be influenced by genetic or environmental factors.

Clearly, further larger longitudinal studies of hypertensive subjects identified by ambulatory recording are necessary to characterise the various adaptive cardiac responses and to ascertain the associated outcomes. As suggested by Devereux et al (353) partition values for any parameter, whether LV mass or relative wall thickness, should not be ascertained by simply describing the upper limit of such parameters in the normal population. Partition values should be found which separate those with an adverse prognosis from those without an adverse prognosis. Septum-to-cavity ratio may have a role in these studies as the measure of relative wall thickness. A value of > 0.26 was present in all of the subjects with significant hypertension in this study and did not occur in any normal subjects. Septum-to-cavity ratio is easier to calculate than mean wall thickness-to-cavity radius ratio and since asymmetric septal hypertrophy is a recognised pattern of left ventricular remodelling in hypertension, it would seem logical to optimise detection of hypertrophy by using this measure to reflect relative wall thickness.

The hypertensive subjects in the current work showed increased diastolic wall thickness measurements and reduced LV end diastolic diameter measurements when compared to normal subjects which has been noted by other authors (391). As such it is not surprising that measures of relative wall thickness were also increased. An LV wall-to-cavity ratio >0.23 was present in 13/15 (87%) of subjects with significant hypertension and a systolic LV wall-to-cavity ratio >0.63 was seen in 7/15 (47%). It is of interest that systolic hypercontractility is seen in approximately half of those with hypertension. Increased ejection fraction in those with hypertension compared with a control population has been reported by other authors (391).

4.52 Hypertensive subjects and subjects with HCM

The difficulty in the differentiation between the cardiac hypertrophy secondary to hypertension and that seen in hypertrophic cardiomyopathy has long been acknowledged (117, 123, 128, 138, 391, 420). Many groups have failed to identify a tool to differentiate the cardiac hypertrophy found in hypertension from that found in HCM. Gibson et al (132) concluded that no accurate differentiation could be made between the group with secondary LVH and those with HCM based on echocardiographic criteria and this was recently alluded to in another study of suggested screening measures for HCM (138). The situation has
remained largely unchanged with any definition of HCM including the proviso that the hypertrophy has to exist in the absence of any other disease known to cause left ventricular hypertrophy (45).

It is clear from the data in chapter 3.5 that none of the wall-to-cavity ratios could discriminate between hypertensive subjects and subjects with HCM. Since all of the patients with significant hypertension were identified by the abnormal septum-to-cavity ratio attempts were made to further discriminate only between subjects with values of septum-to-cavity ratio >0.26 and not to revisit the normal or athletic populations who would have been correctly classified by the combination of septum-to-cavity ratio and systolic LV wall-to-cavity ratio. The most obvious discriminating factor between those with HCM and those with hypertension was the difference in the systolic LV wall-to-cavity ratio. This is not surprising as those with hypertension are subjected to increased afterload in the form of systemic vascular resistance and those with HCM are not. However, since approximately 50% of the hypertensive subjects do have values above normal it might be concluded that adaptive concentric left ventricular hypertrophy may show systolic hypercontractility as a feature.

Contractility index (systolic LV wall-to-cavity ratio/LV wall-to-cavity ratio) was calculated as a further measure of systolic performance. It does this by setting a measure of systolic function against one of diastolic function. In this small study this measure was quite successful in separating those with hypertension from those with HCM even after adjustment to include subjects with similar septal thickness measurements from each group. However, the group of hypertensive subjects in this thesis is small and the graph in Figure 13 C suggests that in bigger populations of subjects with both disorders, the extent of overlap between the populations would be significant and probably too great to propose any cut-off in this measure as a reliable discriminatory test. It does, however, perform better at separating these two conditions than any measure considered in the literature to date and therefore warrants further exploration with larger sample sizes.

As such the proviso remains that HCM should only be diagnosed confidently in the absence of any other condition known to cause LV hypertrophy. From this thesis it can be concluded that any subject with an elevated septum-to-cavity ratio >0.26 should have hypertension excluded as the cause of the hypertrophy. In the case of a subject with elevated readings in clinic, ambulatory recording is helpful in discriminating between a subject with true hypertension and an anxious person who may have underlying HCM. Since the incidence of hypertension increases with age it is likely that a proportion of older patients with HCM will develop concurrent hypertension. Therefore, attention should be paid to serial blood pressure recordings in those with an established diagnosis of HCM, particularly over the age of 40 years.

The athletes who showed septum-to-cavity ratios > 0.26 were of the elite variety in a sport with a considerable isometric element and a history of such sporting attainment should be elicited. Furthermore,
it is important to draw attention to the observation that 50% of those with significant hypertension had elevated septum-to-cavity ratios and normal systolic LV wall-to-cavity ratios and consequently may appear similar to the very few athletes with mildly elevated septum-to-cavity ratio and a normal systolic LV wall-to-cavity ratio. It is particularly important therefore to exclude significant hypertension in these athletes. Septum-to-cavity ratio > 0.26 has been shown to be sufficiently rare in elite athletes in this thesis and from the study by Pelliccia et al (374) to lead to the suggestion that a 24 hour ambulatory recording should be carried out in such athletes before the hypertrophy can be classified as physiological with certainty.
4.6 Magnetic resonance imaging in the assessment of subjects with HCM.

MRI has been used in the evaluation of hypertrophic cardiomyopathy by other authors and has greatly improved detection of disease affected areas of the left ventricle compared with echocardiography (397, 398, 421). Comparisons of left ventricular mass and wall thickness measurements obtained by cross-sectional echocardiography and MRI in HCM have also been published (393, 421). However, transverse MR images and not short axis images were used to compare measurements of left ventricular mass (393) and axial, long or short axis plane MR images were compared to cross-sectional echocardiographic measurements without reference to the views or anatomical landmarks from which they were obtained (421).

In the study by Posma et al (397) 52 patients who had a diagnosis of HCM are reported. In three patients the MRI studies were incomplete and in 19 (37%) the echocardiograms showed inadequate echogenicity for assessment. True short axis images from both techniques are compared in 32 of 52 (62%) patients using hypertrophy scores. These were obtained from four 1cm thick short axis sections from base to apex. The methodology precludes quantitation of muscle mass and absolute wall thickness measurements are compared in a selective and non-standardised sampling method. It is not clear which of the four sections was employed in the direct comparison of absolute wall thickness estimates with echocardiography, and it was reported that MRI wall thickness values for “various” regions correlated well with those obtained by echocardiography. Furthermore, the differences between anatomically analogous measurements from two techniques are incorrectly illustrated by plotting one against another and obtaining a correlation coefficient. The shortcomings of this approach are clearly discussed by Bland and Altman (400) and alluded to by Posma et al in their results from the posterior free wall. In addition, two echocardiographic observers were used in their study introducing the possibility for inter-observer variability and neither M-mode echocardiography or estimates of left ventricular mass were discussed.

In the current work, wall thickness measurements using MRI and echocardiography were compared like for like at the level of the tips of the mitral valve or chordae and therefore this study achieves a more accurate examination of the agreement in values obtained using both techniques in HCM when compared with previous studies (393, 397, 421). In addition, comparisons involving both M-mode and cross-sectional echocardiography and LVM are examined.

Our results show that the best agreement between wall thickness measurements occurred with MRI and echocardiography at the anterior interventricular septum (AIVS) using M-mode echocardiography. This is not surprising because when the M-mode cursor is carefully placed on the parasternal long axis two dimensional image it will preferentially traverse the anterior ventricular septum which is closest to the transducer at right angles, providing a single plane linear image of the septal wall, the resolution of which
is in the region of 1mm (153). In cross-sectional echocardiography the edges of the AIVS are less clear as they are not linear, however a reasonable result was still obtained using this technique.

The posterior left ventricular free wall (PLVFW) is farthest from the ultrasound transducer and attenuation of the ultrasound beam may result in "drop out" of echocardiographic impulses both in M-mode and cross-sectional images (113). In addition, the PLVFW presents a concave surface in the antero-posterior direction and slopes towards the long axis of the heart to reach the apex. This presents a potential for partial volume averaging to affect the MRI estimate of the thickness of the PLVFW in a 1cm thick section. In contrast, the echocardiographic cursor measures wall thickness at a particular point where the cursor is perpendicular to the posterior free wall and the septum. All of these factors probably contribute to the wider spread of the measurement differences in this area of the ventricle.

Comparisons of the measurements of the posterior interventricular septum (PIVS) and the anterior left ventricular free wall (ALVFW) were also good. The spread of the differences concerning the PIVS was wider than with the AIVS. This may be explained by the increased distance from the echocardiographic transducer and the parallel rather than perpendicular orientation of the PIVS relative to the transducer resulting in reduced clarity of the endocardial and epicardial borders. The ALVFW could only be imaged in nine of the ten patients and is vulnerable to interference from the anterior chest wall and overlying lung. However, where echocardiographic imaging was possible a good agreement with MRI was achieved.

The comparison of LV mass shows a huge spread of differences between MRI and echocardiography. This is because echocardiographically determined LV mass is calculated from a single set of measurements entered into a formula which makes geometric assumptions concerning the shape of the ventricle and uniformity of wall thickness. This technique is clearly not applicable in HCM where considerable distortion of normal cardiac anatomy occurs. MRI measures LV mass by summation of sections of myocardium and has been shown to be both an accurate and reproducible technique (393). Figure 4 demonstrates our inter-observer variability using this technique which is excellent with only about 1% mean difference. Interestingly, the largest values of echocardiographic estimates of LV mass (g) in normal adult subjects in this thesis were 184g in females and 254g in males. Comparing these with the MRI estimates of LV mass in those with HCM it can be seen that 2/4 females and 6/6 males with HCM had values below these. In addition, 5/6 males and 1/4 females had values less than 2 sds above the mean for LVM (g) in males (194g) and females (140g) using data from the MRI study of normal subjects by Semelka (396) thus emphasising that LVM measurements are insufficiently sensitive to diagnose HCM.

In conclusion, MRI is a superior technique to echocardiography for the quantification of left ventricular mass in the abnormal ventricle as it does not make invalid geometrical assumptions. We agree with other studies that the inter-observer variability of this technique is excellent. In standardised views there was
good agreement between left ventricular wall thickness measurements obtained with MRI and echocardiography, although the discrepancies between the two techniques did grow with increasing distance from the echocardiographic transducer. The best agreement occurred between the MRI and M-mode echocardiographic measurement of the anterior interventricular septum. A current limitation of MRI is the time taken to determine manually left ventricular wall thickness and muscle mass. Fast, robust computer driven analysis programmes are required to make MRI a practicable option for cardiac assessment.

Both techniques will be important in the evaluation of therapies to reduce left ventricular hypertrophy. Echocardiography is far cheaper, more readily available and takes less operator time (approximately 45 minutes-1 hour for MRI) and could be used to rationalise the timing of sequential MRI scans. Serial echocardiographic studies will undoubtedly be the mainstay of monitoring treatment efficacy in any trials of subjects with HCM, therefore it is likely that changes in wall thickness measurements will be the most easily observed effect. Since HCM preferentially involves the AIVS and in addition this area gave the best agreement between echocardiographic and MRI estimates of wall thickness, it would seem logical to use changes in the echocardiographic measurement of this area to rationalise the use of MRI. All M-mode echocardiographic measurements of AIVS thickness were within a 3mm spread of the MRI measurements and therefore a change in thickness of ≥3mm using sequential M-mode imaging would be likely to result in a significantly changed MRI assessment of AIVS thickness. Since LVM is dependent upon the muscle and hence the thickness of the constituent parts, it is not unreasonable to assume that a significant change in this measurement would also be seen although this obviously requires more study.
BIBLIOGRAPHY


94. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. American Heart Journal 1949,37:161-86.
119. Bulkley BH. Idiopathic hypertrophic subaortic stenosis afflicted: idols of the cave and the

120. Larter WE, Allen HD, Sahn DJ, Goldberg SJ. The asymmetrically hypertrophied septum. Further

121. Goodman DJ, Harrison DC, Popp RL. Echocardiographic features of primary pulmonary


123. Maron BJ, Edwards JE, Epstein SE. Disproportionate ventricular septal thickening in patients with

disproportionate ventricular septal thickening in patients with coronary artery disease. Circulation

ventricular wall thickness in weight lifters: a problem with the definition of ASH. (abstr). American

126. Maron BJ, Henry WL, Roberts WC, Epstein SE. Comparison of echocardiographic and necropsy
measurements of ventricular wall thicknesses in patients with and without disproportionate septal

127. Wei JY, Weiss JL, Bulkley BH. The heterogeneity of hypertrophic cardiomyopathy: an autopsy and

128. Kansal S, Roitman D, Sheffield LT. Interventricular septal thickness and left ventricular

129. Shapiro LM. The differentiation of physiological from pathological left ventricular hypertrophy. In:
25-32.


131. Roeske WR, O'Rourke RA, Klein A, Leopold G, Karliner JS. Noninvasive evaluation of ventricular

132. Gibson DG, Traill TA, Hall RJ, Brown DJ. Echocardiographic features of secondary left

133. Lewis JF, Maron BJ. Hypertrophic cardiomyopathy characterized by marked hypertrophy of the
posterior left ventricular free wall: significance and clinical implications. Journal of the American College

134. Maron BJ. Asymmetry in hypertrophic cardiomyopathy: the septal to free wall thickness ratio


273. Latimer HB. The weight and thickness of the ventricular walls in the human heart. The Anatomical Record 1953;117:713-23.


346. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the


352. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Annals of Internal Medicine 1991;114:345-52.


Appendix

Publications in support of thesis


A comparison of MRI and echocardiography in hypertrophic cardiomyopathy

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Abstract. This study compares MRI and echocardiography as imaging modalities in hypertrophic cardiomyopathy, with particular reference to measurement of left ventricular wall thickness and mass. 10 subjects underwent echocardiography and MRI. Contiguous 10 mm short axis 35° flip angle cine gradient recalled echo MR images were acquired from the apex to the base of the left ventricle at 1.5 tesla. Standard M-mode and cross-sectional echocardiographic views of the left ventricle were obtained. Excellent agreement between measurements occurred with MRI and M-mode echocardiographic assessment of the thickness of the anterior interventricular septum (95% limits of agreement -1.5 to +1.5 mm). Other comparisons of MRI vs M-mode echocardiographic measurements had the following limits of agreement: posterior free wall -3.3 to +2.9 mm; end-diastolic dimension -5 to +8 mm, left ventricular mass -291 to +55.5 g. Comparing MRI with cross-sectional echocardiographic measurements, the limits of agreement were: anterior interventricular septum -2.4 to +1.7 mm, posterior interventricular septum -2.4 to +2.9 mm, posterior free wall -3.4 to +2.5 mm, anterior free wall -2.4 to +1.7 mm, end-diastolic dimension -4.1 to +8 mm. MRI estimates of LVM in systole vs diastole showed good agreement with 95% limits of agreement of -20 to +17 g, with excellent interobserver variability in diastole (-9 to +5 g) and in systole (-7 to +12 g). In conclusion, MRI is superior to echocardiography for the quantification of ventricular mass in the abnormal left ventricle because it does not make invalid geometrical assumptions. Comparisons of wall thickness show greater discrepancy with increasing distance from the echocardiographic transducer. This study suggests that sequential echocardiography could rationalize the need for MRI in left ventricular hypertrophy. A change in anterior septal thickness of ≥ 3 mm on echocardiography merits a further MRI study.

Hypertrophic cardiomyopathy (HCM), a disease with autosomal dominant inheritance, has an estimated prevalence of 0.2% in young adults [1]. Imaging of the heart remains an essential modality in the screening for and diagnosis of the disease since known genetic mutations can only be identified in as few as 50% of kindreds with the disease [2]. HCM has an annual mortality of 6% in children and adolescents [3] and is the commonest cause of sudden death in young athletes [4]. The extent of left ventricular hypertrophy in this disease and in hypertension is an independent and adverse cardiovascular risk factor [5-7]. Techniques which accurately measure left ventricular wall thickness and left ventricular mass will therefore be necessary to evaluate the effectiveness of treatment strategies in attenuating this feature of these diseases [8].

Echocardiography is used to evaluate left ventricular hypertrophy from any cause because it is a relatively cheap, rapid and reproducible technique [9] which accurately measures left ventricular wall thickness and cavity dimensions for both screening and diagnostic purposes [10-12]. Previous studies have shown good agreement between echocardiographic estimations of left ventricular mass and post mortem findings in normal hearts [13].

MRI is a reproducible technique and provides accurate measurements of left ventricular mass in ex vivo cadaver hearts [14, 15], hypertrophied canine hearts [16], and morphologically abnormal human left ventricles [17]. Serial images can be acquired in the short axis plane from which measurements of wall thickness can be made comparable to those obtained by echocardiography.

The purpose of this study was to compare the measurements of left ventricular wall thickness and left ventricular mass obtained using echocardiography and MRI in patients with HCM.
Patients

10 patients with hypertrophic cardiomyopathy, diagnosed by standard echocardiographic criteria [10], formed the study group. All subjects were normotensive. There were six males (mean age 29.3 years, range 14-46 years) and four females (mean age 33, range 17-47 years). Informed consent was obtained in all cases. Four patients were symptomatic with shortness of breath on exertion or palpitations. Six patients had been identified through voluntary screening of family members.

Methods

MRI technique

This was performed on a superconducting MRI machine (Signa, International General Electric, Slough, UK) operating at 1.5 tesla. T1 weighted coronal and long axis oblique images (TR = R-R interval, TE = 12 ms) with respiratory artefact suppression techniques and electrocardiographic gating were acquired initially. Short axis double oblique gradient recalled acquisition in the steady state (GRASS, TR = 66 ms, TE = 17 ms, 30° flip angle) images were obtained as described by Semelka et al [18]. The entire left ventricle was encompassed with 1 cm contiguous sections from apex to the mitral valve annulus. The images were transferred to the remote workstation for subsequent off-line analysis. The depiction of endocardial and epicardial borders was optimized on end-diastolic and end-systolic images for each section using window levels and window widths in accordance with the calculations published by Semelka. The borders were traced manually by outlining the endocardial and epicardial margins with the electronic cursor.

Each diastolic short axis image of the left ventricle was split into four quadrants: anterior interventricular septum (AlVS), posterior interventricular septum (PivS), posterior left ventricular free wall (PLVFW) and anterior left ventricular free wall (ALVFW) (Figure 1). The wall thickness was measured from the thickest part of each quadrant. A line was constructed to transect the left ventricle from the left of the sternum, through the anterior ventricular septum, left ventricular cavity and left ventricular posterior wall (Figure 1). The left ventricular end-diastolic dimension was measured here for comparison with M-mode and cross-sectional echocardiographic measurements. Anatomical landmarks such as the mitral valve, chordae and papillary muscles were noted for each section so that the anatomically appropriate one could be compared with the echocardiographic measurements. The observer performing the MRI wall thickness measurements was blinded to the measurements already obtained by echocardiography.

Left ventricular myocardial volumes were produced by regions of interest placed within the epicardial and endocardial margins respectively. The left ventricular mass was calculated using the sum of the myocardial regions of interest in both systole and diastole multiplied by 1.05 g ml⁻¹, the density of myocardial tissue. This was performed by two observers independent of one another and the results are compared; observer 1 is a consultant radiologist and observer 2 is a research registrar in cardiology.

Echocardiography technique

These were performed by a single observer using an ATL Ultramark 9 with a separate Mitsubishi printer. Standard M-mode and cross-sectional echocardiographic views were obtained at the level of the tips of the mitral valve or chordae. M-mode images were printed along with the cross-sectional reference image (Figure 2). Short axis cross-sectional views were also printed.

Figure 1. A short axis cine MR image from a patient with hypertrophic cardiomyopathy. Markers indicate the four quadrants from which the wall thickness measurements were taken and where the left ventricular end diastolic dimension was measured.

Figure 2. A long axis parasternal M-mode echocardiogram from a patient with hypertrophic cardiomyopathy.
Printed images were analysed by one observer using fine point callipers giving AIVS, left ventricular end-diastolic dimension (LVEDD) and PLVFW measurements from the M-mode prints. Short axis images were divided into four quadrants as for the MRI images, and the thickest part of each quadrant was measured allowing direct comparison of AIVS, PIVS, PLVFW and ALVFW measurements.

An estimate of left ventricular mass was calculated from the M-mode echocardiographic measurements using an equation published by Devereux et al [19].

**Statistical analysis**

Statistical examination of the differences between the measurements from these two techniques was performed according to the methods of Bland and Altman [20].

**Results**

Comparisons of MRI and echocardiographic measurements of the left ventricular wall thickness at the level of the tips of the mitral valve/chordae are shown in Figure 3. The closer of the two echocardiographic estimates (M-mode or cross-sectional) is individually illustrated in Figures 3a–d. The differences between the techniques were calculated by subtracting the echocardiographic measurement from the MRI measurement in each case. From this the mean difference (d), standard deviation of the differences (s) and 95% limits of agreement (d±2s) were calculated. Only nine patients are compared in the anterior left ventricular free wall measurements due to unsatisfactory echocardiographic prints from this area in one patient. Other results are shown in Table 1.

**Anterior interventricular septum**

The excellent agreement between the M-mode echocardiographic and MRI measurements of the AIVS is shown in Figure 3a. There was no significant bias between the techniques with a mean difference of 0 mm and the narrowest 95% limits of agreement (−1.5 to +1.5 mm) obtained for any comparison of wall thickness. This represents a variation of −6 to +6% around the mean measurements.

The comparison of MRI with cross-sectional echocardiography is shown in Table 1. The 95% limits of agreement (−2.4 to +1.7 mm or −4 to +10% variation around the mean measurements) are slightly wider than with M-mode echocardiography.

**Posterior interventricular septum**

The comparison between MRI and cross-sectional echocardiography measurements is shown in Figure 3b. Again, there is no significant bias between the two techniques with a mean difference of 0.27 mm. The 95% limits of agreement are wider than with the AIVS −2.4 to +2.9 mm (a −9 to +14% variation around the mean measurements).

**Posterior left ventricular free wall**

M-mode and cross-sectional echocardiographic measurements compared virtually equally with MRI in this case. The comparison between wall thickness estimates from cross-sectional echocardiography and MRI is shown in Figure 3c as it has slightly narrower 95% limits of agreement than the comparison with M-mode echocardiography. There is no significant bias between the two techniques with a mean difference of −0.44 mm with 95% limits of agreement of −3.4 to +2.5 mm. However, there is a slight suggestion from this graph and the one comparing M-mode echocardiography with MRI (not shown), that echocardiography tended to give higher estimates of the thickness of thinner walls and lower estimates of the thickness of thicker walls when compared with the MRI values.

Table 1. This shows degrees of bias and limits of agreement between measurements not illustrated in the graphs

<table>
<thead>
<tr>
<th>Type of echocardiography</th>
<th>Site of measurement</th>
<th>Bias between MRI and echo</th>
<th>95% limits of agreement of the differences</th>
<th>Percentage variation around the mean measurements</th>
</tr>
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<tbody>
<tr>
<td>M-mode</td>
<td>Posterior left ventricular free wall</td>
<td>0.22 mm</td>
<td>−3.3 to +2.9 mm</td>
<td>−26 to +12%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular end-diastolic</td>
<td>1.2 mm</td>
<td>−5 to +8 mm</td>
<td>−8 to +15%</td>
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<tr>
<td></td>
<td>dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular mass</td>
<td>−117.7 g</td>
<td>−291 to +56 g</td>
<td>−66 to −5%</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>Anterior interventricular septum</td>
<td>−0.36 mm</td>
<td>−2.4 to +1.7 mm</td>
<td>−3 to +9.4%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular end-diastolic</td>
<td>1.9 mm</td>
<td>−4.1 to +8 mm</td>
<td>−8 to +17%</td>
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<tr>
<td></td>
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</table>
Figure 3. This shows four Bland–Altman plots comparing the measurements of left ventricular wall thickness obtained using MRI with those obtained using echocardiography. The mean difference or bias and the 95% limits of agreement are shown in dotted lines. (a) Differences between the MRI and M-mode echocardiographic measurements of the anterior interventricular septum plotted against the mean measurements. (b,c,d) Differences between the MRI and cross-sectional echocardiographic measurements of the posterior interventricular septum, posterior left ventricular free wall and anterior left ventricular free wall, plotted against the mean measurements.

Anterior left ventricular free wall

Figure 3d shows the comparison between cross-sectional echocardiographic and MRI measurements of the ALVFW. There was no significant bias between the two techniques with a mean difference of -0.4 mm and 95% limits of agreement of -2.4 to +1.7 mm (a -13 to +5% variation around the mean measurements).

Left ventricular end-diastolic dimension

The comparisons of M-mode and cross-sectional echocardiography with MRI are very similar (Table 1). There is a small positive bias in the comparison of both types of echocardiography with MRI and similar 95% limits of agreement.
Left ventricular mass (LVM)

The range of LVM estimates using MRI was 119-261 g in systole and 118-260 g in diastole (observer 1). The range using M-mode echocardiographic estimates from the Devereux formula was 189-599 g. Results in Table 1 show that in HCM extrapolation of M-mode measurements using the Devereux formula greatly overestimates the LVM when compared with MRI measurements with a mean difference of -117 g and 95% limits of agreement -291 to -155.5 g (a variation of -66% to +6% from the mean measurements).

There was no significant difference between the MRI estimates of LVM in systole or diastole with a mean difference of -1.6 g and 95% limits of agreement -20 to +17 g (a variation of -12 to +6% around the mean measurements; observer 1).

In addition, there was no significant difference between the measurements by observer 1 and observer 2 of LVM in either systole or diastole. The differences obtained with the diastolic measurements are shown in Figure 4. There was a mean difference of -2.3 g with 95% limits of agreement of -9 to +5 g (a variation of -5 to +1% around the mean measurements). In comparison, the mean difference in systole was 2.7 g with 95% limits of agreement of -7 to +12 g (a variation of -3 to +6% around the mean measurements).

Discussion

MRI has been used in the evaluation of hypertrophic cardiomyopathy and has greatly improved detection of disease affected areas of the left ventricle compared with echocardiography [21-23]. Comparisons of left ventricular mass and wall thickness measurements obtained by cross-sectional echocardiography and MRI in HCM have also been published [14, 21]. However, transverse MR images and not short axis images were used to compare measurements of left ventricular mass [14] and axial, long or short axis plane MR images were compared with cross-sectional echocardiographic measurements without reference to the views or anatomical landmarks from which they were obtained [21].

In the study by Posma et al [23] 52 patients who had a diagnosis of HCM are reported. In three patients, the MRI studies were incomplete and in 19 (37%) the echocardiograms showed inadequate echogenicity for assessment. True short axis images from both techniques are compared in 32 of 52 (62%) patients using hypertrophy scores. These were obtained from four 1 cm thick short axis sections from base to apex. The methodology precludes quantitation of muscle mass and absolute wall thickness measurements are compared in a selective and non-standardized sampling method. It is not clear which of the four sections was employed in the direct comparison of absolute wall thickness estimates with echocardiography, and it was reported that MRI wall thickness values for "various" regions correlated well with those obtained by echocardiography. Furthermore, the differences between anatomically analogous measurements from two techniques are incorrectly illustrated by plotting one against another and obtaining a correlation coefficient. The shortcomings of this approach are discussed clearly by Bland and Altman [20] and alluded to by Posma et al in their results from the posterior free wall. In addition, two echocardiographic observers were used in their study, introducing the possibility for interobserver variability, and neither M-mode echocardiography nor estimates of left ventricular mass were discussed.

In our study, wall thickness measurements using MRI and echocardiography compared like for like either at the level of the tips of the mitral valve or chordae. This study therefore achieves a more accurate examination of the agreement in values obtained using both techniques in HCM when compared with previous studies [14, 21, 23]. In addition, comparisons involving both M-mode and cross-sectional echocardiography and LVM are examined.

Our results show that the best agreement between wall thickness measurements occurred with MRI and echocardiography at the AIVS using M-mode echocardiography. This is not surprising because when the M-mode cursor is carefully placed on the parasternal long axis
two-dimensional image it will preferentially traverse the anterior ventricular septum which is closest to the transducer at right angles, providing a single plane linear image of the septal wall, the resolution of which is in the region of 1 mm [24]. The edges of the AIVS are less clear in cross-sectional echocardiography as they are not linear, although a reasonable result was still obtained using this technique.

The PLVFW is farthest from the ultrasound transducer and attenuation of the ultrasound beam may result in “drop out” of echocardiographic impulses both in M-mode and cross-sectional images [25]. In addition, the PLVFW presents a concave surface in the anteroposterior direction and slopes towards the long axis of the heart to reach the apex. This presents a potential for partial volume averaging to affect the MRI estimate of the thickness of the PLVFW in a 1 cm thick section. In contrast, the echocardiographic cursor measures wall thickness at a particular point where the cursor is perpendicular to the posterior free wall and the septum. All of these factors probably contribute to the wider spread of the measurement differences in this area of the ventricle.

Comparisons of the measurements of the PIVS and ALVFW were also good. The spread of the differences concerning the PIVS was wider than with the AIVS. This may be explained by the increased distance from the echocardiographic transducer and the parallel rather than perpendicular orientation of the PIVS relative to the transducer resulting in reduced clarity of the endocardial and epicardial borders. The ALVFW could only be imaged in nine of the 10 patients and is vulnerable to interference from the anterior chest wall and overlying lung. However, a good agreement with MRI was achieved when echocardiographic imaging was possible.

The comparison of LV mass shows a huge spread of differences between MRI and echocardiography. This is because echocardiographically determined LV mass is calculated from a single set of measurements entered into a formula which makes geometric assumptions concerning the shape of the ventricle and uniformity of wall thickness. This technique is clearly not applicable in HCM where considerable distortion of normal cardiac anatomy occurs. MRI measures LV mass by summation of sections of myocardium and has been shown to be both an accurate [11, 12] and reproducible [14] technique. Figure 4 demonstrates our interobserver variability using this technique which is excellent with only about 1% mean difference.

In conclusion, MRI is a superior technique to echocardiography for the quantification of left ventricular mass in the abnormal ventricle as it does not make invalid geometrical assumptions. In standardized views there was good agreement between left ventricular wall thickness measurements obtained with MRI and echocardiography, although the discrepancies between the two techniques did grow with increasing distance from the echocardiographic transducer. The best agreement occurred between the MRI and M-mode echocardiographic measurement of the anterior interventricular septum. A current limitation of MRI is the time taken to determine manually left ventricular wall thickness and muscle mass. Fast, robust computer driven analysis programmes are required to make MRI a practicable option for cardiac assessment.

Both techniques will be important in the evaluation of therapies to reduce left ventricular hypertrophy. Echocardiography is far cheaper, more readily available and takes less operator time and could be used to rationalize the timing of sequential MRI scans. Serial echocardiographic studies will undoubtedly be the mainstay of monitoring treatment efficacy in any trials of subjects with HCM. It is therefore likely that changes in wall thickness measurements will be the most easily observed effect. Since HCM preferentially involves the AIVS and, in addition, this area gave the best agreement between echocardiographic and MRI estimates of wall thickness, it seems logical to use changes in the echocardiographic measurement of this area to rationalize the use of MRI. All M-mode echocardiographic measurements of AIVS thickness were within a 3 mm spread of the MRI measurements and therefore a change in thickness of 3 mm or more using sequential M-mode imaging would be likely to result in a significantly changed MRI assessment of AIVS thickness. Since LVM is dependent upon the muscle and hence the thickness of the constituent parts, it is reasonable to assume that a significant change in this measurement would also be seen although this obviously requires more study.

Acknowledgments

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References


Diagnosis of hypertrophic cardiomyopathy and screening for the phenotype suggestive of gene carriage in familial disease: a simple echocardiographic procedure

A M Devlin, I Östman-Smith

Abstract

Objectives—To design a new echocardiographic method of screening for hypertrophic cardiomyopathy applicable to children and adults, with a low false positive rate in athletes.

Setting—Regional centre of cardiology, Oxford, UK.

Methods—Forty one patients with hypertrophic cardiomyopathy, 66 first degree relatives from families with familial hypertrophic cardiomyopathy, 262 normal subjects, and 32 athletes were studied by long axis M mode and cross sectional echocardiography to determine the frequency distribution of diastolic and systolic ratios of cardiac wall thickness to cavity diameter.

Results—The best screening measure for hypertrophic cardiomyopathy is diastolic septum to cavity ratio, where a value of 0.26 yielded a 100% detection rate at all ages with 0% false positives in the ordinary population. In comparison, the conventional screening tool of diastolic septum to posterior left ventricular wall ratio of > 1.5 yielded a detection rate of only 75%, for a false positive rate of 2%. In first degree relatives, a septum to cavity ratio > 0.26 yielded a 100% detection rate for an abnormal phenotype suggestive of carriage of a mutation for hypertrophic cardiomyopathy with no obvious false positives. Conventional screening showed a detection rate of only 44%. Athletes with physiological cardiac hypertrophy showed only a 6% false positive rate with diastolic septum to cavity ratio, and could be differentiated from subjects with hypertrophic cardiomyopathy by the absence of hypercontractility shown by a normal systolic left ventricular wall to cavity ratio (cut off < 0.63; 0% false positives).

Conclusions—M mode echocardiographic measurement of the septum to cavity ratio provides a good screening test for hypertrophic cardiomyopathy at all ages. Combining this measurement with systolic left ventricular wall to cavity ratio improves the accuracy further.

Keywords: hypertrophic cardiomyopathy; M mode echocardiography; cross sectional echocardiography

Overt hypertrophic cardiomyopathy (HCM) affecting children and adolescents is not a benign condition, having a reported annual case fatality rate of 5% to 6%.

Thus, HCM is more common than many other congenital conditions regularly screened for, such as hypothyroidism (1:4000) and phenylketonuria (1:10 000). In 1993, Clark and Coots concluded that screening for HCM could not be justified because of the “low sensitivity and specificity of the available screening tests.” Subsequently, the ethical problems and clinical relevance of identifying transmission of a known disease mutation to an asymptomatic offspring were discussed, but more recently Goodwin has argued in favour of family screening.

HCM has autosomal dominant inheritance, but is a genetically heterogeneous condition with variable penetrance. Over 100 different mutations with linkage to seven different chromosomes have been described. All identified gene mutations encoded for contractile proteins, but many relatives with familial HCM have, as yet, unidentified mutations. Thus there is currently no prospect of a definitive screening test based on genetic studies. Furthermore, genetic screening does not differentiate between gene carriers who express the disease and those who do not. Therefore, echocardiography remains an essential component of family screening, as discussed by McKenna et al.

Traditionally, echocardiographic criteria used to diagnose the disease have been based on increased absolute wall thickness, but these are inadequate for screening because of poor sensitivity and specificity (see Discussion below). Furthermore, identification of inappropriate hypertrophy requires individualised interpretation of the wall thickness measurements. This is complicated in subjects of varying and changing size, such as children, and would be difficult for most echocardiographers in district general hospitals, with limited paediatric experience as well as limited experience of HCM. Long axis M mode echocardiography is performed routinely in most echocardiography laboratories, and it is usually easy to obtain good M mode recordings in children and adolescents. A small left ventricular cavity and systolic hypercontractility are additional typical features of hypertrophic cardiomyopathy. It might therefore be anticipated that by
Echocardiographic screening for hypertrophic cardiomyopathy

Compared wall thickness and cavity size measurements in the form of ratios, screening performance would be improved. The use of simple and reproducible ratios, derived from routine measurements, which detect hypertrophy typical of HCM at all ages would represent an advance. An earlier study involving children with HCM successfully used ratios of echocardiographic wall thickness to cavity dimensions as measures to assess progression or regression of hypertrophy. The current study was designed to explore the use of diastolic and systolic wall to cavity ratios to diagnose HCM, particularly in children, and to identify the abnormal phenotype suggestive of gene carriage in familial disease.

Patients and methods

We studied 262 healthy, normotensive subjects (200 children, 62 adults; age range 1 day to 60 years); 41 patients (age range 0.2 to 75 years) with conventionally diagnosed HCM—that is, diastolic septal or left ventricular (LV) wall thickness greater than 15 mm in adults and substantially greater than two standard deviations above the mean for weight in children 

(four infants, 11 children aged 1 to 15 years, and 26 subjects older than 15 years; all normotensive and with other causes of cardiac hypertrophy excluded); and 66 first degree relatives (27 children, 39 adults; age range 0.1 to 72 years, median 30 years) from 18 pedigrees with evidence of genetic transmission of HCM according to accepted criteria. In addition, 32 competitive athletes with significant physiological cardiac hypertrophy were included for comparison, exemplifying findings in secondary cardiac hypertrophy (runners, rowers, pentathletes, weight lifters; all training at least three times per week; aged 14 to 40 years).

Echocardiography was performed with the subjects in the left lateral position, using the fourth or fifth intercostal space. The M mode cursor was positioned so that it cut the septum, cavity, and posterior wall at right angles in the long axis view, just distal to the tips of the mitral valve. M mode traces were measured manually from large prints according to standard American Society of Echocardiography criteria. Cross sectional short axis images were also obtained and measured with electronic calipers to identify cases of HCM predominantly involving areas outside the M mode plane. However, all reported ratios were calculated from long axis M mode measurements.

The following ratios were calculated: diastolic septal thickness to LV end diastolic diameter (septum to cavity ratio), diastolic LV posterior wall thickness to LV end diastolic diameter (LV wall to cavity ratio), systolic LV posterior wall thickness to LV end systolic diameter (systolic LV wall to cavity ratio), diastolic septal thickness to diastolic LV posterior wall thickness (septum to LV wall ratio).

Frequency distribution histograms and statistical analyses were done using Statgraphics software, and goodness of fit with distributions used assessed by Kolmogorov-Smirnov tests. As data from the HCM group tended to show log normal rather than normal distribution, intergroup comparisons were carried out using non-parametric tests (Mann-Whitney U test).

Results

HCM patients and normal subjects

The LV end diastolic diameter was significantly smaller in the HCM group than in the controls (Mann-Whitney U test p < 0.0001). The median value of LV end diastolic cavity diameter in the HCM group (3.8 cm) was 2.1 standard deviations smaller than the median value in normal subjects (4.8 cm), whereas the median value of septal thickness was 2.4 standard deviations greater than the median value in normal subjects. This finding indicates that a small LV cavity is of comparable importance to septal hypertrophy as a disease characteristic. Accordingly, the ratio of wall thickness to cavity diameter is likely to provide increased screening sensitivity when compared to the sensitivity of each measurement used separately.

The wall to cavity ratios at all ages in both healthy controls and HCM patients are compared in the form of frequency distribution histograms in figure 1. The diastolic septum to cavity ratio is the only variable that completely separates the two groups of subjects (figure 1A). With the systolic LV wall to cavity ratio (figure 1B), diastolic LV wall to cavity ratio (figure 1C), and septum to LV wall ratio (figure 1D), more overlap is progressively seen between the two populations. The septum to LV wall ratio, conventionally used for screening, showed a substantial overlap between the populations.

Selection of cut off values for screening

Whilst it is straightforward to identify a cut off value of > 0.26 for the septum to cavity ratio as the value which optimally separates normal from affected individuals in figure 1A, the optimal cut off values for the other ratios are less clear due to the degree of overlap. The distribution of all ratios in both the normal and HCM populations conformed to log normal distributions. Log normal probability density function plots were therefore constructed for each of the ratios and the optimal cut off point was identified by the value at which the tails of the curves intersected. For the diastolic septum to cavity ratio this value is 0.26, which gives a disease detection rate of 100% in our HCM group and a false positive rate of 0% in the normal population (see table 1). The optimal cut off values for the other ratios were 0.63 for systolic LV wall to cavity ratio, 0.23 for diastolic LV wall to cavity ratio, and 1.30 for septum to LV wall ratio. Table 1 illustrates the detection rate and the false positive rate when these cut off points are applied to the disease population and the normal population. For comparison, we have included the observed rates when a septum to LV wall ratio cut off of > 1.50 is used, as advocated by some authors.

The diastolic septum to cavity ratio shows a slight age variation in the normal population and is highest at birth and lowest in the 3 to 5 year age range (figure 2). However, the
Figure 1. Frequency histograms showing the relative frequencies of different ratios in controls and patients with HCM. A: Diastolic septum to cavity ratio. Control subjects 0.12 to 0.26, HCM patients 0.32 to 1.26. B: Systolic left ventricular wall to cavity ratio. Control subjects 0.3 to 0.77 (only infants > 1 year have values > 0.63), HCM patients 0.43 to 3.35. C: Diastolic left ventricular wall to cavity ratio. Control subjects 0.11 to 0.24, HCM patients 0.13 to 0.7. D: Diastolic septum to left ventricular wall ratio. Control subjects 0.69 to 1.71, HCM patients 0.96 to 3.82.

Table 1. A comparison of the detection rate and false positive rate of different echocardiographic ratios in the diagnosis of HCM.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Cut off value</th>
<th>Test positives out of 41 HCM* cases</th>
<th>Detection rate (%)</th>
<th>False positives out of 262 controls</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR†</td>
<td>&gt; 0.26</td>
<td>41</td>
<td>100</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>SYSCAVR‡</td>
<td>&gt; 0.63</td>
<td>40</td>
<td>97.6</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>SYSCAVR (all)</td>
<td>&gt; 0.63</td>
<td>40</td>
<td>97.6</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>SYSCAVR (&gt; 4 years)</td>
<td>&gt; 0.63</td>
<td>30/30</td>
<td>100</td>
<td>0/173</td>
<td>0.0</td>
</tr>
<tr>
<td>LVCAVR§</td>
<td>&gt; 0.23</td>
<td>31</td>
<td>75.6</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>SEPLVR¶</td>
<td>&gt; 1.30</td>
<td>37</td>
<td>90.2</td>
<td>27</td>
<td>11.3</td>
</tr>
<tr>
<td>SEPLVR</td>
<td>&gt; 1.50</td>
<td>31</td>
<td>75.6</td>
<td>5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* Hypertrophic cardiomyopathy.
† Diastolic septum to cavity ratio.
‡ Systolic left ventricular wall to cavity ratio.
§ Systolic LV wall to cavity ratio.
¶ Diastolic LV wall to cavity ratio.

For the SYSCAVR, the values for all subjects, as well as for subjects > 4 years of age, are given separately.

Screening of First Degree Relatives

Bimodal Distribution

Sixty six first degree relatives from 18 pedigrees with familial HCM were examined. With only one exception, all described mutations responsible for familial HCM, which are transmitted in an autosomal dominant manner. Thus, in a sufficiently large population of first degree relatives, 50% of the subjects would be expected to have inherited the mutation, whether or not it is expressed as overt disease. Figure 3 is a frequency histogram showing the diastolic septum to cavity ratios in first degree relatives compared to normal subjects. The frequency distribution in first degree relatives appears bimodal. The first peak mirrors...
Echocardiographic screening for hypertrophic cardiomyopathy

Detection rate and false positive rate in first degree relatives

Of the 32 relatives with septum to cavity ratios > 0.26, 12 subjects fulfilled classical diagnostic criteria for HCM, with diastolic septal thicknesses > 15 mm. A further 18 subjects fulfilled the recently agreed criteria for “affected” by having M mode septal thickness > 13 mm for adults, or by having a septal thickness > 2 SD above the mean for age, weight, and sex for children.

Thus, 30/32 subjects with a septum to cavity ratio of > 0.26 could justifiably be classed as “affected” on M mode wall thickness measurements. Each subject also had additional echocardiographic abnormalities, either systolic hypercontractility with ejection fraction above normal range, or asymmetrical septum hypertrophy with a septum to LV wall ratio > 1.3, or both. The remaining two subjects were adult, normotensive females with M mode septal thicknesses of 12 mm and 11 mm respectively. They both had an abnormally small LV cavity diameter of 3.8 cm. This value is much more than 2 SD below the mean for 4.9 cm for adult females, and would be average for a 22 kg 6 year old child. Consequently, the values for LV wall to septal ratio (specificity for HCM 99.6%) and systolic wall to cavity ratio (specificity in adults 100%) were above normal range. One had significantly increased ejection fraction and the other a septum to LV wall ratio > 1.3. Therefore, these two subjects had five M mode echocardiographic measurements outside the normal range, supporting the diagnosis of an abnormal cardiac phenotype characterised by increased relative wall thickness, a small cavity, and systolic hypercontractility. On short axis cross sectional echocardiography, both these subjects had anterior post septal wall thickness of 13 mm in a small area and would be classified as “borderline” on that count.

The inference, therefore, is that the presence of these M mode features in combination can identify an abnormal cardiac phenotype suggestive of “subclinical” HCM even when the M mode plane does not traverse the area of greatest wall thickness. Moreover, all subjects exhibiting predominantly apical HCM were still correctly identified as abnormal using septum to cavity ratios, even though the M mode beam did not transect the apical septum. In conclusion, the cut off point of 0.26 for the septum to cavity ratio provided no false positives for the identification of a phenotype suggestive of gene carriage.

Conversely, examination of the cross sectional short axis images obtained from the 34 first degree relatives with a septum to cavity ratio of < 0.26, reveals that 34/34 have septal and free left ventricular wall thickness values < 13 mm and within 2 SD for age, sex, and body size. Three adult subjects, all > 20 years of age, showed septum to LV wall ratios > 1.30, but < 1.50 (as did 27 of the normal...
controls), but had no systolic hypercontractility, with all other echocardiographic measurements and ratios in the normal range and with normal electrocardiograms. Consequently, on best clinical criteria, none of the 34 could be classed as "affected" with overt HCM giving a false positive rate for the septum to cavity ratio criterion of 0%.

Table 2 compares the observed detection rates and false positive rates for all three wall to cavity ratios with that of the septum to LV wall ratio and with varying wall thickness criteria, when applied to the population of first degree relatives. In accordance with the results for the overt disease and control populations, the septum to cavity ratio appears superior to the other tests and identifies 49% of the first degree relatives as possessing an abnormal cardiac phenotype.

Detection rate in children

In order to evaluate whether subjects screened in childhood were likely to be correctly categorised by screening with septum to cavity ratio we studied children (age 0 to 15 years) with one parent with HCM, and where prolonged follow up was available. There were 14 subjects, seven had a septum to cavity ratio > 0.26 on initial echocardiogram, seven had a ratio < 0.26. Their progress over time is illustrated in figure 4. It is clear that the children appear to have been correctly separated in abnormal and normal phenotypes, as none of the children with a septum to cavity ratio of 0.26 have crossed into the abnormal range, even during the pubertal growth spurt. Children with initial septum to cavity ratio > 0.26 have all remained abnormal, some increasingly so, with acceleration of septal hypertrophy in the pubertal growth spurt (see figure 4). Thus, like the adults, the children are divided into normal and abnormal populations in the expected proportions for a disease with autosomal dominant inheritance.

### SCREENING OF ATHLETES

The athletes showed cardiac hypertrophy as expressed by significantly greater septal thickness and LV wall thickness when compared to the normal population (Mann-Whitney U test p < 0.0001). Five out of 32 had a septal thickness > 13 mm, and 1/32 > 15 mm. LV end diastolic cavity dimension was also significantly larger in the athletic group (p < 0.0001) when compared to normal adult subjects. The hypertrophy was symmetrical with septum to posterior LV wall ratio < 1.3 in all subjects.

There was a probable 6% false positive rate with two of the athletes, both rowers, having a septum to cavity ratio exceeding the 0.26 cut off (table 2). These two athletes did not have an inappropriately small LV cavity, asymmetrical septal hypertrophy, or systolic hypercontractility implying that the hypertrophy was physiological. Indeed, none of the athletes showed systolic hypercontractility with systolic LV wall to cavity ratios within the normal range (0.38 to 0.59). As a systolic LV wall to cavity ratio > 0.63 shows a 0% false positive rate, and a 100% overt HCM detection rate in the age group that may engage in sports (> 4 years: see table 1), this ratio is an excellent tool to identify true positives among athletes with particularly marked physiological cardiac hypertrophy.

Rowers (n = 17), and other athletes who predominantly perform isometric exercise, had significantly higher septum to cavity ratios than runners (n = 12; p = 0.005), with a mean septum to cavity ratio of 0.23 (SD 0.03) v 0.19 (0.02).
If the currently recommended family screening cut off value for abnormal absolute wall thickness (> 13 mm) was applied to our athletic population, there would be a false positive rate of 5/32 (16%).

**Discussion**

**SCREENING FOR HCM**

In assessing our screening test we are handicapped by the absence of any firm “gold standard” for in vivo diagnosis of HCM. As recently discussed by McKenna et al, the great genetic heterogeneity in HCM, and the varying degree of penetrance of some mutations, means that in some instances the presence of a specific mutation merely reflects increased susceptibility to the disease necessitating close echocardiographic monitoring. With some β myosin heavy chain mutations (for example, Arg403Trp, Arg249Glu, Leu908Val, Gly256Glu) up to 55% of known gene carriers lack echocardiographic wall thickening or ECG changes, and 37% to 75% of adult carriers have a maximum wall thickness < 13 mm. Accordingly, the presence of a mutation per se cannot be considered the gold standard for the diagnosis of overt HCM, particularly when as few as 50% of families have a known mutation in any case. Moreover, the laboratory techniques for screening for an unknown mutation are only available in selected research laboratories, and it remains technically demanding, unless the family is big enough for linkage analysis (three or four affected members) (H Watkins, personal communication). Estimated disease penetrance using conventional echocardiographic criteria averages approximately 80% and increases with age in families with HCM. Yet, since the mutations causing HCM clearly affect all myocardial cells, one might expect that there should be some phenotypic characteristic to identify these hearts, even in the absence of overt disease. Thus we have to find the most sensitive phenotypic indicator of the presence of abnormal myocardial contractile proteins. Our results suggest that in addition to relative septal hypertrophy and systolic hypercontractility, a small left ventricular end diastolic diameter is an important part of the phenotypic expression of the mutation, as it is seen clearly even in subjects with very mild left ventricular hypertrophy. This view is supported by the finding that the mean left ventricular end diastolic diameter of most patients with hypertrophic cardiomyopathy is below the 95th prediction limits for normal subjects even in childhood (Östman-Smith and Devlin, unpublished observation). This result might indicate an abnormality in the Frank-Starling relationship between wall tension and fibre length caused by abnormal myocardial contractile proteins.

Previously, an echocardiographic ratio of diastolic septal thickness to diastolic LV posterior wall thickness of greater than 1.5 was used both to diagnose the disease and to identify affected relatives. However, a septum to LV wall ratio ≥ 1.3 gave only a 55% probability of being affected in a study of known gene carriers. In addition, asymmetric septal hypertrophy has been found in normal individuals, athletic hearts, and different types of heart disease. Symmetrical forms of HCM also exist, particularly in the athletic population where up to 43% of athletes suffering sudden death from HCM exhibited normal septum to LV wall ratios. These observations, together with our results, show that the ratio of septal thickness to posterior wall thickness is unreliable both as a diagnostic and as a screening tool.

Using an absolute diastolic septal wall thickness > 15 mm for screening fails to identify known gene carriers, as does the lower cut off value of 13 mm proposed by a workshop and employed by many authors. For example, in one family with the Arg403Trp β myosin heavy chain mutation, only five out of 22 affected adults had a maximum wall thickness of > 13 mm. The lower cut off of > 13 mm will also be positive in some athletes. Isolated M mode measurements of absolute wall thickness have only been shown to miss 25% of cases of HCM when used in isolation from extensive cross sectional imaging. In our subjects, detailed cross sectional imaging confirmed that no cases of HCM had been overlooked by using long axis M mode diastolic septum to cavity ratios, not even the cases with predominantly apical HCM. The M mode technique gives more accurate measurements of anterior interventricular septal thickness and diastolic and systolic dimensions than does cross sectional echocardiography. In our HCM relatives, the increased septal thickness, which may be mild, and the small LV cavity measurement in combination are sufficiently abnormal to bring the septum to cavity ratio above the 99th centile in affected subjects. As hypertrophy can be very mild or even absent with some mutations, for example, Troponin T, it is unlikely that any one echocardiographic test will truly identify 100% of all cases in the population. However, the septum to cavity ratio performs better than any other echocardiographic test in our HCM relatives.

Recently, new criteria for screening combining electrocardiographic and echocardiographic features applicable to adults have been suggested for simplification of pedigree analysis in affected relatives, but neither the false negative rate nor the false positive rate in the general population has been validated, and the authors advocate its use in affected relatives only. With an anterior septal wall thickness of 12 mm combined with “redundant mitral valve leaflets”, for example, qualifying as “affected”, the false positive rate would probably be high in athletes and significant in the general population. These criteria are also inapplicable in children.

There is an inevitable circularity in applying a screening test which is based on a wall thickness ratio, when absolute wall thickness is the accepted gold standard for in vivo diagnosis. However, the independent confirmation of the validity of our approach is provided by the findings in the first degree relatives. Our results...
phy from HCM. It is also important that
to differentiate physiological cardiac hypertrophy. It is not uncommon to be faced with siblings or
children of HCM patients who are keen athletes, and in whom it is important to be able
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Screening in athletes
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in family members of all ages show that a separation
to cavity ratio > 0.26 identifies the expected proportion of abnormal subjects for a
condition with autosomal dominant inheritance, and as we have shown they are clearly
different from the normal population. Each subject identified as “abnormal” had addi-
tional confirmatory abnormalities of either systolic hypercontractility or an asymmetric
pattern of hypertrophy typical of HCM. The comparisons above and in the tables show that
this ratio is a more effective screening test than earlier tests as it combines a high detection rate with a 0% false positive rate in the normal population, and a low false positive rate in ath-
letes. It is often stated that most cases of familial HCM develop phenotypic expression of
disease only during adolescence.24 The most obvious advance of our septum to cavity ratio is
that it correctly identifies phenotypic abnormalities in first degree relatives as early as the 0
to 12 year age range, as shown by long term follow up (figure 4).

Screening in childhood
Until now, the diagnosis in children has been made when septal thickness measurements are
> 2 SD above the mean, or > 95th centile, for weight or age.14 This procedure requires refer-
ence to complex graphs with no account being taken of small left ventricular cavity size, which
we have shown to be a crucial feature of the disease. Moreover, by definition, this proce-
dure classifies up to 5% of normal subjects with a potential disease label, and has also
proved singularly ineffective in the identification of known gene carriers in childhood.15-17
Yet sudden death may be the presenting event in children with HCM, particularly if they
engage in sports, and Goodwin argues a strong case for screening children in affected families
where the potential for reducing sudden death mortality is greatest.7 The most obvious
advance of our septum to cavity ratio is that it appears to identify phenotypic abnormalities in
first degree relatives as early as the 0 to 12 year age range as shown by long term follow up
(figure 4). It provides a simple and reproduc-
table echocardiographic tool that takes account of reduced LV cavity size, and can be used by
district hospital services for diagnostic pur-
poses and for sequential monitoring at all ages.
When used for diagnostic purposes, confirmatory abnormalities of systolic and diastolic
function should be looked for. A septum to cavity ratio of > 0.26 is above the 99% prediction limits for all normal subjects > 1 year of age (see figure 2) and is an advance in the echocardiographic screening for HCM, par-
ticularly in children by offering the highest
detection rate and lowest false positive rate of any echocardiographic screening method de-
scribed so far.

Screening in athletes
It is not uncommon to be faced with siblings or
children of HCM patients who are keen athletes, and in whom it is important to be able
to differentiate physiological cardiac hypertrophy from HCM. It is also important that

Limitations of single cut off screening and use of
other ratios
The cut off for septum to cavity ratio of > 0.26 arrived at through the analysis of frequency
distributions does leave a grey area where sub-
jects are above the 99% prediction limit, but
still below the cut off. This occurs primarily in
the 3 to 5 year old age group, who demonstrate
the lowest relative wall thickness, and where the
99% prediction limit of septum to cavity ratio is 0.22 (see figure 4). Although this has
not presented a problem in the families studied
so far, it is possible that mildly affected
children may fail to be detected by septum to
cavity ratio alone. In this group, as with the
athletes, the combination of this ratio with systolic LV wall to cavity ratio will be valuable,
as this results in increased specificity. Carriage
of a HCM mutation should be suspected if the
systolic wall to cavity ratio is > 0.63 in any sub-
ject more than 1 year old, and sequential echocardiographic monitoring advised. Like-
wise, a diastolic LV wall to cavity ratio > 0.23
makes further monitoring advisable. Thus a
combined use of these ratios will lessen the
likelihood of missing subjects who are evolving
an abnormal phenotype.

Potential benefits of identifying
asymptomatic individuals
HCM can be rapidly progressive during child-
hood and adolescence in children with echocardiograms previously judged as normal
on standard criteria.26 Sudden death in a previ-
ously asymptomatic individual is a common
presentation in this age group and in
athletes.37 A recent study on complete cohorts

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prospective randomised trial in mild childhood HCM reported in earlier studies from tertiary centres was not due to referral bias. Another recent study confirms that the sudden death rate is much higher in the 0 to 20 year age range, than in the > 30 year age range, and that 50% of the deaths in which the circumstances were known occurred during exercise, meaningful since exercise related activities only comprise a small proportion of each day.

This result supports the widespread practice of counselling against competitive sports for individuals with HCM. Preparticipation screening of competitive athletes is compulsory in Italy, and this has resulted in HCM being a rare cause of sudden death in Italian athletes (2.0% of sudden deaths in athletes as opposed to 7.3% of sudden deaths in the unscreened control population). HCM was identified in 22 athletes in that study, resulting in their disqualification from competitive sports, thereby suggesting a role for preparticipation screening in the prevention of sudden death.

Whether screening of all children in affected families is worthwhile is clearly dependent on whether there is evidence that medical treatment and/or life style modifications reduce mortality. Medical treatment with high dose propranolol, amiodarone, and verapamil have all been reported to be associated with a low annual case fatality rate in retrospective studies, but these studies have lacked contemporary controls. However, a recent retrospective study does have contemporary controls with identical risk factor profiles and shows a statistically significant improvement in survival in childhood HCM treated with high dose propranolol, compared either with no treatment, or with other treatment regimes. The treatment effect is large, with hazard ratio analysis indicating a five to tenfold reduction in the risk of disease related death in subjects treated with high dose propranolol. Thus a case can be made for family screening in relatives with familial HCM and, where resources permit, also for preparticipation screening of athletes.

Whether population screening, for example, in schools, would be justified would be dependent on whether it could be shown that early treatment has a beneficial effect on disease progression, morbidity, and long term outcome even in mild cases of HCM at comparatively low risk of sudden death. As HCM often progresses markedly in the pubertal growth spurt, early childhood may be the optimal window of opportunity in which any pharmacological treatment strategies aimed at the attenuation of the phenotypic expression of the disease could be implemented and followed. In severe childhood HCM, retrospective studies suggest that treatment with high dose propranolol did reduce hypertrophy and late morbidity from arrhythmias. However, a prospective randomised trial in mild childhood HCM is needed to make the case for population screening. Our study suggests that the echocardiographic measurement of septum to cavity ratio provides a powerful tool to identify candidates of all ages for these purposes, including susceptible family members in families where a genetic mutation has not been found. Furthermore, once treatment regimens had commenced, the severity, progression, or regression of the disease at all ages could be monitored using the ratio as shown in the studies of children with HCM and by the data in figure 4.

CONCLUSIONS

A diastolic septum to cavity ratio of > 0.26 in subjects older than 1 year, and > 0.28 in subjects under 1 year where causes of secondary hypertrophy have been excluded, is an excellent diagnostic indicator of overt HCM and of the phenotype suggestive of gene carriage in familial disease. Although it cannot be claimed from a single study that 100% of cases of HCM can be identified using this test, it appears to offer a more sensitive and specific echocardiographic method to detect the condition than those used before. In combination with systolic LV wall to cavity ratio, it is particularly useful in differentiating physiological from pathological hypertrophy in athletes.

We are greatly indebted to Professor N Wald (Wolston Institute of Preventative Medicine, St Bartholomew's and the Royal London School of Medicine and Dentistry, London) for his helpful advice. Dr Devlin was supported by grants from the University of Oxford and the Medical Research Fund of the Faculty of Clinical Medicine, University of Oxford, and from the Children's Echocardiography Fund.

16. Al-Mahdawi S, Chambelan S, Chojnowska L, et al. The electrocardiogram is a more sensitive indicator than...
CLINICAL STUDIES

A Simple Method for Assessing the Regression or Progression of Ventricular Hypertrophy in the Growing Child and Adult: the Value of Left Ventricular Wall-to-cavity Ratios

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Alms: To establish the normal range of diastolic and systolic left ventricular wall-to-cavity ratios.

Methods and Results: Two hundred and sixty-two normal subjects (age 0-40 years), 15 children with valvar aortic stenosis and 11 childhood athletes were studied with M-mode echocardiography. Values of diastolic septum-to-cavity ratio and diastolic left ventricular wall-to-cavity ratio were not influenced by sex nor, in adults, by height, weight or body surface area. There were slight age variations from 0-15 years of age, but not in adults from 15-40 years of age. Values of diastolic left ventricular wall-to-cavity ratio in neonates were 0·18 (95% confidence limits 0·17-0·19); in 3-5 year olds 0·16 (0·15-0·16); and in adults 0·18 (0·17-0·19). In valvar aortic stenosis there is a positive correlation between the Doppler-estimated pressure gradient and the degree of left ventricular hypertrophy, as expressed by both diastolic and systolic left ventricular wall-to-cavity ratio (r=0·90; P<0·00001 and r=0·85; P=0·00006 respectively).

Conclusions: Diastolic septum and left ventricular wall-to-cavity ratios accurately differentiate physiological from pathological left ventricular hypertrophy in the growing child. Because these ratios are independent of sex and body size, they may also be more sensitive than absolute wall thickness in the detection of abnormal left ventricular hypertrophy in adults.

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Key Words: left ventricular hypertrophy; cardiac hypertrophy; aortic stenosis; athletes.

Introduction

There is a clinical need for a simple measure to diagnose and monitor left ventricular hypertrophy that could be used in the growing child, where age-related growth of the heart makes it difficult to assess superimposed pathological left ventricular hypertrophy. Normal ranges of cardiac wall thickness and of left ventricular cavity dimensions measured by M-mode echocardiography have been published for neonates[1-3]. For older children graphs have been published relating left ventricular wall thickness and dimensions to body surface area[4-5], the cube root of weight or cube and square root of body surface area[6-7], or weight and sex[8]. The clinical use of these normal ranges requires access to height and weight and/or computation of body surface area followed by reference to a graph. These normal data were also compiled on stand-alone M-mode transducers rarely used today, when two-dimensional (2D) image guidance for optimal M-line positioning is the norm. Furthermore, the M-mode measurements in most of these studies[1-7] were not performed using the subsequently recommended leading-edge-to-leading-edge convention currently accepted[9].

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Huwez et al. have published normal data obtained on modern equipment on 127 subjects from the age of 7 months to 19.5 years, and derived mathematical formulae to predict the normal range of wall thickness and cavity dimension from the age or the body surface area of the child[14]. This again requires cumbersome calculations for each observation, with no graphs for quick reference, and the data may not be valid for children below 7 months. Most studies give only 90% or 95% prediction limits for normal measurements such that 5–10% of normal children would be classified as abnormal and would risk a spurious disease label in a condition such as hypertrophic cardiomyopathy.

The use of absolute wall thickness measurements alone to diagnose cardiac hypertrophy in adults is also inadequate, since there are clear gender differences. Left ventricular wall thickness in females is on average at least 0.1 cm less than in males[11,12] and, in addition, there is the separate influence of body size. Thus, there is a clear absence of logic in the current use of absolute wall thickness criteria alone for the diagnosis of hypertrophic cardiomyopathy in adults. The diagnostic requirement of a wall thickness of >1.5 cm, or >1.3 cm as recommended for family screening[13], leaves a large grey area between either measurement and the commonly accepted upper limit of normal of 1.1 cm[14] and ignores the normal gender difference.

Therefore, a measure of left ventricular hypertrophy that is independent of age, sex and body size, and where 99% prediction limits were also provided, would offer much to the clinician in a busy outpatient clinic. In addition, it may provide a more sensitive means of detecting pathological hypertrophy.

In previous studies on the treatment of hypertrophic cardiomyopathy (HCM) in children and adults, the ratios of septum and posterior left ventricular wall thickness to left ventricular internal diameter were used to assess progression or regression of hypertrophy[15,16]. These simple ratios appeared to offer a useful tool for the assessment of progression of hypertrophy, especially in growing subjects. The current study has collected measurements from normal children and adults in order to establish the normal ranges and to explore the influence of age and body size on the values of the ratios from birth to adulthood. In order to assess the clinical usefulness of the ratios in the growing heart, values from young subjects with physiological and pathological left ventricular hypertrophy are also included.

**Methods**

**Subjects**

The 262 normal subjects consisted of normal neonates, healthy siblings of children attending the Paediatric Cardiology outpatient clinics, children and adolescents assessed for innocent heart murmurs and found to have structurally normal hearts, and adult normotensive volunteers. Two hundred subjects were children, and 62 were above 15 years of age and defined as adults. Mean and median age of the adult subjects was 27 years with a range of 15.3–59 years, but only one adult was over 40 years of age. Data from 15 patients with left ventricular hypertrophy secondary to valvar aortic stenosis, with normal myocardial function and no significant aortic incompetence, were also obtained (mean age 7.2 years, range 0.2–16 years). Finally, measurements from 11 school age competitive athletes (mean age 15.6 years, range 12–18 years) were studied to ascertain values in physiological hypertrophy in the growing child. They competed in sports involving predominantly isotonic exercise such as running and swimming.

**Echocardiography**

The examination was carried out in the supine position in infants and young children, and in the left lateral position in adolescents and adults. The left ventricle was imaged in a long-axis parasternal view from the third to the fifth intercostal space. The M-mode cursor was positioned on the real-time image so that it transected the septum, cavity and posterior left ventricular wall at right angles at, or just distal to, the tips of the mitral valve leaflets. Many cardiac cycles were recorded, and where possible measurements from three cycles were averaged. Measurements were made manually from recorded prints using fine point callipers and the leading-edge-to-leading-edge convention[19].

**Statistics**

The summary statistics, the linear regression analysis, the confidence limits and the prediction limits were calculated with a computer software programme (Statgraphics Plus). Goodness of fit of the observed data with a normal distribution was tested with the Kolmogorov–Smirnov one sample test. In order to evaluate the correlation between outflow gradients and relative wall thickness without the influence of age-related change, a Z-value for each ratio was calculated for the patients with aortic stenosis. The Z-value was calculated by subtracting the age-specific mean value of the wall-to-cavity ratio for normal subjects from that of the patient, and dividing the difference by the age-specific standard deviation of the mean.

**Results**

**Septum-to-Cavity Ratio**

Figure 1 shows that the mean septum-to-cavity ratio is slightly higher at birth than it is around 3 years of age,
Assessment of Ventricular Hypertrophy

Figure 1. The diastolic septum-to-cavity ratio (SEP­CAVR) plotted on the y-axis, versus the age in years on the x-axis. The best fit with the observed values is found when the linear regression with age is divided in three sections, between birth and 3 years of age, between 3 and 15 years of age, and above 15 years of age. This figure illustrates the individual observations, the predicted mean values at different ages using the linear regressions in these three age bands, with the 99% prediction limit at all ages illustrated. The numerical values of the regression equations are given in Table 1.

The only subject not illustrated is the 59 year old, who with a septum-to-cavity ratio of 0·19, is close to the mean for adults.

Figure 2. The diastolic posterior left ventricular wall-to­cavity ratio (LVCAVR) is plotted on the y-axis versus the age in years on the x-axis. Analysis of the same three age bands (0–3 years, 3–15 years, above 15 years) show the best fit of a regression line with the observed values. The individual observations, the predicted mean and 99% prediction limits using linear regression equations are illustrated in this figure. The numerical parameters of the regression equations are given in Table 1. Abbreviations: LV, left ventricular; y, years.

Left Ventricular Diastolic Wall-to-Cavity Ratio

As illustrated in Figure 2 and Table 1, there is a similar relationship to age as seen with septum-to-cavity ratios. The initial negative regression between these ratios and age from birth to 3 years of age is less steep but still significant (P=0·00002), and the positive regression between 3 years and 15 years is more obvious with a highly significant slope (P=0·00001). In subjects above 15 years of age there is no further change with increasing age. All observed data again fall within a relatively narrow range, with no normal individuals having a left ventricular wall-to-cavity ratio greater than 0·25 or smaller than 0·12. The average ratio is 0·18 both in neonates and in adults, with the lowest mean (0·16) observed in 3–5 year olds. There is no significant skewing in the distribution of the observations at any age group, and the range, confidence limits of the mean and the 95 and 99% prediction limits for a normal distribution in appropriate age bands are given in Table 2.

Systolic Left Ventricular Wall-to-Cavity Ratio

As seen in Figure 3 and Table 1 there appears to be a decrease in the average systolic left ventricular wall-to-cavity ratio in early life, although the slope does not
After 15 years of age there is no further age-related decrease that stops at about 2-5 years of age, followed by a quite reach statistical significance (P=0.07), but the decrease stops at about 2-5 years of age, followed by a significant slow rise until 15 years of age (P=0.0005). After 15 years of age there is no further age-related change. After the age of 1 year, no values in excess of 0.61, or below 0.30, were observed in normal individuals. In adults the mean systolic ratio is 0.47 (95% confidence limits 0.46-0.49). The lowest mean value, 0.43, is observed in pre-school children age 3-5 years (95% confidence limits 0.41-0.45).

None of the three ratios is influenced by sex at any age. For instance, for both septum-to-cavity ratio and left ventricular wall-to-cavity ratio the mean for adult males is 0.18 (standard deviation 0.03 and 0.02, respectively), and the mean for adult females is also 0.18 (standard deviation 0.02 and 0.02; P=0.71 and P=0.93, respectively). In the adults (age greater than 15 years) there is no correlation with body surface area, height or weight for either septum-to-cavity ratio or for diastolic left ventricular wall-to-cavity ratio. Likewise in children, within each age band there was no correlation between these two ratios and height, weight or body surface area. If all children are analyzed together there is a very slight positive correlation between body surface area and left ventricular wall-to-cavity ratio, but this is simply due to the confounding effect of age which is associated with increase in both body surface area and left ventricular wall-to-cavity ratio over the 5-15 years age range.

**Inter-observer Variability**

Inter-observer variability of measurements was assessed by blind measurements of two observers from the M-mode prints of 25 subjects. The mean and 99% prediction limits derived from the 59-year-old is not shown, but her value (0.55) is well within the normal range. Abbreviations: y, years.

![Figure 3](image)

**Correlation to Other Parameters**

None of the three ratios is influenced by sex at any age. For instance, for both septum-to-cavity ratio and left ventricular wall-to-cavity ratio the mean for adult males is 0.18 (standard deviation 0.03 and 0.02, respectively), and the mean for adult females is also 0.18 (standard deviation 0.02 and 0.02; P=0.71 and P=0.93, respectively). In the adults (age greater than 15 years) there is no correlation with body surface area, height or weight for either septum-to-cavity ratio or for diastolic left ventricular wall-to-cavity ratio. Likewise in children, within each age band there was no correlation between these two ratios and height, weight or body surface area. If all children are analyzed together there is a very slight positive correlation between body surface area and left ventricular wall-to-cavity ratio, but this is simply due to the confounding effect of age which is associated with increase in both body surface area and left ventricular wall-to-cavity ratio over the 5-15 years age range.

Potential uses for these simple ratios are illustrated in Figure 4. Figure 4A shows the progression of left ventricular hypertrophy with time in three patients with valvular aortic stenosis, and the effect of surgical valvotomy or balloon valve angioplasty. The increase in relative hypertrophy associated with worsening outflow- gradient and the regression of hypertrophy after successful treatment is well shown by sequential left ventricular wall-to-cavity ratio measurements. As shown in Figure 4B, a good correlation existed between the diastolic left ventricular wall-to-cavity ratio and the outflow gradient in 15 children with aortic stenosis of varying degrees of severity, even without the use of Z-values to correct for age (correlation coefficient 0.90; slope 0.0024, P=0.00001). The diastolic left ventricular wall-to-cavity ratio correlated better than either the systolic left ventricular wall-to-cavity ratio (correlation coefficient 0.85, slope 0.0077, P=0.00006) or the septum-to-cavity ratio (correlation coefficient 0.67, slope 0.0023, P=0.007). This result is probably because the former ratio is least affected by age. Thus, the correlation between Z-values derived from the diastolic left ventricular wall-to-cavity ratios and the Doppler estimated gradient is no better than that obtained using the uncorrected ratios (correlation coefficient 0.89, slope 0.120, P=0.00001). However, the correlation between systolic wall-to-cavity ratio and pressure gradient is improved by using Z-values to correct for age (correlation coefficient 0.86; slope 0.10, P=0.00005), as is the correlation between septum-to-cavity ratio and pressure gradient (correlation coefficient 0.72; slope 0.11, P=0.002). Thus, in summary, the diastolic left ventricular wall-to-cavity ratio appears to be the most convenient measure for monitoring the effect of pressure-overload and can be used without age correction. In practical terms all patients with a Doppler gradient of >40 mmHg had a diastolic left ventricular...
Table 1. Relationship between age and relative thickness of septum and left ventricular wall. This table shows the numerical values of the regression equations of diastolic septum-to-cavity ratio (SEPCAVR), diastolic posterior left ventricular wall-to-cavity ratio (LVCAVR), and systolic posterior left ventricular wall-to-cavity ratio (SYSCAVR). The regression equations have been divided in three age bands according to the linear regression best fit to the observed data.

<table>
<thead>
<tr>
<th>Group</th>
<th>Intercept</th>
<th>S.E.</th>
<th>Slope</th>
<th>S.E.</th>
<th>Corr. Coeff.</th>
<th>T value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPCAVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &lt;3 years</td>
<td>0.218</td>
<td>0.004</td>
<td>-0.0225</td>
<td>0.0027</td>
<td>-0.70</td>
<td>-8.2</td>
<td>0.00011</td>
</tr>
<tr>
<td>SEPCAVR</td>
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<td>0.006</td>
<td>0.0018</td>
<td>0.0007</td>
<td>0.23</td>
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<td>0.010</td>
</tr>
<tr>
<td>age &gt;15 years</td>
<td>0.192</td>
<td>0.012</td>
<td>0.0003</td>
<td>0.0004</td>
<td>-0.10</td>
<td>0.75</td>
<td>n.</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.177</td>
<td>0.004</td>
<td>-0.0121</td>
<td>0.0027</td>
<td>-0.46</td>
<td>-4.46</td>
<td>0.0002</td>
</tr>
<tr>
<td>age &lt;3 years</td>
<td>0.143</td>
<td>0.005</td>
<td>0.0029</td>
<td>0.0004</td>
<td>0.39</td>
<td>4.74</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.188</td>
<td>0.011</td>
<td>-0.0004</td>
<td>0.0004</td>
<td>-0.11</td>
<td>0.86</td>
<td>n.s.</td>
</tr>
<tr>
<td>age &gt;15 years</td>
<td>0.510</td>
<td>0.018</td>
<td>-0.0337</td>
<td>0.01178</td>
<td>-0.24</td>
<td>-1.90</td>
<td>0.07(n.s.)</td>
</tr>
<tr>
<td>SYSCAVR</td>
<td>0.399</td>
<td>0.014</td>
<td>0.0072</td>
<td>0.0017</td>
<td>0.35</td>
<td>4.31</td>
<td>0.0003</td>
</tr>
<tr>
<td>age 2-5 years</td>
<td>0.453</td>
<td>0.034</td>
<td>0.0008</td>
<td>0.0012</td>
<td>0.08</td>
<td>0.63</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

wall-to-cavity ratio of at least 0.22 (=95% prediction limit for infants and adults), and all subjects with Doppler gradients >50 mmHg had left ventricular wall-to-cavity ratios >0.24 (=99% prediction limit for adults).

**Physiological Left Ventricular Hypertrophy in Athletes**

School-age athletes showed significant left ventricular hypertrophy with a mean left ventricular wall thickness of 0.94 (0.16) cm and a septum thickness of 0.94 (0.12) cm, as compared with age-matched controls (n=33) with a mean left ventricular wall thickness of 0.81 cm (0.12; P=0.01), and a septum of 0.84 cm (0.12; P=0.046). However, left ventricular cavity dimension had increased in proportion to the increase in wall thickness, such that the wall-to-cavity ratios remained unchanged, with athletes having mean left ventricular wall-to-cavity ratios of 0.19 (0.03) and septum-to-cavity ratios of 0.19 (0.02) as compared to 0.18 (0.03; P=0.43) and 0.19 (0.03; P=0.76), respectively, in the age-matched controls (see Figure 5 for the distribution of individual values).

**Discussion**

Diastolic wall-to-cavity ratios are independent of sex, weight, height and body surface area, and remain normal in physiological cardiac hypertrophy, thereby offering obvious practical advantages over absolute wall thickness measurements in the detection of pathological left ventricular hypertrophy. Thus, the normal range can be determined by reference to age only, which is a great advantage in the assessment of the growing child. Furthermore, the age-related increase in these ratios is so small that it does not significantly interfere with the ability to detect progression or regression of cardiac hypertrophy in the growing child as illustrated by Figure 4.

It was initially hoped that the wall-to-cavity ratios would be completely independent of age, but it is clear that a biphasic response is observed, although in numerical terms the differences are small. Neonatally, the relative wall thickness ratios are a little higher, particularly of the interventricular septum. Our data on absolute septal thickness used to calculate the wall-to-cavity ratios do in fact suggest that the assumption by Huwez et al. of a simple linear relationship between absolute wall thickness and age is not correct below 1 year of age.

There are probably three factors influencing the high relative wall thickness at birth and in the first 12 months of life. Firstly, the right ventricular contribution to total septal thickness reduces in response to the postnatal fall in right ventricular pressure. Secondly, newborn babies and infants have higher sympathetic nervous tone and heart rate than older children and therefore the Starling curve of the myocardium is probably shifted to the left, i.e. a smaller left ventricular diameter is required for any given workload. Thirdly, the cavity dimension needs to increase rapidly during the first few years of life when the body surface area is increasing more rapidly than
Table 2. Mean, 95% confidence limits of the mean, and prediction limits for relative heart wall thickness in selected age groups. This table shows the mean, median, standard deviation, the 95% confidence limits of the mean, the range of observed values, and the 95% and 99% prediction limits for a normal distribution for children grouped in appropriate size age bands in relation to the relationship between age and wall-to-cavity ratios, and with the values for adults given separately. Within each age group the observed values are normally distributed as tested with the Kolmogorov-Smirnov one sample test, although there is some positive skewing of the observed systolic left ventricular wall-to-cavity ratios in the infant 6-12 month group. The 15 subjects between age 1 month and 6 months of age have not been averaged because of the rapid rate of change in this age band. The age bands are inclusive, so that, for instance, the 1–2 year band includes children with ages between 1.0 to 2.99 years, and so forth.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Median</th>
<th>S.D.</th>
<th>95% C.L.of mean</th>
<th>Range</th>
<th>95% Pred.lim.</th>
<th>99% Pred. lim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 month (n=12)</td>
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<td>0.23</td>
<td>0.02</td>
<td>0.22–0.24</td>
<td>0.19–0.27</td>
<td>0.18–0.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.17–0.19</td>
<td>0.15–0.21</td>
<td>0.14–0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.24</td>
<td>0.44</td>
<td>0.06</td>
<td>0.41–0.48</td>
<td>0.36–0.54</td>
<td>0.33–0.55</td>
<td>0.30–0.58</td>
</tr>
<tr>
<td>Age 6–12 months (n=11)</td>
<td>0.20</td>
<td>0.21</td>
<td>0.02</td>
<td>0.19–0.22</td>
<td>0.17–0.24</td>
<td>0.16–0.26</td>
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</tr>
<tr>
<td></td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
<td>0.16–0.18</td>
<td>0.14–0.21</td>
<td>0.14–0.21</td>
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</tr>
<tr>
<td></td>
<td>0.30</td>
<td>0.48</td>
<td>0.11</td>
<td>0.43–0.58</td>
<td>0.38–0.71</td>
<td>0.36–0.71</td>
<td></td>
</tr>
<tr>
<td>Age 1–2 years (n=36)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
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<td>0.13–0.22</td>
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<tr>
<td></td>
<td>0.15</td>
<td>0.15</td>
<td>0.03</td>
<td>0.14–0.16</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>0.42</td>
<td>0.08</td>
<td>0.40–0.46</td>
<td>0.31–0.61</td>
<td>0.31–0.61</td>
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<tr>
<td>Age 3–5 years (n=56)</td>
<td>0.17</td>
<td>0.16</td>
<td>0.03</td>
<td>0.16–0.17</td>
<td>0.12–0.24</td>
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<tr>
<td></td>
<td>0.16</td>
<td>0.15</td>
<td>0.02</td>
<td>0.15–0.16</td>
<td>0.12–0.21</td>
<td>0.12–0.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>0.42</td>
<td>0.07</td>
<td>0.41–0.45</td>
<td>0.30–0.57</td>
<td>0.33–0.56</td>
<td>0.30–0.57</td>
</tr>
<tr>
<td>Age 6–10 years (n=37)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.03</td>
<td>0.17–0.18</td>
<td>0.12–0.21</td>
<td>0.12–0.21</td>
<td></td>
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<tr>
<td></td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
<td>0.16–0.17</td>
<td>0.13–0.21</td>
<td>0.13–0.20</td>
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</tr>
<tr>
<td></td>
<td>0.46</td>
<td>0.46</td>
<td>0.07</td>
<td>0.43–0.48</td>
<td>0.30–0.59</td>
<td>0.34–0.58</td>
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<tr>
<td>Age 11–15 years (n=33)</td>
<td>0.18</td>
<td>0.18</td>
<td>0.03</td>
<td>0.17–0.19</td>
<td>0.12–0.25</td>
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<tr>
<td></td>
<td>0.18</td>
<td>0.18</td>
<td>0.03</td>
<td>0.17–0.19</td>
<td>0.11–0.24</td>
<td>0.13–0.23</td>
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<tr>
<td></td>
<td>0.48</td>
<td>0.47</td>
<td>0.07</td>
<td>0.46–0.50</td>
<td>0.32–0.62</td>
<td>0.36–0.61</td>
<td>0.32–0.62</td>
</tr>
<tr>
<td>Adult, age &gt;15 years (n=62)</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.18–0.19</td>
<td>0.13–0.23</td>
<td>0.14–0.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.17–0.19</td>
<td>0.13–0.23</td>
<td>0.13–0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.47</td>
<td>0.47</td>
<td>0.07</td>
<td>0.46–0.49</td>
<td>0.30–0.63</td>
<td>0.34–0.61</td>
<td>0.30–0.65</td>
</tr>
</tbody>
</table>

Abbreviations: C.L., confidence limits of the mean; LVCAVR, diastolic posterior left ventricular wall-to-cavity ratio; S.D., standard deviation; SEPCAVR, diastolic septum-to-cavity ratio; SYSCAVR, systolic posterior left ventricular wall-to-cavity ratio.

during later growth, as they are linearly related\(^4\). Thus, a rapid increase in left ventricular diameter in infancy contributes to the reduction in relative wall thickness. The subsequent very slow rise in the relative wall thickness of the left ventricle, occurring from about 3 years of age, may be related to the slow increase in systolic blood pressure that occurs throughout childhood, as it appears to cease at about the same time as adult blood pressure levels are reached.

Clinical Use of Wall-to-cavity Ratios in Children

There is a definite need for a convenient but reliable way of following the progress of left ventricular hypertrophy in the growing child which we now provide in the form of wall-to-cavity ratios. The existing published data relating absolute wall thicknesses to body surface area were obtained by equipment rarely used today and are cumbersome to use\(^4\). They are also insensitive by virtue of looking at each measure in isolation. For instance, a child with a body surface area of 0·8 m\(^2\) could have an interventricular septum on the 95th centile and a left ventricular diastolic diameter on the 5th centile (using data from the graph published by Henry\(^5\)), but actually have a pathologically hypertrophied heart, because the septal wall-to-cavity ratio would be 0·26, well above the 99th centile for a child of 3–5 years of age (99th centile=0·22, see Table 2). Furthermore, the ratios can also be used to monitor left ventricular dilatation in patients with dilated cardiomyopathy, where progressive left ventricular dilatation can be differentiated from age-related growth by a steady fall in wall-to-cavity ratios. A study on children with dilated cardiomyopathy has shown that both diastolic septum-to-cavity ratio and systolic left ventricular wall-to-cavity ratio are significant predictors of outcome (Chernobelska, Eur J Echocardiography, Vol. 2, issue 1, March 2001).
Abbreviations: LV, left ventricular.

This graph shows data from 15 children with valvar aortic stenosis of varying degrees of severity (age range 0-2-16 years). The relationship between left ventricular outflow tract gradient and the resulting left ventricular hypertrophy as expressed by the diastolic wall-to-cavity ratio has been explored previously, but because normal values for this ratio in childhood remain normal in physiological hypertrophy.

The expression of wall thickness and cavity size as a ratio has been explored previously, but because Laplace's law was invoked as a rationale, the left ventricular radius was determined, and used to calculate a radius/wall thickness ratio. In this procedure the value falls with hypertrophy and increases with dilatation, and no normal values for this ratio in childhood have been published. Other authors used systolic wall thickness/systolic left ventricular diameter or diastolic wall thickness/diastolic radius as a predictor of left ventricular systolic pressure in compensated aortic stenosis. The advent of Doppler techniques to predict aortic valve gradients has largely superseded the use of these ratios. It is not suggested that the use of wall-to-cavity ratios is better than a Doppler estimate of the gradient, but it is clear from our observations that

the systolic “Bennett-formula” and the currently illustrated diastolic left ventricular wall-to-cavity ratio ≥0.22 is evidence of a significant aortic valve gradient, and a ratio >0.24 of a potentially dangerous gradient. These values will identify children for whom an examination under sedation is advisable. It is noteworthy that in this study the correlation between relative wall thickness and pressure overload in children is better for the diastolic than for the systolic wall-to-cavity ratio.

A wall thickness/radius ratio has also been used in the study of physiological hypertrophy in athletes. However, for ease of use in a clinical context it is more convenient to use the actual measurement (i.e. left ventricular internal diameter), and to divide the wall thickness by the diameter to get an increase with cardiac hypertrophy, in the way it was used to monitor growing children with hypertrophic cardiomyopathy.

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Figure 4. (A) This figure illustrates the progress with increasing age in three individual patients with valvar aortic stenosis of significant severity. The increasing deviation from normal as the outflow gradient increases, and the reduction in relative left ventricular hypertrophy after successful intervention with surgical valvotomy or balloon dilatation of the aortic valve, is well seen. It is noteworthy that the patient indicated by filled squares, who had a very eccentric valve orifice, had repeated Doppler estimates, including under sedation, suggesting only a modest aortic valve gradient of 36-40 mmHg but because of the marked left ventricular hypertrophy he underwent cardiac catheterization which confirmed severe aortic stenosis with a gradient of 90 mmHg. In this patient the wall-to-cavity ratio served to alert the clinician to a significant underestimation of the outflow gradient as predicted by Doppler measurement. Standard arrows indicate the timing of surgical aortic valvotomy in the patients indicated by filled squares and triangles, whereas the arrow with a filled tip indicates the timing of balloon dilatation of the aortic valve in the patient illustrated by filled circles (who had had a previous neonatal surgical aortic valvotomy).

Abbreviations: LV, left ventricular. (B) This graph shows data from 15 children with valvar aortic stenosis of varying degrees of severity (age range 0-2-16 years). The relationship between left ventricular outflow tract gradient and the Doppler-estimate of the aortic valve gradient (in mmHg) on the x-axis. The best fit linear regression line, (with the 95% confidence limits for the mean) is illustrated. The correlation coefficient is 0.90, the slope 0.0024, and the slope is significantly different from 0 as shown by  < 0.0001; thus, there is a highly significant positive correlation between the gradient and the value of the left ventricular wall-to-cavity ratio.
Figure 5. This graph illustrates the diastolic left ventricular wall-to-cavity ratios in school-age athletes plotted within a graph of the 99% prediction limits for age.

Absolute wall thickness measurements do not differentiate between physiological and pathological hypertrophy and give no consideration to the effects of gender. This is vividly illustrated in a major prevalence study of hypertrophic cardiomyopathy in childhood in which cases were diagnosed on absolute wall thickness criteria alone. This autosomal dominant condition showed a 3:1 male preponderance in the 0–20 year age range, suggesting that this methodology is insufficiently sensitive to diagnose affected females. In contrast, studies using the septum-to-cavity ratio as a diagnostic marker for hypertrophic cardiomyopathy in childhood successfully identified affected subjects with no undue sex bias, using a septum-to-cavity ratio cut-off of >0.26. A systolic LV wall-to-cavity ratio >0.63 was also an excellent screening measure in children over 4 years of age. Furthermore, in childhood hypertrophic cardiomyopathy higher wall-to-cavity ratios correlated with a higher risk of disease-related death and may therefore be useful markers of high-risk individuals.

Clinical Use of Wall-to-cavity Ratios in Adults

The fact that septum and left ventricular wall-to-cavity ratios are not influenced by sex, weight or body surface area in the adult means that they are likely to be more sensitive than the measurement of absolute left ventricular wall thickness in the detection of pathological left ventricular hypertrophy. Thus, these ratios should be an important advance with particular clinical value in adults with hypertension in whom the presence of left ventricular hypertrophy is associated with an adverse prognosis. The effect of anti-hypertensive therapy on regression of left ventricular hypertrophy in this condition could be observed, and conversely the progression of left ventricular outflow obstruction in patients with pressure overload, e.g. due to aortic stenosis, could also be monitored. Use of wall-to-cavity ratios should also reduce the under-diagnosis of adult females with mild HCM suggested by a 3:1 male preponderance in incidence studies using wall thickness criteria alone.

Conclusions

The diastolic left ventricular wall-to-cavity ratio provides a simple and convenient tool to assess the effect of pressure overload on the left ventricle, whilst remaining normal in physiological left ventricular hypertrophy. The fact that wall-to-cavity ratios are independent of sex and body-size increases their sensitivity in the detection of abnormal wall hypertrophy of any aetiology. Thus, they provide a practical advance over the use of absolute wall thickness in the assessment of both children and adults.

Acknowledgements

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References


