The Structural Determinants and Functional Consequences of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy

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‘ I, Dr Christopher Critoph, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed……

Abstract

Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiac condition. Many patients have resting or provocable left ventricular outflow tract (LVOT) obstruction. Symptoms treated with drugs or surgery may improve. There is a need to improve the clinical assessment in individual patients, because of the often poor correlation between symptoms and LVOT gradient, and the association with complications such as stroke, heart failure and sudden cardiac death. In addition, in a proportion of patients with significant LVOT gradients, relief of obstruction does not adequately improve symptoms.

Reduced angulation between the inter-ventricular septum and the aorta is a determinant of LVOT obstruction. However, lack of a standardised method of measurement in HCM without recourse to complex 3-D imaging limits the usefulness of this parameter in routine practice. Transthoracic echocardiography is widely available, and can be used to measure aorto-septal angulation. However, data in HCM are lacking. I validated a simple measurement of aorto-septal angulation using 2-D echocardiography and cardiac magnetic resonance imaging and determined its relation to provocable LVOT obstruction in HCM. I showed this technique to be easy, reproducible, comparable to magnetic resonance imaging, and can be quickly calculated using standard echocardiographic software. Patients have a smaller aorto-septal angle than controls, where it is associated with higher peak LVOT gradient. A reduced aorto-septal angle is highly specific for provocable LVOT obstruction and should prompt further evaluation in symptomatic patients without resting gradients.

I used a non-invasive technique for measuring cardiac output to determine the relation between LVOT obstruction, cardiac output and peripheral oxygen utilisation in patients with HCM during exercise. I demonstrated that cardiac output response to exercise is impaired, caused largely by failure to appropriately augment stroke volume. LVOT obstruction is associated with greater impairment of stroke volume at peak exercise and is an independent and modifiable predictor of cardiac output reserve. However, heterogenous responses are seen between patients who otherwise appear similar using standard clinical criteria. There is therefore a strong argument for the individualisation of therapy in patients with LVOT obstruction. Invasive therapies to reduce gradients may work better in those with genuine obstruction to the outflow of blood, rather than for example myocardial ischaemia or mitral regurgitation. The non-invasive measurement of haemodynamic indices during exercise is practical, aids understanding of the complex physiological basis behind symptoms and may help to tailor therapy for HCM, and in particular LVOT obstruction.

Contents

Tables

Figures

1 Preface

1.1 Statement of originality

The work submitted in this thesis to the University of London is original, and has not been submitted elsewhere for any other professional qualification. Published results are detailed in chapter 9. This thesis has been checked using University College London turnitin plagiarism detection software. Other than the citations listed, no significant similarities or matches were seen.

1.2 Aims and clinical relevance of the thesis

The broad theme of this thesis is LVOT obstruction in HCM, and is split into structural and physiological aspects.

1.2.1 Structural determinants of LVOT obstruction: 3D imaging before and after myectomy surgery in patients with HCM

Surgical myectomy is the gold standard procedure for patients with HCM and drug-refractory symptoms of LVOT obstruction. In current practice patients have trans-thoracic echocardiography prior to the procedure and 2D trans-oesophageal echocardiography (TOE) at the time of surgery. Patients also have conventional coronary angiography to exclude significant coronary disease which could be treated at the time of surgery if needed. A proportion of patients also undergo cardiac magnetic resonance (CMR) imaging as part of their workup. Ventricular septal myectomy substantially reduces the gradient and improves exercise capacity and symptoms. In experienced centres, mortality rates are less than 1% and complications such as atrio-ventricular block and ventricular septal defects rare. These good results, however, belie the challenge that patients with more complex anatomical abnormalities pose for surgical correction. In addition to hypertrophy of the interventricular septum, leaflet elongation or restriction, accessory mitral valve attachments and abnormalities of the papillary muscles and chordae are very common and are often only detected at the time of operation. Various modifications of the standard surgical technique have been proposed to deal with such anomalies including mitral valve plication or patching, chordal remodelling and edge to edge repair, but the choice of technique and their contribution to successful relief of obstruction is difficult to predict peri-operatively. Similarly, variable distribution of hypertrophy between patients often results in sub-optimal resection. This project proposed that all patients

undergo pre and post surgical evaluation with 3D TOE, CMR and computed tomography (CT) and the data integrated to improve surgical planning and ultimately outcome. Although individually these investigations are commonly performed in patients with HCM, this integreation has not been attempted before. Specifically, the original aims were:

1. To characterise the morphological and haemodynamic determinants of left ventricular outflow tract obstruction in individual patients with hypertrophic cardiomyopathy with the intention of improving their subsequent surgical treatment.
2. To create a single, realistic, 4D animation of each individual patient's heart and great vessels which can be used to create a real-time tool combining echocardiography, MR and CT data.

I commenced data collection for this project in Autumn 2010 immediately prior to my out of cardiology program research period. Unfortunately, shortly afterwards due to circumstances beyond my control the surgical myectomy program at The Heart Hospital was temporaily halted, and did not restart until October 2012. During this time, 18 patients had CT scanning pre- LVOT reduction therapy, and 10 had post- operative scanning, having had operations carried out at another centre, or alcohol septal ablation (ASA). As a result, it was only possible to collect preliminary pilot data. A description of methods and results are detailed in the appropriate sections.

The Heart hospital has the largest cohort of patients with HCM in Europe, all of whom undergo cardiopulmonary exercise testing, and many have been investigated with stress echocardiography. It is also the UK's leading centre for interventional LVOT gradient reduction. A unique opportunity therefore existed to expand my project to other aspects of LVOT obstuction in HCM.

1.2.2 Structural determinants of LVOT obstruction: Analysis of aorto-septal angulation using 2-D transthoracic echocardiography

The aorto-septal angle is formed between the plane of the inter-ventricular septum and the aorta. A smaller angulation is an anatomical feature commonly seen in advancing age and hypertension. In addition, in children it has been associated with sub-aortic valve obstruction. Recently, it has been shown to be predictive of LVOT obstruction in HCM using 3D imaging techniques. Whilst a standardised measurement technique using echocardiography has been described, this has never

been applied to patients with HCM, in whom it might be expected to be inaccurate given the highly variable LVOT geometry. In routine clinical practice, aorto-septal angulation in HCM is commonly described as being suggestive of provocable LVOT obstruction. However, on review of the literature few data exist as to its importance in this disease. I therefore sought to determine whether this was an anatomical predictor of provocable LVOT obstruction in a cohort of patients with HCM and no resting obstruction, and whether it could be reliably and accurately measured using transthoracic echocardiography. The result is a description of a novel mechanism by which the risk of provocable LVOT obstruction may be predicted from a standard resting transthoracic echocardiogram of a patient with HCM. This may help identify patients who would benefit from further assessment and treatment.

1.2.3 Functional consequences of left ventricular outflow tract obstruction

The primary aim of this study was to determine the relation between LVOT obstruction, cardiac output and peripheral oxygen utilisation in patients with HCM during exercise using symptom limited cardiopulmonary exercise testing. Compared to some areas of research in HCM, for example genetics, this subject is largely unstudied in the literature, and in particular in recent years. In part, this likely relates to the difficulties in investigating exercise physiology in these patients. Typically HCM cohorts in most hospitals are small, and physiological expertise limited; larger numbers may be needed to determine the relative importance of a variety of complex factors which may have a role in exercise limitation. The techniques available to study exercise physiology, in particular cardiac output, also have their own limitations: invasive techniques carry associated risks (which are often less acceptable to research populations than work done in the 20th century), and non-invasive techniques are either unable to capture the rapid changes in dynamic variables, or are unsuited to use during exercise. I therefore wanted first to validate a non-invasive technique for measuring cardiac output. I chose finger plethysmography, as the design lends itself to use during exercise, and captures beat by beat physiological data which may be of importance in HCM.

The physiological data shed new light on the mechanism of exercise limitation in patients with HCM. Cardiac output response to exercise was shown to be impaired in HCM, driven predominantly by a failure to appropriately augment stroke volume. Peak LVOT gradient was an independent predictor of cardiac output reserve. In some patients, stroke volume impairment is compensated for by an ability to mount an exaggerated heart rate response. Most importantly, the stroke volume response

between patients with LVOT obstruction was heterogeneous, implying that better haemodynamic characterisation of patients may help determine those who may derive maximal benefit from invasive treatment.

1.3 Statement of individual contribution

1.3.1 Physiology study

All cardiopulmonary exercise tests were performed as part of routine patient care at The Heart Hospital by Dr Bryan Mist. I performed finger plethysmography during those tests. All echocardiograms were also performed as part of routine patient care at The Heart Hospital by the imaging department. I analysed all the resulting data.

1.3.2 Aorto-septal angulation study

The original echocardiograms and magnetic resonance scans were all performed by the imaging department at The Heart Hospital. I retrospectively analysed the images and data. Another research fellow Dr Joel Salazar also independently measured the aorto septal angles for the purpose of assessing inter-observer variability.

1.3.3 Myectomy imaging study

I recruited patients from the Heart Hospital, and transported them to Great Ormond Street Hospital where the CT scans were performed by myself and Professor Andrew Taylor, and Dr Claudio Capelli reconstructed the CT images. The cardiopulmonary exercise tests and echocardiograms in these patients were performed by Dr Bryan Mist and the imaging department respectively as part of their routine clinical care at The Heart Hospital. I analysed the resulting data.

2 Introduction

2.1 Definition and classification of the cardiomyopathies

Cardiomyopathies are myocardial disorders in which the heart is structurally and functionally abnormal, in the absence of coronary artery, congenital or valvular heart disease, or hypertension sufficient to cause the observed myocardial abnormality (1). Cardiomyopathies are classified into four main subtypes, based on ventricular morphology and physiology; HCM is defined as left ventricular hypertrophy in the absence of abnormal loading conditions sufficient to explain the degree of hypertrophy (1). HCM is the commonest inherited cardiac disease, with a population prevalence of approximately 1 in 500 (2).

2.2 Genetics and associated syndromes

In one half to two thirds of individuals, HCM is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomeric protein genes (3-5). The commonest are ß-myosin heavy chain, cardiac troponin T, cardiac troponin I, α-tropomyosin, cardiac myosin binding protein C, the essential and regulatory myosin light chains, and cardiac actin. Other genes, such as those encoding α-myosin, titin and proteins of the Z-disc, account for less than 1% of cases (6).

Given the extent of genetic heterogeneity and the variable effect of different mutations, it is not surprising that HCM is characterised by marked heterogeneity in disease severity and outcomes. Clinical manifestations of identical mutations are highly variable, even within the same family, indicating that other genetic and possibly environmental factors influence disease expression (7).

A number of malformation syndromes and other conditions, many of which present in childhood, are associated with HCM. These include Noonan (8-10)and LEOPARD (11) syndromes, Anderson-Fabry disease (X-linked dominant lysosomal storage disorder) (12), Danon disease (13-15) , Pompe disease (glycogen storage disease type IIa) (16,17), primary respiratory chain diseases (18,19) and Friedreich's ataxia (20,21).

2.3 Mitochondrial mutations and hypertrophic cardiomyopathy

Mitochondrial diseases are a group of maternally inherited conditions with a variety of phenotypes. Increasingly mitochondrial mutations are recognised as being associated with cardiomyopathy, which may be hypertrophic in nature (22). Mitochondria are essential components of cellular respiration, and mitochondrial disorders are often associated with profound effort intolerance as a result of skeletal and respiratory muscle abnormalities. Patients with HCM who display these symptoms in excess of the apparent cardiac phenotype can be considered for further assessment to explore the possibility of mitochondrial disease. A raised serum creatinine kinase is a simple investigation which can be suggestive. More specialised tests include electromyography and skeletal muscle biopsy, both of which have been found to be abnormal in some patients with HCM (23). A morphological study of 9 HCM patients found mitochondria were significantly greater in number and smaller in size than in controls (24). In a murine HCM model, mitochondrial mutations are associated with cellular respiratory abnormalities, which therefore may contribute to haemodynamic dysfunction (25). In addition, HCM phenotypic expression in an individual with a causal sarcomeric mutation may be influenced by additional 'modifier' mutations and/or environmental factors, which can include mitochondrial mutations (26). This may be important in the interpretation of the relationship between oxygen consumption (VO_2) and work. Abnormal peripheral muscle oxygen use could affect the 'gross' measurement of oxygen consumption, and also relatively little work may be performed for a given VO_2. Further evidence for abnormal myocardial metabolism was observed by an increased lactate production and higher myocardial oxygen consumption in HCM patients with LVOT obstruction during atrial pacing (27), and by a greater fall in coronary sinus pH during dipyridamole stress in HCM compared to normal controls (28). It is not known whether mitochondrial abnormalities were present in these studies.

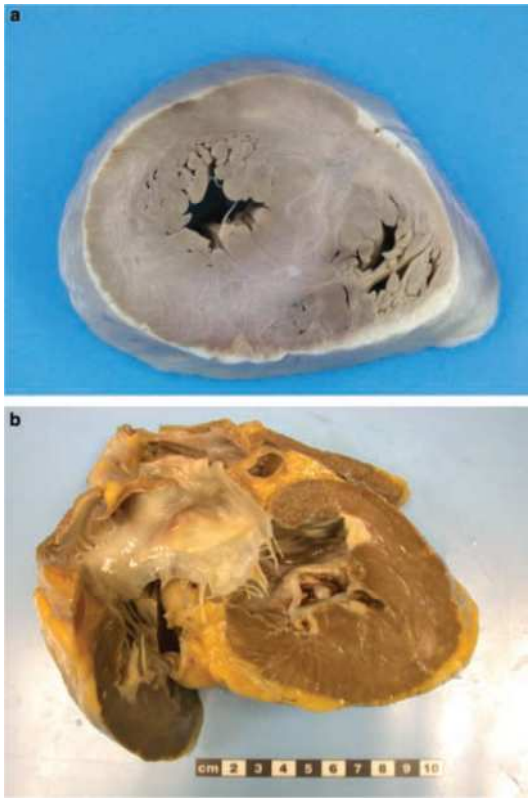
When studying exercise physiology in a patient population with HCM, the absence of genotyping data (as in my cohort) can potentially therefore make interpretation of haemodynamic data more challenging. An observed abnormality during cardiopulmonary exercise testing may for example be influenced by cellular respiration and skeletal muscle function in addition to gross cardiac dysfunction. No patient had an elevated serum creatinine kinase to suggest an underlying muscle disorder, although this does not exclude a problem as levels typically fluctuate.

2.4 Pathology of hypertrophic cardiomyopathy

The hypertrophic phenotype may vary with the underlying genetic aetiology. The most common appearance is asymmetric septal hypertrophy (ASH), but any pattern of ventricular hypertrophy can be seen, including eccentric, concentric and apical. The classical form originally described in 1958 by Sir Donald Teare of St George's medical school has left ventricular basal anterior septal hypertrophy, which bulges into the LVOT causing obstruction to blood flow. A pathological specimen is shown in figure 2.1. Hypertrophy may not be confined to the basal segments; mid-cavity obstruction may be associated with a figure of eight left ventricular configuration, possibly due to high systolic pressures forcing the thinner apical region outwards. This can be associated with aneurysmal dilatation and thrombus formation. Apical HCM was originally thought to be a more benign variant, although is now undifferentiated from other forms in contemptoray risk stratification. The papillary muscles are often anteriorly displaced, and may be multiple, with abnormal insertion into the mitral valve. Primary mitral valve abnormalities are very common, particularly elongated (anterior) leaflets. If LVOT obstruction is present, endocardial thickening may be seen at the point of mitral valve-septal contact, known as a contact lesion. Right ventricular hypertrophy is also seen in a significant number of cases, although when seen should prompt exclusion of other infiltrative conditions.

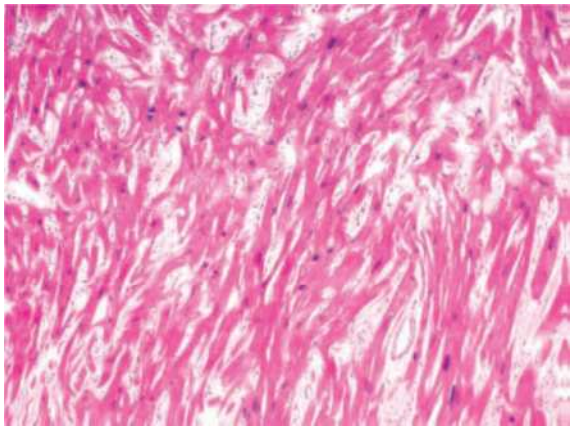
Microscopically, HCM is characterised by myocyte hypertrophy and disarray, interstitial fibrosis and expansion of the interstitial compartment (29,30), figure 2.1. Small intramural coronary arteries are often dysplastic and narrowed due to wall thickening by smooth muscle cell hyperplasia (31). These changes are not confined to areas of hypertrophy, but may be found in apparently macroscopically normal myocardium. Differing microscopic features have no prognostic significance, although extensive fibrosis is associated with a poorer outcome. Myocyte disarray is absent in some other common causes of ventricular hypertrophy such as hypertensive or aortic stenotic heart disease and so may be a useful diagnostic feature.

Figure 2.1. Transverse section of both ventricles at the mid-septal level from a patient with hypertrophic cardiomyopathy (30).



A. The hypertrophy involves both the free and septal walls of the left ventricle with marked asymmetric thickening of the septum. B. Apical variant of HCM.

Figure 2.2. Photomicrograph of myocytes from a patient with familial hypertrophic cardiomyopathy (30)



Normal parallel arrangement of myocytes has been replaced with myocyte disarray and increased connective tissue.

2.5 Clinical features of hypertrophic cardiomyopathy

2.5.1 Physical examination

The cardiovascular examination in most patients is normal. In some, the jugular venous pulsation may have a prominent 'a' wave, caused by reduced right ventricular compliance. The left ventricular impulse is typically sustained, or double, reflecting an atrial impulse followed by left ventricular contraction. LVOT obstruction causes a rapid up and downstroke to the arterial pulse, occasionally followed by a palpable reflected wave, resulting in a bisferiens pulse. On auscultation, LVOT obstruction causes a harsh ejection systolic murmur at the left sternal edge, which increases in intensity during strain phase of the Valsalva or when standing from the squatting position. Most patients with LVOT obstruction also have mitral regurgitation (caused by abnormal coaptation of the mitral valve leaflets during systole). This causes a pansystolic, high frequency murmur at the apex, radiating to the axilla. A third or fourth heart sound is common.

2.5.2 Natural history

HCM can present at any age, from infancy to old age (32). Many patients follow a stable and benign course, with a low risk of adverse events. In some series, HCM is the most common cause of sudden death in young people (33,34) but the majority of patients are asymptomatic and therefore often remain undiagnosed. Long-term, many patients develop progressive heart failure symptoms caused by a gradual deterioration in left ventricular function. This so-called "end-stage" is characterised by severe impairment of contractile performance and is associated with a poor prognosis (35). Diastolic function is impaired in the majority of patients and may in some individuals resemble restrictive cardiomyopathy (36).

2.5.3 Sudden cardiac death

HCM is one of the commonest causes of sudden cardiac death in the young. Most contemporary studies report an annual incidence of sudden death in HCM populations of 0.5-1% per year, rising to 2% or higher in certain groups (37-42). The mechanism of sudden cardiac death is rarely documented. Factors that contribute to a propensity to ventricular arrhythmia include: dispersion of repolarisation which increases susceptibility to triggered arrhythmias; myocyte disarray and areas of conduction block which predispose to re-entry arrhythmias; and abnormal ion fluxes causing after-

depolarisations and triggered activity. Other morphological and physiological factors may influence the vulnerability of the underlying substrate, such as myocardial ischaemia, LVOT obstruction and diastolic dysfunction.

2.5.4 Heart Failure

End-stage HCM develops at all ages, but in the majority of patients, the time from onset of heart failure symptoms to diagnosis of severe systolic impairment is about 10-15 years (35). The development of severe systolic heart failure is associated with a poor prognosis, with rapid progression to death or transplantation and an overall mortality rate of up to 11% per year (35). The prevalence of severe systolic impairment in HCM using conventional echocardiographic criteria ranges from 2% to nearly 10%, with an annual incidence of less than 1% (35,43). However, the true incidence of systolic left ventricular impairment may be much higher as clinically significant reductions in systolic performance may occur while the measured ejection fraction remains within the normal range on account of the hypertrophied myocardium and small left ventricular cavity.

2.5.5 Stroke

The annual incidence of stroke varies from 0.56%-0.8%/year rising to 1.9% for patients in patients >60 years old (44). The major cause is atrial fibrillation (AF) which affects about a quarter of HCM patients, with an incidence of up to 3% per annum (45,46). A meta-analysis by Guttmann et al showed the prevalence of AF in HCM to be 22.5%, and in those patients the prevalence of thromboembolism was 27.1% (46). The odds ratio for stroke in AF patients is 17.7 (95% CI, 4.1 to 75.9; P=0.0001; 23% of strokes are fatal (44)). Risk factors for AF include age and left atrial dilation (a consequence of diastolic dysfunction, LVOT obstruction and mitral regurgitation) (45,46).

2.5.6 Infective endocarditis

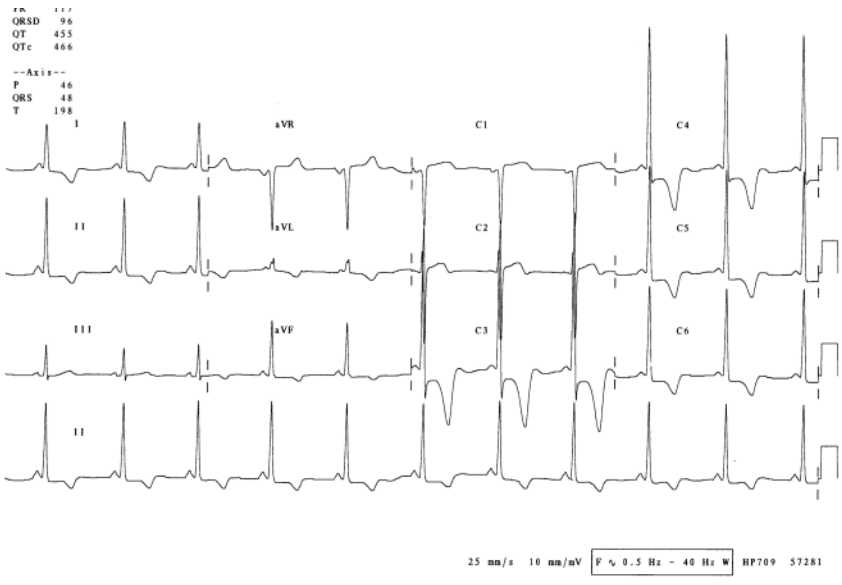
Patients with obstructive HCM have an increased risk of developing infective endocarditis, usually on the anterior mitral valve leaflet (47). The incidence of infective endocarditis is 1.4 per 1000 person-years (95% CI, 0.5 to 3.2) (3.8 per 1000 person-years (95% CI, 1.6 to 8.9 in patients with obstruction), compared with 1.7 – 6.2 cases per 100,000 years in the general population (48).

2.6 Diagnosis of Hypertrophic Cardiomyopathy

2.6.1 Electrocardiography

The resting 12-lead electrocardiogram (ECG) is abnormal in 95% of patients with HCM. The commonest abnormalities are ventricular hypertrophy, repolarisation abnormalities, pathological Q waves and left atrial enlargement. Giant negative T waves in the mid-praecordial leads are characteristic of apical HCM (49), figure 2.3. A short PR interval without ventricular pre-excitation is common. Atrioventricular conduction delay (including first-degree block) is rare except in particular subtypes of hypertrophic cardiomyopathy (e.g. PRKAG2 mutations and mitochondrial disease) (50,51).

Figure 2.3. Twelve lead electrocardiogram from a patient with apical hypertophic cardiomyopathy

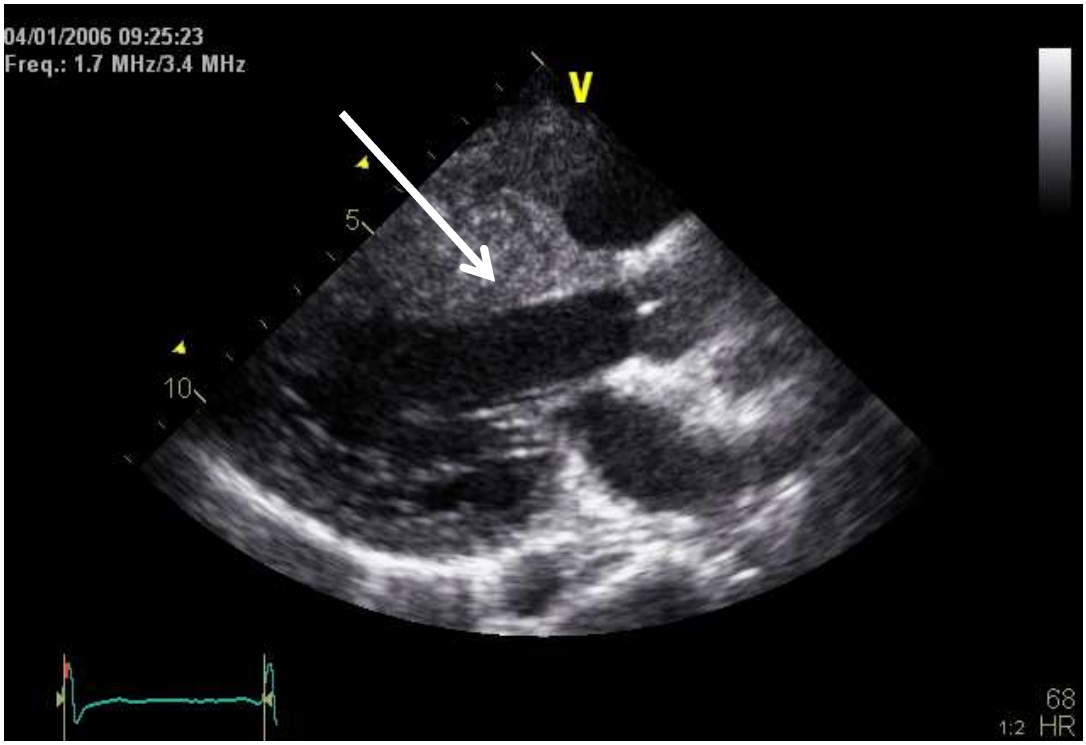


Note marked left ventricular hypertrophy and giant negative T waves in the praecordial leads.

2.6.2 Echocardiography

The diagnosis of HCM relies on the demonstration of a maximal left ventricular wall thickness (MWT) more than two standard deviations from the normal (typically ≥13mm in an adult) (52), figure 2.4. The hypertrophy is typically asymmetric, involving the interventricular septum more than other segments, but any pattern of left ventricular hypertrophy including concentric , eccentric, distal and apical is consistent with the diagnosis of HCM (53-56).

Figure 2.4. Parasternal long axis echocardiographic view from a patient with hypertrophic cardiomyopathy



Note marked hypertrophy of the inter-ventricular septum (arrowed)

Left ventricular systolic function assessed from changes in ventricular volume during the cardiac cycle, is typically increased, but regional and long-axis function is usually reduced (57). A proportion of adults with HCM develop progressive myocardial thinning, global left ventricular systolic impairment and cavity dilatation (35). Characteristically, patients with HCM have diastolic left ventricular impairment demonstrated by reduced early diastolic (Ea) velocities in the mitral annulus and septum and reversal of the ratio of early to late diastolic velocities (Ea/Aa). Abnormalities of the mitral valve and its apparatus are extremely common in HCM, and are readily assessed using echocardiography.

2.6.3 Cardiac Magnetic Resonance Imaging

CMR provides a detailed assessment of cardiac morphology as well as accurate assessment of systolic function. It also permits tissue characterisation, particularly detection of myocardial scarring by the assessment of delayed gadolinium enhancement. Many patients with HCM have areas of patchy gadolinium hyper-enhancement and studies suggest that the extent of gadolinium enhancement correlates with risk factors for sudden death and with progressive left ventricular remodelling (58,59).

2.6.4 Cardiac Catheterisation

Left and right heart catheterisation is rarely necessary to make a diagnosis of HCM. The main indications are exclusion of coronary artery disease and much less commonly assessment of cardiac output, filling pressures and intraventricular pressure gradients in patients with severe symptoms. Endomyocardial biopsy is occasionally indicated when an infiltrative or metabolic disease such as amyloidosis, or Anderson-Fabry disease is suspected.

2.6.5 Ambulatory ECG Monitoring

Ambulatory electrocardiographic monitoring is important in the assessment of symptoms and in the prediction of arrhythmic risk. Non-sustained ventricular tachycardia (VT) occurs in approximately one fifth of adults with HCM. Most episodes are relatively slow, asymptomatic, and occur during periods of increased vagal tone. In contrast, sustained VT is uncommon, and may occur in association with apical aneurysms (60). Paroxysmal supraventricular arrhythmias occur in 30-50% of patients; sustained AF is present in 5% of patients at diagnosis, and develops in a further 10% in the subsequent 5 years (45,61).

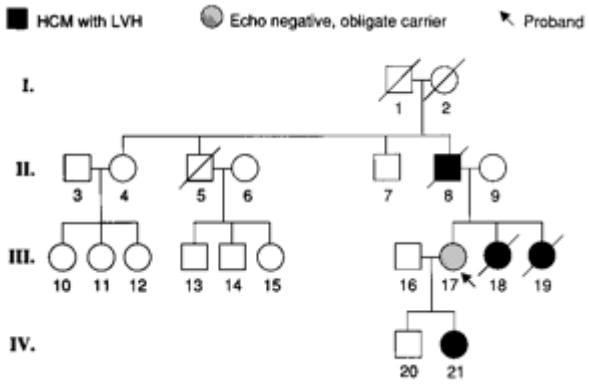
2.7 Clinical management of hypertrophic cardiomyopathy

The treatment of most patients with HCM focuses on the counselling of family members, the management of symptoms, and the prevention of disease-related complications. Exceptions include lysosomal storage diseases, such as Pompe and Anderson Fabry disease where specific therapies are available.

2.7.1 Genetic counselling and evaluation of families

All patients with HCM should be counselled on the implications of their diagnosis for other family members (34). Analysis of carefully constructed family pedigrees can reassure relatives who are not at risk of inheriting the disease (figure 2.5).

Figure 2.5. Example of a pedigree from a family with a history of hypertrophic cardiomyopathy



HCM – hypertrophic cardiomypathy, LVH – left ventricular hypertrophy.

Circles – female, squares – male, line through shape – dead, white shape - unaffected

For those who are at risk, current guidelines recommend screening with a 12-lead ECG and echocardiogram at intervals of 12-18 months, usually starting at the age of 12 years, unless there is a family history of premature sudden death, the child is symptomatic or a competitive athlete, or there is a clinical suspicion of left ventricular hypertrophy, until full growth and maturation is achieved (34). Thereafter, if there are no signs of disease expression, clinical screening should be performed every five years, as left ventricular hypertrophy can develop well into adulthood. Modified diagnostic criteria that take into account the high probability that otherwise unexplained ECG and echocardiographic findings in first-degree relatives reflect incomplete disease expression should be used when evaluating other family members.

When genetic testing is available, affected individuals should be counselled on the purpose of the test, the likely mode of inheritance, and the potential hazards and limitations of genetic testing. These include:

- Psychological consequences of a test result, for example:
    - Anger
    - Depression
    - Guilt
    - Change in family relations / dynamics
- Financial consequences of a test result, for example increased insurance premiums
- Possibility of discrimination
- Inability of a test to predict the natural history of the condition
- Genetic abnormalities of uncertain clinical significance
- Potential lack of treatment strategy once a diagnosis has been made

2.7.2 Symptom management

In patients with symptoms caused by LVOT obstruction, the aim of treatment is to reduce the outflow tract gradient. Typically, symptoms include chest pain, syncope or pre-syncope and breathlessness. These are, of course, also seen in patients with HCM without LVOT obstruction. Clues to help discrimate include symptoms made worse by exertion (particularly of sudden onset such as running for a bus), dehydration, any form of Valsalva, alcohol and eating are more commonly seen with LVOT obstruction. Patients often report symptoms which initially occurred in early adulthood, and may have adapted their lives to cope wih them. Options for treatment include negatively inotropic drugs (ß-blockers, disopyramide and verapamil), atrio-ventricular sequential pacing, percutaneous alcohol septal ablation of the inter-ventricular septum and surgery. This will be discussed in more detail later.

Approximately 60 to 70% of patients improve with medical therapy but high doses are frequently required and side effects are common (34). Dual-chamber pacing using a short-programmed atrio-ventricular delay to produce maximum pre-excitation while maintaining effective atrial function can reduce the outflow gradient by 30 to 50%, but provides little objective improvement in exercise capacity in most patients (62). Selective injection of alcohol into a septal branch of the left anterior descending coronary artery to create a localised septal infarction can be effective, but is associated

with atrio-ventricular block requiring a pacemaker in 5-20% of patients and is unsuitable for all patients because of variation in coronary artery anatomy and co-existent mitral valve abnormalities (63).

Surgery is considered in patients with significant outflow obstruction (gradient >50 mmHg) and symptoms refractory to medical therapy. The most commonly performed surgical procedure, ventricular septal myectomy, substantially reduces the gradient and improves exercise capacity and symptoms. In experienced centres, mortality rates are less than 1% and complications such as atrio-ventricular block and ventricular septal defects are rare (64).

Therapeutic options in patients without LVOT gradients are limited predominantly to pharmacological therapy. ß-blockade, calcium antagonists such as verapamil and diltiazem can relieve chest pain and dyspnoea. In patients with paroxysmal nocturnal dyspnoea and chronically raised pulmonary pressures diuretics can be effective, but the dose and duration of therapy should be minimised particularly in patients with severe diastolic impairment or labile obstruction. At present, pharmacological therapy of systolic heart failure in HCM is initiated only when patients develop symptoms and a low ejection fraction. The drugs used (ACE inhibitors (or angiotensin receptor blockers), ß-adrenoreceptor blockers, diuretics and digoxin) are identical to those employed at an earlier stage in patients with dilated cardiomyopathy. In HCM, the benefit of treatment at this later stage is unknown, but it may not substantially improve prognosis.

2.7.3 Management of atrial arrhythmia

Anticoagulation should be considered in all patients with sustained or paroxysmal AF (46). Treatment with amiodarone is effective in maintaining sinus rhythm and in controlling the ventricular response during paroxysmal episodes. The addition of a low-dose ß-blocker, verapamil or diltiazem may be required for rate control. In general, the principles of managing AF in patients with HCM are similar to those in other conditions, with the proviso that the threshold to use anticoagulation should be lower.

2.7.4 Prevention of sudden cardiac death

The published annual incidence of sudden cardiac death in patients with HCM has declined from between 2-4% to 1% or less (65,66). The reasons for this change are complex and relate not only to medical intervention but also to the identification of patients with milder disease. Sudden cardiac death occurs throughout life with a maximum incidence in adolescence and young adulthood, often without warning signs or symptoms (67). Although there is an excess of deaths during or after strenuous exertion, most occur during mild exertion or sedentary activities (34). The mechanism underlying most sudden cardiac deaths is thought to be ventricular tachyarrhythmia, but conduction disease and thrombo-embolism may account for some cases (34). Rapid AF and myocardial ischaemia appear to be important triggers for sudden ventricular arrhythmia (68).

Although sudden death rates are generally low, when it occurs it is often without warning in young and often mildly symptomatic patients. There is therefore a need to accurately identify high risk patients. This is challenging because of the different aetiologies of HCM, a heterogeneous clinical phenotype and evolution of the arrhythmogenic substrate with time. Nevertheless, traditionally a high risk cohort were identified using a small number of readily determined clinical parameters (table 2.1) (34,69).

Table 2.1 – 'Traditional' risk factors for sudden death in hypertrophic cardiomyopathy

Ventricular tachycardia	Sustained or non-sustained on Holter ECG
Familial sudden hypertrophic cardiomyopathy-related death	(particularly in a first degree relative and/or multiple in occurrence)
Syncope	one or more episode, and particularly if recurrent, exertional, or in the young
Abnormal blood pressure response with exercise	a fall or sustained failure to rise ≥20 mm Hg during exercise or recovery
Extreme left ventricular hypertrophy	maximum left ventricular thickness ≥30 mm from echocardiogram

The risk associated with individual risk factors is cumulative (70). Prior to 2014, the presence of two or more conventional risk factors prompted consideration of an implantable cardioverter defibrillator (ICD), as patients with ≥2 risk factors have a 4% to 5% annual risk of sudden cardiac

death (34,71). More problematic are patients that have only a single risk factor (up to 25% of patients). When assessing the need for ICDs in this group, age, symptoms and the presence of so called 'minor' risk factors such as LVOT obstruction were taken into account and balanced against the risk of complications of ICD therapy, particularly in young people (69). These factors are all taken into account in contemporary risk stratification, which uses a sophistiscated algorithm (which can be accessed online) to predict 5 year sudden cardiac death risk (70).

Patients with HCM and risk factors should refrain from intense exercise. This of course has significant implications for many patients, underlining the importance of accurate diagnosis.

2.7.5 Role of electrophysiological testing in HCM

Current guidelines suggest that electrophysiological testing might have a role in some borderline cases (72), but 36% percent of patients have inducible sustained VT (73). VT induced by aggressive protocols may be associated with a higher risk of cardiac events but as the predictive accuracy for sudden death is very low routine use of electrophysiology testing is not recommended (73). One study has suggested that paced ventricular electrogram fractionation may have greater value for predicting sudden cardiac death than conventional invasive criteria or the non-invasive risk factors, but the exact role of this technique requires corroboration in larger populations (74).

2.7.6 Exercise testing in HCM

Cardiopulmonary exercise testing is an important part of the assessment of patients with HCM, providing information on clinical status as well as influencing risk assessment (75,76). It should be a part of the assessment of all new patients attending cardiomyopathy clinic, whether as part of a screening process or in patients with proven disease. Subsequent testing will depend on clinical status: any change in symptomatology, response to drug or outflow tract gradient reduction therapy; transplant assessment; or simply to assess progress over time should all include quantification of exercise tolerance using cardiopulmonary exercise testing.

There are various modes of exercise that can be employed when testing. Simple methods may be designed predominantly to identify provocable LVOT gradients, such as postural manoeuvres, hand-grip exercise and dobutamine infusion. Other modalities designed to better simulate physiological stress in normal life include bicycle ergometer (both upright and supine) and treadmill. Bicycle ergometer studies have the advantage that it is practically easier to make multiple blood pressure recordings, record accurate ECG tracings, quantify power output (measurement of watts) and is generally better accepted by patients, many of whom are not used to treadmills.

Any mode of exercise testing where the aim is to assess maximal oxygen uptake should utilise large muscle groups, and be amenable to performance without prior training which may influence the results achieved. It should avoid undue pressor effects of isometric exercise. In the majority of cases the test should begin with submaximal exercise to allow physiological adaptation; the exception to this is the attempt by a clinician at provocation of a latent LVOT gradient by sudden near maximal effort. The physician and physiologist must determine an individual patient's ability to perform any such test so that diagnostic information is captured. Upright, symptom limited exercise testing is safe in HCM and acceptable to patients. It provides a quantitative assessment of a patient's exercise tolerance, particularly when combined with metabolic functional testing.

2.8 Exercise physiology in hypertrophic cardiomyopathy

Patients who do not report symptoms are often found to have sub-optimal exercise tests when objectively measured and exercise capacity is not well predicted in HCM from conventional markers such as magnitude of left ventricular hypertrophy or peak LVOT gradient (75,77,78). Exercise intolerance is common in HCM, although the exact mechanisms in each individual are likely to vary. A number of variables have been shown to be of importance, including myocardial ischaemia, diastolic dysfunction, chronotropic incompetence, ventilation perfusion mismatch, an inability to augment cardiac output on exercise, and LVOT obstruction, each of which will be discussed. Determining the interplay of these factors in a patient is challenging. LVOT obstruction is often targeted to reduce symptoms, although a significant number of patients continue to experience symptoms even after successful gradient reduction therapy. This is likely due to the complex interaction of these variables. A number of physiological parameters have been studied in HCM with varying degrees of success and importance. However, most of this work, particularly during exercise,

dates from the 1990s or earlier. In particular, the majority of invasive haemodynamic studies are over two decades old. Perhaps this is in part explained by the difficulties in investigating such dynamic variables. There has also been an increased focus on underlying genetic mechanisms behind the disease, risk management, and treatment. In addition, the numbers of patients studied with significant LVOT obstruction in most studies investigating exercise physiology in HCM is small, and the modes used to investigate them often invasive with technical limitations (discussed later).

HCM is a common condition, and prevalence of obstruction is high. There is a need to characterise haemodynamic responses to exercise in a larger number of patients. Current practice in many medical specialities often aims to use non-invasive alternatives to traditional invasive techniques, and there have been technological advances in non-invasive haemodynamic monitoring which have not been applied to this population. The large population of patients seen at the Heart Hospital with HCM, and the availability of non-invasive haemodynamic monitoring make this an ideal environment to add to the research literature. It is clear that despite attention to treatment of LVOT obstruction, a significant number of patients remain functionally limited. There is therefore the need for a greater understanding of the physiological basis for symptoms, which may then translate to improvement in treatment.

2.8.1 Oxygen consumption

Peak VO_2 is routinely measured in patients as an objective assessment of cardiovascular and respiratory performance. Individuals with HCM usually have a reduced peak oxygen consumption and a lower anaerobic threshold compared with healthy age-matched controls (75,79-81). Additionally, some neuromuscular conditions are associated with a hypertrophic cardiomyopathy phenotype. Some sarcomere protein gene mutations are expressed in skeletal muscle and could conceivably affect exercise performance, via reduced peripheral oxygen extraction and anaerobic threshold.

In Sharma's study of 135 patients with HCM, 98% were limited to a peak VO_2 <80% predicted, and less than 1.5% of patients achieved more than their predicted value (75). Increasing New York Heart Association (NYHA) functional class was loosely correlated with peak VO_2. The independent determinants of functional limitation were LVOT obstruction, abnormal blood pressure response (ABPR) and chronotropic incompetence.

It is well recognised that patients with HCM who claim they are asymptomatic often have an objective impairment in VO_2 when assessed (81). Recent retrospective data from 182 minimally symptomatic patients with obstructive HCM have suggested an association between impaired peak VO_2 and prognosis (82). The severity of LVOT obstruction and percent predicted peak VO_2 were identified as independent predictors of death and severe symptoms (NYHA III or IV), suggesting closer follow up of patients with poor exercise tolerance may be necessary. Furthermore, they identified cut off values that predicted adverse events (table 2.2). To my knowledge most studies do not report the amount of exercise performed by patients with HCM, and therefore the effect of detraining on haemodynamics and oxygen consumption is unknown.

Table 2.2. Risk stratified by oxygen consumption in hypertophic cardiomyopathy (82)

% predicted VO_2	Risk	4-year event free survival (%)
>80	Low	85.4
60-80	Moderate	67.2
<60	High	58.5

Frenneaux et al investigated the relationship between haemodynamic indices measured invasively and respiratory gas analysis in 23 patients with HCM (8 with LVOT obstruction) (81). Maximal oxygen consumption was reduced in 11 of 13 patients who were in NYHA class I and who denied limitation of exercise capacity and in all 10 patients who were in functional class II or III. Haemodynamic results of this study are discussed in the appropriate sections.

Jones et al investigated the exercise VO_2 response of 50 patients with HCM (11 with resting LVOT obstruction) using cycle ergometry and respiratory gas analysis (79). They demonstrated a reduction in peak VO_2 and anaerobic threshold. Specifically, 59% of patients achieved less than 60% peak VO_2 and only 2 patients >80%. The anaerobic threshold was <60% predicted in 31 patients and >80% in only 3 patients. The slope of the oxygen uptake/ work rate relationship (a major determinant of the subject's aerobic efficiency) was decreased in 16 patients (32%). The maximum oxygen pulse (numerically equivalent to VO_2 / heart rate, or the product of stroke volume x arterio-venous (A-V) oxygen difference) was reduced as a percentage of the predicted value, and became flat at high work rates in 32 patients. There was a significant correlation between anaerobic threshold and peak VO_2, work efficiency (the slope of increase in VO_2 as a function of work rate) and maximum oxygen pulse. The slope of change in ventilation against change in carbon dioxide output (VE / VCO_2) for the sub-anaerobic threshold range was increased in 36 patients (72%) and was inversely correlated with

anaerobic threshold. The authors concluded that exercise intolerance in HCM could be caused by failure of stroke volume augmentation, ventilation perfusion mismatch and abnormal peripheral oxygen utilisation. No further differentiation between these possibilities could be made from their data.

Sharma et al demonstrated an additional impairment to maximal VO_2 in HCM patients with an ABPR to exercise than those without (75). These findings have also been demonstrated in smaller numbers by Ciampi (ABPR 63% ±11% vs 78% ±15%) (83).

In patients with non-obstructive HCM, VO_2 and minute ventilation / carbon dioxide ratio ($\dot{V}E / \dot{V}CO_2$) at peak exercise correlate modestly (negative and positive respectively) with resting haemodynamics including pulmonary artery systolic, diastolic and mean pressures and pulmonary capillary wedge pressure (84).

2.8.2 Blood pressure response to exercise

An ABPR to exercise has been seen in approximately one third of HCM patients, is associated with an increased risk of sudden cardiac death (37,85-88) and makes up part of contemporary risk stratification algorithms (34). Several researchers have noted those with ABPR tend to be younger (83,87,88). A normal blood-pressure response is usually defined as a gradual increase of at least 20 mm Hg in systolic blood pressure during exercise. An ABPR may take one of several forms: an increase or decrease in systolic blood pressure during exercise < 20 mm Hg compared with baseline; an initial increase in systolic blood pressure with a subsequent fall >20 mm Hg compared with peak blood-pressure value; a continuous decrease in systolic blood pressure throughout the exercise test >20 mm Hg compared with baseline (85-88). These last two conditions are termed “hypotensive blood pressure response,” while the first condition represents a flat response.

There are a variety of explanations for this, including abnormal vasodilatation of non-exercising vascular beds triggered by inappropriate firing of left ventricular baroreceptors (85) and abnormal cardiac output responses (83,89), which itself has several explanations, including ischaemia and LVOT obstruction (90-93).

A recent study by Heffernan et al investigated the correlation between pulse pressure (arterial systolic minus diastolic blood pressure) and an ABPR to exercise (94). Interestingly they found in a

group of 70 patients with HCM that pulse pressure at rest was significantly greater in patients who went on to demonstrate an ABPR (n = 19) than in the patients without an ABPR to exercise. There was no difference in systolic, diastolic or mean arterial pressure (MAP) between the groups. Those within the greatest tertile of pulse pressure at rest were 4.8 times more likely to have an ABPR than those within the lowest tertile (95% confidence interval 1.24 to 18.2, $p < 0.05$). In their study there was no difference in pulse pressure or ABPR rates between obstructive and non-obstructive groups. They proposed that this may be a useful tool to identify those patients who may have an ABPR.

The increased pulse pressure was felt to be a manifestation of increased arterial stiffness and augmented pressure from wave reflections, both of which have the effect of increasing cardiac energetic demand, reducing myocardial oxygen supply / consumption, reducing sub-endocardial perfusion (95) impairing cardiac systolic and diastolic function, and blunting stroke volume (96). In patients with HCM in whom these abnormalities often exist, it may be difficult to determine cause and effect.

Patients with HCM have been shown to have greater arterial stiffness than controls, particularly in the setting of associated myocardial fibrosis (97). The underlying reason is uncertain, although may relate to abnormal endothelial function. This is discussed in more detail in section 6.2.4. This group demonstrated age and aortic stiffness (assessed using MRI) to be independently associated with maximal VO_2 (98). It seems reasonable then that a wide pulse pressure in patients with HCM reflects increased aortic stiffness, and thus a propensity to ABPR and impaired exercise capacity for all the reasons cited above. What is less easily explained by this theory is the increased incidence of ABPR in young people, when aortic stiffness should be a phenomenon associated with older age. Traditional markers of 'severity' seen in younger patients with ABPR could be associated with an increased aortic stiffness.

An increase in arterial stiffness in the vasculature containing baroreceptors (shown in hypertension and aortic stenosis) could explain the reduction in sensitivity to afferent arterial pressure stimuli in HCM patients with ABPR. This would result in a reduction of baroreceptor afferent firing per given unit of arterial pressure change, less inhibition of sympathetic outflow (altering peripheral vascular tone), and lessened amplification of cardiac vagal tone (altering left ventricular contractility) (99). Thaman et al demonstrated a lower resting baroreflex sensitivity and exaggerated changes in baroreflex sensitivity during lower body negative pressure in a group of HCM patients with high prevalence of ABPR (100). It seems plausible then that in the presence of baroreceptor dysfunction, autonomic control of vascular function should also be impaired and contribute to ABPR to exercise.

Yoshida et al found evidence of sub-endocardial ischaemia during exercise in patients with HCM (90). They used left ventricular cavity dilatation measured using thallium-201 scintigraphy after exercise as a marker of sub-endocardial hypoperfusion and found a higher prevalence in those with an abnormal compared to those with normal blood pressure response (47.1 vs. 10%, $p < 0.0002$). On multivariate logistic regression left ventricular cavity dilatation was independently associated with ABPR (odds ratio 3.76, 95% confidence interval 1.61 to 8.76). Sub-endocardial ischaemia could contribute to a worsening of systolic performance on exercise and the resulting ABPR (91-93).

Ciampi felt the reasons for an ABPR to exercise were a cascade beginning with systolic impairment due to an inability to tolerate an increased end systolic volume, then a reduction in cardiac output which then manifests as a hypotensive response (83). These authors felt the observed responses were consistent with myocardial ischaemia.

Kim demonstrated an improvement in exercise capacity and ABPR when LVOT obstruction was abolished by ASA (101) suggesting the cavity gradient may have a role in the blood pressure response. In their group 9 patients with an ABPR had this resolved following treatment. 17 of their 20 patients demonstrated a symptomatic improvement with an increase in exercise duration and VO_2.

2.8.3 Myocardial perfusion and ischaemia

Evidence for myocardial ischaemia during dipyridamole stress has been demonstrated in HCM patients by invasively monitoring changes in coronary sinus pH (28). This study demonstrated a larger fall in pH in HCM patients symptomatic with chest pain. There was a correlation between maximal pH change and higher heart rates upon stress. Myocardial ischaemia has also been demonstrated by lactate production during atrial pacing (27). In this study, those with resting LVOT obstruction had higher myocardial VO_2, lower coronary resistance and higher basal coronary flow than those without obstruction. Interestingly in both groups there was evidence of symptomatic myocardial ischaemia beyond heart rates of 130 beats / minute, with exhaustion of transmural coronary flow reserve in those with LVOT obstruction. In the non-obstructive group, evidence of ischaemia occurred at lower coronary flow rates with lower myocardial VO_2, suggesting a lower threshold to symptoms upon stress. Marked elevation in filling pressures were noted in both groups.

Perfusion defects on nuclear imaging, both fixed and reversible, are common amongst patients with HCM in the absence of stenotic coronary disease (90,91). In the study by Yamada et al fixed

perfusion defects detected during dipyridamole stress in patients with HCM were associated with syncope, larger LV cavity dimensions and reduced exercise capacity (91).

Abnormalities of coronary vasodilatation have been demonstrated in HCM compared with controls using positron emission tomography to assess regional myocardial blood flow after pharmacological dilation using dipyridamole (102). Resting blood flow was similar between groups. Although a reduction in coronary resistance was seen in all groups, this was significantly less in those with HCM, which was also associated with a history of chest pain.

2.8.4 Left ventricular systolic function and cardiac output

Accurate measurement of left ventricular systolic function is notoriously difficult in routine clinical practice, yet is an important determinant of exercise capacity in health. It has been the focus of extensive research in HCM. Pump function must be sufficient to supply exercising muscles with sufficient blood and oxygen to perform work, and to the respiratory muscles to allow efficient respiration. In non-obstructive HCM, a reduction in systolic performance was observed in about half of patients in a study using continuous ventricular monitoring with a cadmium telluride detector (CdTe-VEST) (92). Systolic dysfunction was not related to the degree of septal hypertrophy. These findings were replicated by Okeie et al, who also demonstrated regional wall motion abnormalities in hypertrophied segments on dobutamine stress in the absence of coronary disease (93).

Ciampi et al demonstrated a difference in end systolic volume (using nuclear scintigraphy) on exercise between HCM patients with and without ABPR to exericse (83). In those with a normal response, end systolic volume increased less. Both groups were noted to have a reduction in ejection fraction on exercise, with a greater fall in the ABPR group. In their small (ABPR = 8, NBPR = 14) group of patients, there was a small increase in stroke volume on exercise in the NBPR group, and a fall in the ABPR group (3% ±28% and -21% ±21% respectively). Their nuclear data were however averaged over 60 second intervals, and taken at baseline, 3 minutes of exercise and peak exercise only. This infrequent sampling rate is inadequate to monitor physiological changes during an exercise test. Similarly, cardiac output response to exercise was shown to be an increase of 94% ± 44% in the NBPR group and only 49% ±44% in ABPR group. This implies augmentation of heart rate to be the mechanism for an increase in cardiac output in the ABPR group.

The same group had previously shown a statistically significant increase in ejection fraction and stroke volume in control subjects compared with the reverse in HCM (89). Overall HCM patient's stroke volume fell by 5% ± 27% relative to baseline. When subdivided into NBPR and ABPR groups, stroke volume increased in the former and fell in the latter (2 ±27% and -18±21% over baseline). Cardiac output increased on exercise in both groups, although significantly more in controls (132% ± 70% vs 78% ± 50% compared with baseline). Heart rates have been shown to rise appropriately in HCM patients on exercise both with and without ABPR (83,89).

Frenneaux et al showed a significant correlation between peak exercise cardiac index (measured using Fick method) and the change in index from baseline with maximal VO_2 (81). There was no correlation with diastolic parameters (discussed in the relevant section) and the authors concluded that cardiac output was a major determinant of exercise capacity but that the role of diastolic function and other parameters required further investigation.

Jones et al investigated the relationship of gas exchange indices during incremental exercise in patients with HCM. They found a low maximum value of oxygen pulse and felt this was consistent with the failure to continue to increase stroke volume during exercise (79). They noted that the possibility that this pattern of oxygen pulse may have been associated with a decreasing stroke volume and further widening of the A-V oxygen content difference could not be excluded.

2.8.5 Systemic vascular resistance

Counihan and co-workers assessed forearm vascular responses to supine and upright exercise in patients with HCM (85). Their normal control population demonstrated a mean decrease in forearm blood flow of 12% during exercise. Approximately two thirds of their patients had a 'normal' response to exercise, and in one third they noted either a failure to decrease or an increase in blood flow. There was an association in this latter group with younger age, family history of HCM and sudden cardiac death. They also noted an association with smaller cavity dimensions, leading them to conclude that this comparatively large increase in wall stress during exercise may activate left ventricular mechanoreceptors which play a part in an abnormal vascular response. When the investigators went on to perform upright exercise, they found 79% of those patients with abnormal forearm vascular response on exercise also had a systemic hypotensive response to upright exercise. Of the remaining 'normal' response group, 63% actually had what were described as abnormal

oscillations in recovery (defined as a rapid decrease of 10 mm Hg or more and subsequent increase in systolic blood pressure of more than 10 mm Hg from the minimum recovery blood pressure).

In the ABPR group there was no association between peripheral haemodynamic indices and LVOT gradient, although those with abnormal responses had smaller left atrial and left ventricular end diastolic size. There was also a significant association with a family history of sudden cardiac death, prompting the authors to conclude that abnormal peripheral responses could be a marker of haemodynamic instability causing this increased risk. In a subset of HCM patients studied invasively, there was no significant difference in peak cardiac index between those with and without ABPR to exercise although this was marginally higher in the former group (86). Cardiac index increased fivefold in both groups though magnitude of increase was greater in hypotensive patients, implying blood pressure change on exercise was not related to cardiac output. There was no difference in LVOT obstruction between groups suggesting that obstruction was not a factor in exercise hypotension.

In the more recent paper by Ciampi, they showed a fall in systemic vascular resistance (SVR) on exercise in both NBPR and ABPR groups (-34% ±26% and -28% ± 26%, respectively, over baseline; *P* =NS). SVR was not measured directly but a global assessment was made by calculating it according to the following formula: SVR = 80 x (MAP / cardiac output), and was considered to be 100% at the beginning of the study, subsequently expressed relative to this value. This group had previously demonstrated a similar fall in SVR between normal controls and HCM (89). Although there was a trend to a greater decrease in the control group this did not reach statistical significance. The difference in methodology (in addition to the omission of right atrial pressure from the calculation) may explain the findings contradictory to the work on local SVR by Counihan and Frenneaux (85,86). Global SVR is the sum of different adaptation processes to exercise: the local effect of exercise metabolites, cortical influences, reflex activation of metabolic receptors in skeletal muscle, and increased ventricular baroreceptor activity (103). As such the local changes observed by Counihan and Frenneaux are unlikely to be reflected in the more general assessment performed by Ciampi's group.

2.8.6 Diastolic function

Diastolic dysfunction has been shown to cause impaired exercise tolerance in non-HCM populations. Cardiac output during exercise depends on the left ventricle increasing its ability to fill without adversely increasing left atrial pressure (104). Historical studies demonstrated resting diastolic abnormalities and increased left atrial pressure in HCM patients compared with controls (105,106), and diastolic dysfunction has long been regarded a contributor to exercise limitation (81,107,108). The abnormalities of filling have been proposed as a contributory mechanism to exercise limitation (81), and are compounded by the reduced filling time encountered at higher heart rates on exercise.

The optimal technique to measure diastolic function, particularly on exercise due to technical considerations, is not clearly established. Conventional Doppler indices of left ventricular diastolic function do not correlate with symptoms or exercise capacity in patients with HCM (109,110). The mitral valve Doppler profile is affected by variables independent of diastolic function, such as filling (111) and have not been shown to correlate with invasively measured diastolic parameters (112).

An early study in 52 patients with HCM using transthoracic echocardiography showed that exercise capacity was determined by passive LV diastolic function, as assessed by the resting left atrial M-mode and Doppler-derived pulmonary venous flow velocities (113). Left atrial fractional shortening and the pulmonary venous systolic filling fraction were however the only determinants of the maximum VO_2 ($r = 0.70$; $p < 0.001$). However, correlation coefficients were low, and no attempt was made to study Doppler indices on exercise. This group did not show any significant correlation between mitral valve Doppler parameters and peak VO_2. A more contemporary study using tissue Doppler showed that early diastolic mitral annular velocities are reduced in patients with HCM and unlike conventional Doppler indices alone, the transmitral E to lateral Ea ratio correlates with NYHA functional class and exercise capacity (114). However in that study the correlation between the transmitral E to lateral Ea ratio and VO_2 was relatively modest, suggesting that other factors such as a reduced stroke volume response, ventilation / perfusion mismatch, and abnormal peripheral oxygen utilisation also influence exercise capacity.

Abnormal Doppler diastolic indices have been identified with similar frequency in patients with (78%) or without (83%) LVOT obstruction, as well as in patients with (84%) or without (80%) cardiac symptoms (109). However, patients with non-obstructive HCM showed more severe alterations in the Doppler indexes of diastolic function than did patients with obstruction.

Frenneaux et al showed no correlation between indices of diastolic function (pulmonary capillary wedge pressure (PCWP) – at rest and peak, and the change during exercise, left atrial size) and maximal VO_2 in 23 HCM patients studied invasively (81). Despite the lack of correlation with cardiac

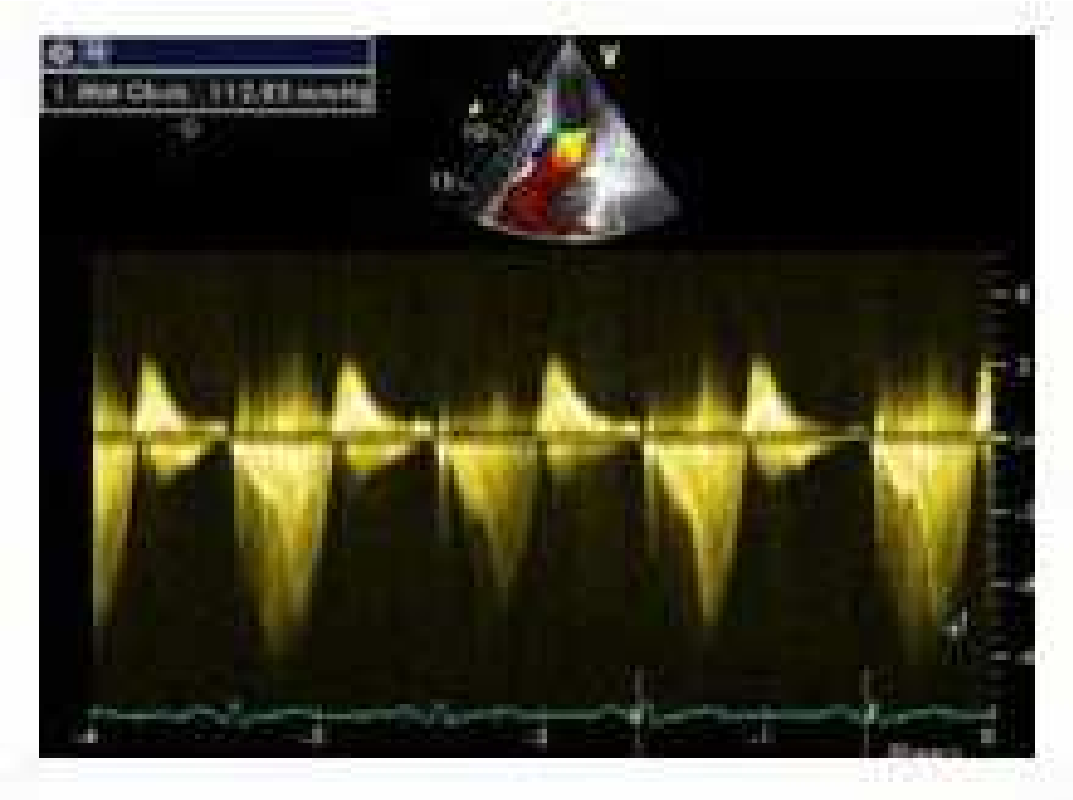
index, abnormal responses of PCWP to exercise were observed, and the authors felt their population was representative of a wider HCM population. They excluded anyone with severe mitral regurgitation as the resulting increase in left atrial pressure may have affected their results. Similarly no significant relationship has been shown between left atrial pressure and exercise capacity in a general heart failure population (115,116). PCWP itself is a reflection of left atrial pressure assuming there is no trans-pulmonary gradient. In the longer term elevations may point towards diastolic dysfunction. However, it does not really represent a good measure of left ventricular filling, or indeed the 'stiffness' which may accompany an inability to augment stroke volume at higher heart rates and therefore influence exercise capacity.

Dumont et al attempted to quantify left ventricular stiffness by using the ratio of PCWP (derived from the E/Ea ratio) to LV end-diastolic volume (assessed by CMR) (117). By using a different definition of resting diastolic dysfunction to Frenneaux, they found a LV stiffness level of 0.18 mm Hg/ml had 100% sensitivity and 75% specificity (area under the curve 0.84) for predicting <7 metabolic equivalents (METs) achieved. In their study there were inverse correlations between METS achieved and age, heart rate deficit, E/Ea ratio, left ventricular stiffness and wall thickness and a positive correlation with left ventricular volume, although only left ventricular stiffness was associated with an impaired exercise capacity on multivariate analysis. Whilst often measured, MWT has not been shown to be a determinant of exercise capacity in HCM (118).

2.9 Left ventricular outflow tract obstruction

LVOT obstruction by definition implies an obstruction to the forward flow of blood being ejected from the left ventricle. However, it is a complex phenomenon which is incompletely understood. What is clear is that it is common, often associated with significant symptoms and a worse prognosis, and is commonly targeted as a treatment strategy. It can be detected during physical examination, and usually quantified using echocardiography by measuring the pressure gradient between the left ventricular cavity and the aorta (figure 2.6). Under resting conditions, 25% of patients have obstruction to the LVOT, whilst up to 70% of symptomatic patients may have latent, or provocable LVOT obstruction during manoeuvres that increase contractility or reduce afterload and preload (119,120).

Figure 2.6. Echocardiographic doppler profile demonstrating a significant left ventricular outflow tract gradient.



2.9.1 Mechanism

LVOT obstruction has long been recognised as an important phenomenon in HCM. However despite being the subject of intense scrutiny the complex underlying mechanism of LVOT obstruction remains incompletely defined. Essentially four anatomical features predispose an individual heart to LVOT obstruction, but their pathophysiological interaction may be complex: the muscular hypertrophy extending into the outflow tract (121); abnormal mitral valve leaflets capable of moving anteriorly (122-128); the mitral valve annular position in the cavity and the size and orientation of papillary muscles which position the mitral valve leaflets into the path of blood leaving the ventricle (124,129-132). The relative importance of each factor in any given individual can be difficult to determine, but is usually seen in combination with hyperdynamic ejection (133).

2.9.1.1 Systolic anterior motion of the mitral valve

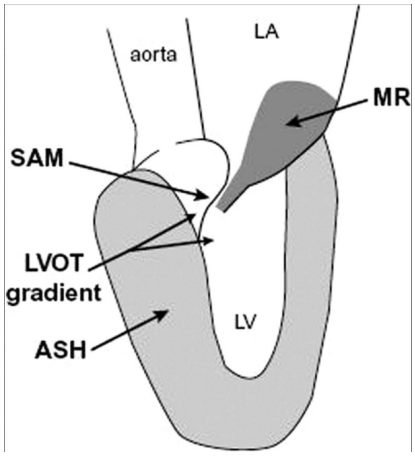
In most cases, obstruction is associated with systolic anterior motion (SAM) of the mitral valve, in which the anterior mitral valve leaflet and/or its sub-valvular apparatus move towards and makes contact with the ventricular septum in systole (figure 2.7). The most commonly accepted explanation for SAM is that septal hypertrophy, and consequent narrowing of the outflow tract, increase the velocity of blood above the mitral valve. The leaflet tips are projected into this stream, exposing them to the hydrodynamic force of drag and pushing them further towards the septum (134-136). The leaflet tips may also be exposed to the "sucking" effect of Venturi forces generated by the high velocity blood in the LVOT (137-139). The relative contribution of each of these mechanisms remains unclear, and in practice may vary between individuals with differing ventricular and valvular geometry. Most patients with SAM have a posteriorly directed jet of mitral regurgitation, but the presence of complex jets (e.g. anteriorly-directed or central) suggests additional mitral valve abnormalities.

Experimental and observational data suggest that abnormalities of the sub-valvular apparatus such as anterior papillary muscle displacement and primary mitral valve abnormalities such as accessory mitral tissue create leaflet "slack" to allow SAM at low flows (136,140). Systolic obliteration of the ventricular cavity can also produce a high velocity gradient in the mid-ventricle (141) and right ventricular outflow tract obstruction is common in Noonan syndrome and some metabolic disorders (142).

2.9.1.2 Primary mitral valve abnormalities

The heterogeneity of mitral valve abnormalities has long been recognised (127). Enlargement of mitral valve leaflets is a feature of both obstructive and non-obstructive HCM, suggesting that this is a primary abnormality rather than a consequence of being stretched over time with LVOT obstruction (127). 3D imaging modalities have helped shed light on the specific role of the mitral valve in LVOT obstruction (143,144). Using 3D echocardiography, Kim et al investigated the relative effects of mitral valve anatomy and geometry on LVOT obstruction (140). They found that mitral annular areas, annular height and mitral leaflet areas were larger in patients with resting obstruction than non-obstructive HCM and controls.

Figure 2.7. Systolic anterior motion of the mitral valve (145).



ASH: Asymmetric septal hypertrophy; LVOT: left ventricular outflow tract; MR: mitral regurgitation; SAM: systolic anterior motion of the mitral valve

This cartoon demonstrates anterior movement of the mitral valve during systole as a result of ASH, causing both LVOT obstruction and mitral regurgitation.

2.9.1.3 Papillary muscle abnormalities

Anterior displacement of the papillary muscles has the effect of interposing the mitral valve leaflets into the LVOT, pushing them into the septum (134,136,146,147). This also reduces the ability of the posterior leaflet to coapt with the anterior leaflet. Additional congenital abnormalities such as a solitary or multi-headed papillary muscle or direct insertion into the mitral valve leaflets, are commonly seen. Papillary muscle abnormalities have been cited as a potential cause for residual LVOT gradients after ASA therapy (147). In addition they have provided a potential target for surgical therapies (129,148-150). If a mitral valve ring is required at surgery the shape can potentially exert an effect over LVOT obstruction. A flat ring exerts more stress on the leaflets which decreases leaflet slack (151,152).

2.9.2 Provocable left ventricular outflow tract obstruction

In contrast to a fixed obstruction such as aortic stenosis, LVOT obstruction is to a varying degree dynamic; that is, subject to change and influence by factors such volume loading, heart rate and

contractility. Traditionally clinical assessment for LVOT obstruction was made at rest. It is now well recognised that latent, or provocable obstruction must be actively sought during clinical assessment. Provocable LVOT obstruction should be excluded in patients with suggestive symptoms and no resting LVOT gradient (120,153,154) as it is associated with reduction in functional class (155). Furthermore, interventional treatment improves both exercise tolerance and outcome (156,157).

Common stress techniques to provoke obstruction during Doppler echocardiography include physiological (Valsalva manoeuvre, exercise) or non-physiological (drug administration e.g. sub-lingual nitrate). However, few data exist on methods for determining which patients may benefit from further investigation with stress echocardiography, which is a decision primarily based on clinical opinion. At the heart hospital current practice aims to replicate situations which might provoke patient symptoms in day to day life. Standard Bruce protocol exercise tests are therefore not ideal due to the graded nature of exertion. We perform exercise in the upright position, with the intention of rapidly increasing the incline and speed of the treadmill to simulate, for example, hurrying for a bus. Doppler echocardiography is then performed immediately, still in the upright position, on cessation of exercise at the limit of effort tolerance.

2.9.3 Clinically important associations

In addition to symptoms, there is an association between LVOT obstruction and various disease related complications. Traditionally, it was considered to be a risk factor which may prompt the clinician towards more aggressive treatment in an otherwise equivocal case (158) 194, 196]. LVOT obstruction is now part of contemporary risk stratification, appearing in a recently published sophisticated algorithm (70) . LVOT obstruction is also associated with stroke. In an unselected HCM population, prevalence was found to be 6% and incidence 0.8% per year (44). Embolic phenomenon are largely related to AF, and in a recent large metanalysis of 7381 patients (including 33 studies), overall prevalence in HCM patients with AF was 27.09% (95% CI 20.94% to 33.25%). Death from heart failure, or NYHA class III or IV symptoms are more common in patients with LVOT obstruction (relative risk, 2.7; $P<0.001$), especially in those aged over 40 ((159). However, no excess incidence in heart failure has been seen in patients with severe obstruction. Provocable LVOT obstruction is associated with functional impairment and heart failure symptoms,(154,155,159) and there is good evidence that invasive treatments should be offered to these patients (156,157).

2.9.4 Treatment of LVOT obstruction

In patients with symptoms caused by LVOT obstruction, the aim of treatment is to reduce the outflow tract gradient. Options include negatively inotropic drugs (ß-blockers, disopyramide and verapamil), atrioventricular sequential pacing, percutaneous ASA of the interventricular septum and surgery. With both invasive procedures, results are improved with experience and higher volume centres should be preferred for referral.

2.9.4.1 Medical

Approximately 60 to 70% of patients improve with medical therapy but high doses are frequently required and side effects are common (34). β-blockers are recommended as first line treatment for exercise intolerance in HCM, particularly in patients with LVOT obstruction (34). Diastolic characteristics and ischaemia are improved by reducing heart rate and improving filling time. Although β blockade is useful for rate-control in the treatment of atrial arrhythmia (common in HCM), and are used to help prevent ventricular arrhythmia (34), a mortality benefit has not been clearly established and they do not appear to adequately protect against sudden cardiac death (160). A recent trial of bisoprolol in patients with provocable obstruction demonstrated a significant reduction in outflow tract gradient (161).

Non-dihydropyridine calcium channel blockers are frequently used in the treatment of both non-obstructive and obstructive HCM, with verapamil being the most common agent. Negative chronotropic and inotropic effects help to reduce the gradient in patients with obstruction and improve symptoms. However, as with β blockers contemporary trial data is scant (162-166). The use of verapamil is not uncommonly restricted by side effects including constipation and peripheral oedema, although haemodynamic consequences such as depression of sino-atrial function, hypotension and rarely pulmonary oedema should also be recognised (167). Diltiazem is routinely used in non-obstructive patients and improves diastolic relaxation and filling (168), and ischaemia on exercise (169).

Disopyramide is a class 1a anti-arrhythmic agent used as an adjunct in medical therapy of patients with obstruction to improve haemodynamics and exercise tolerance (170-172), often prior to invasive septal reduction therapy. It has been shown to be safe (173) although should be concomitantly administered with either β blockers or rate slowing calcium channel blockers as atrio-ventricular nodal conduction can be accelerated. QT interval must be monitored after prescription to exclude significant lengthening. Other common side effects limiting its use are related to anticholinergic action, such as dry eyes and mouth, constipation and urinary retention.

2.9.4.2 Right ventricular apical pacing

Dual-chamber pacing using a short-programmed atrio-ventricular delay has been used as a less invasive method of treating LVOT obstruction. Initial work investigating the effects of RV apical pacing appeared promising, showing improvement in symptoms and haemodynamics in the first few months after pacemaker implantation in patients with resting and provocable LVOT obstruction (174), with benefit maintained at one year (175). Later prospective randomised studies showed little objective evidence of benefit, with significant placebo effect, although there is some suggestion older patients may respond more favourably (62,176). Lastly, pacing has been shown inferior to surgery (177).

2.9.4.3 Alcohol septal ablation

ASA is a trans-catheter interventional procedure designed to treat LVOT obstruction. Either femoral or radial routes may be used. A septal perforator vessel is identified, and balloon occlusive angiography performed following which a contrast agent is injected. This is visualised using echocardiography, with the intention of localising dye to the point of SAM septal contact. Once a suitable target vessel has been identified, a small quantity of neat alcohol is injected. This has the effect of initially stunning the myocardium, followed in subsequent months by necrosis and regression of hypertrophy with the intention of reducing LVOT gradients. The procedure is generally well tolerated. Standard risks of coronary angioplasty include bleeding, vascular damage, arrhythmia, tamponade, myocardial infarction, stroke, emergency bypass surgery and death with a

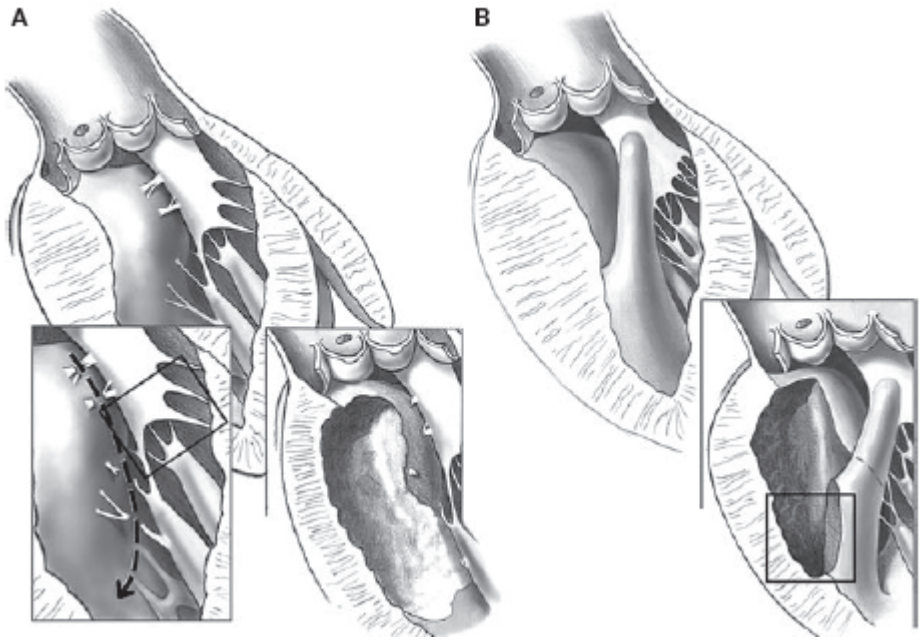
typical figure of 1% quoted. The main additional risk related specifically to ASA is the need for permanent pacing due to damage to the conduction system, with rates up to 18% (178,179). Commonly patients develop a right bundle branch block pattern on ECG following the procedure (178,180).

With respect to exercise, a meta-analysis of 42 published series of ASA showed an improvement in mean NYHA class from 2.9 at presentation to 1.2 at 1 year($P<0.001$) (181). At 1-year follow-up, peak VO_2 increased from 17.8 to 23.6 mL/kg/min ($P < 0.001$) and mean exercise capacity on a treadmill increased from 325.3 to 437.5 seconds ($P <0.001$).

2.9.4.4 Surgical myectomy

Surgical myectomy remains the gold standard treatment for drug-refractory LVOT obstruction. Whilst overall operative success rates are very good, it is difficult pre-operatively to determine factors pertaining to the actual surgery which may influence the post-operative symptoms. Surgical technique has changed over the years, with many centres abandoning the classical Morrow procedure in favour of an extended myectomy. The original Morrow operation involved access to the heart via an oblique aortotomy, and a trench shaped resection was made into the LVOT basal septum (figure 2.8). An extended myectomy results in a shallower trough, with the resection border extending either laterally or posteriorly. The advantage of this approach is that the surgeon may deal with more eccentric patterns of distribution of hypertrophy. Typically, patients have a left bundle branch block pattern on ECG following myectomy.

Figure 2.8. Surgical myectomy for hypertrophic cardiomyopathy with left ventricular outflow tract obstruction (182).



Panel A: a standard rectangular Morrow myectomy trough. Panel B: an extended midventricular resection due to extensive hypertrophy and anomalous papillary muscle insertion

Potential disadvantages include impaired left ventricular contractility of the resected muscle post-operatively (possibly due to ischaemia or scar) and an increased likelihood of conduction problems. In addition, it can be challenging for the surgeon to directly visualise the area to be resected, particularly whilst on cardio-pulmonary bypass. Optimal pre and intra-operative imaging discussed with the surgeon is therefore important for a successful outcome. At present, this usually includes CMR, 2-D transthoracic and 3-D trans-oesophageal echocardiography.

In a recent report on surgical outcomes a mitral valve procedure was necessary in 13.5% (115/851), including mitral valve replacement in 41.7% (48/115) (183). These data support the need for a comprehensive patient specific assessment prior to surgery where the potential need for contemporary mitral valve procedures (Alfieri, plication or papillary muscle re-orientation) can be assessed.

No randomised controlled trials exist comparing myectomy and ASA. A recent meta-analysis of 5 studies including 183 patients undergoing ASA and 168 myectomy showed the ASA group tended to

be older (mean age 54.4 +/- 6.3 vs. 45.0 +/- 4.4 years, P = 0.02), although similarly symptomatic and with equivalent LVOT gradients (81.4 +/- 14.3 mmHg in ASA vs. 77.4 +/- 15.5 mmHg in myectomy, P = 0.2) (179). Both treatments were effective at gradient reduction, although lower figures were achieved in the surgical group (18.2 +/- 6.7 vs. 10.8 +/- 6.3 mmHg, P < 0.001). Reduction in NYHA class was similar (1.5 +/- 0.3 in ASA vs. 1.3 +/- 0.2, P = 0.2). In hospital mortality was similar, although more patients having ASA required a pacemaker (18.4 +/- 7.9 vs. 3.3 +/- 3.9%, P = 0.04).

A historical study in 1979 of 29 patients following myectomy showed an improvement in peak VO_2 from 16 to 21 ml/min/kg (P<0.005) (184). Interestingly, surgery was associated with a significant increase in cardiac index during maximal exercise (5.0 to 5.7 litres/min per m^2, P<0.05). Another from 1992 investigating exercise improvement following myectomy identified preoperative impairment in peak VO_2, and a post-operative reduction in LVOT gradient and LV filling pressures as multivariable predictors of a positive change in peak VO_2 at 6 months (185).

It is clear that randomised studies are required to fully investigate the differences between ASA and myectomy. However, the heterogenous nature of HCM makes accurate randomisation difficult, and the nature of the treatments means blinding is impossible. Furthermore, bias in individual centres is evident from the literature, and appropriate trials with large numbers of patients seem unlikely.

2.9.5 Unanswered questions

It is now widely accepted that LVOT pressure gradients can cause breathlessness, chest pain and syncope and that their treatment with negative inotropic drugs or invasive reduction of septal thickness results in clinical improvement (34). However, this does not explain the enormous variability in symptoms associated with identical degrees of obstruction and the poor correlation between LVOT gradients and objective measures of exercise capacity. Nor does it explain the unfortunate clinical scenario of ongoing symptoms following ‘successful’ gradient reduction. There is therefore the need for further understanding of the phenomenon, particularly its relation to exercise.

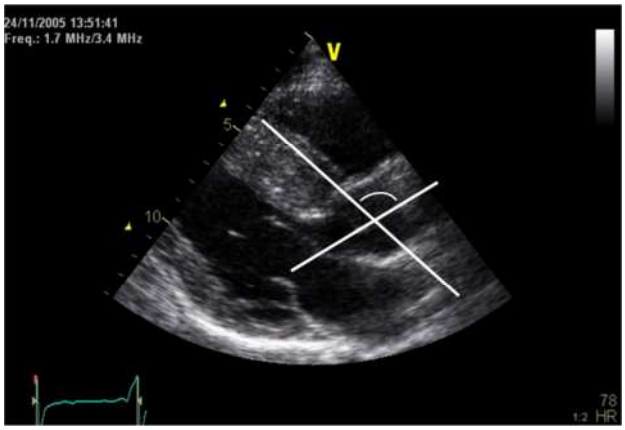
It is increasingly recognised that assessment of cardiac parameters at rest in patients with any cardiac disease is unrepresentative of the physiology behind symptoms, and efforts should be made to perform investigations during exercise. With regard to HCM with LVOT obstruction, the gold standard for diagnosing provocable obstruction is stress echocardiography during exercise in the upright position. However, whilst this approach has proved useful for diagnosis of provocable

obstruction, it provides little haemodynamic information on the functional consequences, which may have implications for the correct treatment.

2.10 Aorto-septal angulation

In addition to abnormalities of the mitral valve discussed above, other geometric LVOT abnormalities are frequently seen in HCM. One of these is aorto-septal angulation. The aorto-septal angle is the angle formed between the aorta and the interventricular septum (figure 2.9).

Figure 2.9. Aortoseptal angulation



Transthoracic parasternal long axis echocardiogram demonstrating the plane of the inter-ventricular septum (longer line), the aorta, and the aorto-septal angle between the two.

Whilst a standardised measurement technique using echocardiography has been described (186), this has never been used in patients with HCM, in whom it might be expected to be difficult to apply given the highly variable LVOT geometry. The most commonly adopted in the literature is the angle formed by the long axis of the ascending aorta and the plane of the ventricular septum, initially described by Fowles and colleagues (186-190). The normal range of aorto septal angle in patients without structural heart disease in the Fowles' study was 128^{o} ± 1.9 (SEM), range 122-132. However, patient numbers have been small (Barkhordarian, 21; Olafiranve 75; Sigfusson 45; Kleinert 58) and in most studies no attempt was made to assess inter-observer variability. However, Sigfusson used 2 independent examiners and found an excellent inter-observer correlation (r=0.997, mean inter-observer difference 4.8%).

Aorto-septal angulation is an anatomical feature commonly seen in advancing age, hypertension and aortic stenosis (186,187,190-192). In addition, in children it has been associated with sub-aortic

valve obstruction. In the case of aortic stenosis, increased aorto-septal angulation can be associated with ASH (186). Abnormal flow in the LVOT made worse by acute angulation can increase left ventricular intra-cavity pressure (193). In turn, re-modelling may be adversely affected.

Although not uncommonly seen in HCM, it has been little investigated. Recently however, aorto-septal angulation has been shown to be predictive of LVOT obstruction in HCM using 3D imaging techniques (191). Whether this is a pathological feature of HCM or a secondary result of the already abnormal ventricular geometry is not known. Fluid modelling studies testing the effect of variable flow angulation have demonstrated that the Shear stress on the basal septal surface increases with a steeper aorto-septal angle (194), which in animal models is associated with vascular obstruction (195). A steep angle is also associated with increased arterial pressure wave reflection and central blood pressure, which is known to impact left ventricular hypertrophy (188).

In routine clinical practice, aorto-septal angulation in HCM is commonly described as being suggestive of provocable LVOT obstruction, prompting further assessment often with stress echocardiography. However the lack of a standardised method of measurement that can be used in patients without recourse to complex 3-D imaging techniques limits the usefulness of this parameter in day to day practice.

Diagnosis and treatment of provocable LVOT obstruction is recommended. However, access to stress echocardiography is highly variable, dependent on equipment and expertise. A simple tool that could help predict those patients who go on to develop significant gradients would be of benefit.

I therefore had two aims. Firstly I sought to determine whether aorto-septal angulation could be reliably and accurately measured using a modification of the existing standard transthoracic echocardiography technique, and validate this against CMR. Secondly I investigated whether this was an anatomical predictor of provocable LVOT obstruction in a large cohort of patients with HCM and no resting obstruction.

2.10.1 LVOT orifice area

One would expect that the geometric changes in the LVOT during obstruction would result in a reduced cross sectional area, and this has been demonstrated in several studies. An early 3D echocardiographic study of 25 patients with HCM and SAM measured the minimal LVOT area in real time and compared it to the maximal velocity of blood flow, and used a 2D measurement of SAM-septal distance as 'control'(196). The LVOT area ranged from 0.6 to 5.2 cm^2 (mean: 2.2 +/- 1.4 cm^2),

and a highly significant inverse correlation was seen with blood velocity. A poorer although still highly significant inverse correlation was seen between SAM – septal distance, prompting the authors to conclude that 3D echocardiography is a useful tool for assessing patients with HCM. No attempt was however made to evaluate the added benefit that this technique has on diagnosis or treatment. However, the same group later performed real-time 3D echocardiography in 10 patients undergoing myectomy. The exact location of SAM was shown with a predominant involvement of the medial portion of the mitral valve in 4 patients and the middle portion in 6 patients. The smallest area of the LVOT significantly increased after myectomy (1.4 +/- 0.7 vs 4.8 +/- 1.8 cm^2, p <0.01). Whether the addition of 3D contributed to additional operative benefit through improved intra-operative anatomical visualisation was not directly assessed (197). Not surprisingly in Kim's study (140) the minimal LVOT area during systole, reflecting the combination of septal hypertrophy and SAM, was smallest in patients with LVOT obstruction and smaller in patients without obstruction than in controls (0.56±0.31 versus 2.75±0.66 versus 4.05±0.70 cm^2; *P*<0.001). The LVOT area in diastole also showed similar trends (3.33±1.01 versus 5.80±1.28 versus 7.92±1.44 cm^2; *P*<0.001). The minimal systolic LVOT area showed an excellent inverse correlation with peak LVOT pressure gradient in patients with ASH (exponential curve fitting, *R*2=0.83, *P*<0.001).

2.11 Measurement of cardiac output

Physiological assessment of cardiac performance during exercise is an important part of clinical assessment of the cardiovascular system. Peak VO_2 in particular has been shown to be of prognostic significance in heart failure and can be used to guide treatment (198-200). However, peak VO_2 is determined not only by cardiac output, but also by non-cardiac factors such as age, gender, respiratory disease, haemoglobin concentration and level of training (201).

Most reference methods for the estimation of cardiac output are invasive, costly and often require specialised catheter laboratory facilities and staff. A number of non-invasive alternatives, including impedance cardiography (202), nuclear scintigraphy (202), Doppler echocardiography (203,204), magnetic resonance imaging (205-207), and respiratory gas analysis (208) can be used to measure resting cardiac output, but most of these methods are unsuited to routine clinical use during exercise, particularly above the anaerobic threshold because they provide only periodic assessment and are unable to capture rapid changes in physiologic variables. A summary of these technique is shown in table 2.3. No single technique to date has been shown to be able to continuously measure cardiac output accurately and non-invasively. Most methods suffer the drawback that determination

of cardiac output is made over several cardiac cycles. At rest this is usually not important, but cardiac output can be highly variable on exercise leading to inaccuracies of measurement. Even postural changes in cardiac output may not be accurately evaluated with these techniques. They do not provide a continuous assessment, desirable for the monitoring of dynamic variables in which changes could be missed by periodic assessment. There is, therefore, a need for a method that accurately measures dynamic cardiac output during exercise.

2.11.1 The Fick principle

First described in 1870 by Adolf Fick, this is the principal that VO_2 is proportional to the rate of blood flow, and the affinity of Haemoglobin for oxygen. By measuring the VO_2 over time, and the oxygen concentration of both arterial and venous blood it is possible to calculate cardiac output from the equation:

Oxygen consumption (VO_2) = (Q x C_a) – (Q x C_v)

Where

VO_2 = oxygen consumption (L/min) measured using a respiratory flow meter

C_a = Oxygen concentration of arterial blood (usually taken from a peripheral artery)

C_v = Oxygen concentration of mixed venous blood (taken from the pulmonary artery)

Q = Cardiac output

When rearranged: $Q = \frac{VO2}{Ca-Cv} \times 100$

Each gram of haemoglobin can carry 1.34 g of oxygen, therefore:

$$oxygen\ content\ per\ 100ml\ blood\ (arterial\ or\ venous)$$
$$= Hb\left(\frac{g}{dL}\right) x\ 1.34\ x\ blood\ oxygen\ saturation\ (\%)$$
$$+ 0.0032\ x\ partial\ pressure\ of\ oxygen\ (to\ account\ for\ oxygen\ dissolved\ in\ blood)$$

This technique is often considered the gold standard, but is invasive and performed in a cardiac catheterisation laboratory. It is not therefore not well suited to (maximal) exercise. Another major disadvantage of this technique is an inability to perform rapidly enough to capture the dynamic nature of physiologic exercise variables. Its use tends to be restricted therefore to diagnostic

procedures at rest, for example in the assessment of patients being considered for heart transplantation.

Table 2.3 Comparison of cardiac output measurement techniques

	Pros	Cons
Direct Fick	Gold standard accuracy (at rest)	Invasive Requires cardiac catheter laboratory Not well suited to maximal exercise Not continuous data
Pulmonary artery thermodilution	Accurate (at rest)	Invasive Requires cardiac catheter laboratory Not well suited to maximal exercise Time consuming Not continuous data
Doppler echocardiography	Non-invasive inexpensive	Dependent on operator experience and good echo window Not well suited to exercise
Impedence cardiography	Non-invasive	Motion artefact on exercise Limited at high workloads
2D echocardiography	As for doppler echo	As for doppler echo
CMR	Highly accurate Non-invasive Additional data provided	Expensive Difficulty resolving fast moving structures during exercise limits use
Inert gas techniques	Non-invasive	Only interval recordings Complicated respiratory manoeuvres required
Invasive pulse pressure analysis	Continuous recording Additional data provided	Invasive Requires calibration Expensive Not well suited to exericse
Finger plethysmography	Inexpensive Non-invasive Continuous recording Suited to exercise – although not validated	Affected by peripheral vasoconstriction Learning curve for use

2.11.2 Pulmonary artery thermodilution

A pulmonary artery catheter is inserted with its tip at a terminal artery. A known quantity of cold saline at a known temperature is injected into the right atrial port, and the temperature measured distally, the cooled blood having traversed a thermistor in the catheter. Cardiac output can then be estimated by measuring the area under the 'thermodilution curve'. Often several recordings are made and averaged. Differing cardiac outputs will deliver different curves. This method suffers the same disadvantages of the Fick method, namely being invasive and time consuming. Accurate delivery and recording of cold injectate, baseline temperature changes, hypovolaemia, and the need for cardiac output to remain constant while a stroke volume assessment are made are all potential limitations (209-211).

2.11.3 Doppler echocardiography

Cardiac output can be measured using Doppler using the following equations:

Cardiac output (Litres/minute) = (stroke volume (ml) x heart rate (bpm)) ÷ 1000

Stroke volume = Doppler velocity time integral x aortic valve cross sectional area (CSA) (cm^2)

The valve CSA can be calculated from:

$$CSA = \pi r^2$$

Where r = radius of the aortic valve orifice.

The Doppler signal can either be obtained from a supra-sternal notch or an apical window.

This method is non-invasive, inexpensive and provides continuous data but there are several limitations. Estimating CSA depends on operator experience, a good echocardiographic window, and being able to be aligned to the direction of flow. These latter two points are often difficult to achieve on exercise, particularly in the upright position. Aortic CSA may also change with posture. Any inaccuracies are compounded by using the square of the value used in the equation. Doppler derived stroke volume has been shown to be comparable under resting conditions to modelflow, although differences were noted during tilting (212). The trans-oesophageal route can be used by using the

Doppler profile from the descending aorta. This method is still often used in the intensive care setting to measure resting values but obviously not suited to exercise.

2.11.4 Invasive pulse pressure analysis

Pulse pressure methods use the waveform within an artery to derive information on cardiac output, and can be performed non-invasively and invasively. Simple non-invasive methods (eg sphygmomanometry and tonometry) tend to be inaccurate as both cardiac and peripheral changes will affect the waveform. Invasive methods include LiDCO (LiDCO Ltd, London, England) and PiCCO (PULSION Medical Systems AG, Munich, Germany). Both techniques involve inserting an arterial catheter and measuring the waveform continuously from which cardiac output can be derived using the method described by Wesseling (213). Both must also be calibrated. LiDCO uses lithium dilution via a peripheral artery and vein. PiCCO used a trans-pulmonary thermodilution technique: similar to trans pulmonary thermodilution, cold saline is injected into a central vein, and a thermodilution curve derived from temperature data obtained at a peripheral artery (often radial or femoral). Once calibrated this method will give continuous haemodynamic information. However, calibration itself can be difficult to accurately reproduce, and should be repeated following any change in posture / therapy or clinical status change. This later method also gives an estimation of cardiac filling volumes, intrathoracic blood volume and extra-thoracic lung water. Both techniques are time consuming, expensive, and poorly suited to assessment of cardiovascular physiology on exercise. FloTrac (Edwards Lifesciences LLC, USA) is a self-calibrating pulse pressure device which derives cardiac output through analysis of the pressure waveform from an arterial catheter (214). Pulse contour analysis needs correction if it is to be accurate over changing haemodynamic conditions.

2.11.5 Impedance cardiography

Impedance cardiography measures the change in trans-thoracic impedance over the cardiac cycle: as intra-thoracic blood flow and volume increase the impedance falls (215). This is a non-invasive technique, providing continuous data, which has been used with some success particularly in the heart failure population (216). Contemporary utility on exercise is however relatively limited, partly

due to motion artefact. Moore et al demonstrated good agreement between cardiac output as assessed by impedance cardiography and CO_2 re-breathing in healthy young males at sub-maximal exercise (217). There was also a similar correlation with VO_2 in both groups. However, beyond a workload of 120 W both methods were limited.

2.11.6 2D echocardiography

2D echocardiography has been used to assess cardiac output by tracing the endocardial border in end systole and end diastole to generate the left ventricular area, from which a volume is derived. Stroke volume is calculated by subtracting the left ventricular end systolic volume from the end diastolic volume Multiplying by the heart rate and dividing by 1000 will give the cardiac output in litres per minute. Inherent inaccuracies with this technique are well known, largely due to difficulties in endocardial border definition, and are compounded when used during exercise. 3D echocardiography may help to resolve these issues to some extent. However cardiac motion with respiration significantly degrades the image quality, thus limiting its use during exercise.

2.11.7 Magnetic resonance imaging

At rest, velocity encoded phase contrast MRI is highly accurate and reproducible when used to measure flow in large vessels. An assessment of cardiac output is often made as part of a routine CMR assessment. The utility of CMR on exercise is yet to be proven and is the subject of on-going research. Certainly the ability of current technology to resolve fast-moving structures is limited, which makes interpretation of exercise data difficult.

2.11.8 Inert gas re-breathing techniques

Inert gas re-breathing techniques have been extensively used for the calculation of cardiac output (218-223). However, this method can only provide estimates of cardiac output at intervals during the exercise test, and is technically challenging to perform, particularly in individuals with poor exercise capacity. Patients must perform respiratory manoeuvres including breath holds at times indicated by

the person carrying out the test, making this technique unsuitable for routine clinical practice. On exercise small A-V oxygen differences introduce error (217). In addition, in order to validate the technique the assumption of steady state cardiac output is made, however performing the test will introduce small changes in both circulation and ventilation (224).

2.11.9 Finger plethysmography

Finger plethysmography is a relatively inexpensive technique that provides a continuous beat to beat assessment of cardiac output and additional parameters such as peripheral resistance. Early studies on exercise appeared promising although accuracy was suboptimal without correction (225,226). My hypothesis was that a contemporary, commercially available finger plethysmography device using pulse waveform analysis with brachial cuff calibration would be comparable in the measurement of cardiac output during submaximal exercise to a previously validated acetylene (C_2H_2) uptake technique (227). Furthermore, if this was the case it could then be used to non-invasively assess haemodynamic responses during routine clinical cardio-pulmonary exercise tests. The specific technique is discussed in more detail in chapter 3.

2.12 Cardiac output response to exercise in normal individuals

In normal individuals stroke volume, heart rate (and hence cardiac output) all rise during exercise and total peripheral resistance (TPR) falls (228-231). Historical studies have calculated normal ranges for cardiac output and VO_2. For adult males maximal VO_2 is in the range 25 to 62 ml/kg per min and cardiac output between 13 to 25 litres/min (232). These parameters have been shown to reduce with age (233) although the relationship of cardiac output to VO_2 between age groups or sexes at submaximal exercise does not change (218).

Stroke volume normally increases up to exercise intensities of 40–60% of peak VO_2 in sedentary young subjects and then plateaus or falls slightly (234,235). Endurance training can affect this trend. In trained individuals assessed using graded cycle ergometry, stroke volume increases from baseline to 40% peak VO_2 in men and women of all age groups (218). In this study between 40-70% peak VO_2 the stroke volume continued to increase in men but not in women. At nearly maximal VO_2, younger

men continue to increase stroke volume slightly whilst older men maintained the same level. Younger women maintained stroke volume at this intensity whilst older women did not. TPR calculated by MAP divided by cardiac output was higher at rest in older versus younger patients, although all groups demonstrated a similar reduction on exercise.

Although there are some contradictory data from previous studies looking at the relationship between VO_2 and cardiac output between men and women (220,236) (218), overall conclusions are that there are no significant gender differences in cardiac output at a given VO_2 in people of similar ages, which has been replicated elsewhere 162]. In the case of HCM, no gender differences were noted in the assessment of exercise capacity in HCM by Frenneaux et al (86).

2.12.1 Relationship between oxygen consumption and cardiac output

The relationship between VO_2 and cardiac output is linear. Several historical studies have investigated this using a variety of techniques to measure cardiac output, including both invasive and non-invasive (237) (238-241). A much more recent study by Proctor et al noted the slopes of the cardiac output :VO_2 relationship across submaximal levels of cycling were similar among all four groups tested (young / old men and young / old women) despite variations in resting and peak values (218). They used the acetylene inhalation technique during submaximal cycle ergometry in a chronically endurance trained population and found regression values between 5.4–5.9 l/l.

Relatively few data exist on the cardiac output : VO_2 response to exercise in HCM. However, this has been evaluated in heart failure. In patients awaiting transplantation for heart failure calculation of the ratio of cardiac output : VO_2 slope predicts survival (242). They characterised patients as either normal or abnormal compared to a reference value of cardiac output = 5 VO_2 + 3 (threshold determined through an analysis of several studies (220,243-245)). They did not report the values for gradients, but that 55% had an abnormal (flat) response. Patients with a normal cardiac output response to exercise had a survival of 95% at 1 year, whereas survival in those with a reduced cardiac output response was 72% ($P < 0.0001$). No attempt was made to determine the physiological cause for this flat response. The authors felt this method added additional information as a prognostic tool and one that could be used to better predict those with a greater need for transplantation.

3 Methods - physiology

Much of the physiological methodology between the validation study and testing in patients is common to both. I have therefore initially described general principles before detailing the differences in appropriate sections. The study complied with the declaration of Helsinki and NHS research governance arrangements. In chapter 4 I have presented the methods used to assess the *anatomical* component, and how I investigated the role of aorto-septal angulation with respect to LVOT obstruction in HCM.

3.1 Non-invasive measurement of cardiac output during exercise using finger plethysmography

Measurement of the finger arterial waveform to non-invasively continuously assess blood pressure has been practiced since the early 1980s. The accuracy of recording both at rest and on exertion with Finapres (FINger Arterial PRESsure) / Portapres (Finometer medical systems, Amsterdam) is well established (246). An image of a contemporary machine used in my work is shown in figure 3.1.

Figure 3.1. Image of the Finapres equipment

Finometer pro and brachial calibration cuff (Finapres Medical Systems, the Netherlands)

3.1.1 Volume clamp technique

These devices measure blood pressure using the volume clamp method, developed by Czech physiologist Penaz in the early 1970s. This is based on the dynamic pulsatile unloading of finger arterial walls (246). An artery is kept at a constant diameter by pressure from a surrounding inflatable cuff, despite changes in pressure with the cardiac cycle. Diameter changes are detected with an infrared photo-plethysmograph built into a finger cuff housing an inflatable bladder (fig 3.2).

Figure 3.2. Finapres finger cuff (Finapres Medical Systems, the Netherlands)

This cuff contains an inflatable bladder and an infrared photo-plethysmograph to record physiological data.

This in turn is attached to the main unit via an air hose and separate electric cable. During systole if an increase in arterial diameter is detected the cuff rapidly inflates to keep the size constant. At zero transmural pressure the artery is not collapsed (which would require cuff pressure > intra-arterial pressure) but 'unloaded'. This is the arteries unstressed diameter (246,247). Intra-cuff pressure equals intra-arterial pressure at this point. The unloaded diameter is close to the average diameter at a pressure where the amplitude of the pulsations in the plethysmogram is largest (246). Changes in stress and tone of smooth muscle in the arterial wall and in haematocrit affect the unloaded diameter, and therefore this diameter is subject to change and must be calibrated. The finometer does this repeatedly, using a system designed to monitor the pressure waveform of the artery and adjust cuff pressure accordingly to maintain diameter (247). It analyses the waveform at differing pressure levels, and is not affected by changes in smooth muscle tone. In practice, the cuff inflates to a constant pressure initially every 10 beats, becoming less frequent the longer the pressure waveform remains unchanged. Monitoring is temporarily suspended during these inflations.

3.1.2 Waveform analysis

Finger pressure waveforms may differ substantially from the more proximal originating waveforms (248-250). The systolic pressure waveform is augmented as it moves from brachial to finger level (251,252). This is due to the pressure waveform being affected by changes in vessel compliance, and reflection along the arterial tree. At any point in the course, the pressure waveform can be thought of as a combination of the forward and reflected wave (253). In young healthy patients finger systolic pressure may overestimate brachial systolic pressure due to this over-amplification (248,249). As arterial diameter decreases towards the peripheries, a pressure gradient develops which has the effect of underestimating the mean finger arterial pressure compared with brachial (248). There is a reduction in pulse pressure amplification with increasing age (253) and vasoactive agents (254) but an enhancement with heart rate (255). Assumption of the upright position from supine will therefore alter the finger arterial pressure waveform by a combination of the effects of reflex increase in heart rate and changes to vascular tone. The resultant effect would be a higher systolic and lower diastolic and mean finger than brachial arterial pressure. An anti-resonance model and a regression based level correction can be performed on the finger arterial pressure waveform to allow for these effects (256,257). Following correction the reconstructed bias for systolic pressure is 0mmHg and 1mmHg following 20 minute head-up tilt (258). Diastolic pressure is not affected by reconstruction (256,257).

The finger waveform is further corrected by taking a return to flow measurement using a standard brachial blood pressure cuff, corrected for the hydrostatic height of the finger with respect to the heart level. The device has met clinical and research diagnostic criteria of the British Hypertension Society and Association for the Advancement of Medical Instrumentation (AAMI) (reconstructed finger pressure minus BAP: systolic, 3.7 mmHg; mean, 0.7 mmHg; diastolic, 1.0 mmHg)(256,259,260).

3.1.3 Modelflow method

Cardiac output is calculated by the finometer using the Modelflow method (213). The reaction of the aorta to the arrival of blood ejected from the left ventricle is described by a model of aortic input impedance (aortic characteristic impedance, arterial compliance, and TPR) (261-263). The finometer simulates this model and applies it to the measured arterial pressure waveform in the finger, and

the resulting waveform is integrated during systole to calculate stroke volume and from here cardiac output by multiplying by the heart rate.

The aortic impedance during systole depends on the mechanical properties of the aorta, which are influenced by the intra-arterial pressure (as blood remaining within the aorta from the previous heart beat will offer resistance to further pulsatile flow towards it) and the external pressure exerted on the walls (i.e. trans-mural pressure) (264). Two of the model parameters, aortic characteristic impedance and arterial compliance (aortic elasticity), are derived from the age- and sex-dependent aortic pressure–area relationship (265) and so patient's age, sex, height and weight are manually entered. This is because the reaction of the CSA of the aorta to pressure is non-linear, increasing rapidly at lower pressures and more slowly at higher pressures, characteristics which vary between individuals (266). An elastic aorta will expand with minimal rise in pressure, but it is well recognised that aortic compliance decreases with ageing (267). The aortic impedance and arterial compliance are the major determinants of systolic inflow, with peripheral resistance of less importance (213).

TPR is obtained by iteration and varied with each heartbeat. A reasonable initial value of TPR is assumed at the start of the simulation. This value is entered into the model with aortic impedance to derive cardiac output. The next beat ratio of arterial pressure to cardiac output defines a new value for peripheral resistance, which is then used in the next model and so on. After a few heartbeats the readings stabilise, but the model will continue to update on a beat by beat basis.

It has been suggested that in order to quantitatively assess an absolute value for cardiac output, the finometer should be calibrated against a known method for example thermodilution at baseline, because an individual's aortic size (needed for the calculation) cannot be assumed (264,268-270). However, the accuracy of measuring relative changes in cardiac output against baseline has been demonstrated, as this is not influenced by changes in aortic size (213,226,271). It is well recognised that conventional echocardiographic assessment of cardiac output in itself may differ to invasive measurements, particularly in the upright position adopted during exercise. Doppler measurements taken from a transducer positioned in the supra-sternal notch are technically more feasible than 2D measurements, particularly on exercise (204). However in that study they only achieved diagnostic quality 2D studies in 30% of subjects. Christie et al demonstrated an increase in aortic size of 2-3% when assessed by echocardiography on assumption of an upright posture from supine, but no further changes were observed during exercise up to 80% of maximum workload (204). A constant aortic size on exercise would support the validity of using the finometer to assess cardiac output

during upright exercise. The prevalence of aortic dilatation in HCM has been reported as 4%, similar to that for the general population, with similar mean aortic size (272,273).

There is no perfect gold standard for the accurate measurement of cardiac output on exercise. Early studies comparing cardiac output derived by arterial pulse contour analysis of porta-pres derived data showed a lower precision and accuracy compared to CO_2 re-breathing, although this was prior to implementation of contemporary algorithms, and lacked the brachial calibration of current equipment (274). The validity of the technique outside of normal physiology has been questioned: Modelflow has been shown to underestimate cardiac output via both brachial artery cannulation and Finapres compared with thermodilution in normal individuals subjected to whole body heat stress (275). However, Modelflow derived cardiac output has been shown to follow changes in inert-gas rebreathing derived values during static exercise in the upright position (276). In addition, fast changes in cardiac output are tracked by modelflow across various experimental protocols (268,277,278), postural stress (212,264) static (276) and dynamic (225,226,279) exercise.

Although the accuracy of measurement of relative changes in cardiac output has already been shown, in order to determine the accuracy of my absolute values for cardiac output using the Finapres algorithms, it was first necessary to perform validation studies at rest and sub-maximal exercise (see section 3.2.2) compared against a previously validated technique.

3.2 Cardiopulmonary exercise testing investigative protocol

Similarities exist between the protocols used for the validation study, and the subsequent clinical cardiopulmonary exercise tests in patients with HCM. I have therefore outlined common points before describing the specifics of each protocol.

3.2.1 Common points

Peak VO_2 is the product of cardiac output and the A-V oxygen difference, and therefore abnormalities of oxygen utilisation will affect VO_2 independent of cardiac output. It is therefore important (although often overlooked) that respiratory function is determined and assessed in conjunction with other haemodynamic data when interpreting the results of a cardio-pulmonary exercise test. Formal arterial and venous blood sampling is impractical, but I sought to minimise

potential error by measuring respiratory function. In my cohort of patients and controls all subjects performed 3 flow volume loops prior to exercise testing , and FEV_1, FVC and their ratio were calculated. Anyone with a significant impairment was subsequently excluded. Time of day, caffeine intake and smoking on the day of the exercise test were not routinely documented and unstandardised.

Non-invasive beat-to-beat cardiac output assessment was made using a finometer and beatscope software (Finapres Medical Systems, the Netherlands). A finger cuff was attached to the index finger of the left hand. During preliminary data collection I found that the optimal signal was recorded with the patient's hand and forearm in a fairly neutral position. Excessive plantar or dorsiflexion on occasion interrupted the finometer tracing, presumably by compressing the arterial wall against the ergometer handlebars. I therefore had a bespoke moulded plastic splint made by the hand therapy department at University College London Hospital in order to minimise this problem. Meticulous attention to positioning of the finger cuff and avoidance of sudden movement has previously been shown to be important for optimal data collection (212).

Patients were asked to grip the ergometer handlebars lightly and if possible to keep their hand in the same position throughout the test duration. The automatic blood pressure cuff was attached to the ispilateral upper arm and both were attached to the Finapres hardware. Arterial blood pressure waveforms were measured continuously in the finger using the photoplethysmography method (200 Hz sampled analogue waveform). A height correction unit was used to compensate for hydrostatic blood pressure changes in the finger waveforms.

Signals from a 12 lead ECG were displayed continuously for observation, and recorded at regular intervals during the exercise and in the recovery phase. Citations were inserted into the software during the test to form a permanent record of any relevant details, for example a non-invasive BP recording, any symptoms reported, any reduction in quality of the tracing and a possible cause if known.

All subjects were given the opportunity to become familiar with the cycle ergometer. The saddle height and handlebars were individually adjusted. A previously calibrated and electronically braked cycle ergometer (Ergoselect 200P, Ergoline, Germany) was used to exercise the subjects in an upright position. This system provides an actual "zero" load with unloaded cycling—that is, a "motor assist" overcomes the mechanical resistance normally present at zero load cycling (often 20 to 30 W or more). Simultaneous 12 lead electrocardiography was performed throughout the test.

The exercise tests were performed during working hours, in an air conditioned exercise laboratory (average temperature of 21°C) with full resuscitation facilities and two investigators present at all times. All subjects were told what was expected of them and were appraised of the signals to be used to communicate with those in attendance during the test.

3.2.2 Validation study protocol: acetylene inhalation technique

Volunteers were familiarised with the technique of C_2H_2 inhalation prior to exercise (280). The breathing circuit was flushed with test gas and the multi-gas sensor calibrated. Patients were connected to the mouthpiece of a SensorMedics Encore Vmax 229 machine (Yorba Linda, California). A nose clip was positioned. A certified gas mixture (CareFusion, Basingstoke) containing 0.3% carbon monoxide, 0.3% methane, 0.3% acetylene, 21% oxygen and balance nitrogen was inhaled to vital capacity and then exhaled at a slow, constant rate of 0.5L/second to residual volume. This flow rate was achieved as follows: exhalation flow rate was displayed graphically on a computer screen, overlayed on a fixed line representing 0.5L/second. The participant therefore exhaled at a rate attempting to match the line. Measurement of inhaled and exhaled carbon monoxide concentrations were used to calculate lung diffusion capacity. Measurement of inhaled and exhaled unabsorbed / diluted methane were used to calculate alveolar volume. Normal values of these gases exclude significant diffusion limitation across the pulmonary circulation, which may affect C_2H_2 absorption and hence calculation of cardiac output. Continuous assessment of the decreasing slope of C_2H_2 concentration in expired gas reflects the uptake of C_2H_2 into the pulmonary circulation and is used to calculate the right heart cardiac output (280,281). In the absence of intra-cardiac shunting this equals left ventricular cardiac output. Mathematically, the relation between gas absorption and pulmonary capillary blood flow is expressed as follows:

$$\dot{Q}_C = \frac{\ln (F_A/F_{A_0})}{\ln [(V_A + \alpha_t V_t)/(V_{A_0} + \alpha_t V_t)]} * \frac{\dot{V}_E}{\alpha_b} * \frac{60*1{,}000}{760}$$

where F = fraction of gas; V = volume of gas; $\dot{V}$ = flow rate; α= bunsen coefficient for solubility of acetylene in tissue (t) or blood (b); A = alveolar; A_o = at full inspiration; IF = inspiratory flow; I = inspiratory; E = expiratory and DS = dead space (227).

Three baseline recordings of cardiac output were obtained using the C_2H_2 technique with simultaneous finger plethysmography recording. The exact time point of each C_2H_2 inhalation was

marked on the finger plethysmography waveform for retrospective analysis. Volunteers were then exercised on a bicycle ergometer (Ergoselect 200P, Ergoline, Germany) using a 10W ramp protocol to a pre-determined workload chosen to reflect sub-maximal exercise, based on a subjective assessment of their level of fitness, age and resting heart rate. The workload was then fixed and a further three cardiac output measurements were made at steady state using the C_2H_2 technique with simultaneous finger plethysmography recording. A single investigator performed respiratory gas analysis and another independently assessed finger plethysmography data. The mean values for cardiac output over 5 consecutive heart beats with a stable pulse pressure waveform collected contemporaneously with C_2H_2 inhalation were used for comparison.

3.2.2.1 Statistics

Advice on statistical testing was obtained from Allan Hackshaw, Professor of epidemiology and medical statistics, University College London. All continuous variables are presented as mean ± standard deviation (SD). Analysis of all variables was carried out using SPSS statistical software version 19 (SPSS for Windows, IBM, USA). The means of 3 resting and 3 exercise cardiac output values from each method were assessed using two tailed independent t tests and Pearson's correlation coefficient. A Bland Altman plot of the differences between cardiac output values and their mean was used to determine agreement between techniques. The fractional differences between finger plethysmography derived cardiac output and the reference C_2H_2 method were calculated to determine whether they fell within a 10% margin of accuracy.

3.2.3 Cardiopulmonary exercise test protocol

In patients with HCM, with the exception of amiodarone, cardioactive medications were withdrawn for a minimum of 24 hours prior to the exercise test as is standard practice at the Heart Hospital. One minute of baseline cardiorespiratory data was collected before the subjects began the incremental ramp after one minute of unloaded pedalling. The work rate for the incremental exercise ranged from 5 to 15 W/min and was based on patients' account of daily physical activity, age, sex, and medical history. The aim was to achieve an exercise time of 10 minutes by selecting the

appropriate exercise ramp rate for each patient. Subjects rode to the limit of tolerance. A record was made of the subject's reason for termination of exercise, which fell into one of several categories: general fatigue, tired legs, breathlessness, chest pain, dizziness. The reason for stopping is however subjective, as sensations such as those above vary between individuals. Blood pressure was determined by auscultation at three minute intervals during the test and recovery phase. A single investigator (Dr Bryan Mist) performed respiratory gas analysis and another (Dr Chris Critoph) independently assessed finometer data.

Cardiac power output, in watts, was calculated from the equation:

Cardiac power output = (CO x MAP) x K

where MAP is the mean arterial pressure in mmHg, CO is the cardiac output in L/min and K the conversion factor 2·22 x 10^{-3} (282).

A-V oxygen difference at different workloads was derived from the Fick equation:

$$A-V\ oxygen\ difference = \frac{Oxygen\ Consumption\ (VO2)}{Cardiac\ Output}$$

An picture of a participant during the exercise test is shown in figure 3.3

Figure 3.3 Participant performing an exercise test

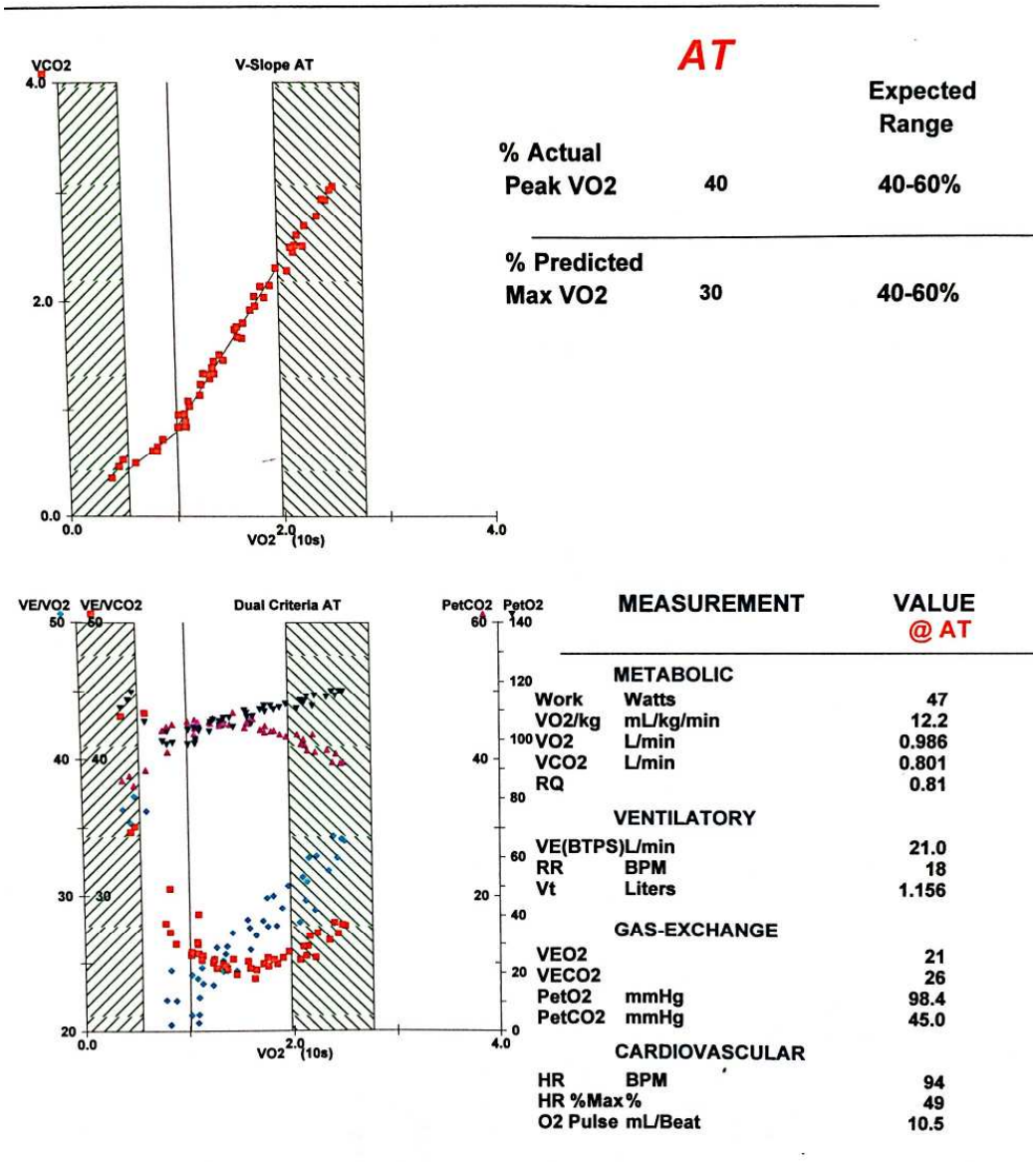
Mouthpiece, finometer, ECG electrodes and blood pressure cuff are attached and the individual is performing incremental bicycle exercise (volunteer permission to reproduce image granted).

3.2.4 Oxygen uptake measurement

The formula of Wasserman et al was used to calculate the predicted peak VO_2. Importantly, the normal values for predicted VO_2 were adjusted for an individual's weight (283,284). This is because

an overweight person would have a higher predicted VO_2 than an age and sex matched individual who was of 'normal weight', and thus would be less likely to achieve an 'appropriate' VO_2. Alternatively two individuals of the same age, height and weight should have different predicted VO_2 if one person was overweight and the other lean. Patients breathed room air through a disposable, low resistance (approximately 1.2 cm/l/min at 12 l/min), low dead space (39 ml) flow meter. The flow meter was calibrated with a three litre syringe, using a range of flows. Respiratory gas was sampled continuously from the mouthpiece and analysed using a zirconia cell for oxygen and an infrared sensor for carbon dioxide (Sensormedics Vmax Encore 229, Viasys Healthcare, UK). These signals underwent analogue to digital conversion for breath by breath calculation of VO_2 and VCO_2, using algorithms based on the procedure of Beaver et al (285). The anaerobic threshold was determined from the plot of VCO_2 against VO_2, as described by Beaver et al (285) and Sue et al(286), where the slope of this linear relation increases owing to a rise in VCO_2 (V slope) (fig 3.4). Further confirmation of the anaerobic threshold was provided from VE/VCO_2, VE/VO_2, end tidal PCO_2, and end tidal PO_2 relations, as described by Whipp et al (287), VE being ventilation (expired volume per minute). The linear region of the plot of VO_2 against work rate(fig 3.5) has been shown to be a major determinant of the subject's aerobic efficiency.

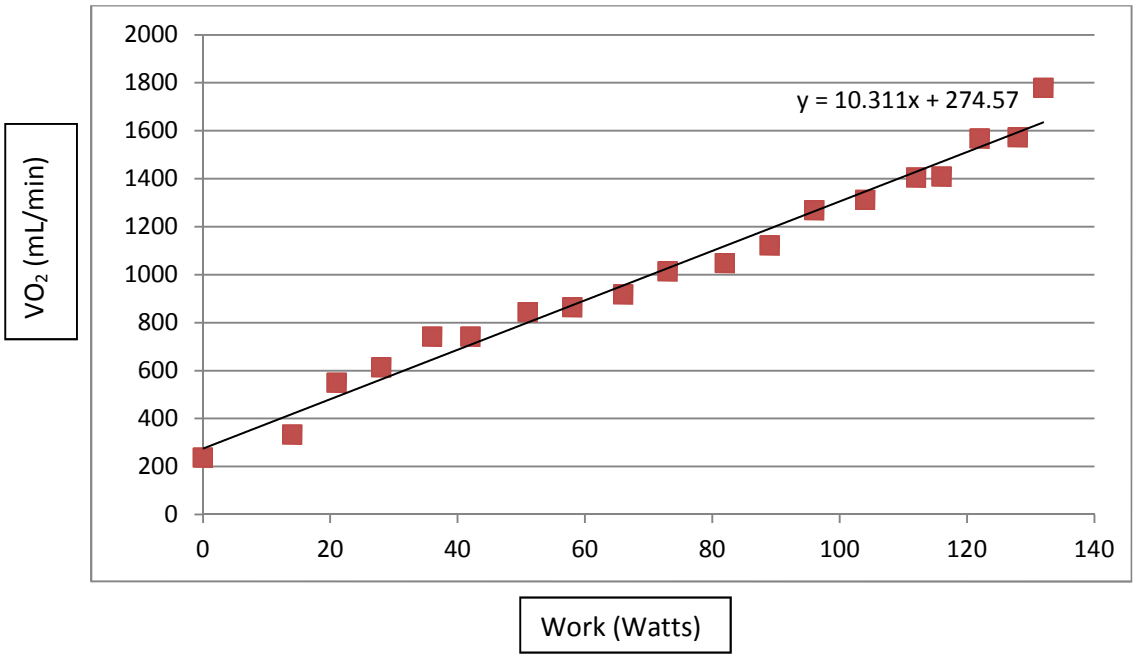
Figure 3.4. Example of respiratory data collected during an exercise test and determination of anaeorobic threshold (285,286).



AT – anaerobic threshold, BPM – beats per minute, HR – heart rate, PCO_2 - partial pressure of cardbon dioxide, $PETCO_2$ – end tidal cardon dioxide tension, $PETO_2$ - end tidal oxygen tension, PO_2 - partial pressure of oxygen, RQ – respiratory quotient, VCO_2 - carbon dioxide production, VE – ventilatory equivalent, VE/VCO_2 - ventilatory equivalent for carbon dioxide, VE/VO_2 - ventilatory equivalent for oxygen, VO_2- oxygen consumption.

Profile of response of VCO_2 (uppermost panel), ventilatory equivalent for VO_2 and VCO_2 (lower panels), and end tidal PO_2 and end tidal PCO_2 (lower panel) as a function of oxygen uptake during an exercise test in a patient with hypertrophic cardiomyopathy.

Figure 3.5. The profile of VO_2 response, as a function of work rate, in a cardiopulmonary exercise test in a patient with hypertrophic cardiomyopathy



VO_2 – oxygen consumption. Note the normal slope of the relationship between oxyen consumption and work in this patient.

It should be noted that the peak VO_2 mostly but not always corresponded to the last time point of the exercise test. All were within 60 seconds of the test termination. The corresponding cardiac output value was always taken, even if there was a slightly higher or lower value at the point of exercise termination, to ensure reproducible methodology. This peak VO_2 value was scrutinised on a breath by breath basis to ensure that all values were reasonable. If, for example, a patient took a very small breath amongst their normal tidal breaths, this would produce a very low VO_2 value. Conversely if a very large breath was taken the value would be very high. Outlying values such as these are immediately obvious when reviewing the breath by breath VO_2 data and are routinely edited in clinical practice to ensure the final peak VO_2 value is not falsely influenced. This explains the sometimes apparent disparity between the peak VO_2 value documented during the exercise test and the 30 second averaged readings obtained throughout exercise.

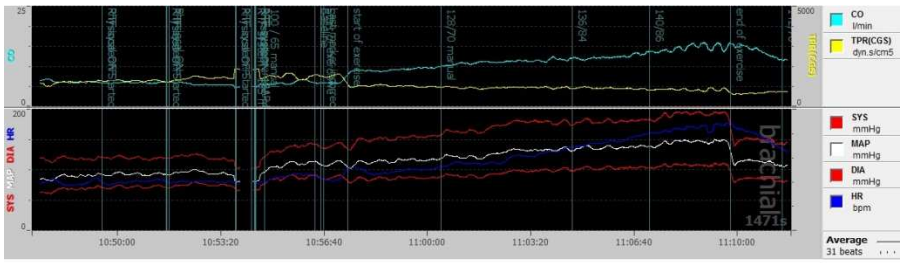
3.2.5 Data capture using finger plethysmography and Beatscope

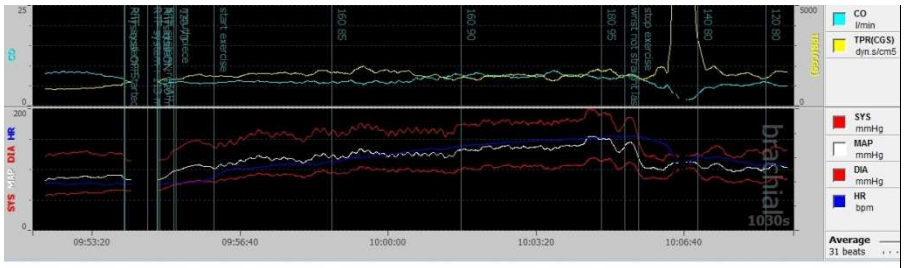
Screen shot examples of data from Beatscope software are shown in figure 3.6. Time is on the x axis, and on multiple y axes are plotted cardiac output, TPR, systolic, diastolic and mean arterial blood pressure, and peripheral pulse waveform.

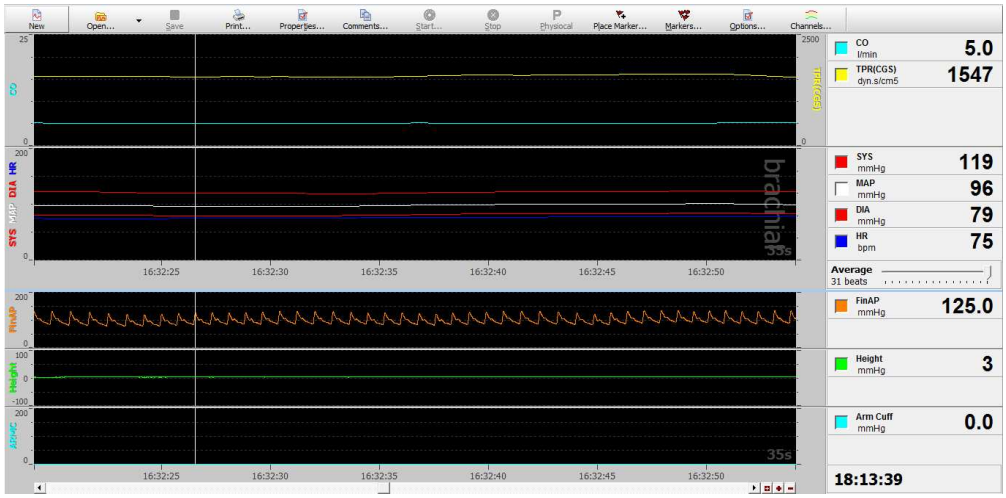
3.2.6 Analysis of an individual finger plethysmography dataset

The text file generated by Beatscope was imported into an Excel database, with fields for different haemodynamic parameters separated into columns. The raw data was imported into one worksheet, and the time of respiratory mouthpiece insertion, start of exercise, and end of exercise were noted. Baseline data was defined as that in the immediate 30 second interval preceding exercise. The cell corresponding to the start of baseline recording was entered into a formula that automatically divided and averaged subsequent data into 30 second intervals. The exact times of any data not meeting acceptable criteria for analysis were recorded, then any remaining acceptable data for a given 30 second interval were averaged manually. An example of the resulting data table is shown in table 3.1.

Figure 3.6. Screen shots from Beatscope of (A) normal and (B) flat cardiac output response to exercise. Panel (C) shows a close up to demonstrate the arterial waveform and measured haemodynamic indices at the point of the vertical white line.







Time is on the x axis, and on multiple y axes are plotted cardiac output (pale blue), TPR (yellow), systolic (red), diastolic (red) and mean (white) arterial blood pressure, heart rate (dark blue), and peripheral pulse waveform (orange).

Table 3.1. Example of individual patient's exercise test. The total time is divided into 30 second intervals, with corresponding mean cardiac output, stroke volume and heart rate.

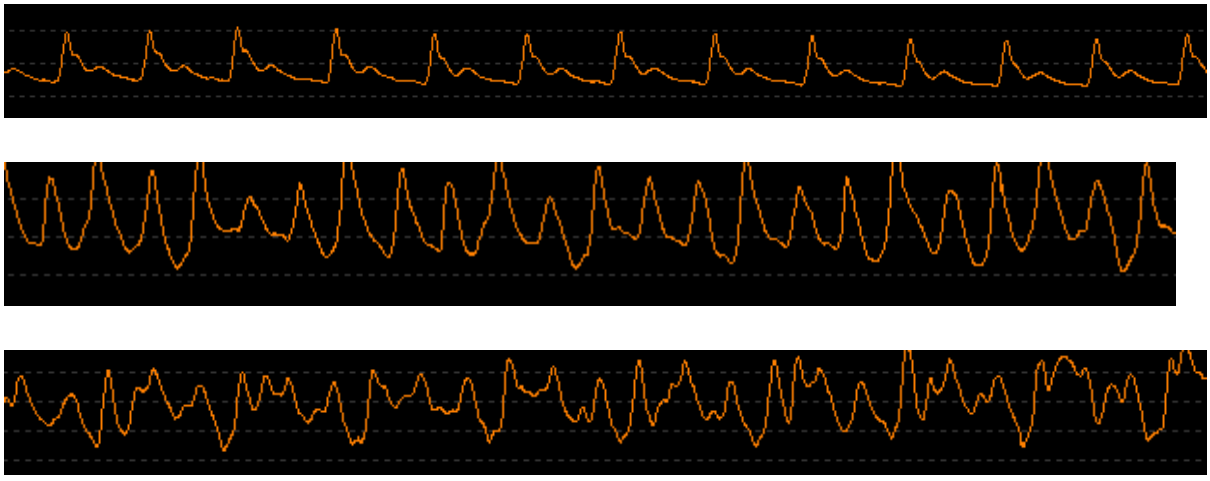
Time (seconds)	Cardiac output (L/min)	Stroke volume (ml)	Heart rate (bpm)
30	5.2	80	65
60	7	100	70
90	7.3	99	74
120	7.5	96	78
150	7.8	95	82
180	8.0	91	88
210	8.3	87	95
240	8.5	85	100
270	8.7	84	104
300	9.0	83	109
330	9.9	85	116
360	10.6	88	121
390	11.4	90	127
420	12	89	135
450	12.4	89	139
480	12.9	87	148
510	13.6	88	154
540	14.4	90	160
570	14.9	90	166
600	15.8	93	170
630	16.5	95	174

These data were then exported into another spread sheet, with additional columns for work (watts) and VO_2 (L/min). From this, a graph of cardiac output versus VO_2 was drawn, and the slope and intercept calculated. The cardiac output and VO_2 at baseline, 25, 50, 75, 100, 150, 200 and 250 watts (as applicable) was documented. Lastly a graph of VO_2 : work ratio was drawn and the slope calculated from the plots derived from breath by breath data recorded on the Sensormedics workstation. Each individual patient's demographic, echocardiographic, respiratory and haemodynamic (both measured and derived) data was then tabulated in a master database as described in section 3.3.5.

The data displayed on screen (fig 3.6) are an average of 30 consecutive heart beats. Whilst not used for offline calculation, they provide a good intra-test guide as to quality of signal, and are useful in the assessment of outlying data points. Each heart beat contributes a line on a text file saved to the computer's hard disk. When an exercise test is complete therefore, there are the same numbers of lines as there were heart beats during the test. Each line comprises a value for: systolic, diastolic, mean arterial blood pressure, stroke volume, TPR, cardiac output, heart rate etc. Therefore over a 10 minute exercise test at a mean heart rate of 120bpm the file would be composed of 1200 lines of data.

Each patient's file was imported into a new Excel 2010 software database (Microsoft Office) for initial analysis. The first step was to compare exercise duration from respiratory data to that recorded using finometer to ensure they were identical and corresponded to the same time period. Baseline, exercise, and where available recovery data were then averaged every 30 seconds and the results displayed graphically. These data were then reviewed alongside the original beatscope graph (fig 3.6). The individual pressure waveform for a patient's exercise test was then scrutinised. Examples of good, acceptable and poor waveforms are shown in figure 3.7.

Figure 3.7. Examples of (A) good, (B) acceptable and (C) unacceptable finger plethysmographic pulse wave tracings. Note both (B) and (C) were recorded during maximal exercise.



If a waveform was deemed to be of insufficient quality to be reliable, the data from that time period was excluded. In order to record a value for a 30 second period of exercise, a minimum of 5 seconds of data with an accompanying acceptable pressure waveform had to be present. If an exercise test terminated during a 30 second period, only the data up to the point of exercise termination was included.

During my initial analysis, the absolute and percentage change in cardiac output, heart rate and stroke volume were measured from baseline to the 30 second interval prior to anaerobic threshold. Absolute values and percentage change were then measured for the same parameters at the point of highest VO_2 for which corresponding haemodynamic data was available. A third global assessment from baseline to peak VO_2 was also calculated. However, in practice, I felt that any slight inaccuracy in measuring anaerobic threshold would have a knock on effect on the time point at which cardiac output was measured, and therefore affect both baseline to anaerobic threshold and anaerobic threshold to peak results. To remedy this, I felt that rather than measuring the cardiac output at different points in time, a more standardised method would be to use measure the cardiac output at given workloads. This would also have the advantage of making comparison between individuals and groups easier. I had both respiratory and haemodynamic data for every 30 second interval of the exercise test, and therefore was able to determine values for cardiac output and VO_2 at any given workload. I chose workloads of 0, 25, 50, 75, 100, 150, 200 and 250 watts, and measured VO_2, stroke volume and heart rate (and derived cardiac output and A-V oxygen difference) at each, as I felt this would be the best way of evaluating dynamic changes.

3.3 Study cohort

3.3.1 Inclusion criteria

Consecutive patients fulfilling conventional task force criteria for the diagnosis of HCM (34) attending the cardiomyopathy clinic at The Heart Hospital between July 2011 to June 2012, who were due to have cardiopulmonary exercise testing as part of their routine clinical care were enrolled.

3.3.2 Exclusion criteria

- Patients under the age of 16
- Exercise limiting disease other than cardiac, eg severe peripheral vascular or joint disease

- Endurance athletic trained individuals (patient reported)
- Significant pulmonary disease (defined as FEV_1 or FVC <80% predicted in accordance with NICE guidelines for the diagnosis of chronic obstructive pulmonary disease (288))
- More than moderate valvular heart disease (European Association of Echocardiography guidelines (289,290))
- Cardiac pacing
- Pulmonary hypertension (defined as mean pulmonary artery systolic pressure ≥25mmHg)
- Left ventricular systolic dysfunction (defined as an ejection fraction measured by echocardiography using Biplane Simpson's method <55%)
- Permanent AF
- A pre-existing diagnosis of anaemia

3.3.3 Statistics

Continuous variables are presented as mean ± standard deviation (SD). Analysis was carried out using SPSS statistical software version 19 (SPSS for Windows, IBM, USA). Differences between two groups were assessed using independent 2 sample t test and within groups at different workloads using paired t test. One way analysis of variance (ANOVA) with homogeneity of variance testing, and post hoc Bonferonni or Games-Howell corrections were used as appropriate to assess differences between multiple groups. Pearson's coefficient was used to assess for correlation. Linear regression analysis was used to assess the predictors of cardiac reserve in patients. A p value <0.05 was considered significant.

3.3.4 Echocardiography

All patients underwent detailed transthoracic echocardiographic examination according to British Society of Echocardiography protocol. The following parameters were entered into a microsoft excel spread sheet:

- Maximal left ventricular wall thickness (mm)
- Left ventricular diastolic cavity dimension (mm)
- Valvular lesions (none / mild / moderate / severe)
- Left ventricular systolic function (normal / mild / moderate / severe impairment)
- An ejection fraction was calculated by Simpson's method. If images were of insufficient quality, where possible another modality (eg MRI) was used (n=4), and in the absence of this a visual assessment was made (n=19).
- Left ventricular diastolic function (Grade 1-4)
- Septal and lateral S wave, E wave and lateral E/E' were documented. If a patient was in AF the average of 5 consecutive beats was taken.
- Left Atrial size (mm, taken from parasternal long axis view)
- Resting LVOT gradient (mmHg)
    - Care was taken to ensure the LVOT and not mitral regurgitation Doppler profile was interrogated.
- Provocable LVOT gradient (following Valsalva manoeuvre - maximal attempted exhalation against a closed airway for as long as is tolerated)
    - Defined as a peak LVOT gradient ≥50mmHg during provocation.

The gradient on Valsalva provocation was documented in every patient to give some measure of propensity for provocable obstruction. It is however recognised that this will fail to identify a proportion of patients with provocable LVOT obstruction (120). This is partly because it is often performed in the lying position where preload is reduced and partly because the manoeuvre fails to adequately increase afterload and contractility in the same manner as for example exercise. The Heart Hospital protocol is for patients to perform the Valsalva manouvre in the upright position, including after squatting if possible to maximise the sensitivity of the test. However the frequency with which squatting was performed was not documented.

Following routine clinical assessment, patients suspected of having provocable obstruction during exercise with no significant gradient at rest or during Valsalva manoeuvre were referred for and underwent symptom limited bicycle ergometer or treadmill exercise echocardiography to determine their maximum provocable LVOT gradient. This minimises the chance of grouping a patient incorrectly, and is considered a gold standard in clinical practice for elucidating LVOT obstruction. In practice, 11 patients had this investigation. A patient was classed as having non-obstructive hypertrophic cardiomyopathy if the resting LVOT gradient was <30mmHg, obstructive HCM if

≥30mmHg, and provocable HOCM if the gradient induced by provocation manoeuvre or exercise was ≥50mmHg. It is clear however that some patients who by this definition fall into the resting obstruction cohort also have an increase of this gradient on exercise and may therefore also be considered provocable. I also therefore assessed LVOT gradient as a continuous variable. These thresholds are determined by convention (291). A gradient of ≥50 mm Hg is usually considered to be the threshold at which LVOT obstruction becomes haemodynamically important. This concept comes from studies that demonstrate progressive impedance to flow above this value (56).

3.3.5 Master database

All demographic, echocardiography, respiratory and haemodynamic data was recorded in a database as follows:

- Demographic Data
    - Unique patient identifier
    - Date of birth
    - Age
    - Gender
    - Ethnicity
    - Weight (kg)
    - Height (cm)
    - Body surface area (calculated using the mosteller formula (292))
    - Reason for stopping exercise
    - Haemoglobin
    - Diagnosis code
        - Normal control
        - HCM without LVOT obstruction
        - HCM with LVOT obstruction
    - Smoking history
    - Level of exercise
        - An assessment of patient's training / physical status was made:
        - 0 = no regular physical activity

        - 1 = some regular physical activity
        - 2 = regular aerobic physical activity (≤3 sessions per week)
        - 3 = trained athlete
    - NYHA functional class
    - Medication (including time since last dose)
    - History of previous intervention for LVOT obstruction
    - Risk factors for sudden cardiac death
        - History of ICD insertion
        - Family history sudden cardiac death
        - MWT ≥30mm
        - History of syncope
        - ABPR to exercise
        - History of non-sustained VT
- Heart Rate Data
    - Resting heart rate
    - Predicted peak heart rate (220 – age women, 210 – age men)
    - Peak heart rate achieved
    - Percent predicted heart rate achieved
    - Heart rate at 25, 50, 75, 100, 150, 200, 250 Watts (where applicable)
    - Heart rate deficit (predicted heart rate – achieved heart rate)
    - Heart rate at 1 minute
    - Percent fall in heart rate at 1 minute
    - Heart rate at 3 minutes
    - Percent fall in heart rate at 3 minutes
    - Change in heart rate (peak heart rate – resting heart rate)
    - Chronotropic incompetence (defined as a failure to reach 80% predicted heart rate)

- Respiratory data
    - FEV_1
    - FVC
    - FEV_1 : FVC ratio
    - Weight corrected predicted VO_2
    - Baseline VO_2
    - Peak VO_2

- Percent predicted VO_2
- VO_2 at 25, 50, 75, 100, 150, 200, 250 Watts (where applicable)
- Respiratory exchange ratio
- Anaerobic threshold
- Gradient of VO_2 : work ratio

- Haemodynamic data
  - Blood pressure
    - Baseline systolic blood pressure (mmHg)
    - Baseline diastolic blood pressure (mmHg)
    - Baseline MAP (mmHg)
    - Resting pulse pressure (mmHg)
    - Peak exercise systolic blood pressure (mmHg)
    - Peak exercise diastolic blood pressure (mmHg)
    - Peak exercise MAP (mmHg)
    - Blood pressure response (mmHg)
  - Stroke volume
    - Baseline stroke volume (ml)
    - Stroke volume at 25, 50, 75, 100, 150, 200, 250 Watts (ml, where applicable)
  - Cardiac output
    - Cardiac output pre-mouthpiece (L/min)
    - Baseline cardiac output (L/min) and index (L/min/m^2)
    - Peak cardiac output (L/min) and index (L/min/m^2)
    - Delta cardiac output (L/min)
    - Percent change cardiac output
    - Cardiac output at 25, 50, 75, 100, 150, 200, 250 Watts ((L/min), where applicable)
    - Cardiac output at peak VO_2
  - Peak cardiac power (watts)
- Cardiorespiratory data
  - Peak workload (watts)
  - Gradient of the slope of Cardiac output : VO_2
  - Intercept of the slope of Cardiac output : VO_2
  - Oxygen extraction (gradient of the slope of VO_2: cardiac output (ml/100ml blood)
  - A-V oxygen difference at rest (ml/100ml)

    - A-V oxygen difference at 25, 50, 75, 100, 150, 200, 250 Watts (where applicable)
    - Delta A-V oxygen difference
- Echocardiographic data
    - Maximal wall thickness (mm)
    - Left atrial size (mm)
    - Left atrial size index (mm/m^2)
    - Left ventricular end-diastolic diameter (mm)
    - Left ventricular end-diastolic diameter (mm/m^2)
    - LVOT gradient at rest (mmHg)
    - LVOT gradient on Valsalva provocation (mmHg)
    - LVOT gradient during exercise (mmHg, where available)
    - Left ventricular ejection fraction
    - Tissue doppler velocities
        - Septal Ea
        - Septal S
        - Lateral Ea
        - Lateral S
        - Lateral E:Ea ratio
    - Valvular heart disease >moderate
    - Presence of pulmonary hypertension

Patient data were grouped according to diagnosis for statistical analysis. Details of specific tests used will be described in the relevant sections.

4 Methods – anatomy

4.1 Assessment of the effect of aorto-septal angulation on provocable left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

This was a retrospective cohort study. The study complied with the declaration of Helsinki and NHS research governance arrangements. I reviewed the images and case-notes of 179 consecutive patients fulfilling conventional diagnostic criteria for HCM (34) from our dedicated cardiomyopathy clinic, in whom there was a clinical suspicion of provocable obstruction but no resting gradient, referred for stress echocardiography between August 2004 and December 2008. None of the patients had received interventional gradient reduction therapy (myectomy/ASA). Contemporaneous peak oxygen consumption measured during symptom limited upright bicycle ergometer exercise testing, functional class and medication data were recorded in all patients. The control group consisted of 25 age and sex matched individuals referred for transthoracic echocardiography to investigate symptoms of chest pain or breathlessness, who were subsequently found to have normal studies, with no history of hypertension, myocardial or valvular heart disease.

Resting transthoracic echocardiography was performed using vivid i7 (GE Vingmed Ultrasound, Horten, Norway) and Philips Sonos 7500 (Philips Medical Systems, Andover, MA, USA) platforms using standard acquisition protocols (British Society of Echocardiography). Exercise echocardiography was performed using the same equipment, simultaneously with symptom-limited exercise on an upright bicycle ergometer using a ramp protocol. Echocardiographic parameters were measured according to European Society of Echocardiography guidelines (289,290,293) using EchoPAC (GE) software. Basal septal thickness was measured in the parasternal short axis view. SAM was defined as incomplete if there was any movement of the mitral valve leaflets or chordae toward the ventricular septal endocardium without septal contact; and as complete when there was contact with the ventricular septum during systole. Mitral regurgitation was graded as none, mild, moderate or severe at rest and during provocation (290). LVOT gradient was measured using continuous wave Doppler in the apical 5 chamber view at rest, during exercise at 2 minute intervals, immediately on cessation of exercise and 2 minutes into recovery. The maximal value was then reported. Care was taken to interrogate the LVOT and not a mitral regurgitation or mid cavity obstruction Doppler profile. Resting LVOT obstruction was defined as a peak LVOT gradient ≥30 mmHg, and provocable

LVOT obstruction was defined as a gradient ≥50mmHg during provocation. The smallest LVOT diameter below the aortic valve annulus during ventricular systole was measured in the parasternal long axis view.

The mode of provocation is important. Valsalva is commonly performed to elicit a gradient during echo, and has been used for decades (294,295). However, this has been shown to significantly underestimate both the presence of provocable obstruction and the magnitude of the gradient demonstrated during exercise. Exercise echocardiography, particularly in the upright position, is the best method of diagnosing a latent gradient being more reproducible, and has the advantage of being able to correlate imaging data with patient symptoms (119). Exercise triggers LVOT obstruction because of increased contractility and an increase in heart rate which limit filling, particularly if performed in the upright position when outflow tract gradients become higher still (296,297). Rapid changes in preload during recovery represent the most likely explanation for the post exercise development of outflow obstruction. Maron demonstrated that the Valsalva manoeuvre had a sensitivity of only 40% for identifying the presence of an exercise-induced outflow gradient (119). The specificity was 100% for assessing whether patients without obstruction at rest would generate a gradient with exercise (positive predictive value, 100%; negative predictive value, 60%). In patients with both a Valsalva-induced and an exercise-induced gradient, the outflow obstruction generated during the Valsalva manoeuver significantly underestimated the magnitude generated during exercise. Exercise gradients exceeded Valsalva by 24±25 mm Hg (for the 30 to 49 mm Hg exercise-provocable group; P=0.04) and by 65±46 mm Hg (for the ≥50 mm Hg exercise-provocable group; P<0.0001). Interestingly in this cohort 84% of those with an exercise induced gradient of >50mmHg were in NYHA functional class II. What is not known is how many of these will go on to develop symptoms or indeed a deteriorating physiological picture.

The LVOT gradient may reduce quickly on cessation of exercise in the supine position (296,297). A similar study aimed to reproduce patient's mode of exercise (i.e. patient do not often immediately lie down following a period of exercise) and noted a continued increase in LVOT gradient on cessation of exercise in the orthostatic position (298). This group contained patients with both resting and latent obstruction, although a significant number were on cardiac medication which may have reduced the gradient. Following immediate cessation of exercise, venous return is reduced as peripheral muscles stop contracting leading to an increased intraventricular gradient. The obstruction may then be ameliorated on assumption of a supine position after exercise. The authors postulated this is the mechanism by which patients often experience symptoms of syncope / pre-syncope following exercise.

4.1.1 Measurement of aorto-septal angle

A parasternal long axis view taken at the R wave of the surface electrocardiogram was used for analysis. The image was analysed using a DICOM image viewer (SOBOX version 2.3.0.1). The aorto-septal angle was measured using a modification of the technique originally described by Fowles (186), and defined as the angle between a line drawn along the border of the right and left inter-ventricular septum (parallel to the proximal right ventricular endocardial border) and a line drawn through the long axis of the aortic root (figure 4.1), where a value of 180 degrees would be a straight line from septum to aorta and reducing values represent increasing angulation.

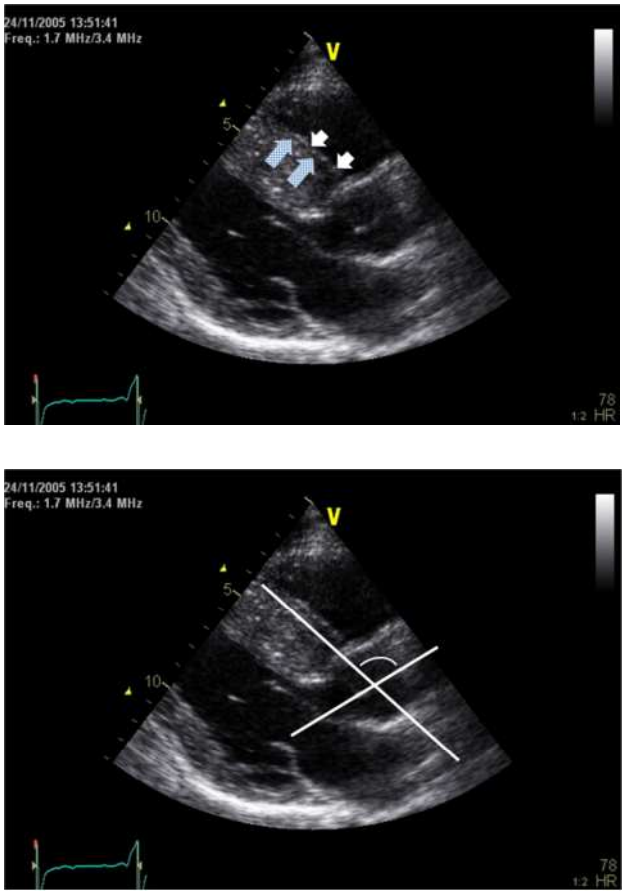
An additional cardiologist (Dr Joel Salazar) trained in echocardiography and cardiomyopathy assessed all images, and measured the aorto-septal angle as above. In 29 patients, contemporaneous CMR images were available, and 3-D datasets were loaded onto a standard offline work station (Leonardo, Siemens Medical Solutions) for analysis of the LV-aortic root angle. This angle was measured in a multi-planar reformatted LVOT view (intended to replicate the echocardiographic images) using the same reference lines as for echocardiography.

4.1.2 Statistics

Normally distributed variables are presented as mean ± standard deviation (SD), and non-normally distributed data as median and interquartile range. Analysis was carried out using SPSS statistical software version 19 (SPSS for Windows, IBM, USA). The mean value of the angle measured by two observers was used as an independent variable, and assessed alongside the above additional echocardiographic parameters using a linear regression model to determine the univariate predictors of the peak provocable LVOT gradient. Significant factors were then entered into a stepwise elimination model to determine multivariate predictors. A similar model was used to determine the predictors of the aorto-septal angle. Binary logistic regression and receiver operator characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of the aorto-septal angle alone or in combination with resting incomplete SAM to detect the presence of provocable LVOTO. Differences between two groups were assessed using independent 2 sample t test. One way ANOVA with homogeneity of variance testing, and post hoc Bonferonni or Games-Howell corrections were used as appropriate to assess differences between multiple groups. Inter-observer variability was assessed using a two-way mixed model intra-class correlation coefficient

(absolute type) and Pearson's correlation. Intra-observer variability was not assessed. Agreement between echocardiography and CMR measured angles was assessed using Pearson's correlation coefficient and Bland-Altman analysis. For all tests a p value <0.05 was considered significant.

Figure 4.1. Transthoracic echocardiogram, parasternal long axis view: example of construction of reference lines for aorto-septal angle calculation.



Panel A: The septal line was drawn along the junction of left and right inter-ventricular septum (checked arrows), parallel to the proximal right endocardial border (white arrows). Panel B: The aorto-septal angle was defined as the angle between the septal line, and a line drawn through the long axis of the aortic root where a value of 180 degrees would be a straight line from septum to aorta and reducing values represent increasing angulation.

4.2 CT imaging of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy undergoing invasive septal reduction therapy

Cardiac CT scanning can be performed in most patients, with rare contra-indications. Spatial resolution is very good (0.4mm), and with contemporary scanners the ionising radiation dose is low. Pre-and post-operative imaging is therefore feasible. Many patients with HCM have ICDs or pacemakers precluding them from MRI scanning. Whilst leads and generators can degrade CT images making resolution of small structures more difficult, adequate images in these cases are still achievable. Additonally, imaging of the lung fields may yield further clinically useful information. This technique was therefore chosen to assess cardiac structure before and after myectomy surgery.

Patients were recruited from specialist cardiomyopathy clinics at the Heart Hospital, who were being assessed for LVOT gradient reduction therapy. Initially this included myectomy surgery only, although was expanded to include ASA following continued suspension of the surgical program. The study complied with the declaration of Helsinki and NHS research governance arrangements (REC reference number 08/H0713/51).

Patients had their CT scan at Great Ormond Street Hospital, using a 64 slice Siemens Somatom Definition scanner, supervised by Prof Andrew Taylor. Scans were retrospectively ECG-gated and used 100mls Omnipaque 350 contrast. Auto bolus tracking was performed with a region of interest drawn in the ascending aorta from a scout scan, and triggered at 100HU. Coverage began at the mid aortic arch and included the whole heart.

CT image data were reconstructed by using Mimics software (Materialise, Ann Arbor, Mich). All reconstructions were executed by one operator (Claudio Capelli) with 8 years of experience. Image elaboration for each CT data-set took 4-5 hours. The Digital Imaging and Communications in Medicine data were imported into the Mimics software for image processing. These data were viewed in two dimensions (transverse, coronal, and sagittal sections) and in 3D after segmentation. Segmentation masks were then used to detect the region of interest—in this case, the left ventricle.

Thresholding was the first action performed to create a segmentation mask. The region of interest was selected by defining a range of gray values. The boundaries of this range were the lower and upper threshold values. All pixels with a gray value in this range were highlighted in a mask. To detect the inner arterial wall, two suitable threshold values were chosen.

Next, a region-growing algorithm was used to eliminate noise and separate structures that were not connected. Finally, manual editing functions were used to draw, erase, or restore parts of the image by clicking on single pixels. When the region of interest was completely selected, the software constructed a 3D model of the structure by means of pattern recognition and interpolation algorithms. In this way, it was possible to generate the volume of the ventricle wall.

Once the first 3D model was generated 2 subsequent functions were performed. First, the dedicated wrap was using to create a more uniform surface of the left ventricle. This tool was found useful in consideration of the complex ventricle structure and to filter small inclusions or close small holes. Following sensitivity analysis the following parameters were set up and kept consistent for each data set: smallest detail = 0.5 mm and closing distance = 0.5 mm. Finally, a smoothing algorithm (smoothing factor 1.0, iterations =3) was applied. These values were the results of a sensitivity analysis performed on the entire cohort of reconstructions to identify the optimal setting to model all the anatomies in this study without creating artefacts (i.e. increasing too much the smoothing factor may lead to unrealistic anatomies). The values of such sensitivity analysis are reported to guarantee repeatability of this study if the same commercially available software is used. The obtained volume was eventually automatically calculated.

Volumes were calculated for the best systolic and diastolic frame pre and post-operatively. The difference between the pre and post operative figures was intended therefore to represent the volume of muscle resected plus any changes attributable to remodelling in the intervening period.

4.2.1 Statistics

Normally distributed variables are presented as mean ± standard deviation (SD), and non-normally distributed data as median and interquartile range. Analysis was carried out using SPSS statistical software version 21 (SPSS for Windows, IBM, USA). Differences between groups were assessed using independent 2 sample t tests. For all tests a p value <0.05 was considered significant.

5 Results

5.1 Cardiac output measurement validation study

5.1.1 Cohort

The study cohort consisted of 24 healthy volunteers (12 male, ages 35 ± 8 years, height 174 ± 8cm, weight 72 ± 13kg) with no history of cardiorespiratory disease. These volunteers were all National Health Service employees at the time of testing.

Valid results at rest and on exercise were achieved in 20 of 24 participants. Two participants were unable to successfully perform the respiratory manoeuvres required to measure cardiac output using the C_2H_2 technique, and a further 2 participants had inconsistent finger pulse pressure waveforms and were excluded. The overall correlation between all finger plethysmography and C_2H_2 data obtained during rest and exercise was $r^2 = 0.872$, $p < 0.0001$ (Figure 5.1).

5.1.2 Rest

Resting heart rate was 77 ± 11 beats per minute. Mean finger plethysmography derived cardiac output was 5.3 ± 1.1 L/min (5.7 ± 0.8 L/min in men and 4.9 ± 1.2 L/min in women). Corresponding mean C_2H_2 uptake cardiac output was 5.2 ± 1.2 L/min (5.7 ± 0.8 L/min in men 4.6 ± 1.4 L/min in women). There was no significant difference between the results obtained with each technique at rest (p=0.712). The correlation coefficient was 0.902, $p < 0.0001$. Mean difference (bias) between techniques was -0.1 L/min with a standard deviation (precision) of 0.5 L/min. Bland Altman plots for rest and exercise are shown in figure 5.2. The mean fractional deviation from C_2H_2 uptake derived cardiac output at rest was -4 ± 15% (0 ± 9% in men and -8 ± 18% in women (figure 5.3)). At rest, 3 of the 20 finger plethysmography values differed by >10% from the corresponding C_2H_2 values.

Figure. 5.1. Graph showing correlation between acetylene and finger plethysmography derived cardiac output

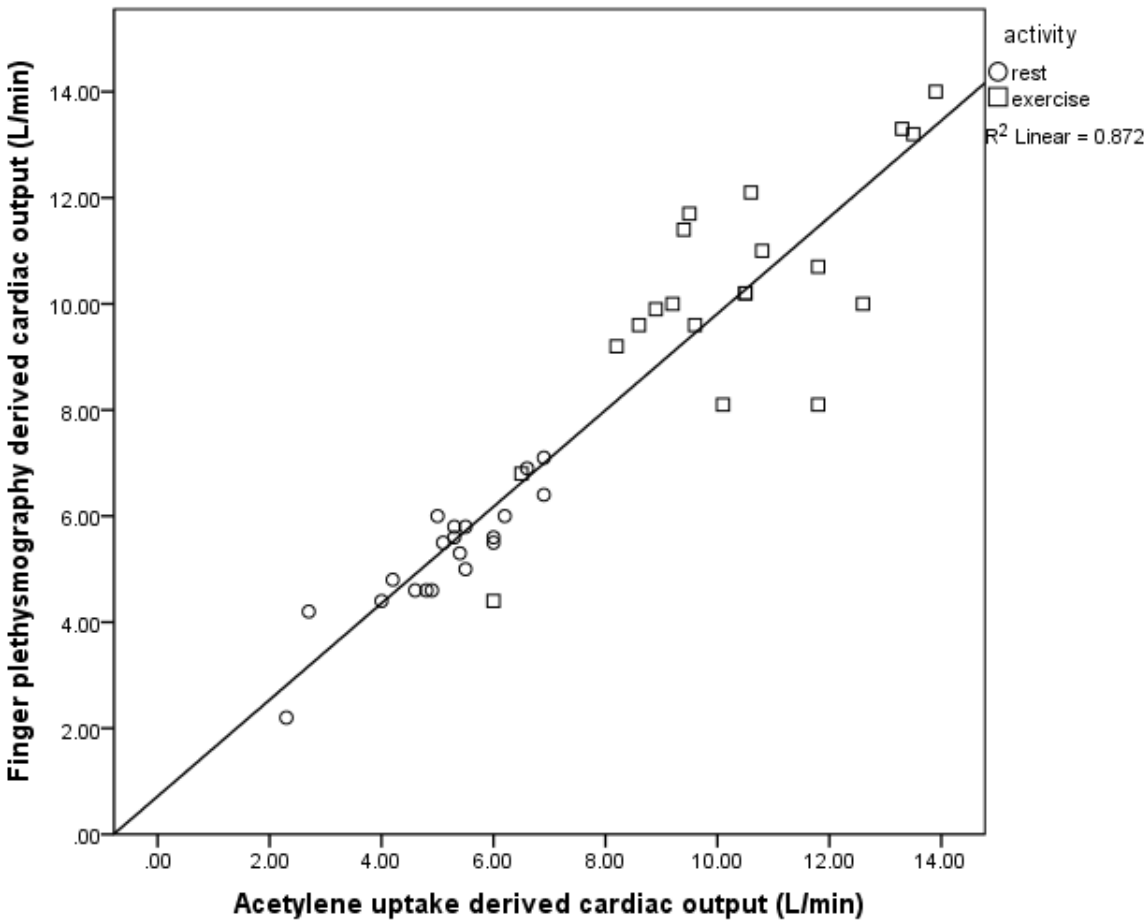
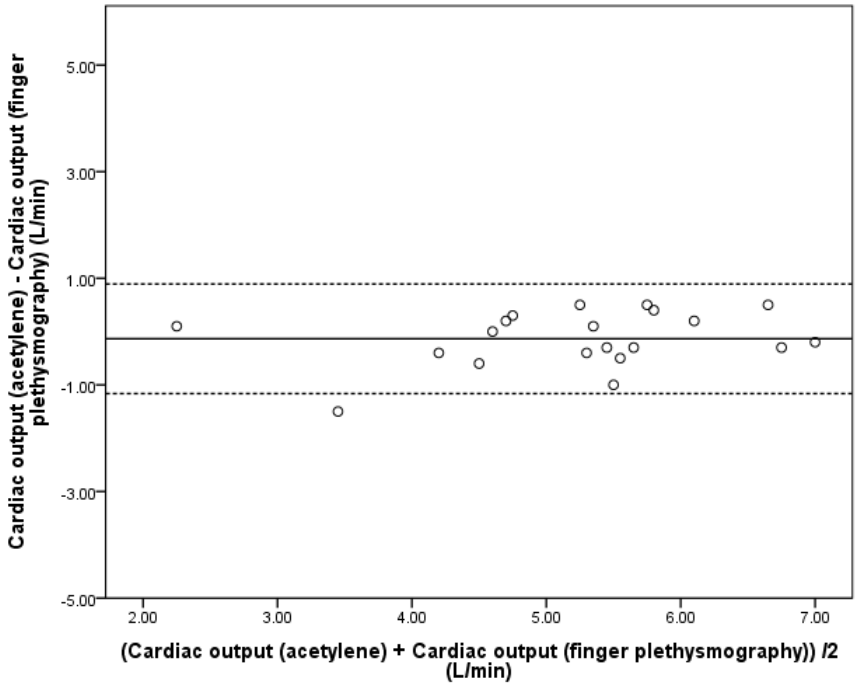
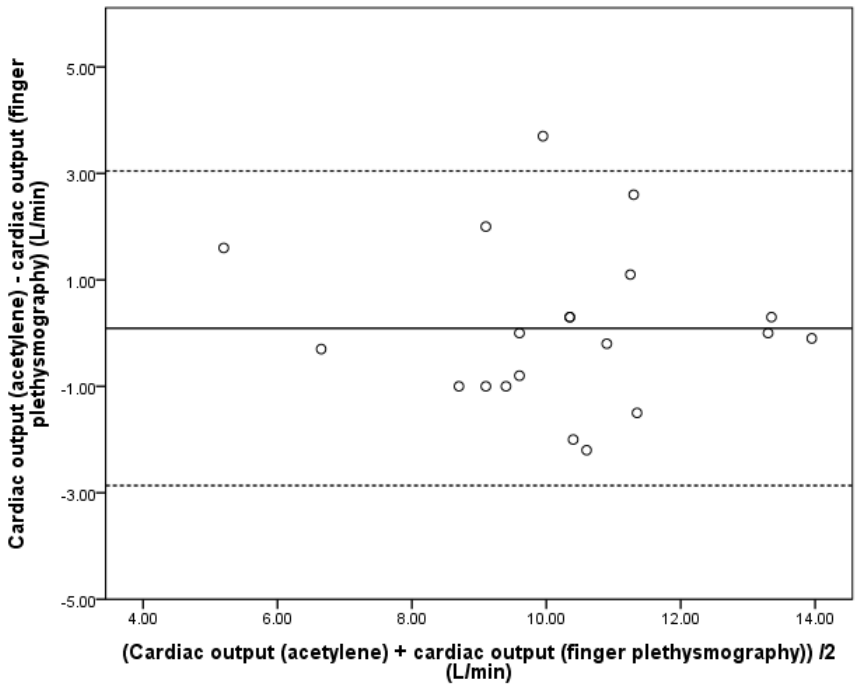


Figure. 5.2 Bland-Altman plot showing difference between (a) resting and (b) sub-maximal exercise cardiac output acetylene uptake and finger plethysmography values plotted against their mean.



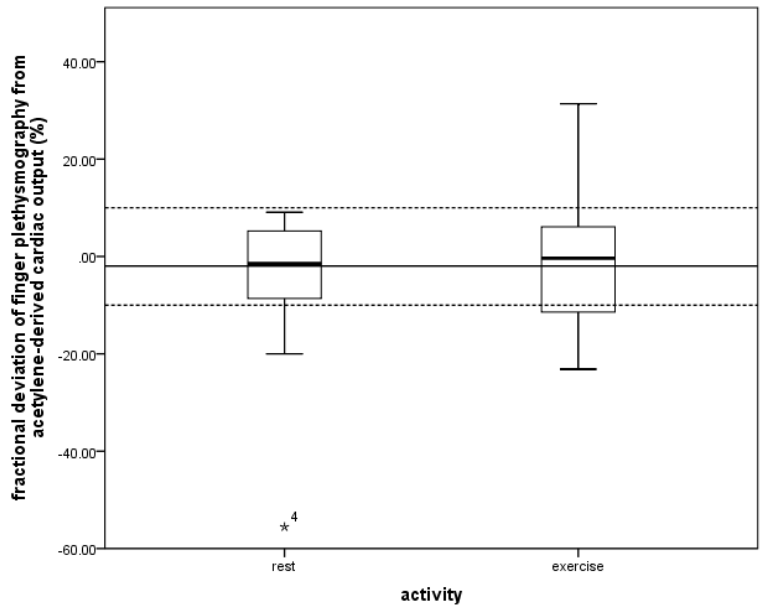
A



B

Solid lines represent mean differences, dotted lines represent mean differences ± 1.96 x SD.

Figure 5.3 Fractional difference between finger plethysmography derived cardiac output and the acetylene uptake method.



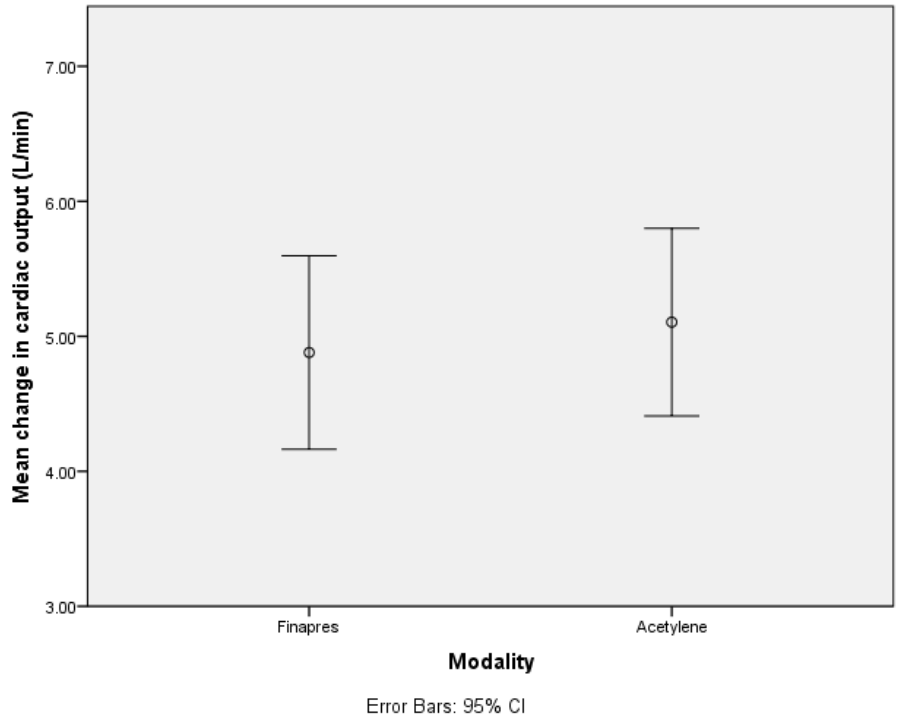
Solid line represents mean difference, dotted lines represent ±10%**.** Top whisker - highest case within 1.5 times inter-quartile range, top of box – third quartile, middle line – median, bottom of box – first quartile, bottom whisker – lowest case within 1.5 times inter-quartile range

5.1.3 Exercise

Mean exercise duration was 7 minutes 23 (± 68) seconds. Time taken to complete three steady state C_2H_2 technique cardiac output measurements was 76 ± 12 seconds. Heart rate during sub-maximal exercise was 120 ± 15 beats per minute at a workload of 77 ± 24 Watts. Mean finger plethysmography derived cardiac output was 10.2 ± 2.3 L/min (11.1 ± 1.9 L/min in men and 9.2 ± 2.2 L/min in women). Corresponding mean C_2H_2 uptake cardiac output was 10.3 ± 2.1 L/min (11.6 ± 1.8 L/min in men and 8.9 ± 1.6 L/min in women). There was no significant difference between the results obtained during exercise (p=0.898). The combined correlation coefficient was 0.767, p<0.0001. Mean difference between techniques was 0.1 L/min (± 1.5 L/min). The mean fractional deviation from C_2H_2 uptake derived cardiac output on exercise was 0 ± 15% (3 ± 15% in men and -2 ± 15% in women). On exercise 10 of the 20 finger plethysmography values differed by >10% from the corresponding C_2H_2 uptake (figure 5.3).

The mean absolute rise in cardiac output from rest to sub-maximal exercise was 5.1 ± 1.5 L/min (C_2H_2) and 4.9 ± 1.5 L/min (finger plethysmography, p=0.64), figure 5.4. The mean percentage increase in cardiac output from rest to sub-maximal exercise was 50 ± 9% (C_2H_2) and 47 ± 7% (finger plethysmography, p=0.374).

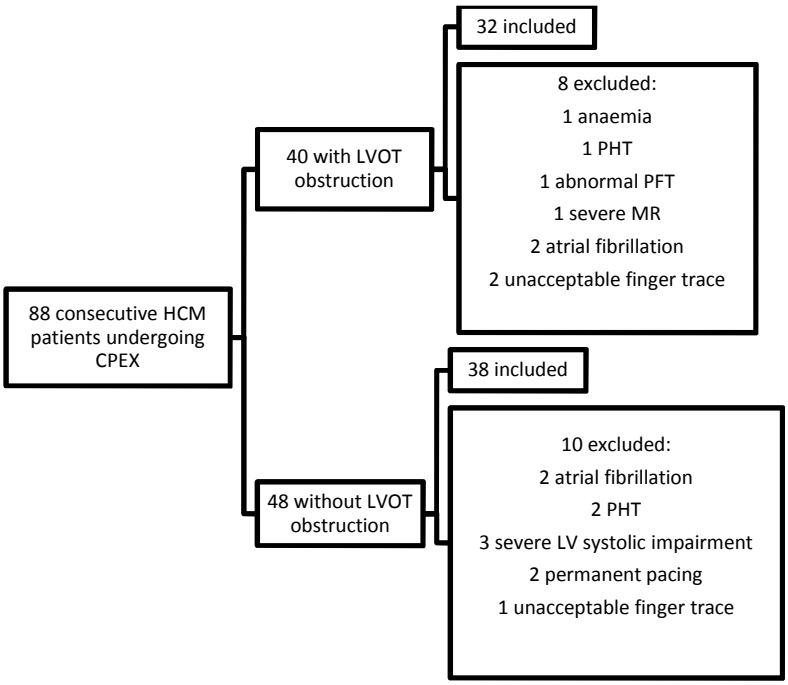
Figure 5.4. Graph demonstrating the difference between techniques for the measurement of mean increase in cardiac output from rest to sub-maximal exercise



5.2 The effect of left ventricular outflow tract obstruction on cardiac output response to exercise in hypertrophic cardiomyopathy

Eighty-eight consecutive patients with HCM undergoing cardiopulmonary exercise testing as part of their routine clinical evaluation were assessed. A consort diagram showing patients included and reasons for exclusion is shown in Figure 5.5.

Figure 5.5. Consort diagram demonstrating characteristics of HCM patients included and reasons for exclusion



CPEX – cardiopulmonary exercise test, HCM – hypertrophic cardiomyopathy, LV – left ventricular, LVOT – left ventricular outflow tract, MR – mitral regurgitation, PFT – pulmonary function test, PHT – pulmonary hypertension,

The final cohort consisted of 70 consecutive adult patients (55 male, age 47 ± 13 years) with HCM attending a dedicated cardiomyopathy clinic undergoing cardiopulmonary exercise testing as part of their routine clinical evaluation and twenty eight normal healthy volunteers (14 male, age 41 ± 12 years). Fifteen on the normal volunteers had participated in the validation study. Patients with anaemia, respiratory disease (defined as FEV_1 or FVC <80% predicted), valvular heart disease, cardiac pacing, pulmonary hypertension (defined as mean pulmonary artery systolic pressure ≥25mmHg), left ventricular systolic dysfunction (defined as an ejection fraction <55% measured by

echocardiography using Biplane Simpson's method) or permanent AF were excluded from the study. Where possible medication was discontinued for 3 half-lives prior to exercise as per hospital protocol. Patients were telephoned by nursing staff in advance of their appointment. If patients required medication for symptomatic reasons and could not be withheld the time and date of dosage was documented. The control group consisted of individuals who had no medical history of cardiovascular or other systemic disorders. None was involved in heavy exercise or athletic training. I attempted to age and sex match the control group to the patients, although the mean age of the controls was slightly lower than the patients due to difficulties recruiting 'older' volunteers. It was not possible to recruit the same number of individuals to the control group. They were employees of the national health service at the time of testing. They should have undergone echocardiography to confirm the absence of cardiac disease, although this was not performed. None reported any cardiac symptoms.

5.2.1 Statistics

Professor Allan Hackshaw (Professor of medical statistics, University College London) reviewed my data and advised on appropriate statistical testing. Continuous variables are presented as mean ± standard deviation (SD). Analysis was carried out using SPSS statistical software version 19 (SPSS for Windows, IBM, USA). Differences between two groups were assessed using independent 2 sample t test and within groups at different workloads using paired t test. One way ANOVA with homogeneity of variance testing, and post hoc Bonferonni or Games-Howell corrections were used as appropriate to assess differences between multiple groups. Pearson's coefficient was used to assess for correlation. Linear regression analysis was used to assess the predictors of cardiac reserve in patients. A p value <0.05 was considered significant.

5.2.2 Demographics

Descriptive clinical and echocardiographic statistics are shown in table 5.1. Thirty eight (54%) patients had non obstructive HCM and 32 patients had LVOT obstruction (22 (31%) patients with resting obstruction and 10 (14%) with provocable obstruction). Patients with obstruction had a

worse functional class (p=0.004), larger maximal wall thickness (19 ± 5 vs 17 ± 4 mm, p=0.019) and larger E:Ea ratio at the lateral mitral valve annulus, (p<0.0001) than those with non-obstructive HCM. There was no difference in left atrial size or left ventricular end diastolic dimension between patient groups.

5.2.3 Workload

Peak workload (Watts) achieved was higher in controls (199 ± 67 W, range 80-365) than non-obstructive (148 ± 53 W, range 33-269, p=0.001) and obstructive groups (101 ± 47 W, range 26 – 194, p<0.0001). Patients without obstruction achieved a higher peak workload than obstructive patients (p=0.002). Five non-obstructive patients and no patient with obstruction achieved a workload >200W; 14 and 8 patients, respectively, achieved a workload between 150 and 200W (Figure 5.6). No attempt was made to statistically compare patient groups at workloads above 150W due to small numbers. I initially sought to evaluate haemodynamic responses before, at, and after anaerobic threshold. However, I found the anaerobic threshold was not always determined with a high enough degree of precision (ie to the exact percent), and I thought that by evaluating the haemodynamic parameters at specific workloads this would allow better comparison between groups. I acknowledge however that the haemodynamic responses will have differed before and after anaerobic threshold, and therefore this would have been of interest and importance.

Table 5.1. Descriptive clinical and echocardiographic statistics for cohort

	Normal controls	HCM without LVOT obstruction	HCM with LVOT obstruction
Number	28	38	32
Male	14 (50%)	32 (84%)	23 (72%)
Age (years)	41 ± 12	46 ± 13	48 ± 14
Height (cm)	172 ± 9	174 ± 7	172 ± 10
Weight (kg)	73 ± 15	90 ± 19*	86 ± 18†
Body surface area (Mosteller formula, m^2)	1.87 ± 0.23	2.07 ± 0.25†	2.02 ± 0.25*
NYHA class I	28 (100%)	25 (66%)†	9 (28%)*, **
NYHA class II	0	12 (32%)†	18 (56%)*, **
NYHA class III	0	1 (3%)†	5 (16%)*, **
NYHA class IV	0	0	0
Left ventricular end diastolic diameter (mm)		48 ± 6	46 ± 5
Left ventricular maximal wall thickness (mm)		17 ± 4	19 ± 5**
Left atrial size (mm)		43 ± 6	43 ± 6
LVOT gradient rest (mmHg)		6 ± 4	55 ± 39**
LVOT gradient peak (mmHg)		11 ± 10	82 ± 31**
Ejection fraction (%)		66 ± 8	68 ± 4
Lateral mitral valve annulus E:Ea ratio		8.4 ± 3.6	13.6 ± 5.9**
Previous alcohol septal ablation		1	0
Previous myectomy surgery		4	1
Usual Medication (withheld >48 hours) Beta blocker		15	21
Calcium channel blocker		4	6
ACE inhibitor		3	2
Amiodarone		1	0

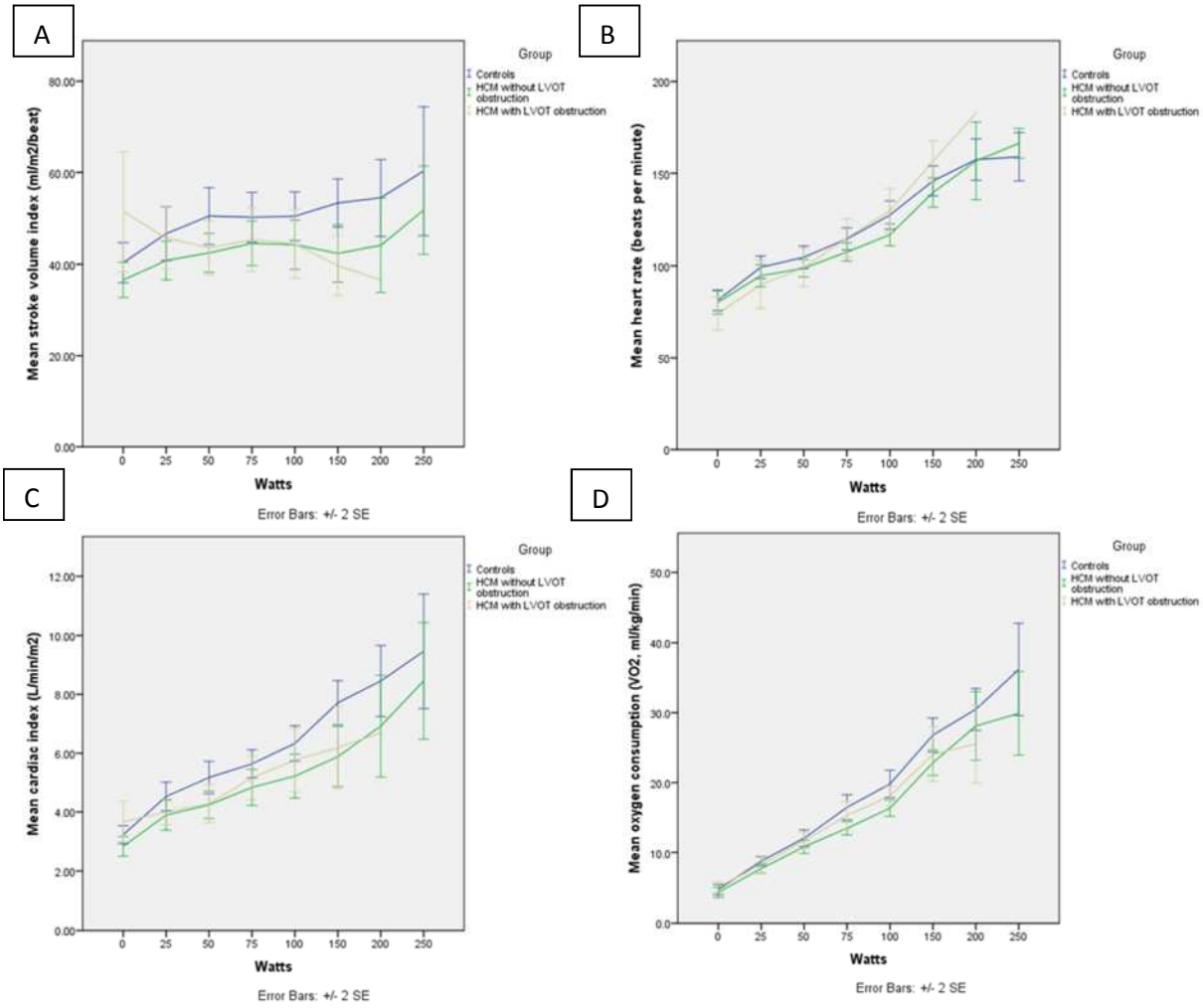
ACE – angiotensin converting enzyme, HCM – hypertrophic cardiomyopathy, LVOT – left ventricular outflow tract, NYHA – new york heart association

* HCM with LVOT obstruction vs controls $p<0.05$

† HCM without LVOT obstruction vs controls $p<0.05$

** HCM with LVOT obstruction vs HCM without LVOT obstruction $p<0.05$

Figure 5.6. Haemodynamic and respiratory parameters during exercise in individuals with good exercise tolerance.



HCM – hypertrophic cardiomyopathy, LVOT – left ventricular outflow tract
Stroke volume index (A), heart rate (B), cardiac index (C) and oxygen consumption (D) during bicycle exercise in controls and patients with non-obstructive, and obstructive hypertrophic cardiomyopathy who were able to exercise at workloads >150 Watts.

The number of individuals in each group at specific workloads was:

Workload	0	25	50	75	100	150	200	250
Normals	28	28	28	28	28	28	13	5
HCM with LVOT obstruction	32	32	28	23	16	8	2	0
HCM without LVOT obstruction	38	38	37	35	32	19	5	3

5.2.4 Oxygen consumption

Peak VO_2 was higher in controls than patients (34.7 ± 7.7 vs 22.4 ± 6.1 ml/kg/min, p<0.0001). There was no significant difference in peak VO_2 between patients with and without LVOT obstruction (20.5 ± 6 vs 24.1 ± 5.9 ml/kg/min, p=0.066). At low workloads (<50W) absolute and relative change in VO_2 were comparable (table 5.2, Figure 5.7d) between controls and patients. Above 50W, VO_2 was higher in controls than patients. Patients with LVOT obstruction had a higher VO_2 at baseline through to 75W than patients without obstruction (table 5.3, Figure 5.7d). Above 75W, VO_2 was similar between patient groups.

5.2.5 Stroke volume index

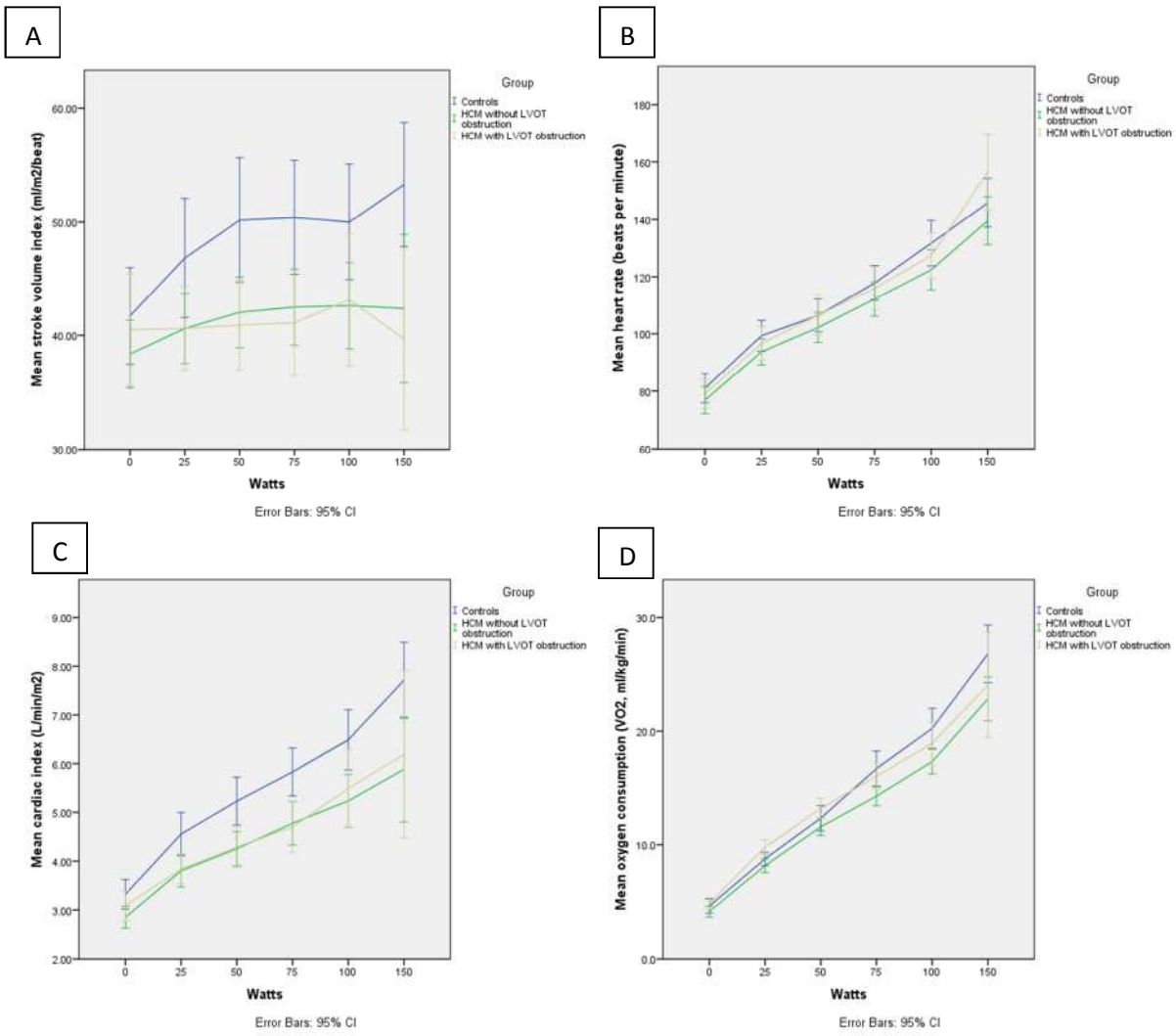
In the control group there was an increase in stroke volume index (SVI) from baseline to 50W (p<0.0001) and 100W (p<0.0001), with a further rise from 100W to 150W (p=0.006), (table 5.2). In the non-obstructive patients, there was an initial rise in SVI from baseline to 50W (p=0.014) and 100W (p=0.021) but no additional rise was seen between 100W and to 150W (p=0.655).

In patients with LVOT obstruction there was a failure to augment SVI at all workloads. In the small number of patients able to achieve workloads ≥150W, SVI continued to fall in those with LVOT obstruction (fig 5.4). However, analysis of individual patient data demonstrated heterogeneous responses, with some resembling that seen in the controls (Figure 5.8).

Resting SVI values were similar in patients and controls. The absolute and percentage rise in SVI was greater at all workloads in controls when compared to patients (table 5.2, Figure 5.7a). Between patient groups absolute SVI was comparable at rest and at all workloads. However, the percentage rise from baseline was significantly higher in the non-obstructive group at workloads above 75W (table 5.3, Figure 5.7a).

Baseline SVI correlated with peak workload achieved in the obstructive group (R = 0.417, p =0.018) but not in those without obstruction (r= - 0.186, p=0.264) or controls (r= -0.088, p=0.658). However although the correlation was statistically significant the attributable impact is likely to be very low, and therefore not much variability in peak workload achieved is likely to be due to baseline SVI or left ventricular end systolic volume.

Figure 5.7. Haemodynamic and respiratory parameters during exercise



HCM – hypertrophic cardiomyopathy, LVOT – left ventricular outflow tract.

Stroke volume index (A), heart rate (B), cardiac index (C) and oxygen consumption (D) during bicycle exercise from 0 – 150 Watts in controls and patients with non-obstructive, and obstructive hypertrophic cardiomyopathy.

The number of individuals in each group at specific workloads was:

Workload	0	25	50	75	100	150
Normals	28	28	28	28	28	28
HCM with LVOT obstruction	32	32	28	23	16	8
HCM without LVOT obstruction	38	38	37	35	32	19

Table 5.2. Cardio-respiratory parameters in normal individuals and patients with hypertrophic cardiomyopathy during bicycle exercise between 0-150 Watts

	Workload (Watts)					
	0	25	50	75	100	150
Number						
Normal	28	28	28	28	28	28
HCM	70	70	65	58	58	27
VO_2 (ml/kg/min)						
Normal	4.6 ± 1.6	8.8 ± 1.5	12.3 ± 2.9	16.7 ± 4	20.2 ± 4.5	26.8 ± 5.9
HCM	4.5 ± 1.4	8.9 ± 2	12.3 ± 2.4	15 ± 2.6	17.9 ± 3.2	23.2 ± 4.4
p	0.648	0.72	0.907	0.04	0.009	0.017
Heart rate (bpm)						
Normal	81 ± 13	99 ± 14	106 ± 15	118 ± 16	132 ± 20	146 ± 20
HCM	78 ± 14	95 ± 15	104 ± 17	114 ± 17	124 ± 18	144 ± 18
p	0.311	0.196	0.523	0.292	0.093	0.813
SVI (ml/m^2/beat)						
Normal	42 ± 11	47 ± 13	50 ± 14	50 ± 13	50 ± 13	53 ± 13
HCM	39 ± 11	41 ± 10	42 ± 10	42 ± 10	42 ± 10	42 ± 12
p	0.346	0.014	0.001	0.001	0.001	0.002
Cardiac Index ($L/min/m^2$)						
Normal	3.3 ± 0.8	4.6 ± 1.1	5.2 ± 1.3	5.8 ± 1.3	6.5 ± 1.6	7.7 ± 1.8
HCM	3 ± 0.8	3.8 ± 0.9	4.3 ± 1	4.7 ± 1.2	5.3 ± 1.4	6 ± 2.1
p	0.037	0.002	<0.0001	<0.0001	0.002	0.003
TPR (dyn.sec/cm5)						
Normal	1360 ± 375	1088 ± 420	997 ± 346	915 ± 276	876 ± 303	739 ± 196
HCM	1427 ± 386	1264 ± 426	1181 ± 380	1042 ± 300	999 ± 313	952 ± 326
p	0.433	0.071	0.031	0.063	0.106	0.009

HCM – hypertrophic cardiomyopathy, SVI – stroke volume index, TPR – total peripheral resistance, VO_2 – oxygen consumption

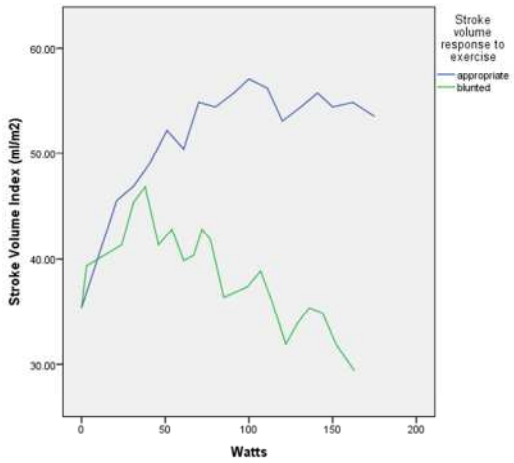
Table 5.3. Cardio-respiratory parameters in patients with hypertrophic cardiomyopathy with and without left ventricular outflow tract obstruction during bicycle exercise between 0-150 Watts

	Workload (Watts)					
	0	25	50	75	100	150
Number						
HCM with LVOTO	32	32	28	23	16	8
HCM without LVOTO	38	38	37	35	32	19
VO_2 (ml/kg/min)						
HCM with LVOTO	4.9 ± 1.4	9.7 ± 1.8	13.2 ± 2.3	16 ± 2.6	18.9 ± 3.5	24.1 ± 5.5
HCM without LVOTO	4.1 ± 1.4	8.2 ± 1.8	11.6 ± 2.3	14.3 ± 2.4	17.3 ± 3	22.8 ± 4
p	0.003	<0.0001	0.006	0.014	0.105	0.521
Heart rate (bpm)						
HCM with LVOTO	79 ± 14	97 ± 16	107 ± 18	116 ± 18	127 ±14	157 ± 16
HCM without LVOTO	77 ± 14	94 ± 14	102 ± 16	112 ± 17	122 ±19	140 ± 17
p	0.518	0.423	0.309	0.421	0.38	0.026
SVI (ml/m^2/beat)						
HCM with LVOTO	41 ± 14	41 ± 10	41 ± 10	41 ± 11	43 ± 11	40 ± 9
HCM without LVOTO	38 ± 9	41 ± 9	42 ± 9	42 ± 10	43 ± 10	42 ± 13
p	0.441	0.997	0.648	0.614	0.871	0.626
Cardiac Index (L/min/m^2)						
HCM with LVOTO	3.1 ± 0.9	3.8 ± 0.9	4.3 ± 1.1	4.7 ± 1.2	5.5 ± 1.5	6.2 ± 1.9
HCM without LVOTO	2.8 ± 0.7	3.8 ± 1	4.3 ± 1	4.8 ± 1.3	5.2 ± 1.5	5.9 ± 2.2
p	0.209	0.87	0.9	0.828	0.582	0.744
TPR (dyn.sec/cm5)						
HCM with LVOTO	1389 ± 404	1285 ± 420	1187 ± 389	1011 ± 315	908 ± 233	969 ± 324
HCM without LVOTO	1459 ± 372	1246 ± 436	1176 ± 378	1063 ± 293	1044 ± 341	946 ± 336
p	0.453	0.709	0.917	0.519	0.17	0.879

HCM – hypertrophic cardiomyopathy, LVOTO – left ventricular outflow tract obstruction, SVI – stroke volume index, TPR – total peripheral resistance, VO_2 – oxygen consumption

Figure 5.8. Differing haemodynamic responses during exercise in two individual patients with hypertrophic cardiomyopathy and resting left ventricular outflow tract obstruction

A



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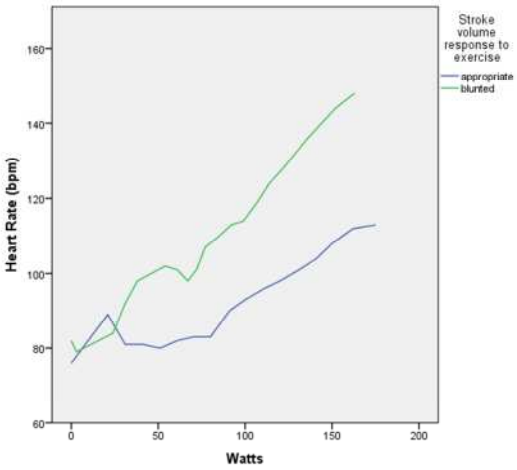

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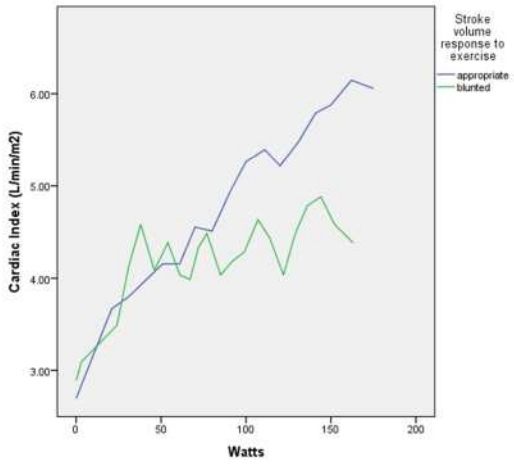


Examples shown are of stroke volume index (A), heart rate (B) and cardiac index (C) response during incremental exercise. The patient with an appropriate stroke volume response was a 37 year old man, New York Heart Association (NYHA) class I, maximal wall thickness 17mm, left atrial size 44mm, left ventricular end diastolic dimension 48mm, ejection fraction 65%, resting left ventricular outflow tract (LVOT) gradient 46 mmHg (increasing to 87mmHg with Valsalva provocation). The patient with a blunted stroke volume response was a 40 year old man, NYHA class II, maximal wall thickness 16mm, left atrial size 38mm, left ventricular end diastolic dimension 46mm, ejection fraction 73%, resting LVOT gradient 31 mmHg (increasing to 106mmHg with Valsalva provocation).

5.2.6 Heart rate

Between workloads of 0-150 W, there was no difference in absolute or change in heart rate between patients and controls (table 5.2, figures 5.5b). At peak exercise, heart rate (146 ± 27 vs 173 ± 17 bpm, p<0.0001) and heart rate reserve (62 ± 26 vs 88 ± 15 bpm, p<0.0001) were lower in patients.

Heart rate at peak exercise was lower in obstructive compared to non-obstructive patients (138 ± 29 vs 152 ± 24 bpm, p=0.035). At individual workloads heart rate was similar in obstructive and non-obstructive HCM (table 5.3, Figure 5.7c) until 150 W when heart rate was greater in patients with obstruction (N = 8 obstructive, 19 non-obstructive , 157 ± 16 vs 140 ± 17 bpm, p=0.026). Above 150W, patients with LVOT obstruction had the highest heart rates of any group (Figure 5.6), although the patient numbers were small.

In the group with LVOT obstruction, 9 patients (28%) were in functional class I, and of these only 1 had chronotropic incompetence (defined as a failure to reach 80% predicted peak HR) which itself was marginal (76%). 3 of 16 patients achieving >100W and 0 of 8 patients achieving >150W had chronotropic incompetence.

5.2.7 Cardiac index

Cardiac index was higher at rest in patients than controls (3.3 ± 0.8 vs 3 ± 0.8 L/min/m^2, p=0.037), although during exercise at all workloads both absolute values and magnitude of increase were lower (table 5.2, Figure 5.7c). Peak cardiac index was higher in controls than patients (9.4 ± 2.9 vs 5.5 ± 1.9 L/min/m^2, p<0.0001) as was cardiac output reserve (11.6 ± 6 vs 5.3 ± 3.4 L/min, p<0.0001).

Resting (3.1 ± 0.9 vs 2.8 ± 0.7 L/min/m^2, p=0.209) and peak (5.3 ± 1.8 vs 5.8 ± 2 L/min/m^2, p=0.302) cardiac index were similar in obstructive and non-obstructive HCM although cardiac reserve was lower (4.4 ± 2.7 vs 6.3 ± 3.6 L/min, p=0.025) in the obstructive group. The increase in cardiac index in those with obstruction was significantly lower than that observed in the non-obstructive group at 75W only. There was a trend towards a difference at 50W and 100W (table 5.3).

5.2.8 Relationship of cardiac index to oxygen consumption

The mean slope of the relationship between cardiac output and VO_2 was higher in normal controls than patients with HCM (5 ± 1.8 vs 3.4 ± 2.1, p=0.001). The slopes were similar in patients with and without LVOT obstruction (3.3 ± 2.4 vs 3.5 ± 1.8, p=0.661). The linear region of the plot of VO_2 against work rate was similar in controls and HCM (10.5 ± 1.1 vs 10.5 ± 1.1, p=0.992), although 4 patients had an abnormal slope (<9). One might expect that the slope would be more shallow in patients with HCM, and this finding may therefore be indicative that the sample size is too small to show a statistically significant difference.

5.2.9 Arterio-venous oxygen difference

Analysis of the A-V oxygen difference at different workloads is shown in table 5.4. There were no differences in A-V oxygen difference at rest between controls and patients. The difference was significantly wider at all levels of exercise in patients. A-V difference was greater in patients with LVOT obstruction during submaximal exercise, although this did not reach statistical significance.

In the subgroup of patients able to achieve workloads of ≥150W, patients with LVOTO had the same resting A-V oxygen difference as HCM (6.9 ± 2.6 vs 6.1 ± 2.5 ml/100ml, p=0.281), but this became significantly higher during sub-maximal (50W, 12.2 ± 3.5 vs 9.7 ± 3.1 ml/100ml, p=0.011) and maximal (19.3 ± 4.8 vs 15.5 ± 4 ml/100ml, p=0.007) exercise.

The maximum oxygen pulse (A-V oxygen difference x stroke volume) was reduced in patients compared to controls (18 ± 4 ml / beat vs 21 ± 4, p=0.001), although there was no difference in patients with and without LVOT obstruction 18 ± 5 ml / beat vs 17 ± 3, p=0.415).

5.2.10 Predictors of cardiac reserve

Univariable analysis of the predictors of cardiac reserve in patients is shown in table 5.5. Resting ejection fraction, left ventricular end diastolic dimension and left atrial size did not correlate with the increase in cardiac output on exercise. Age, gender, peak LVOT gradient and E:Ea ratio at the

lateral mitral valve annulus were all significantly associated with cardiac output reserve and were entered into a stepwise multivariable analysis model. The final significant multivariable factors were age (β -0.11, CI -0.162 - -0.057, p<0.0001), peak LVOT gradient (β -0.018, CI -0.034 - -0.002, p=0.031) and gender (β-2.286, CI -0.162 - -0.577, p=0.01).

Table 5.4. Arterio-venous oxygen difference during exercise in patients with hypertrophic cardiomyopathy vs controls

	Normal Controls	HCM without LVOT obstruction	HCM with LVOT obstruction
A-V O_2 at rest (ml/100ml)	5.8 ± 2.5	6.5 ± 2.6	7.1 ± 2.6
A-V O_2 at 25W	7.9 ± 2.8*	9.9 ± 3.7	11.3 ± 3.6
A-V O_2 at 50W	9.6 ± 3.2*,†	12.5 ± 3.9	13.7 ± 4
A-V O_2 at 100 W	12.7 ± 3.9	15.5 ± 5.1	15.6 ± 4.1
A-V O_2 at 150 W	14.4 ± 4.7†	18.8 ± 5.4	17.9 ± 6.8
A-V O_2 at peak exercise	14.8 ± 4†	18.4 ± 6	17 ± 4.5
Δ A-V O_2	8.9 ± 3†	11.6 ± 4.9	9.9 ± 3.7

A-V O_2 – arterio-venous oxygen difference, LVOT – left ventricular outflow tract.

* HCM with LVOT obstruction vs controls p<0.05

†HCM without LVOT obstruction vs controls p<0.05

Table 5.5. Univariate predictors of cardiac reserve during exercise in hypertrophic cardiomyopathy

	Correlation coefficient (r)	P value	β	Lower CI	Upper CI
Age	-0.511	<0.0001	-0.128	-0.183	-0.073
Female Gender	-0.376	0.002	-3.093	-5.043	-1.144
Maximal wall thickness	0.22	0.083	0.163	-0.022	0.347
Left atrial size	-0.037	0.773	-0.021	-0.164	0.123
Left ventricular end diastolic diameter	0.04	0.757	0.024	-0.129	0.176
Peak left ventricular outflow tract gradient	-0.273	0.03	-0.022	-0.041	0.002
Ejection Fraction	0.145	0.258	0.07	-0.052	0.192
Lateral mitral valve annulus E:Ea ratio	-0.286	0.027	-0.178	-0.334	-0.021

5.2.11 Predictors of stroke volume augmentation

Univariate analysis of the predictors of increase in stroke volume from baseline to 75 W in patients with hypertrophic cardiomyopathy is shown in table 5.6. Variables with a p-value <0.2 were entered into a stepwise multivariate analysis model. The final predictors were peak LVOT gradient (p=0.047) and the change in heart rate to 75 W (p<0.0001), overall r=0.56, p<0.0001.

Univariate analysis of the predictors of increase in stroke volume from baseline to peak exercise in patients with hypertrophic cardiomyopathy is shown in table 5.7. Variables with a p-value <0.2 were entered into a stepwise multivariate analysis model. The final predictors were peak LVOT gradient (p=0.002), MWT (p=0.001) and heart rate reserve (p=0.006), overall r=0.511, p<0.001.

Table 5.6. Predictors of percentage stroke volume augmentation (%) from baseline to moderate exercise (75W)

	Correlation coefficient (r)	P value	β	Lower CI	Upper CI
Age	0.014	0.92	0.023	-0.439	0.485
Female Gender	-0.146	0.277	-11.316	-31.979	9.348
Maximal wall thickness	0.144	0.285	0.706	-0.605	2.017
Left atrial size	0.284	0.032	0.953	0.084	1.822
Left ventricular end diastolic diameter	0.008	0.955	0.029	-1.004	1.063
Peak left ventricular outflow tract gradient	-0.263	0.048	-0.141	-0.281	-0.001
Ejection Fraction	-0.002	0.989	-0.006	-0.829	0.818
E/Ea lateral	-0.123	0.374	-0.562	-1.819	0.695
change in heart rate to 75W (bpm)	-0.51	<0.0001	-0.742	-1.079	-0.404

5.2.12 Blood pressure

MAP at rest (90 ± 12 vs 90 ± 8 mmHg, p=0.791) and peak exercise (108 ± 16 vs 114 ± 13 mmHg, p=0.117) was similar in patients and controls. Resting systolic (118 ± 18 vs 124 ± 17 mmHg, p=0.154) and mean arterial (88 ± 11 vs 92 ± 12 mmHg, p=0.099) blood pressure was similar in patients with and without obstruction; patients with obstruction had a lower peak systolic (152 ± 28 vs 168 ± 29 mmHg, p=0.018) and mean arterial (104 ± 16 vs 112 ± 16 mmHg, p=0.033) blood pressure than non-obstructive patients. Magnitude of blood pressure response in patients with obstruction was 34 ± 21 vs 44 ± 21 mmHg (p=0.106). An ABPR (failure to increase systolic blood pressure >20mmHg) during exercise was seen 13 (19%) patients (8 (25%) with vs 5 (13%) without LVOT obstruction,

p=0.2). There were no differences in resting pulse pressure, heart rate, heart rate reserve, VO_2, peak cardiac output, cardiac reserve and peak and delta SVI between patients with and without an ABPR to exercise.

Table 5.7. Predictors of stroke volume augmentation (%) from baseline to peak exercise

	Correlation coefficient (r)	P value	B	Lower CI	Upper CI
Age	-0.161	0.207	-0.374	-0.962	0.213
Female Gender	-0.057	0.659	-4.309	-23.766	15.149
Maximal wall thickness	0.272	0.031	1.861	0.174	3.547
Left atrial size	0.117	0.361	0.609	-0.713	1.931
Left ventricular end diastolic dimension	-0.082	0.525	-0.449	-1.855	0.957
Peak left ventricular outflow tract gradient	-0.193	0.129	-0.141	-0.325	0.042
Ejection Fraction	0.099	0.442	0.44	-0.698	1.578
E/Ea lateral	-0.089	0.499	-0.505	-1.99	0.98
Heart rate reserve	-0.198	0.12	-0.237	-0.537	0.063

5.2.13 Total peripheral vascular resistance

There was no difference in TPR at rest between patients and the control group (1360 ± 375 dyn.sec/cm5 vs 1427 ± 386, p=0.433). During exercise, TPR was higher in patients than controls (table 5.8, Figure 5.9a). There was no significant difference in TPR at rest or during exercise in patients with and without LVOT obstruction (table 5.3). There was no difference in TPR at rest between patients with and without an ABPR to exercise (1333 ± 316 dyn.sec/cm5 vs 1449 ± 399, p=0.334). During exercise, TPR was lower in patients with an ABPR, with values similar to normal individuals (table

5.8, Figure 5.9b). Although lower at all workloads, this was statistically significant at 25 and 100 watts only. This may be a reflection of statistical power, as the numbers of patients with an ABPR to exercise was small. Ninteen percent of patients were found to have an ABPR to exericse, which is slightly lower than one third of cases reported in previous (larger) series (85,86).

5.2.14 Cardiac power

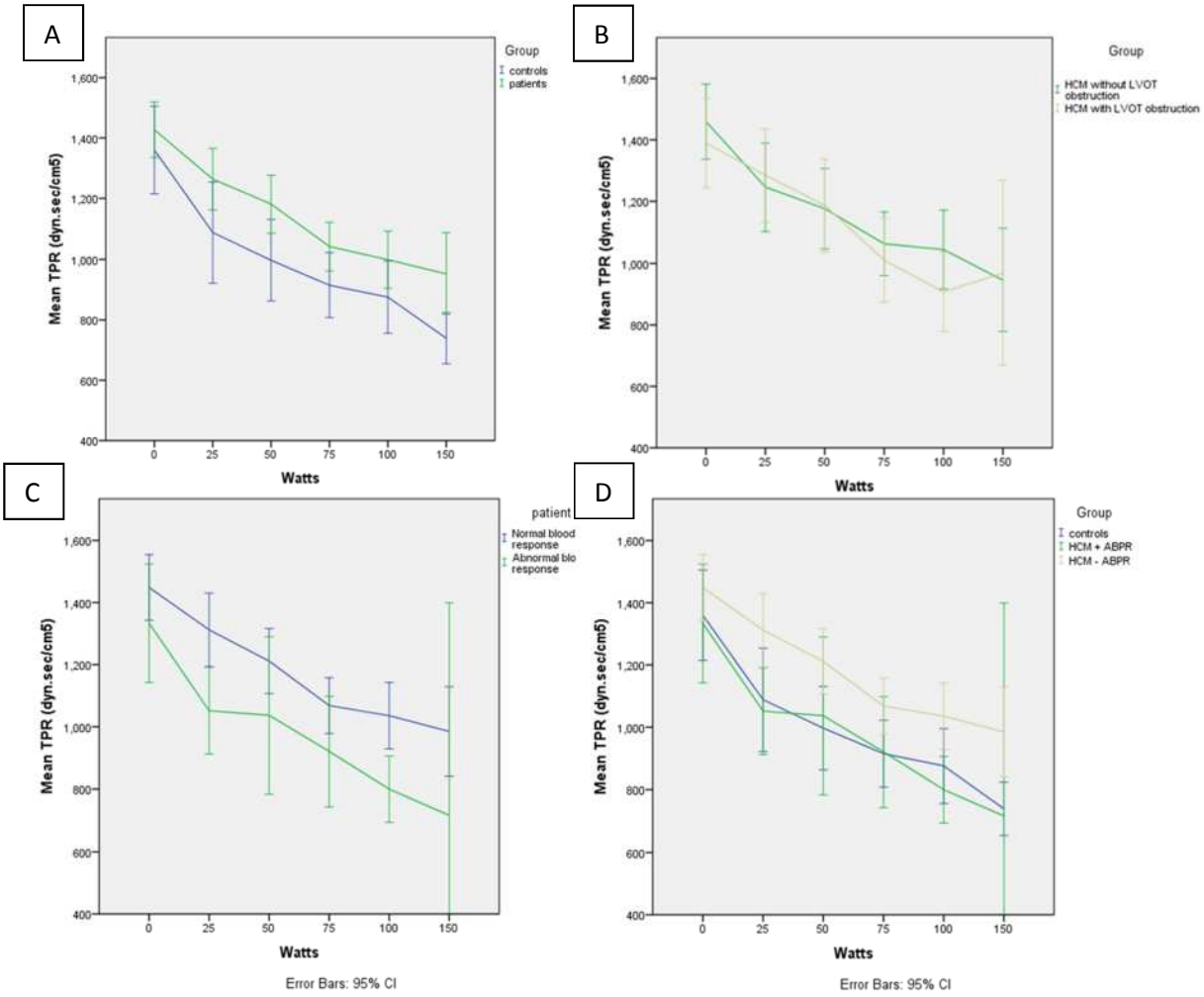
There was a trend towards lower peak cardiac power in patients with LVOT obstruction (2.51 ± 1.14 vs 3.04 ± 1.28 W, p=0.086). There was no relationship between peak cardiac power output and the number of conventional risk factors for SCD, p=0.534. Three (9%) patients with HCM and 12 (40%) with HOCM had peak cardiac power values <1.96W (p=0.04).

Table 5.8. Total Peripheral Resistance in patients with hypertrophic cardiomyopathy with and without an abnormal blood pressure to exercise during bicycle testing between 0-150 Watts

Workload (Watts)	Parameter	Patients without ABPR	Patients with ABPR	P Value
0	Number	57	13	
	TPR (dyn.sec/cm5)	1449 ± 399	1333 ± 316	0.334
25	Number	57	13	
	TPR (dyn.sec/cm5)	1312 ± 447	1052 ± 231	0.005
	Percent change in TPR from baseline	-7 ± 30	-19 ± 16	0.184
50	Number	52	11	
	TPR (dyn.sec/cm5)	1212 ± 377	1037 ± 377	0.168
	Percent change in TPR from baseline	-13 ± 23	-18 ± 23	0.508
75	Number	47	10	
	TPR (dyn.sec/cm5)	1068 ± 306	921 ± 249	0.16
	Percent change in TPR from baseline	-21 ± 21	-29 ± 8	0.057
100	Number	38	7	
	TPR (dyn.sec/cm5)	1036 ± 325	800 ± 114	0.002
	Percent change in TPR from baseline	-25 ± 19	-34 ± 15	0.245
150	Number	22	3	
	TPR (dyn.sec/cm5)	985 ± 325	716 ± 275	0.187
	Percent change in TPR from baseline	-28 ± 24	-34 ± 11	0.679

ABPR – abnormal blood pressure response, TPR – total peripheral resistance

Figure 5.9. Total peripheral resistance (dyn.sec/cm5) during increasing bicycle workload between (A) controls and patients with HCM (B) patients with and without LVOT obstruction (C) patients with and without an abnormal blood pressure response to exercise (D) controls and patients with and without an abnormal blood pressure response to exercise



ABPR – abnormal blood pressure response, CI – confidence intervals, HCM – hypertrophic cardiomyopathy, LVOT – left ventricular outflow tract, TPR – total peripheral resistance

5.3 The influence of aorto-septal angulation on provocable left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

On the day of exercise 19 patients were found to have a LVOT gradient at rest ≥30mmHg at rest and were excluded from analysis. The final study cohort therefore consisted of 160 patients (105 males, age 48 ± 14 years). Descriptive demographic and echocardiographic statistics are shown in table 5.9. 12 (8%) patients were unable to perform exercise and underwent measurement of the LVOT gradient following the administration of sublingual glyceryl tri-nitrate in combination with Valsalva manoeuvre. 59 (37%) patients were taking either a beta blocker or calcium channel blocker and were unable to discontinue before the test for symptomatic reasons; a further 40 (25%) patients withheld these drugs for a minimum of 48 hours prior to study. No patient was taking any other medication likely to have impacted upon pre- or afterload. Provocable LVOTO was present in 60 (38%) patients. There was no difference in absolute (22.0 ± 8.1 vs 20.3 ± 7 ml/kg/min, p=0.199) or percent predicted (71 ± 20 vs 68 ± 19 %, p=0.415) peak oxygen consumption between patients with or without provocable LVOTO. 12 (20%) patients with and 10 (10%) without provocable LVOTO were in NYHA class III (p=0.097).

5.3.1 Aorto-septal angle

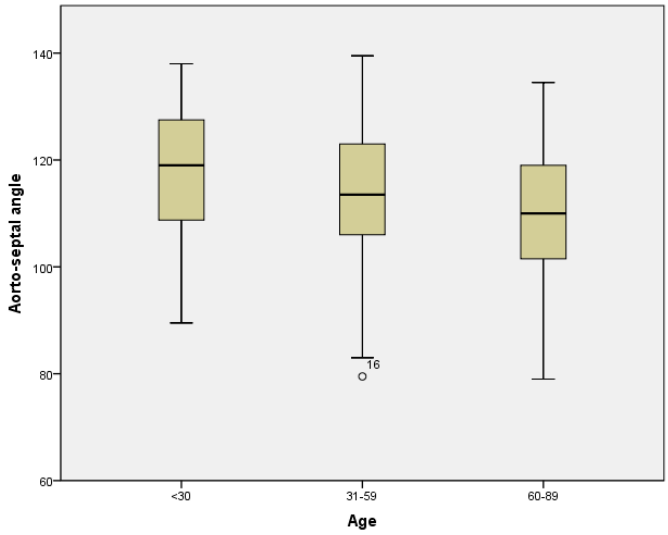
Patients with HCM had a smaller aorto-septal angle than controls (113^0 ± 12 vs 126^0 ± 6, p<0.0001). There was no difference in aorto-septal angle between men and women (112^0 ± 13 vs 114^0 ± 11, p=0.297). There was a weak negative correlation between aorto-septal angle and both age (r= -0.242, p=0.002) and height (r= -0.181, p=0.036). With increasing age, there was a trend towards a steeper aorto-septal angle, p=0.083, Figure 5.10. There was no relationship between aorto-septal angle and body weight. There was no correlation between aorto-septal angle and basal septal thickness or LVOT systolic diameter.

Table 5.9. Patient demographics, clinical and echocardiographic characteristics

	Patients with HCM		Controls
Demographics & baseline data			
Age (years)	50 (19), range 16-82		47 (11)
Male gender	105 (66%)		16 (64%)
Height (cm)	173 (14)		171 (18)
Weight (kg)	82 ± 16		79 ± 14
Peak oxygen consumption (ml/kg/min)	19.0 (11.4)		n/a
Percent predicted peak oxygen consumption	67 (32)		n/a
Medication			
Calcium antagonist or beta-blocker on day of test	59 (37%)		
Calcium antagonist or beta-blocker withheld >48 hours pre-test	40 (25%)		
New York Heart Association functional class			
2	138 (86%)		
3	22 (14%)		
Echocardiographic parameters			
Basal septal thickness (mm)	16 ± 4		9 ± 1
Left ventricular outflow tract systolic diameter (mm)	19 ± 3		27 ± 3
Aorto-septal angle (degrees)	113 ± 12 (range 79-140)		126 ± 6
Left ventricular outflow tract gradient (mmHg),	Rest	Provocation	
Whole cohort	7 (6)	28 (69)	3 ± 1
<30	160 (100%)	81 (51%)	
30-49	-	19 (12%)	
50-69	-	12 (8%)	
≥70	-	48 (29%)	
Systolic anterior motion of the mitral valve			
None	82 (51%)	62 (39%)	25 (100%)
Incomplete	78 (49%)	39 (24%)	
Complete	0	59 (37%)	
Mitral regurgitation			
None	19 (12%)	17 (11%)	16 (64%)
Mild	139 (87%)	120 (75%)	9 (36%)
Moderate	2 (1%)	20 (13%)	
Severe	0	3 (2%)	

Normally distributed data mean ± standard deviation, non-parametric data median (inter-quartile range). Note no change in parameters with provocation in normal controls.

Figure 5.10. Box plot showing aorto-septal angle by age group



Top whisker - highest case within 1.5 times inter-quartile range, top of box – third quartile, middle line – median, bottom of box – first quartile, bottom whisker – lowest case within 1.5 times inter-quartile range.

5.3.2 Relationship between echocardiographic variables and provocable LVOT obstruction

Univariate analysis of echocardiographic variables and their relationship to peak provocable LVOT gradient is shown in table 5.10. Aorto-septal angle (β: -1.18; CI -1.68, -0.68; p<0.0001), incomplete SAM at rest (β: 30.59; CI 18.15, 43.04; p<0.0001) and degree of resting mitral regurgitation (β: 20.61; CI 2.64, 38.59; p=0.025), overall r=0.508, p<0.0001, were independently associated with peak provocable LVOT gradient.

Table 5.10. Univariate predictors of peak provocable left ventricular outflow tract gradient

Factor	r	β	CI		P
			Lower	Upper	
Aorto-septal angle	0.319	-1.165	-1.708	-0.622	<0.0001
Basal septal thickness	0.048	-0.613	-2.618	1.392	0.547
Incomplete systolic anterior motion of the mitral valve (rest)	0.366	33.06	19.861	46.259	<0.0001
Mitral regurgitation grade (rest)	0.197	25.604	5.535	45.677	0.013
Left ventricular outflow tract systolic diameter	0.014	-0.24	-2.949	2.469	0.861

The aorto-septal angle was smaller in patients with provocable LVOTO ($108^0 \pm 12$ vs $116^0 \pm 12$, p<0.0001), Figure 5.11. When grouped by LVOT gradient, a smaller aorto-septal angle was found in patients with increasingly severe LVOTO, p=0.004, Figure 5.12.

Figure 5.11. Histogram showing variation in aorto-septal angle between patients with hypertrophic cardiomyopathy with and without provocable left ventricular outflow tract obstruction (LVOTO).

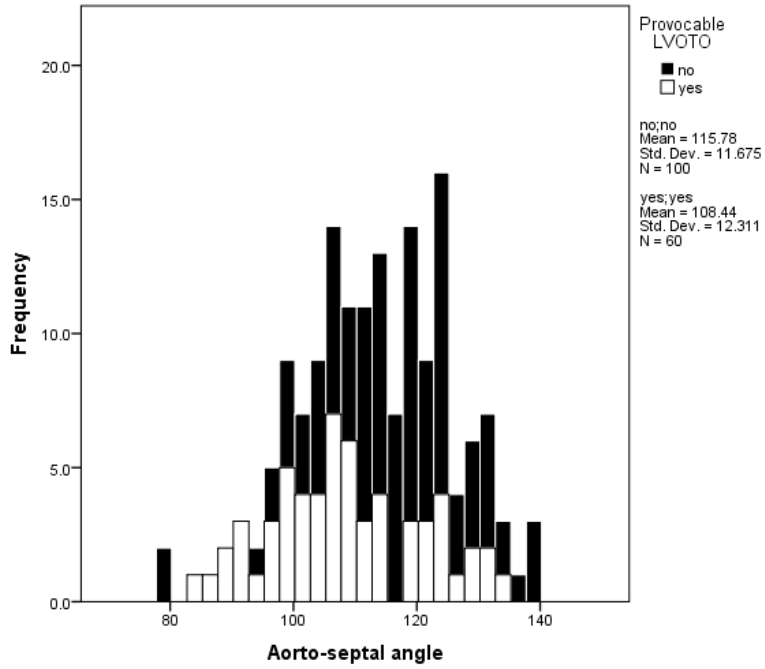
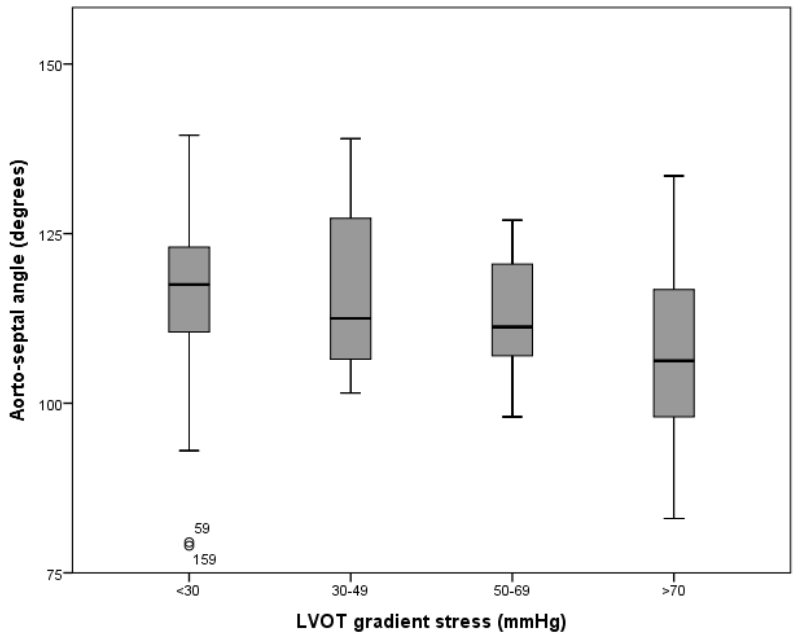


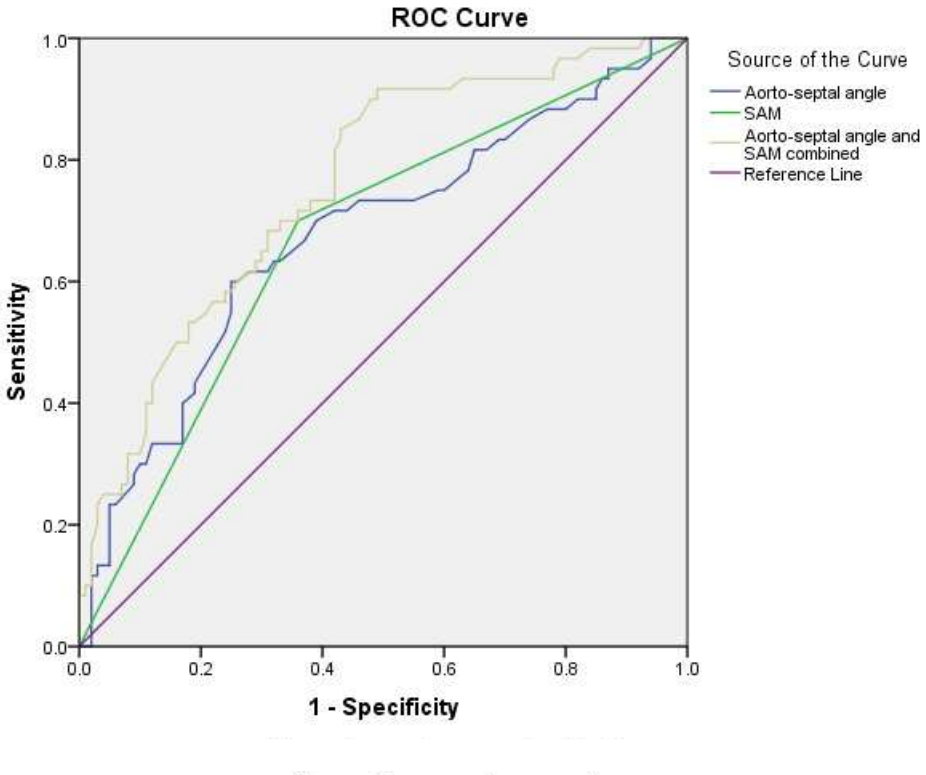
Figure 5.12. Box plot showing decreasing aorto-septal angle with increasing severity of provocable left ventricular outflow tract gradient.



LVOT - left ventricular outflow tract. Top whisker - highest case within 1.5 times inter-quartile range, top of box – third quartile, middle line – median, bottom of box – first quartile, bottom whisker – lowest case within 1.5 times inter-quartile range.

Area under receiver operator curves for aorto-septal angle, incomplete rest SAM, and the two parameters combined for the prediction of provocable LVOTO were 0.68 (95% CI 0.59 – 0.76, p<0.0001), 0.67 (95% CI 0.58 – 0.76, p<0.0001 and 0.76 (95% CI 0.68 – 0.83, p<0.0001), respectively (Figure 5.13). Sensitivity, specificity and positive predictive value for SAM and aorto-septal angulation are shown in table 5.11.

Figure 5.13. Receiver operator characteristic curves showing the probability that aorto-septal angle, presence of systolic anterior motion of the mitral valve and both combined predict patients who develop provocable left ventricular outflow tract obstruction during exercise.



ROC – receiver operating characteristic, SAM - systolic anterior motion of the mitral valve

Table 5.11. Sensitivity, specificity and positive predictive value to predict provocable left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy using resting echocardiographic parameters.

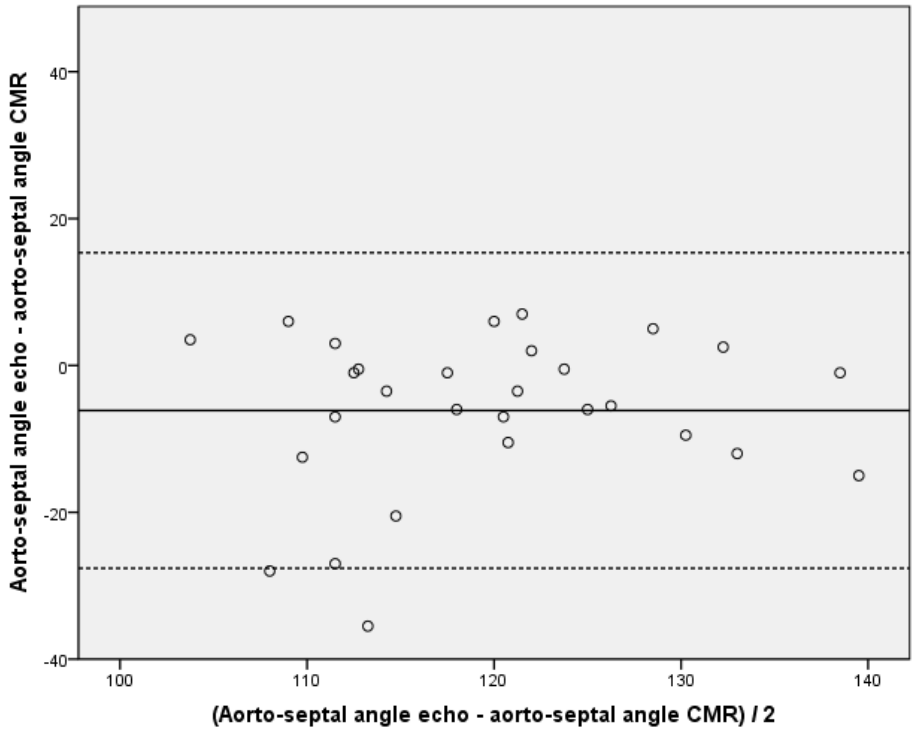
	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Incomplete SAM rest	70	64	54
Aorto-septal angle ≤ 100^{o} N=25 (16%)	27	91	59
Aorto-septal angle ≤ 100^{o} and incomplete SAM rest N=8 (5%)	12	99	88
Aorto-septal angle ≤ 110^{o} N=37 (23%)	62	71	56
Aorto-septal angle ≤ 110^{o} and incomplete SAM rest N=19 (12%)	23	95	74

SAM – systolic anterior motion of the mitral valve

5.3.3 Reproducibility

All images were deemed usable for the purpose of angle measurement by both observers. The intra-class correlation coefficient of the aorto-septal angles measured by the two observers was 0.90 (95% CI 0.87-0.93, p<0.0001), with Pearson's coefficient r=0.82, p<0.0001). Correlation between the aorto-septal angle measured using echocardiography and CMR was r=0.50, p=0.006. The mean difference between the echocardiography angle – CMR angle was -6^{o} (SD 11). A Bland-Altman plot of the differences in angle measured using the two modalities plotted against their mean is shown in Figure 5.14.

Figure 5.14. Bland-Altman plot of the differences between aorto-septal angulation measured using transthoracic echocardiography and cardiac magnetic resonance (CMR) imaging. Solid line represents mean, dashed line represents mean ± 2 standard deviations



CMR - cardiac magnetic resonance

5.4 CT imaging before and after left ventricular outflow tract gradient reduction therapy

In total, 21 patients had a CT scan prior to planned LVOT reduction therapy (16 myectomy, 5 ASA). As previously discussed, this project was hampered by by temporary halting of the myectomy surgical program. As such, the final study cohort consisted of 10 patients, who had pre and post-operative CT scans between May 2010 and August 2012. Tabulated data and illustrative figures follow. Two patients were operated on at the Heart Hospital, and 7 at St Georges Hospital, London. One patient had ASA at the Heart Hospital. In those operated on at the Heart Hospital, the myectomy sample was weighed. Of the 10 patients, reconstructions were not possible in 2 patients due to inadequate scan resolution. In the remaining 8 patients' pre-operative CT scans, all diastolic images were adequate, and 5 systolic images were adequate. In the post-operative scans, 7 diastolic and 6 systolic images were adequate.

Table 5.12. Surgical and functional data for study cohort

ID	age	procedure	tissue removed (grams)	complications	NYHA pre	NYHA post	time pre-op CT to surgery (days)	Time to post-op CT (days)
1	44	extended septal myectomy, PFO closure, AV repair, LAA excision	10.7	required aortic valve repair	3	1	27	219
2	56	septal myectomy, LAA excision	4	none	2	2	15	184
3	46	myectomy		Atrial fibrillation requiring hospitalisation	3	2	381	363
5	51	myectomy		stroke, pericarditis, wound infection requiring VAC dressing and re-operation	3	2	283	356
6	36	myectomy		coronary artery fistula	3	2	164	207
7	67	myectomy		none	3	2	24	188
11	59	myectomy, maze, LAA excision		amiodarone thyrotoxicosis	3	2	353	209
13	45	myectomy CABG and PFO closure		bleeding requiring return to theatre	3	2	322	193
20	45	myectomy		pericardial effusion, became infected with pseudomonas, sternal destruction and pain. Small VSD 40mmHg	3	2	134	235
16	42	Alcohol septal ablation		none	3	2	113	286

CABG- Coronary artery bypass grafting, CT- computed tomography, LAA- Left atrial appendage, NYHA- New York Heart Association, PFO- Patent foramen ovale, VAC- vacuum assited closure, VSD- Ventricular septal defect

Table 5.13. Pre and post operative cardiopulmonary exercise testing

ID	VO_2 (ml/kg/min^{-1}) pre	% predicted VO_2 pre	VO_2 (ml/kg/min^{-1}) post	% predicted VO_2 post	change in VO_2 (%)
1	11.6	55	9.8	47	-16
2	13.5	45	n/a	n/a	n/a
3	na	Na	n/a	n/a	n/a
5	23.3	72	24.2	n/a	4
6	24	60	23.4	63	-3
7	13.3	49	16.3	64	23
11	17.4	58	13.5	48	-22
13	16.1	50	13.7	44	-15
20	16.2	47	n/a	n/a	n/a
16	24	68	n/a	n/a	n/a

VO_2 – oxygen consumption

Table 5.14. Echocardiographic parameters for the study group

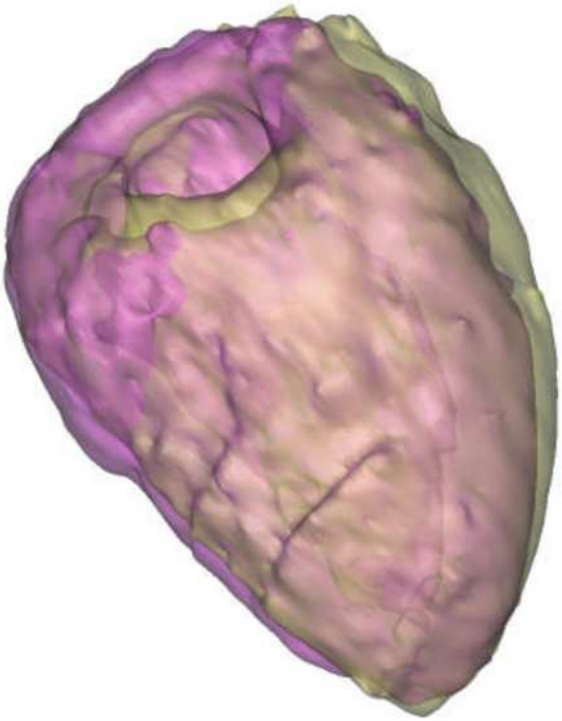
ID	LA (mm)	LVEDD (mm)	BST pre (mm)	BST post (mm)	Change in BST (%)	MWT (mm)	EF pre (%)	EF post (%)	E/E' pre	E/E' post
1	39	47	16	11	-31	16	65	60	10	n/a
2	45	44	16	9	-44	16	65	56	12	12
3	40	49	19	12	-37	19	60	50	9	af
5	42	40	18	9	-50	18	72	50	n/a	9
6	36	35	33	9	-73	33	68	60	n/a	7
7	41	42	18	13	-28	18	75	65	n/a	10
11	51	48	18	13	-28	19	66	60	n/a	n/a
13	56	63	18	10	-44	18	65	65	13	10
20	45	43	15	13	-13	15	60	60	9	n/a
16	45	51	14	14	0	16	60	60	5	10

BST- basal septal thickness, EF- ejection fraction, LA- left atrial dimension, LVEDD- left ventricular end diastolic diameter, MWT- maximal wall thickness, SAM- systolic anterior motion of the mitral valve

ID	SAM		LVOT gradient (mmHg)						Mitral regurgitation		
	pre	post	Pre-op rest	pre-op Valsalva	pre-op stress	Post-op rest	Post op Valsalva	post op stress	Pre-op rest	pre-op stress	Post-op
1	2	0	100	123	n/a	13	13	n/a	mild	n/a	mild
2	1	1	42	62	65	8	8	50	mild	Mild	mild
3	2	0	116	n/a	n/a	11	11	n/a	mild	n/a	mild
5	1	0	48	55	104	5	5	n/a	mild	mod	mild
6	1	0	7	22	90	8	8	16	trace	Mild	mild
7	1	1	80	105	n/a	40	52	75	mild	n/a	mild
11	1	0	15	45	105	4	4	n/a	mild	n/a	mild
13	2	1	107	n/a	n/a	11	11	n/a	mild	n/a	mild
20	2	0	63	63	n/a	3	3	n/a	mild	n/a	mild
16	1	0	6	11	64	4	4	11	trace	n/a	trace

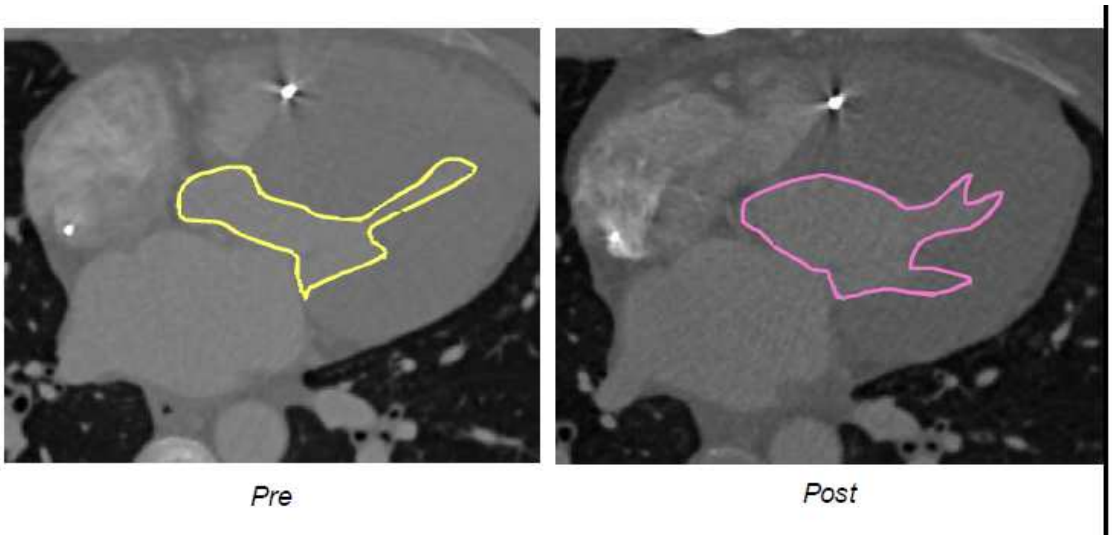
LVOT – left ventricular outflow tract, SAM – systolic anterior motion of the mitral valve

Figure 5.15. Assessment of myocardial volume change pre- and post- operatively



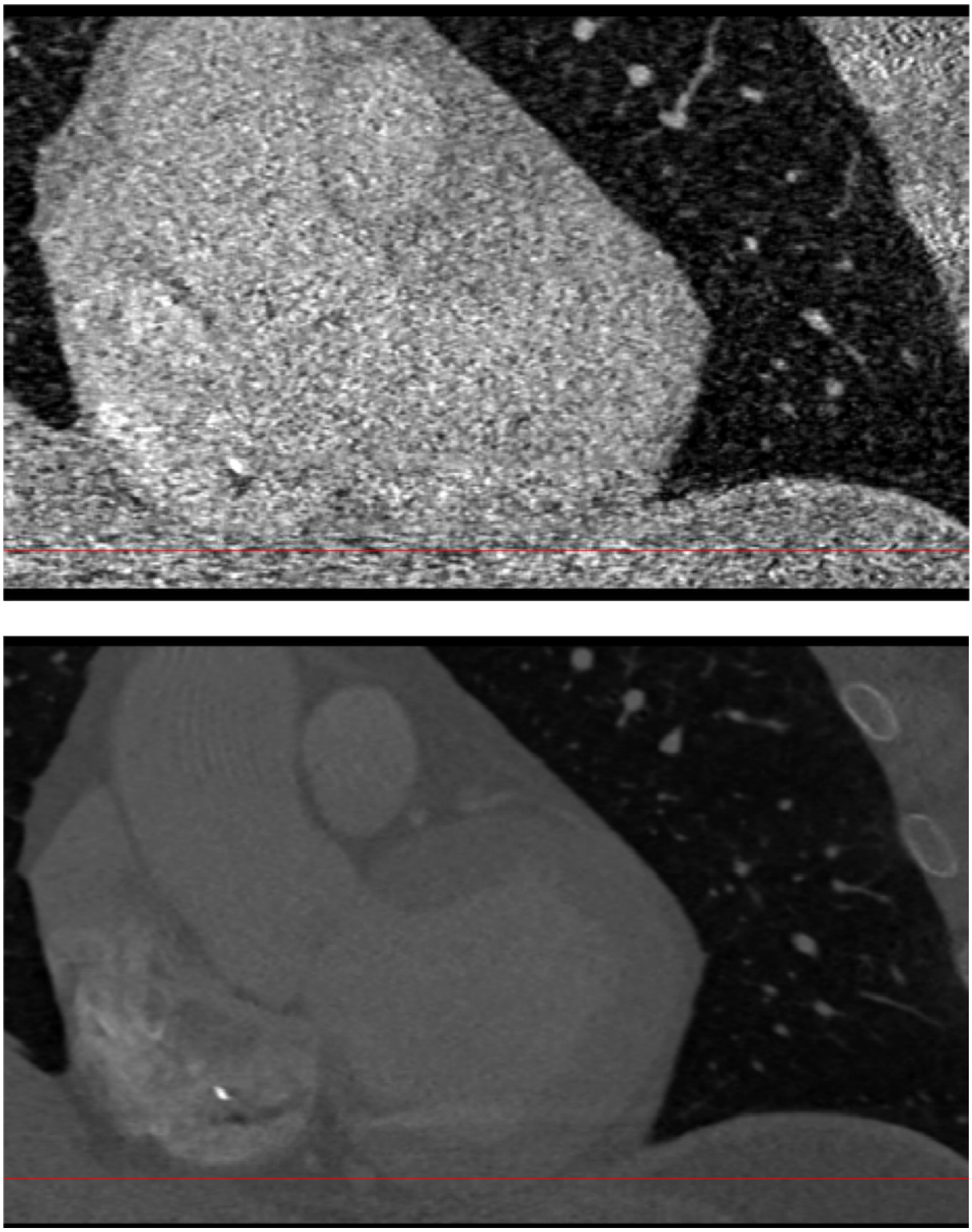
The yellow image is pre-operative, and the purple image post-operative. By subtracting the volume of one from the other it is possible to assess change in myocardial volume.

Figure 5.16. Assessment of change in intra-cardiac blood volume



By tracing the endocardial border before and after surgery, it is possible to determine the change in blood volume of the left ventricular cavity

Figure 5.17. Example of how imaging issues can affect accurate data collection.



Panel A: best systolic frame. Panel B: best diastolic frame. Note significant degradation of images as the heart moves during systole (patient weight 124 kg)

Figure 5.18 Changes in diastolic ventricular volume following left ventricular outflow tract gradient reduction therapy

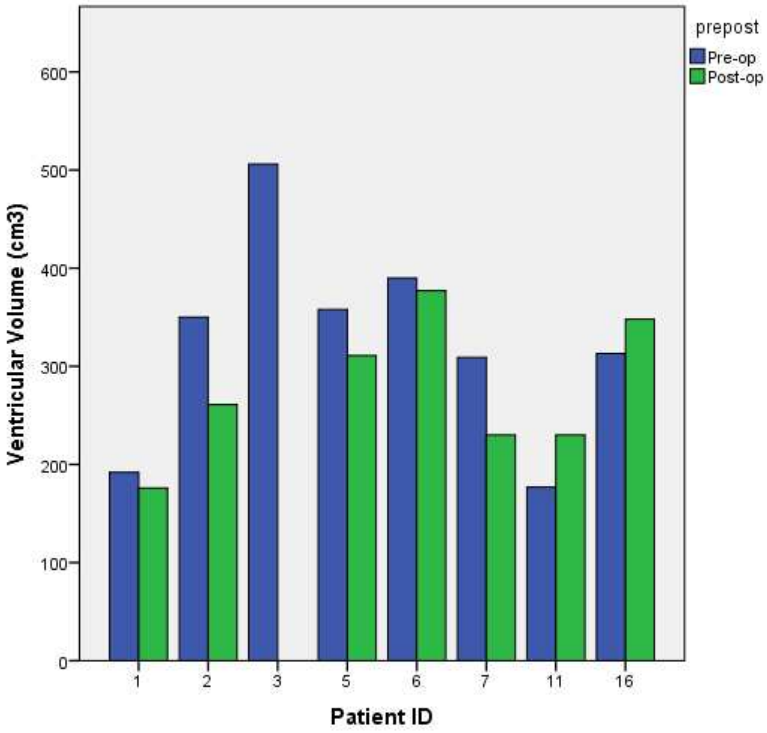


Figure 5.19 Changes in systolic ventricular volume following left ventricular outflow tract gradient reduction therapy

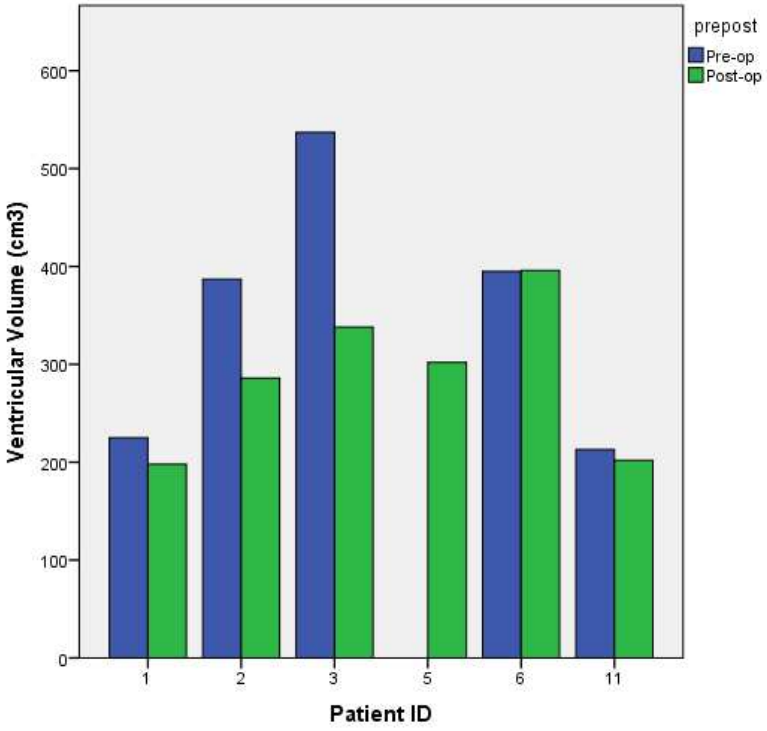


Table 5.15. Measured post-operative changes in cardiac ventricular volume

Patient	difference in volume (diastole, cm^3)	difference in volume (systole, cm^3)	Mass of tissue removed at operation (g)
1	-16	-26	10.7
2	-89	-101	4
3		-199	
5	-47		
6	-14	1	
7	-78		
11	53	-12	
16	35		N/A – Alcohol septal ablation

5.4.1 Statistical analysis

Median time from pre-operative CT to myectomy was 149 (304) days, and from surgery to post-operative CT was 214 (112) days.

Mean pre-operative VO_2 was 17.7 ± 4.9 ml/kg/min^{-1} (56 ± 9% predicted). Post-operative VO_2 was 16.8 ± 5.8 ml/kg/min^{-1} (53 ± 10% predicted), p=0.752. Mean change in VO_2 post-operatively was -5 ± 17%.

Mean pre-operative LA size was 44 ± 6mm, LVEDd 46 ± 8 mm, BST 19 ± 5mm, EF 66 ±5%. Post operative mean BST was 11 ± 2 mm (a reduction of 35 ± 20%, p=0.001), EF 59 ± 5% (p=0.012).

Mean pre-operative LVOT gradients (mmHg) were 58 ± 42 (rest), 61 ± 38 (Valsalva), 86 ± 20 (exercise). Mean post-operative LVOT gradients (mmHg) were 13 ± 12 (rest, p=0.008) and 14 ± 16 (Valsalva, p=0.006).

Mean change in diastolic volume was a reduction of 22 ± 54 cm^3, and in systolic volume was a reduction of 67 ± 84 cm^3.

6 Discussion

6.1 Assessment of finger plethysmography as a tool for the measurement of cardiac output on exercise

Finger plethysmography with brachial calibration appears to be a useful tool for the non-invasive assessment of haemodynamics on exercise and provides additional information to that of routine respiratory gas analysis.

In this study I examined the values for cardiac output at rest and sub-maximal exercise in a cohort of normal individuals derived from finger plethysmography and the single breath C_2H_2 uptake technique. At rest there was good agreement between the techniques. There was a good correlation between techniques at both rest and exercise, although correlation does not necessarily denote accuracy. At rest the C_2H_2 technique values were very slightly lower than finger plethysmography, a trend which was reversed on exercise. Given the difficulties of assessment of cardiac output on exercise, the spread of results in this study suggest that the precision of values is within acceptable limits, and could identify a deficit in cardiac reserve likely to be of significance in clinical practice. The magnitude of rise in cardiac output from rest to exercise was consistent with the workload achieved using both techniques.

Inert gas rebreathing techniques have been extensively used for the calculation of cardiac output (208,218). They are non-invasive, relatively inexpensive and can be performed in conjunction with routine cardio-pulmonary exercise tests. In our institution non-invasive cardiac output measurement is routinely performed using a single breath C_2H_2 technique, the accuracy of which is comparable to re-breathing techniques (299). However, the respiratory manoeuvres are technically challenging to perform, particularly at high workloads and in individuals with cardiorespiratory disease. Inert gas techniques have been validated against invasive techniques at rest (227,300-302) and during exercise (203,303-307) in both health and disease states and thus provide a valid measure against which other non-invasive techniques can be measured.

Cardiac output is calculated by the finometer using the Modelflow method (213). The dynamic changes in aortic dimensions during the cardiac cycle are described by a model of aortic input impedance (aortic characteristic impedance, arterial compliance and TPR) (261-263). The finometer

simulates this model and applies it to the measured arterial pressure waveform in the finger. The resulting waveform is integrated during systole to calculate stroke volume and hence cardiac output by multiplying by the heart rate.

The aortic impedance during systole depends on the mechanical properties of the aorta, which are influenced by the intra-arterial pressure (as blood remaining within the aorta from the previous heart beat will offer resistance to further pulsatile flow towards it) and the external pressure exerted on the walls (i.e. trans-mural pressure) (264). Two of the model parameters, aortic characteristic impedance and arterial compliance (aortic elasticity), are derived from the age- and sex-dependent aortic pressure–area relationship (265) and so age, sex, height and weight are manually entered. This is because the relationship between the cross-sectional area of the aorta and pressure is non-linear, increasing rapidly at lower pressures and more slowly at higher pressures, characteristics which vary between individuals (266). An elastic aorta will expand with minimal rise in pressure, but it is well recognised that aortic compliance decreases with ageing (267). The aortic impedance and arterial compliance are the major determinants of systolic inflow, with peripheral resistance of less importance (213).

Early studies comparing cardiac output derived by arterial pulse wave analysis of Portapres (Finapres Medical Systems, the Netherlands) derived data showed a lower precision and accuracy compared to CO_2 re-breathing, although this was prior to implementation of contemporary algorithms (274). Modelflow derived cardiac output has been shown to correlate with inert-gas rebreathing derived cardiac output during *static* exercise in the upright position (276). Changes in cardiac output are tracked by Modelflow across various experimental protocols (268,277,278) and postural stress (212,264). Two studies have examined finger plethysmography during dynamic exercise (225,226). Sugawara et al used exercise in the semi-supine position on a bicycle ergometer and compared finger plethysmography derived cardiac output with that calculated using the Doppler velocity profile of flow in the ascending aorta taken from a non-imaging transducer in the supra-sternal notch whereas Tam et al used an open-circuit C_2H_2 technique. Importantly both methods used the Portapres device, which lacks the brachial calibration cuff of the Finapres, which improves the accuracy of the pressure measurement being entered into the Modelflow equation (256,308). In comparison to this previous work assessing finger plethysmography on exercise, the additional use of brachial calibration appears to improve accuracy compared with Doppler and C_2H_2 techniques respectively. In addition, I felt the use of a splint to maintain the hand in a neutral position may have helped improve the peripheral pulse wave signal which could be compromised by forceful gripping of handlebars during exercise. The index (rather than middle) finger was splinted for participant

comfort whilst wearing the splint. Bland Altman analysis of uncorrected data in the former study showed a mean difference of 1.8 L/min (SD 1.9 L/min). In the latter study the mean difference was 1.83 L/min (SD 4.11 L/min) improving to 0.24 L/min (SD 3.48 L/min) following correction by an independent method. Recently Bartels et al published a study comparing the Nexfin monitoring system (BMEYE B.V.,Amsterdam, The Netherlands) with an inert gas rebreathing technique (309). This also uses pulse contour analysis and was found to reliably measure cardiac output on exercise in normal individuals, and my data supports the use of finger plethysmography for the measurement of cardiac output on exercise despite the differences in equipment and methodology.

Routine cardio-pulmonary exercise testing does not incorporate an assessment of the cardiac output response to exercise which alongside respiratory data may be fundamental to both diagnosis and an understanding of symptoms in patients with cardiac disease. Whilst the limitations of non-invasive techniques of assessing haemodynamic variables on exercise are acknowledged, finger plethysmography with brachial calibration may provide useful adjunctive information during cardio-pulmonary exercise testing.

6.1.1 Limitations - general

Time of day, caffeine intake and smoking on the day of the exercise test were not routinely documented and unstandardised, and might have been of influence. Two volunteers were excluded because a reliable finger plethysmography trace could not be achieved. The ability of a participant to exhale at a constant flow rate of 0.5L / second during exercise was variable due to breathlessness, although was achieved in the majority of cases.Two people were excluded due to a failure to successfully perform the respiratory manoeuvres, a common barrier to effective employment of the C_2H_2 technique in clinical practice. In some cases the forced expiration and maximal inhalation manoeuvres required for the C_2H_2 uptake technique altered the finger plethysmography waveform amplitude. In these cases values with a stable waveform immediately preceding the respiratory manoeuvres were used. In no case did the time of acquisition of corresponding values differ by more than seven seconds.

6.1.2 Limitations - HCM

The acetylene inhalation technique to calculate cardiac output has not been validated in patients with HCM. One might imagine this to be problematic to perform, as patients may have abnormalities of anatomical and physiological deadspace and VQ mismatching, given the alterations in VE/VCO_2 slopes. This may affect tissue and plasma solubility of the gases used in the calculation of cardiac output. In turn, this may affect the reliability of the method as a tool for validation of finger plethysmography in this population. I did not have the resources to validate finger plethysmography against an invasive technique, particularly during exercise.

The Finapres technique makes several assumptions of normality when calculating cardiac output, for example aortic size and pressure waveform reflection along the arterial tree, each of which may be affected by abnormalities of arterial compliance and peripheral resistance. LVOT obstruction itself may alter the measured arterial waveform as blood flow is abnormal during cardiac ejection. Aortic elastic properties (strain, distensibility and stiffness) assessed using echocardiography (310) and CMR (97),and arteriograph-derived pulse wave velocity and augmentation index (310) have been shown to be abnormal in HCM. The lack of validation during exercise of the method against a technique known to be accurate in HCM is therefore a significant limitation.

6.2 Functional consequences and associations of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

Several assumptions have been made in the interpreting of these finger plethysmography data, including the central and peripheral arterial waveform, and the compliance, size and elasticity of the aorta in patients with HCM which pose significant limitations. Notwithstanding those assumptions, these data indicate that cardiac index during exercise in HCM is limited by a failure to augment SVI and to a lesser extent heart rate at peak exercise. Patients with resting LVOT obstruction have a greater reduction in cardiac reserve than non-obstructive patients at all stages of exercise and a fall in SVI at higher workloads accompanied by a compensatory increase in heart rate. Within the cohort with LVOT obstruction, different patterns of stroke volume responses were observed in patients that otherwise appeared similar using standard clinical and echocardiographic criteria.

Patients with LVOT obstruction who were able to achieve higher workloads had a larger resting stroke volume than those who were more limited. Furthermore, within the cohort of patients with LVOT obstruction, different patterns of stroke volume responses could be elicited in patients who otherwise appeared similar using standard clinical and echocardiographic criteria. These findings suggest that non-invasive cardiac output measurement might be of value in selecting those patients who would most benefit from invasive treatments to reduce LVOT gradients. Lastly, for the first time, I demonstrated that during early exercise, VO_2 is higher in patients with LVOT obstruction, but fails to increase during exercise. The mechanism appears to be an abnormal increase in A-V oxygen difference during exercise compared to normal individuals.

6.2.1 Mechanisms of impaired cardiac output response

There are many potential mechanisms for an impaired cardiac output response to exercise in patients with HCM, including LVOT obstruction, systolic and diastolic dysfunction, mitral regurgitation, chronotropic incompetence and myocardial ischemia. The incidence and prevalence of severe systolic impairment in HCM is relatively low (35,43) although contractile impairment is often overlooked as clinically significant reductions in systolic performance may occur while the measured ejection fraction remains within the normal range. Relatively little is known about cardiac output

and stroke volume response during exercise, due to the difficulties in accurate measurement of dynamic physiological variables.

A few studies using continuous nuclear ventriculography have shown that patients with non-obstructive HCM have a reduction in systolic performance on exercise unrelated to the degree of septal hypertrophy (83,92,93). My findings show that the cardiac response to exercise is severely constrained by an inability to increase stroke volume and, to a lesser extent, heart rate. At the extremes of work in the LVOTO group, high compensatory heart rate responses that coincided with a fall in stroke volume were evident in some patients.

Although VO_2 may be influenced by several factors, a linear relationship exists between VO_2 and cardiac output in normal individuals during exercise (235). Previous invasive work in HCM showed a significant association between the rise (but not resting or peak) in cardiac index on exercise and peak VO_2 (81). I used the cardiac reserve, measured non -invasively from baseline as a dependant variable to assess exercise limitation in HCM and investigate the association with several haemodynamic parameters. Stroke volume may fall at peak exercise in normal individuals, and so the measurement at peak VO_2 may be difficult to interpret. I therefore also assessed the percentage change in stroke volume at both peak and sub-maximal workloads as a dependent variable to remove some of the influence of resting left ventricular cavity size, and gain more information on dynamic change. The haemodynamic measurements made non-invasively in this study are comparable with previous radionuclide (89,311) studies. Peak exercise cardiac output values were slightly lower than in invasive studies by Frenneaux (81,107), although my cohort were older with lower peak VO_2 which may explain this. The resting values for cardiac output may seem slightly higher than one would expect which in part is explained by an anticipation reaction to the imminent exercise test.

6.2.2 Left ventricular outflow tract obstruction and stroke volume

In normal individuals at low levels of exercise, cardiac output increases linearly as result of an increase in both stroke volume and heart rate (243). Stroke volume increases as a result of an increase in left ventricular filling pressure (increased inotropy) and end diastolic volume and to a smaller extent by a fall in end systolic volume (increased preload) through the Starling mechanism (230,243).

Whether LVOT obstruction represents a true physical barrier to the ejection of blood during left ventricular systole, and therefore what role it plays in stroke volume and exercise limitation in HCM has not been proven and remains a source of controversy. Discrepancies are often seen between exercise limitation and the magnitude of left ventricular outflow tract gradient (81,110) implying additional factors are important. Despite this, successful treatment of LVOT obstruction is often reported to be accompanied by an improvement in functional class, maximal VO_2 and blood pressure response (101,184,312). However, reduction of LVOT gradient is not always associated with an improved exercise capacity (176), the mechanism by which this occurs is incompletely understood. It may be that patient selection can be refined to target those patients with LVOT obstruction who neither augment stroke volume on exercise nor mount a compensatory tachycardic response and therefore may benefit more.

I hypothesised that LVOT obstruction results in reduced anterograde aortic flow, which could be measured during exercise using finger plethysmography. My results suggest that patients with HCM are unable to augment their stroke volume during exercise compared to normal individuals, but importantly that the presence of LVOT obstruction further limits the cardiac output response.

A few studies using continuous nuclear ventriculography have shown that patients with non-obstructive HCM have evidence of a reduction in systolic performance on exercise that is unrelated to the degree of septal hypertrophy (83,92,93).

Stroke volume was an important determinant of exercise capacity in 23 patients with HCM studied invasively, although only 4 of these had LVOT obstruction (107). Another early invasive study did not demonstrate any significant relationship between the incidence and magnitude of resting LVOT gradient and peak VO_2 (108). However, in the presence of obstruction, radionuclide and echocardiographic indices of impaired left ventricular systolic performance and atrial systolic failure were related to percent predicted VO_2. In the non-obstructive group, diastolic function was of more importance in identifying those with a reduction in percent predicted VO_2 <70%.

Jones et al investigated the relationship of gas exchange indices during incremental exercise in patients with HCM compared to a control group (79). They found a low maximum value of oxygen pulse in patients (numerically equivalent to the product of stroke volume x A-V oxygen difference). Although not measured directly, they felt this was consistent with the failure to continue to increase stroke volume during exercise although a widening of the A-V oxygen difference could not be excluded (79). Only 12 patients with LVOT obstruction were included in the cohort, but no additional differences in submaximal or maximal exercise response were seen compared to patients without

obstruction. The same investigators later showed in a larger study the magnitude of LVOT gradient to be inversely proportional to peak VO_2, anaerobic threshold and oxygen pulse (75). My results expand on these findings, demonstrating not only a failure of stroke volume augmentation, but also, for the first time, a widening of the A-V oxygen difference, and heterogenous haemodynamic responses between otherwise clinically similar patients.

In comparison, an early study in 1984 using radionuclide angiography in 57 patients (26 with obstruction at rest) investigated the proportion of blood ejected from the left ventricle during systole, and concluded there was no difference between those patients with and without obstruction, although ejection was earlier in both groups compared to normal individuals (313).

My results showed that MWT was higher in patients with obstruction, and a univariate predictor of stroke volume augmentation from base to peak exercise with a weak positive correlation. However, the β value of 1.861 is very small when considering the units of wall thickness measurement are millimetres, therefore so is the magnitude of its influence, and was not significant in multivariate analysis. Potentially this could reflect some patients with longstanding 'burnt out' disease with thinner myocardium, who despite 'normal' ejection fraction by Simpsons method do have left ventricular contractile impairment and as such are likely to have depressed cardiac output response to exercise.

LVOT obstruction was the only consistently significant multivariate predictor of cardiac reserve, stroke volume augmentation at both moderate and intense physical activity. As expected, age was negatively correlated with cardiac reserve, as was female gender on account of size. Heart rate reserve was weakly negatively correlated with stroke volume augmentation from base to peak exercise; similarly the delta heart rate at 75W was weakly negatively correlated with stroke volume augmentation at this workload. Viewed inversely, this suggests that patients with an impairment of stroke volume augmentation maintain their cardiac output through tachycardia, which is consistent with the other heart rate data collected.

6.2.3 Diastolic function

I used resting E/Ea ratio as a marker of diastolic function, and found it to be significantly higher in patients with LVOT obstruction than non-obstructive disease, and a significant univariate predictor of cardiac reserve.

The ability to increase diastolic dimensions on exercise plays an important role in increasing stroke volume. During exercise at higher heart rates, filling time is shorter therefore magnifying the importance of volume. During pharmacological provocation of LVOT obstruction in HCM, the development of LVOT obstruction causes prolongation of systole at the expense of diastolic time (314). In addition, patients with obstruction have been shown to have abnormally short resting diastolic times compared to controls. This is aggravated during exercise, where significant reductions in filling time are seen compared with both controls and non-obstructive HCM (311). In this study by Plehn loss of diastolic filling time was associated with lower stroke volume at both rest and exercise, and at peak exercise was a significant multivariate predictor of the rise in cardiac output. There was a positive correlation between baseline outflow gradient and the corresponding loss of diastolic time in patients with obstruction, although the effect on cardiac reserve was not directly assessed. In my cohort peak heart rate and heart rate reserve was significantly lower in patients with LVOT obstruction which coupled with a reduction in stroke volume augmentation further reduces cardiac output response.

6.2.4 Relation between cardiac output and oxygen consumption

The relationship between cardiac output and VO_2 is assumed to be linear (237,238) and the slope similar across different age groups (218). In this study the mean slope of the relationship between cardiac output and VO_2 was higher in normal controls than patients with HCM, consistent with the observation that cardiac output response to exercise is limited and therefore A-V oxygen difference must be widened to perform work.

At maximal exercise, oxygen extraction reaches values of 14-18 ml / 100 ml blood (234,235,243). In my study the A-V oxygen difference was similar between patients and controls at rest, but became wider in patients from early to peak exercise, possibly to help compensate for an inability to appropriately increase cardiac output. This implies that the impairment of stroke volume augmentation in HCM, and the additional barrier to flow posed by mechanical LVOT obstruction is associated with a chronic increase in oxygen extraction, akin to the effects of athletic training. Whilst at first glance the ability for patients with HCM to appear trained in this way seems counter-intuitive, it does make sense in going part way to explain the large number of patients (and

undiagnosed individuals) who have relatively few symptoms despite anatomically significant heart muscle disease.

However, a wide A-V oxygen difference is not necessarily the result of supra-normal oxygen kinetics because fractional oxygen extraction is related to the ratio of the diffusive oxygen capacity to the perfusive oxygen delivery (ie blood flow to the exercising muscle) (315). When blood flow to exercising muscle is reduced (for example in HCM) the ratio of diffusion to perfusion becomes relatively exaggerated, and oxygen extraction is increased. The relationship between factors affecting oxygen diffusion and perfusion therefore determines overall A-V oxygen extraction, although both are affected in cardiovascular disease. Chronic heart failure (CHF), for example, causes a multitude of deleterious effects in peripheral muscle, including increased vasoconstriction and metaboreflex (316), and decreased endothelial function (317), capillarity (318) and functional capillarity haematocrit (315). However, a wider A-V oxygen difference in CHF does not necessarily lead to improved exercise performance because the capacity of skeletal muscle to use oxygen is impaired with reductions in mitochondrial oxidative enzyme activity and volume density as well as mitochondrial dysfunction (319,320). Similarly, patients with HCM and β myosin heavy chain (321) and to a lesser extent troponin T (322) mutations have been shown to have peripheral abnormalities of oxygen metabolism and in these patients with both muscle diffusion and perfusion abnormalities, it may be that a relatively higher degree of dysfunction in the former causes a reduced capacity for overall A-V oxygen transport and consequently more severe impairment of exercise performance.

Abnormal endothelial function may also contribute to exercise intolerance in HCM. Although the underlying mechanism is uncertain, endothelial dysfunction has been demonstrated in several ways in patients with HCM. Stressor tests to measure endothelium-dependent vasomotor function in the coronary arteries are abnormal (323,324). Microvascular dysfunction is common in HCM, in part related to myocardial hypertrophy, causing impairment of myocardial perfusion (325). Other biochemical markers of endothelial dysfunction have been shown to be elevated in HCM compared to healthy individuals (326-328) with higher values in patients with LVOT obstruction.

Although to my knowledge A-V oxygen difference has not been investigated in HCM, data exists in CHF literature suggesting that patients with systolic impairment (left venricular ejection fraction ≤40%) have a higher resting A-V oxygen difference than those with normal ejection fraction, which becomes wider still on exercise (329). Another study directly measuring A-V oxygen difference in CHF patients showed higher values at rest, anaerobic threshold and peak exercise in patients with lower compared to higher peak VO_2 (330). During exercise, patients with severe heart failure have a

greater capability to divert blood from tissue not actively involved in exercise to exercising muscle (331) possibly as a result of neuro-humoral activation. In this context a wide A-V difference must occur with a significant local oxygen transport abnormality.

Exercise training in CHF has been shown to improve peripheral structural and functional oxygen transport (including both widening of the A-V oxygen difference and uptake at a local level) without increasing central cardiac output (332-334). The underlying mechanism is unclear, although does not appear to be associated with a reduction in circulating catecholamine levels, a marker of chronic over-activation of the sympathetic nervous system, common in CHF. Similarly, drugs that affect oxidative function and muscle oxygen diffusing capacity may have a positive effect on exercise tolerance in heart failure (335,336) (337,338).

In my study patients with LVOT obstruction had slightly higher values for A-V oxygen difference. If we assume that oxygen kinetics and diffusion are similar between patients this implies that reduced muscle perfusion as a consequence of obstruction determines the observed increased A-V oxygen difference in that sub-group. The ability to actually utilise extracted oxygen effectively has not been assessed here, and a large A-V oxygen difference may not necessarily correlate with functional status because of impaired cellular metabolism in the exercising muscle. This may be due to chronic degenerative changes in the skeletal muscle such as those seen in heart failure with poor nutritional flow. Alternatively, primary abnormalities of muscle oxygen utilisation such as is recognised in mitochondrial disease may be the cause (339), and the potential for overlap syndromes with HCM has previously been discussed.

The relationship between cardiac output and VO_2 is assumed to be linear (237,238) and the slope similar across different age groups (218). The slope in my control group is in good agreement with previous physiological studies (234,238,340). In my study the mean slope of the relationship between cardiac output and VO_2 was higher in normal controls than patients with HCM, and the flatter slope seen in patients suggests a larger increase in VO_2 is required for a given rise in cardiac output, consistent with the observation that the cardiac output response to exercise is limited and therefore A-V oxygen difference must be widened to perform work. Although the slopes were similar, VO_2 was significantly higher in patients with obstruction at rest and during early exercise despite no significant difference in cardiac or stroke volume index at low workloads, in keeping with a wider A-V oxygen difference. This may provide part of the explanation for the relative lack of symptoms in some patients with obstruction.

6.2.5 Heart rate

Eight patients with obstruction achieved a workload of ≥150W. In these individuals the enhanced exercise capacity was driven by a disproportionate tachycardia at higher workloads. Chronotropic incompetence (defined as a failure to achieve a maximal predicted heart rate >80% predicted) is relatively common in HCM and associated with a reduction in VO_2 (75). These results suggest patients with a 'normal' chronotropic response have the advantage of being able to increase cardiac output through a disproportionate rise in heart rate even during a continued fall in stroke volume, which may be an additional explanation for the apparently good functional status of some patients with LVOT obstruction.

6.2.6 Cardiac power

Cardiac power is thought to be a more direct measurement of cardiac work (242,341), and either as a continuous variable or dichotomized at a level of 1·96W, is the best predictor of outcome in patients with congestive heart failure (282). I found there was a trend towards a lower peak cardiac power in patients with LVOT obstruction, and a significantly higher proportion of patients in this group fell below the 1.96W threshold. Although overall peak cardiac power did not correlate with the number of risk factors for SCD, 2 patients with 3 risk factors had very low values (1.5 ± 0.1W). Prospective data is needed to identify if cardiac work predicts mortality in HCM.

6.2.7 Blood pressure response and peripheral resistance

In spite of a poor cardiac output response, most patients with HCM had mean arterial pressures during exercise similar to control values due to a compensatory increase in TPR. However, within the patient cohort a subgroup had an ABPR and yet inappropriately 'normal' TPR values. This observation is consistent with prior data showing that approximately one third of patients with HCM fail to augment systolic pressure due to excessive vasodilatation (85,86). The mechanism remains unproven but in part is probably explained by excessive LV mechanoreceptor stimulation. As a similar ABPR has been reported in aortic stenosis, it might be expected that increased left ventricular

afterload associated with LVOT obstruction is the trigger for mechanoreceptor activity, but there was no correlation between the magnitude of blood pressure response and peak resting LVOT gradient. This suggests that other factors such as heterogeneous stress-strain relations within the myocardium caused by patchy myocyte disarray and fibrosis are responsible.

Counihan et al showed no association between peripheral haemodynamic indices and LVOT gradient, although those with abnormal responses had smaller left atrial and left ventricular end diastolic size (85). There was also a significant association with a family history of SCD, prompting the authors to conclude that abnormal peripheral responses could be a marker of haemodynamic instability causing this increased risk. In a subset of HCM patients studied invasively, there was no significant difference in peak cardiac index between those with and without ABPR to exercise although this was marginally higher in the former group (86). Cardiac index increased fivefold in both groups though magnitude of increase was greater in hypotensive patients, implying change in blood pressure during exercise was not related to cardiac output. There was no difference in LVOT obstruction between groups suggesting that this was not a factor in exercise hypotension. My results concur, as I found no difference in the incidence of ABPR to exercise in patients with and without LVOT obstruction. Nor were there differences in heart rate, heart rate reserve, VO_2, peak cardiac output, cardiac reserve or peak stroke volume between patients with and without an ABPR to exercise.

In contrast, cardiac output response during exercise was assessed using ambulatory radionuclide monitoring in 43 patients with HCM by Ciampi (89) who demonstrated that in patients with an ABPR, ejection fraction and stroke volume fell more ($p = 0.032$ and $p = 0.009$, respectively) and cardiac output increased less ($p = 0.001$) than they did in patients with HCM with a normal blood pressure response. The incidence of significant LVOT obstruction in their cohort was the same in both normal and ABPR groups. Impaired cardiac output response was related to an increase in left ventricular end diastolic and systolic volumes, potentially secondary to myocardial ischaemia which could be related to increased oxygen demand seen with higher heart rates during exercise (342).

Resting pulse pressure was shown in a study of 70 patients with HCM to be a predictor of ABPR, although MAP did not differ significantly between groups (94). The ABPR group also had a higher resting pulse pressure. My results contradict this, as pulse pressure was nearly identical in patients with normal and abnormal responses (47 ± 13 vs 47 ± 12 mmHg, $p=0.975$). Peak and increase in systolic blood pressure was lower in patients with LVOT obstruction, although I found a similar proportion of patients with ABPR in each group.

The relationship between peripheral resistance, mean arterial and venous pressure and cardiac output is expressed as follows:

$$Total\ Peripheral\ Resistance = \frac{Mean\ Arterial\ Pressure - Mean\ Venous\ Pressure}{Cardiac\ Ouput}$$

It was not possible to measure mean central venous pressure, which was assumed to be relatively constant between groups for the purpose of calculating TPR. Patients with LVOT obstruction had a lower peak MAP and cardiac output than those without. One may therefore expect TPR to be similar between the groups, which I demonstrated. By comparison, patients overall had a similar MAP, and a lower cardiac output at peak exercise to controls; I found the TPR to be correspondingly higher in patients. It is interesting to note that patients with an ABPR during exercise have very similar TPR absolute values to normal individuals. MAP and TPR during exercise were lower in patients with an ABPR, with an appropriately similar rise in cardiac output. My non-invasive data is in close agreement with the results demonstrated in previous invasive studies (86), although in my study TPR in the ABPR group fell earlier in the course of exercise. These results show that in the majority of patients with HCM, the primary cardiovascular abnormality during exercise is an inability to augment cardiac output, but that a proportion of patients have an independent abnormality of peripheral vascular response which is associated with exercise hypotension.

6.2.8 Clinical implications

This study shows that patients with HCM have a complex response to physical exercise that is dominated by a limited cardiac output reserve. LVOT obstruction imposes an additional burden by further compromising SV during exercise. In addition, I demonstrated heterogeneous haemodynamic responses between patients with similar clinical characteristics. This implies that in individual patients, the predominant mechanism of exercise limitation is likely to vary, with central and peripheral mechanisms playing a greater or lesser role. Recent supporting evidence for this comes from a study reporting paradoxical falls in LVOT obstruction during exercise in some patients (343). The corollary is that the response to therapy will also vary. For example, blunting of the relative tachycardia towards peak exercise with ß-blockade might adversely affect cardiac output reserve and increase symptoms. Similarly patients with similar degrees of LVOT obstruction may have a variable response to invasive gradient reduction strategies depending on the degree to which

LVOT obstruction contributes to exercise intolerance. I hypothesise that non-invasive haemodynamic assessment of individual patient exercise responses may improve the targeting of pharmacological and invasive therapies.

Debate exists as to the effect on VO_2 of therapies designed to reduce LVOT gradients. The reduction of LVOT obstruction by ASA (101,312) or myectomy (184) is associated with an improvement in VO_2. Although both procedures effectively treat LVOT obstruction, myectomy has been shown to be superior to ASA in terms of objective improvement in exercise parameters (344). This improvement was shown in a recent large surgical series to extend to patients with provocable obstruction but no significant resting gradient (156). In 249 patients symptoms and functional class were similar to patients with high resting gradients, and surgical success rates were comparable. In comparison, Nishimura demonstrated no significant change in VO_2 despite a reduction in LVOT obstruction with DDD pacing (176).

No study has prospectively evaluated the effect of LVOT obstruction reduction therapy on cardiac output response to exercise. It would seem plausible that either ASA or myectomy should increase the capacity for stroke volume augmentation on exercise and thus improve the response. Difficulties to overcome however include the use of negatively inotropic agents commonly prescribed to patients with symptomatic HCM, and their effect on cardiac output which would be difficult to correct for. Indeed, it is interesting to note that in patients in whom stroke volume limitation is deemed contributory to symptoms, that negatively inotropic agents exert a beneficial effect. In addition, negative chronotropy should in theory improve filling on one hand, but if stroke volume is limited on exercise, the ability to increase heart rate should be important to increase cardiac output and thus perform work. The original studies investigating the effect of beta blockers (345-347) and calcium channel antagonists (162-166) were in small numbers of patients with largely surrogate echocardiographic or cardiac catheter based endpoints.

6.2.9 Limitations

Time of day, caffeine intake and smoking on the day of the exercise test were not routinely documented and unstandardised and may have been of influence. The study of cardiovascular parameters during high intensity exercise is technically challenging, particularly using invasive methods. Finger plethysmography has been validated at sub-maximal exercise only, and not in

patients with HCM. However, the workloads achieved and values measured in this cohort during maximal exercise are comparable to those in normal individuals during my validation study (348) and in HCM using invasive techniques by others (86). At high workloads the number of patients in the obstruction group was small making it difficult to show statistical differences between groups.

There were more males in the controls, although there was no gender difference between patient groups and heterogeneity of haemodynamic response was seen in both sexes. Because of the relatively small sample size, I could not stratify haemodynamic responses based on gender without the requirement for many more comparison groups which in itself may introduce error. Based on their NYHA functional class, I feel this cohort is representative of the wider HCM population, however I acknowledge there may be an element of referral bias towards more symptomatic patients given this hospital's tertiary referral status.

I cannot exclude the possibility that patients deemed to be non-obstructive at rest did not develop LVOT obstruction on exercise. However, any patient with symptoms suggestive of provocable obstruction on clinical review had an upright symptom limited stress echocardiogram to document an exercise induced gradient. In addition if this were the case, it would likely strengthen my results.

6.3 Structural determinants of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

6.3.1 Aorto-septal angulation

The main findings of this study are that patients with HCM have a smaller aorto-septal angle than controls, and individuals who develop provocable LVOT obstruction during exercise have a smaller angle than those without obstruction. The angle can be easily and reliably measured using standard 2-D transthoracic echocardiography in patients with HCM, and is more specific than the presence of SAM for the identification of provocable LVOT obstruction.

6.3.2 Determinants of provocable LVOT obstruction and aorto-septal angulation

A variety of structural features are associated with LVOT obstruction including anterior displacement of papillary muscles (140), reduced LVOT area (196) and primary mitral valve abnormalities (127,143,144), but the essential component in the majority of patients is contact between the mitral valve and the inter-ventricular septum caused by SAM of the anterior and less commonly the posterior leaflets. Incomplete SAM at rest has long been recognised as a clue to the presence of provocable LVOT obstruction but this study demonstrates for the first time that reduced aorto-septal angle has a higher specificity when used as a single measure. The relatively low sensitivity of both parameters is expected given the high prevalence and complexity of LVOT obstruction, which is related to many additional factors.

Variation in LVOT geometry is characteristic not only of HCM, but also of aortic valve disease and hypertension in which a 'sigmoid' configuration is common, particularly with advancing age and reduction in left ventricular cavity size (349-353). In adults, a smaller aorto-septal angle is associated with increased aortic pressure wave reflection and higher central blood pressure (300) although no causal relationship has been demonstrated to date and in children a smaller aorto-septal angle is a highly sensitive, specific and positive predictive marker for the development of sub-aortic stenosis (354) and can be used as an echocardiographic feature to identify individuals at risk (190).

Previous studies have recognised the importance of LVOT geometry in provocable obstruction. Minimal systolic mitral-septal distance (measured using M-Mode in parasternal long axis view) has been shown to be a predictor of patients with provocable LVOT obstruction (297). In contrast in the study by Shah there was no correlation between the change in LVOT gradient on exercise and LVOT diameter measured at the onset of systole using the initial echo of the anterior mitral leaflet in the parasternal long axis view (120). Indeed the only independent predictors were a history of presyncope/syncope, incomplete/complete SAM at rest and Wigle score. The difference in methodology explains the discrepancy in results. I feel that retrospective measurement of mitral-septal distance using M-mode would be difficult to accurately achieve, and so measured the LVOT diameter in the parasternal long axis view using standard criteria. I found that the systolic LVOT diameter did not influence the presence or magnitude of LVOT gradient. This measurement is however distal to the point of SAM-septal contact and relatively fixed, and therefore the lack of variation is not surprising given the dynamic nature of provocable LVOT obstruction.

Data on the importance of LVOT diameter in predicting patients with provocable obstruction are conflicting possibly due to differences in methodology (120,297,355). Due to the dynamic nature of provocable LVOT obstruction, measurement of this parameter may often be distal to the point of SAM-septal contact and relatively fixed, therefore may not accurately reflect 3-D LVOT area. The lack of an unequivocal association is not therefore surprising. I measured the LVOT diameter using 2-D images in the parasternal long axis view and found no influence on the presence or magnitude of LVOT gradient.

6.3.3 Technique of aorto-septal angulation measurement

CMR or computed tomography imaging provide a 3-D measurement of aorto-septal angulation, which has been shown to predict LVOT obstruction provoked using Valsalva or amyl nitrite independent of basal septal thickness (191). Real-time 3D echocardiography has been shown to be superior to 2D in the measurement of myocardial hypertrophy, left ventricular volume, ejection fraction and mass (356), and can accurately identify resting and provocable LVOT obstruction in patients with HCM (357). Although widespread availability and expertise is currently lacking, this may be a useful future tool for the assessment of aorto-septal angulation. In current clinical practice however routine scanning of all patients with HCM using these modalities is often not possible, and

for the specific purpose of measuring the aorto-septal angle I feel my methodology using standard transthoracic echocardiography is accurate and robust.

A variety of methods have been used for measurement of the aorto-septal angle using 2-D trans-thoracic echocardiography. The most commonly adopted is the angle formed by the long axis of the ascending aorta and the plane of the ventricular septum, which has excellent inter-observer correlation (186,187,189,190). Whilst 2-D echocardiography has been used multiple times to measure aorto-septal angulation, it has not been evaluated in HCM. The left ventricular endocardial border in HCM rarely forms a straight line, particularly in patients with a basal septal bulge. I recognised the difficulties of finding consistent echocardiographic landmarks from which to accurately quantify the aorto-septal angle from standard 2-D images in HCM, and so attempted to determine reference lines which would be most consistently applicable across echocardiographic studies and between observers. I therefore modified the method originally described by Fowles (186). Instead of using a line bisecting the septum at the level of the mitral valve leaflets and 2cm apically, I constructed one at the junction of the left and right inter-ventricular septum, parallel to the proximal right endocardial border. I hypothesised that this technique would be a more accurate representation of the true septal orientation in HCM and more likely to fit a straight line. The quality of echocardiographic images varies between individuals, and in a minority of patients fit to a straight line can be challenging. However, the results of my inter-observer analysis support the reliability of my method across a large number of studies, and comparison with CMR data shows acceptable agreement. 3-D imaging techniques including CMR and computed tomography are the gold standard for measuring aorto-septal angulation. In my retrospective cohort data a minority of patients had CMR images available. Although it may have been statistically underpowered, the gold standard technique should have been assessed first for the prediction of provocable LVOT obstuction. I could have then compared how 2-D echocardiography compared against this. Compared to the 2004-2008 when these data were collected, the majority of patients attending the HCM clinic at the Heart Hospital now undergo CMR. It would therefore be of interest to repeat this work prospectively.

6.3.4 Clinical relevance and applicability

Patients with refractory symptoms and resting LVOT obstruction should be considered for myectomy (198,358) or ASA (179,181,359). Provocable LVOT obstruction is associated with functional impairment and heart failure symptoms (154,155,159) and there is good evidence that invasive

treatments should be offered to these patients (156,157). Therefore a simple clinical tool which helps identify patients at risk of developing provocable LVOT obstruction would be of benefit.

I propose that reduced aorto-septal angle serve as a 'red flag' for the presence of provocable LVOT obstruction, even in the absence of resting SAM on 2-D echocardiography, and prompt further evaluation with stress echocardiography. Availability of expertise for stress echocardiography in patients with HCM is variable, although it can be performed safely (360), and as such the relatively low sensitivity of aorto-septal angle measurement demonstrated here is of less importance. However the high specificity is likely to identify patients who may then benefit from treatment. As used here, current guidelines to diagnose provocable LVOT obstruction recommend use of either a treadmill or bicycle in combination with Doppler echocardiography during and / or immediately following exercise (198).

I have demonstrated my methodology for aorto-septal angle quantification using standard 2-D transthoracic echocardiography provides a simple, relatively inexpensive, robust method, which is comparable to magnetic resonance and provides additional information which may be of clinical benefit to patients with HCM. Furthermore, the results may be equally relevant in other patients with reduced aorto-septal angle, for example those with hypertension and the elderly. Further study in these groups is warranted.

6.3.5 Limitations

This is a retrospective observational study on a consecutive cohort of patients selected for stress echocardiography from a specialist cardiomyopathy clinic. I did not assess specific abnormalities of the mitral valve and supporting structures. Only symptomatic patients were referred for stress echocardiography, and so the relevance of aorto-septal angulation in asymptomatic patients is unknown. One third of patients were unable to discontinue medication for symptomatic reasons; this reflects real-world practice, but may have underestimated prevalence and magnitude of LVOT obstruction. The fact that some patients continued on these medications for symptomatic reasons may have introduced a confounding factor, as it is uncertain if there are specific characteristics in this population, for example a propensity to aorto-septal angulation.

Basal septal thickness was relatively modest in my cohort. However, increase in this measurement is associated with a reduction in aorto-septal angle (191). Inclusion of patients with more prominent

basal septal hypertrophy may therefore be expected to increase sensitivity and specificity of aorto-septal angulation for the diagnosis of provocable LVOT obstruction. I did not assess for intra-observer variability with repeated measures, which in retrospect would have been a useful way of strengthening recommendation for the technique.

6.4 CT assessment of cardiac morphology before and after myectomy surgery

6.4.1 Changes in left ventricular volume

The major finding in this cohort is that in 6 of 8 of cases there was a reduction in cardiac volume following relief of LVOT obstruction. In the two patients whose volumes increased, one had myectomy sugery and one ASA. Both had a reduction in NYHA class from three to two, although the surgical patient had a reduction in VO_2 from 17.4 ml/kg/min^{-1} (58% predicted) to 13.5 ml/kg/min^{-1} (48% predicted).

While one might expect that ventricular volumes would be increased rather decreased by a reduction in left ventricular septal thickness, the net effect is likely to be extremely small. For example, in one case, only just over 4g of tissue was removed but, the difference in diastolic volume post-operatively was 89 cm^3. If we assume a cardiac mass density of 1.05 g/cm^{-3}(361), this would equate to a tissue mass of 93g. It is much more likely that the reduction in left ventricular volumes represents reverse remodelling following the relief of LVOT obstruction. This phenomenon is poorly studied in HCM but is well recognisd in aortic stenosis. Regression in left ventricular hypertrophy following surgical aortic valve replacement has been demonstrated, particularly in the first six months (362,363). In another study of 24 patients using CMR, left ventricular diastolic volume index, having been high pre-operatively, decreased rapidly in the first six months, with further reduction at one year (364). However, left ventricular mass/volume, a 3D measure of ventricular geometry, remained unchanged over 4 years. In patients undergoing trans-catheter aortic valve implantation for aortic stenosis, reverse remodelling has been demonstrated using CMR six months following the procedure, identified by a reduction in LV mass index (365). However, left ventricular diastolic volume index, ejection fraction and stroke volume did not change.

Circumferential strain and rotation have been shown to decrease in patients following myectomy surgery (366). Data from patients with operated aortic stenosis suggests that unloading a chronically pressure overloaded ventricle normalises low preoperative longitudinal and abnormally high circumferential strain (367). Given the haemodynamic similarities between the conditions, one would expect a similar result following myectomy in HCM. The mechanical outcome shown in the two studies above was similar, although pre-operative longitudinal strain was not as low in HCM, and did not normalise post-operatively. One may speculate what effect these mechanical forces have on ventricular reverse remodelling in HCM, and it does not seem unreasonable that a reduction in afterload and 'net strain' could have the effect of reducing ventricular volume over time.

With regard to functional parameters, there was a small but statistically significant reduction in ejection fraction post-operatively. This may be partly as a result of a reduction in afterload, but may also reflect a change in septal activation which is extremely common following surgery. Diastolic parameters assessed using echocardiography remained unchanged.

6.4.2 Relationship to symptoms

It is widely accepted that invasive treatment of LVOT obstruction increases exercise capacity, and it has been reported that VO_2 also increases. A meta-analysis of 42 published series of ASA showed an improvement in mean NYHA class from 2.9 at presentation to 1.2 at 1 year($P<0.001$) (181). At 1-year follow-up, peak VO_2 increased from 17.8 to 23.6 mL/kg/min ($P < 0.001$) and mean exercise capacity on a treadmill increased from 325.3 to 437.5 seconds ($P <0.001$). A historical study in the 1970s of 29 patients following myectomy showed an improvement in peak VO_2 from 16 to 21 ml/min/kg ($P<0.005$) (184). Interestingly, surgery was associated with a significant increase in cardiac index during maximal exercise (5.0 to 5.7 litres/min per m^2, $P<0.05$). Another from 1992 investigating exercise improvement following myectomy identified preoperative impairment in peak VO_2, and a post-operative reduction in LVOT gradient and left ventricular filling pressures as multivariable predictors of a positive change in peak VO_2 at 6 months (185).

In my cohort 6 patients had pre and post operative exercise tests: in 3 the peak VO_2 fell, in 1 it increased and in 2 it remained the same. Despite this, all of these patients reported an improvement in functional class. In 8 patients, a reduction in 1 NYHA class from 3 to 2 was seen; 1 patient moved from class 3 to 1, and 1 remained in class 2. Interestingly, the only patient whose VO_2 increased was the same individual who still had a significant LVOT gradient at follow up (40mmHg at rest). Whilst a

reduction in VO_2 yet an improvement in symptoms following surgery seems counter-intuitive, this is exactly what my experience of seeing these patients in the clinical scenario has been over the last few years. However, the absolute change in VO_2 seen in this cohort and my clinical experince is relatively small. The timing of a cardio-pulmonary exercise test is likely to be of importance, as performed too early may be confounded by post-operative recovery time and de-training. In addition, there are several alternative explanations for an improvement in symptoms unrelated to oxygen consumption, including a reduction in mitral regurgitation and ischaemia and increase in skeletal and respiratory muscle perfusion.

I demonstrated that AV oxygen extraction in HCM is increased. The reason for this is uncertain, but I believe it to be a compensatory mechanism to allow a patient with a severe reduction in exercise cardiac output to be able to perform work. If one considers the Fick equation, by improving cardiac output through myectomy surgery, this obviates the need for an increased AV oxygen difference and perhaps the observed increase in VO_2 in the literature is a reflection of this. I do acknowledge however that this may be an over-simplification of what may be a complex physiological adaptation with considerable difficult in determining which is the chicken and which the egg. It would therefore be of great interest to perform non-invasive haemodynamic assessment on patients before and at least two post myectomy timepoints.

6.4.3 Limitations

Whilst the number of patients with complete datasets before and after myectomy surgery is small, I believe that it has still been possible to explore the concept of reverse remodelling in patients undergoing invasive LVOT reduction therapy. This project has shown some promising pilot data, but also highlighted several difficulties. From a logistic viewpoint, there was a significant delay in time in many cases (in 4 around 1 year) from pre-operative imaging to surgery. The effect this may have had on remodelling is unknown.

The original intent was to use multi-modality imaging to optimise morphological information that can be displayed to a surgeon before myectomy. Unfortunately a significant number of patients with HCM undergoing LVOT reduction therapy will have an ICD, precluding the use of MRI. In this cohort 50% of the patients had an ICD. Leads and generators can also degrade CT images making resolution of small structures more difficult.The original plan had been to utilise 3-D echocardiography.

Although 2 of the patients were operated on here and had this investigation intra-operatively, it was not possible to access the raw data due to technical restrictions by the hardware manufacturers. The remaining patients did not undergo 3-D echocardiography at the surgical centre.

7 Conclusions

7.1 Use of finger plethysmography for the measurement of cardiac output on exercise

Finger plethysmography with brachial calibration determined cardiac output values at rest are not significantly different to those obtained using the single breath C_2H_2 uptake technique in normal individuals. During sub-maximal exercise the agreement was less precise, although the measured relative rise in cardiac output from rest to sub-maximal exercise was similar between techniques. Finger plethysmography was easier to perform during exercise than the single breath C_2H_2 uptake technique. Overall these results support the use of finger plethysmography to measure cardiac output at sub-maximal intensity, although caution and clinical acumen should be exercised when using the results to make clinical decisions.

7.2 Functional consequences of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

Cardiac output response to exercise is impaired in HCM, caused largely by a failure to appropriately augment stroke volume. LVOT obstruction is associated with a greater impairment of stroke volume at peak exercise and is an independent and modifiable predictor of cardiac output reserve. During exercise patients with HCM widen their A-V oxygen difference further than normal individuals. The non-invasive measurement of haemodynamic indices during exercise is practical, aids understanding of the complex physiological basis behind symptoms and may help to tailor therapy for HCM, and in particular LVOT obstruction.

7.3 Structural determinants of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

7.3.1 Aortoseptal angulation

Measurement of aorto-septal angulation using transthoracic echocardiography in patients with HCM is easy, reproducible, comparable to magnetic resonance imaging, and can be calculated using standard echocardiographic software. Patients with HCM have a smaller aorto-septal angle than controls, where it is associated with higher peak LVOT gradient. A reduced aorto-septal angle is highly specific for provocable LVOT obstruction and should prompt further evaluation in symptomatic patients without resting obstruction.

7.3.2 Multi-modality imaging to optimise myectomy surgery in HCM

CT scanning of patients with HCM undergoing myectomy or ASA is feasible, and potentially could help with pre-operative surgical planning. Combination with other modalities including CMR and 3-D echocardiography should be explored in suitable patients. Reverse remodelling was demonstrated post-operatively in the majority of patients by a reduction in left ventricular volume.

7.4 Implications of this thesis for future work

A number of questions have occurred to me during the collection and analysis of these data. The most striking question, is if patients with HCM and LVOT obstruction have an impaired cardiac output response to exercise, predominantly driven by a blunted stroke volume, then what is the impact of successful gradient reduction therapy on that response? If it is normalised, is this associated with functional improvement? At first glance this should be straightforward to investigate: we routinely perform cardio-pulmonary exercise testing before and after myectomy surgery for example, so simply measure haemodynamic parameters using finger plethysmography at the same time. Firstly however, there is the need for robust validation of finger plethysmography during exercise in patients with HCM. Unfortunately even with this validation, a number of

methodological concerns may muddy the water: most patients being assessed for interventional procedures are dependent on negatively inotropic drugs pre-operatively, and in the majority of cases when sufficient time has elapsed post-operatively for a patient to be able to perform an exercise test, medication has often changed. It would be very difficult to accurately account for the effect of medication on haemodynamic parameters during exercise. Despite this however, it does seem intuitive to collect these data for analysis. Lastly, this work has raised interesting questions regarding the mechanism behind the observed increased A-V oxygen difference in HCM during exercise, which has no good explanation in the literature.

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9 Appendix

9.1 Abbreviations

ABPR - abnormal blood pressure response

AF - atrial fibrillation

ANOVA - analysis of variance

ASA – alcohol septal ablation

ASH - Asymmetric septal hypertrophy

A-V – Arterio-venous

CHF – Chronic heart failure

CI – Cardiac Index

CMR - Cardiac Magnetic Resonance

CSA - Cross sectional area

ECG – Electrocardiogram

FEV_1 – Forced expiratory volume in 1 second

FVC – Forced vital capacity

HCM – Hypertrophic cardiomyopathy

ICD – Implantable cardioverter defibrillator

LVOT - Left ventricular outflow tract

MAP - Mean arterial pressure

MET - metabolic equivalents

MWT - maximal wall thickness

NICE – National institute for health and care excellence

NYHA - New York Heart Association

PCWP - pulmonary capillary wedge pressure

PPM – permanent pacemaker

SAM – systolic anterior motion

SCD - sudden cardiac death

SVI – stroke volume index

SVR - systemic vascular resistance

TPR – Total peripheral resistance

VO_2 - oxygen consumption

VT – ventricular tachycardia

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9.5 Publications associated with this thesis

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Critoph CH, Patel V, Mist B, Elliott PM. Cardiac Output Response and Peripheral Oxygen Extraction During Exercise Among Symptomatic Hypertrophic Cardiomyopathy Patients with and without Left Ventricular Outflow Tract Obstruction. Heart. 2014 Apr;100(8):639-46 (appended below).

Critoph CH, Pantazis A, Esteban MTT, Salazar-Mendiguchía J, Pagourelias ED, Moon JC, Elliott PM. The influence of aorto-septal angulation on provocable left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Open Heart. 2014;1: e0000176. Doi:10.1136/openhrt-2014-000176 (appended below).

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