# Surgical management of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

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I, Richard Collis 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 and referenced appropriately in the thesis.

Richard Collis

Signed……

# Abstract


### Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac condition affecting 1 in 500 of the population with a largely genetic autosomal dominant pattern of inheritance. Left ventricular outflow tract obstruction (LVOTO) is the most common clinical feature occurring in up to two thirds of patients with HCM leading to clinical symptoms and premature death. Different management strategies exist for LVOTO including pharmacological and invasive interventional techniques.

### Objectives

The main aim of this thesis is to examine and evaluate current clinical practices and outcomes using varying surgical techniques in the management of LVOTO in HCM.

### Methods

A systematic review of the literature and meta-analysis were performed in accordance with the PRISMA statement. Individual observational studies were also performed comprising of various surgical populations using a large relational database of patients with HCM in a single specialist cardiomyopathy clinic located in London, UK.

### Results

*Meta-analysis:*

Contemporary early (<30 days) and late (>30 days) mortality following septal myectomy were 1.4% (CI 0.8, 2.4) $I^2$ 9.0%, p = 0.36 and 0.7% (CI 0.3, 1.2) $I^2$ 70.7%, p < 0.05 respectively.

Observational Study:

Three hundred and forty seven patients underwent surgical intervention for LVOTO (1988-2015). Median follow-up was 5.2 years (interquartile range 1.9-7.9). The mean resting LVOT gradient improved post-operatively from 71.9 ± 39.6 mmHg to 13.4 ± 18.5 mmHg (P < 0.05). Overall, 72.4% of patients improved by >1 New York Heart Association (NYHA) class. There were 5 perioperative deaths and 20 late deaths (>30 days). 58.9% of patients undergoing mitral valve replacement alone did not improve their NYHA class. Long-term (>30 days) complications included atrial fibrillation (29.6%), transient ischaemic attack/stroke (2.4%) and heart failure hospitalisation (3.2%). There were 16 repeat surgical interventions at 3.0 years.

**Conclusions**

Septal myectomy is a safe procedure resulting in symptomatic improvement in the majority of patients. Ongoing clinical follow-up, surveillance and medical therapy is recommended after surgery.

# Impact Statement

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac condition affecting 1 in 500 of the population. Hypertrophic cardiomyopathy is associated with premature death due to heart failure, arrhythmias, stroke and sudden cardiac death. Left ventricular outflow tract obstruction (LVOTO) can occur in up to two thirds of patients with HCM due to underlying pathological and physiological processes resulting in a pressure gradient and turbulence of blood flow across the left ventricular outflow tract (LVOT). Left ventricular outflow tract obstruction is associated with exertional clinical symptoms and carries a poorer prognosis in HCM.

Management of patients with LVOTO includes pharmacological and invasive techniques aimed at alleviating the pressure gradient across the LVOT and improving clinical symptoms. In drug refractory cases a surgical technique of septal myectomy is the gold standard in managing patients with LVOTO according to international guidelines.

Early surgical outcomes have been reported through case series and observational studies since initial surgeries in the late 1960's. Long term outcomes of patients undergoing septal myectomy is not robust in the literature as evidenced by a systematic review and meta-analysis carried out as part of this research work. Further to this, the mechanism of LVOTO in patients can be complex with involvement of the mitral valve and sub-valvular structures. Long term outcomes, again, in these patients is lacking in the literature.

This thesis examines and evaluates the current practices of surgical techniques, since the first surgical outcome studies were published. Studies were evaluated from different geographical regions and surgical centre size. Long term outcomes were evaluated utilising different surgical techniques in the management of LVOTO in a large specialised cardiomyopathy centre. This showed similar low mortality rates in both early and long term follow-up. However, in spite of this, the incidence of non-fatal disease related complications following surgical intervention remains high during long term follow-up. According to the surgical technique utilised, differences in clinical outcomes were evident. This not only highlights the importance and need for ongoing clinical surveillance after surgical intervention but also the importance of careful individualised surgical planning prior to intervention.

This thesis demonstrates that septal myectomy is a safe procedure in the management of LVOTO with good clinical outcomes in the vast majority of patients. In a smaller cohort of patients with LVOTO careful surgical planning is required to select the most appropriate surgical technique including intervention to the mitral valve with mitral valve repair or mitral valve replacement. Ongoing clinical follow-up, surveillance and medical therapy is recommended after surgery.

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# Acronyms

2D: Two Dimensional

ACE: Angiotensin Converting Enzyme

AF: Atrial Fibrillation

AFD: Anderson Fabry Disease

AHA: American Heart Association

AR: Aortic Regurgitation

AS: Aortic Stenosis

ASA: Alcohol Septal Ablation

ASH: Asymmetric Septal Hypertrophy

AV: Atrioventricular

CAD: Coronary Artery Disease

CMR: Cardiac Magnetic Resonance

CPET: Cardiopulmonary Exercise Test

CRT: Cardiac Resynchronisation Therapy

CT: Computed Tomography

CVA: Cerebrovascular Accident

ECG: Electrocardiogram

ESC: European Society of Cardiology

HCM: Hypertrophic Cardiomyopathy

ICD: Implantable Cardioverter Defibrillator

IQR: Interquartile Range

IR: Incidence Rate

LA: Left Atrium

LV: Left Ventricle

LVH: Left Ventricular Hypertrophy

LVOT: Left Ventricular Outflow Tract

LVOTO: Left Ventricular Outflow Tract Obstruction

MCO: Mid Cavity Obstruction

MRI: Magnetic Resonance Imaging

NSVT: Non-Sustained Ventricular Tachycardia

NYHA: New York Heart Association

PPM: Permanent Pacemaker

RA: Right Atrium

RV: Right Ventricle

SAM: Systolic Anterior Motion

SCD: Sudden Cardiac Death

TIA: Transient Ischaemic Attack

TOE: Transoesophageal Echocardiogram

TTE: Trans-thoracic Echocardiogram

UK: United Kingdom

USA: United States of America

VF: Ventricular Fibrillation

VSD: Ventricular Septal Defect

VT: Ventricular Tachycardia

# Introduction

## *1.1* ***Background***

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac condition affecting 1 in 500 of the population with a largely genetic autosomal dominant pattern of inheritance.[1-4] There is a heterogeneous phenotype to this condition with features including obstruction of the left ventricular outflow tract (LVOTO), heart failure, atrial and ventricular arrhythmias.[5] Hypertrophic cardiomyopathy can lead to premature death from heart failure, stroke or ventricular arrhythmias.[6-9] The diverse clinical phenotype seen in HCM can cause debilitating clinical symptoms including dyspnoea, chest pain and syncope. Symptoms relate to presenting clinical features of the condition. Management of individual clinical features can improve symptoms and patient outcomes with pharmacological therapies and invasive interventions which have evolved over the years. International guidelines published by the European Society of cardiology (ESC) and the American Heart Association (AHA) provide physicians with a detailed overview of the condition and management of individual clinical presentations.[6,8]

Initial references to enlarged and hypertrophied hearts date back to the 17$^{th}$ and 18$^{th}$ centuries from physicians and anatomists including Theophile Bonet, William Harvey, Jean Baptiste Morgagni and Giovanni Maria Lancisi.[10] The first modern description of HCM arises from a published series in 1958 by Dr Donald Teare, an esteemed British pathologist working at St

George's Hospital in London.[11] This published case series, described 8 unrelated individuals, between the ages of 14 and 44, who died of sudden cardiac death (SCD). The patients in this series were found to have asymmetrical septal hypertrophy (ASH) of the left ventricle and characteristic patterns of myocardial fibrosis. Various other complications were reported in this series including atrial fibrillation (AF) and cerebral embolism.[11] The comprehensive description of these patients also highlighted many of the main pathological and clinical features which to this date are pivotal in the diagnosis and management of HCM. An addendum to this paper by Teare himself reported a sudden death in one first degree relative of a patient from this initial case series with similar autopsy findings. This highlighted the first notions of a familial nature to this condition.[11] Following this, different research groups studied the clinical associations and inherited nature of this disease. These studies led to various descriptive names for this condition in the literature including "idiopathic hypertrophic subaortic stenosis", "obstructive cardiomyopathy" and "hypertrophic cardiomyopathy". Advances in our scientific and clinical understanding of this condition have been made through years of clinical research. This includes the introduction of a surgical technique by Dr Andrew Morrow, Chief of Surgery at the National Institute of Health (NIH), Bethesda, Maryland, USA. In 1961, Morrow was the first surgeon to perform a myectomy operation to alleviate LVOTO, the most common complication seen in patients with HCM.[12] In this series of 25 patients with idiopathic hypertrophic subaortic stenosis, he performed a combination of subaortic ventriculomyotomy along with limited resection of hypertrophied muscle tissue to relieve obstruction of the left ventricular

outflow tract (LVOT). Of those, 21 were followed up (1-8 years) with 15 patients asymptomatic and 6 patients experiencing mild symptoms on follow-up.[12] Although, the Morrow operation has adapted to include a more extensive muscular resection, the technique is still used to this day in the surgical management of LVOTO.

Dynamic LVOTO occurs in up to two thirds of patients with HCM under resting or provoked conditions.[13,14] The dynamic nature of LVOTO arises from physiological changes affecting both contractility and loading conditions of the heart. The presence of LVOTO can lead to symptoms such as shortness of breath, chest pain and syncope. Many strategies to alleviate these symptoms exist to improve clinical outcomes such as pharmacological interventions and more invasive therapeutic approaches including surgery, alcohol septal ablation and dual chamber pacing.[6] Pharmacological intervention is first line in the management of LVOTO however when drug refractory cases arise, the surgical technique of septal myectomy remains the gold standard in treating LVOTO. It has been long recognised that associated abnormalities of the mitral valve (MV) apparatus may also need to be addressed at the time of surgery to fully treat and alleviate the underlying obstruction.[15-17]

Despite significant advances in our understanding of the mechanism of LVOTO further studies are still required to determine patient outcomes following surgical intervention.

## 1.2 Definition, Diagnosis & Diagnostic Challenges

### *1.2.1 Definition*

Hypertrophic cardiomyopathy belongs to a heterogeneous group of disorders that are defined by a structurally and functionally abnormal myocardium called cardiomyopathies. Previously these disorders were classified as primary or secondary according to heart involvement with or without systemic organ involvement. Clinical guidelines, as set out by international bodies like the European Society of Cardiology (ESC) have adopted a more pragmatic approach in the classification of these conditions according to morphological structure and function of the heart in each condition. These include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and unclassified cardiomyopathy.[5,6] *Hypertrophic cardiomyopathy is defined as an increase in left ventricular wall thickness not solely explained by abnormal loading conditions e.g. hypertension or aortic stenosis.*[6]

### *1.2.2 Diagnosis*

The diagnosis of HCM is based on demonstration of an unexplained increase in left ventricular wall thickening in any myocardial segment using any imaging modality including two dimensional echocardiography, magnetic resonance imaging (MRI) or computed tomography (CT) of the heart.[6]

In adults, a left ventricular wall thickness ≥ 15mm, unexplained by abnormal loading conditions is diagnostic of HCM; however, a left ventricular (LV) wall thickness ≥ 13mm in patients with a first degree relative with HCM is also considered diagnostic. In children the diagnosis of HCM requires a left ventricular wall thickness of more than two standard deviations greater than the predicted mean value.[6]

### *1.2.3 Differential Diagnosis*

It is important when diagnosing a patient with HCM that careful consideration is made to out rule other acquired causes of left ventricular hypertrophy. It should be noted however that in certain patients more than one potential aetiology can coexist. Below are some examples of clinical scenarios where challenges to a diagnosis can be seen including;

- Mild hypertrophy
- Athlete's heart[18,19]
- Angulation of the aorta with a basal septal bulge[20]
- Hypertension[21]
- Aortic Stenosis (AS)[22]

## 1.3 Epidemiology

Data from a large American study of over 4000 individuals with echocardiograms in a general population estimated that HCM occurs with a

prevalence of 0.17%.[1] This estimation of 1 in 500 could in fact be more frequent when we take other potentially affected family members into account.[1-3] Most studies report a male preponderance which is yet to be explained, but may reflect selection bias and screening patterns.[6,23] The condition affects patients with a similar prevalence worldwide, however phenotypic differences are seen among various ethnicities. The condition affects all age groups with an age related prevalence.[24,25]

### 1.4 Histopathology

The diagnosis of HCM is clinical but certain characteristics are seen histologically. Specifically, cardiac myocyte hypertrophy and disarray with the cells organised in a chaotic and disorganised fashion as can be seen in *Figure 1*. Interstitial fibrosis is seen between the myocytes which can be regional or patchy in nature. The smaller coronary arteries in the muscle wall can show medial hypertrophy, leading to a reduced cross-sectional area and a reduction in coronary flow reserve and micro vascular ischaemia.[26,27]

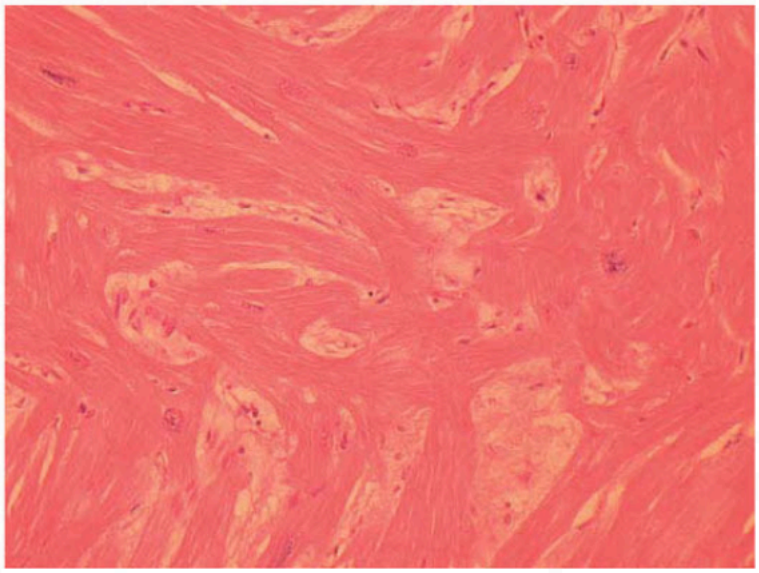


Figure 1: Histological changes of hypertrophic cardiomyopathy with myocyte disarray and fibrosis. (Courtesy of Dr Michael Ashworth, Institute of Child Health, London.)

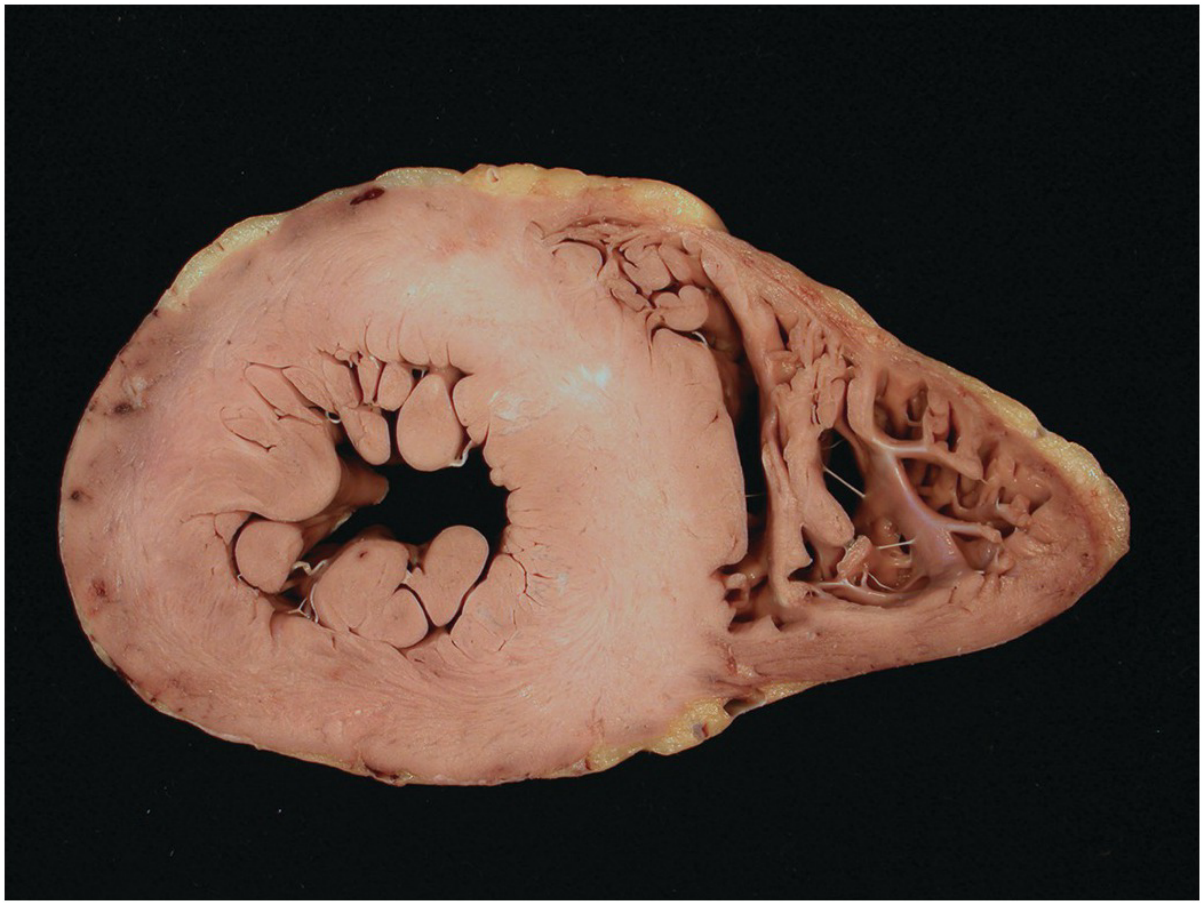


Figure 2: Cross-sectional image of the left and right ventricle showing hypertrophy of the left ventricle. (Courtesy of Dr Michael Ashworth, Institute of Child Health, London.)

### 1.5 Aetiology

In adults, HCM is most commonly caused by mutations in genes that encode proteins of the cardiac sarcomere with an autosomal dominant pattern of inheritance accounting for up to 60% of cases.[28,29] A smaller number of cases are caused by rarer genetic conditions including malformation syndromes, inborn errors of metabolism, neuromuscular and mitochondrial

conditions. Other non-genetic conditions including amyloidosis and endocrinopathies can cause a similar cardiac phenotype with left ventricular wall thickening and should be screened for in high risk populations.[30-33] An illustrated chart of the various aetiologies can be seen in *Figure 3*.[6]

### *1.5.1 Sarcomeric Gene Mutations*

Hypertrophic cardiomyopathy is mainly a disease of autosomal dominant inheritance however, less commonly autosomal recessive inheritance or de novo mutations can also be seen.[28] Disease penetrance is often incomplete and is age and gender dependant. [8,25,34-36] The most common mutations are seen in genes encoding myosin binding protein C (MYBPC3) and beta-myosin heavy chain (MYH7) which are found in 80% of familial cases. Other genes less commonly affected include troponin I (TNNI3), troponin T (TNNT2), alpha-tropomyosin (TPM1), regulatory myosin light chain (MYL2), essential myosin light chain (MYL3), and actin (ACTC1).[28,34-36] Patients with genetic mutations tend to be younger at presentation and have higher rates of familial disease and familial SCD. Observational studies have reported varying phenotype-genotype correlations.[37,38] Non-sarcomeric genetic mutations can mimic HCM phenotypically and are discussed below in *section 1.5.2*.

Genetic testing allows for the identification of family members who have disease causing mutations but do not have left ventricular hypertrophy (LVH). In many of these patients the ECG will be abnormal, and some may

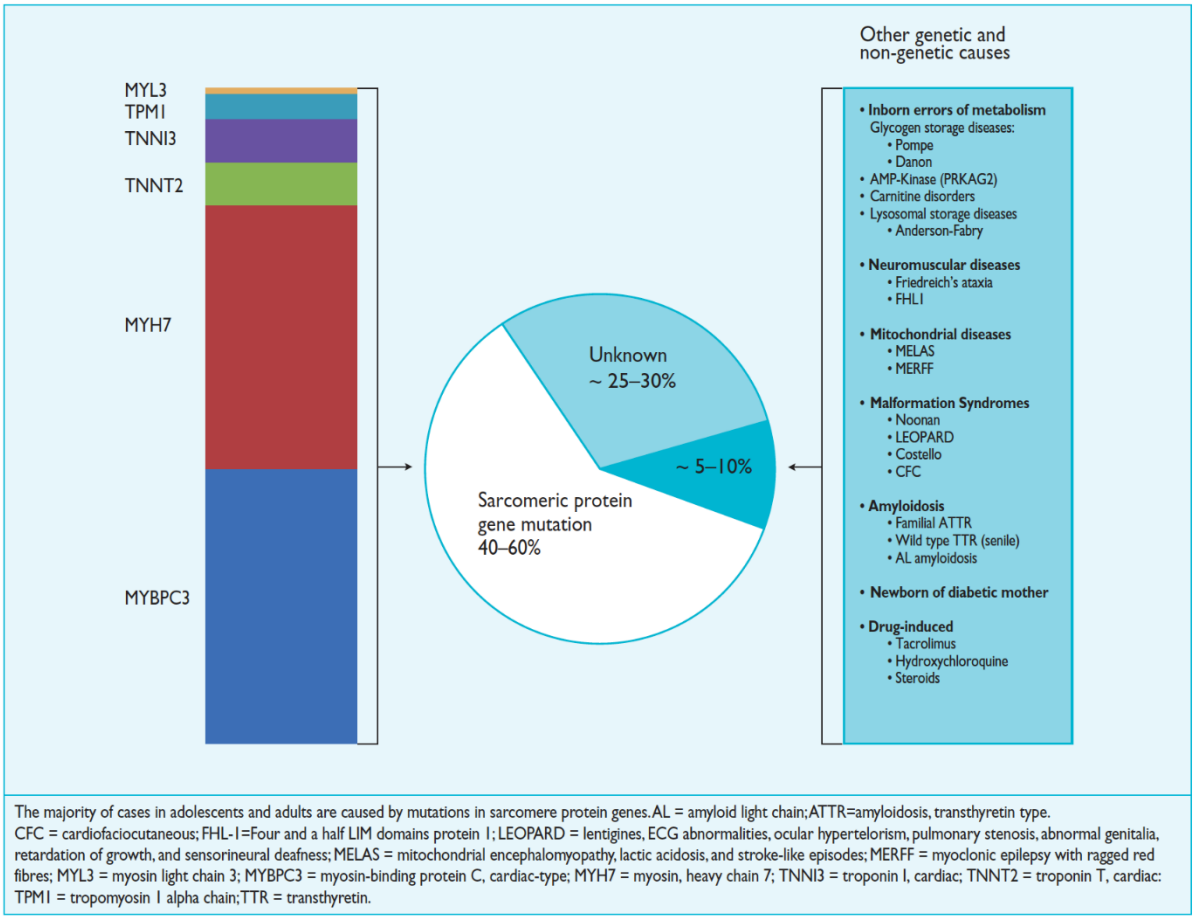
have fibrosis seen on Cardiac Magnetic Resonance (CMR) or elongated mitral leaflets. The identification of pathogenic mutations can facilitate early pre-symptomatic diagnosis and family planning along with genetic testing and is therefore recommended by international guidelines for cascade screening.[6]

### *1.5.2 Rarer Aetiologies*

Rarer genetic causes of hypertrophy can be seen in 5-10% of adult patients and include Anderson Fabry disease (*GLA*), Danon disease (*LAMP2*), PRKAG2, Noonan and LEOPARD syndrome (RAF1, PTPN11, BRAF, MAP2K1), Amyloidosis (TTR) and Friedrichs ataxia (FXN).[6,36,41-47]

Mitochondrial disorders due to underlying mutations in mitochondrial DNA can lead to abnormalities of energy production affecting high energy organs like the heart. Many of these cases can present with cardiomyopathies in particular hypertrophic cardiomyopathy in 20-40% of children with mitochondrial disease.[48]

Systemic conditions can also present with cardiac hypertrophy along with other cardiac abnormalities and remain important factors to consider in the diagnosis. These include amyloidosis, acromegaly, phaeochromocytoma.[33]




The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Figure 3: Aetiology of hypertrophic cardiomyopathy.[6]

### 1.6 Left Ventricular Outflow Tract Obstruction

Obstruction of the left ventricular cavity is the most common clinical feature associated with HCM and can occur at various levels in the LV. Most commonly obstruction is seen in the LVOT, causing exertional symptoms in patients due to the impedance of blood flow during systole.[13,49] Up to one third of patients with HCM will have LVOTO under resting conditions with a further one third having evidence of obstruction under provoked conditions.[13] Less commonly patients can present with more distal obstruction of the mid

cavity due the presence of hypertrophied papillary muscles or abnormally orientated muscles which can present with similar symptoms to LVOTO.[50-53]

### *1.6.1 Definition and Diagnosis*

The presence of LVOTO is defined by a peak systolic pressure gradient ≥30mmHg across the LV outflow tract under resting or provoked conditions.[6] Pressure gradients are dynamic depending on loading conditions and contractility. These are assessed most commonly using 2D transthoracic echocardiography (TTE) and continuous wave Doppler measurements which estimate a forward flow velocity and systolic pressures in the heart just below the point of mitral-septal contact. In certain equivocal cases or cases where clinical and echocardiographic examination are discrepant pressure gradients can also be assessed using cardiac catheterisation with direct measurement of pressure gradients in the LVOT.[6] Although LVOTO is defined as a gradient across the LVOT ≥30mmHg, a value of ≥50mmHg is used clinically as a threshold for the invasive management of LVOTO.[6,9]

### *1.6.2 Pathophysiology of LVOTO*

The mechanism of LVOTO has been debated for many years. Obstruction of the LVOT was initially thought solely to be due to hypertrophy of the basal interventricular septum but it is now known that in addition to hypertrophy extending in to the outflow tract, LVOTO has a more complex mechanism involving anterior movements of the MV leaflets, annular position of the MV and abnormalities of the submitral apparatus including chordae and papillary

muscles. [13-17,54-56] Late diastolic inflow and early systolic outflow of blood causes pressure and physiological changes within the left ventricular cavity. Narrowing of the LVOT from hypertrophy which led to increased blood flow velocity in the LVOT, creating hydrodynamic forces which suck the leaflets towards the septum creating a Venturi effect. Other forces however are potentially believed to dominate include a pushing or dragging force due to abnormal flow of blood which gets behind and lateral to the MV pushing it into the septum and LVOT. This results in the phenomenon of systolic anterior motion (SAM) of the mitral leaflets and impedance of normal blood flow as seen in *Figure 6*.[15] As SAM progresses with early systolic outflow a larger surface of the leaflets are exposed to the push and drag effect potentiating these forces. Evidence of the drag and push effect as the dominant mechanism of action comes from evidence of LVOTO and SAM in the absence of significant hypertrophy and intermittent evidence of posterior leaflet SAM.[15]

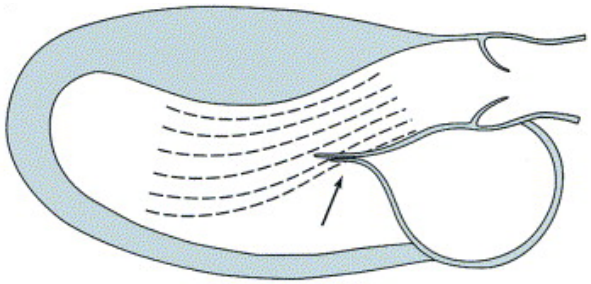


Figure 6: Illustration showing the movement of the anterior mitral leaflets towards the hypertrophied septum resulting in obstruction of the LVOT.[15]

Anatomical abnormalities that contribute to and exacerbate SAM include a narrowed LVOT due to septal hypertrophy, abnormalities of the MV including elongation of the anterior mitral leaflet or primary valve abnormalities and abnormal submitral attachments including hypertrophied, apically displaced papillary muscles and abnormal chordae. Systolic anterior motion of the anterior MV leaflet also results in reduced MV leaflet coaptation during systole resulting in MR which is posteriorly directed into the left atrium. This understanding of MV involvement is important as LVOTO can occur with mild hypertrophy and obstruction due to elongation of the anterior mitral leaflet. On the other hand, a more central jet of MR may indicate intrinsic MV disease. LVOTO is dynamic and the degree of obstructions is affected by a number of factors including loading conditions of the heart and contractility. This is evidenced from changes in the degree of LVOTO with various maneuvers and exercise which will be discussed below.

### *1.6.3 Clinical Presentation of LVOTO*

#### *1.6.3.1 Clinical History*

A detailed clinical history can provide many clues to a diagnosis of HCM even prior to the development of a clinical phenotype and can be drawn from a thorough evaluation of presenting symptoms, past medical history and family history. Generation of a family pedigree provides a detailed family history of not only HCM but also other cardiovascular conditions such as arrhythmias, strokes, heart failure and systemic conditions. Many patients

with HCM will be asymptomatic at presentation and quite often the diagnosis will be incidental or found on screening after a diagnosis in a relative.[57] The presence of LVOTO in HCM leads to symptoms of breathlessness, chest pain and lightheadedness most notably on exertion or post prandially.[13,57]

*1.6.3.2 Physical Examination*

William Osler said, “There is no more difficult art to acquire than the art of observation”. As in the case with many clinical conditions, HCM can provide many clues to an examining eye.

Left ventricular hypertrophy can lead to the presence of a sustained apical impulse. This in combination with SAM of the MV can cause turbulence of blood flow across the LVOT which can be heard on auscultation yielding a classic crescendo – decrescendo early systolic murmur. [13,49,54,55] This can be heard best over the lower left sternal edge. Unlike the murmur of aortic stenosis or subaortic stenosis, the murmur associated with LVOTO does not typically radiate to the neck. This can also be evaluated further clinically by performing manoeuvres such as the Valsalva manoeuvre, in which there is forced expiration against a closed glottis, or on changing from a squatting to upright position which reduces preload on the heart. These manoeuvres increase the intensity of the murmur associated with LVOTO compared to aortic or subaortic stenosis which usually reduces on intensity.

Systolic anterior motion leads to varying degrees of mitral regurgitation (MR). This is due to an underlying eccentric jet of blood into the left atrium during ventricular systole. This can be heard as a mid-late systolic murmur at the apex on auscultation. The more classical holosystolic murmur of MR can also be heard in patients with intrinsic MV disease due to central jet of MR.[17,56]

Prominent “a waves” of the jugular veins are seen due to forced atrial contraction and reduced right ventricular compliance. In advanced disease, signs such as pitting oedema, elevation of the jugular venous pressure and hepatomegaly may be present. Arterial pulses can have characteristic features such as brisk upstroke and jerky pulsations in the presence of obstruction.

### *1.6.4 Diagnostic Investigation of LVOTO*

#### *1.6.4.1 Electrocardiography*

An ECG is the most common initial investigation in patients with suspected HCM. A minority of patients with HCM will have a normal ECG. This was evidenced from an observational study showing a normal ECG in <6% of patients with echocardiographic evidence of HCM.[57] Although a relatively sensitive tool, ECG abnormalities are not specific for HCM or LVOTO and many abnormalities seen are also found in other cardiac abnormalities.[58]

The most common ECG changes seen in HCM are repolarisation abnormalities, hypertrophy and Q-waves. Abnormalities in individual leads give a clue as to the distribution of hypertrophied tissue; for example, giant T-wave inversion in the mid precordial leads can indicate an apical variant of hypertrophy. P-wave abnormalities can indicate atrial enlargement and the combination with hypertrophy on an ECG is highly suggestive of HCM.[57-59] An example of these abnormalities can be seen in an ECG of a patient with HCM in *Figure 4*.[60] Other electrical abnormalities can also be identified on ECG and associated with HCM e.g. atrial and ventricular arrhythmias.[61,62] Atrioventricular nodal delay is rare in HCM but can commonly be seen in rarer forms of HCM such as PRKAG2 mutations and metabolic disease.[44,45] Ambulatory ECG monitoring for 24-48 hours provides useful information particularly in the assessment of SCD risk and identification of atrial fibrillation.[62] Prolonged monitoring with implantable loop recorders are useful in the evaluation of symptoms such as syncope.

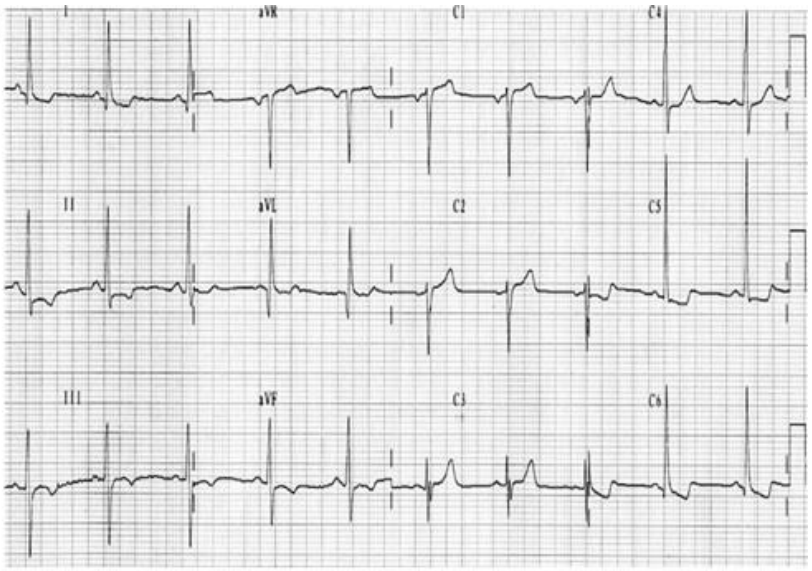


Figure 4: ECG illustrating hypertrophy, repolarisation abnormalities and abnormal Q waves.[60]

*1.6.4.2 Echocardiography*

*a) Transthoracic Echocardiography*

Two dimensional 2D TTE is the gold standard diagnostic imaging tool in HCM and LVOTO.[6,9] This technique allows for a detailed assessment of the distribution of hypertrophy as well as the presence or absence of LVOTO using Doppler techniques. This imaging modality also allows for the assessment of cardiac structure, atrial and ventricular functioning as well as valvular abnormalities such as MR which is commonly seen with LVOTO.

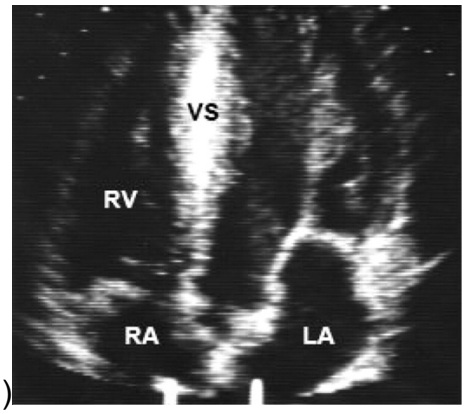
A diagnosis of HCM is made from the presence of unexplained left ventricular hypertrophy (LVH) ≥15mm in one or more left ventricular myocardial segments or ≥13mm in the presence of a family history with a

first degree relative.[6,9] This wall thickening can affect any part of the left ventricular wall but most commonly is seen in the basal interventricular septum giving a classical picture of ASH.[63] Other areas of thickening which are less commonly seen include the anterior free wall, posterior wall or confined to the apical region. This thickening can be taken in a variety of views but for consensus standard measurement is taken in diastole in the parasternal long axis view at the level of the MV.[63-65]

Continuous wave Doppler gives a non-invasive estimation of the pressure gradient across the LVOT. A peak gradient of ≥30mmHg is diagnostic of LVOTO and is best measured in the 5-chamber long axis apical view of the heart.[6] As already noted, LVOTO is dynamic and influenced by factors which alter cardiac contractility and loading conditions and therefore can occur under both resting or provoked conditions. It is therefore important in standard evaluation of gradients across the LVOT to perform provocation manoeuvres. If a high clinical suspicion exists based on symptoms it may be necessary to attempt further provocation with exercise testing to rule out latent LVOTO if Valsalva or other manoeuvres fail to produce a significant gradient.[13,15,17] Exercise induced provocation is preferable to pharmacological provocation as it most closely mimics daily life.[66] If a gradient is documented it is important to rule out other causes of obstruction unrelated to HCM such as sub aortic stenosis. This is evident in a study of patients with HCM evaluating LVOTO which showed 53% of patients without resting LVOTO to have evidence of LVOTO on provocation.[13] Despite this, even though a gradient of ≥30mmHg is diagnostic of LVOTO a value of

≥50mmHg is treated as haemodynamically significant for therapeutic management.[6]

Echocardiography also allows for an assessment of the MV and the presence or absence of SAM.[13-17] Other abnormalities seen in HCM which can lead to obstruction include elongation of the mitral leaflets, altered mitral length and abnormalities of the sub-mitral apparatus such as thickening and anterior displacement of the papillary muscles and abnormal fibrotic attachments.[17] Depending on the echocardiographic windows the MV may need more detailed imaging particularly if considering surgical intervention. It is important to measure the size of the left atrium in patients with HCM as a significantly enlarged left atrium is a poor prognostic marker and carries a risk for the development of AF.[67,68] Echocardiography can also be used to physiologically or pharmacologically provoke a gradient across the LVOT which subsequent measurement of dopplers. Different exercise techniques can be utilised including upright assessments with a treadmill or while seated using a bicycle ergometer. It is unclear which is the preferred technique. It may be that by naturally provoking a gradient in an upright position, this could lead to a more natural provocation of the gradient across the LVOT which seen in everyday life.

5 a) 

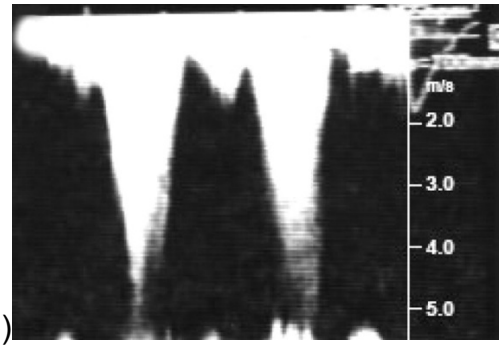
5 b) 


Figure 5:

a) Apical 5-chamber long-axis view showing septal hypertrophy on 2D TTE

b) Continuous-wave Doppler showing increased velocities across the LVOT of 5 m/s (100 mm Hg).[13]

*b) Transoesophageal Echocardiography (TOE)*

Transoesophageal echocardiography is a useful alternative imaging method in patients with poor transthoracic echogenic windows. It is particularly useful if a more detailed assessment is required on the underlying mechanism of obstruction and if any MV pathology.[69,70] TOE is useful during septal reduction therapy to help guide the procedure and evaluate any potential complications.[71]

### *1.6.4.3 Cardiovascular Magnetic Resonance*

Cardiovascular Magnetic Resonance imaging provides detailed imaging of cardiac structure and functioning in patients with HCM.[16,72] It can accurately assess the underlying pathology of LVOTO and any valvular pathology

however with good 2D TTE images CMR provides similar information.[73] Obstruction of the LVOT can be assessed with phase velocity flow mapping but standard 2D TTE is the imaging modality of choice for assessing this. Cardiovascular Magnetic Resonance does however provide other added information compared to a 2D TTE such as patterns of fibrosis through late gadolinium enhancement.[72]

#### *1.6.4.4 Cardiac Computed Tomography (CT)*

Cardiac CT scanning is also used in imaging of cardiac morphology and allows for imaging of the coronary arteries if required. The use of cardiac CT is reserved for when more detailed imaging is required over 2D TTE and CMR is not suitable.[74]

### *1.6.5 Management of LVOTO*

The use of negative inotropic pharmacological intervention and invasive intervention have both been shown to reduce LVOT gradients and improve symptoms.[75,76] This has been further reported and recommended in management guidelines.[6,8,9,25,77] Left ventricular outflow tract obstruction under both resting and provoked conditions has adverse effects on long-term outcomes in HCM in particular those with more severe symptoms and advanced NYHA functional class. Left ventricular outflow tract obstruction has been shown to carry an increased risk of stroke, heart failure and

death.[78,79] It has also been shown to be a risk factor for SCD and is an important consideration in the presence of other risk factors for Implantable Cardioverter Defibrillator (ICD) therapy.[64] It is unclear whether alleviation of this gradient reduces the risk of SCD and the treatment of LVOTO is aimed towards symptomatic improvement. Treatment may be beneficial in those with minimal symptoms with other complications of HCM such as left atrial enlargement.[6]

#### *1.6.5.1 Pharmacological management of LVOTO*

Initial therapy with medications such as β-blockers, non-dihydropyridine calcium antagonists and disopyramide therapy along with the elimination of potential exacerbating factors can improve symptoms. This is recommended as first line therapy in the management of LVOTO.[6,9] All three pharmacological therapies have been shown to reduce LVOT gradients in LVOTO. β-blockers and non-dihydropyridine calcium antagonists including verapamil and diltiazem are negative inotropic medications which reduce contractility and heart rate, prolong diastole and increase left ventricular filling times.[75,76] Either of these two medications are recommended as monotherapy first line treatment.[6,9] Disopyramide has also been shown to reduce LVOT gradients in HCM and is recommended as add-on therapy to β-blocker or non-dihydropyridine calcium antagonist in the pharmacological management.[80] Due to the anti-cholinergic side effects disopyramide is sometimes poorly tolerated by patients. As well as medication, avoidance of factors which trigger LVOTO or volume depletion is recommended such as,

dehydration, diuretics and vasodilators such as Angiotensin Converting Enzyme (ACE) inhibitors, nitrates and dihydropyridine calcium antagonists.[81]

#### *1.6.5.2 Invasive management of LVOTO*

A large proportion of patients respond to initial medical therapy but approximately 25% remain refractory and require further management of their symptoms.[49] As per international guidelines, patients who remain symptomatic despite maximal medical therapy with LVOT pressure gradients ≥50mmHg are recommended for consideration of septal reduction therapy and dual chamber pacing as seen in the flow chart in *Figure 7*.[6,9] For this reason, demonstration of a significant LVOT gradient is paramount in patients with HCM. Absence of a significant resting gradient in the presence of symptoms should prompt further provocation testing to rule out latent LVOTO. Standardised provocation measures are used including the Valsalva manoeuvre andexercise.[62]

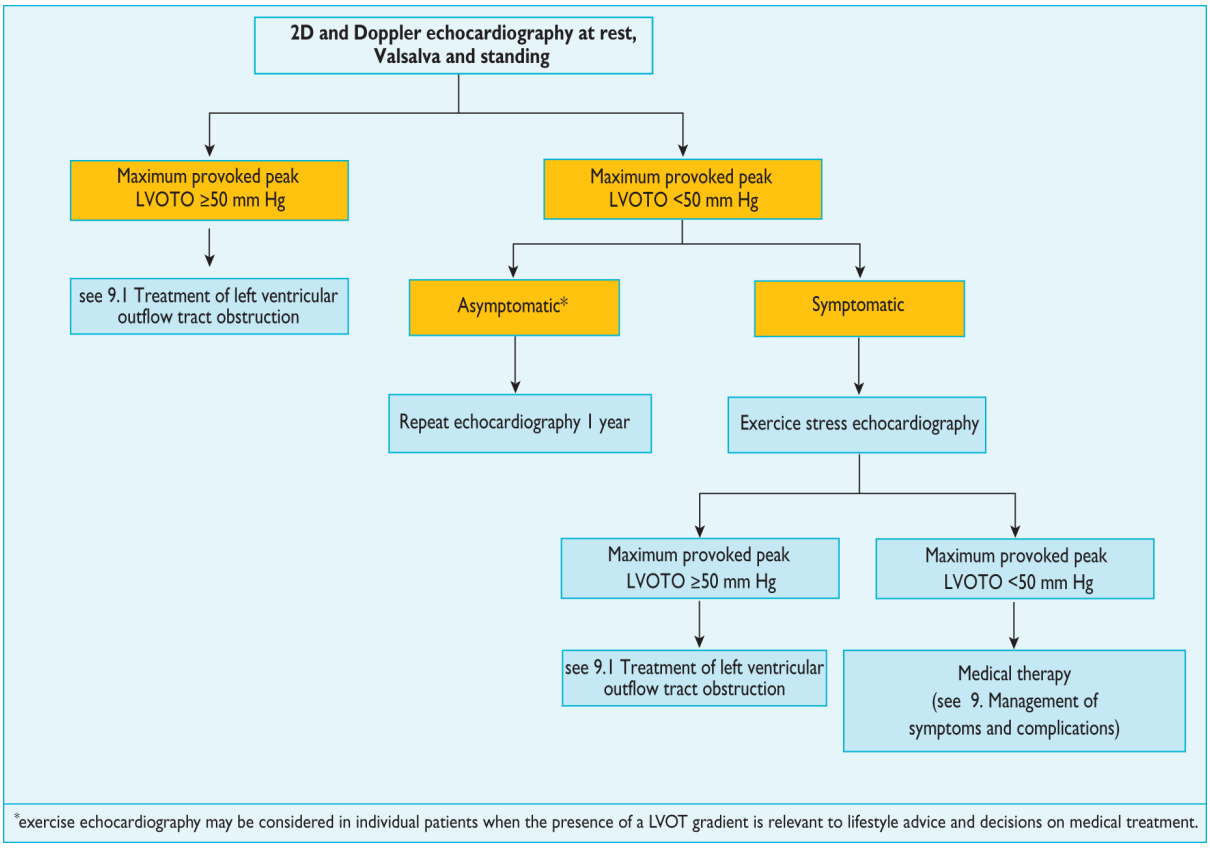



Figure 7: Flowchart for the assessment and management of LVOTO.[6]

Septal reduction therapy can be performed using a surgical approach via a septal myectomy or percutaneously via cardiac catheterisation and injection of alcohol into a septal perforator artery. Both have been shown to reduce septal wall thickening and improve symptoms by improving the flow of blood through the LVOT.

A septal myectomy is carried out through a midline sternotomy with transaortic visualisation of the ventricular septum through the aortic valve. A rectangular trough is created in the basal septum and extended distally

below the point of mitral septal contact known as a Morrow procedure and can be seen in *Figure 8*.[12] This procedure has been adapted over the years to a more extensive septal myectomy.[82] This allows for alleviation of LVOT gradients and improvement of symptoms. Surgical intervention also allows for concomitant procedures to be carried out at the same time of septal myectomy such as intervention on the MV.[83,84] Complications of this procedure include heart block, ventricular septal defect (VSD) and other surgical complications however these are rare in experienced centres.[85-87]

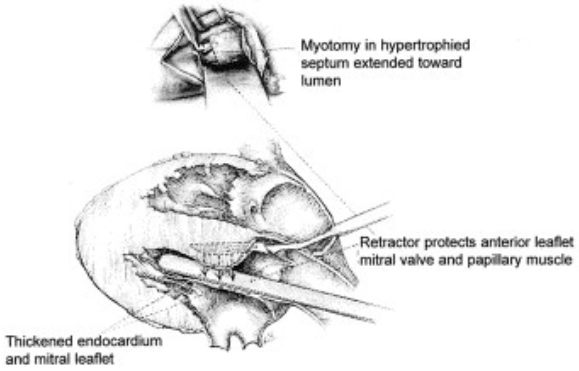



Figure 8: Illustration of the Morrow procedure.[15]

Mitral valve abnormalities that are seen in patients with HCM can be intrinsic including annular, leaflet or chordal calcification or fibrosis or abnormalities more specific to HCM patients including elongation of MV leaflets or abnormal mitral attachments.[17] Abnormal MV attachments, commonly seen with LVOTO include anterior papillary muscle displacement, thickened bifid papillary muscles, direct insertion of papillary muscle into the anterior MV leaflet or fibrotic chordal attachments. In certain cases where there is

involvement of both the mitral and sub-mitral apparatus in the mechanism of LVOTO these can be managed with a combination of septal myectomy and repair or replacement of the MV. Mitral valve intervention may also be more suitable for patients who have limited septal hypertrophy who are not amenable to a septal myectomy. Controversy remains over the most appropriate type of MV repair in patients with LVOTO and rates of MV intervention with septal myectomy varies from 8% to 25% in large centres.[84,85]

Further options to address MV abnormalities include multiple surgical approaches which have been advocated such as the following;

1. An extended septal myectomy can be performed by extending the resection in a fan like fashion moving distally in the septum to open the LVOT further and reduce obstruction.
2. Mitral valve repair
    - Edge-to-edge Alfieri repair: Following a standard septal myectomy the MV is inspected and the central free edges of the A2 and P2 scallops of the MV are approximated using a suture. In doing this a double orifice is created leading to alleviation of SAM and relief of LVOTO as seen in *Figure 9*. If an Alfieri repair is contemplated, assessment of the posterior MV leaflet length is important, as excess length can lead to bileaflet prolapse with SAM making this type of repair less likely to be effective.

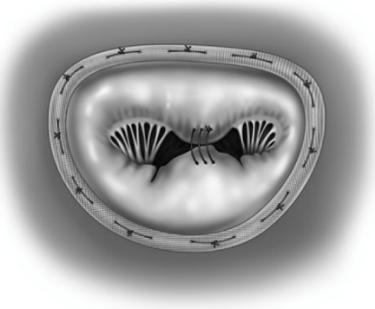


Figure 9: Edge-to-Edge Alfieri mitral repair.[88]

- Anterior MV leaflet extension: Following septal myectomy an autologous pericardial patch is harvested and cut to an oval shape. The anterior mitral leaflet is incised longitudinally. The patch is sewn onto the ventricular surface of the leaflet at the site of the incision by using sutures to stiffen the valve leaflet and alleviate obstruction as seen in *Figure 10*.

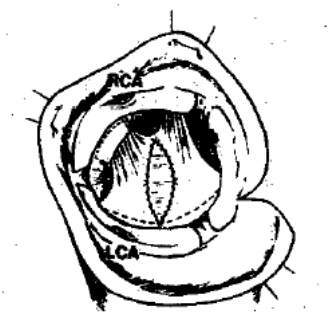



Figure 10: Anterior mitral valve leaflet extension using an oval harvested autologous pericardial patch.[89]

- Mitral valve plication: Following a septal myectomy the MV is shortened by creating a horizontal plication of the anterior

MV leaflet. When an appropriate slack is noted, sutures are placed in a horizontal orientation through the fibrotic area of the leaflet to plicate, shorten the valve leaflet and eliminate obstruction. An illustration of this technique can be seen in *Figure 11*.

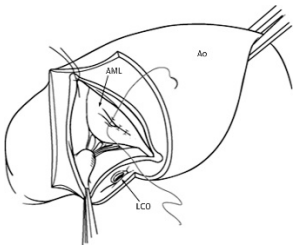



Figure 11: Mitral valve plication of the anterior leaflet.[90]

- Selective cutting of fibrosed secondary chordae: Ferrazi et al. describe a procedure to relieve LVOTO due to fibrosed secondary chordae. This is performed following mobilisation of the papillary muscles and a septal myectomy. Secondary mitral chordae *(Figure 12)* inserting beyond the free margin and rough zone of the mitral leaflet are then examined and selectively cut if judged to tether the anterior MV leaflet.[91]

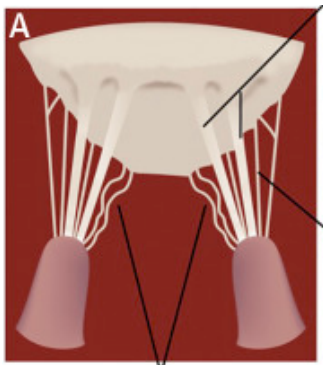



Figure 12: Slack mitral valve chordae tethered to anterior leaflet.[91]

3. Mitral valve replacement as performed in a similar fashion to standard replacement techniques and has been reported to alleviate obstruction of the LVOT and improve clinical symptoms since its first introduction by Cooley et al. in the 1970's for the management of LVOTO.[92] In recent years its use has been limited to selected cases due to complications associated with valve replacement and newer surgical techniques of repair as described above.

Alcohol Septal Ablation is a percutaneous procedure carried out through a cardiac catheterisation of the first or second septal perforating coronary arteries. A small amount of ethanol is injected into the artery which supplies the area of the basal septum creating a small localised infarct. Overtime the septal muscle remodels and results in an increase in LVOT diameter and relief of obstruction and symptoms.[93] Complications of an ASA include heart block, arrhythmias, VSD and other catheterisation related complications such as coronary artery dissection.[93-95]

The benefits of different septal reduction therapy procedures have been debated for many years. Current guidelines recommend septal myectomy as the gold standard in the management of symptomatic drug refractory LVOTO as it alleviates LVOT gradients in >90% of patients with symptomatic improvement in >75% of patients.[6,9] The majority of patients will have classical basal septal hypertrophy. Increasingly awareness of abnormalities with the MV apparatus are identified contributing to LVOTO.[16,17] These abnormalities include elongation of the MV leaflets as well as abnormalities of the mitral attachments.[83,84] Ventricular septa with limited hypertrophy of <18mm can be seen in HCM patients who may not be amenable to septal reduction therapy due to the risk of ventricular perforation. Although similar mortality rates are seen with septal myectomy and ASA there is less opportunity to address these anatomical abnormalities of the MV apparatus using ASA and a surgical approach is recommended instead by international guidelines.[96]

The use of dual chamber pacing to treat LVOTO has been investigated in individual studies.[97-99] Dual chamber DDD pacing with short AV delay causes preexcitation of the interventricular septum with paradoxical movements of the interventricular septum and movements away from the LV wall during systole. This movement can increase the size of the LVOT and reduce velocities in the LVOT mitigating obstruction. Other potential mechanisms in DDD pacing include a negative inotropic effect which can lead to a decrease

in ejection acceleration and early mitral valve forces. Dual chamber pacing has a role in patients with significant comorbidities, unsuitable for septal reduction therapy to alleviate LVOT gradients and improve symptoms. Reported outcomes from pacing studies have shown variable improvement in symptoms but a potential benefit is possibly seen in an older population.[100]

Other variants of obstruction can occur in HCM including more distal obstruction of the left ventricular cavity with mid cavity obstruction (MCO).[60,61,96] This can occur due to a number of mechanisms including distal septal and lateral wall hypertrophy, hypertrophied papillary muscles or direct insertion of the anterolateral papillary muscle directly into the anterior MV leaflet. This leads to a reduction in left ventricular cavity size and due to narrowing of the mid cavity.[101] This may or may not be seen in the context of a left ventricular apical aneurysm which can lead to an increased risk of thrombus formation and ventricular arrhythmias.[102] Rarely other variants of HCM can occur including right ventricular hypertrophy with right ventricular outflow tract obstruction. These variants can be more difficult to treat but pharmacological therapy with negative inotropic agents are first line therapy before more invasive surgical measures are considered.[6,9]

### *1.7 Other Clinical Features*

### *1.7.1 Heart Failure*

Heart Failure symptoms can ensue in the presence or absence of obstruction caused by diastolic and systolic dysfunction.

#### *a) Diastolic dysfunction*

The underlying pathophysiology of HCM leads to myocyte hypertrophy with fibrosis and expansion of the interstitium which can contribute to the stiffening of the myocardium and development of diastolic dysfunction with prolonged left ventricular relaxation time and compensatory increases in left ventricular filling times.[26] Left atrial enlargement is common in patients with diastolic dysfunction.[103,104]

Symptoms of heart failure can be exacerbated by concomitant LVOTO or uncontrolled tachyarrhythmias.[105] Management is aimed at improving left ventricular filling using negatively inotropic medications including b-blockers, and non-dihydropyridine calcium channel blockers (Verapamil or Diltiazem). Loop diuretics can be used if clinical signs of overload are present, but these should be used cautiously particularly in the presence of LVOTO.[6,9]

#### *b) Systolic dysfunction*

Reduction in left ventricular systolic function is relatively common in HCM.[106] Progression to systolic dysfunction is associated with a poor prognosis.

Secondary pulmonary hypertension can lead to severe exertional and non-exertional symptoms in these patients.[106,107]

Management of systolic dysfunction is as per the usual heart failure guidelines with b-blockers, angiotensin converting enzyme inhibitors, aldosterone receptor blockers and mineralocorticoid receptor antagonists however a cut off for the introduction of medical therapy is recommended at <50%.[108]

### *1.7.2 Arrhythmias*

#### *a) Ventricular arrhythmias*

Hypertrophic cardiomyopathy carries a risk of ventricular tachyarrhythmias and SCD with a rate close to 1%.[7,109-111]

Non-sustained ventricular tachycardia (NSVT) occurs in approximately 20% of patients with HCM with increasing prevalence with age, left ventricular wall thickness and degree of myocardial fibrosis.[112,113] It carries an increased risk for SCD forming an important factor in assessing the risk of sudden cardiac death in patients with HCM in particular when associated with exercise.[114]

Sustained monomorphic ventricular tachycardia (VT) ≥30 seconds is uncommon in patients with HCM. Its presence should prompt investigation

for an apical left ventricular aneurysm where it is more commonly seen.[115] As in all cases of significant ventricular arrhythmia the presence of coronary artery disease should be excluded if associated atherosclerotic risk factors are present or a high clinical suspicion of coronary disease.[6]

Although pharmacological therapy has been shown to suppress arrhythmias there is no clear evidence that its use reduces the risk of SCD.[116] Implantable Cardioverter Device therapy is recommended in patients with aborted SCD due to the increased risk of further ventricular arrhythmias. Specific risk factors for SCD have been identified in HCM and the ESC recommend the use of a risk calculator to aid in this assessment. The calculator estimates a 5-year risk in patients >16 years of age as seen in *Figure 13*.[113] The calculator has not been validated after myectomy or alcohol septal ablation.[113]

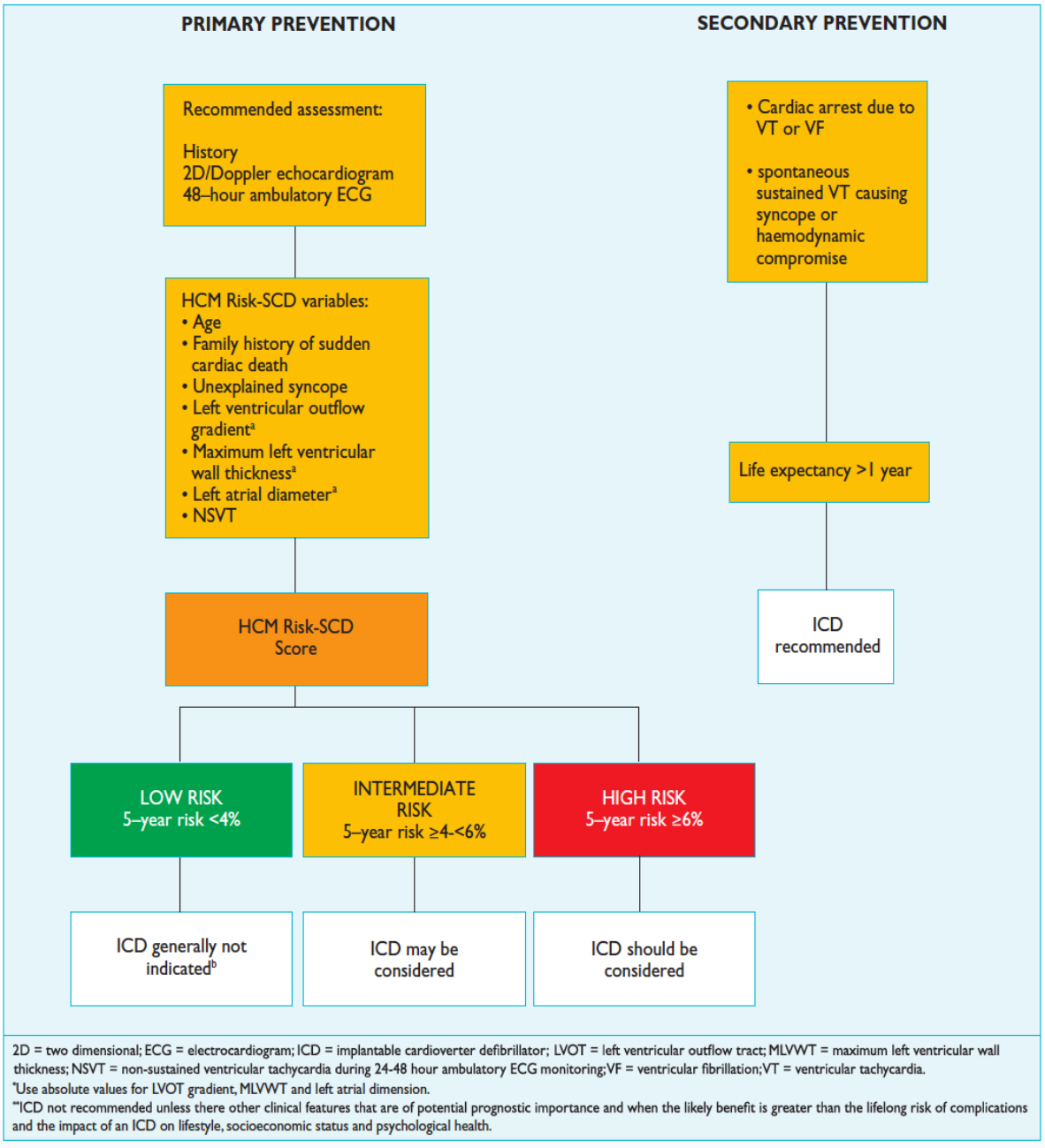



Figure 13: Flowchart for ICD consideration in hypertrophic cardiomyopathy. The flowchart illustrates a systematic approach to management using the HCM Risk-SCD model and organising individuals based on their SCD risk estimate at 5 years.[113]

*b) Atrial arrhythmias*

Atrial Fibrillation is the most common arrhythmia seen in HCM with a prevalence of 22% reported in a large meta-analysis.[117] The development of AF carries an increased rate of all-cause mortality and cardiovascular mortality secondary to heart failure and stroke.[117] It has been proposed that the development of AF may accelerate disease progression or may simply act as a marker of advanced disease. Predictors of the development of AF in HCM include female sex, age, left atrial diameter, New York Heart Association (NYHA) class, hypertension and vascular disease.[118] In a study of almost 5000 patients with HCM, 3.6% of patients reached the primary endpoint of a thromboembolic event.[119]

The management of AF in HCM is similar to that of other aetiologies as set out by the ESC guidelines including anticoagulation for thromboprophylaxis. There is a significant increased risk of AF in HCM and the use of risk scores such as the $CHA_2DS_2$-VASc score does not correlate in HCM when compared to the general population and should therefore not be used in this cohort.[6] It is unclear when to anticoagulate in patients with no history of AF but guidelines recommend regular prolonged ECG monitoring in those with dilated left atria >45mm given its association with the development of AF.[6]

*c) Bradyarrhythmias*

Atrioventricular (AV) block is relatively uncommon in HCM and its presence should raise the suspicion of aetiologies other than sarcomeric disease and rarer conditions. The management of AV block should be based on the

general guidelines for bradyarrhythmias including the removal of any AV blocking agents and pacing where required.[6]

### *1.7.3 Other common cardiac conditions*

#### *a) Coronary Artery Disease (CAD)*

Older studies report incidences of up to 20% of CAD in adult HCM patients but there is a lack of contemporary data.[120] Patients with HCM however, presenting with chest pain is usually secondary to underlying microvascular ischaemia or LVOTO. Investigation of underlying coronary artery disease should be considered in those with typical chest pain and risk factors associated with the development of atherosclerosis.[121]

#### *b) Valvular Heart Disease*

Mitral regurgitation is the most common valvular abnormality in HCM.[17] This is frequently seen as a result of SAM in LVOTO resulting in an eccentric jet of MR.[14-17] Mitral valve abnormalities seen in HCM include elongation of the MV leaflets, altered mitral height and abnormalities of the submitral valve apparatus including abnormally aligned or thickened papillary muscles and fibrotic chordal attachments.[15,16] These abnormalities are important and need to be addressed particularly if considering septal reduction therapy as intervention of the MV with a repair or replacement may be required if significant MR is present.

Intrinsic MV abnormalities can also be seen in HCM as are seen in the general population including valve degeneration in older patients. This should be managed in concordance with guidelines on the management of valvular disease with particular attention to the presence of concomitant LVOTO if considering surgical management.[6]

Aortic stenosis can cause a clinical conundrum in HCM. As per guidelines the presence of increased left ventricular wall thickening in any myocardial segment ≥15mm in the absence of abnormal loading condition defines HCM.[6] Although the hypertrophy is usually mild, AS can cause asymmetrical hypertrophy and tends to correlate with the severity of valve stenosis.[22] It is important to determine if LVOTO is present when considering surgical intervention.[6]

Mild aortic regurgitation (AR) can be seen in up to one third of patients with HCM however severe AR is uncommon.

### *1.7.4 Mortality*

The annual incidence rate of mortality in patients with HCM has reduced from older studies and is estimated at 1% in contemporary reports.[7] Common causes of death in HCM include SCD, heart failure and stroke related deaths.

The risk of SCD is associated with cardiomyopathies and varies depending on the underlying subtype. Sudden cardiac death although rare in HCM, is the most common mode of death seen in HCM and carries an estimated annual incidence rate of 0.8% peaking in early adulthood. It is most commonly associated with ventricular arrhythmias and bradyarrhythmias to a lesser extent.[7]

There are many risk factors which have been identified as carrying a higher risk of SCD including non-sustained ventricular tachycardia (VT), severe LVH, unexplained syncope and abnormal blood pressure response to exercise as described above.[108] The absence of these risk factors typically carries a lower risk of SCD.[108] The 2014 ESC guidelines on HCM recommended the use of a clinical calculator to aid in the clinical decision of need for ICD implantation (HCM RISK–SCD) [http://www.doc2do.com/hcm/webHCM.html].[6] On the other hand, survivors of ventricular fibrillation (VF) or sustained VT are at very high risk of a subsequent event and should all receive an ICD for secondary prevention.[122]

Less commonly deaths occur due to other cardiovascular causes including heart failure and stroke (0.5% and 0.07% respectively).[7] It is important to manage these clinical features appropriately as discussed above, as many of these features can be prevented and treated through the use of various pharmacological agents.

# 2. Aims and Objectives

The main aim of this thesis is to evaluate the outcomes following surgical management of LVOTO in HCM. Clinical outcomes will be explored in a stepwise approach by examining current and past surgical practices from the literature and variances in surgical techniques. I aim to then analyse surgical techniques including the short and long term outcomes in a large heterogenous cohort of patient with LVOTO and HCM in the United Kingdom (UK).

## 2.1 Current and past surgical practices

*Outcomes following the surgical management of left ventricular outflow tract obstruction; A systematic review and meta-analysis.*

The gold standard in the management of LVOTO in HCM is surgical intervention. This practice largely comes from expert consensus in international guidelines based on evidence published from large single centre institutions. There is inconsistent reporting of all short and long term outcomes in these studies which can make it difficult to draw direct conclusions when considering best clinical practice. In performing a thorough review of the published literature in this cohort I aim to systematically review clinical outcomes including morbidity and mortality and quantitatively evaluate mortality by meta-analysis.

## 2.2 **Clinical outcomes in a large heterogenous UK based cohort**

*Long-term outcomes for different surgical strategies to treat left ventricular outflow tract obstruction in hypertrophic cardiomyopathy.*

Following systematic review and meta-analysis of the data I aim to carry out a retrospective analysis of short- and long-term outcomes in patients undergoing a range of different surgical approaches for the relief of LVOTO in a large specialist cardiomyopathy centre.

## 2.3 **Individual surgical techniques in the management of LVOTO**

*Individualised surgical strategies for left ventricular outflow tract obstruction in hypertrophic cardiomyopathy.*

On exploration of current and past surgical practices a number of varying surgical approaches are utilised in the management of LVOTO largely dependent on the underlying clinical phenotype and local surgical preferences. The aim of this study is to evaluate these surgical approaches in further detail and explore the outcomes of various approaches adopted in our institution.

## 2.4 Alfieri mitral valve repair in the management of LVOTO

*Early and medium-term outcomes of Alfieri mitral valve repair in the management of systolic anterior motion during septal myectomy.*

Edge to edge repair of the MV is a technique developed by Ottavio Alfieri and colleagues in Milan, Italy. This technique was performed on a small cohort of patients with LVOTO in our specialised cardiomyopathy centre. The aim of this study is to evaluate this cohort of patients and analyse their clinical outcomes.

# 3. Methods

As described in *Chapter 2,* studies were performed using a stepwise approach to evaluate the short- and long-term clinical outcomes of patients undergoing surgical intervention for the management of LVOTO in HCM. I performed a systematic review of published literature and used this to identify gaps in our clinical knowledge which could then further be evaluated in a large heterogenous cohort of patients with LVOTO and HCM.

## *3.1 Outcomes Following the Surgical Management of Left Ventricular Outflow Tract Obstruction; A Systematic Review and Meta-Analysis*

### *3.1.1 Systematic Review*

A systematic review of the literature and meta-analysis was carried out in accordance with the PRISMA statement.[123] A systematic literature search was performed using both the PubMed and Web of Science databases. Search terms which were applied to the search included “myectomy”, “myotomy”, “myomectomy”, “hypertrophic cardiomyopathy”, “idiopathic hypertrophic subaortic stenosis”, “mitral valve replacement”, “mitral valve repair” “outcome”, “prognosis”, “mortality”. These search terms were applied to titles and abstracts and the search was restricted to observational studies, clinical trials, comparative studies, controlled clinical trials, meta-analyses,

randomised controlled trials, systematic reviews, journal articles, full texts, humans, and English language.

Original articles were reviewed and selected by two independent reviewers (Richard Collis, Oliver Watkinson) to determine eligibility for the study. The search criteria were not limited to the date of publication. Criteria for selection were based on documented mortality rates following surgical intervention for LVOTO in HCM with surgeries including, septal myectomy alone, septal myectomy with mitral valve repair, septal myectomy with mitral valve replacement and mitral valve replacement alone. Case reports, editorials, systematic reviews and previous meta-analyses were removed. Articles unrelated to the topic along with those without a documented mortality rate were removed and database searches were corrected for duplicates. The reference lists of selected papers were scrutinised for additional eligible papers. The last search was carried out on 11/11/2015.

Variables extracted from each study included age, sex, date of study, date of publication, study location, New York Heart Association (NYHA) class, LVOT gradient, perioperative mortality, late mortality, cardiovascular mortality, rates of VSD, stroke, permanent pacemaker (PPM) insertion and surgical re-intervention including myectomy, MV repair and replacement. Where reported, echocardiographic parameters including left ventricular ejection fraction, left ventricular end diastolic diameter, maximum left ventricular wall thickness, left atrial diameter and LVOT gradients were collected.

Early complications were defined as those occurring within the first 30 days post-operatively or during a post-operative stay. Long-term outcomes were defined as those occurring after this period. Sudden cardiac death and cardiovascular deaths were defined as per individual studies.

### *3.1.2 Meta-Analysis*

Studies reporting prevalence data for different types of mortality were included in the meta-analysis. Not all studies provided standard error (SE) of the prevalence and so SE was calculated using the prevalence data and sample size in each study and the same formula commonly used for binomial proportion.[124] Assuming that the estimated values for prevalence follow a normal distribution for large number of studies, we calculated 95% confidence intervals (CI) for population prevalence. The incidence rate for each study was calculated using the number of new cases and median follow-up time provided by the study. SE of incidence rate was calculated assuming Poisson distribution of number of new cases. A random effect meta-regression model was then used to combine both the prevalence and incidence data and to obtain the pooled (overall) prevalence and incidence for different types of mortality separately. The overall prevalence (or incidence) rate was the weighted average of the prevalence (or incidence) across different studies, where weights were calculated using measures of precision (inverse of the variance of the prevalence). Intra- and inter-study variances were used in the calculation of precision. The intra-study variance

was the variance of the prevalence (incidence) obtained as above (square of SE) for each study. The inter-study variance, a parameter of the random effects meta-regression model, was estimated using method of moments. The inter-study variance was used to adjust for the heterogeneity in prevalence (or incidence) between studies. Heterogeneity from variability in outcomes between studies was further assessed using the $I^2$ statistic.[124] The $I^2$ statistic ranged from 0% - 100% and determined the percentage of variance that is attributable to study heterogeneity. The higher the $I^2$ percentage the higher the heterogeneity was involved. A p-value determined the probability of the null hypothesis that there was no heterogeneity between studies. When $p < 0.05$, I rejected the null hypothesis and considered there was heterogeneity across studies. A random effect meta-analysis was conducted to obtain an overall prevalence (or incidence) rates of different types of mortality. The analysis was further extended for different subgroups based on surgical technique and study year to see if the results vary across the subgroups. To reduce centre bias, studies from the same centre were isolated according to study period and the largest cohort was used in the meta-analysis. Paediatric studies were excluded from the meta-analysis. Selected studies with a non-classical baseline population were also excluded from the meta-analysis. All these computations were conducted using Stata V.11 and Comprehensive Meta-Analysis V.3.

### 3.2 *Long-Term Outcomes for Different Surgical Strategies to Treat Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy.*

### *3.2.1 Study Design*

This study is an observational cohort study comprising all patients with HCM undergoing surgical intervention and treatment for LVOTO. Patients were followed up at a specialist cardiomyopathy clinic located sequentially at St George's Hospital (1988-2003), The Heart Hospital, University College London (2003-2015) and St Bartholomew's Hospital (2015-present). The majority of patients were operated on by three surgeons (Professor Christopher McGregor, Professor Victor Tsang, Mr Venkatachalam Chandrasekaran). Hypertrophic cardiomyopathy was defined as a wall thickness ≥15mm in any left ventricular myocardial segment in the absence of other abnormal loading conditions or ≥13mm in the presence of a family history of HCM.[3] Surgical intervention was considered in accordance with international guidelines in patients with drug refractory symptomatic LVOTO.[6] This eligibility was defined as a LVOT gradient ≥50 mmHg and was documented under resting conditions or provoked using Valsalva manoeuvre and exercise echocardiography when clinically indicated. Patients underwent routine echocardiography including Valsalva provocation as part of standard clinical assessment follow-up. In cases where there was a clinical suspicion of LVOTO but no significant LVOTO on resting echocardiography, patients underwent exercise echocardiography with upright treadmill exercise testing (Bruce protocol) when clinically appropriate or bicycle ergometer to determine if an exercise induced provocable gradient was evident. Patients were included if at least one year follow-up data was available. Patients with rare phenocopies of HCM including lysosomal storage diseases, metabolic

conditions or malformations were excluded. Eight patients undergoing a septal myectomy also had AS and received an aortic valve replacement. These patients were not included in the analysis. Ten patients received a concomitant aortic valve replacement for underlying AR or mixed aortic valve disease with mild AS only and were included in the study.

### *3.2.2 Clinical Assessment*

All patients were assessed in a specialist clinic and their data were stored on a relational database. Background history was documented including previous arrhythmia or cardiovascular complications. Atrial fibrillation and VT documented on 12-lead ECG or prolonged ECG monitoring and a family history of HCM or SCD were defined as in previous studies.[113,125] Clinical assessment included documentation of New York Heart Association (NYHA) class, a 12-lead ECG and a TTE. Maximum left ventricular wall thickness, left ventricular ejection fraction by visual assessment, left atrial dimensions and LVOT pressure gradients at rest and with Valsalva provocation were documented. Exercise stress echocardiography using a bicycle ergometer was performed on clinical grounds to detect a provoked gradient when no resting LVOT gradient was documented. Cardiopulmonary exercise testing was carried out using a bicycle ergometer in accordance with published methods.[125] Peak oxygen consumption, percentage target heart rate achieved, and systolic and diastolic blood pressure responses to exercise were documented. Prior to surgery, patients were presented at a joint cardiothoracic conference to a team of cardiac surgeons and cardiologists

specialising in inherited cardiovascular disease to determine the most suitable management plan. Individuals with significant LVOTO who were considered unsuitable for septal myectomy typically had mild hypertrophy or co-existent severe MV disease unrelated to obstruction and were considered for alternative surgical approaches.

### *3.2.3 Follow-Up*

After surgical intervention, all patients were followed-up and assessed post-operatively by both surgical and medical teams at 6 weeks and then at regular intervals based on their clinical condition. For the purposes of this analysis, clinical data were reviewed from follow-up clinics at 1, 5 and 10 years post-operatively. Perioperative complications and death were defined as events occurring during a perioperative stay or within the first 30 days post-operatively. Long-term outcomes (occurring at least 30 days after surgical intervention) used in the analysis were: stroke or TIA's, new onset AF, PPM implantation and heart failure hospitalisations, defined as an acute admission to hospital with shortness of breath and/or fluid overload requiring treatment with intravenous diuretics. Patients were included if at least 1 year had lapsed since their surgery and clinical and echocardiographic data were available.

### *3.2.4 Study Endpoints*

In this study the primary survival endpoint was all-cause mortality. Secondary endpoints included cardiovascular death, SCD, aborted SCD, repeat

cardiovascular operation for the further management of LVOTO and heart transplantation. Other long term clinical outcomes assessed included the prevalence of non-fatal morbidities including atrial fibrillation, heart failure, stroke. Cardiovascular death was defined as death secondary to SCD, stroke or heart failure. Sudden cardiac death was defined as witnessed sudden death within 1 hour following the onset of new cardiovascular related symptoms or nocturnal deaths with no recent history of worsening cardiovascular symptoms. Aborted SCD was defined as successful defibrillation with spontaneous restoration of the patient's circulation. This definition included appropriate ICD shocks due to ventricular arrhythmias. Death due to heart failure was defined as death preceded by signs and symptoms of heart failure of > 1 hour duration or clinical presentation of the patient with cardiogenic shock. These definitions were consistent with previous studies from our institution.[113,125]

### *3.2.5 Statistical Analysis*

Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) based on distribution and normality of the data. Tests of normality were carried out using the Shapiro–Wilk test. Comparisons were made with the use of Student's t-test, Mann–Whitney U-test, ANOVA and Kruskal–Wallis test based on normality of the data. All primary and secondary endpoints were assessed as above and the cumulative probability of an endpoint was analysed using the Kaplan–Meier survival method with log-rank testing to provide a statistical comparison between groups.

Clinical predictors were selected according to baseline demographics and echocardiographic parameters to evaluate if any effect on clinical outcome. A previous history of known AF, heart failure, CAD and prior procedural intervention for LVOTO were noted but were not included in the analysis due to low case numbers. All independent variables were measured on a dichotomous or continuous scale. Relief of LVOT gradients to <30mmHg determined the dependant dichotomous outcome variable for assessment. A univariate regression analysis was first performed on each independent variable followed by a binomial logistic regression of all independent variables. All assumptions for a logistic regression were considered and fitted the model for analysis. Continuous variables were linearly related to the logit of the dependant variable which were assessed using a Box-Tidewell test. A Bonferroni correction was applied for statistical significance. No outliers were noted on analysis with studentised residuals. The regression model adequacy and fit were assessed using the Hosmer and Lemeshow goodness of fit test and Nagelkerke R square test.

A p-value of <0.05 was considered significant for this study. Statistical analysis was performed using SPSS version 24 (SPSS Inc, Chicago, IL, USA).

### 3.3 Evaluation of Clinical Outcomes using Individual Surgical Strategies

### *3.3.1 Study Design*

Between 2003 and 2015, a sub-group of 203 consecutive patients of our entire cohort were evaluated after undergoing surgical management of LVOTO in HCM in a national specialised cardiomyopathy unit at the Heart Hospital, University College London Hospital. No patients were excluded. All patients were operated on by 1 of 2 surgeons (Professor Christopher McGregor and Professor Victor Tsang).

### *3.3.2 Clinical Assessment*

All patients were assessed in a specialist cardiomyopathy clinic. Baseline demographic, clinical and echocardiographic data were documented as explained in *3.2.2*.

### *3.3.3 Surgical Technique*

The surgical technique utilised in our institution by these two surgeons is described as follows. In the operating theatre patients underwent anaesthetic preparation. Following a median sternotomy and before cardiopulmonary bypass, direct simultaneous pressure measurements were carried out with needles in the aorta and the left ventricle. Provocation measures were performed following a bolus of isoproterenol (5μg) intravenously and repeated if an increase in the heart rate and/or reduction in the blood pressure was not attained. This procedure evaluated a provoked LVOT gradient from the operating theatre table. During the study period, the

surgical technique of septal myectomy evolved from the classical Morrow myectomy to the Danielson modification of the classical Morrow myectomy.[12,82] These surgical techniques have been described in further detail in Chapter 1 of this thesis. After the initial planned surgery and cessation of cardiopulmonary bypass, a TOE was performed to assess the LVOT and the MV. Direct simultaneous pressure measurements were repeated in a similar procedure using needles in the aorta and left ventricle with and without provocation as done pre-bypass. These values were evaluated by the operating surgeon for potential significant residual LVOT gradient. Indications to resume bypass and perform further surgery at this point were principally due to a significant residual gradient and/or persistent SAM related MR. Mitral valve intervention was pre-planned in certain cases based on a clinical decision at the joint surgical and medical meeting. Further surgical decisions of concomitant MV intervention were made at the time of surgery following direct visualisation of the MV and evaluation of pressure gradients. Mitral valve repairs were performed concomitantly to a septal myectomy in selected cases and types of MV repair included approaches such as a trans-atrial Alfieri edge-to-edge repair, trans-aortic mitral plication, cleft repair, division of papillary muscles or artificial chordal repair. Mitral annuloplasty was avoided in all patients as this can precipitate SAM of the anterior mitral leaflet causing further obstruction of the LVOT. Mitral valve replacements were done at the time of septal myectomy using the standard techniques, and MV replacement was done alone without septal myectomy again using the standard techniques. Perioperative complications were defined as those occurring within the first 30 days following surgery.

### *3.3.4 Follow-Up*

All patients were followed up clinically as documented in *3.2.3*.

### *3.3.5 Statistical Analysis*

Statistical analysis was performed as documented in *3.2.5*.

## 3.4 Investigation of Clinical Outcomes of Septal Myectomy and Concomitant Alfieri Mitral Valve Repair

### *3.4.1 Study Design*

A retrospective analysis was carried out in a sub-cohort of patients with LVOTO and HCM who had a concomitant septal myectomy and Alfieri mitral repair for management of LVOTO by a single surgeon (Professor Christopher McGregor). A diagnosis of HCM was again defined as per international guidelines.[3] No patient had undergone previous management of LVOTO with surgery, ASA, or dual-chamber pacing. Preoperative clinical assessment was undertaken by a team of specialist HCM cardiologists in a national referral centre. Review board ethical approval was obtained for data collection and reporting.

### *3.4.2 Patient Profiles*

The study consisted of 11 consecutive patients (7 male), having an Alfieri repair as part of septal myectomy surgery for LVOTO with HCM from April 2009 to August 2015 out of a total of 123 septal myectomy patients operated on in that same period. The mean age of the Alfieri repair patients was 47.5 ± 13.9 years. All patients preoperatively had drug refractory symptomatic LVOTO at rest (n = 8) or on provocation with the Valsalva manoeuvre (n = 3). The potential use of an adjunctive Alfieri repair was considered and discussed in patients with reduced septal thickness or those with intrinsic MV abnormalities necessitating a MV repair. The aim of the Alfieri repair was to reduce anterior leaflet SAM by attachment to a normal or tethered posterior leaflet. Specific attention was made to posterior mitral leaflet length to avoid bi-leaflet anterior motion post Alfieri repair. The indications for an Alfieri repair in this series included: elongated anterior MV leaflets (n = 5), leaflet prolapse (n = 2), significant residual SAM related MR, or residual unacceptable LVOT gradients on provocation after septal myectomy following the discontinuation of cardiopulmonary bypass (n = 4). Eight patients had concomitant surgery to suture close the orifice of the left atrial appendage and one had a MAZE procedure for AF.

### *3.4.3 Clinical Assessment and Follow-Up*

Patients were clinically assessed and followed up as documented in *3.2.2* and *3.2.3*.

### *3.4.4 Surgical Assessment and Technique*

Perioperative TTE was performed prior to and following cardiopulmonary bypass. After median sternotomy and before cardiopulmonary bypass, direct simultaneous pressure measurements were performed with needles in the aorta and left ventricle. Provocation was measured following a bolus of Isoproterenol (5µg) intravenously and repeated if an increase in heart rate and/or reduction in blood pressure was not achieved. The technique of septal myectomy was based on the Danielson modification of the classic Morrow Myectomy as described in Chapter 1 of this thesis and in previous published literature.[12,82] The Alfieri repair was performed via a posterior left atriotomy by approximating the central free edges of the A2 and P2 scallops of the MV using a pledgeted 4-0 Gore-Tex (W&L Gore and Associates, Newark, DE) suture.[126,127] After cardiopulmonary bypass TOE was done to assess the LVOT and MV function. In addition, direct simultaneous pressure measurements were repeated with and without provocation as done pre-bypass. Indications to resume bypass and perform an Alfieri repair at this point were a significant residual gradient, and/or persistent SAM related MR. Mitral annuloplasty was avoided in all patients.

### *3.4.5 Statistical Analysis*

Statistical analysis was performed as documented in *3.2.5*.

# 4. Results

## *4.1 Outcomes Following the Surgical Management of Left Ventricular Outflow Tract Obstruction; A Systematic Review and Meta-Analysis.*

### *4.1.1 Search Strategy*

The results of the search strategy are shown in *Figure 13*.[128]

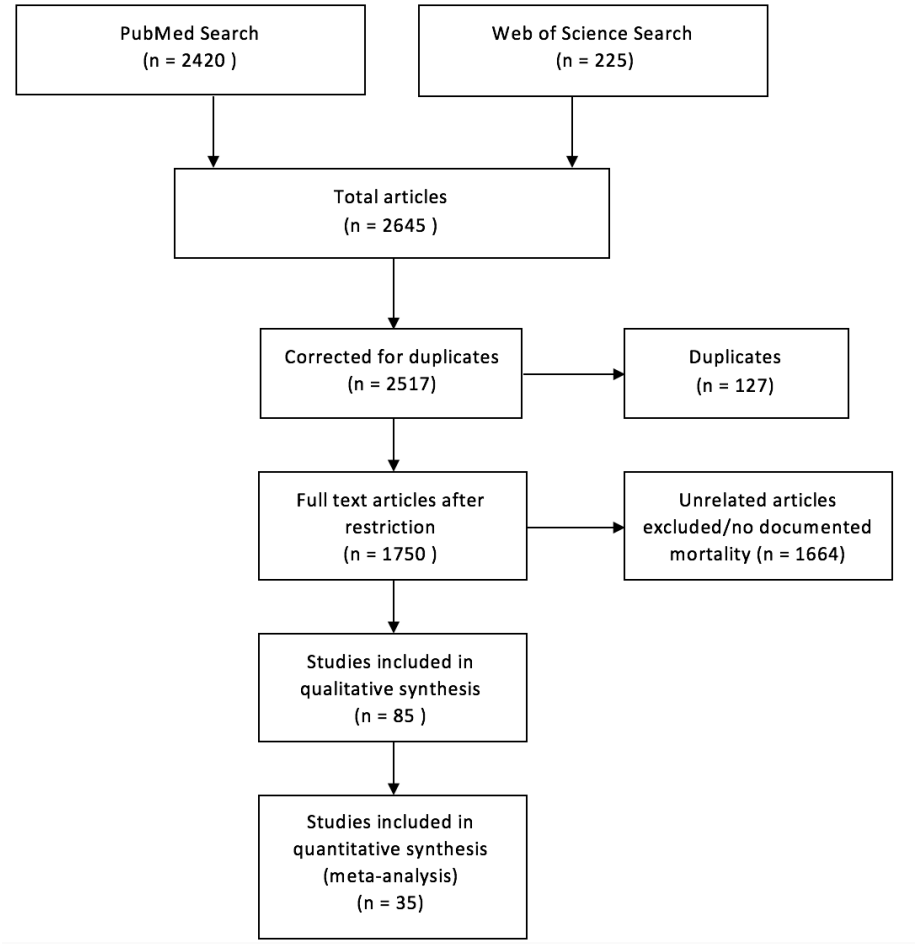



Figure 13: Flow diagram of search strategy methodology.[128]

Eighty-five papers were included in the systematic review and can be seen in *Table 1.*

| ***Author*** | **Location** | **Year** | **FU (Yrs)** | **Cohort** | **SM** | **SM & MV** | **SM & MVR** | **SM & MVR/MVrep** | **MVR alone** |
|---|---|---|---|---|---|---|---|---|---|

| | | | | | | Rep | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Tajik et al*[129] | Mayo Clinic, USA | 1974 | 7.0 | 43 | 38 | 1 | 1 | - | 0 |
| *Morrow et al*[130] | NHLBI, Maryland, USA | 1975 | 5.7 | 83 | 83 | - | - | - | - |
| *Koch et al*[131] | NHLBI, Maryland, USA | 1980 | 4 | 20 | 20 | - | - | - | - |
| *Jeffrey et al*[132] | St Luke's Hospital, Wisconsin, USA | 1981 | 5.8 | 20 | 17 | 0 | 3 | - | 1 |
| *Beahrs et al*[133] | Mayo Clinic, USA | 1982 | 13.4 | 40 | 40 | 0 | 0 | 0 | 0 |
| *Binet et al*[135] | Centre Chirurgical Marie Lanuelongue, France | 1983 | 8.2 | 76 | 73 | 0 | 3 | - | 0 |
| *Maron et al*[136] | NHLBI, Maryland, USA | 1983 | 5.8 | 240 | 240 | - | - | - | - |
| *Rothlin at al*[134] | University Hospital, | 1983 | 7.6 | 63 | 58 | 0 | 5 | - | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Zurich, Switzerland | | | | | | | | |
| *Schaffer et al*[137] | Sick Kids, Toronto, Canada | 1983 | 6.1 | 3 | 3 | 0 | 0 | - | 0 |
| *Fighali et al*[138] | Texas Heart Institute, USA | 1984 | 4.0 | 36 | 12 | 0 | 11 | - | 13 |
| *Cooper et al*[139] | NHLBI, Maryland, USA | 1987 | 4.5 | 52 | 52 | 0 | 0 | - | 0 |
| *Leachman et al*[141] | Texas Heart Institute, USA | 1987 | 10.0 | 54 | 0 | 0 | 0 | 0 | 54 |
| *Williams et al*[140] | Sick Kids, Toronto, Canada | 1987 | 3.0 | 61 | 60 | 1 | 0 | - | 0 |
| *Krajcer et al*[142] | Texas Heart Institute, USA | 1988 | 9.8 | 185 | 127 | 0 | 0 | - | 58 |
| *Cecchi et al*[147] | NHLBI, Maryland, USA | 1989 | 7.0 | 18 | 17 | - | - | - | 1 |
| *Lewis et al*[148] | NHLBI, Maryland, USA | 1989 | 3.4 | 18 | 12 | 0 | 0 | - | 6 |
| *McIntosh et al*[145] | NHLBI, Maryland, USA | 1989 | 2.0 | 58 | 0 | 0 | 0 | - | 58 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Mohr et al*[144] | Mayo Clinic, USA | 1989 | 5.1 | 115 | 109 | 0 | 2 | - | 4 |
| *Siegman et al*[146] | NHLBI, Maryland, USA | 1989 | 4.8 | 28 | 24 | 0 | 0 | - | 4 |
| *Walker et al*[143] | Western General Infirmary, Edinburgh, UK | 1989 | 8.2 | 21 | 11 | 0 | 0 | - | 10 |
| *Seiler et al*[149] | University Hospital, Zurich, Switzerland | 1991 | 9.4 | 79 | 79 | - | - | - | - |
| *Cohn et al*[150] | Brigham & Women's Hospital, Boston, USA | 1992 | 6.5 | 31 | 31 | 0 | 0 | - | 0 |
| *McIntosh et al* | NHLBI, Maryland, USA | 1992 | 2.2 | 36 | 0 | 35 | 1 | 0 | 0 |
| *Delahaye et al*[152] | Hopital Cardiovasculaire et Pulmonologique, Lyon, Fr. | 1993 | 5.7 | 47 | 21 | 0 | 24 | - | 2 |

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|---|---|---|---|---|---|---|---|---|---|
| *Schulte et al*[153] | Heinrich Heine University Hospital, Dusseldorf, Germany | 1993 | 8.2 | 364 | 338 | 7 | 19 | - | 0 |
| *Stone et al*[151] | NHLBI, Maryland, USA | 1993 | 10.1 | 17 | 14 | 0 | 1 | - | 2 |
| *Ten Berg et al*[154] | St Antonius Hospital, Nieuwegein, Netherlands | 1994 | 6.8 | 38 | 30 | 0 | 8 | - | 0 |
| *Heric et al*[156] | Cleveland Clinic, USA | 1995 | 3.7 | 178 | 136 | 4 | 17 | - | 3 |
| *Schoendube et al*[155] | Klinikum RWTH Aachen, Germany | 1995 | 7.0 | 58 | 0 | 58 | 0 | - | 0 |
| *Kofflard et al*[159] | University Hospital Dijkzigt, Rotterdam, Netherlands | 1996 | - | 20 | 12 | 8 | 0 | - | 0 |
| *Mc Cully et al*[157] | Mayo Clinic, USA | 1996 | 2.4 | 65 | 60 | 3 | 2 | - | 0 |

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|---|---|---|---|---|---|---|---|---|---|
| *Robbins et al*[160] | Stanford University, USA | 1996 | 6.1 | 158 | 133 | 0 | 5 | - | 0 |
| *Theodoro et al*[158] | Mayo Clinic, USA | 1996 | 6.4 | 25 | 23 | 2 | 0 | - | 0 |
| *Gol et al*[161] | Cardiology Clinic, Ankara, Turkey | 1997 | 3.7 | 69 | 62 | 4 | 3 | - | 0 |
| *Schonenbeck et al*[162] | University Hospital, Zurich, Switzerland | 1998 | 11.7 | 110 | 98 | 10 | 2 | - | 0 |
| *Schutle et al*[163] | Heinrich Heine University Hospital, Dusseldorf, Germany | 1999 | 8.5 | 368 | 368 | 0 | 0 | - | 0 |
| *Havndrup et al*[164] | Copenhagen, Denmark | 2000 | 3.6 | 11 | 9 | 0 | 2 | - | 0 |
| *Merrill et al*[165] | Vanderbilt University, USA | 2000 | 6.6 | 22 | 21 | 0 | 1 | - | 0 |
| *Qin et al*[166] | Cleveland Clinic, USA | 2001 | 0.4 | 26 | 26 | - | - | - | - |

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|---|---|---|---|---|---|---|---|---|---|
| *Firoozi et al*[167] | St George's Hospital, London, UK | 2002 | 3.8 | 24 | 24 | - | - | - | - |
| *Minami et al*[168] | Heart Center NRW, Bad Oeynhausen, Germany | 2002 | 5.5 | 125 | 110 | 0 | 15 | - | 0 |
| *Van der Lee et al*[169] | Erasmus Medical Centre, Rotterdam, Netherlands | 2003 | 3.4 | 29 | 0 | 29 | 0 | - | 0 |
| *Jiang et al*[170] | Anzhen Hospital, Beijing, China | 2004 | 2.0 | 11 | 11 | - | - | - | - |
| *Minakata et al*[171] | Mayo Clinic, USA | 2004 | 2.8 | 56 | 54 | 2 | 0 | - | 0 |
| *Stassano et al*[172] | Texas Heart Institute, USA | 2004 | 21.9 | 18 | 0 | 0 | 18 | - | 0 |
| *Balaram et al*[178] | St Luke's-Roosevelt Centre, NYC, USA | 2005 | 2.4 | 19 | 0 | 19 | 0 | - | 0 |
| *Minakata et al*[176] | Mayo Clinic, USA | 2005 | 5.8 | 13 | 13 | 0 | 0 | - | 0 |

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|---|---|---|---|---|---|---|---|---|---|
| *Minakata et al*[177] | Mayo Clinic, USA | 2005 | 8.6 | 56 | 49 | 7 | 0 | - | 0 |
| *Ommen et al*[175] | Mayo Clinic, USA | 2005 | 5.8 | 289 | 289 | - | - | - | - |
| *Ralph-Edwards et al*[173] | Toronto General Hospital, Canada | 2005 | 2.3 | 48 | 48 | 0 | 0 | - | 0 |
| *Woo et al*[174] | Toronto General Hospital, Canada | 2005 | 7.7 | 338 | 325 | 0 | 0 | 13 | 0 |
| *Swistel et al*[179] | St Luke's-Roosevelt Centre, NYC, USA | 2006 | 3.1 | 42 | 4 | 34 | 3 | - | 1 |
| *Elbardissi et al*[183] | Mayo Clinic, USA | 2007 | 1.9 | 16 | 14 | 2 | 0 | - | 0 |
| *Monteiro et al*[181] | Mayo Clinic, USA | 2007 | 3.0 | 150 | 150 | - | - | - | - |
| *Nagueh et al*[180] | DeBakey Heart Centre, Texas, USA | 2007 | 1.5 | 20 | 20 | - | - | - | - |
| *Vural et al*[182] | Bursa Yuksek Ihtisas | 2007 | 1.1 | 24 | 9 | 15 | 0 | - | 0 |

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|---|---|---|---|---|---|---|---|---|---|
| | Hospital, Turkey | | | | | | | | |
| *Kaple et al*[186] | Cleveland Clinic, USA | 2008 | 3.8 | 115 | 0 | 67 | 35 | - | 13 |
| *Smedira et al*[185] | Cleveland Clinic, USA | 2008 | 3.6 | 323 | 323 | 0 | 0 | - | 0 |
| *Wan et al*[187] | Mayo Clinic, USA | 2009 | 5.6 | 32 | 0 | 28 | 4 | - | 0 |
| *Brown et al*[188] | Mayo Clinic, USA | 2010 | 3.6 | 416 | 345 | 62 | 9 | - | 0 |
| *Kwon et al*[189] | Cleveland Clinic, USA | 2010 | 0.9 | 182 | 143 | 0 | 0 | 39 | 0 |
| *Schaff et al*[190] | Mayo Clinic, USA | 2010 | 2.6 | 44 | 43 | 0 | 1 | - | 0 |
| *Ball et al*[193] | Toronto General Hospital, Canada | 2011 | 7.2 | 287 | 287 | - | - | - | - |
| *Knyslov et al*[192] | National Institute of Cardiovascular Surgery, Ukraine | 2011 | 3.8 | 28 | 28 | - | - | - | - |
| *Lisboa et al*[191] | Heart Institute, Sao Paolo, Brazil | 2011 | 9.6 | 34 | 26 | 8 | 0 | - | 0 |

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|---|---|---|---|---|---|---|---|---|---|
| *Balaram et al*[194] | St Luke's-Roosevelt Centre, NYC, USA | 2012 | 5.6 | 132 | 32 | 86 | 14 | - | 0 |
| *Hickey et al*[195] | Sick Kids, Toronto, Canada | 2012 | 8.2 | 32 | 32 | - | - | - | - |
| *Iacovani et al*[86] | Ospedali Riuniti, Bergamo, Italy | 2012 | 1.7 | 124 | 115 | 7 | 2 | - | 0 |
| *Schaff et al*[196] | Mayo Clinic, USA | 2012 | - | 749 | 639 | 95 | 15 | - | 0 |
| *Altarabseh et al*[201] | Mayo Clinic, USA | 2013 | 8.3 | 127 | 97 | 29 | 1 | - | 0 |
| *Cambra et al*[200] | Hospital Universitari I Politecnic La Fe, Spain | 2013 | 2.2 | 69 | 66 | - | - | 3 | 0 |
| *Desai et al*[85] | Cleveland Clinic, USA | 2013 | 6.2 | 699 | 518 | 154 | 27 | 0 | 0 |
| *Kunkala et al*[198] | Mayo Clinic, USA | 2013 | 1.6 | 56 | 56 | - | - | - | - |
| *Orme et al*[197] | Mayo Clinic, USA | 2013 | 4.7 | 239 | 239 | - | - | - | - |

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|---|---|---|---|---|---|---|---|---|---|
| *Wang et al*[201] | Fuwai Hospital, Beijing, China | 2013 | 0.9 | 93 | 74 | 9 | 10 | - | 0 |
| *Cho et al*[204] | Mayo Clinic, USA | 2014 | - | 52 | 48 | 4 | 0 | - | 0 |
| *Efthimiadus et al*[208] | AHEPA, Thessaloniki, Greece | 2014 | 1.4 | 32 | 29 | 3 | 0 | - | 0 |
| *Geske et al*[203] | Mayo Clinic, USA | 2014 | 3.1 | 306 | 306 | - | - | - | |
| *Helder et al*[209] | Mayo Clinic, USA | 2014 | 2.6 | 16 | 15 | 1 | 0 | - | 0 |
| *Kunkala et al*[206] | Mayo Clinic, USA | 2014 | 4.6 | 23 | 23 | 0 | 0 | - | 0 |
| *Panaich et al*[210] | NIS, USA | 2014 | - | 665 | 665 | - | - | - | - |
| *Samardhi et al*[207] | Prince Charles Hospital, Brisbane, Australia | 2014 | 3.8 | 23 | 20 | 1 | 2 | - | 0 |
| *Sedehi et al*[205] | Stanford University, USA | 2014 | 13.7 | 171 | 171 | 0 | 0 | - | 0 |
| *Steggerda et al*[202] | St Antonius Hospital, | 2014 | 9.1 | 102 | 102 | - | - | - | - |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Nieuwegein, Netherlands | | | | | | | | |
| *Parry et al*[211] | Toronto General Hospital, Canada | 2015 | 4.4 | 211 | 209 | 2 | 0 | - | 0 |
| *Vriesendorp et al*[212] | Erasmus Medical Centre, Rotterdam, Netherlands | 2015 | 8.3 | 139 | 24 | 98 | 14 | - | 0 |

Table 1: Journal articles included in the systematic review. "-": Not reported in study; FU: Mean Follow-Up Duration; SM: Septal Myectomy without Mitral Valve Intervention; SM & MV Repair: Septal Myectomy and Mitral Valve Repair; SM & MVR: Septal Myectomy and Mitral Valve Replacement; SM & MVR/MVrep: Septal Myectomy and unspecified Mitral Valve Replacement or Repair; MVR: Mitral Valve Replacement.[128]

Following exclusion of multiple studies from the same centres, 35 papers were included in the final meta-analysis. The systematic review included 9738 patients from 1958 -2012. All studies were observational and used retrospective data collection. The median number of patients per study was 56 (IQR 25 -127). The mean age at surgery was 45.2 years and 55.1% were men; the mean follow-up was 5.5 years.

### *4.1.2 Systematic Review*

#### *4.1.2.1 Geographical Location*

Fifty-seven (67.1%) studies came from North American centres (7557 patients) and 23 (27.1%) from European centres (2020 patients). The remainder comprised of 2 studies from China, 1 from Australia and 1 from Brazil. Of the 57 articles from North America, 21 (36.8%) were published from the Mayo Clinic in Rochester, Minnesota. This introduced bias in the meta-analysis due to overlapping cohorts from the same centre. We sought to eliminate this bias in the meta-analysis as described above. The origin of individual studies is shown in *Table 1*.

#### *4.1.2.2 Surgical Procedures*

The 85 studies included patients undergoing septal myectomy alone, septal myectomy with concomitant MV intervention and MV replacement alone. 11 studies (12.9%) focused on MV intervention in the surgical management of LVOTO which were analysed separately in the meta-analysis. Selected cohorts reported outcomes in patients undergoing redo surgical procedures and one reported outcomes in patients undergoing apical myectomy which were not included in the meta-analysis.[176,190]

*4.1.2.3 Clinical Assessment*

Sixty-eight studies (80.0%) referenced NYHA class and 47 studies (55.3%) reported a mean improvement of 1.4. Mean ejection fraction reduced from 65.4% (CI 65.0, 65.6) preoperatively to 59.4% (CI 59.0, 59.8) postoperatively. Left ventricular end diastolic diameter increased from 42.5mm (CI 42.3, 42.8) to 45.0 mm (CI 44.6, 45.5) postoperatively. Mean maximum wall thickness reduced from 22.1mm (CI 22.0, 22.2) to 17.1mm (CI 16.7, 17.4) postoperatively. The mean left atrial diameter reduced 45.9mm (CI 45.6, 46.2) to 45.3mm (CI 45.2, 45.4) postoperatively. Mean resting peak left ventricular outflow tract gradient reduced from 74.0 mmHg (CI 73.0, 75.0) to 9.2mmHg (CI 8.9, 9.4) postoperatively.

*4.1.2.4 Early Complications*

Sixty-eight studies (80.0%) documented rates of at least one non-fatal perioperative complications. Permanent pacemaker insertion was the most frequently documented complication with 60 studies (70.6%) reporting rates of perioperative PPM insertion. Fewer studies documented other perioperative complications with 31 studies (36.5%) documenting rates of VSD and 24 studies (28.2%) documenting rates of perioperative CVA *(Table 2)*. Twenty-one studies (24.7%) documented postoperative AF with 5 studies (5.9%) documenting specific new onset of AF postoperatively.

| ***Author*** | **Year** | **Cohort** | **VSD** | **CVA** | **PPM** |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| *Tajik et al*[129] | 1974 | 43 | 0.0% | - | 2.3% |
| *Morrow et al*[130] | 1975 | 83 | 6.0% | - | 3.6% |
| *Koch et al*[131] | 1980 | 20 | - | - | 10.0% |
| *Jeffrey et al*[132] | 1981 | 20 | 5.0% | - | 0.0% |
| *Beahrs et al*[133] | 1982 | 40 | - | 2.5% | 2.5% |
| *Rothlin at al*[134] | 1983 | 63 | 1.6% | - | 6.3% |
| *Maron et al*[136] | 1983 | 240 | - | - | 1.7% |
| *Williams et al*[140] | 1987 | 61 | 1.6% | 1.6% | 1.6% |
| *Cooper et al*[139] | 1987 | 52 | 7.7% | - | - |
| *Lewis et al*[148] | 1989 | 18 | 5.6% | - | - |
| *Mohr et al*[144] | 1989 | 115 | 1.7% | - | 5.2% |
| *Siegman et al*[146] | 1989 | 28 | 17.9% | - | 7.1% |
| *Cohn et al*[150] | 1992 | 31 | - | - | 6.5% |
| *Stone et al*[151] | 1993 | 17 | - | - | 5.9% |
| *Ten Berg et al*[154] | 1994 | 38 | 2.6% | - | 2.6% |
| *Heric et al*[156] | 1995 | 178 | 1.1% | 2.8% | 9.6% |
| *Theodoro et al*[158] | 1996 | 25 | 0.0% | - | 4.0% |
| *Robbins et al*[160] | 1996 | 158 | 1.3% | 0.6% | 2.5% |
| *Mc Cully et al*[157] | 1996 | 65 | - | 1.5% | 1.5% |
| *Gol et al*[161] | 1997 | 69 | 10.1% | - | - |
| *Schonbeck et al*[162] | 1998 | 110 | 0.9% | - | 4.5% |
| *Merrill et al*[165] | 2000 | 22 | 0.0% | - | 0.0% |

| | | | | | |
|---|---|---|---|---|---|
| *Havndrup et al*[164] | 2000 | 11 | - | - | 0.0% |
| *Qin et al*[166] | 2001 | 26 | - | - | 7.7% |
| *Minami et al*[168] | 2002 | 125 | 1.6% | - | 7.2% |
| *Firoozi et al*[167] | 2002 | 24 | - | - | 4.2% |
| *Jiang et al*[170] | 2004 | 11 | - | 9.1% | - |
| *Minakata et al*[171] | 2005 | 13 | 7.7% | - | 7.7% |
| *Ommen et al*[175] | 2005 | 289 | 0.7% | - | 1.0% |
| *Woo et al*[174] | 2005 | 338 | 1.8% | - | 6.2% |
| *Minakata et al*[176] | 2005 | 56 | - | - | 1.8% |
| *Vural et al*[182] | 2007 | 24 | - | - | 0.0% |
| *Elbardissi et al*[183] | 2007 | 16 | - | - | 12.5% |
| *Nagueh et al*[180] | 2007 | 20 | - | - | 10.0% |
| *Smedira et al*[185] | 2008 | 323 | 0.6% | 0.6% | 6.8% |
| *Kwon et al*[189] | 2010 | 182 | - | 0.0% | 8.8% |
| *Schaff et al*[190] | 2010 | 44 | - | - | 0.0% |
| *Ball et al*[193] | 2011 | 287 | 1.4% | 1.0% | 6.3% |
| *Lisboa et al*[191] | 2011 | 34 | - | 5.9% | 2.9% |
| *Hickey et al*[195] | 2012 | 32 | - | 3.1% | - |
| *Iacovani et al*[86] | 2012 | 124 | - | - | 3.2% |
| *Schaff et al*[190] | 2012 | 749 | - | - | 3.6% |
| *Cambra et al*[199] | 2013 | 69 | 1.4% | 1.4% | 4.3% |
| *Wang et al*[201] | 2013 | 93 | - | - | 3.2% |

| | | | | | |
|---|---|---|---|---|---|
| *Altarabseh et al*[200] | 2013 | 127 | - | - | 0.8% |
| *Desai et al*[85] | 2013 | 699 | - | - | 6.9% |
| *Samardhi et al*[207] | 2014 | 23 | 0.0% | 4.3% | 13.0% |
| *Steggerda et al*[202] | 2014 | 102 | 1.0% | 2.0% | 8.8% |
| *Efthimiadus et al*[208] | 2014 | 32 | 3.1% | - | 3.1% |
| *Cho et al*[204] | 2014 | 52 | 3.8% | - | 3.8% |
| *Panaich et al*[210] | 2014 | 665 | - | 2.6% | - |
| *Kunkala et al*[206] | 2014 | 23 | - | - | 0.0% |
| *Sedehi et al*[205] | 2014 | 171 | - | - | 6.4% |
| *Parry et al*[211] | 2015 | 211 | 0.9% | 0.0% | 5.7% |
| ***Studies focusing on mitral valve Intervention*** | | | | | |
| *Krajcer et al*[142] | 1988 | 185 | - | 0.5% | 2.7% |
| *McIntosh et al*[145] | 1989 | 58 | - | - | 8.6% |
| *Delahaye et al*[152] | 1993 | 47 | 2.1% | 4.3% | - |
| *Schoendube et al*[155] | 1995 | 58 | - | 1.7% | 5.2% |
| *Van der Lee et al*[169] | 2003 | 29 | - | - | 0.0% |
| *Stassano et al*[172] | 2004 | 18 | - | - | 0.0% |
| *Minakata et al*[171] | 2004 | 56 | - | 3.6% | 5.4% |
| *Balaram et al*[178] | 2005 | 19 | - | - | 5.3% |
| *Swistel et al*[179] | 2006 | 42 | - | 0.0% | 4.8% |
| *Wan et al*[187] | 2009 | 32 | - | - | 3.1% |
| *Balaram et al*[194] | 2012 | 132 | 0.8% | 1.5% | 3.8% |

Table 2: Early complications. "-": Not reported in study.[128]

*4.1.2.5 Long-Term Follow-Up*

Forty-five articles (52.9%) documented long-term complications following surgery. Re-operation for LVOTO or heart transplantation was most frequent (43 articles (50.6%); *Table 3)*. Late PPM was reported in 10 studies (11.8%) with rates ranging from 0%-6.4%. On late follow-up only 7 studies (8.2%) reported on stroke (range: 1.1% - 8.6%). Seven studies (8.2%) reported heart failure related hospitalisations after surgery (range: 0% - 13.6%). One study reported 6 heart failure hospitalisations during follow-up in a cohort of 44 patients undergoing apical myectomy.[190]

| ***Author*** | **Year** | **Cohort** | **CVA** | **PPM** | **HF** | **Reintervention** | **Transplant** |
|---|---|---|---|---|---|---|---|
| *Morrow et al*[130] | 1975 | 83 | - | 2.4 % | - | - | - |
| *Jeffrey et al*[132] | 1981 | 20 | 5.0 % | - | - | 5.0% | - |
| *Beahrs et al*[133] | 1982 | 40 | - | 2.5 % | - | - | - |
| *Rothlin at al*[134] | 1983 | 63 | - | 4.8 % | - | 3.2% | - |
| *Schaffer et al*[137] | 1983 | 3 | - | - | - | 33.3% | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Mohr et al*[144] | 1989 | 115 | - | - | - | 0.0% | - |
| *Stone et al*[151] | 1993 | 17 | - | - | - | 11.8% | - |
| *Schulte et al*[153] | 1993 | 364 | - | - | - | 0.3% | - |
| *Ten Berg et al*[154] | 1994 | 38 | - | 2.6 % | - | 0.0% | - |
| *Heric et al*[156] | 1995 | 178 | - | - | - | 1.1% | - |
| *Theodoro et al*[158] | 1996 | 25 | - | - | - | 8.0% | 4.0% |
| *Mc Cully et al*[157] | 1996 | 65 | - | - | - | 3.1% | - |
| *Gol et al*[161] | 1997 | 69 | - | - | - | 0.0% | - |
| *Schonbeck et al*[162] | 1998 | 110 | - | 6.4 % | - | 5.5% | - |
| *Merrill et al*[165] | 2000 | 22 | - | - | - | 0.0% | 0.0% |
| *Havndrup et al*[164] | 2000 | 11 | - | - | - | 0.0% | - |
| *Minami et al*[168] | 2002 | 125 | - | - | - | 2.4% | - |
| *Minakata et al*[176] | 2005 | 13 | - | - | - | 7.7% | - |
| *Ommen et al*[175] | 2005 | 289 | - | - | - | - | - |
| *Woo et al*[174] | 2005 | 338 | 5.9 % | - | 13.0 % | 3.3% | 1.5% |
| *Minakata et al*[177] | 2005 | 56 | - | - | - | 12.5% | 3.6% |
| *Smedira et al*[185] | 2008 | 323 | - | 5.9 % | - | 3.1% | - |
| *Kwon et al*[189] | 2010 | 182 | - | - | - | 0% | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Schaff et al*[190] | 2010 | 44 | 6.8 % | 4.5 % | 13.6 % | 2.3% | 2.3% |
| *Ball et al*[193] | 2011 | 287 | - | - | - | - | 1.0% |
| *Lisboa et al*[191] | 2011 | 34 | - | 2.9 % | - | 2.9% | - |
| *Hickey et al*[195] | 2012 | 32 | - | - | - | 6.3% | - |
| *Iacovani et al*[86] | 2012 | 124 | - | 0.8 % | - | 0.8% | - |
| *Altarabseh et al*[200] | 2013 | 127 | - | - | - | 6.3% | - |
| *Desai et al*[85] | 2013 | 699 | 1.9 % | - | 4.1% | 3.4% | 0.1% |
| *Kunkala et al*[198] | 2013 | 56 | - | - | 1.8% | 0.0% | - |
| *Samardhi et al*[207] | 2014 | 23 | - | - | - | - | - |
| *Steggerda et al*[202] | 2014 | 102 | 4.9 % | - | 5.9% | 1.0% | - |
| *Kunkala et al*[206] | 2014 | 23 | - | 0.0 % | - | - | - |
| *Parry et al*[211] | 2015 | 211 | - | - | - | 0.0% | - |
| ***Studies focusing on mitral valve Intervention*** | | | | | | | |
| *Leachman et al*[141] | 1987 | 54 | - | - | - | 7.4% | - |
| *Krajcer et al*[142] | 1988 | 185 | 1.1 % | - | - | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *McIntosh et al*[145] | 1989 | 58 | 8.6 % | - | - | 5.2% | - |
| *Delahaye et al*[152] | 1993 | 47 | 2.1 % | - | - | 2.1% | - |
| *Stassano et al*[172] | 2004 | 18 | 11.1 % | - | - | 38.9% | - |
| *Minakata et al*[171] | 2004 | 56 | - | - | - | 1.8% | - |
| *Balaram et al*[178] | 2005 | 19 | - | - | 0.0% | 0.0% | - |
| *Swistel et al*[179] | 2006 | 42 | - | - | 0.0% | 0.0% | - |
| *Kaple et al*[186] | 2008 | 115 | - | - | - | 5.2% | - |
| *Vriesendorp et al*[212] | 2015 | 139 | - | - | - | 2.9% | 1.4% |

Table 3: Long term outcomes. "-": Not reported in study.[128]

### *4.1.3 Meta-analysis*

Thirty-five studies were included in the meta-analysis as illustrated in *Figure 13* above.

#### *4.1.3.1 Early Mortality*

The overall incidence of early perioperative mortality in septal myectomy studies, without MV intervention, was 2.7% (CI 0.7, 9.6) $I^2$ 58.7%, $p<0.05$ *(Figure 14).* There was a decline in perioperative mortality over time with an incidence of 5.2% (CI 3.4, 7.8) $I^2$ 42.9%, $p=0.06$ in studies prior to 2000 and

1.4% (CI 0.8, 2.4) $I^2$ 9.0%, p=0.36 in contemporary studies since 2000 (between groups p<0.05).

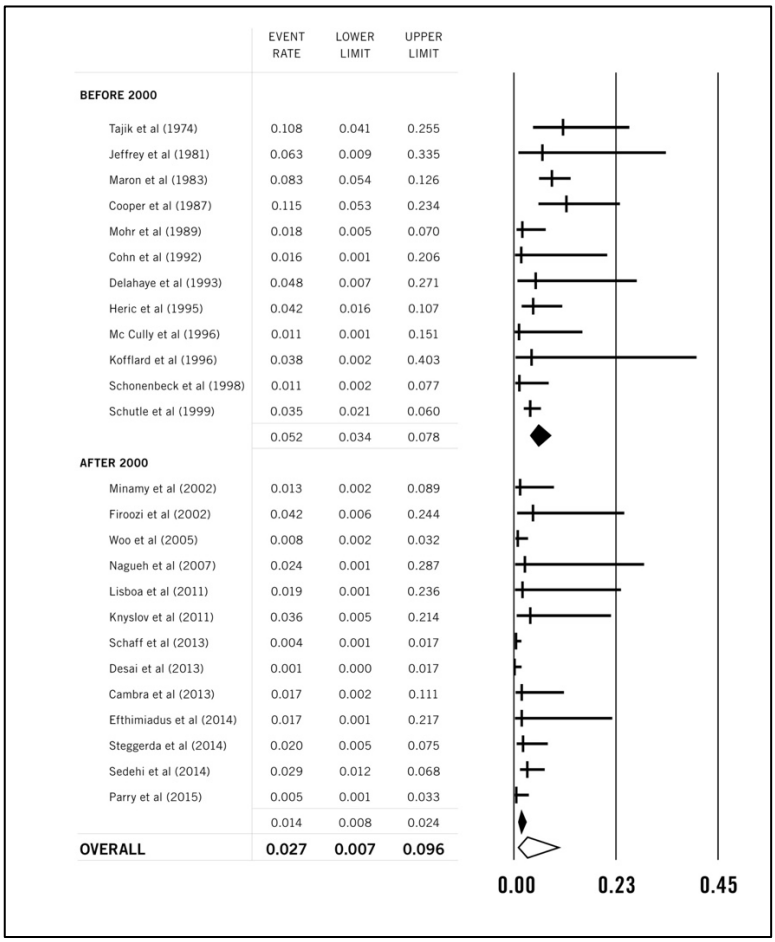


Figure 14: Meta-analysis of incidence of early perioperative mortality over time in septal myectomy studies.[128]

The incidence of early perioperative mortality in patients undergoing MV intervention, as seen in *Figure 15*, was 1.4% (CI 0.5, 3.7) $I^2$ 0%, p=0.70 in studies reporting outcomes in septal myectomy with MV repair, 7.3% (CI 2.4, 20.3) $I^2$ 0%, p=0.73 in studies reporting outcomes in septal myectomy and MV replacement and 7.9% (CI4.3, 14.1) $I^2$ 0%, p=0.93 in studies reporting

outcomes in MV replacement alone (between groups p<0.05). Studies including MV replacement, however, were older compared to those focusing on MV repair *(Figure 15).*

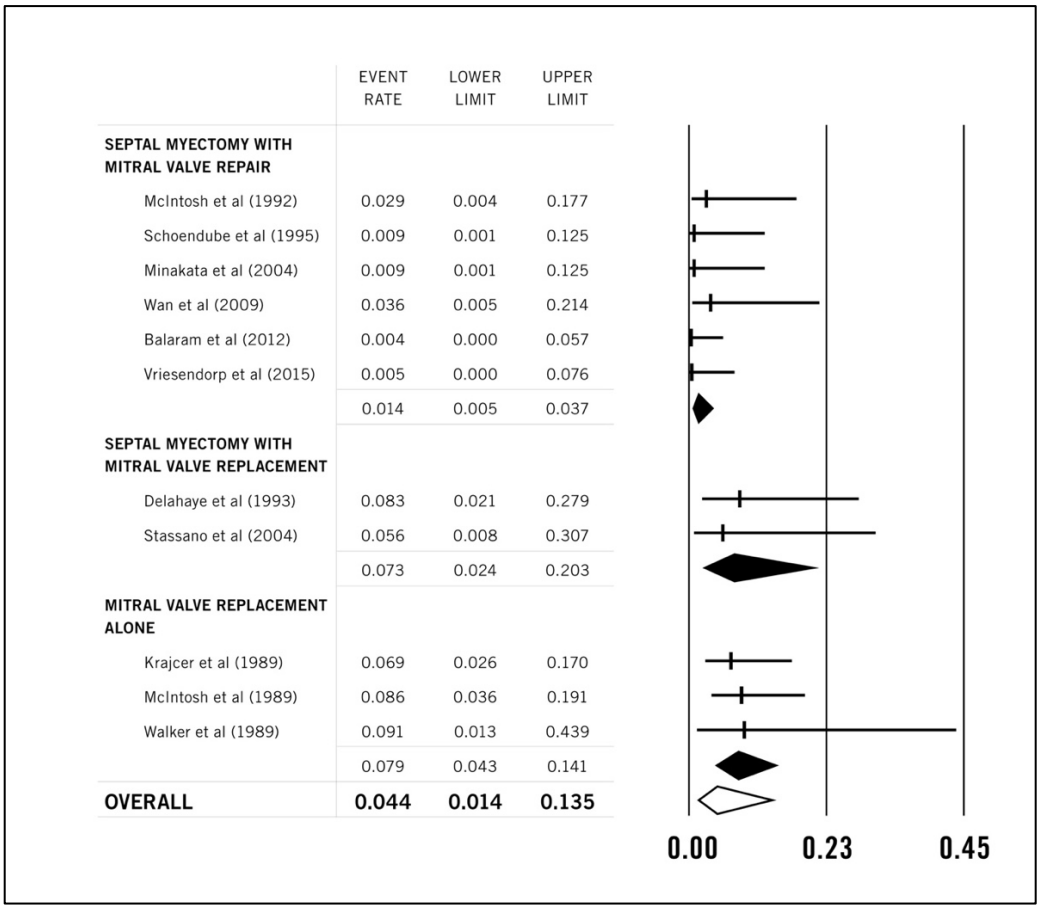


Figure 15: Meta-analysis of incidence of early perioperative mortality in MV intervention studies.[128]

*4.1.3.2 Late Mortality*

The overall annual incidence rate (IR) of late mortality (>30days) following septal myectomy surgery was 1.3% (CI 0.1, 2.5), $I^2$ 75.6%, p<0.05 (*Figure 16)*. There was a similar temporal decline in late mortality: IR prior to 2000

was 2.0% (CI 1.2, 2.8) $I^2$ 2.5% p=0.38 and after 2000 was 0.7% (CI 0.3, 1.2) $I^2$ 70.7%, p<0.05 (between groups p<0.05).

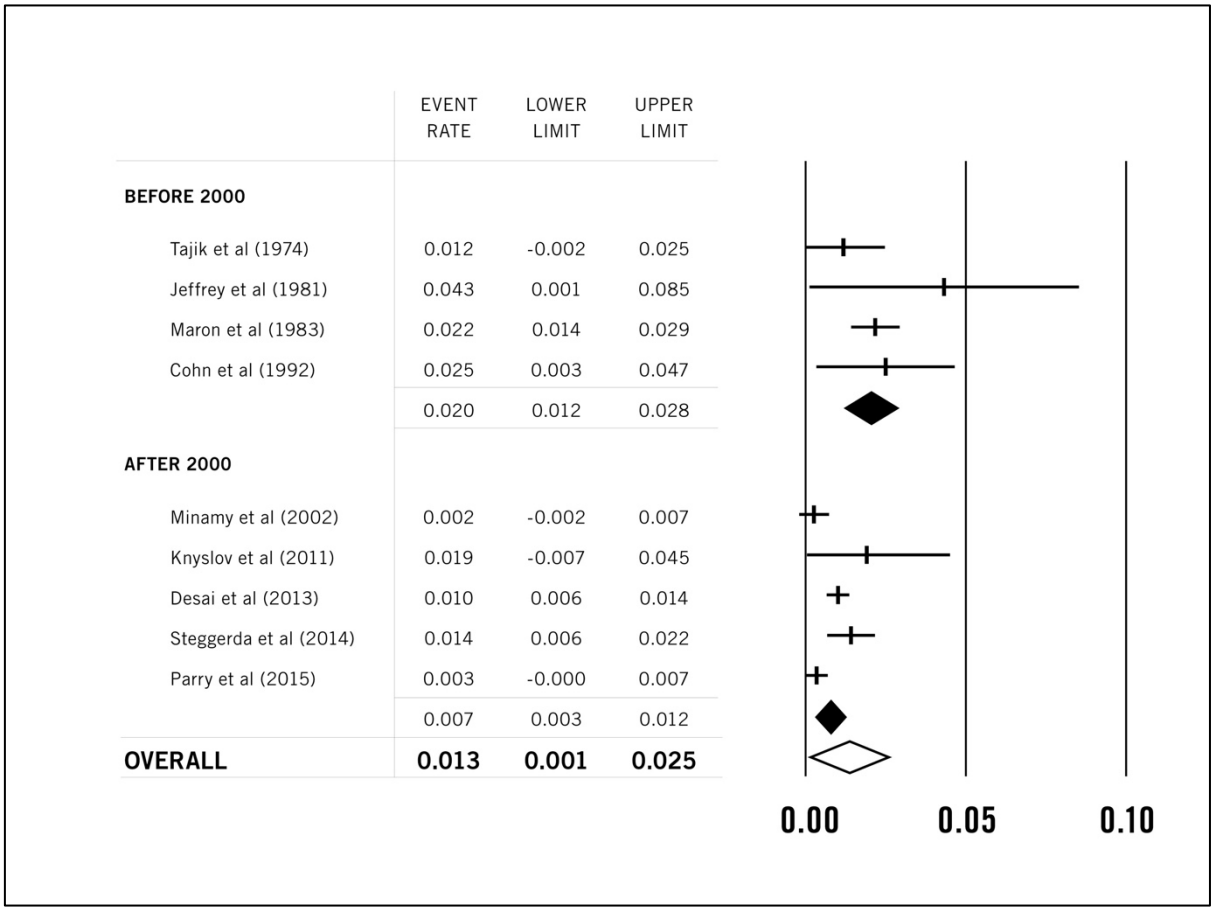


Figure 16: Meta-analysis of annual IR of late mortality (>30 days) over time in septal myectomy studies.[128]

As seen in *Figure 17* the overall annual IR of late mortality (>30days) in those undergoing MV intervention, was 1.1% (CI 0.5, 1.7) $I^2$ 51.3%, p<0.05. The annual IR of late mortality in studies reporting outcomes in septal myectomy with MV repair was 1.1% (CI 0.3, 1.8) $I^2$ 59.2%, p<0.05, in studies reporting outcomes in septal myectomy and MV replacement was 0.8% (CI -

0.8, 2.3) $I^2$ 0%, p=1.00 and in studies reporting outcomes in MV replacement alone was 1.5% (CI 0.3, 2.8) $I^2$ 40.7%, p=0.19 (between groups p=0.73).

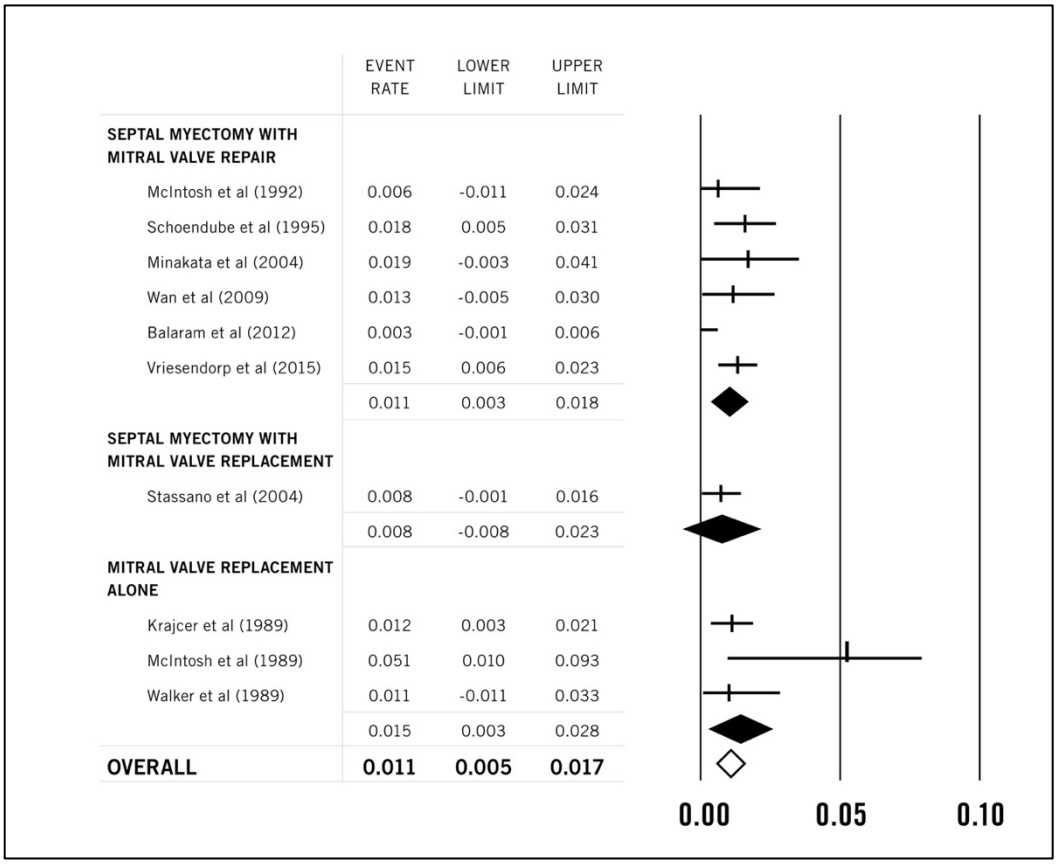


Figure 17: Meta-analysis of annual IR of late mortality (>30 days) in MV intervention studies.[128]

*4.1.3.3 Morbidity*

*4.1.3.3.1 Early Morbidity*

The overall incidence of a VSD was 2.2% (CI 0.9, 5.7) $I^2$ 48.6%, p<0.05. Contemporary studies since 2000, showed a decline in the incidence of VSD

to 1.4% (0.8, 2.3) $I^2$ 0%, p<0.05. The overall incidence of perioperative CVA was 2.1% (CI 1.5, 3.1) $I^2$ 1.0%, p=0.44. The overall prevalence of perioperative PPM insertion was 5.0% (CI 4.0, 6.2) $I^2$ 25.69%, p=0.09 which did not differ significantly overtime in comparing contemporary to earlier studies (p=0.22).

#### *4.1.3.3.2 Late Morbidity*

The overall incidence of reintervention was 2.8% (CI 1.8, 4.3) $I^2$ 60.6% p<0.05 with an annual IR of reintervention of 0.3% (CI 0.2, 0.4) $I^2$ 52.5%, p<0.05.

## *4.2 Evaluation of long-term clinical outcomes following surgery*

### *Long-Term Outcomes for Different Surgical Strategies to Treat Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy*

#### *4.2.1 Patient Characteristics*

347 patients (217 males) undergoing surgery between 1988 and 2015 were included in the study. The median age at diagnosis of HCM was 39.7 ± 17.6 years and age at time of surgery was 47.0 ± 16.7 years. Prior to surgery, 23 patients had undergone dual chamber pacemaker insertion to treat LVOTO

and 15 had undergone alcohol septal ablation with no improvement in symptoms.

Patients were divided into groups based on their surgical intervention: Group A (n=272) septal myectomy alone; group B (n=33) septal myectomy with MV repair; group C (n=22) septal myectomy with MV replacement; and group D (n=20) MV replacement alone. Mitral valve repair procedures included intervention on papillary or chordal attachments, valve leaflet plication, Alfieri and cleft repair of the MV leaflets. The characteristics of each surgical group are summarised in *Table 4*.

| | **Total** | **Group A** | **Group B** | **Group C** | **Group D** | **P (ANOVA between groups)** |
|---|---|---|---|---|---|---|
| *N* | 347 | 272 (78.4%) | 33 (9.5%) | 22 (6.3%) | 20 (5.8%) | |
| ***Demographics*** | | | | | | |
| *Male* | 217 (62.5%) | 171 (62.9%) | 23 (69.7%) | 13 (59.1%) | 10 (50%) | 0.533 |
| *Age at Diagnosis (years)* | 39.7+/- 17.6 | 38.0+/- 17.4 | 42.3+/- 16.1 | 49.4+/- 17.0 | 51.5+/- 17.7 | <0.05* |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Age at Surgery (years)* | 47.0+/- 16.7 | 44.9+/- 16.0 | 48.6+/- 16.8 | 55.8+/- 15.1 | 62.4+/- 16.1 | <0.05* ^ |
| *BMI (units)* | 28.6+/- 5.1 | 28.8+/- 5.4 | 27.1+/- 3.2 | 29.5+/- 4.7 | 26.9+/- 4.1 | 0.167 |
| ***Past Medical History*** | | | | | | |
| *Prior history of AF* | 44 (12.7%) | 27 (9.9%) | 6 (18.2%) | 4 (18.2%) | 7 (35.0%) | <0.05* |
| *History of any VT* | 16 (4.6%) | 13 (4.8%) | 2 (6.1%) | 0 (0%) | 1 (5.0%) | 0.754 |
| *History of VF* | 4 (1.2%) | 3 (1.1%) | 1 (3.0%) | 0 (0%) | 0 (0%) | 0.664 |
| *Hypertension* | 83 (23.9%) | 60 (22.1%) | 7 (21.2%) | 10 (45.5%) | 6 (30.0%) | 0.342 |
| *Diabetes Mellitus* | 12 (3.5%) | 9 (3.3%) | 1 (3.0%) | 1 (4.5%) | 1 (5.0%) | 0.091 |
| *TIA/Stroke* | 7 (2.0%) | 5 (1.8%) | 1 (3.0%) | 0 (0%) | 1 (5.0%) | 0.667 |
| *Coronary Artery Disease* | 12 (3.5%) | 10 (3.7%) | 1 (3.1%) | 1 (4.5%) | 0 (0%) | 0.781 |
| *Peripheral Vascular Disease* | 1 (0.3%) | 1 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.094 |
| *PPM* | 29 (8.4) | 20 (7.4%) | 2 (6.1%) | 3 (13.6%) | 4 (20.0%) | 0.181 |
| *ICD* | 44 (12.7%) | 38 (14.0%) | 3 (9.1%) | 2 (9.1%) | 1 (5.0%) | 0.552 |
| ***Family History*** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *HCM* | 103 (29.7%) | 86 (31.6%) | 10 (30.3%) | 4 (18.2%) | 3 (15.0%) | 0.108 |
| *SCD* | 63 (18.2%) | 51 (18.8%) | 7 (21.2%) | 4 (18.2%) | 1 (5.0%) | 0.166 |
| *HCM with SCD* | 31 (8.9%) | 26 (9.6%) | 4 (18.2%) | 2 (9.1%) | 1 (5.0%) | 0.654 |

Table 4: Demographic of surgical population.[213] * Post hoc analysis reveals statistical difference between groups A and D. ^ Post hoc analysis reveals statistical difference between Group A and C and Group B and D.

Patients in group D were older at diagnosis and at the time of surgery (62.4 in group D vs 44.9-48.6 in groups A, B and C). Patients in group D had higher prevalence of AF (35%) and hypertension (30%) at baseline compared to other groups. The mean left ventricular wall thickness prior to surgery was smallest in group D, with 11 of 20 patients having a maximum left ventricular wall thickness less than 17.0 mm. Mitral regurgitation was more severe in those undergoing a MV procedure, particularly in those requiring a MV replacement (*Table 5*). All patients in group D had a planned MV replacement. In group C, 13 of the MV replacements were unplanned and were carried out at the time of intervention due to persistence of MR despite septal myectomy and/or MV repair.

### *4.2.2 Perioperative Course for Each Surgical Subgroup*

There were 5 perioperative deaths (3 in Group A, 1 in Group B, 0 in Group C and 1 in Group D). The mean by-pass time was 93.3+/-47.2mins overall and 81.9+/-41.1mins, 121.8+/-35.0mins, 157.1+/-21.6mins, 124.3+/-37.5mins respectively in Groups A to D. 121 concomitant procedures were carried out including 18 coronary artery bypass grafts, 10 aortic valve replacements, 11 maze procedures (9 radiofrequency pulmonary vein isolation), 55 left atrial appendage removal and 21 other minor procedures. The mean length of hospital stay was 11.3 days (9.5, 11.7, 17.2, 18.8 days respectively for groups A to D).

Perioperative complications are documented in *Table 5*.

| | **Total** | **Group A** | **Group B** | **Group C** | **Group D** |
|---|---|---|---|---|---|
| *Death* | 5 (1.4%) | 3 (1.1%) | 1 (3.0%) | 0 (0%) | 1 (5.0%) |
| | | | | | |
| *VSD* | 4 (1.2%) | 4 (1.5%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *LV Rupture* | 1 (0.3%) | 1 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | | | | | |
| *Unplanned AV Surgery* | 2 (0.6%) | 2 (0.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | | | | | |
| *Postop AF* | 84 (24.2%) | 56 (20.6%) | 9 (27.3%) | 9 (40.9%) | 10 (50.0%) |
| *New Postop AF* | 56 (16.1%) | 42 (15.4%) | 5 (15.2%) | 5 (22.7%) | 4 (20.0%) |
| | | | | | |
| *TIA* | 5 (1.4%) | 4 (1.5%) | 0 (0%) | 1 (4.5%) | 0 (0%) |
| *Stroke* | 8 (2.3%) | 6 (2.2%) | 0 (0%) | 0 (0%) | 2 (10.0%) |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| *PPM* | 24 (6.9%) | 21 (7.7%) | 2 (6.1%) | 0 (0%) | 1 (5.0%) |
| *ICD* | 10 (2.9%) | 8 (2.9%) | 1 (3.0%) | 1 (4.5%) | 0 (0%) |

Table 5: Perioperative complications.[213]

There were 4 VSD's requiring repair, all of which were in Group A with maximum left ventricular wall thickness of 15mm, 16mm, 18mm, 21mm respectively. There was 1 left ventricular rupture of the lateral wall which was repaired successfully at the time of septal myectomy. There were 2 unplanned aortic valve repairs due to aortic valve injury during surgery. All remaining aortic valve procedures were carried out for pre-existing aortic regurgitation.

There were 8 perioperative strokes and 5 TIA's. Of these 13 cases, 4 had previously documented AF and 4 had new onset AF. Five patients had no documented AF. One patient had an air embolus and one patient had a deep vein thrombosis with an associated patent foramen ovale and paradoxical embolism. Pre-operatively the mean left atrial diameter in patients who suffered a perioperative CVA was 50.5+/-13.7mm with a mean left atrial area of 41.5+/-19.1cm$^2$.

Twenty-four patients required a perioperative PPM insertion for high grade atrioventricular heart block. Nine patients had an ICD inserted for primary prevention in the perioperative period and 1 patient for secondary prevention

of aborted SCD following an in hospital cardiac arrest with successful defibrillation.

### *4.2.3 Symptoms Following Surgery*

In the cohort as a whole, 95.1% of patients described symptoms of dyspnoea preoperatively. NYHA functional class improved from a mean of 2.5+/-0.6 to 1.6+/-0.6 at one year. Overall, 75% of patients in the entire cohort described an improvement in symptoms with an improvement in NYHA class of at least one class. The change in NYHA class varied between the surgical subgroups (*Figure 18*) with the greatest change in group B (mean 1.2+/-0.7) followed by Group A (0.9+/-0.7), Group C (0.8+/-0.7) and Group D (0.4+/-0.7), p=0.08). In Group D, NYHA class remained unimproved at 1 year in 62.0% of patients compared to 27.5% in Group A. Clinical response, ≥1 NYHA class was compared to those who did not improve postoperatively as illustrated in *Figure 18*.

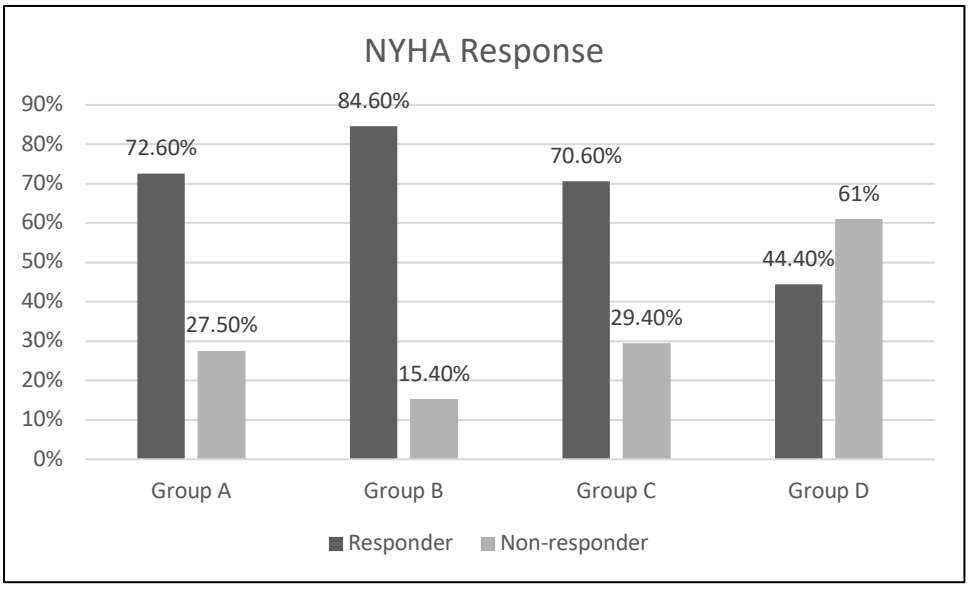

Figure 18: Changes in NYHA class pre and postoperatively at 1 year.[213]

Symptoms other than dyspnoea are described in *Table 6*.

| | Group A | Group B | Group C | Group D |
|---|---|---|---|---|
| ***Chest Pain*** | | | | |
| *Preop* | 49.10% | 42.40% | 34.80% | 25% |
| *Postop* | 8.50% | 0% | 8.70% | 0% |
| | | | | |
| ***Palpitations*** | | | | |
| *Preop* | 36.40% | 27.30% | 21.70% | 25% |
| *Postop* | 16.30% | 9.10% | 4.30% | 5% |
| | | | | |
| ***Presyncope*** | | | | |
| *Preop* | 32.90% | 36.40% | 21.70% | 20% |
| *Postop* | 7.40% | 9.10% | 13% | 0% |
| | | | | |
| ***Syncope*** | | | | |
| *Preop* | 12.70% | 6.00% | 21.70% | 15.00% |
| *Postop* | 2.20% | 3% | 4.30% | 0% |

Table 6: Pre and postoperative symptoms.[213]

Preoperatively 162 patients (46.2%) described symptoms of exertional chest pain; 114 patients (32.8%) and 46 patients (13.3%) described symptoms of presyncope and syncope, respectively; and with 122 patients (35.2%) complained of palpitations. On follow-up at one year, 50 patients (14.4%) described exertional chest pain; 27 patients (7.8%) had symptoms of presyncope and 8 (2.3%) patients had further episodes of syncope; 51 patients (14.7%) described symptoms of palpitations.

### *4.2.4 Changes in Echocardiographic Parameters at 1 Year*

The mean resting LVOT gradient improved from 71.9+/-39.6mmHg preoperatively to 13.4+/-18.5mmHg postoperatively ($p<0.05$). This gradient improved significantly in all groups. There was a similar reduction in maximum left ventricular wall thickness in all groups except Group D with a significant difference on analysis between groups ($p<0.05$). This was similar for septal wall thickness. Left ventricular end diastolic diameter increased in group A and B but was seen to reduce in in those undergoing MV replacement in group C and D. Ejection fraction reduced in those undergoing myectomy and increased in group D. Changes in echocardiographic variables are documented in *Table 7.*

| | Group A | | | P | Group B | | | P | Group C | | | P | Group D | | | P | P (ANOVA between grp) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Preop | Postop | Diff. | | Preop | Postop | Diff. | | Preop | Postop | Diff. | | Preop | Postop | Diff. | | |
| *MWT* | 21.0+/-4.8 | 16.8+/-4.6 | -4.1+/-4.7 | <0.05 | 19.8+/-4.4 | 16.6+/-3.5 | -2.7+/-4 | <0.05 | 19.2+/-3.6 | 16.4+/-3.6 | -4.7+/-3.9 | <0.05 | 17.7+/-3.4 | 16.7+/-4.5 | -1.1+/-3.4 | 0.26 | <0.05* |
| *IVS* | 19.7+/-4.7 | 14.3+/-4.3 | -5.3+/-5 | <0.05 | 18.9+/-4.5 | 14.2+/-3.7 | -4.1+/-4.5 | <0.05 | 18.2+/-3.3 | 15.2+/-3.9 | -4.3+/-3.6 | <0.05 | 16.9+/-3.6 | 16.6+/-4.4 | -0.5+/-3.7 | 0.66 | <0.05* |
| *PWT* | 11.1+/-2.8 | 10.3+/-2.4 | -0.7+/-2.9 | <0.05 | 10.6+/-2.4 | 9.8+/-1.3 | -0.7+/-2.4 | 0.16 | 11.0+/-3.1 | 10.6+/-1.9 | -0.7+/-3.5 | 0.49 | 11.1+/-2 | 12.1+/-3 | 1.5+/-3 | 0.14 | 0.1 |
| *LAD* | 46.9+/-7.8 | 45.9+/-7.4 | -1.1+/-6.2 | <0.05 | 48.0+/-7.9 | 46.1+/-7.6 | -2.3+/-6.5 | 0.09 | 49.1+/-8.4 | 48.0+/-9.4 | -1.6+/-6.1 | 0.47 | 50.5+/-9.5 | 51.9+/-7.5 | 0.8+/-9.3 | 0.76 | 0.6 |
| *LAA* | 30.4+/-8 | 26.9+/-7.2 | -2.5+/-7.7 | <0.05 | 29.4+/-7.6 | 28.6+/-8.6 | -2.9+/-4.9 | 0.07 | 32.3+/-6.2 | 28.9+/-5.9 | -3.6+/-5.3 | <0.05 | 35.8+/-11 | 30.2+/-10.1 | -3.4+/-6.1 | 0.13 | 1.0 |
| *LVEDd* | 44.6+/-6.4 | 47.9+/-6.7 | 3.4+/-6.6 | <0.05 | 45.8+/-5.3 | 47.0+/-5.2 | 0.9+/-6.1 | 0.45 | 46.8+/-5.9 | 45.8+/-6.4 | -0.6+/-4.5 | 0.55 | 48.7+/-6.9 | 42.2+/-6.9 | -3.5+/-3.5 | <0.05 | <0.05* |
| *EF* | 69.1+/-7.4 | 61.9+/-7.6 | -7.0+/-9.3 | <0.05 | 69.4+/-8.5 | 63.8+/-8.4 | -4.4+/-11.6 | 0.14 | 67.8+/-8.4 | 57.2+/-8 | -11.4+/-10.6 | <0.05 | 65.1+/-9 | 64.5+/-11 | 2.6+/-7.5 | 0.4 | <0.05^ |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Resting LVOT Grad* | 73.8+/- 39.6 | 14.2+/- 20 | - 61.0+/- 39 | <0.05 | 68.2+/- 34 | 15.8+/- 15.4 | -56.1+/- 31.5 | <0.05 | 62.9+/- 38.8 | 5.7+/- 4.3 | -53.2+/- 33.2 | <0.05 | 71.8+/- 45.6 | 8.9+/- 10.3 | -52.6+/- 47.4 | <0.05 | 0.7 |
| *MR* | 2.2+/- 0.9 | 1.5+/- 0.7 | -0.8 | | 2.9+/- 0.7 | 1.6+/-1 | -1.2 | | 2.8+/- 0.8 | 0.9+/- 0.7 | -1.9 | | 3.2+/- 0.8 | 0.2+/- 0.4 | -3.0 | | - |
| *AR* | 0.5+/- 0.7 | 0.9+/- 0.9 | -0.2 | | 0.5+/- 0.8 | 1.0+/- 0.9 | -0.3 | | 1.1+/-1 | 1.1+/- 0.9 | 0.1 | | 1.1+/- 0.9 | 0.9+/- 0.9 | 0.2 | | - |

Table 7: Echocardiographic parameters pre and post operatively with difference at 1 year. * Post hoc analysis reveals statistical difference between groups A and D. ^ Post hoc analysis reveals statistical difference between Group C and D.[213]

*4.2.5 Changes in Functional Status Using Cardiopulmonary Exercise Testing*

There was no change in per cent predicted or absolute peak $VO_2$ following surgery. There was an improvement in percent predicted target heart 0.70 to 0.74 ($p<0.05$) and in systolic blood pressure response to exercise (32.4mmHg to 38.7mmHg ($p<0.05$)). Although full CPET data was not available in those undergoing a MV replacement there appeared to be a poorer response in both groups C and D which show a reduction in predicted VO2, target heart rate and systolic blood pressure response postoperatively (*Table 8)*.

| | **Group A (n=123)** | **Group B (n=7)** | **Group C (n=3)** | **Group D (n=1)** |
|---|---|---|---|---|
| ***Absolute VO2 (mL/min/Kg)*** | | | | |
| *Preoperative* | 18.4+/-67.8 | 19.3+/-8.3 | 12.1+/-4.0 | 13.0 |
| *Postoperative* | 18.0+/-6.4 | 21.0+/-7.4 | 14.3+/-2.8 | 16.3 |
| | p=0.43 | p=0.36 | p=0.08 | |
| ***Target HR (%)*** | | | | |
| *Preoperative* | 70.3% | 79.8% | 61.1% | 77.6% |
| *Postoperative* | 74% | 71.3% | 71.6% | 52.3% |
| | p<0.05 | P=0.06 | p=0.30 | |
| ***SBP Response (mmHg)*** | | | | |
| *Preoperative* | 32.0 | 33.6 | 30.0 | 20.0 |
| *Postoperative* | 40.4 | 42.1 | 20.0 | 5.00 |
| | p<0.05 | p=0.33 | p=0.23 | |

Table 8: Changes in cardiopulmonary exercise testing at one year.[213]

*4.2.6 Long Term Outcomes*

Median follow-up was 5.2 years (IQR 1.9 – 7.9 years). 191 patients continue to be followed up at St. Bartholomew's Hospital and 122 patients are followed by local physicians. 9 patients were lost to follow-up.

*4.2.6.1 Mortality*

Excluding perioperative deaths, there were 20 deaths during follow-up (15 in Group A, 2 in Group B, 2 in Group C, and 1 in Group D). There were 5 cardiovascular deaths, 1 from SCD, 3 from heart failure and 1 from a stroke. There were 7 non-cardiac deaths and 8 who died of unknown causes.

Estimated survival rates *(Figure 19)* for all-cause mortality post-operatively at 1, 5 and 10 years respectively were 98.4%, 96.9%, 91.9% in group A; 97.0%, 92.4%, 61.6% in group B; 100.0%, 100.0%, 55.6% in group C; and 94.7%, 85.3%, 85.3% in group D ($p<0.05$). Estimated survival rates including appropriate ICD shock therapy at 1, 5 and 10 years were 98.4%, 96.9%, 91.1% in group A; 97.0%, 92.4%, 61.6% in group B; 100.0%, 100.0%, 55.6% in group C; and 94.7%, 85.3%, 85.3% in the group D ($p<0.05$).

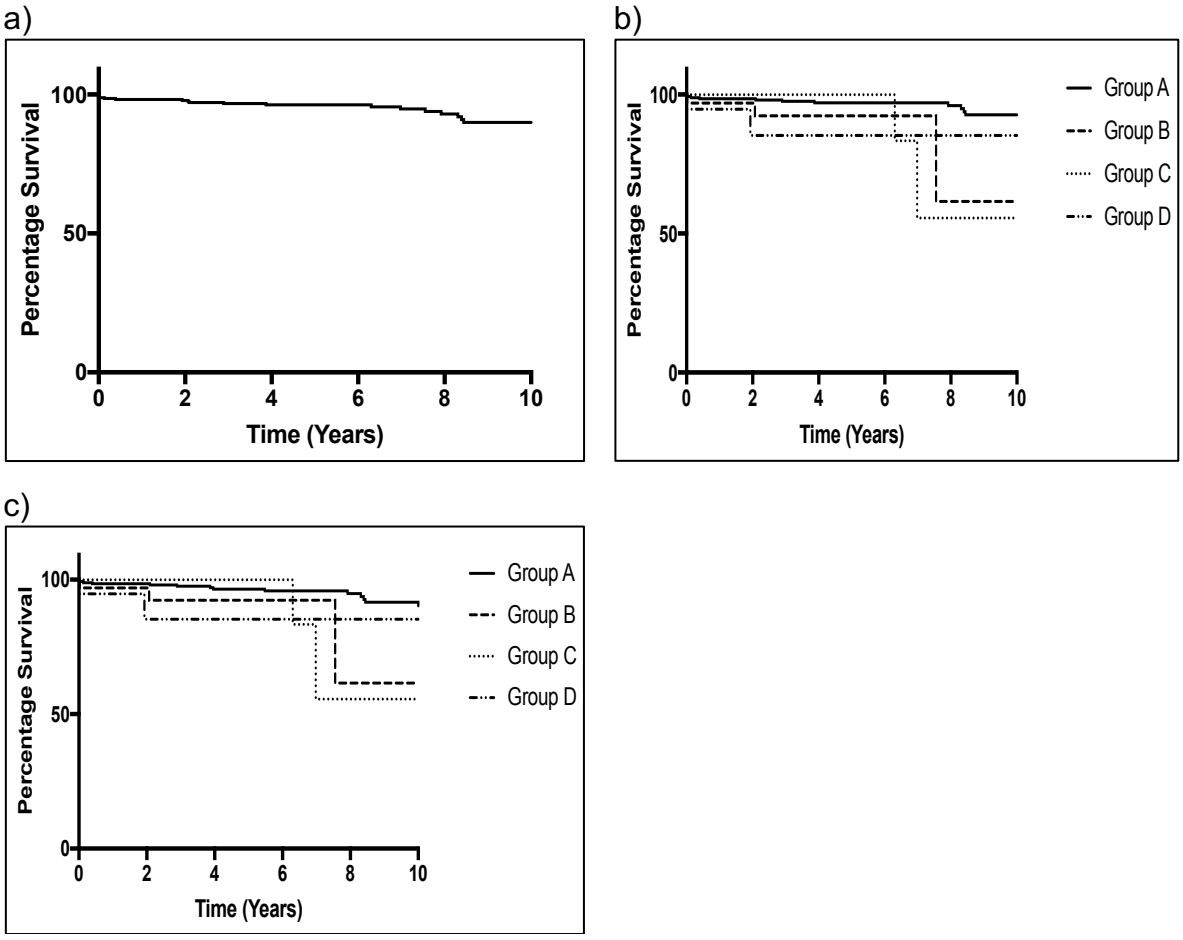


Figure 19: Kaplan- Meier curves for survival analysis in the surgical groups at 10 year follow-up. (a): K-M Overall survival analysis; (b): K-M survival analysis by groups; (c):K-M analysis for appropriate ICD shock or death.[213]

*4.2.6.2 Morbidity*

At follow-up, 72 patients (20.7%) had documented paroxysmal AF and 31 patients (8.9%) persistent AF. There were 4 TIAs and 4 strokes, three of which were

presumed cardioembolic as seen in *Table 9*. The mean left atrial diameter was 51.5+/-8.0mm postoperatively in this subgroup.

| | Total | Group A | Group B | Group C | Group D |
|---|---|---|---|---|---|
| | | | | | |
| *Paroxysmal AF* | 72 (20.7%) | 51 (18.8%) | 9 (27.3%) | 4 (18.2%) | 8 (40.0%) |
| *Persistent AF* | 31 (8.9%) | 22 (8.1%) | 2 (6.1%) | 3 (13.6%) | 4 (20.0%) |
| | | | | | |
| *Postop TIA* | 4 (1.2%) | 1 (0.4%) | 1 (3.0%) | 2 (9.1%) | 0 (0%) |
| *Postop Stroke* | 4 (1.2%) | 3 (1.1%) | 0 (0%) | 0 (0%) | 1 (5.0%) |
| | | | | | |
| *Late PPM* | 9 (2.6%) | 6 (2.2%) | 0 (0%) | 2 (9.1%) | 1 (5.0%) |
| *Late ICD* | 45 (13.0%) | 40 (14.7%) | 3 (9.1%) | 2 (9.1%) | 0 (0%) |
| *Late CRT* | 19 (5.5%) | 18 (6.6%) | 1 (3.0%) | 0 (0%) | 0 (0%) |
| | | | | | |
| *Heart Failure Admission* | 11 (3.2%) | 8 (2.9%) | 1 (3.0%) | 2 (9.1%) | 0 (0%) |
| | | | | | |
| *Reintervention* | 16 (4.6%) | 14 (4.9%) | 2 (6.3%) | 1 (4.5%) | 1 (5.0%) |
| *Redo Myectomy* | 7 (2.0%) | 6 (2.2%) | 0 (0%) | 0 (0%) | 1 (5.0%) |
| *Redo MVR* | 8 (2.3%) | 5 (1.8%) | 2 (6.1%) | 1 (4.5%) | 0 (0%) |
| *Redo MV Repair* | 1 (0.3%) | 1 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *Redo AVR* | 3 (0.9%) | 3 (1.1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | | | | | |
| *Transplant* | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| *Death* | 20 (5.8%) | 15 (5.5%) | 2 (6.1%) | 2 (9.1%) | 1 (5.0%) |

Table 9: Long-term outcomes following surgical intervention.[213]

Nine patients (2.6%) received a PPM and 45 patients (13.0%) an ICD. All ICDs were inserted for primary prophylaxis purposes on late follow-up. Nine of these 45 patients undergoing ICD insertion had CRT-D devices. There were 10 CRT-P devices inserted on follow-up. In total 99 patients had an ICD in situ postoperatively which was either inserted before or after the operation; there were 3 appropriate ICD shocks for VT/VF and 5 inappropriate shocks during the follow-up period.

The median time to first heart failure hospitalisation was 5.2 years (IQR 0.9 -6.4 years). Sixteen patients underwent a second surgical procedure with a median time to reintervention of 3.0 years (IQR 0.3 – 5 years): 7 re-do myectomies, 8 MV replacements, 1 MV repair and 3 aortic valve replacements.

### *4.2.7 Predictors of Clinical Outcomes Following Septal Myectomy Surgery*

#### *4.2.7.1 Baseline Demographics and Frequency Statistics*

272 patients (171 males) undergoing a septal myectomy alone without the use of concomitant MV intervention for the management of LVOTO in HCM between 1988 and 2015 were evaluated for predictors of clinical outcomes. The median age at time of surgery was 44.9 ± 16.0 years. The baseline demographics and echocardiography parameters are shown in *Table 10*. Median follow-up was 5.8 years (IQR 2.2 – 8.9).

| | N=272 |
|---|---|
| ***Demographics*** | |
| *Male* | 171 (62.9%) |
| *Age at Surgery (years)* | 44.9+/-16.0 |
| *BMI (units)* | 28.8+/-5.4 |
| ***Echocardiography*** | |
| *Max LV Wall Thickness (mm)* | 21.0+/-4.8 |
| *Left Atrial Diameter (mm)* | 46.9+/-7.8 |
| *LV End Diastolic Diameter (mm)* | 44.6+/-6.4 |
| *Ejection Fraction (%)* | 69.1+/-7.4 |
| *Resting LVOT Gradient (mmHg)* | 73.8+/-39.6 |

Table 10: Baseline demographics and echocardiography parameters.

*4.2.7.2 Univariate Regression Analysis*

Independent variables were first analysed using a univariate regression to evaluate independent predictors of outcome following surgery. The results of this univariate analysis are shown in *Table 11*.

| | P value | OR | Lower CI | Upper CI |
|---|---|---|---|---|
| ***Baseline Demographics*** | | | | |
| *Age at Surgery* | 0.12 | 0.96 | 0.93 | 0.99 |
| *Sex* | 0.59 | 13 | 0.49 | 3.5 |
| *BMI* | 0.19 | 0.93 | 0.82 | 1.04 |
| ***Echocardiography*** | | | | |

| | | | | |
|---|---|---|---|---|
| *Max LV Wall Thickness* | 0.91 | 1 | 0.9 | 1.13 |
| *Left Atrial Diameter* | 0.68 | 0.98 | 0.91 | 1.06 |
| *LV End Diastolic Diameter* | 0.08 | 0.93 | 0.86 | 1 |
| *Ejection Fraction* | 0.08 | 0.82 | 0.65 | 1.02 |
| *Resting LVOT Gradient* | 0.18 | 1 | 0.99 | 1.02 |

Table 11: Univariate regression analysis.

*4.2.7.3 Binomial Logistic Regression*

A binomial logistic regression analysis was then performed to evaluate the effects of independent variables on the elimination of LVOTO following surgery. The logistic regression model was not statistically significant; $\chi^2$ 8.12, p=0.42. The results of the logistic regression can be seen in *Table 12*.

| | **B** | **P value** | **Adjusted OR** | **Lower CI** | **Upper CI** |
|---|---|---|---|---|---|
| ***Baseline Demographics*** | | | | | |
| *Age at Surgery* | -0.04 | 0.65 | 0.96 | 0.8 | 1.15 |
| *Sex* | 0.88 | 0.68 | 2.41 | 0.04 | 158.06 |
| *BMI* | -0.32 | 0.90 | 0.97 | 0.59 | 1.59 |
| ***Echocardiography*** | | | | | |
| *Max LV Wall Thickness* | 0.89 | 0.28 | 2.43 | 0.49 | 12.14 |
| *Left Atrial Diameter* | 0.14 | 0.36 | 1.15 | 0.85 | 1.55 |
| *LV End Diastolic Diameter* | -0.19 | 0.33 | 0.83 | 0.57 | 1.21 |

| | | | | | |
|---|---|---|---|---|---|
| *Ejection Fraction* | -0.28 | 0.35 | 0.76 | 0.43 | 1.35 |
| *Resting LVOT Gradient* | 0.06 | 0.65 | 0.96 | 0.98 | 1.15 |

Table 12: Binomial logistic regression analysis.

### *4.3 Evaluation of clinical outcomes using individual surgical strategies*

Of the 203 patients in the study, baseline demographics are documented in *Table 13*.

| | **N (%)** |
|---|---|
| *Age at Surgery* | 48.6+/-14.6 |
| *Male* | 132 (65.0%) |
| ***Past Medical History*** | |
| *Atrial Fibrillation* | 28 (13.8%) |
| *Previous PPM* | 14 (6.9%) |
| *Previous PPM for LVOTO* | 9 (4.4%) |
| *Previous ASA* | 11 (5.4%) |
| *Stroke* | 3 (1.5%) |
| *Peripheral Vascular Disease* | 1 (0.5%) |
| *Diabetes Mellitus* | 9 (4.4%) |
| *Hypertension* | 58 (28.6%) |

Table 13: Baseline demographics.[214]

Eleven patients (5.4%) previously underwent ASA for the management of LVOTO with recurrence of symptoms.

#### *4.3.1 Surgery*

The mean cardiopulmonary bypass-time was 92.9+/-47.8 minutes with a mean length of hospital stay of 10.5+/-7.8 days. The mean weight of septal tissue removed, available in 87 patients (42.3%), weighed 6.6+/-4.3 grams. Surgical procedures are illustrated in *Table 14*.

| | **N (%)** |
|---|---|
| ***Septal Myectomy*** | 159 (78.3%) |
| ***Septal Myectomy with MV repair*** | 25 (12.3%) |
| *Plication* | 4 |
| *Edge-to-edge Alfieri repair* | 11 |
| *Cleft repair* | 3 |
| *Division of papillary muscles* | 1 |
| *Chordal repair* | 6 |
| ***Septal Myectomy with MVR*** | 9 (4.4%) |
| ***MVR alone*** | 10 (4.9%) |
| ***Concomitant Procedures (in 22 patients)*** | 27 |
| *CABG* | 4 (2.0%) |
| *Planned aortic valve replacement* | 3 (1.5%) |
| *MAZE* | 9 (4.4%) |
| *Resection of subaortic membrane* | 7 (3.4%) |
| *Closure of PFO* | 3 (1.5%) |
| *Closure of ASD* | 1 (0.5%) |

Table 14: Surgical procedures.[214]

One hundred and fifty-nine patients (78.3%) had a septal myectomy alone. Twenty-five patients (12.3%) had a septal myectomy with MV repair which included edge-to-edge (Alfieri) repair, valve plication, cleft repair, chordal repair and division of papillary muscle. Nine patients (4.4%) underwent a septal myectomy with MV replacement. In six of these nine patients concomitant MV replacements were unplanned following unsuccessful repair, the remainder were planned replacements. Ten patients (4.9%) had a MV replacement alone without a septal myectomy. Other concomitant procedures included coronary artery bypass grafting (n=4), aortic valve replacement (n=3), surgical MAZE with or without pulmonary vein radiofrequency ablation (n=9), resection of subaortic membrane (n=7), closure of a patent foramen ovale (n=3) or atrial septal defect (n=1). Forty-six patients (22.7%) underwent closure of the left atrial appendage at the time of surgery. Anatomical and echocardiographic indications for individual surgical approaches to the MV are shown in *Table 15*.

| ***Type of MV intervention (N = each group)*** | **ASH <18mm** | **Angulation of aorta** | **Long AMVL** | **Abnormal MV attachments** | **Myxomatous MV** | **Prolapse** | **MR** | **SAM** |
|---|---|---|---|---|---|---|---|---|
| *Papillary division (1)* | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Cleft Repair (3)* | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 3 |
| *Plication (4)* | 1 | 1 | 3 | 0 | 0 | 1 | 4 | 4 |
| *Chord Repair (6)* | 1 | 0 | 0 | 3 | 2 | 1 | 4 | 5 |
| *Alfieri (11)* | 4 | 3 | 5 | 2 | 1 | 2 | 9 | 10 |
| *SM and MVR (9)* | 2 | 1 | 3 | 2 | 3 | 1 | 9 | 9 |
| *MVR alone (10)* | 7 | 1 | 1 | 0 | 6 | 0 | 7 | 9 |

Table 15: Anatomical and echocardiographic indications for individual surgical mitral intervention. Numbers in each column represent the number of patients with the listed specific indication. ASH: Asymmetric Septal Hypertrophy; AMVL: Anterior MV leaflet; MR: Grade 3 or 4 MR.[214]

### *4.3.2 Early Mortality*

Operative survival was 99.0% with 2 perioperative deaths within 30 days of surgery. One patient, a 67-year-old female sustained a VSD identified on an intraoperative TOE following a septal myectomy with staple excision of the left atrial appendage. This was repaired immediately through a right ventriculotomy using bovine pericardial patches and continuous prolene sutures to close the defect and the right ventricle. This patient developed progressive low cardiac output and died on day 3. A second patient, a 30-year-old male, undergoing an extended septal myectomy for severe concentric left ventricular hypertrophy and pulmonary vein isolation for the

management of AF developed an aortic valve tear to the left coronary cusp which was repaired using two 8-0 prolene sutures. This patient died on day 3 from heart failure in the setting of AR, severe diastolic dysfunction and external pacemaker dysfunction. Survival at 1 year was 98.5% with 1 further death at 4 months due to heart failure postoperatively. There were no other deaths within the first year of surgery.

*4.3.3 Complications*

Fifty-six patients (27.6%) had documented postoperative AF, thirty-nine of which were new onset of postoperative AF. There were 2 perioperative TIA's (1.0%) with 4 perioperative strokes (2.0%). One stroke was assumed cardioembolic in nature in the setting of new onset AF. The remaining cases had no documented AF. Thirteen patients (6.4%) had a PPM device inserted for AV block. Ten patients (4.9%) had an ICD in the perioperative period, 3 of which were implanted to treat complete AV block in the setting of associated risk factors for SCD. The remaining 7 patients had an ICD implanted based on risk factors associated with SCD. As described above, 3 patients (1.5%) suffered a VSD requiring repair intraoperatively. One additional patient developed an acquired Gerbode defect postoperatively which was successfully surgically repaired.[215] Two patients (1.0%) had an unplanned aortic valve repair due to a new valve tear intraoperatively. Two patients (1.0%) required further operative intervention during the initial surgical stay. These patients who initially underwent septal myectomy with MV repair required reintervention with MV replacement on day 4 and 14 respectively due to severe MR.

*4.3.4 Clinical and Echocardiographic Outcomes*

The mean NYHA Class improved from 2.6+/-0.5 preoperatively to 1.6+/-0.6 postoperatively at 1 year ($p<0.05$). The vast majority of patients improved symptomatically with 78.7% of patients improving by at least one NYHA class postoperatively, with 19.5% of patients remaining in the same NYHA functional class and a minority of patients (1.7%) in a higher NYHA function class at 1 year. At the 1 year follow-up, postoperative echocardiographic data were available in 83.7% of patients. Echocardiographic variables are shown in *Table 16*.

| | **Preoperative** | **Postoperative** | **P-Value** |
|---|---|---|---|
| *IVS (mm)* | 19.1+/-4.1 | 13.9+/-4.0 | <0.05 |
| *PWT (mm)* | 10.8+/-2.8 | 10.1+/-2.3 | <0.05 |
| *LAD (mm)* | 47.2+/-7.7 | 45.8+/-7.1 | <0.05 |
| *LAA ($cm^2$)* | 30.6+/-8.0 | 27.1+/-7.0 | <0.05 |
| *LVEDd (mm)* | 46.0+/-5.9 | 48.9+/-6.3 | <0.05 |
| *EF (%)* | 69.0+/-6.8 | 62.1+/-8.4 | <0.05 |
| *Resting Grad (mmHg)* | 70.6+/-40.3 | 11.0+/-10.5 | <0.05 |
| *Provoked Grad (mmHg)* | 91.1+/-39.8 | 24.5+/-32.0 | <0.05 |
| *MR grade* | 2.4+/-0.9 | 1.4+/-0.7 | |

Table 16: Pre and post-operative echocardiographic variables.[214]

The mean interventricular septal wall thickness reduced from 19.1+/-4.1mm preoperatively to 13.9+/-4.0mm postoperatively ($p<0.05$). Resting LVOT gradients reduced from 70.6+/-40.3 preoperatively to 11+/-10.5mmHg after surgery at 1 year ($p<0.05$). One hundred and eighty-three patients (90.1%) had no evidence of resting or provoked LVOTO on the postoperative echocardiogram at 1 year.

## *4.4 Investigation of clinical outcomes of septal myectomy and concomitant Alfieri MV repair*

### *Early and Medium-Term Outcomes of Alfieri Mitral Valve Repair in the Management of Systolic Anterior Motion During Septal Myectomy*

#### *4.4.1 Patient Characteristics*

There were no perioperative or late deaths. The median follow-up duration was 6.6 years (IQR 1.2-7.4). No patient was lost to follow-up. Septal tissue excised at myectomy weighed a mean of 4.3+/-3.6 grams. Intraoperatively, pre-bypass, the mean resting LVOT gradient was 40.7+/- 19.9mmHg and on provocation with Isoproterenol was 115.8+/-30.4mmHg. Following surgical resection and Alfieri repair, the mean resting LVOT gradient reduced to 8.3+/-9.8mmHg and on provocation was 25.8+/-9.2mmHg. The mean hospital stay was 10+/-3 days.

One patient required a MV replacement on day 4 postoperatively due to severe MR. This was a 46-year-old man who preoperatively had a right atrial pressure of 21mmHg, pulmonary pressures >60mmHg, severe concentric LVH, complete SAM and severe MR with a significantly dilated left atrium. He firstly underwent an extended septal myectomy (10 grams of tissue removed), with a MAZE procedure and planned Alfieri repair. Intraoperatively there was resolution of obstruction with no significant gradient on provocation. Postoperatively, over the following days, he required increasing inotropic support to maintain adequate circulation. Echocardiography revealed severe MR. A MV replacement, inserting a 33mm St

Jude mechanical prosthesis, was performed on day 4. The papillary muscles were found to be thickened and fibrosed. The patient was discharged home well on day 12. He had one hospitalisation at 2.7 years for management of heart failure with diuresis, and continues to be symptomatically well on latest follow-up at 6 years. Another patient had a brief episode of AF perioperatively, successfully chemically cardioverted. One patient, a 73-year-old man, with preoperative first degree AV block and left bundle branch block had a planned prophylactic dual chamber pacemaker inserted postoperatively.

### *4.4.2 Clinical Outcomes*

At 1 year follow-up, the mean NYHA class had improved from 2.6+/-0.9 preoperatively to 1.6+/-0.7 and on most recent follow-up (median 6.6 years) was 1.7+/-0.4. Nine of the 11 patients showed an improvement in NYHA functional class to NYHA Class I/II, while 2 patients remained in the same functional class (NYHA III). One of the 2 patients who remained in the same functional class, was diagnosed with lung and liver metastases of unknown primary. They subsequently underwent chemotherapy with an ongoing good response. The other patient was a 64-year-old with multiple comorbidities limiting their functional capacity, including ongoing smoking, chronic obstructive pulmonary disease and severe osteoarthritis, subsequently having a knee replacement and who remains limited (NYHA III) at 7 years.

### *4.4.3 Late Complications*

There were no other late complications in the series.

*4.4.4 Echocardiographic Outcomes*

Echocardiographically (*Table 17*), the mean interventricular septal wall thickness reduced from 17.5+/-3.0mm preoperatively to 15.5+/-3.8mm at 1 year ($p<0.05$) and 16.1+/-3.5mm at most recent follow-up (median 6.6 years). Changes in left atrial diameter and left ventricular end diastolic dimensions were not significant at 1 year or on most recent follow-up compared to preoperatively. The mean grade of MR improved from 2.7+/-0.8 preoperatively to 1.0+/-0.9 at 1 year, and 0.7+/-0.6 at most recent follow-up. The mean resting LVOT gradient reduced from 59.8+/-28.2mmHg preoperatively to 20.7+/-16.6mmHg at 1 year ($p<0.05$) and 16.2+/-15.7 at most recent follow-up ($p<0.05$). All 11 patients had documented SAM on the preoperative echocardiogram. No patient had SAM on the postoperative echocardiogram at 1 year.

| | **Preoperatively** | **1 Year (n=11)** | **P Value (Comparison at 1 year and preoperatively** | **Most recent follow-up (n=11)** | **P Value (Comparison on most recent follow-up and preoperatively)** |
|---|---|---|---|---|---|
| *Interventricular Septal Thickness (mm)* | 17.5+/-3.0 | 15.5+/-3.8 | <0.05 | 16.1+/-3.5 | 0.07 |

| | | | | | |
|---|---|---|---|---|---|
| *Posterior Wall Thickness (mm)* | 9.6+/-2.1 | 9.7+/-0.9 | 0.77 | 11.1+/-2.3 | 0.22 |
| *Left Atrial Diameter (mm)* | 46.6+/-8.7 | 47.7+/-8.1 | 0.89 | 44.3+/-8.8 | 0.23 |
| *Left Ventricular End Diastolic Diameter (mm)* | 45.5+/-4.9 | 45.4+/-5.4 | 0.88 | 43.5+/-6.5 | 0.41 |
| *Ejection Fraction (%)* | 72.0+/-9.8 | 64.4+/-9.9 | 0.59 | 62.2+/-6.2 | <0.05 |
| *Resting Gradient (mmHg)* | 59.8+/-28.2 | 20.7+/-16.6 | <0.05 | 16.2+/-15.7 | <0.05 |
| *Mitral Regurgitation* | 2.7+/-0.8 | 1.0+/-0.9 | | 0.7+/-0.6 | |

Table 17: Mean echocardiographic variables with pre and post-operative comparisons using paired t-tests (significance, $p<0.05$).[216]

# 5. Discussion

Surgical management of LVOTO by septal myectomy is considered by expert consensus to be the gold standard in the management of drug refractory symptomatic cases in HCM, with excellent outcomes in a majority of cases. The earliest surgical approaches in the management of LVOTO included the standard septal myectomy introduced by Morrow and MV replacement by Cooley.[12,92] In the vast majority of patients, septal myectomy is the only procedure required to treat LVOTO in HCM however increasingly MV repair techniques are utilised concomitantly with septal myectomy to manage LVOTO. Multiple large surgical series have reported the outcomes of septal myectomy alone, but with increasing MV intervention being utilised to manage LVOTO, further analysis of clinical outcomes is required.

## *5.1 A systematic review and meta-analysis of early and late clinical outcomes following the surgical management of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy*

### *5.1.2 Overview*

In patients with obstructive HCM randomised controlled trials are unlikely to compare surgical intervention and medical therapy. The reason lies with the inherent challenges that exist in the design of clinical studies in this population including relatively low prevalence, heterogeneity of the condition and low event

rates requiring very large numbers of patients to power a study.[217] For these reasons, systematic reviews and meta-analyses of the literature will remain the major source of evidence for the study of surgical treatments for LVOTO in HCM. Although smaller meta-analyses of selected studies have been reported and published, for the first time, I investigate and evaluate extensively pooled data on early and late mortality as well as early and late morbidity since initial surgical reports in the literature.

Although septal myectomy is the surgery of choice in the vast majority of patients with LVOTO, this review also examines various other surgical techniques including septal myectomy with concomitant MV repair, septal myectomy with concomitant MV replacement as well as MV replacement alone. The findings from this review show that in experienced centres operative mortality in septal myectomy is low with similar low operative mortality rates in studies reporting outcomes in septal myectomy with MV repair. Contemporary data however, on the use of MV replacement in LVOTO are less robust and therefore difficult to draw conclusions from. Higher operative mortality rates however, were seen in earlier studies. In this current study we identify gaps in evidence from the literature particularly with respect to the reporting of perioperative complications and long-term disease related morbidity following surgical treatment.

*5.1.3 Geographical location*

The majority of reported data on surgical intervention come from large specialised centres, mostly in North America, including one quarter from a single institution, the Mayo Clinic in Rochester, Minnesota, USA. This concentration of data on reported clinical experiences from a small number of these specialised centres means that the good surgical outcomes seen in the literature may not be representative of results from less experienced low volume surgical units. Some recently published evidence suggesting that this is the case come from an audit of North American centres carrying out septal myectomy procedures that reports an incidence of early mortality of 3.8% in high volume centres and 15.6% in low volume centres.[218] Furthermore, ASA has been introduced in recent years as an alternative to surgical septal reduction therapy which may have resulted in a reduction in the number of septal myectomy surgeries performed in certain regions such as Europe. This is evident from our systematic review results with trends showing fewer publications from European centres over this period. In recent years however, this has changed further with more publications from European centres. This may reflect the publication of European guidelines recommending surgery as the gold standard in the management of LVOTO in suitable patients.

### *5.1.4 Early complications*

This systematic review and meta-analysis demonstrate improved clinical outcomes following the surgical management of LVOTO since its first introduction in the 1950's. Similar falls in reported late mortality were seen, although the impact of surgery on these later complications is more difficult to determine. Meta-analysis showed operative mortality to be highest in the 18-39

and over 60-year-old age groups at 6.1% and 9.2%, respectively. It is unclear why these age groups were more vulnerable, but the fact that their late mortality was similarly higher than other cohorts suggests that they may have more severe underlying disease or comorbid conditions that increased their surgical risk. The incidence of complications arising directly from removal of septal muscle such as a VSD and need for PPM insertion perioperatively was low, particularly in contemporary studies but there was limited reporting noted of other early perioperative complications such as AF and stroke.

### *5.1.5 Late complications*

While this review and meta-analysis confirms the success of surgery in treating symptoms attributable to LVOTO, the underlying myocardial disease clearly retains the potential for progression in spite of surgical intervention and alleviation of obstruction. While most series included data on long-term survival, less than 22% in this study reported the incidence of non-fatal complications such as AF, stroke and heart failure on long-term follow-up. Documentation of long-term morbidity was less robust than the reporting of early complications. This may be accounted for by the fact that many studies are reported by large tertiary specialised referral centres that discharge patients to local physicians following surgery with little sufficient clinical data on long term outcomes. This represents a major gap in current knowledge as most series suggest that patients with and without LVOTO are at risk of adverse outcomes and the impact of surgery on the incidence of non-fatal disease related morbidity is unknown. Following this analysis, it is clear further studies are required to assess long-term non-fatal outcomes.

*5.1.6 Comparison of different surgical approaches*

Mitral valve replacement for the management of LVOTO was introduced in the 1970s as a mechanism to alleviate LVOTO and improve symptoms, however higher complication rates with this procedure meant in more recent years that it has been reserved primarily for individuals considered unsuitable for myectomy.[92] In this review, studies investigating outcomes following MV replacement alone, although older, reported higher perioperative mortality rates.[141-143] More recently a study from Stassano et al, show a reduced perioperative mortality rate of 5.6% in a MV replacement cohort but overall documentation of perioperative complications and late morbidities in these studies were low.[172] Contemporary studies have focused on incorporating patients undergoing MV replacement into a wider surgical cohort with low rates of specific outcomes in individual surgical MV approaches compared to septal myectomy. Other more recent studies have focused specifically on septal myectomy with MV repair using a variety of surgical techniques as discussed in Chapter 1 of this thesis. [155, 159, 169, 171, 178, 179, 186, 187, 189, 212] Techniques for MV repair can involve plication of the MV leaflet, extension of the anterior MV leaflet with a patch repair, edge to edge (Alfieri) stitch repair or reorientation of papillary muscles. With improved imaging techniques and surgical advances, MV repair using one of the above techniques in combination with septal myectomy is increasingly advocated and taking precedence in the management of LVOTO in HCM. This preference for MV repair over MV replacement may reflect improved surgical technique as well as a less invasive procedure without the need for MV replacement and associated complications that can occur with

anticoagulation. From this review however, studies comparing outcomes of different MV interventions including MV replacement with septal myectomy alone are lacking and need further evaluation.

### *5.1.7 Limitations*

Many cohorts extracted from the systematic review came from the same centres which created bias. We aimed to eliminate this by removing studies from the meta-analysis with overlapping patient cohorts from the same institution.

### *5.1.8 Learning points*

1) Contemporary operative mortality rates following septal myectomy and septal myectomy with concomitant MV repair are low.
2) Contemporary outcome data on the use of MV replacement in the management of LVOTO in HCM is less robust compared to a standard septal myectomy or septal myectomy with concomitant MV repair techniques.
3) Long term outcome reports of morbidity are less robust than that of early perioperative complications following surgical management of LVOTO in HCM.
4) Several surgical techniques are utilised to repair the MV concomitantly at the time of septal myectomy in the management of LVOTO in HCM but studies comparing the clinical outcomes of different MV interventions are lacking.

## *5.2 Long-term outcomes for different surgical strategies to treat left ventricular outflow tract obstruction in hypertrophic cardiomyopathy*

### *5.2.1 Overview*

Literature reviews show us that the majority of studies investigating septal myectomy in HCM have focused on long-term mortality rather than morbidity.[175,193,211] This is evidenced from the low reporting rates of non-fatal complications such as AF, stroke and heart failure on long term follow-up. This, we appreciate may relate to the lack of long term clinical follow-up data in specialised centres with many of these patients being followed up locally after receiving specialised care. This is an inherent limitation of studies involving this cohort of patients across many centres. The novel finding in our cohort study is that in spite of low procedural and long-term death rates, the incidence of non-fatal disease related complications after surgical treatment of LVOTO is relatively high during follow-up. This illustrates the importance and the need for ongoing clinical surveillance and medical therapy after surgical intervention for LVOTO. We also identify an older cohort of patients that have LVOTO associated with milder hypertrophy but severe MR who respond less well to intervention.

### *5.2.3 Surgical intervention*

Single centre studies and meta-analyses show that septal myectomy is an effective and successful procedure with a low mortality rate in high volume

specialist centres. Relatively few recent studies have reported on the outcomes of MV replacement surgery in patients with HCM.[141-143] The findings in the present study are broadly in line with the published literature in that a reduction in resting LVOTO to less than 30 mmHg was achieved in more than 90% of patients undergoing septal myectomy alone with an operative mortality and an annual all-cause approximately 1%. The change in symptoms, as measured by NYHA class was also similar to published data in that 75% of patients reported an improvement.[96] Patients undergoing septal myectomy and MV repair had similar outcomes to those treated with septal myectomy alone, but those receiving MV replacements had poorer outcomes with less symptomatic benefit in spite of a similar reduction in LVOT gradients. These findings suggest that patients with LVOTO and other indications for MV surgery need to be carefully selected for intervention and that further study is required to optimise surgical strategies in this group.

### *5.2.4 Mitral valve replacement surgery*

Mitral valve replacement in the surgical management of LVOTO was first advocated in the 1970s by Cooley, but subsequent studies have reported higher rates of perioperative and late mortality compared to septal myectomy alone leading to its limited use for this indication in recent years.[92,141-143] Nevertheless, MV abnormalities that contribute to LVOTO are common in patients with HCM and as result, numerous valve sparing repair procedures have been explored. In the present outcomes study, MV replacement was considered the most appropriate management in a minority of patients. Although numbers are small in group D, undergoing a MV replacement alone

without septal myectomy for LVOTO, they had higher perioperative mortality and higher stroke rates compared to patients undergoing septal myectomy alone. Of patients treated with MV replacement alone in our cohort nearly two thirds had no improvement in NYHA class at 1 year. I do appreciate that baseline demographics differed and individuals undergoing MV replacement were significantly older and had more comorbidities including AF and hypertension which may have accounted for their poorer clinical outcomes. It is also to be noted that their cardiac morphology also differed in that they had less septal hypertrophy, greater degrees of MR and larger left atria. Together these findings suggest that the patients undergoing MV replacement had a more severe cardiac phenotype and potentially more advanced disease than those undergoing septal myectomy alone. This may also account for their poorer surgical outcomes which were seen in our results.

### *5.2.5 Exercise performance outcomes following surgery*

Very few studies have investigated changes in exercise performance after surgical treatment for LVOTO. In the sub-set of patients that underwent CPET before and after surgery there was an improvement in systolic blood pressure response but no change in peak oxygen consumption. The lack of improvement in pVO2 seems counterintuitive given the improvement in NYHA class reported by most patients, but it probably reflects the complex mechanism of exercise limitation in HCM. For example, it is possible that the relief of SAM related MR and exercise induced myocardial ischaemia could result in symptomatic improvement without an increase in left ventricular stroke volume sufficient to increase peak oxygen consumption. Similarly, the increase in exercise blood

pressure might reflect changes in centrally mediated vascular behaviour during exercise rather than an increase in cardiac output. Whatever the explanation, these findings suggest that peak oxygen consumption may be an unreliable indicator of the success of surgical intervention for LVOTO.

### *5.2.6 Predictors of Clinical Outcomes Following Septal Myectomy Surgery*

The data on predictors of various clinical outcomes in HCM has been studied in recent years including AF and SCD.[113,118,119] These studies have led to the development of highly valuable clinical tools which help in the clinical assessment and management of patients with HCM.[113] The data for prediction of clinical outcomes following surgery in the management of LVOTO is less robust despite it being the most common complication associated with the underlying condition. Desai et al. suggest that increasing age and residual post-operative AF are potential indicators of clinical outcome. This report assessed various surgical approaches including MV interventions.[85]

Surgical success in this current study was determined by elimination of obstruction and absence of significant LVOT gradients >30mmHg on 1-year TTE assessment. Following surgery in our cohort resting LVOT gradients were reduced below 30mmHg in over 90% of patients undergoing surgery, which was in line with previous published reports. This again highlights the success associated with this procedure over the years. As evidenced by statistical analysis in this study no strong predictors of surgical success were associated with individual baseline variables.

### *5.2.6 Learning Points*

1. Septal myectomy in the management of LVOTO in patients with HCM is a safe procedure and results in symptomatic improvement in the majority of patients.
2. Ongoing clinical surveillance and medical therapy is still required following surgery as disease related complications such as AF, heart failure and stroke are common following successful surgical treatment of LVOTO.
3. Indications for MV surgery need to be carefully planned and selected for intervention and the surgical approach should be tailored towards the MV abnormalities contributing to LVOTO in individual patients.
4. Several surgical techniques are utilised to repair the MV concomitantly at the time of septal myectomy in the management of LVOTO in HCM but studies comparing the clinical outcomes of different MV interventions are lacking.
5. In the absence of strong predictors of surgical success, there is an importance in adopting an individual surgical approach in the management of patients with LVOTO in HCM as well as close clinical follow-up of patients post-operatively.

## *5.3 Individualised surgical strategies for left ventricular outflow tract obstruction in hypertrophic cardiomyopathy*

### *5.3.1 Overview*

Many large surgical series from single centres have reported the outcomes of septal myectomy alone, which reflect in part, referral patterns to large US centers.[85,175,219] The earliest surgical approaches in the management of LVOTO include the standard septal myectomy introduced by Morrow et al. (1961) and MV replacement by Cooley et al. (1971); both of which have been shown to be successful in improving symptoms and alleviating LVOT gradients however clinical outcomes vary with these procedures.[12,92] Mitral abnormalities play an important role in the mechanism of LVOTO in individual patients such as those with limited hypertrophy, and we believe an individualised surgical approach is necessary for optimal surgical management.[16] This study of individual surgical techniques reflects the experience of surgery for LVOTO in HCM in a large national specialised centre with referral of a wide heterogenous phenotypic variation performing >70% of such procedures in UK practice over the period of the study.

### *5.3.2 Surgical Planning*

Surgical planning including preoperative and intraoperative imaging techniques, such as TTE and TOE are essential in the characterisation of varying phenotypic abnormalities commonly seen in this population of patients with LVOTO in HCM. These imaging modalities allow for strategic and accurate

surgical planning in a multidisciplinary setting to address causes of MR and SAM seen in LVOTO. Abnormalities of the MV in LVOTO can be intrinsic or more specifically related to the underlying physiology and morphology in HCM. Intrinsic MV abnormalities can pre-exist similar to the general population, in patients with HCM. These intrinsic abnormalities include annular, leaflet or chordal calcification or fibrosis. These abnormalities may need to be addressed at the time of the surgical intervention. More specific abnormalities of the MV apparatus, commonly seen in HCM patients can contribute to the classical mechanism of LVOTO. These abnormalities include both elongation of the MV leaflets, typically the anterior leaflet, and abnormalities of the sub-mitral attachments.[220] Abnormal MV attachments, commonly seen with LVOTO include anterior papillary muscle displacement, thickened bifid papillary muscles, direct insertion of papillary muscle into the anterior MV leaflets or fibrotic chordal attachments. In more complex cases in which there is involvement of both the mitral and sub-mitral apparatus, these cases can be managed with a combination of septal myectomy and repair or replacement of the MV. The use of an extended septal myectomy can address this issue to some extent by extending the resection in a fan like fashion moving distally in the septum but in other cases intervention on the valve or sub-valvular apparatus is required. Elongation of the MV leaflets, in particular the anterior leaflet results in SAM related MR. In cases of limited septal hypertrophy, MV replacement has been performed as primary surgery in the past, however, a range of newer surgical techniques for MV repair have evolved to address such cases in which adequate resection is technically challenging.[194,212,221]

*5.3.3 Surgical approaches to the mitral valve*

Multiple surgical approaches have been advocated in the presence of elongated leaflets with post septal myectomy SAM and/or MR with good outcomes, including the edge to edge Alfieri repair, MV plication and anterior MV leaflet extension using a pericardial patch.[19-21] The edge to edge Alfieri repair was our preferred surgical approach to address elongated anterior mitral leaflets with SAM related MR with good resolution of LVOT gradients and improved symptoms. The Alfieri technique has been used successfully in MR of various aetiologies.[221] There have been no early or late mortalities in this group of 11 patients in the current study, who documented good medium-term outcomes. If an Alfieri repair is contemplated, assessment of the posterior MV leaflet length is important, as excess length can lead to bileaflet prolapse with SAM making this type of repair less likely to be effective. Ferrazi et al. report good outcomes in patients undergoing a limited septal myectomy with trans aortic selective division of fibrosed secondary chordae attached to the anterior MV leaflet body believed to be contributing to SAM from the submitral apparatus.[91] Controversy remains over individual techniques of MV repair in patients with LVOTO. The rate of concomitant MV intervention with septal myectomy has varied across centres from 8% in a recent large study of over 2000 patients from the Mayo Clinic operated on with septal myectomy for LVOTO to 25% in a paper from the Cleveland Clinic.[84,85]

The advantage of MV repair is that it obviates the need for MV replacement and its associated complications.[222] Late survival following septal myectomy with MV repair was superior to septal myectomy with MV replacement in a large

Mayo clinical experience.[84] Contemporary data on MV replacement alone for relief of LVOTO in HCM in the literature is less robust than that for septal myectomy. Initial studies reported by Cooley et al. showed good symptomatic relief and resolution of gradients. Further long-term studies by the same group showed good outcomes at ten years.[142] Other early studies showed similar symptomatic and gradient reduction with MV replacement, however, higher mortality rates and complication rates were seen in these cohorts.[143,145] More recent studies of MV replacement in patients with LVOTO have reported on septal myectomy with MV replacement rather than MV replacement alone.[84,172,186,187] Mitral valve replacement alone is a successful approach in cases unsuitable for repair or when used alone in those patients with thinner septae unsuitable for septal myectomy. In selected older patients with atypical phenotypes and multiple comorbidities in whom septal myectomy alone was felt unlikely to be adequate and who were felt to be unsuitable for multiple bypass runs, an upfront decision to perform MV replacement alone was made in this series.

### *5.3.4 Strategic planning process*

We developed a flowchart which can be seen in *Figure 20* and illustrates a pathway for consideration in the strategic planning of surgery in the management of non-classical LVOTO in HCM. These non-classical phenotypes include aortic angulation, limited hypertrophy, abnormally distributed hypertrophy and/or abnormalities of the MV or sub-mitral apparatus as described above. It is important to adopt a stepwise approach in the planning of individual cases which needs to be re-evaluated intraoperatively following the

initial procedure and initial bypass run to evaluate if further intervention is needed to the MV. This avoids or limits the potential for re-operation in the future. The recent Mayo study of 174 patients surgically managed with septal myectomy and MV intervention revealed no difference in ICU length of stay, hospital length of stay or late mortality in those undergoing single or multiple cardiopulmonary bypass runs indicating the safety of this approach in appropriate patients.[84]

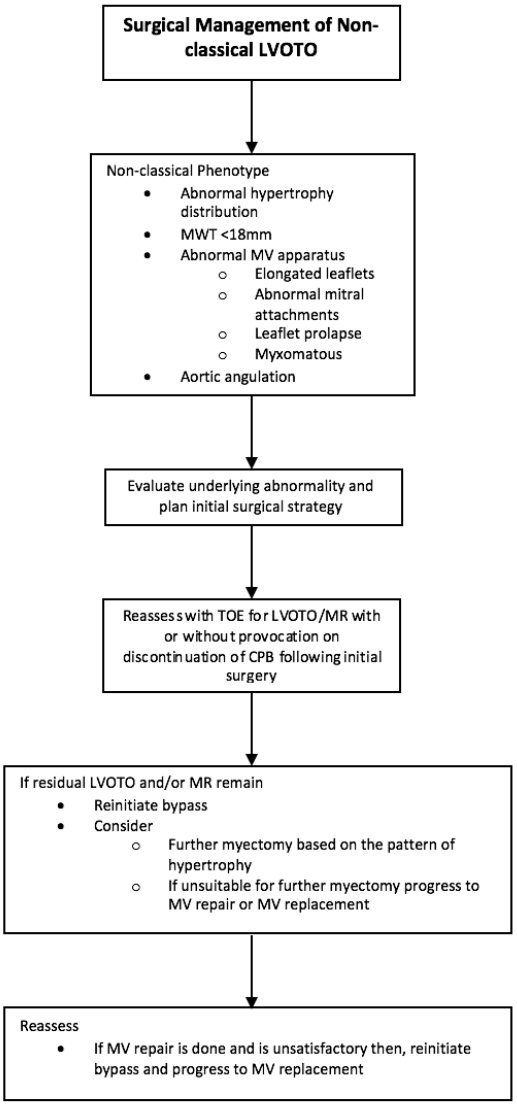


Figure 20: Flowchart in decision making for surgical management.[214]

MWT: Maximum Wall Thickness of Left Ventricular Septum.

### 5.3.5 Surgical outcomes

Hospital volume plays an important role in mortality outcomes of surgery for HCM. A recent national database study analysing 6386 septal myectomies reported that surgery in lower volume centres was an independent predictor of mortality in the USA.[218] In high volume centres early surgical outcomes following septal myectomy have shown very low mortality rates with good resolution of symptoms.[85,86,175,218] Mortality within this current study is low and comparable to current reported outcomes in high volume centres for septal myectomy.[219] Additionally, 21.7% of patients included in the current study had MV surgery and 10.8% had concomitant non-mitral surgery. This study reports good echocardiographic follow-up with 83.7% of all patients at 1 year, a rate which is not available in many other studies of this size. Almost 80% of patients in this study showed an improvement in NYHA class postoperatively comparable to previous large studies.[174,175] Over 90% of patients demonstrated a resolution of obstruction with a LVOT gradient of <30mmHg on postoperative echocardiography at 1 year. This individualised approach to the management of LVOTO in variable phenotypes of HCM adopted by our institution has not compromised, at least, 1 year surgical, clinical and echocardiographic outcomes.

### *5.3.6 Limitations*

This study represents a single centre, retrospective consecutive experience representing limitations inherent to this study design. We acknowledge that as a national referral centre with a large population of HCM patients attending for regular clinical review that this may introduce referral bias, however, we believe that, a more variable set of phenotypes may be seen within such an environment, requiring a more individualised surgical approach.

### 5.3.7 Learning points

1. In a vast majority of patient isolated septal myectomy alone is required to manage LVOTO in HCM however a non-classical phenotype exists which requires an individualised surgical planning approach to address potential abnormalities with the MV.
2. Various surgical approaches exist to address a non-classical phenotype in HCM including the edge-to-edge Alfieri MV repair technique utilised in our institution.

## *5.4 Early and medium-term outcomes of Alfieri mitral valve repair in the management of systolic anterior motion during septal myectomy*

### *5.4.1 Overview*

An isolated septal myectomy is the only surgical procedure required in the vast majority of patients with a classical phenotype and distribution of hypertrophy to

alleviate LVOTO.[84,223] The 8% incidence of septal myectomy with concomitant MV repair in this study (11 of 123 overall septal myectomy cases) is consistent with the 7% rate reported recently in the largest study to date of over 2000 patients from the Mayo Clinic, which was also discussed subsequently in an editorial.[84,224] The type of MV repair was not described in this study from the Mayo Clinic. A number of surgical techniques have been utilised on the MV to eliminate SAM in the context of septal myectomy which have been described previously.[91,155,169,194] The optimal surgical strategy remains uncertain.[84] Systolic anterior motion of the anterior MV leaflet after septal myectomy can result in residual unacceptable levels of LVOTO and/or MR post procedure. As in the Mayo study, if further septal resection was judged inappropriate due to limited septal thickness, MV repair was our preferred approach to reduce this residual LVOTO and/or MR whenever possible, and avoid the limitations of valve replacement.[84,222,225]

### *5.4.2 Edge to edge Alfieri mitral valve repair*

Alfieri and colleagues introduced a technique in 1995 describing an edge to edge repair to approximate the central MV edges creating a double orifice to alleviate MR.[126] This technique has been studied in larger cohorts undergoing surgery for primary MR unrelated to LVOTO in HCM with good long term outcomes.[126,127,221,226,227] On analysis of previous studies of long term follow-up following an Alfieri repair, reports showed rates of freedom from reoperation of 90% at 5 years and survival rates of 94% at 5 years.[127] There are few papers describing an Alfieri repair in the context of LVOTO in HCM. These reports show only short term results with limited echocardiographic follow-up. In a

subgroup of 14 patients who underwent and Alfieri repair without annuloplasty after septal myectomy at the Cleveland Clinic, two patients required subsequent MV replacement.[221] This study, using the trans aortic Alfieri repair technique, reported an encouraging early experience of an Alfieri repair in HCM, but had limited follow-up data compared to the longer clinical and echocardiographic follow-up in this current study. A further study by Shah et al, focused on perioperative complications following trans aortic Alfieri repair in 24 patients with LVOTO in HCM with short, limited follow-up data with one early mortality from a VSD.[228] Recently Obadia et al, report outcomes in 22 patients with trans aortic Alfieri repair after septal myectomy with shorter follow-up and early echocardiographic data only.[229] The remainder of the literature consists of case reports.

*5.4.3 Alfieri repair outcomes*

Our data reports, for the first time, medium term clinical and echocardiographic outcomes with a median follow-up of 6.6 years. Interventricular septal wall thickness was reduced from 17.5+/-3.0 mm preoperatively to a mean of 15.5+/-3.8 mm postoperatively at 1 year. An Alfieri repair was performed rather than further resection either because residual thickness was such that a further resection was regarded as high risk for VSD, or the patient had a known mitral leaflet abnormality. This partly reflects the varying clinical phenotype of patients in HCM, with less hypertrophy seen in the sub group of patients treated in this study compared to Obadia et al, who report a mean septal wall thickness preoperatively of 25mm. In the current study, functional outcomes, assessed

using NYHA classification, were comparable to a recent meta-analysis looking at long term follow-up in general septal reduction therapy.[96]

As in the Cleveland series, a concomitant mitral annuloplasty, almost uniformly done at the time of general mitral repair including the Alfieri repair was avoided in this series of HCM patients, to avoid any propensity to worsen SAM.[221] The use or lack of use of mitral annuloplasty in the subset of patients with MV repair after septal myectomy was not reported in the large Mayo series or by the studies from Shah et al and Obadia et al.[84,228,229] The avoidance of annuloplasty has not compromised the results of and Alfieri repair in the current series at medium term follow-up.

The relative merits of trans atrial Alfieri repair, done in this study, versus trans aortic Alfieri repair remain to be clarified by larger series with longer follow-up. In the context of LVOTO and HCM there is limited experience with the trans aortic approach.[221,228,229] Literature on the Alfieri repair for other aetiologies of MR has principally used the trans atrial approach which was utilised in this cohort.

The favourable early and medium term clinical and echocardiographic outcomes in the current study demonstrate the benefit of trans atrial Alfieri repair for the prevention or treatment of SAM at the time of septal myectomy in the management of LVOTO. There was no early or late mortality, few early or late complications and good symptomatic and echocardiographic outcomes.

### *5.4.4 Limitations*

This paper represents a small, single centre, single surgeon, retrospective analysis of clinical experience using an Alfieri repair concomitantly to a septal myectomy in the management of LVOTO in HCM. The sample size is small, so that conclusions must be guarded, but appears to be the largest study to date looking at more medium term as well as early, clinical and echocardiographic outcomes of the Alfieri repair for the treatment of SAM post septal myectomy in HCM. The absence of measured, documented MV morphometry is a weakness in this, as in most relevant studies.

# 6. Conclusions

This thesis aimed to evaluate the surgical management of LVOTO in patients with HCM. A stepwise approach was taken to examine current and past surgical practices and techniques with regards to clinical outcomes.

Following systematic review and meta-analysis of the published literature it is evident that the contemporary surgical management of LVOTO in specialist centres is associated with low operative mortality rates. Inconsistencies do however exist in reporting short- and long-term clinical outcomes following surgical intervention which can make it difficult to draw direct conclusions and in deciding the best clinical practice for these patients. The reporting of long-term morbidity is less robust than that of early complications. Further studies are needed to investigate the long-term outcomes for different surgical approaches to the management of LVOTO and to determine the impact of relief of LVOTO on non-fatal disease related complications.

In a high volume specialised cardiomyopathy centre, septal myectomy for the management of LVOTO in patients with HCM is a safe procedure and results in symptomatic improvement in the majority of patients. It is clear that ongoing clinical surveillance and medical therapy is still required following surgery as disease related complications such as AF, heart failure and stroke are common following successful surgical treatment of LVOTO. Mitral valve replacement is utilised in the management of patients with LVOTO in certain cases and is associated with higher mortality and morbidity and is less successful in

improving symptoms. The characteristics of patients requiring MV replacement suggest that this group is potentially at higher pre-operative risk and has a different phenotype to the majority of patients undergoing surgical treatment for LVOTO.

Predictors of clinical outcomes in patients with LVOTO in HCM has been assessed. In those patients undergoing septal myectomy for LVOTO the data is not robust and therefore difficult to make predictions given this current study. Further evaluation is required to investigate this in larger cohorts.

On exploration of current and past surgical practices, it is evident that a number of varying surgical approaches are utilised in the management of LVOTO largely dependent on the underlying clinical phenotype and local surgical preferences. Individualised surgical approaches to the management of LVOTO in HCM include septal myectomy alone or varying concomitant interventions to the MV. Low mortality rates and good clinical outcomes were again observed in the same large UK based cardiomyopathy centre. Given the varying phenotypes that exist in HCM surgical strategy should be individualised depending on the underlying mechanism of obstruction with appropriate evaluation of the MV.

A frequently utilised surgical approach to the MV in the management of LVOTO is a technique developed by Ottavio Alfieri and colleagues in Milan, Italy. This technique was performed on a small cohort of patients in our specialised

cardiomyopathy centre. This study demonstrated good early and medium term, clinical and echocardiographic outcomes in 11 consecutive patients using trans-atrial Alfieri repair without annuloplasty, as adjunctive therapy, for the prevention or treatment of SAM at the time of septal myectomy in the management of LVOTO in HCM. The study performed, supports the ongoing utility of this approach to address a sometimes difficult surgical challenge.

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# 8. Appendix

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*8.2 Supervision*

Primary Supervisor: Professor Perry Elliott, Institute of Cardiovascular Science, UCL

Secondary Supervisor: Dr Petros Syrris, Institute of Cardiovascular Science, UCL

*8.3 Location of research*

Barts Heart Centre, Barts Health NHS Trust, London, EC1A 7BE

*8.4 Contributors*

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*8.5 Publications arising from completion of research programme*

- Collis RA, Rahman MS, Watkinson O, Guttmann OP, O'Mahony C, Elliott PM. Outcomes following the surgical management of left ventricular outflow tract obstruction; A systematic review and meta-analysis. Int J Cardiol. 2018. 265:62-70.
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- Collis R, Tsang V, Pantazis A, Tome-Esteban M, Elliott PM, McGregor CGA. Individualized surgical strategies for left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Eur J Cardiothorac Surg. 2018. 53(6):1237-43.
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*8.6 Word count: 32,996*