# Hypertrophic Cardiomyopathy

## Update on Prognosis and Therapy

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ISBN: 90-8559-149-X

Cover design, layout and printing:
Optima Grafische Communicatie
P.O. Box 84115
3009 CC Rotterdam
The Netherlands
www.ogc.nl

# Hypertrophic Cardiomyopathy

## Update on Prognosis and Therapy

Hypertrofische cardiomyopathie

nieuwe inzichten in prognose en therapie

**PROEFSCHRIFT**

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
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Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 8 maart 2006 om 15.45 uur

door

**Christiaan van der Lee**
geboren te Bergschenhoek

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Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Ter nagedachtenis aan mijn moeder
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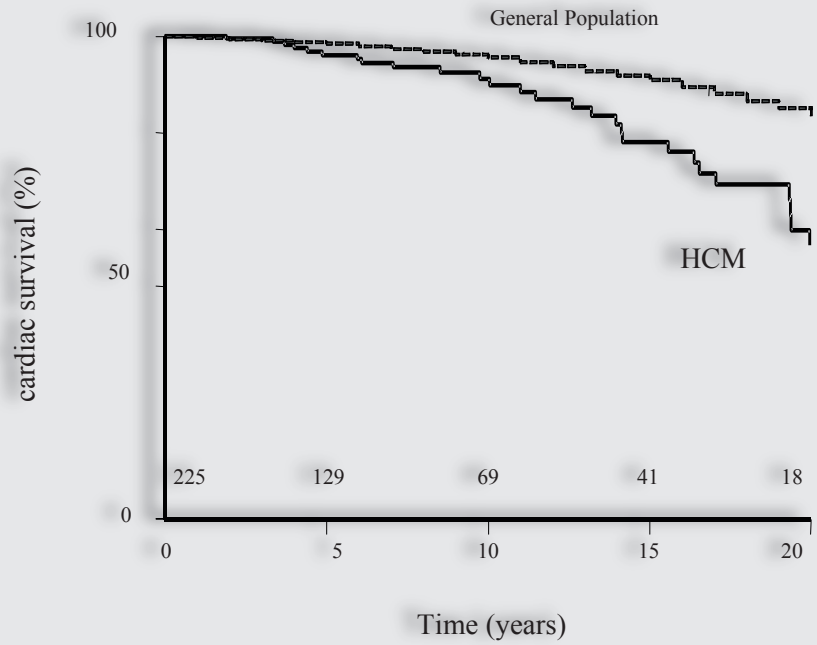
# Introduction



## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex cardiac disease with heterogeneity in genotype, clinical expression, prognosis and therapeutic modalities.[1,2] The disease, which is defined as a hypertrophied left ventricle in the absence of apparent causes of hypertrophy, is caused by mutations in genes encoding for sarcomeric proteins.[3] The prevalence of HCM in the general population is 0.2%.[4] The clinical presentation may vary from non-symptomatic to severely disabled.[5] Sudden cardiac death is the most devastating complication in the natural history of HCM, often occurring in young, previously asymptomatic patients.[6] Since the introduction of HCM as a clinical entity in 1958,[7] extensive research has been performed regarding genetics, diagnosis, prognosis and therapy. However, correct diagnosis and optimal management of HCM patients may still offer difficulties to the physician. For instance, only recently it became apparent that even with a normal echocardiogram, patients may be carrier of a HCM-causing mutation.[8,9] Therefore, optimal management of HCM patients requires extensive knowledge of the natural history, the extensive genetic variations and the indications for medical and invasive treatment.

## PROGNOSIS AND TREATMENT

The first data on the natural history of HCM were initially derived from referral-based populations, which consisted of young, often seriously disabled patients referred for advanced care.[10] These patients personify a selected minority and their clinical course seems to represent the worst end of the disease spectrum. Annual cardiac mortality rates in these populations were as high as 4%-6%.[11-14] In contrast, recent data suggest that HCM has a fairly benign prognosis.[15-19] Yet, the continuous research for new knowledge of risk markers still remains important to identify patients at increased risk for (sudden) cardiac death.

Therapeutic strategies in HCM are multifaceted and may vary during the course of the disease. The general advise for patients who remain symptomatic, despite optimal medical treatment, and demonstrate a left ventricular outflow tract (LVOT) gradient of ≥ 50 mm Hg, is invasive treatment.[20] Currently, the two most frequently used invasive therapies are surgical septal myectomy and percutaneous transluminal septal myocardial ablation (PTSMA).

Septal myectomy entails partial resection of the hypertrophied septum of the left ventricle to alleviate the LVOT obstruction. Since HOCM patients often demonstrate abnormalities of the mitral valve or its subvalvular apparatus, we frequently combine septal myectomy with mitral leaflet extension (MLE).[21]

PTSMA, introduced as an alternative to surgery, entails the injection of highly concentrated ethanol into one or more septal perforator branches of the left descending coronary artery to produce a localised septal myocardial infarction, resulting in remodelling (shrinkage) of the septum, enlargement of the narrowed outflow tract and reduction of the LVOT gradient. Compared to surgery, the definite role of PTSMA in HOCM has not been established yet.

## PERSPECTIVES OF THE PRESENT THESIS

The aim of the present thesis is to evaluate the natural history in the largest "Dutch" community-based cohort of HCM patients and to present the follow-up outcome of HOCM patients with drug-refractory symptoms after PTSMA and septal myectomy in combination with MLE.

After a mean follow-up of 8 years, we describe the outcome of 225 HCM patients, referred to the Thoraxcenter between 1970 and 1999. In this population, we studied prognosis as well as risk markers for sudden cardiac death and clinical deterioration.[22] The non-referral base of the study population allowed us to evaluate prognosis and to calculate mortality rates, which are regarded as representative for the "average" HCM patient. Furthermore, nine consecutive female patients out of this HCM population were followed during pregnancy and delivery.[23] From this experience, we tried to formulate a general advise on the management during and after pregnancy.

Septal myectomy in combination with MLE, a modified mitral valve repair technique originally developed by Carpentier,[24] is a surgical technique, developed in the Thoraxcenter, to treat symptomatic HOCM patients with an enlarged anterior mitral valve leaflet. Previously, we demonstrated the superiority of this combined technique as compared to myectomy alone. In the present thesis, we describe the long-term follow-up outcome of 29 patients, treated with this combined surgical approach. The study emphasizes on the multifactorial origin of the LVOT obstruction and in particular on the role of the mitral valve in this process. Furthermore, the study examined the safety and durability of this modified technique, in particular in respect to the mitral valvular function.

We studied the outcome of the largest cohort of HCM patients, who underwent PTSMA in the Netherlands. Patients underwent the procedure at the Thoraxcenter of the EMC Rotterdam or The Antonius Ziekenhuis Nieuwegein. The purpose of the study was to identify predictors of outcome after PTSMA and to compare our results to the outcome of other centers. Furthermore, we studied the value of two additional techniques, that have been introduced to optimize the PTSMA procedure. The first

technique, myocardial contrast echocardiography (MCE), was evaluated on its use as a tool to predict the site and size of the septal myocardial infarction. The correlation of MCE-related parameters to the MRI-determined volume and location of the septal myocardial infarction distinguished this study from other studies. The second technique, intracardiac echocardiography, using the Acunav®-probe, continuously provides the operator with high quality images which may be beneficial to guide the PTSMA procedure. We evaluated this technique on operator-dependency and on its value as PTSMA-guide.

Currently, only few centers have studied whether PTSMA is equally effective as septal myectomy in HCM patients.[25-27] We describe the 1-year follow-up results of 43 patients, who underwent PTSMA, and of 29 patients, who underwent surgery.[28] We compared the outcome of the two techniques in respect to hemodynamic and clinical outcome to obtain more insight in the advantages and disadvantages of each of the two therapies. We evaluated the role of PTSMA in relation to surgery and compared our findings to the studies of others.[25-27]

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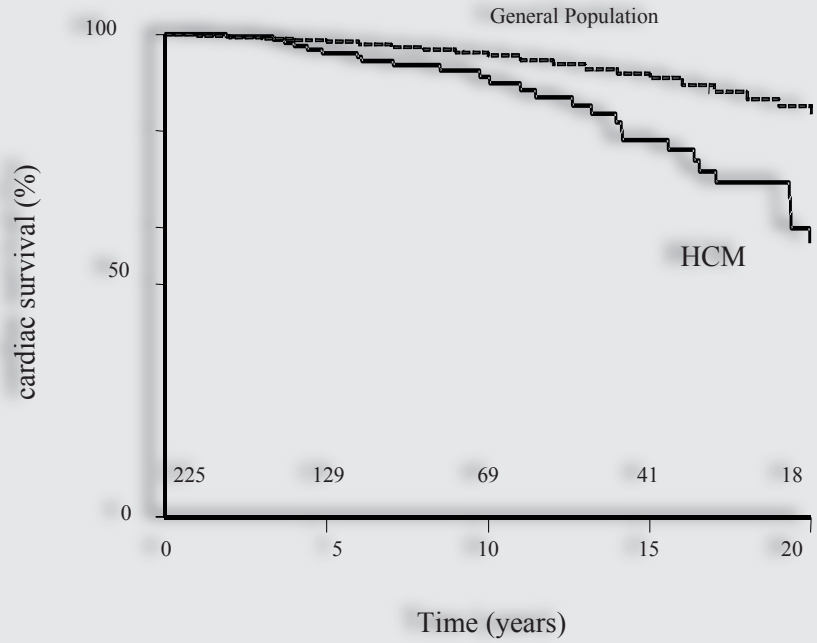
# 2

# Hypertrophic cardiomyopathy in daily practice: an introduction on diagnosis, prognosis and treatment

C. van der Lee, M. Kofflard, M. Geleijnse, F. ten Cate

*Netherlands Heart J 2005;13:452-460*



## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex, inherited cardiac disease that has been subject of intense investigation since its first description in 1957. Over the past 40 years, understanding has evolved regarding the diagnosis, prognosis and treatment of HCM. Analyses of HCM populations from non-referral centers have refined the insights in the natural history and the occurrence of sudden cardiac death, which is the most devastating component of its natural history. Therapeutic strategies are diverse and may vary during the course of the disease. Optimal therapy depends on symptoms, hemodynamic findings and the presence of risk factors for sudden cardiac death. At present, invasive therapy for patients with obstructive HCM and drug-refractory symptoms includes surgery or percutaneous transluminal septal myocardial ablation.

This report summarises the diagnostic criteria, clinical course and therapeutic management of HCM. Also, attention is paid to certain issues of special interest in this disease.

### Diagnosis

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease, first described as a clinical entity in 1957.[1] The diagnosis is based on the echocardiographic existence of a hypertrophied, non-dilated left ventricle (LV) in the absence of apparent causes for hypertrophy such as aortic valve stenosis and hypertension.[2] The disease is caused by mutations in genes encoding for the proteins of the cardiac sarcomere.[3] Usually, the left ventricular wall is thickened with a varying degree of hypertrophy, ranging from mild (13-15 mm) to massive (>30 mm). [4-6] Adults with increased left ventricular thickness secondary to diseases such as amyloidosis, metabolic diseases such as glycogen storage disease and Anderson-Fabry disease and syndromes such as Friedreich's ataxia and Noonan's syndrome are usually excluded from HCM. Routine physical examination is often not a reliably tool to suspect nor to establish HCM. A typical systolic heart murmur is only in patients with the obstructive type of HCM (HOCM). The murmur, which often increases with a Valsalva manoeuvre, originates from obstruction of blood flow in the left ventricular outflow tract (LVOT). This obstruction is caused by the hypertrophied septum and systolic anterior motion of the anterior mitral valve (SAM). The Venturi mechanism, flow drag of the leaflets and/or anterior displacement of the papillary muscles, which allows the mitral valve to protrude into the outflow tract, may cause the latter phenomenon. As a result of SAM, a posterior directed mitral regurgitation jet may frequently be visualized due to malcoaptation of the anterior and posterior mitral valve leaflets (figure 1A). In HOCM, color-flow Doppler echocardiography typically demonstrates turbulence

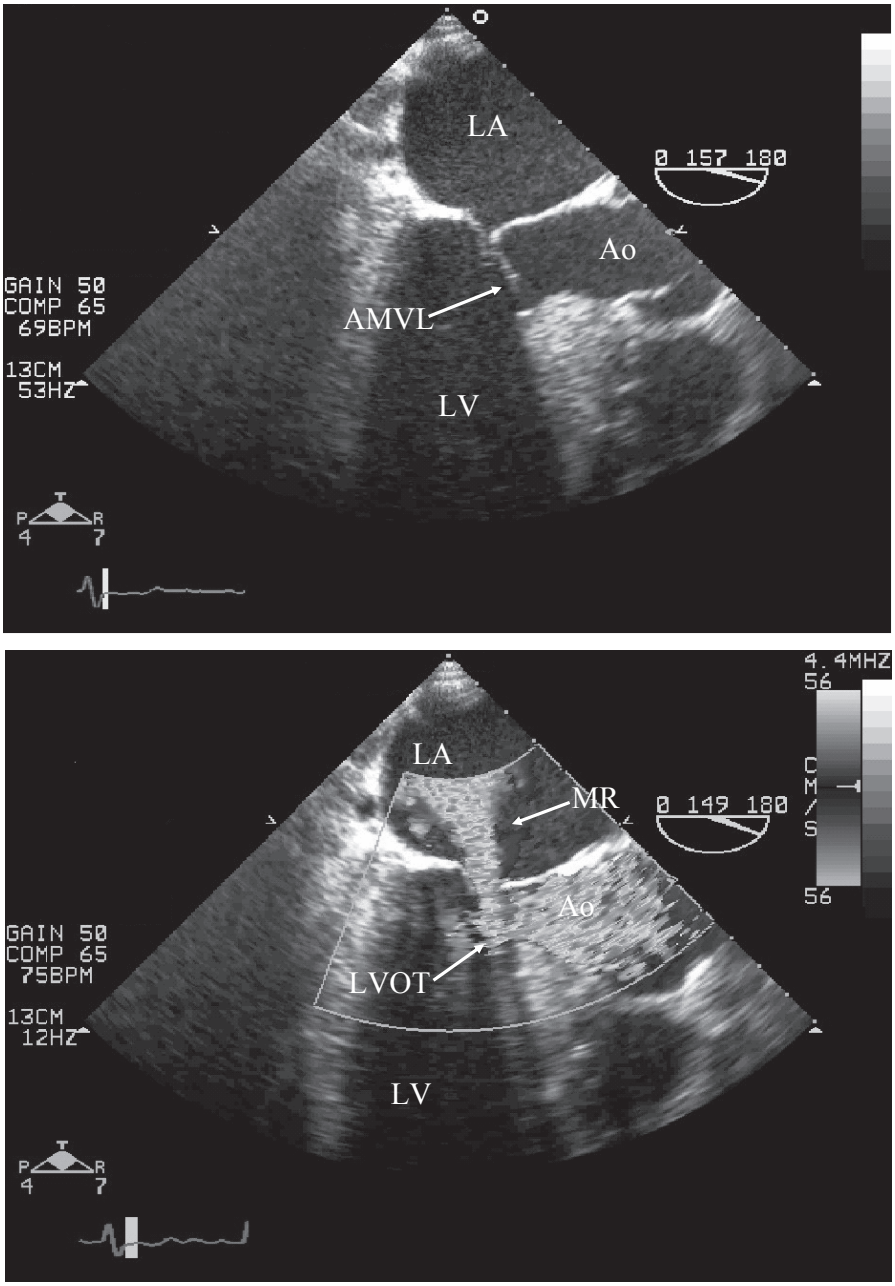



**Figure 1.** Esophageal multiplane echocardiography.

Panel A: Cross sectional view through the LVOT at approximately 160 degrees shows SAM of the anterior mitral valve leaflet (AMVL). Mal-coaptation of the anterior and posterior mitral leaflets is clearly seen.

Panel B: With color-flow imaging, the mitral regurgitation jet, which is directed towards posterior, is visualized. Also note the turbulent flow within the LVOT, which is caused by the obstruction.

Abbreviations: Ao = Ascending Aorta. LA = Left Atrium. LV = Left Ventricle. LVOT = Left Ventricular Outflow Tract. MR = Mitral Regurgitation jet.

of blood flow in the LVOT and, if present, a posterior directed mitral regurgitation jet (figure 1B). Doppler echocardiography is used to record the typical "dagger-shaped" signal (figure 2) and to calculate the severity of obstruction using the simplified Bernoulli equation ($P = 4v^2$). LVOT obstruction is observed in approximately 25% of patients with HCM.[7]

The 12-lead electrocardiogram demonstrates abnormalities in 75 to 95% of all patients, including signs of left atrial enlargement, left ventricular hypertrophy, T-wave abnormalities, pathological Q-waves and atrial fibrillation.[8,9] Electrocardiography remains an important tool of screening at any age, especially since it may be the only abnormal finding even in the presence of a normal echocardiogram. Originally, a normal echocardiogram at adulthood was thought to exclude the diagnosis of HCM. Advances in genetic research, however, provided evidence that individuals with a disease-causing mutation may develop hypertrophy at any stage in life. For instance, late-onset left ventricular hypertrophy (even after middle age) has been demonstrated in patients with a myosin-binding protein C (MYBPC) or troponin T mutation.[10-13] If the specific genetic mutation is unknown, first degree family members of patients with HCM should therefore undergo routine echocardiographic screening every two years at young age and every 5 years after adolescence.[14] In individuals with co-existing hypertension or in highly trained athletes, the diagnosis

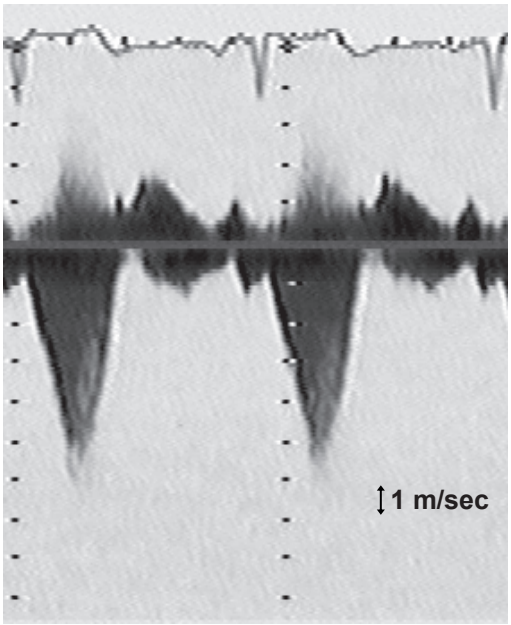



**Figure 2.** Continuous wave Doppler, characteristic for the dynamic outflow tract obstruction in HOCM patients. Note the late-peaking "dagger-shaped" appearance of the velocity envelope.

may be more difficult since these circumstances may contribute to LV hypertrophy. However, hypertensive patients without HCM usually have concentric LV hypertrophy. In these individuals, the extent of the hypertrophy usually does not exceed 15 mm and SAM is usually absent.[15] In the presence of mild hypertrophy and a positive HCM family history, genetic testing might be the only tool to exclude the presence of HCM in hypertensive individuals. In trained athletes, left ventricular hypertrophy is always mild (≤ 16 mm), left atrial enlargement and diastolic dysfunction are absent, at electrocardiography prominent q-waves are absent and regression of hypertrophy can be demonstrated on deconditioning.[16,17]

**Prevalence**

Epidemiological studies, using echocardiography estimate the prevalence of HCM at approximately 1 in 500 persons.[18] This number may be an underestimation since not all genetically affected patients necessarily demonstrate the echocardiographic abnormalities. In theory, genetic screening is the best method to estimate the true prevalence of HCM in the society. However, it is thought that a large number of mutations still await identification and besides that, genetic screening is complex, time-consuming and expensive.



**Pathology**

The distribution of hypertrophy in HCM is heterogeneous, characteristically asymmetrical and in about one-third of the patients localized in a single segment.[2] The anterior septum is usually predominantly involved in the hypertrophic process. However, concentric, apical, and atypical distributions are also present. Right ventricular hypertrophy can coexist with left ventricular hypertrophy, yet right ventricular hypertrophy unaccompanied with hypertrophy of the left ventricle is not observed in patients with HCM. Apical hypertrophy is most often seen in the Japanese HCM population. This type is often associated with negative T-waves on the electrocardiogram and LVOT obstruction is usually absent.[19] The main pathological findings in patients with HCM are hypertrophy and disorganisation of the myocardial cells called "myocyte disarray", medial hypertrophy of the intramyocardial coronary arteries (small vessel disease) and interstitial fibrosis.[20-22] Myocardial disarray has been observed in normal hearts and in individuals with congenital heart disease, but in these settings the disarray is usually mild. Extensive myocyte disarray, occupying substantial portions of the left ventricular wall, is a highly sensitive and specific marker for the diagnosis of HCM.[7]

Symmetrical and asymmetrical left ventricular hypertrophy is also seen in several metabolic and syndromic diseases, and diseases like amyloidosis and phaeochromocytoma. However, myocyte disarray is absent in these diseases, mutations in

the sarcomeric genes are lacking and the clinical course of most of these diseases differs from the patient with HCM.[22] The disorganisation of the cellular architecture and myocardial fibrosis in HCM probably serve as arrhythmogenic substrates which predispose to electrical instability as noted by the presence of extensive cellular disarray in young patients who die suddenly.[20] The substrate is likely the source of fatal ventricular tachyarrhythmia leading to sudden death in these patients, either primarily or in association with triggers as myocardial ischemia, hypotension, supraventricular tachyarrhythmia's, diastolic dysfunction, LVOT obstruction and physical exertion.[7]

**Genetic mutations**

HCM is an inheritable disease with an autosomal, dominant pattern.[23] The disease is caused by mutations in one of ten genes, each encoding for proteins of the cardiac sarcomere.[24] The most commonly affected proteins are ß-myosin heavy chain, cardiac troponin T and MYBPC.[25-27] To a lesser extent, mutations have been described in the cardiac troponin I, regulatory and essential myosin light chains, titin, α-tropomyosin, α-actin and α -myosin heavy chain.[24,28-30] In HCM, most gene abnormalities are missense mutations that result in a single amino acid substitution within or close to important functional domains.[31] For instance, the β-myosin heavy chain protein consist of 1936 amino acids and in one of the most reported mutations, the β-myosin heavy chain $Arg^{403}Gln$, the amino acid arginine is replaced by glutamine at coding position 403. In the Dutch HCM population, a mutation in the MYBPC gene is responsible for at least 45% of patients with HCM and in 60% of them the 2373insG mutation is the causal genetic defect.[32] Interestingly, the phenotypical expression of the disease varies not only between individuals with an identical genetic mutation but also exhibits interfamilial phenotypic variation, whereby affected individuals from the same family display distinct clinical and morphological manifestations.[22] This indicates that the phenotypical expression of the mutation is influenced by multifactorial causes such as sex, life-style, risk factors and modifier genes.[33-35]

**Clinical course**

The first data concerning the natural history of HCM were derived from hospital-based populations. However, the cohort of patients in these tertiary centers comprised for the most seriously disabled patients referred for advanced care. These patients personify a selected minority and their clinical course seems to represent the worst end of the disease spectrum. Annual mortality rates in these patients were as high as 4% - 6%.[36-40] We now know that these figures are not representative for the "average" patient with HCM and data from non-referral centers suggest a more benign prognosis with an annual mortality of less than 1%.[41-47] Follow-up of

the HCM population in the Thoraxcenter of the Erasmus Medical Center disclosed similar mortality rates: cardiac death was 0.8%/year and sudden cardiac death was 0.6%/year, respectively.[48] It is important to realise that the majority of patients with HCM may remain a lifetime without symptoms. If the patient has symptoms, typical complaints are dyspnoea, exertional angina, palpitations and (pre)syncope.[45] Dyspnoea, which is the most common complaint, can result from a variety of mechanisms, such as diastolic dysfunction, LVOT obstruction, marked mitral regurgitation and severe left ventricular systolic dysfunction in patients with "end stage" disease. Exertional chest pain occurs in approximately 25% of patients with HCM, usually in the setting of a normal coronary arteriogram. The development of angina may be induced by an increase in myocardial oxygen demand or a reduction in myocardial blood flow and oxygen supply. Factors that increase myocardial oxygen demand are myocyte hypertrophy, increased myocardial mass, and LVOT obstruction, whereas impaired vasodilator reserve, small vessel disease, and inadequate capillary density reduce myocardial blood flow. Approximately 20% of patients have complaints of (pre)syncope. Syncope is a complex entity since multiple mechanisms may be involved, leading to an inadequate cardiac output or abnormal peripheral vascular reflex. These mechanisms include supraventricular and ventricular tachyarrhythmia's, conduction abnormalities and atrioventricular nodal block, LVOT obstruction, myocardial ischemia during exertion, diastolic dysfunction and ventricular baroreflex activation with inappropriate vasodilatation.[48]



Sudden death (SD) is the most tragic event in this disease and it can be the first manifestation of HCM in patients who are unaware of their disease or in those who are mildly symptomatic.[49] The prevention of SD in the individual patient remains one of the most challenging goals in the management of HCM. SD can occur at any age, at rest but in many cases during vigorous exercise. The patients at higher risk for SD comprise approximately 10-20% of the total HCM population. They may be identified by the presence of one or more of the following risk factors: 1) survivors of sudden cardiac death, 2) spontaneous (non)sustained ventricular tachycardia, 3) family history of multiple sudden deaths at young age, 4) (pre)syncope, 5) hypotensive blood-pressure response during exercise or 6) extreme LVH.[31,39,50-54] To date, there are no convincing data that patients with LVOT obstruction or patients with a specific causal gene are at particularly high risk for SD.[44,55,56]

High-risk patients were generally treated with either ß-blockers, verapamil or antiarrhythmic drugs like amiodarone.[55,56] However, none of these drugs are proven to be effective in preventing SD.[7] The automatic implantable cardioverter-defibrillator (ICD) is the first device to treat potential fatal arrhythmias effectively and to alter the natural history of the HCM patient.[57-60] Recently, the ICD proved to be very effective in patients who had survived a cardiovascular collaps.[57] Primary prevention

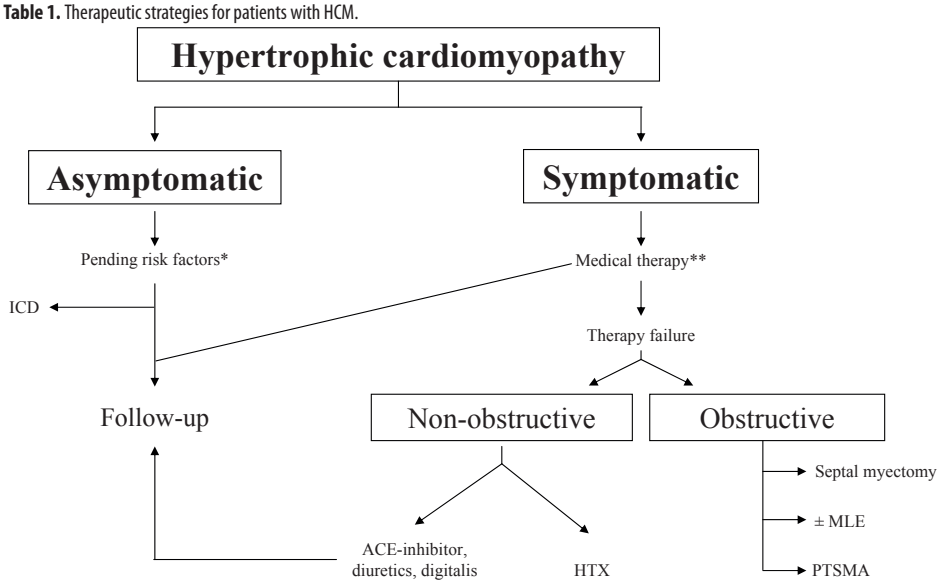
in high-risk patients may also be effective. The American College of Cardiology and the European Society of Cardiology stated to implant the ICD in HCM patients who survived SD and advised ICD therapy in patients having two or more risk factors, other than surviving a cardiac arrest.[14]

## THERAPEUTIC MANAGEMENT

### Medical treatment

Therapeutic strategies in HCM patients are multifaceted and may vary during the course of the disease. The choice for the optimal therapy depends mainly on the presence of symptoms, a LVOT gradient, and the presence of risk factors for SD (Table 1). Medical treatment is usually not indicated in the absence of symptoms. In patients with dyspnoea, chest pain and/or (pre)syncope, ß-blockers or the calcium antagonist verapamil are the preferable drugs to relieve complaints.[61,62] Both drugs are negative inotropic and chronotropic and reduce myocardial ischemia and angina trough lowering heart rate, left ventricular contractility and myocardial wall stress during systole. By decreasing heart rate and reducing ischemia, left ventricular filling improves, which may consequently diminish symptoms of dyspnoea and (pre)syncope. Moreover, ß-blocking agents may reduce the exercise-generated

**Table 1.** Therapeutic strategies for patients with HCM.




* = Risk factors as described in text.

** = Medical therapy as described in text. HTX = Heart Transplantation. MLE = Mitral Leaflet Extension. AICD = Automatic Implantable Cardioverter Device.

increase in obstruction. Verapamil should be administered with caution in patients with obstruction since this drug may aggravate the LVOT gradient and increase clinical symptoms.[63]

Disopyramide, an antiarrhythmic drug with negative inotropic properties may serve as an alternative in patients with obstruction, who are unresponsive to treatment with ß-blockers or verapamil.[64-66] The drug may be combined with low doses of a ß-blocker to potentiate its effect.[67] Unfortunately, disopyramide frequently causes intolerable side effects in elderly patients because of its vagolytic properties.

An estimated 5% of the patients progress to a dilated type of cardiomyopathy with signs of heart failure. In this group, symptoms are treated with diuretics, digitalis, ACE-inhibitors, and ß-blockers. If patients do not respond to medical therapy, heart transplantation may be considered.[68,69]

**Invasive therapy**

Invasive therapy is indicated in patients with persisting symptoms, despite optimal medical treatment and a LVOT gradient of more than 50 mm Hg.

**Surgical therapy**

Cleland described the first invasive procedure to treat HOCM patients; further developments were accomplished by Morrow in the late 1960s.[70,71] The Morrow procedure entails partial resection of the hypertrophied septum. Mortality rate was high in the first series of patients but the results dramatically improved with growing experience of the surgeon and increased understanding of the pathophysiology of HOCM.[67,72-74] Recent results from experienced centers report mortality rates of <2%.[75-79] Originally, a rectangular septal through was created, starting directly under the aortic annulus, which is usually the thinnest portion of the septum, and ending just below the tip of the mitral leaflets. This approach could lead to several complications, including a ventricular septum defect, conduction disturbances and aortic valvular regurgitation.[80] Nowadays, a 2-3 mm subaortic muscular ring is preserved at operation to prevent these serious complications.

Preferably, resection of the septal bulge is performed to the base of the papillary muscles (extended myectomy). In doing so, not only the LVOT is widened but also the direction of blood flow is changed. Before surgery, the midseptal bulge redirects the flow direction so that it comes from a lateral and posterior direction. In this way, flow gets behind the mitral valve and pushes it to the septum (flow drag). After extended myectomy, flow tracks more anteriorly and medially abolishing SAM and obstruction (Figure 3A and B).[81,82]

Intraoperative transoesophagial echocardiography is frequently used to judge the maximal septal thickness, distance of maximal thickness from the aortic annulus, lo-

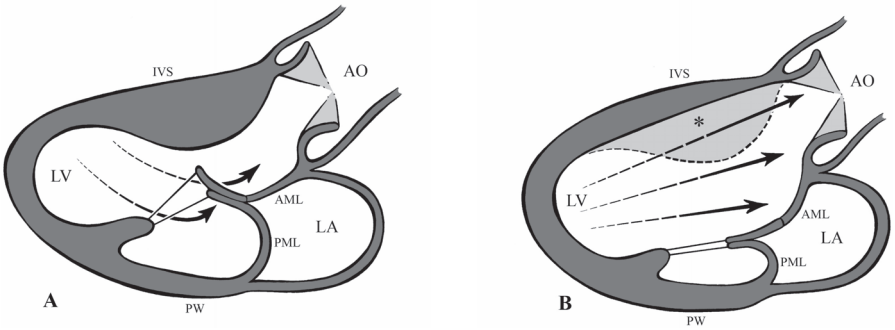



**Figure 3.** Panel A: The streamlines of flow circumvent the hypertrophied septum, which bulges into the outflow tract. The flow may hit the anterior mitral leaflet on its posterior surface, dragging it toward the septum. Abnormal mobility of this leaflet is facilitated due to leaflet elongation and anterior displacement of the papillary muscles.
Panel B: Once the streamlines of flow have been straightened by septal myectomy (dashed area indicated by asterisk), blood flow runs directly from the apex towards the outflow tract. Also, the flow hits the leaflet on its anterior surface, pushing the leaflet towards posterior.
Abbreviations: AML = Anterior Mitral Leaflet. AO = Ascending Aorta. IVS = InterVentricular Septum. LA = Left Atrium. LV = Left Ventricle. PML = Posterior Mitral Leaflet. PW = LV Posterior Wall.

cation of mitral valve and septal contact, expansion of the septal bulge towards the apex, anatomy of the mitral valve and its subvalvular apparatus and to guide surgical intervention. Abnormalities of the mitral valve and subvalvular apparatus include an increase in length of the anterior mitral valve leaflet, increase in mitral valve area, abnormal laxity of the mitral valve, anterior position of the papillary muscles and hypertrophy as well as fusion of the papillary muscles.[82] These abnormalities may lead to residual SAM even after a successful myectomy resulting in inadequate relief of obstruction and persistence of mitral regurgitation.[83-86] Therefore, some surgeons have applied several modifications to the (extended) myectomy procedure. First, mitral valve replacement has been performed in these patients. Although this approach has superior hemodynamic results compared to myectomy, the application of this technique is limited due to serious complications related to the long-term use of anticoagulants in these often young patients.[87] Alternative techniques that often combine septal myectomy with a mitral valve repair technique, have been developed to provide an optimal surgical outcome.[88-91]

McIntosh *et al.* introduced a combined approach of septal myectomy and mitral leaflet plication in patients with elongated and enlarged anterior mitral leaflets.[88] This technique aims at shortening the abnormal anterior mitral valve to counteract its property to protrude into the LVOT during systole. First, the region of leaflet-septal contact, which is characterized by a small fibrotic area, is identified. At this point, interrupted sutures are placed perpendicular to the long axis of the leaflet. Leaflet tissue is not resected to avoid restriction in leaflet mobility (figure 4A).

Swistel *et al.* described an alternative mitral valve repair technique in combination with myectomy and papillary muscle mobilization.[92] In contrast to the technique

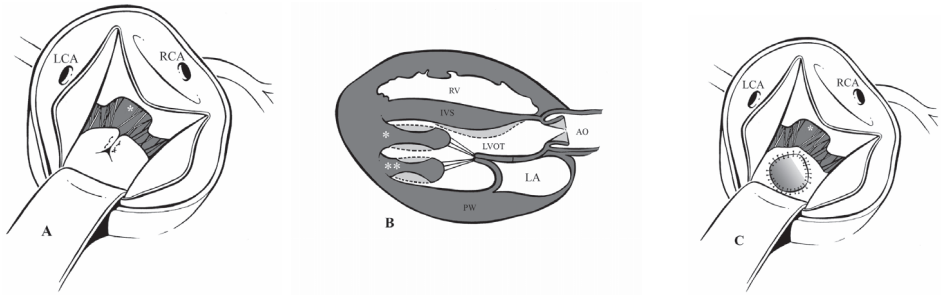



**Figure 4.** Panel A: *Mitral plication:* One (or more) sutures are placed perpendicular to the long-axis of the mitral leaflet, starting at the chordal insertion into the leaflet, near the fibrotic contact lesion to prevent residual systolic anterior motion after completed septal myectomy (indicated by the asterisk).

Panel B: *Papillary mobilisation:* Partial resection (indicated by the dashed lines) of the anterior lateral (asterisk) and the posteromedial (double asterisk) papillary muscles, which separates them from each other and from the myocardial wall. Mobilisation also allows them to assume a more posterior position in the left ventricle. Site of septal myectomy is clearly seen. RV = Right Ventricle.

Panel C: *Mitral leaflet extension:* Through an oblique incision in the ascending aorta, the septal hypertrophy and the anterior mitral leaflet are visualized. The myectomy trough (indicated by the asterisk) and the inserted patch are clearly seen.

**Abbreviations:** AO = Ascending Aorta. IVS = InterVentricular Septum. LA = Left Atrium. LCA = Left Coronary Artery. LV = Left Ventricle. PW = LV Posterior Wall. RCA = Right Coronary Artery.

described by McIntosh *et al.*, the plication sutures are applied in a medial-lateral position, which will not only shorten but also stiffen the anterior mitral valve leaflet to prevent its post-operative movement into the LVOT.

Messmer *et al*. described a technique to correct the hypertrophied papillary muscles by partial resection of the papillary muscles.[93] The technique aims to reduce the diameter of the papillary muscles and separate them from the myocardial wall and from each other (Figure 4B). This allows the papillary muscles to assume a more posterior position in the left ventricle and it permits the mitral valve to assume its more normal posterior position, explicitly out of the LVOT. Both mitral plication methods have resulted in satisfactory hemodynamic outcome in patients who were at risk of residual SAM and LVOT obstruction after septal myectomy alone.

Normally, surgical therapy for HOCM is performed by a transaortic approach. The transmitral approach is an alternative approach, especially in patients with an obstruction at the mid-ventricular or at papillary muscle level.[94] First, the mitral valve is visualized through a left atriotomy. The anterior mitral valve leaflet is detached from the annulus, leaving both commissures intact. By pushing the leaflet aside, the left ventricular cavity is opened and the region of myocardial hypertrophy as well as the obstructive lesion (the contact area between septum and mitral leaflet) may be more carefully identified. The thickened septum that bulges into the LVOT is resected. This method especially allows careful inspection of the portion of the left ventricle that reaches towards the apical region and creates both the possibility to excise myocardial tissue at this level and to mobilize and resect part of the hypertrophied papillary muscles. In the presence of a prominent SAM, the surgeon may

additionally perform a mitral leaflet plication with sutures placed in such a manner to approximate the redundant and thickened primary chordae tendinae. The transmitral approach has limited applicability but may be preferred in the paediatric group or in patients with a complex type of LV obstruction, due to limitations of the transaortic view.

In our institution, a new surgical technique has been developed to treat symptomatic patients with HOCM and an enlarged anterior mitral valve leaflet.[95] The technique entails septal myectomy in combination with anterior mitral leaflet extension via a transaortic approach. After myectomy, a gap is created in the anterior mitral leaflet trough a longitudinal incision, starting at the subaortic hinge point towards the rough zone. Then, an oval autologous pericardial patch is inserted using three running sutures (Figure 4C). The patch creates a horizontal, but not a vertical widening of the leaflet. It appears counterintuitive to enlarge a leaflet, which itself is already abnormally enlarged (Figure 5). Why then does leaflet extension work? First, the pericardial patch is grafted in the center portion of the anterior leaflet, where SAM typically reaches a maximum. By extending the patch across the bending point of the mitral valve, we hypothesize that we stiffen the central parts of the buckling

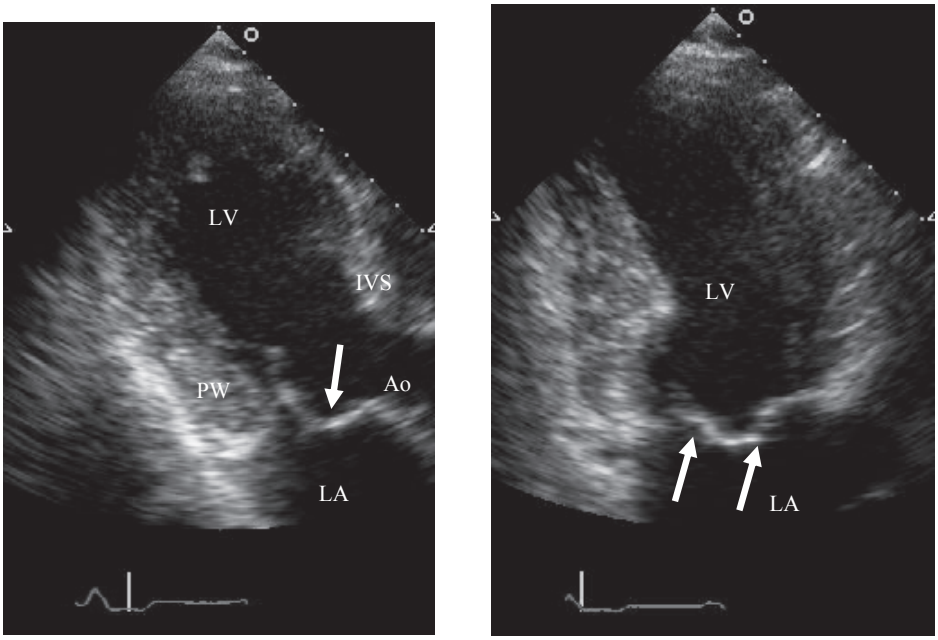



**Figure 5.** Panel A: Post-operative two-dimensional echocardiogram from the apical three chamber long-axis view. The site of the inserted pericardial patch is clearly seen (arrow). Residual systolic anterior motion is absent.
Panel B: Two-dimensional echocardiogram from the apical two chamber long-axis view. The echocardiographic still-frame clearly demonstrates the pericardial patch, which has been inserted into the anterior mitral valve leaflet (between arrows).
Abbreviations: AO = Ascending Aorta. IVS = InterVentricular Septum. LA = Left Atrium. LV = Left Ventricle. PW = LV Posterior Wall.

anterior leaflet, preventing abnormal mobility.[96-98] Second, stiffening of the valve may counteract Venturi forces. Third, the widening of the leaflet may cause a lateral shift of the chordae attaching central portions of the valve, subsequently stretching and erecting these chordae thus enhancing leaflet coaptation. Fourth, mitral leaflet extension could also add positively to maintenance of valve tethering once the streamlines of flow are normalized by septal myectomy.[81] Recently, we described the sustained improvement of this method during long-term follow-up.[78]

Refinement and modifications of the classical Morrow resection resulted in more effective surgical methods to treat symptomatic HOCM patients. As previously mentioned, complication rates are low and clinical outcome is excellent.[77,99]

## ALTERNATIVE INVASIVE THERAPIES

A subset of patients, who might benefit from operation, may not be ideal surgical candidates due to concomitant diseases or advanced age. Others may not have access to the few experienced surgical centers. Therefore, two treatment modalities have been proposed as alternatives to surgery. First, dual-chamber pacing was considered to be beneficial in reducing both symptoms and the LVOT gradient.[100,101] Randomized, crossover clinical trials, however, could not confirm the beneficial results of the initial studies: the reduction in LVOT obstruction was unpredictable and significantly less when compared to surgical therapy. Besides that, the amelioration in functional class was believed to be a placebo effect.[102,103]

Percutaneous transluminal septal myocardial ablation (PTSMA) is another interventional technique.[104] Ethanol is introduced into one or more septal perforator branches of the left descending coronary artery (LAD) to produce a localised myocardial infarction, which in turn results in shrinkage of the basal septum, enlargement of the narrowed LVOT and reduction of the outflow gradient and mitral regurgitation. The procedure is considered a success if the residual LVOT gradient is <30 mm Hg or there is at least a 50% reduction in LVOT obstruction immediately after the procedure. Due to remodelling of the left ventricle, the LVOT gradient will even decrease weeks to months after PTSMA. With regard to clinical outcome, mortality (<2%) is comparable to surgical therapy.[105-108] Furthermore, non-randomized studies show that myectomy and PTSMA are similarly associated with subjective improvement in NYHA functional class.[105-107] However, surgery yields a more favourable outcome with respect to fewer early complications, greater exercise capacity and oxygen consumption and from time to time more complete relief of obstruction.[109] The early complications after PTSMA relate to anterior myocardial infarction due to leakage of alcohol in the LAD, dissection of the LAD and myocardial infarction

distal to the septal myocardium due to abnormal anatomy of the septal branches. The application of myocardial contrast echocardiography (MCE) has diminished these complications and adverse results are now reported infrequently.[110,111] Yet, the risk for permanent pacemaker therapy is up to ten times greater with PTSMA as compared to myectomy and the potential risk of life-threatening ventricular tachyarrhythmia's emanating from myocardial necrosis is of particular concern in HCM given the unpredictable arrhythmogenic substrate.[14,109,112]

Until recently, only three studies have compared the results of surgical myectomy to PTSMA.[105-107] These nonrandomised studies reported that surgical myectomy and PTSMA are equally effective at reducing LVOT obstruction and lead to similar subjective improvements in functional capacity. It is true that the resting LVOT gradient is significantly lower in the myectomy group than in the PTSMA group after three months,[106] but the residual LVOT gradient is comparable one year after intervention.[105,107] The greatest difference comparing the two interventional strategies in these three studies is the incidence of complete heart block necessitating permanent pacemaker therapy (2 to 8% after surgery vs. 15 to 24% after PTSMA, respectively).[105-107] Just recently, Ralph-Edwards *et al.* reported the results of a nonrandomised study comparing PTSMA versus isolated myectomy.[113] There were no deaths during post-procedure hospitalization, but during two year follow-up cardiac related death occurred in 6% after PTSMA versus 0% after myectomy underscoring the possibility of late-onset ventricular tachyarrhythmia's in the presence of a healed intramyocardial scar in patients with an already unstable electrophysiologic substrate. The patients undergoing PTSMA had significantly higher post-interventional resting LVOT gradients, and the NYHA functional class as well as residual SAM were significantly worse. The optimal composite outcome at follow-up, defined as survival, NYHA functional class I, no post-procedure pacemaker placement, and a follow-up resting LVOT gradient of less than 20 mm Hg was noted in 22% of patients in the PTSMA group and 73% of patients in the myectomy group.

Recently, we have compared the outcome in HOCM patients with an enlarged anterior mitral valve leaflet after PTSMA or surgical intervention in 43 and 29 patients, respectively.[108] At surgery, myectomy was combined with anterior mitral leaflet extension, as described before. In our study, the equivalence of PTSMA versus surgery was observed with regard to the effect on the LVOT obstruction and the improvement in functional class at 1-year follow-up. However, mitral regurgitation and residual SAM of the mitral valve were less after surgical intervention. Of importance, PTSMA was related with more peri-procedural complications and re-interventions due to persistence of the LVOT obstruction: death 5% vs. 0%; large anterior myocardial infarction 2% vs. 0%; permanent pacing 9% vs. 0%; re-intervention 9% vs. 3% after PTSMA and surgery respectively.

At present, septal myectomy remains the gold standard to treat patients with HOCM. Structural LVOT anomalies including the mitral apparatus, direct insertion of a papillary muscle into the anterior mitral leaflet, fusion of the papillary muscles to the ventricular septum, as well as fibrous attachments between the septum and the mitral valve may result in persistence of obstruction after PTSMA. During operation, the surgeon may widen and reconstruct the LVOT by treating these morphologic abnormalities under direct visualisation. PTSMA is a selective alternative to surgery, especially in patients without structural anomalies of the mitral valve and subvalvular apparatus and important comorbidity or at advanced age.[114] To define the role of PTSMA in the treatment of HOCM, it would be necessary to perform a randomised trial in a large population comparing these two treatment modalities.[115] However, such a study is difficult to achieve due to the heterogeneity of the disease, the limited number of patients and the many centers required worldwide to obtain sufficient data in a reasonable time span.[115]

## ISSUES OF SPECIAL INTEREST



### Pregnancy

Pregnancy is accompanied by major physiological changes. Cardiac output increases by 30 to 50% due to augmentation in plasma volume, there is a modest increase in heart rate and a decrease in peripheral resistance. In addition, cardiac output increases by a further 20% during labour due to increased venous return with each uterine contraction and sympathetic response to stress and pain.[116,117] These physiological demands may be expected to affect the course of pregnancy. However, most data suggest that pregnancy is generally well tolerated in HCM patients despite the often marked hypertrophy, the diastolic dysfunction and the LVOT obstruction in the HCM-affected heart.[14,116-118] In asymptomatic patients, clinical deterioration during pregnancy is uncommon.[118] Yet, in patients with cardiac complaints before pregnancy, progression of symptoms of heart failure may occur in a minority of patients. Careful monitoring and collaboration with a dedicated cardiologist may minimize complications in patients who have signs of heart failure. Maternal mortality appears to be confined to women with a high-risk clinical profile.[14]

### Endocarditis

Infective endocarditis is a known, yet uncommon complication of HCM.[119] Endocarditis in HCM is almost exclusively confined to patients with a LVOT obstruction under basal conditions and to nonobstructive patients with intrinsic mitral valve disease, such as mitral valve prolapse.[14,119] In most cases, the site of vegetations is the

anterior mitral valve leaflet. However, vegetations can also be present on the aortic valve or the endocardium of the LVOT at the point of mitral-septal contact.[120,121] Patients with the nonobstructive type of HCM, including those with a LVOT obstruction under provocation, are at negligible risk for endocarditis and consequently do not require prophylaxis.[119] Antibiotic prophylaxis for endocarditis is only indicated in patients with the obstructive type of HCM and in patients with intrinsic mitral valve disease.

**Participation in sport**

Although SD is a long-recognized entity in HCM, the recent deaths of several well-known athletes have focused new attention on this devastating and often unpredictable complication of HCM. Several studies have found that HCM is the principal cause of SD in young athletes under 35 years of age, accounting for approximately one third of cardiac arrests in the USA.[122-124] SD in HCM is usually the result of an interaction between triggers (myocardial ischemia, diastolic dysfunction, LVOT obstruction, systemic arterial hypotension and supraventricular tachyarrhythmias) and an unstable electrophysiological substrate (myocardial disarray, myocardial fibrosis and expansion of the interstitial collagen compartment) which may lead to fatal ventricular tachyarrhythmias.[14,56] Physical exertion may also constitute a trigger of SD in patients with HCM and there is indirect evidence that identification and disqualification of individuals with HCM from competitive sports may prevent SD.[7,14,124,125] In the 26th Bethesda conference report guidelines are presented for athletic eligibility or withdrawal of the athletes from sports. The guidelines state that young athletes with HCM are discouraged from participating in competitive sports, with the exception of low-intensity sports such as walking, golf and bowling.[126,127] For older athletes (>35 years), a less restrictive policy is probably a more proper approach. If risk factors for SD are absent, modest, nonvigorous physical activities may be permitted. There is no evidence that genetically affected family members without phenotypical expression of the disease are at increased risk for SD. Therefore, in the absence of a family history of SD and cardiac symptoms, participation in sports activities is not discouraged in these individuals.[14] The incidence of SD from cardiovascular diseases in young athletes is as low as 1 to 2 in 100.000 athletes. This means that extensive pre-participation screening is not feasible in this population considering the cost-benefit relation and the expected large numbers of false-positive results. In 2004, a meeting of the ad-hoc working group on Sudden Cardiovascular Death in sport, held under the umbrella of the International Olympic Committee, discussed about measures that can help prevent SD. The results were summarized in the "Lausanne Recommendations", which seek to identify athletes at risk of sudden cardiac death in order to advise them accordingly. The most important recommendation com-

prises cardiovascular screening of young competitive athletes before participation, including questions concerning the athletes' personal and family history, a physical examination and a 12-lead ECG. The European Society of Cardiology recommends similar measures in a consensus document concerning pre-participation screening of young competitive athletes for prevention of sudden death[122]. The recommendations can detect patients with a cardiovascular disease like HCM and prevent fatal events by excluding these individuals from sport participation.[123]

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# 3

## Hypertrophic cardiomyopathy in a large community-based population: Clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration

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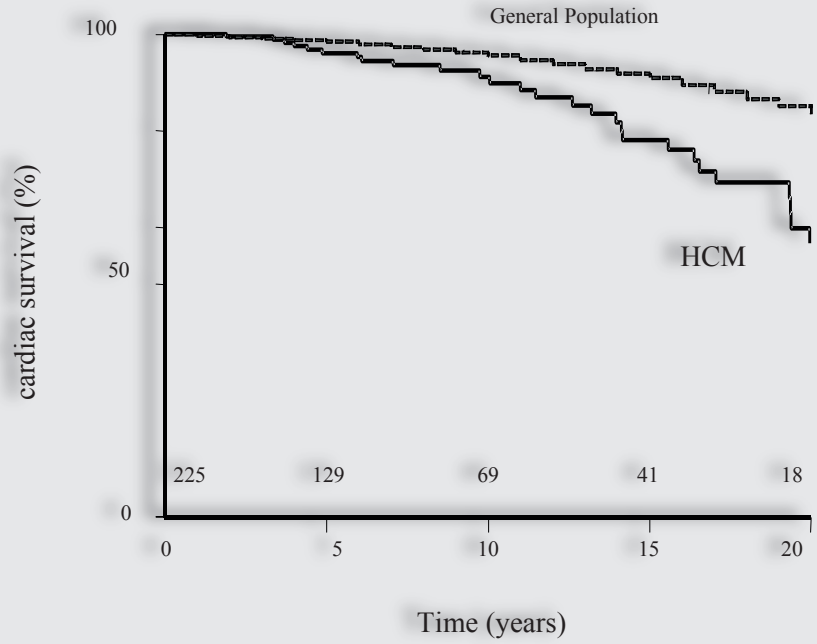
*J Am Coll Cardiol 2003;41:987-993*



## ABSTRACT

**Objectives.** This study evaluates the clinical course and identifies risk factors for sudden cardiac death and clinical deterioration in hypertrophic cardiomyopathy (HCM) in a large community-based population. Comparison was made with data from 6 tertiary referral and six non-referral institutions.

**Background.** HCM is a disease with marked heterogeneity in clinical presentation and prognosis. Risk factors for sudden cardiac death are not well defined in patients free of referral bias.

**Methods.** Between 1970 and 1999, 225 consecutive patients, mean age (± SD) 41 ± 16 years, were examined and followed at yearly intervals.

**Results**. Forty-four deaths were recorded of which 27 cases were cardiovascular. Fourteen patients died suddenly, six were successfully resuscitated and seven patients died of congestive heart failure. The annual mortality, the annual cardiac mortality and annual mortality due to sudden death were 1.3%, 0.8% and 0.6% respectively. At least one New York Heart Association (NYHA) functional class deterioration was reported in 33% of the patients with a significant (≥ 50 mm Hg) left ventricular outflow tract (LVOT) gradient in contrast to 7% without obstruction. The presence of syncope was related to sudden cardiac death ($p<0.05$). Younger age and more severe functional limitation discriminates patients from in hospital-based centers from the ones in community-based centers.

**Conclusions.** HCM is a benign disease in an unselected population with a low incidence of cardiac death. Syncope was associated with a higher incidence of sudden cardiac death and patients with a significant LVOT obstruction were more susceptible to clinical deterioration.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex cardiac disease with a heterogeneous genetic, morphologic and clinical spectrum.[1,2] In recent years, numerous mutations in different genes, encoding for proteins of the cardiac sarcomere, have been found to be responsible for this disease.[3-6] Unfortunately, the same mutation will not always result in identical morphological and clinical features.[7,8] Environmental as well as genetic factors may modify the phenotypic expression of the mutated gene.[3,8,9]

The diverse clinical and genetic characteristics make it difficult to establish general guidelines for the treatment of symptoms and to predict which patient is prone to sudden death. Most of our knowledge concerning the natural history and risk for premature sudden cardiac death (SCD) has been derived from the study of hospital-based populations.[10-18] These studies reported an annual mortality rate of 2 to 4% in adults and 6% in children. However, the clinical outcome and perception of risk factors in HCM is profoundly affected by a bias in patient selection.[19] Studies from non-referral centers suggested a more benign clinical course and fairly favorable prognosis with an annual mortality of ≤ 1%.[20-26] However, risk factors for SCD in patients with HCM have not been extensively studied in these community-based populations. The purpose of the present study was to evaluate the clinical course and to identify the presence of risk factors for SCD and clinical deterioration in a population of relatively unselected patients with HCM.

We compare our results with the results from hospital-based and community-based populations.

## METHODS

### Patient selection

Before 1979, only M-mode echo and 2 DE and no Doppler were available in our institution and the diagnosis of HCM was also made by the presence of typical clinical, electrocardiographic and/or angiographic findings. The diagnosis of HCM was later on based on the echocardiographic finding of a non-dilated hypertrophic left ventricle in the absence of diseases known to cause ventricular hypertrophy[1,2] Patients who visit our HC clinic are relatively unselected and consist of patients who are: 1) diagnosed and treated at our centre; 2) referred from the community for establishment of the diagnosis or advice on management; 3) transferred from outlying hospitals for advanced care; 4) self-referred family-members of patients.

### Follow-up

Between 1970 and 1999, 225 consecutive patients were examined initially and followed at yearly intervals. The population included 113 patients reported earlier.[22] The other 112 patients consisted of patients who were brought to our attention from 1990. At first visit, clinical characteristics including age at diagnosis of HCM, family history of HCM or sudden death in a first degree relative at a young age (<40 years), or both, symptoms, New York Heart Association (NYHA) functional class and the drugs prescribed, were recorded. Physical examination and baseline laboratory studies were performed including ECG, M-mode and two-dimensional echocardiography (as well as Doppler echocardiography after 1985) and in the majority of patient's 24-hour ambulatory Holter monitoring was carried out. Cardiac catheterization was performed only in patients with symptoms refractory to medical therapy in whom surgical treatment was considered. Follow-up information was obtained within 6 months from August 1999 at the outpatient clinic or, if the patient moved out of Rotterdam, from their private cardiologist. No patient was lost to follow-up. Cardiac death was defined as death caused by congestive heart failure or sudden death. All deaths witnessed within one hour of onset of symptoms or in subjects known to be normal functioning 24 hours before, were assumed to be SCD. Patients, who were successfully reanimated after cardiac arrest during follow-up, were classified as SCD for the purpose of analysis.



### Review of the literature on prognosis in patients with HCM

To compare our study findings, we reviewed the literature on prognosis in HCM in both hospital-based and community-based institutions. A total of 9 studies from 6 hospital-based centres and 6 studies from 6 community-based centres were found for comparison.

### Statistics

Data are expressed as mean value ± SD. Cumulative survival estimates and 95% confidence intervals (CIs) were calculated according to the Kaplan-Meier method. Among patients subgroups the log-rank test was used to evaluate differences in survival between subgroups. The yearly cumulative mortality rate was calculated on the basis of all available follow-up time. To assess risk factors for cardiac death and clinical deterioration univariate and multivariate analysis was performed using the Cox regression model.

The chi-squared test was used to compare clinical characteristics from referral and non-referral centers.

## RESULTS

### Baseline characteristics

The clinical characteristics of the 225 patients with HCM are listed in Table 1. The majority of the patients were male (n = 130). At first visit, 63 patients (28%) were younger than 30 years and 20 (9%) were older than 65 years. The mean age (± SD) at diagnosis of HCM was 37 ± 17 years and 41 ± 16 years at presentation to our institution. A positive family history of HCM was present in 110 patients (49%), of whom 52 patients (23%) also reported a sudden death in a first degree relative. Reported symptoms included angina in 58 patients (26%), dyspnea in 81(36%), syncope in 43 (19%) and palpitations in 43 patients (19%). At presentation, 100 patients (44%) were

**Table 1.** Baseline characteristics of 225 patients with HCM.

| | Number (%) |
|---|---|
| Patients | 225 |
| Male/Female | 130 (58%) / 95 (42%) |
| Age (y) | |
| <30 | 63 (28%) |
| 30-65 | 142 (63%) |
| >65 | 20 (9%) |
| mean age (years ± SD) | |
| at diagnosis | 37 ± 17 |
| at initial visit | 41 ± 16 |
| Family history | |
| Positive | 110 (49%) |
| Positive + SD | 52 (23%) |
| Symptoms | |
| Angina pectoris | 58 (26%) |
| Dyspnea | 81 (36%) |
| Syncope | 43 (19%) |
| NYHA | |
| I | 100 (44%) |
| II | 101 (45%) |
| III | 24 (11%) |
| IV | 0 |
| Therapy | |
| Beta-blocker | 47 (21%) |
| Ca-antagonist | 72 (32%) |
| Beta-blocker and Ca-antagonist | 16 (7%) |
| Antiarhythmics | 18 (8%) |
| Other | 11 (5%) |
| No medication | 61 (27%) |
| Interventricular septal width | |
| ≥ 25 mm | 30 (13%) |
| < 25 mm | 195 (87%) |
| LVOT gradient (mm Hg) | |
| ≥ 50 mmHg (at rest/provocation) | 98 (44%) |

asymptomatic or had trivial symptoms (NYHA functional class I), 101 patients (45%) had mild symptoms of exertional angina and/or dyspnea (class II) and 24 patients (11%) were moderately symptomatic (class III). Initially, patients were treated with beta-blocking agents, calcium antagonists, a combination of beta-blocking agents and calcium antagonists, antiarrhytmics or other cardiac therapy in 47 (21%), 72 (32%), 16 (7%), 18 (8%) and 11 patients (5%) respectively. Sixty-one patients (27%) did not take medication.

At echocardiography, mean interventricular septum width was 21 ± 4 mm (range 16 - 40 mm), thirty patients (13%) had marked left ventricular hypertrophy (interventricular septal width ≥ 25 mm). Left ventricular outflow tract (LVOT) gradient, at rest or provocation was ≥ 50 mmHg in 98 patients (44%), as determined by Doppler echocardiography or cardiac catheterization. At the initial visit, 7 patients (3%) presented with persistent atrial fibrillation (AF). Episodes of ventricular tachycardia (VT) on 24-hour ambulatory Holter monitoring were registered in 73 of the 149 patients, in whom recordings were available. At presentation, two patients had been treated by septal myectomy for LVOT obstruction.

### Clinical outcome

During follow-up 44 deaths were reported. Twenty-seven deaths (mean age 49 ± 17 years) could be attributed to cardiovascular causes: 20 (mean age 44 ± 15 years) of these died suddenly, of whom 6 were successfully resuscitated from a witnessed cardiac arrest and 7 patients (mean age 64 ± 10 years) died of congestive heart failure (3 patients underwent orthotopic heart transplantation which is considered a heart failure death). Seventeen patients (mean age 63 ± 16 years) died of non-cardiac causes: four patients died from cerebrovascular accidents and thirteen deaths



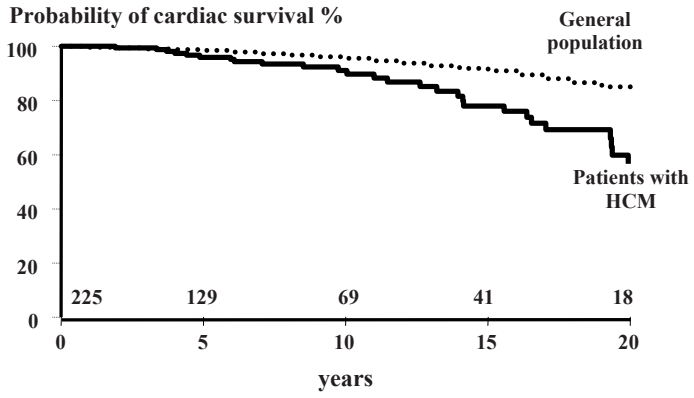



**Figure 1.** Kaplan-Meier survival curve of 225 patients with hypertrophic cardiomyopathy (HCM) and aged-matched controls. Numbers above horizontal axis refer to number of patients at each follow-up period.

were associated with chronic obstructive lung disease (3 patients) or malignant diseases (10 patients). The annual mortality, the annual cardiac mortality and the annual mortality for sudden death was 1.3%, 0.8% and 0.6% respectively. The 5, 10 and 15 years cumulative cardiac survival in our population was 96%, 91% and 78% respectively (Figure 1).

During follow-up, 57 patients underwent septal myectomy, either alone (29 patients) or in combination with anterior mitral leaflet extension (22 patients)[27], mitral valve replacement (3 patients) or coronary artery bypass grafting (3 patients). There was 1 perioperative death. After surgical intervention, fourty-seven patients (82%) had improvement of symptoms and 36 patients (63%) were symptom-free. A total of 10 patients had implantation of a permanent pacemaker, three because of post-operative AV-block, three for sick sinus syndrome, three for treatment of the LVOT obstruction and one patient received an implantable cardioverter-defibrillator after successfully treated ventricular fibrillation.

**Magnitude of left ventricular hypertrophy**

Thirty patients had marked left ventricular hypertrophy at presentation. SCD was demonstrated in 5 of these patients (17%) compared to sudden death of 15 (13%) in 195 patients without marked hypertrophy. There was no significant difference in survival for patients with or without marked left ventricular hypertrophy ($p = 0.10$ and $p = 0.13$ respectively).

**Presence of LVOT obstruction**

At the initial evaluation, 98 patients had a LVOT obstruction. SCD was established in 10 (10%) of 98 patients with obstruction and in 10 (8%) of 127 patients without obstruction respectively. No differences in cardiac death and SCD were found for this variable. During follow-up (mean $7.5 \pm 7$ years) deterioration in at least one functional NYHA class was experienced by 33 patients (33%) with a LVOT gradient and in the 57 patients who underwent septal myectomy functional deterioration was present in 24 cases (42%) (figure 2). In contrast, only 9 patients (7%) had functional deterioration in the non-obstructive group of 127 patients (mean follow-up $8.4 \pm 6.7$ years) (figure 3). In the patients who had surgery, the LVOT gradient did not change over time. However, "end stage" disease with deteriorated systolic function was established in 4 of the 41 not-operated patients with a LVOT obstruction.

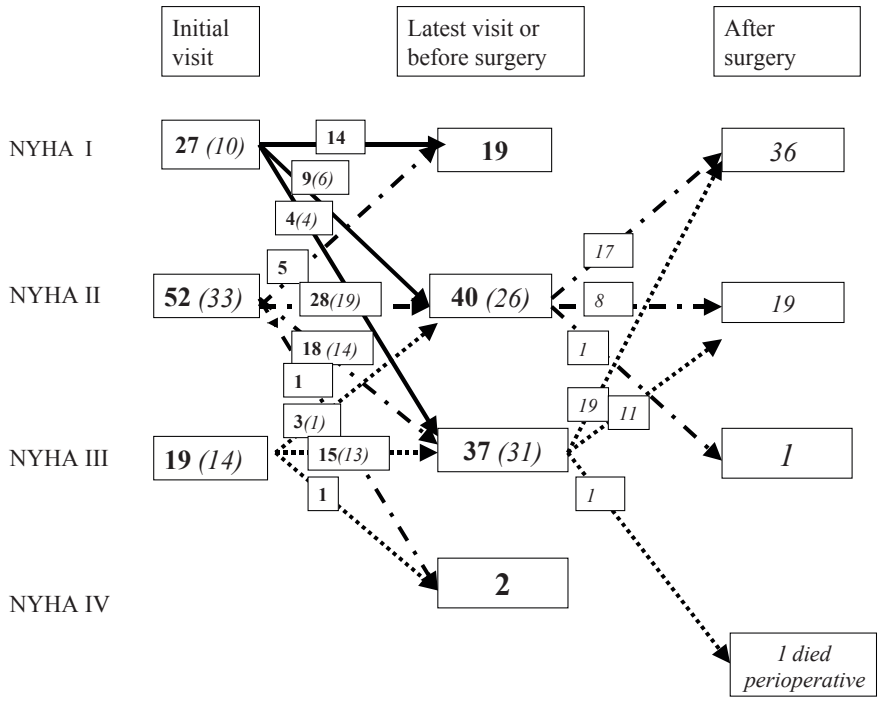





**Figure 2.** Chart showing New York Heart Association (NYHA) classification in patients with a left ventricular outflow tract gradient of ≥ 50 mm Hg at rest or provocation. The total number of patients with obstructive hypertrophic cardiomyopathy is expressed in **bold** (n = 98). The patients treated by surgical therapy are expressed in *italics* (n = 57). The first column represents the NYHA class of the patients at presentation to our institution. The second column represents the NYHA class of nonoperated patients at their latest visit or the NYHA class of patients treated by surgery just before operation. The third column represents the NYHA class of patients treated by surgery at their latest visit.

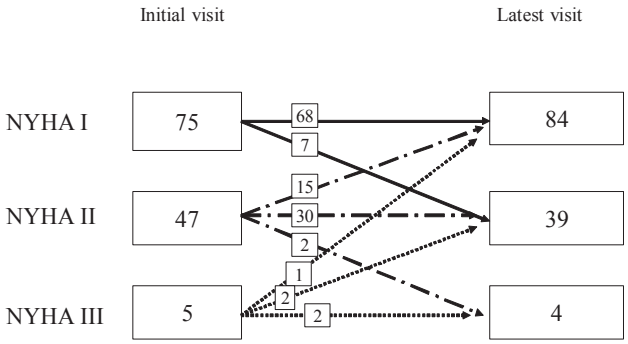



**Figure 3.** Chart showing New York Heart Association (NYHA) functional classification in 127 patients without a left ventricular outflow tract gradient. The first column represents the NYHA class of the patients at presentation to our institution. The second column represents the NYHA class of the patients at their latest visit.

### Presence of AF

At the latest visit, 24 patients (mean age 57 ± 11 years) had persistent AF. Persistent AF was present at initial evaluation in 7 patients. Cardiac death and SCD was noted

in 4 (16%) and 2 (8%) patients with persistent AF compared to 23 (11%) and 18 (9%) patients in sinus rhythm, p = 0.49 and p = 0.89 respectively. The presence of AF had no influence on functional deterioration as assessed by the NYHA classification; p = 0.10. One patient with persistent AF died from an ischemic cerebrovascular accident.

**Presence of VT**

Episodes of non-sustained and/or sustained VT on 24-hour Holter monitoring were present in 73 of 149 patients in whom one or more recordings were available. SCD was established in 8 (11%) patients with VT and 6 (8%) patients without VT on 24-hour Holter monitoring respectively. There was no significant difference in cardiac death and SCD in patients with VT on 24-hour Holter monitoring, p = 0.76 and p = 0.78 respectively. Sustained VT was demonstrated in only 7 patients of whom one patient died suddenly.

**Multivariate statistical analysis**

For the purpose of analysis, patients were divided according to known or suspected risk factors for SCD including age, family history of HCM and/or sudden death, history of syncope, NYHA classification, presence of AF, presence of VT on 24-hour ambulatory monitoring, severe left ventricular hypertrophy (≥ 25 mm) and LVOT obstruction (≥ 50 mm Hg). By multivariate analysis, only syncope was an independent predictor for SCD: RR 4.3 (95% confidence interval 1.8-5.9). Furthermore, only a LVOT obstruction was an independent predictor for functional deterioration during the follow-up period: RR 1.16 (95% CI 1.08 – 1.25) for every increase of 10 mm Hg.

**Review of the literature on prognosis in HCM**

Nine reports originated from 6 referral centers and as a consequence the population in these studies consisted of highly selected patients (Table 2).[13-21] In the other six reports patients came from 6 nonreferral centers and in these studies the population was considered non-selected (Table 3).[22-27]

From the available data it can be appreciated that both annual mortality and annual cardiac mortality is distinctly higher in referral centers compared with nonreferral centers, 2.4% to 5.9% versus 0.0% to 2.0% and 1.5% to 3.5% versus 0.0% to 1.3% respectively. In general, the most striking differences comparing baseline characteristics in hospital-based and community-based populations were the younger age and the more severe functional impairment of patients in referral centers ($p<0.001$ and $p<0.001$ respectively). This might well produce the discrepancy in clinical outcome in selected patients.

**Table 2.** Clinical features of patients with HCM studied in referral centers.

| | Patients (N) | Mean F/U (yrs) | Mean Age (yrs) | Fam History *HCM* + SD (%) | Syncope (%) | NYHA III/IV (%) | LVOT Gradient (%) | AF (%) | VT (%) | Mort / yr (%) | CardMort / yr (%) | SDmort / yr (%) | RF CardMort | RF SDmort |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Swan et al. [10] | 85 | 4.0 | 32 * | _ | _ | 13 | _ | 5 | _ | 3.5* | 3.5 | | | |
| Hadarson et al. [11] | 119 | 4.6 | 30 | _ | 30 | 17 | _ | 9 | _ | 3.5* | 3.5 | | | 1 |
| Shah et al. [12] | 190 | 5.2 | _ | _ | _ | 36 | _ | _ | _ | 3.4 = 5.1 ≠ | | | | |
| McKenna et al. [13] | 254 | 6.0 | 34 | 14 | 21 | 12 | 55 | 6 | _ | Overall 3.9 * <15 yrs: 5.9 ≥ 15 yrs: 2.6 | | | | 1,2,3,4 |
| Maron et al. [14] | 99 | 3.0 | 38 | _ | _ | 18 | 54 | 2 | 19 | 2.3 | 2.3 | | | 5 |
| Koga et al. [15] | 136 | 5.1 | 38 | _ | _ | _ | 24 | 11 | _ | 3.7 | | Overall 2.6 <20 yrs: 7.9 | | 1,6 |
| Romeo et al. [16] | 125 | 7.6 | 34 | 10 | 28 | 62 | 35 | 6 | 16 | 3.4 | 3.0 * | | 7,8 | |
| Seiler et al. [17] | 139 | 8.9 | 37 | _ | _ | _ | _ | 3 | _ | 3.6 = 2.4 ≠ | 3.2 * 1.5 * | | | |
| Maki et al. [18] | 309 | 9.4 | 43 | 15 * | 16 | _ | 17 | 10 * | _ | | | 1.0 | | 9,10 |

Abbreviations: AF = Atrial Fibrillation, LVOT = Left Ventricular Outflow Tract, Mort = Mortality, NYHA = New York Heart Association, RF = Risk Factors, SD = Sudden Death, VT = Ventricular Tachycardia.

Risk factors for Cardiac or Sudden Death: 1 = Young age, 2 = Syncope, 3 = Positive Family history for HC and presence of Sudden Death in one or more first degree relatives, 4 = Dyspnea (functional class III or IV according to the NYHA), 6 = positive exercise test, 7 = decreased left ventricular systolic function, 8 = increased pulmonary wedge pressure, 9 = LVOT-gradient, 10 = Abnormal blood pressure response during exercise.

* estimated from data; = medical therapy; ≠ surgical therapy

**Table 3.** Clinical features of patients with HCM studied in non-referral centres.

| | Patients (N) | Mean F/U (yrs) | Mean Age (yrs) | Fam History *HCM* + SD | Syncope (%) | NYHA III/IV (%) | LVOT Gradient (%) | AF (%) | VT (%) | Mort / yr (%) | CardMort / year (%) | SDmort / year (%) | RF CardMort | RF SD mort |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shapiro et al. [20] | 39 | 3.1 | 55 | 5 | 23 | 20 | _ | 15 | 5 | 0.0 | 0.0 | 0.0 | | |
| Spirito et al. [21] | 25 | 4.4 | 44 | _ | 0 | 4 | 20 | 4 | 20 | 0.0 | 0.0 | 0.0 | | |
| Cannan et al. [23] | 37 | 7.7 | 59 | _ | 11 | _ | _ | _ | _ | | 0.7 | _ | | |
| Cecchi et al. [24] | 202 | 10.0 | 41 | _ | 16 | 9 | 20 | 18 | 40 | 0.6 | 0.6 | 0.1 | 1 | |
| Kyriadikis et al. [25] | 174 | 6.2 | 47 | 13 | 24 | 10 | 33 | 5 | 9 | 1.0 | 1.0 | 0.4 | 1,2,3 | |
| Maron et al. [26] | 277 | 8.1 | 47 | _ | 19 | 9 | 31 | 11 | 49 | 1.3 | 1.3 | 0.7 | 1,4, 5, 6 | |
| Present Study | 225 | 8.0 | 41 | 23 | 19 | 11 | 44 | 18 | _ | 2.0 * | 0.8 | 0.6 | | 2 |

Abbreviations as in Table 2.

Risk factors for Cardiac or Sudden Death: 1 = Functional class, 2 = Syncope, 3 = Ventricular tachycardia, 4 = Atrial fibrillation, 5 = LVOT gradient, 6 = marked left ventricular hypertrophy.

* estimated from data

## DISCUSSION

The natural history of HCM has been the subject of much debate among researchers. Observational studies from tertiary referral centres have estimated the annual cardiac death to be 2-4% in adults[10-17] and as high as 6% in children.[13,28] These studies from major referral institutions have been influenced by selection biases.[19] In community-based studies, patients with HCM have a more favourable prognosis with an annual mortality of approximately 1 percent.[20-26]

Patient-selection biases might lead to misleading conclusions about the significance of risk factors for sudden death. The present study investigates the role of risk factors for sudden death in a community-based population of patients with HCM.

### Clinical characteristics in selected and unselected patients

At the time of the initial visit, mean age was 41 years and almost 90% of the patients had no or mild cardiac symptoms. These findings are comparable with two other large unselected community-based trials from Cecchi et al.[24] and Kyriadikis et al.[25] and in contrast with the findings in tertiary referral centres. This dissimilarity in clinical characteristics has undoubtedly influenced clinical outcome. However, we can only speculate how younger age and more severe functional limitation adversely influence prognosis in hospital-based patients with HCM. A malignant family history with sudden death at young age or surviving cardiac arrest and presence and symptoms of HCM in the very young have been related with adverse outcome and this might persuade the general cardiologist to refer these patients to institutions known to have special interest in HCM.[1] Second, the management of patients with HCM is difficult once symptoms appear. Myocardial ischemia, abnormal diastolic function and LVOT obstruction may all result in symptoms of angina, dyspnea and syncope.[1] The contribution of each of these mechanisms to the clinical picture differs from patient to patient. The general cardiologist may choose to refer the patient if his client becomes severely symptomatic.[1]

### Clinical outcome and risk factors for sudden death

The annual cardiac mortality in our study was 0.8%. Cardiac death is caused by heart failure or occurs sudden and unexpected. Many HCM patients who die suddenly are adolescent persons or young adults and have previously been symptom-free.[29] The stratification of risk of sudden death remains unsettled. There seems to be agreement among investigators that there is a small subgroup of patients who are particularly at high risk for sudden death. Especially, patients who have survived cardiac arrest, young patients with a family history of multiple sudden cardiac deaths and those with a malignant gene mutation are at substantial risk for premature death. Young

age[11,13,15], syncope[13,30], family history of HCM and SCD[13,30], functional cardiovascular status[13], presence of VT[17], positive exercise test[15,31], presence of a LVOT gradient[18], marked left ventricular hypertrophy[32] and an abnormal blood pressure response during exercise[33] are also reported as risk factors of SCD. These data are derived from hospital-based populations and are therefore influenced by referral bias. The latter phenomenon plays a less important role in community-based populations with HCM.

However, none of the community-based institutions have examined the role of risk factors for sudden death. In the studies by Cecchi et al. and Kyriakis et al. risk factors for combined sudden and heart failure-related HCM death were reported. Nevertheless, it is obvious that the process leading to death in patients with intractable congestive heart failure differs from the mechanism causing sudden unexpected death in patients with HCM. Heart failure results from systolic and/or diastolic dysfunction and SCD results from ventricular tachycardia or fibrillation, either as a primary event or as a secondary phenomenon triggered by myocardial ischemia, diastolic dysfunction, LVOT obstruction, hypotension or supraventricular tachycardia.[1,34] In our study, risk factors for cardiac death due to congestive heart failure could not be detected. However, syncope was associated with SCD at multivariate analysis.

Syncope is a complex entity since several mechanisms may be responsible for this symptom including supraventricular and ventricular tachyarrhythmias, bradyarrhythmias, heart block, diastolic dysfunction, myocardial ischemia, autonomic dysfunction and LVOT obstruction. Since the contribution of each of these mechanisms differs from patient to patient the treatment of syncope must be individualized.

At multivariate analysis, only a significant LVOT gradient was related to deterioration in functional state.

### Study limitations

HCM can be caused by a mutation in one of the genes that encode proteins of the cardiac sarcomere. At present, there are obstacles to the translation of HCM genetic research into practical clinical applications and routine clinical strategy. Exercise-induced hypotension is common in young patients with HCM and this finding has been associated with an increased risk of sudden death. However, until 1999 we did not routinely perform exercise-tests in patients with HCM.

### Conclusions

The results in our study show that prognosis of HCM in a community-based population is benign and confirm the current opinion on the natural history in HCM. The most striking finding was a substantial difference in the clinical stability of patients

with and without LVOT obstruction. In non-obstructive patients, a prolonged stable clinical course is noticed. In obstructive patients, we found a progressive decline in functional status during follow-up. Furthermore, syncope was the only risk factor associated with sudden death.

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# 4

## Hypertrophic cardiomyopathy: a fascinating disease with a benign prognosis

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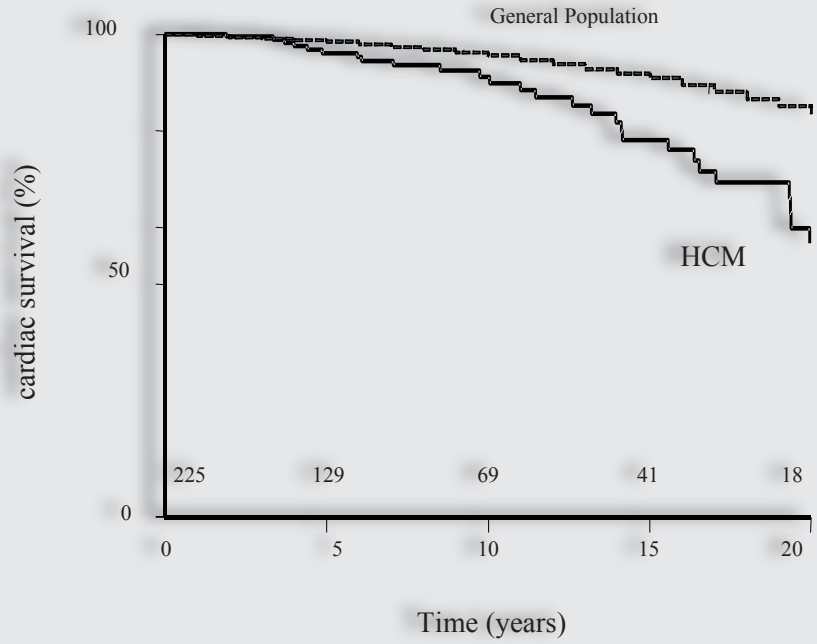
*cf. GAVscoop 2000;4:4-11*



## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease in respect to genetics, morphology and clinical appearance. In 1957, Brock first described the disease as a clinical entity, which is characterized by a non-dilated, hypertrophied left ventricle (LV) in the absence of underlying pathology, such as hypertension or aortic valve stenosis.[1,2]

Within the past years, HCM has been object of extensive research. The insights in prevalence and natural history of this disease have been enlarged. In this report, we give an overview of the various facets with special attention to prevalence, clinical presentation, prognosis and treatment modalities. First, we describe the anatomy and genetic changes that characterize this cardiac disease.

### Anatomy

HCM is usually diagnosed using two-dimensional echocardiography, which will demonstrate the characteristic features of asymmetrical, myocardial hypertrophy. The hypertrophy usually becomes apparent before adolescence but a normal echocardiogram at adultery does not exclude the development of hypertrophy at a later period in life, since development of HCM at an advanced age has been described.[3,4]

In the Western world, 90% of the patients demonstrate hypertrophy either in the septum and/or the lateral border of the LV.[5,6] Normally, the thickness of the left ventricular wall is less than 11 millimetres whereas in HCM patients, it may exceed 15 millimetres. In approximately 5% of Western patients, hypertrophy is solely restricted to the LV apex. Apical HCM, however, is found in almost three-quarters of the Asian HCM patients.[7]

The site of hypertrophy is also of prognostic significance: apical HCM is associated with a benign prognosis.[8] Besides myocardial hypertrophy, HCM expresses several other distinctive features such as a chaotic structure of the myocardial fibres (myocardial disarray)[9], small vessel disease with thickening of the media wall[10] and myocardial fibrosis presumably due to micro-infarctions.[11] The mitral valvular apparatus frequently demonstrates abnormalities, including enlargement and abnormal mobility of the anterior mitral valve leaflet (AMVL).[12]

HCM can be divided into two types: an obstructive and a non-obstructive from. Approximately, 25% of the patients demonstrate the obstructive form. The flow obstruction, which begins at the level of the left ventricular outflow tract (LVOT), is caused by the hypertrophied septum that bulges into the LVOT and an abnormal mobility of the AMVL, which is dragged into the LVOT. The echocardiographic still-frame (Figure 1) demonstrates the bending of the AMVL towards the septum during systole. This phenomenon is called systolic anterior motion.

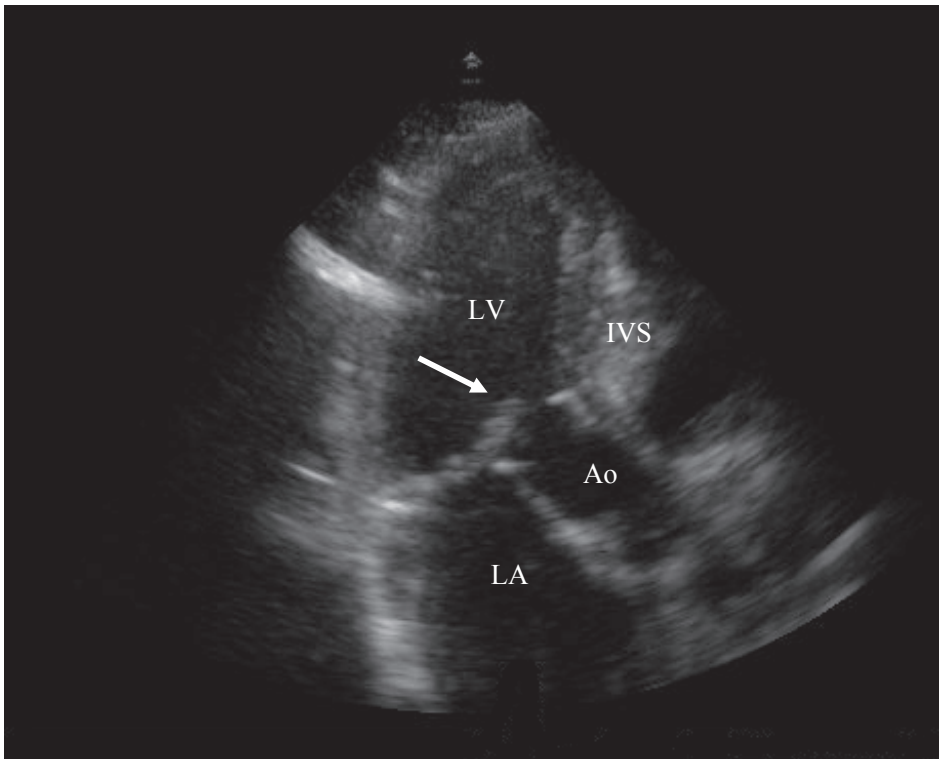





**Figure 1.** Transthoracic echocardiographic still-frame. Apical 3-chamber view. The arrow indicates the site of systolic anterior motion of the anterior mitral valve leaflet. Outflow tract obstruction is created in the presence of septal hypertrophy and systolic anterior motion.
Ao = Aorta Ascendens. IVS = InterVentricular Septum. LA = Left Atrium. LV = Left Ventricle.

The LVOT gradient is dynamic, i.e. it can fluctuate over time. The severity of the obstruction is dependent on several factors, i.e. activation of the sympathetic nervus system, physical activity of the patient or blood pressure. Physical exercise for instance increases both pulse rate and myocardial contractility, which will result in an increase of the LVOT gradient.

The gradient can be measured non-invasively, using transthoracic echocardiography, at the level of the LVOT and it is expressed as a velocity value (in meters per second). At the catheterization laboratory, the gradient is determined using an invasive method. After positioning a catheter in the cavity of the LV, the ventricular pressure is measured. Then, the catheter is pulled back into the LVOT and the aorta ascendens, respectively. This allows determination of the difference in pressure between the LV and the LVOT, which is representative for the LVOT gradient. The pull back of the catheter into the aorta ascendens allows separate determination of a pressure gradient over the aortic valve.

Non-obstructive HCM may be divided according to the left ventricular systolic function, which can either be normal or reduced. The reduced systolic LV function

in this HCM form may be caused by myocardial ischemia or infarctions. HCM may eventually progress to a dilated cardiomyopathy.[13]

### Genetics

Familiar HCM is characterized by gene mutations encoding for cardiac sarcomeric proteins of the contractile apparatus.[14] The disease is characterized by a dominant, autosomal inheritance pattern.

Momentarily, more than 100 different mutations located on 8 different genes have been identified. Several authors have investigated the correlation between genotype and phenotypical expression. In other words, the authors investigated whether a specific mutation in HCM individuals or family members leads to a specific disease expression and/or prognosis.[15,16] The outcome of these investigations, however, demonstrated again the heterogeneity of HCM. Although certain genetic mutations seem to negatively influence prognosis of certain families, no linear correlation has been found between unrelated patients, who had identical genetic mutations. Apparently, lifestyle, risk-factors and (environmental) modifier-genes may influence the prognosis of the patient.

### Prevalence

In several echocardiographic surveys, the prevalence of HCM in the Western world has been estimated at 1 in 500 persons.[17,18] Theoretically, determination of gene mutations would be a more precise method to estimate the prevalence of HCM since certain individuals are carrier of a genetic mutation without expressing the disease. In practice, however, genetic screening is expensive and labour intensive. Besides, this method would only be effective if all HCM mutations were known.

## CLINICAL PRESENTATION

The majority of HCM patients are asymptomatic. Referral to the HCM outpatient clinic is often initiated after the incidental detection of a cardiac murmur or as a screening routine after the diagnosis of HCM has been established in a family member. Physical examination usually does not reveal the diagnosis although a typical cardiac murmur may be present during systole, which may be aggravated with the Valsalva manoeuvre. A mitral regurgitation murmur may be noted, often in patients who also demonstrate a systolic anterior motion on 2-D echocardiography. The 12-lead electrocardiogram is abnormal in approximately 75% of the HCM patients. It usually indicates the presence of left ventricular hypertrophy but signs of patho-

logical Q-waves or left atrial enlarged may also be present. The electrocardiogram of patients with apical HCM typically demonstrates "giant negative T-waves".

The most striking complication of HCM is sudden cardiac death (SCD), which can occur in any HCM patient, independent of the presence of complaints or the type of hypertrophy.

Symptoms include angina pectoris, dyspnoea, and palpitations or (near-) syncope and may be aggravated by several mechanisms including:

*1) Abnormal diastolic function*. During diastole, blood enters the LV cavity. In the presence of diastolic dysfunction, blood entrance into the LV is impaired. The left ventricular pressures in these patients are usually raised and the amount of blood that enters the ventricle during diastole is reduced. During exercise, pulse rate increases and the diastolic filling period (i.e. the time interval during which blood enters the LV) is shortened. This results in a reduction of stroke volume. Also, diastolic dysfunction may result in raised pulmonary pressure, which consequently leads to symptoms of dyspnoea.

*2) Left ventricular outflow tract obstruction*. LVOT obstruction develops during ventricular contraction (systole). Contractile forces are increased in the presence of a gradient and raise the left ventricular oxygen demand. This may cause a disruption of the balance between oxygen delivery and consumption, which results in symptoms of angina pectoris. If the gradient is extremely high, the ejection fraction may be substantially impaired causing hypotension and syncope.



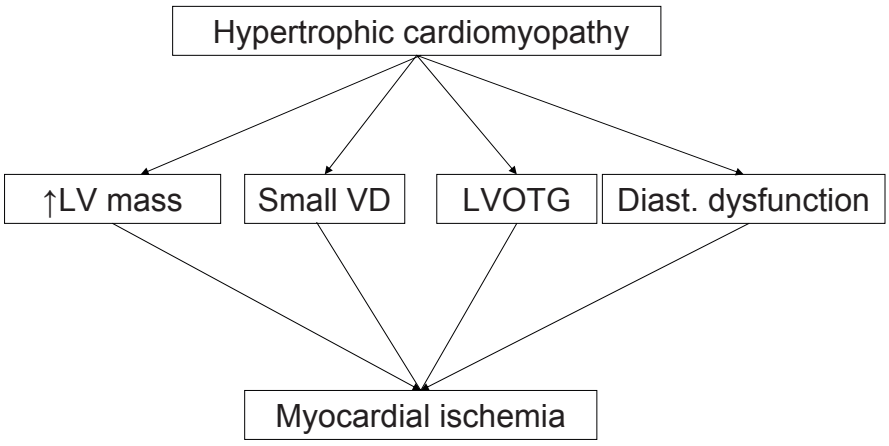



**Figure 2.** Simplified scheme of factors, which might induce or promote myocardial ischemia in HCM.
↑ LV = increased Left Ventricular mass due to hypertrophy. VD = Vessel Disease. LVOTG = Left Ventricular Outflow Tract Gradient. Diast = Diastolic.

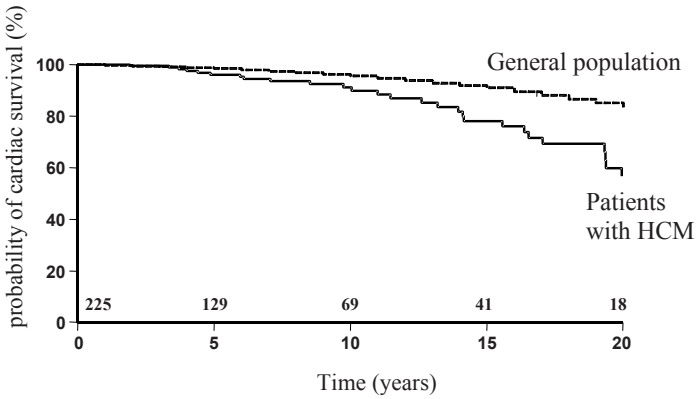
*3) Myocardial ischemia without coronary artery disease*. HCM patients often demonstrate small vessel disease. The luminal diameter of the intramural coronary vessels is often reduced due to thickening of the media. This as well as other factors (figure 2) may cause reduced oxygen delivery to the myocardium resulting in complaints of severe angina pectoris.

Each of the above mentioned factors might contribute to the patients' symptoms. The influence as well as the contribution of each of these factors needs to be assessed in the individual patient to optimize medical or invasive therapy.

## PROGNOSIS

The natural history of HCM has been object of extensive research. Until recently, annual cardiac mortality was estimated at 2 to 6% for adults and at 4 to 6% for children.[19] These data, however, appeared to be derived from hospital-based populations including severely symptomatic patients who were referred to tertiary centers for advanced care. These patients are not comparable to the "average" HCM patient. Recent analysis from non-referral centers demonstrated that the natural history of HCM follows a more benign course. Annual cardiac mortality is now estimated at 0.6 to 1%. The risk of SCD is dramatically lower as previously estimated. Analysis of 225 patients, followed at our HCM outpatient clinic, demonstrated an annual cardiac mortality of 0.8% (Table 1). Patients in this group are relatively unselected and consist of patients who are: 1) diagnosed and treated at our center; 2) referred from the community for establishment of the diagnosis or advice on management;

**Table 1.** Cumulative survival diagram of 225 unselected HCM patients followed at our HCM outpatient clinic. Figures above the horizontal axis indicate the patients "at risk". The annual cardiac mortality is 0.8%. Survival rates after 5, 10, 15 years are 96%, 90% and 78%, respectively.



3) transferred from outlying hospitals for advanced care; 4) self-referred family-members of patients.

### Risk stratification for sudden cardiac death

The most striking complication in HCM patients is SCD. Although only a minority of the HCM population is at high risk for SCD, each individual patient should be carefully screened for risk factors. Patients at increased risk for SCD are: 1) survivors of "out-of-hospital" cardiac arrest,[20,21] 2) those with a positive family history of SCD[22] or 3) those with malignant genetic mutations[23]. The influence of the third factor is still subject of debate. Other proposed factors to increase the risk for SCD include the presence of: 1) symptoms at a young age,[24] 2) syncopal attacks,[25] 3) (non-)sustained ventricular tachycardia at 24-hours ambulatory ECG monitoring,[26] 4) atrial fibrillation,[27] 5) a significant LVOT gradient[28] or 6) exercise-induced hypotension.[29] The contribution of each factor, however, is currently unknown.

An automatic implantable cardioverter defibrillator (ICD) is the only device which has proven to alter the natural history of HCM. Candidates for ICD implantation are patients who were successfully resuscitated from "out-of-hospital" cardiac arrest, who experienced syncope due to ventricular arrhythmias or had a recording of sustained ventricular tachycardia (lasting more than 30 seconds) during 24-hours ambulatory ECG monitoring.



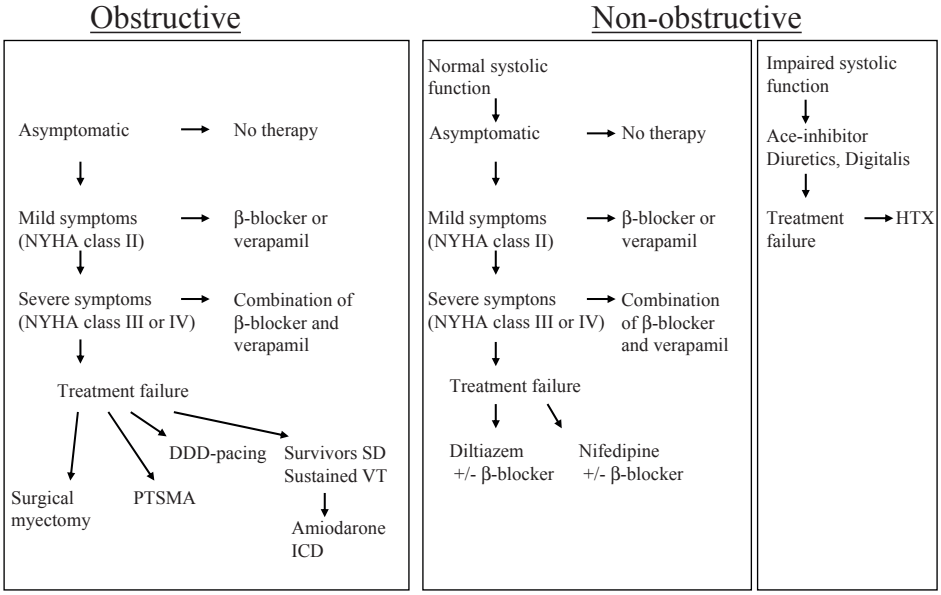
## TREATMENT STRATEGIES

Table 2 demonstrates a therapeutic flowchart for HCM patients. The choice of treatment mainly depends on the severity of symptoms and/or the presence of a significant LVOT obstruction (≥ 50 mm Hg).

### Non-obstructive hypertrophic cardiomyopathy

Merely three-quarters of HCM patients do not demonstrate a LVOT gradient. These patients are initially screened for risk factors and followed at the outpatient. In the presence of complaints, i.e. angina or dyspnoea, patients are treated with either beta-blockers or calcium antagonists. Both drugs reduce cardiac oxygen consumption by lowering the pulse rate and cardiac contractility. Besides, blood flow into the LV during diastole will improve. Thus, symptoms of dyspnea or dizziness may be reduced.[30-32] In patients who remain symptomatic, beta-blockers may be combined with calcium antagonists. Of notice, medical therapy has not proven to be of positive influence on the prognosis of HCM.

**Table 2.** Therapeutic flow chart as used in our HCM outpatient clinic.
DDD-pacing = Dual chamber pacing. HTX = Heart Transplantation. ICD = automatic Internal Cardioverter Defibrillator. NYHA = New York Heart Association. PTSMA = Percutaneous Transluminal Septal Myocardial Ablation. SD = Sudden Death. VT = Ventricular Tachycardia.




Treatment of patients with HCM and a reduced LV systolic function is similar to patients with heart failure, including ACE-inhibitors, diuretics or possibly digitalis.[33]

## Obstructive hypertrophic cardiomyopathy

Symptomatic patients with HOCM are initially treated with beta-blockers, calcium antagonists or a combination of these drugs. Calcium antagonists, however, must be prescribed with caution since the drug may aggravate the LVOT gradient due to arterial vasodilatation.[34] Patients, who remain symptomatic despite optimal medical treatment in the presence of a LVOT gradient of at least 50 mm Hg, are candidates for invasive treatment. At present, several invasive procedures have been proposed.

*1) Surgical treatment (septal myectomy)*. Cleland described the first invasive procedure to treat HOCM patients, further developments were accomplished by Morrow in the late 60's.[35,36] The technique entails partial removal of the hypertrophied septum to enlarge the LVOT outflow tract. In the vast majority of patients, septal myectomy results in reduction of the LVOT gradient and leads to a dramatic improvement of symptoms.[37,38] The increase in surgical experience has lowered operative mortality from 8% to less than 2%. Furthermore, refinement of the surgical technique has decreased the operative complication rate. Surgery, however, may be encountered by several complications, including 1) conduction disturbances necessitating the im-

plantation of a permanent pacemaker (0-15%), 2) ventricular septal defects, caused by too extensive resection of septal myocardium or 3) damaging of the papillary muscles or chordae, attached to the mitral leaflets, resulting in mitral regurgitation. Surgical myectomy is performed in a few selected centers by experienced surgeons in the field. Under these conditions, mortality and morbidity rates are very low.

*2) Permanent pacemaker implantation*. Dual-chamber pacemaker implantation has been introduced as an alternative to surgery. Initially, it appeared an effective therapy to reduce the LVOT obstruction and to ameliorate clinical symptoms. The hypothesized working mechanism is complicated. Pacing alters the depolarization as well as the contraction pattern of the ventricles. Usually, the basal septum is the first myocardial segment that contracts during systole and that consequently bulges into the LVOT. Consequently, the LVOT diameter reduces just before the LV ejects most of the blood through the LVOT into the aorta. Therefore, it would be beneficial to start the depolarization and contraction pattern at the apical region. This could be achieved by placing a ventricular pacemaker lead in the right ventricle. During ventricular pacing, the contraction of the LV starts at the apex and moves towards the basal septum. Under these conditions, most blood has been ejected into the aorta and the consequences of LVOT narrowing due to septal contraction during the late systolic phase, are minimized. The preliminary results achieved by pacing were promising, demonstrating reduction of the LVOT gradient and improvement of the clinical condition. The results of a randomized double-blinded trial, comparing several periods of alternating pacing in the same patients, were discouraging.[39] The results of this study indicated that clinical improvement was at least partly based on a "placebo-effect" and reduction of the LVOT gradient was significantly less as compared to surgical myectomy. In our clinic, pacemaker implantation to treat HOCM is only considered if the surgical risk is deemed to high due to the presence of co-morbidity and/or an advanced age.

*3) Percutaneous transluminal septal myocardial ablation*. Recently, Dr. Sigwart introduced percutaneous transluminal septal myocardial ablation (PTSMA), a new modality to treat patients with HOCM and drug-refractory symptoms.[40] The technique entails the injection of ethanol into one or more septal arteries arising from the left anterior descending artery. The ethanol induces a myocardial infarction within the myocardial area provided by this septal artery. As a result, septal hypertrophy diminishes, the LVOT widens due to remodeling and consequently, the LVOT gradient reduces. Since the introduction of PTSMA, more than 300 patients have been treated by this technique. The short-term results are promising, morbidity rate is low and gradient reduction is significant.[41] The first PTSMA procedure in the Neth-

erlands was performed at the Dykzigt Hospital in 1999. The advantage of PTSMA, performed at the catheterization laboratory, is its less invasive character as compared to surgery. In addition, the duration of in-hospital stay is reduced. Whether the effects of PTSMA will lead to sustained improvement during long-term follow-up and whether the procedure is capable of competing with surgical myectomy cannot be exactly determined at present. An important question that remains to be answered is whether the induction of a septal myocardial infarction by injection of ethanol may induce ventricular arrhythmias during long-term follow-up.

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# 5

## Pregnancy in hypertrophic cardiomyopathy: follow-up in nine patients with twenty pregnancies

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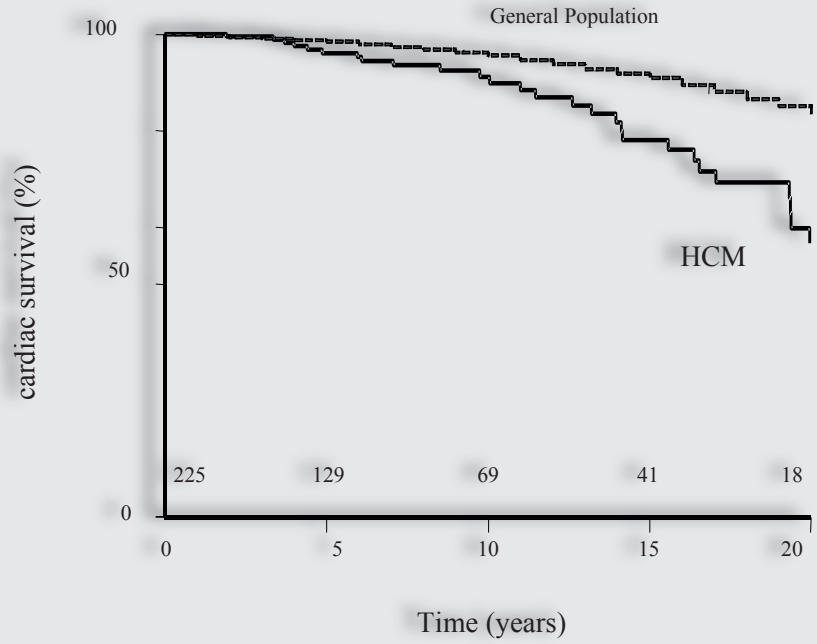
*Cardiology 2000;12:461-465*



**SUMMARY**

Hypertrophic cardiomyopathy is a heterogeneous disease with a wide spectrum of clinical and hemodynamic manifestations. Pregnancy is generally considered a safe undertaking in patients with hypertrophic cardiomyopathy; nevertheless cardiac symptoms can develop or deteriorate during pregnancy. Between 1988 and 1998, the authors followed 9 consecutive patients during pregnancy and delivery. A general advise on the management during and after pregnancy as well as recommendations for delivery are described.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease characterized by a diversity in anatomical, hemodynamic and clinical presentation.[1-4] The clinical picture may differ from patient to patient: although the majority is asymptomatic, some patients have symptoms of angina, heart failure or syncope.[5,6] Pregnancy and delivery is usually well tolerated in patients with HCM.[7,8] However, the combination of physiological changes and altered hemodynamic state in pregnancy and delivery may worsen symptoms and induce venous pulmonary congestion.[7,9] Therefore, advise concerning pregnancy and delivery should be individualized in these patients. We report the outcome of nine pregnant women with HCM and present general advice for management of pregnancy and delivery.

## METHODS

Between 1988 and 1998, nine consecutive patients with HCM out of the Thoraxcenter cardiomyopathy clinic were followed during pregnancy and delivery. The diagnosis of HCM was based on the echocardiographic finding of a nondilatated hypertrophied left ventricle in the absence of known causes of left ventricular hypertrophy.[10] At the time of the initial visit, clinical characteristics including age at diagnosis, family history of HCM or presence of sudden cardiac death in a first degree relative, or both, history of syncope or sudden death, symptoms, New York Heart Association functional class and pharmacological therapy were recorded. Physical examination and baseline laboratory studies were performed, including twelve-lead electrocardiography and echocardiography. Furthermore, clinical characteristics, physical and echocardiographic examination were reevaluated before pregnancy, at midgestation and within 3 months after delivery by one cardiologist (FTC). Cardiac follow-up was intensified if the gynecologist, who followed the patient during pregnancy in the outpatient clinic, suspected a deterioration of the cardiac condition. All patients had undergone 24-hour Holter monitoring before pregnancy. Information on delivery was obtained from the patients' gynecologist.

## RESULTS

### Baseline characteristics

The clinical characteristics of 9 study patients are listed in Table 1. One patient (patient no. 2) already had delivered to 2 children before the diagnosis of HCM was

**Table 1.** Clinical characteristics of pregnant patients with hypertrophic cardiomyopathy

| Pt. number | Year of birth | Family history SD | Syncope | NYHA class | Medication | | LVOTG (mmHg) | VT on Holter | Year of operation | Pregnancies |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pre | During | | | | |
| 1 | 1962 | + | + | I | – | – | 15 | + | 1984 | 1988, 1990 |
| 2 | 1966 | 0 | 0 | II | – | – | 25 | 0 | | 1986*, 1987*, 1991 |
| 3 | 1967 | 0 | 0 | I | V | V | 5 | + | | 1994, 1995 |
| 4 | 1958 | + | + | II | – | – | 4 | + | 1985 | 1994 |
| 5 | 1967 | + | + | I | – | D | 10 | + | 1991 | 1988(A), 1989, 1989(A) 1993, 1995 |
| 6 | 1957 | + | 0 | I | – | – | 5 | + | | 1992(A), 1993, 1995 |
| 7 | 1966 | + | + | II | Dis | Dis | 50 | + | 1986 | 1988(A), 1991, 1994 |
| 8 | 1964 | – | 0 | II | V | V, B | 36 | 0 | | 1997 |
| 9 | 1962 | + | 0 | I | – | – | 12 | 0 | 1995 | 1996(A), 1998 |

A = spontaneous abortion, B = beta-blocker, D = diuretic, Dis = disopyramide, LVOTG = left ventricular outflow tract gradient, NYHA = New York Heart Association, pre = medical therapy before pregnancy, SD = sudden death, V = Verapamil, VT = Ventricular Tachycardia, + = present, 0 = absent, (–) = no therapy, * = not included in the study.

made. Since we included only patients who could be followed during pregnancy and labour, we eliminated these pregnancies from our study. Nine patients were included with 20 pregnancies. The mean age at first presentation to our institution was 22 ± 6 years. Seven patients reported a family history of HCM, of whom 6 patients also reported sudden death in a first-degree relative at a young age (<40 years). Four women had experienced one or more syncopal attacks before pregnancy. Five women were asymptomatic before pregnancy, the symptoms recorded in the remaining patients included dyspnea in 4 patients and exertional angina in 3 patients. All symptomatic patients were in functional class II according to the New York Heart Association. Five women had undergone septal myectomy because of the presence of a left ventricular outflow tract (LVOT) obstruction ≥ 50 mm Hg at rest and complaints of angina or dyspnea despite therapy with betablockers and/or verapamil. In 4 patients this procedure took place before the first pregnancy. The LVOT gradients, as presented in Table 1, were evaluated one to six months before the first pregnancy in 6 patients, before the third pregnancy in patient no. 2 and before the fourth pregnancy in patient no. 5, respectively. All patients were in sinus rythm during the study. On 24-hour Holter monitoring, five patients had one or more episodes of nonsustained ventricular tachycardia and in one patient (no. 4), an episode of sustained ventricular tachycardia was recorded without symptoms.



### Follow-up during pregnancy

During pregnancy, four patients were treated with drugs, of whom 2 patients used verapamil (Table 1). Patient no. 3 discontinued verapamil at the first trimester of both pregnancies and restarted the drug after delivery. Patient no. 8 continued

verapamil throughout pregnancy. At midterm evaluation, the LVOT gradient had increased from 36 mm Hg before pregnancy to 90 mm Hg. Verapamil was discontinued at 21 weeks because of the increase in the LVOT obstruction and was replaced by metoprolol. On echocardiographic examination, four weeks later, the LVOT gradient had decreased to 30 mm Hg. Pregnancy and delivery were uncomplicated afterwards. In patient no. 7 disopyramide was stopped during the first trimester of both pregnancies and restarted after delivery. Two patients (no. 2 and no. 5) had worsening of symptoms during pregnancy. Patient no. 2 was seen in our outpatient clinic at 38 weeks of her third pregnancy for progression of angina and dyspnea on exertion. At physical examination, there were no overt signs of heart failure and she fulfilled her term without pharmacological therapy. Symptoms disappeared after delivery. Diuretic therapy was indicated in one patient (no. 5) at the end of the fourth pregnancy for relief of symptoms of heart failure. Doppler echocardiography revealed that the LVOT gradient did not change significantly during pregnancy in 8 of 9 patients.

**Delivery**

Nine women had 20 pregnancies, five of whom ended in spontaneous abortion. The first pregnancy of patient no. 5 ended in the delivery of a stillborn child at 27 weeks. This patient was hospitalized because of excessive vaginal bleeding due to abruptio placentae. After delivery, the patients' recovery was uncomplicated. Autopsy of the female fetus of 640 grams did not reveal any cardiac abnormality. The remaining four spontaneous abortions took place in the first trimester of pregnancy; autopsy was not performed in these cases. No child nor mother died in the perinatal period. Thirteen children were born by vaginal delivery, two intrauterine growth retarted children were born by cesarean section at 39 weeks because of fetal distress. The birthweight averaged 2868 ± 716 gram (range 1280 – 4160 gram) and the ranges of the Apgar score were 6 to 10 and 7 to 10 after 5 and 10 minutes respectively. Endocarditis prophylaxis because of distinct anterior motion of the mitral valve and concomitant mitral valve regurgitation was administered in 9 of 16 deliveries.

**Follow-up after delivery**

Uptill now, cardiac abnormalities are not found on echocardiographic examination in the 15 live-born children after a mean follow-up of 5 ± 3 years (range 0.5 - 10 years). Two women (no. 4 and 7) had cardiac events during follow-up. Both patients were transmitted to local hospitals after resuscitation because of ventricular fibrillation, 5 and 8 months respectively after the latest pregnancy. Patient no. 7 stayed comatose. Patient no. 4 recovered without neurological injury, she was treated by implantation of a cardioverter defibrillator because of periods of sustained ventricu-

lar tachycardia despite antiarrhythmic drug therapy. In the other 7 patients, clinical status was not different as compared to the period before pregnancy.

## DISCUSSION

In this paper, we report the outcome of 20 pregnancies in 9 patients with HCM. Our cohort represents the heterogeneity in clinical presentation of this disease: while 5 patients were asymptomatic, 4 patients had complaints of angina or dyspnoe, 6 patients had ventricular tachycardia on 24-hour Holter monitoring and septal myectomy because of LVOT obstruction had been performed in five patients. From 20 pregnancies, 15 children were born alive, 13 by vaginal delivery and two by cesarean section. The results of our study show that pregnancy is generally well tolerated in patients with HCM.

Five pregnancies ended in spontaneous abortion. The number of abortions in our cohort is higher than expected (normally 10% of pregnancies end in a spontaneous abortion in the first trimester). It is not known whether HCM in the fetus caused the abortion since autopsy was not routinely performed.



### Hemodynamic changes during pregnancy and its influence on hypertrophic cardiomyopathy

During pregnancy, important changes in the hemodynamic state take place. There is a reduction in the peripheral resistance beginning from the 12th week of gestation,[11] nevertheless blood pressure is unchanged in most patients since cardiac output is increased by 30-50%.[12] In the last trimester, compression of the inferior caval vein by the expanding uterus can result in a decrease of venous return.[13,14] During delivery, pain and stress causes sympathetic stimulation which leads to an increase in heartrate and contractility and furthermore the Valsalva manoeuvre may reduce venous return.[13,14]

The increase in contractility and decrease in pre- and afterload can augment the obstruction in patients with obstructive HCM, which in turn may lead to deterioration of the clinical condition.[9,13,14] In patients with HCM and diastolic dysfunction, the increase in intravascular volume and rise in heartrate is detrimental and may cause worsening of symptoms and pulmonary venous congestion.[15]

### Drug therapy during pregnancy in hypertrophic cardiomyopathy

If the patient is asymptomatic, therapy with drugs should be avoided. In symptomatic patients, beta-adrenergic blocking agents are prescribed traditionally. Beta-blockers reduce myocardial oxygen demand and relief symptoms of angina

and dyspnea through lowering heart rate, reducing left ventricular contractility and reducing the exercise generated increase in obstruction.[3,16,17] The use of these drugs in pregnancy is relatively safe. There are no reports indicating that therapy with beta-blockers results in fetal malformation.[18] Intra-uterine growth retardation, neonatal bradycardia and neonatal hypoglycaemia are reported in a small number of patients.[7,8,19,20] Verapamil is also widely used in the management of patients with HCM. Like beta-adrenergic blocking drugs, verapamil reduces myocardial oxygen consumption by its negative inotropic and chronotropic effect. Moreover, the drug may have a benificial effect on diastolic function.[21,22] In patients with obstructive HCM, verapamil may increase the LVOT gradient through the vasodilatating properties of the drug.[23] No teratogenic effects have been described in patients treated with verapamil for acute management of maternal supraventricular arrhythmias.[24] The effects of chronic administration of verapamil on the course of pregnancy is still unclear.

**Recommendations during labour and delivery in hypertrophic cardiomyopathy**

The use of betamimetic drugs for tocolysis is contraindicated in patients with obstructive HCM, because the LVOT gradient increases and symptoms may worsen.[8] Analgesia during labour is useful to diminish sympathetic stimulation.[13,14] Epidural analgesia is not contraindicated, however adequate volume-expansion and careful blood pressure monitoring is necessary, to avoid hypotension especially in patients with obstructive HCM.[25,26] Hemodynamic monitoring by pulmonary artery catheterization should be considered in patients who are severely symptomatic or have signs of heart failure to guide drug therapy.[9] According to the statement of the American Heart Association patients with HCM are at moderate risk for acquiring endocarditis.[27] In our institution, antibiotic prophylaxis is recommended in patients with distinct systolic anterior motion of the mitral valve and LVOT obstruction, and in patients with moderate to severe mitral regurgitation. In general, vaginal delivery is considered safe and cesarean section is reserved for obstetric indications.

**General recommendations**

The risk of inheritance in familial HCM is 50%. However, it is important to note that patients with identical gene mutations display variable clinical manifestations or even fail to express the disease.[28-30] In HCM patients with a child's wish it is important to explain the risk of inheritance and the risk of worsening of symptoms during pregnancy. Cardiac follow-up during pregnancy is necessary for the surveillance of the patients' clinical condition, to start or change therapy if symptoms worsen or to hospitalize the patient if there are overt signs of heart failure. Postpartum blood loss should be replaced by intravenous fluids, especially in patients with obstructive

HCM, because of the potential aggravation of the pressure gradient across the LVOT. After birth, echocardiographic evaluation should be performed every 2 to 5 years in children (or sooner when cardiac symptoms develop) lasting until adulthood to recognize signs of HCM.

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# 6

# Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy

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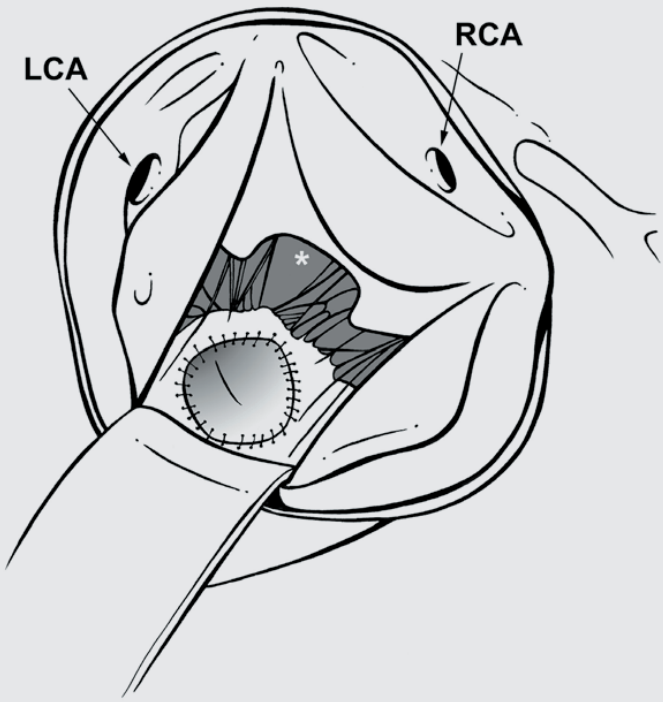
*Circulation 2003;108:2088-2092*



## ABSTRACT

**Background:** Mitral leaflet extension (MLE) combined with septal myectomy is a new surgical approach to treat hypertrophic obstructive cardiomyopathy (HOCM) and an enlarged mitral leaflet area. The study presents the long-term clinical results and outcome of this technique.

**Methods and Results:** MLE entails grafting a glutaraldehyde-preserved autologous pericardial patch onto the center portion of the anterior mitral valve leaflet. Twenty-nine patients with HOCM were studied. Mean follow-up (± SD) was 3.4 ± 2.1 years (range 3 months to 7.7 years). The preoperative calculated mitral leaflet area was 16.7 ± 3.4 $cm^2$. New York Heart Association functional class improved significantly from 2.8 ± 0.4 to 1.3 ± 0.4 ($P<0.05$), width of the interventricular septum decreased from 23 ± 4 to 17 ± 2 mm ($P<0.05$), left ventricular outflow tract gradient decreased from 100 ± 20 to 17 ± 14 mm Hg ($P<0.01$), severity of mitral regurgitation graded on a scale from 0 to 4+ decreased from 2.5 ± 0.9 to 0.5 ± 0.6 ($P<0.01$), and severity of the systolic anterior motion of the mitral valve graded on a scale from 0 to 3+ decreased from 2.9 ± 0.3 to 0.5 ± 0.7 ($P<0.01$) postoperatively. There were no deaths associated with surgery.

**Conclusions:** Long-term follow-up shows sustained improvement in functional status, reduction of outflow tract obstruction, and attenuation of mitral regurgitation and systolic anterior motion of the mitral valve. In this respect, the new technique widens the surgical applications in HOCM.

## INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HOCM) is a heterogeneous disease characterized by asymmetrically distributed left ventricular hypertrophy and left ventricular outflow tract (LVOT) obstruction.[1] Dynamic LVOT obstruction is induced by thickening of the interventricular septum and systolic anterior motion (SAM) of the mitral valve. Several invasive therapeutic modalities have been developed to diminish outflow tract obstruction by reduction of the interventricular septum width. The most commonly performed intervention is surgical myectomy according to the technique developed by Morrow et al.[2] Hypertrophic cardiomyopathy, however, frequently presents with several anatomic alterations of the mitral valve apparatus, including increased mitral leaflet area (MLA), length, and laxity, as well as anterior displacement of the papillary muscles.[3-12] These structural abnormalities, which are not corrected after a successful myectomy, may predispose to residual SAM and result in a suboptimal outcome with persistence of outflow obstruction and mitral regurgitation (MR).[13-15] We therefore performed anterior mitral leaflet extension (MLE), one of several repair techniques originally developed by Carpentier[16], in combination with myectomy in patients with HOCM and an enlargement of the anterior mitral leaflet. We have shown that the combined technique resulted in good short-term functional and hemodynamic outcome compared with myectomy alone in these patients.[17] In this report, we present the long-term follow-up results of this combined surgical approach.

## METHODS

### Patient selection

Patients are selected for surgery at our hypertrophic cardiomyopathy clinic on the basis of the following indications: (1) a significant LVOT gradient ≥ 50 mm Hg at rest or on provocation and (2) New York Heart Association (NYHA) functional class II to IV despite optimal medical treatment consisting of beta-blocking agents, calcium channel blockers, or both. Cardiac catheterizations for invasive hemodynamic measurements and visualization of the coronary anatomy and transthoracic echocardiography were performed routinely before surgery. The echocardiographic images were collected by a single echocardiographer and stored on videotape for off-line analysis.

The mitral valve leaflet area was used as a selection criterion to perform MLE in conjunction with myectomy. First, the mitral valve opening area was measured offline from transthoracic echocardiographic images in the parasternal short-axis

view by tracing the innermost margins of the mitral valve at the point of maximal opening. The demarcated area was calculated with a dedicated software program.[18] Next, the leaflet area was calculated with the formula previously validated by Klues et al: mitral valve leaflet area = 4.64 + 2.17 × mitral valve opening area.[19]

Between 1991 and 1999, 32 patients were accepted for surgical correction, and 29 patients met the selection criteria for MLE. The final decision to perform MLE was made perioperatively by the surgeon after visual inspection and epicardial echocardiographic observation of papillary muscle length and mitral valve laxity, as well as leaflet area. If, in the surgeon's view, these morphometric abnormalities made myectomy alone unlikely to yield optimal results, the leaflet-extending patch was additionally grafted. The surgical procedures, which were approved by the local institutional review committee, were performed by one surgeon (LAvH). All subjects gave oral informed consent.

**Surgical technique**

Cardiac surgery was performed by standard techniques of cardiopulmonary bypass with moderate hypothermia and crystalloid cardioplegic arrest (St Thomas's solution). An autologous pericardial patch was harvested, trimmed of fat and extraneous tissue, immersed for 10 minutes in 0.62% glutaraldehyde, and then placed in a normal saline bath. The patch was treated with glutaraldehyde for ease of manipulation and collagen cross-linking. After the ascending aorta was opened by an oblique incision, myectomy was performed to the left of an imaginary line through the nadir of the right coronary cusp with a locally designed electrocautery device, described in detail elsewhere.[20] The entire surgical procedure was monitored with epicardial echocardiography by the surgeon.

When, in the surgeon's opinion, adequate septal myectomy had been achieved, anterior MLE was performed. The procedure has been explained previously.[21] In brief, a gap was created in the anterior mitral leaflet through a longitudinal incision, starting at the subaortic hinge point to the rough zone. Then, an oval autologous pericardial patch, 2.5 cm wide and 3 cm long, was grafted onto the center portion of the anterior mitral leaflet with 2 running polypropylene sutures. The surgical results were assessed with transesophageal and epicardial echocardiography immediately after the patient was weaned from bypass and at a systolic blood pressure of ≥ 100 mm Hg, with special attention to the width of the interventricular septum, the residual LVOT gradient, MR, and SAM. None of the patients had an indication for reinstitution of cardiopulmonary bypass because of a suboptimal surgical result.

### Follow-up

The clinical characteristics collected before the intervention included assessment of symptoms, NYHA functional class, and drugs prescribed. Physical examination and baseline laboratory studies were performed, including electrocardiography, transthoracic echocardiography, and cardiac catheterization.

The echocardiographic data were reviewed by 2 physicians who were unaware of the patient's medical history. Echocardiography was performed 1 week before surgery and was subsequently repeated 1 week, 3 months, and at yearly intervals after surgery.

At the site of myectomy, the mean interventricular septal thickness was calculated from the septal width in diastole from both the parasternal short-axis and long-axis views. The severity of the MR was graded (on a scale from 0 to 4+) by color flow Doppler echocardiography. The severity of the SAM of the anterior mitral valve was determined from the 2D images and was graded on a scale from 0 to 3+ depending on the mitral-septal distance (grade 0 indicates no SAM and grade 3+ indicates brief or prolonged contact between mitral valve and septum). Peak LVOT gradient was estimated with Doppler echocardiography by the modified Bernoulli equation ($P = 4V^2$), where P is the pressure gradient and V is Doppler-determined blood velocity. MLA was calculated as described above from the preoperative echocardiograms.

Follow-up information was obtained at the hypertrophic cardiomyopathy clinic by 1 cardiologist (FJtC). Because echocardiography has become a non-invasive and standard routine to assess postoperative results, repeated catheterization was not performed in this group.

### Statistical Analysis

Data are expressed as mean ± SD values. The paired Student's t test was determined to compare continuous variables. Preoperative and postoperative patient characteristics compared were NYHA functional class, number of drugs prescribed, width of the interventricular septum, LVOT gradient, severity of MR, and grade of the SAM of the anterior mitral valve leaflet.

## RESULTS

### Baseline clinical characteristics

The baseline characteristics of the 29 patients are listed in Table 1. Fifteen patients were male. Mean age was 44 ± 13 years (range 21 to 64 years). The majority of patients (76%) had class III symptoms according to NYHA classification, and 24% of patients had class II symptoms. Two patients had been resuscitated successfully from

**Table 1.** Baseline characteristics of the 29 patients with hypertrophic obstructive cardiomyopathy treated with myectomy and mitral leaflet extension.

| | N(%) |
|---|---|
| Sex (M/F) | 15(52%)/14(48%) |
| Mean age (years ± SD) | 44 ± 13 |
| Follow-up (years ± SD) | 3.4 ± 2.1 |
| Symptoms | |
| dyspnea | 19 (66%) |
| angina | 14 (48%) |
| (pre) syncope | 7 (24%) |
| out of hospital resuscitation | 2 (7%) |
| NYHA class | |
| II | 7 (24%) |
| III | 22 (76%) |
| Medical therapy | |
| Betablocker (b) | 12 (41%) |
| Calciumantagonist (c) | 11 (38%) |
| Combination (b) and (c) | 6 (21%) |

Abbreviations: NYHA = New York Heart Association, SD = sudden death; M = male, F = female, N = number.



an out-of-hospital cardiac arrest. All patients were treated with drugs. Beta-blocking agents, calcium antagonists or the combination of these drugs were prescribed in 41%, 38%, and 21% of patients, respectively. Interventricular septal thickness averaged 23 ± 4 mm (range 17 to 35 mm), and mean left ventricular posterior wall thickness was 13 ± 3 mm (range 9 to 19 mm). The mean LVOT gradient was 100 ± 20 mm Hg. Most patients had moderate to severe MR (mean grade 2.5 ± 0.9). All patients had typical marked SAM of the anterior mitral valve leaflet (mean grade 2.9 ± 0.3). The calculated MLA was 16.7 ± 3.4 $cm^2$ (normal<12 $cm^2$). Significant coronary artery disease was demonstrated in a single patient in whom bypass grafting was performed simultaneously during the MLE and myectomy procedure.

## Clinical Outcome

Preoperative and postoperative data at 3 months and at the latest follow-up are presented in Table 2. The mean follow-up was 3.4 ± 2.1 years (range 3 months to 7.7. years). None of the patients died during surgery or during short-term follow-up. One surgical complication occurred at 3 months' follow-up and involved a patient with rapid-onset dyspnea. Echocardiography revealed a severe MR jet at the side of the inserted patch. At acute surgical intervention, the patch appeared dehiscent because of a loosened suture. After correction, the patient's clinical course was uncomplicated. During the follow-up period, patients were either asymptomatic or had mild symptoms (70% of them were in NYHA functional class I, and 30% were in class II). The number of cardiac drugs prescribed decreased significantly; before

**Table 2.** Pre- and postoperative characteristics at three months and at the latest visit in 29 patients with hypertrophic obstructive cardiomyopathy treated with myectomy and mitral leaflet extension.

| | Pre | Post* | Post** |
|---|---|---|---|
| Clinics | | | |
| NYHA Class | 2.7 ± 0.5 | 1.4 ± 0.5 | 1.3 ± 0.4 |
| Number of drugs | 1.5 ± 0.7 | 0.6 ± 0.8 | 0.5 ± 0.7 |
| Echocardiography | | | |
| IVS (mm) | 23 ± 4.0 | 18 ± 2.5 | 17 ± 2.3 |
| LVOTG (mm Hg) | 100 ± 21 | 19 ± 15 | 17 ± 14 |
| MR (grade) | 2.6 ± 0.7 | 0.5 ± 0.7 | 0.5 ± 0.6 |
| SAM (grade) | 2.9 ± 0.3 | 0.6 ± 0.6 | 0.5 ± 0.7 |
| LA (mm) | 47 ± 8 | 45 ± 10 | 45 ± 9 |
| MLA ($cm^2$) | 16.7 ± 3.4 | | |

*post-operative follow-up at three months. ** post-operative follow-up at latest visit.
Abbreviations: IVS = Interventricular Septal Width. LA = Left Atrium. LVOTG = Left Ventricular Outflow Tract Gradient. MR = Mitral Regurgitation. NYHA = New York Heart Association functional class. SAM = Systolic Anterior Motion. MLA = Mitral Leaflet Area.

intervention, the number of cardiac drugs used was 1.5 ± 0.7, whereas after surgery, the number of drugs decreased to 0.5 ± 0.7. In 1 of the 2 patients with atrial fibrillation before surgery, sinus rhythm was restored and was maintained under medical treatment postoperatively. No patient needed permanent cardiac pacing. In relation to the preoperative data, we found a mean reduction in septal thickness of 5.9 ± 2.3 mm after the surgical procedure. Moreover, short-term follow-up demonstrated that the LVOT gradient, MR, and SAM of the mitral valve were significantly reduced. At the latest patient visit, the beneficial results were maintained compared with the data at 3 months' follow-up.

Preoperative and postoperative echocardiograms from the same patient after MLE and myectomy are shown in figure 1.

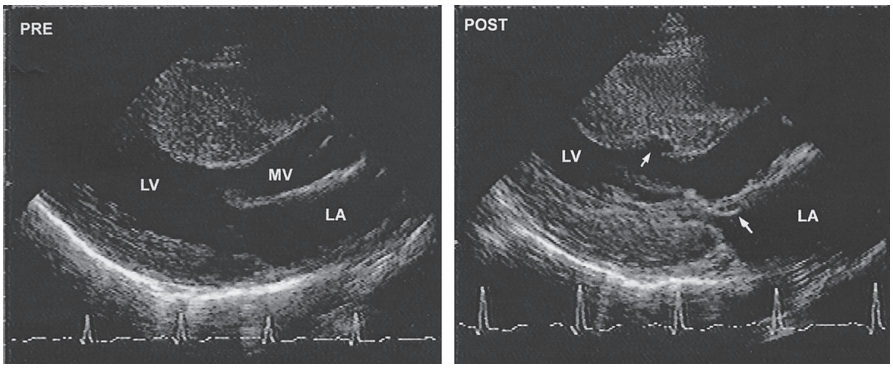



**Figure 1.** Preoperative (PRE) and postoperative (POST) 2D echocardiograms in parasternal long-axis view in a patient treated by combined approach. Arrows in the postoperative image indicate respectively site of myectomy and patch in anterior mitral leaflet. LV indicates left ventricle; MV, mitral valve; and LA, left atrium.

## DISCUSSION

An obstructive outflow tract gradient is present in 20% to 25% of HOCM patients[1] and results primarily from septal hypertrophy. Besides the myocardium, the anatomy of the mitral valve apparatus also frequently appears anomalous and may add to the obstruction component. Normally, the mitral valve leaflets coapt below the outflow tract as they are pulled posteriorly by the papillary muscles, where they do not impede the outward-directed blood flow. Well-recognized elements that may disrupt this coaptation mechanism are valve elongation and anterior displacement of the papillary muscles, which predispose to SAM.[4-12,19,22,23] Consequently, outflow tract obstruction and MR may persist after successful surgical myectomy. Therefore, mitral valve replacement has been alternatively performed to counteract residual SAM in patients regarded as less-suitable candidates for septal myectomy.[4,14,24-26] The thromboembolic complications due to long-term use of anticoagulants restrict the beneficial use of an artificial valve prosthesis.[27] Mitral leaflet plication has been introduced as a successful alternative to mitral valve replacement.[4]

At our institute, we developed an alternative surgical procedure after septal myectomy that aims to reduce the risk of a residual outflow obstruction due to SAM of the mitral valve. The technique entails septal myectomy in combination with a patch of autologous pericardium inserted into the anterior mitral valve leaflet. Initially, patients treated with the combination of myectomy and MLE were selected primarily on the basis of the echocardiographic findings of an elongated MLA. After a short-term follow-up period, we concluded that application of the combined technique resulted in superior hemodynamic results compared with myectomy alone. In the present study, we report the long-term follow-up results of this alternative approach in a larger patient population. Within the next period, 29 of 32 patients selected for surgical myectomy demonstrated an enlarged mitral valve leaflet area (16.7 ± 3.4 $cm^2$), which was significantly above values of a control group of patients (<12 $cm^2$). Clinical and hemodynamic parameters including functional class, reduction of the LVOT gradient, and attenuation of MR and SAM showed sustained improvement during this period. In 90% of the patients treated with the combined technique, SAM was reduced to grade 0 (absent) or grade I (mild). It is important to realize that the severity of MR is related to the presence of SAM.[28] Indeed, mitral valve incompetence was absent or trivial in 97% of patients in the present study.

We regard MLE as a safe addition to myectomy because there was no mortality in the present study. In addition, no ventricular septal defects or complete AV block was seen. One patient needed reoperation because of a dehiscent pericardial patch. Mitral valve function was maintained without echocardiographic observation of a

restricted mitral valve opening. In this respect, the combined technique might serve as a good alternative to septal myectomy alone in selected patients.

**MLE: Why Does It Work?**

In most patients with hypertrophic cardiomyopathy, the abnormal motion of the mitral valve in systole plays a key role in creating the outflow tract obstruction.[6,7] Several factors may be responsible for this phenomenon. The Venturi mechanism and flow drag of the leaflets due to increased mitral leaflet length, laxity, and anterior displacement of the papillary muscles allow the valve to protrude in the outflow tract.[4] Also, inward displacement of the papillary muscles toward each other results in chordal slack in the central leaflet portion and consequently SAM in the central portion of the valve.[5] To counteract these forces, the pericardial patch is grafted in the center portion of the anterior leaflet, where SAM typically reaches a maximum.[5,8,11,23] By extending the patch across the bending point of the mitral valve, we hypothesize that we stiffen the central parts of the buckling anterior leaflet, preventing abnormal mobility. In addition, the patch increases the width of the leaflet, which results in a horizontal extension. The widening of the leaflet may cause a lateral shift of the chordae attaching central portions of the valve. This displacement stretches the chordae, erects them, and enhances leaflet coaptation.[28]

Enlargement of the leaflet area could also add positively to maintenance of valve tethering once the streamlines of flow are normalized by septal myectomy.[28] During systole, the blood flow in the septal hypertrophied heart is forced to go around the septum and flows partially toward the posterior part of the anterior leaflet. The force of this streamline of flow pushes the valve into the LVOT. After septal myectomy, the flow stream straightens, hitting the mitral valve onto the anterior surface and pressing the leaflets toward the left atrium. The force that directs the enlarged valve posteriorly is linear to the leaflet area exposed to that flow. In fact, the patch appears tightened in systole, the anterior leaflet is directed toward the left atrium, and SAM and MR are abolished (Figure 1).

Septal myectomy is the most widely used surgical therapy in drug-refractory hypertrophic cardiomyopathy, with beneficial results in reducing outflow obstruction and MR. Because the outflow tract obstruction is multifactorial in origin, several different methods besides the classic myectomy have been developed to treat this heterogeneous disease. The present study cohort consisted of selected patients who demonstrated enlarged MLAs and typical SAM, as previously described by Klues et al[19]. This subset of patients with obstructive cardiomyopathy is particularly predisposed to residual SAM after a successful myectomy and would therefore benefit from the MLE procedure.

Mitral valve plication is another approach to avoid residual obstruction in selected patients.[3] It was designed to avoid mitral valve repair with a prosthesis, and hemodynamic results were encouraging, as in the present study. The selection criteria for plication included not only a relatively thin ventricular septum or an abnormal mitral valve apparatus but also a persistent obstruction after myectomy. In the present study, we did not treat previously operated patients. Also, we could not compare MLE to the results with valve prosthesis because this has not been a routine procedure at our institute.

Recently, percutaneous transluminal septal myocardial ablation (PTSMA) has been introduced as a new, nonsurgical approach to reduce septal width.[29] The procedure leads to localized thinning and contractile dysfunction of the septum, expansion of the LVOT, and thus reduction of the LVOT gradient. The anatomy of the mitral valve apparatus, however, remains unaltered, and at this moment, it is unknown whether comparable results can be obtained in this patient group with PTSMA. The present technique appears especially useful for patients with failed PTSMA and persisting MR.



## CONCLUSIONS

MLE in combination with myectomy is an effective and safe treatment for patients with HOCM. Long-term follow-up demonstrates sustained improvement in functional class, reduction of obstruction, and reduction in the severity of SAM and MR. Because the present technique offers a broadening of the surgical possibilities, we believe that MLE could become the preferred choice in persistent LVOT and SAM after PTSMA. The technique appears to be especially effective in patients with an enlarged anterior MLA. Future randomized studies will need to examine the status of the different techniques in patients with hypertrophic cardiomyopathy and obstruction.

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# 7

# Percutaneous transluminal septal myocardial ablation in hypertrophic cardiomyopathy

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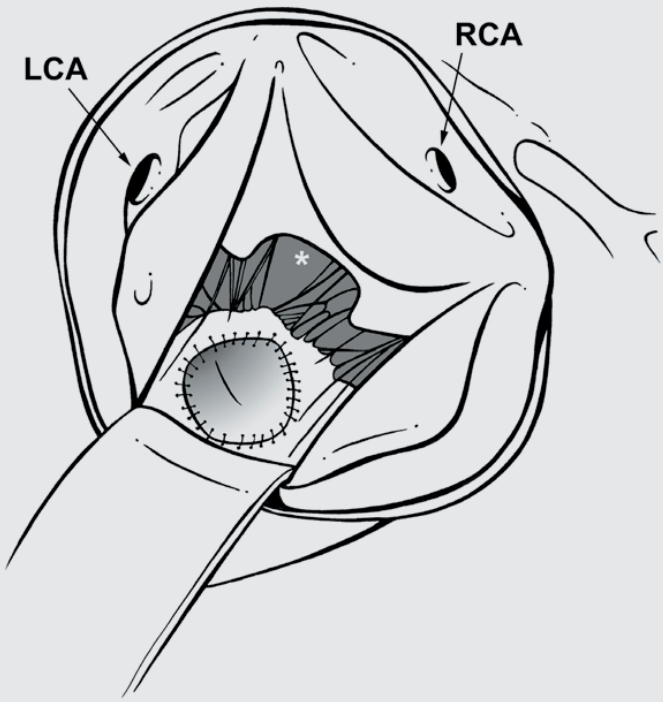
*Netherlands Heart J 2001;9:75-77*



## ABSTRACT

**Background:** Percutaneous transluminal septal myocardial ablation (PTSMA) is a new interventional technique to treat patients with hypertrophic obstructive cardiomyopathy.

**Methods:** Small doses of ethanol 96% were injected into a targeted septal artery causing a chemical myocardial infarction. Three patients were evaluated, including a follow-up of three months.

**Results:** There were no complications during the procedure. Left ventricular outflow tract gradients reduced from 120 ± 40 mm Hg to 25 ± 5 mm Hg. At follow-up, all three patients showed improvement in validity.

**Conclusion:** The method requires an echocardiographic contrast determination of the myocardium at risk for ethanol treatment, in addition to hemodynamic monitoring.

## INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HOCM) is defined as a primary, mostly familiar and genetically determined myocardial hypertrophy. In about 30% of cases, the disease presents with a dynamic obstruction of the left (and occasionally of the right) outflow tract.[1,2]

Therapy in severely symptomatic patients aims at reducing the extent of the left ventricular outflow tract (LVOT) obstruction, either medically using negative inotropic drugs or surgically by myo-myectomy.[2] Recently, DDD pacing has also been proposed as an alternative therapeutic option.

In 1994, Sigwart injected a small amount of absolute ethanol into the first septal branch of the left anterior descending coronary artery of a patient with HOCM.[3] The objective of this approach was to induce a small, localized myocardial infarction in the septal myocardium overlying the LVOT, in effect producing a chemical myo-myectomy without the need for open heart surgery.[3,4] Since then several studies have appeared describing the long-term effects in large groups with HOCM patients. The method, which is called percutaneous transluminal septal myocardial ablation (PTSMA), not only decreases the LVOT gradient, but also improves exercise capacity. The purpose of this report is to describe the first experience with PTSMA in the Netherlands.

Description of the method and the role of myocardial contrast echocardiography for targeted delivery of ethanol into the septal artery branch of choice are described.

## PATIENTS AND METHODS

Between October 1999, when PTSMA for HOCM was initiated in our institution (with the help of Professor U. Sigwart from the Royal Brompton Hospital, London, UK) and December 1999, three patients were treated. Inclusion criteria for PTSMA were moderate or severe symptoms (NYHA functional class II or III) despite optimal medical treatment and a pressure gradient across the LVOT (both measured using transthoracic cardiac echo Doppler and invasively during cardiac catheterization) of ≥ 50 mm Hg at rest. Detailed clinical data are shown in Table 1, and the study protocol is presented in Table 2.

The 2D echo Doppler examination was performed using the guidelines of the American Society of Echocardiography. LVOT gradients were assessed using continuous wave Doppler at rest and after the Valsalva manoeuvre. Mitral regurgitation and systolic anterior motion (SAM) of the mitral valve were graded on a 0-3 scale,

**Table 1.** Clinical characteristics of the three study patients.

| Patient | NYHA | | IVS | | LVOTG | | MR | | SAM | | LA | | LV ED/ES | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | 3 | 2 | 20 | 18 | 64 | 30 | 2+ | 1+ | 3 | 2 | 50 | 50 | 40/19 | 40/19 |
| 2 | 3 | 1 | 18 | 16 | 150 | 16 | 2+ | 1+ | 2 | 1 | 40 | 40 | 42/25 | 42/25 |
| 3 | 3 | 1 | 19 | 17 | 150 | 30 | 3+ | 1+ | 3 | 1 | 39 | 40 | 31/18 | 31/18 |

Clinical and echocardiographic characteristics of the three PTSMA-treated patients. Data are presented before and three months after the procedure. Abbreviations: NYHA = New York Heart Association functional class. IVS = Interventricular septum (mm). LVOTG = Left ventricular outflow tract gradient (mm Hg). MR = Mitral regurgitation (grade). SAM = Systolic anterior motion (grade). LA = Left atrium (mm). LV ED/ES = Left ventricular end-diastolic and end-systolic dimensions (mm). For further explanation see text.

**Table 2.** Study protocol

| | Before | During | 3 months follow-up |
|---|---|---|---|
| Clinical examination | X | X | X |
| ECG | X | X | X |
| 2D-echo/Doppler | X | X | X |
| CAG | X | | |
| Haemodynamics | X | X | |
| Exercise test | X | | X |



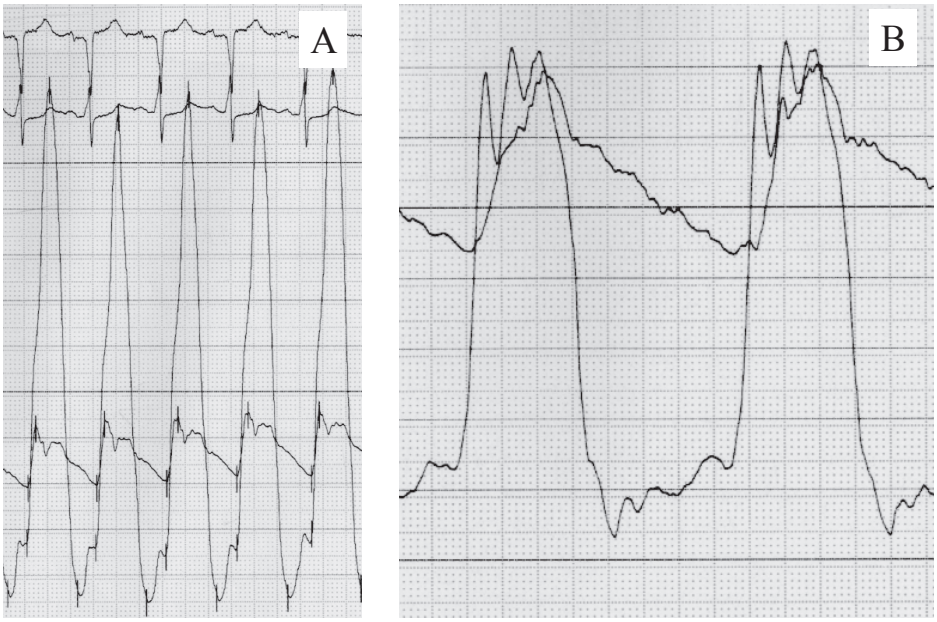



**Figure 1.** Left ventricular outflow tract gradient. The LV-pressure curve in relation to the aortic pressure curve before (panel A) and after (panel B) the procedure is depicted. There is a significant reduction of the LVOT-pressure gradient after the procedure.

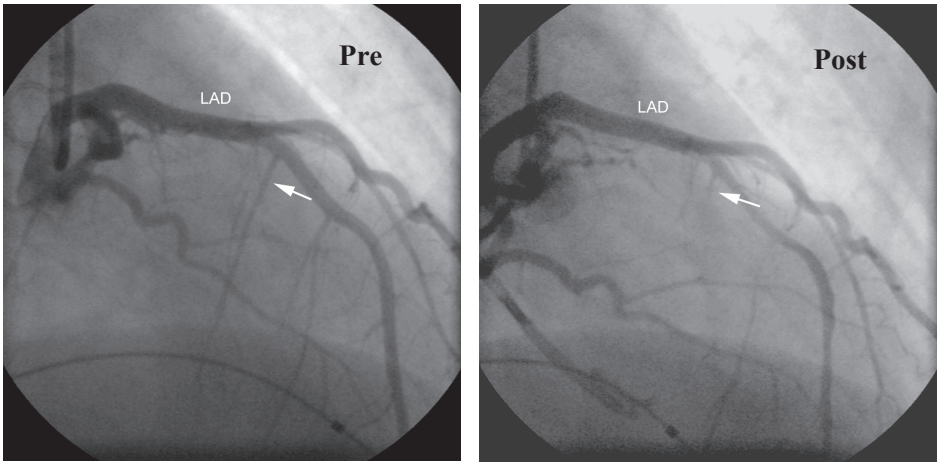



**Figure 2.** Coronary arteriography before and after PTSMA. Observe that the septal branch disappeared after the procedure.

where 0 = absent and 3 = severe with complete septal mitral apposition. Symptom-limited bicycle exercise test in the upright position was performed using 20W protocol (increased by 20W every minute) under continuous monitoring of heart rate and blood pressure.

## Intervention

The patients underwent PTSMA as described by Sigwart.[3] The right and the left femoral arteries were cannulated using a standard Judkins technique.

Professor Sigwart performed the first investigation in our department. A 6F pacemaker lead was placed in the right ventricle, an 6F pigtail catheter was positioned into the left ventricle and a 7F Judkins guiding catheter in the ascending aorta. The LVOT gradient was measured at rest, during the Valsalva manoeuvre and after a ventricular extra systole. Continuous monitoring of the LVOT pressure gradient was performed during the whole procedure (figure 1). After an i.v. standard bolus of 10,000 U heparin, the ostium of the left coronary artery was intubated and the large first septal branch identified on the coronary arteriogram. This was followed by insertion of a 0.014 inch guide wire into this septal branch and then a 2.0 x 10 mm balloon was placed in the proximal part of the target artery (figure 2).

When a satisfactory balloon position was achieved, the guide wire was pulled back and 1 ml of echo contrast agent (Sonovue, Altana Pharma, Bracco, Italy) was injected through the balloon catheter shaft during simultaneous registration of transthoracic 2D echo (figure 3A). This makes it possible to determine the part of the myocardium supplied by the targeted septal artery and also to visualize any leakage of contrast, which appears in the left ventricular cavity. If this was the case, the balloon was repositioned and the procedure repeated. If no leakage occurred and the myocardial

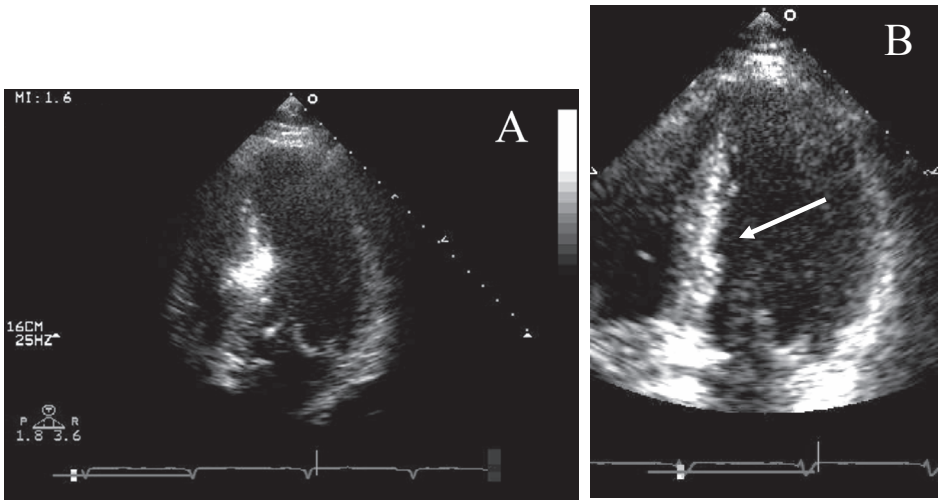



**Figure 3.** *Panel A.* Two-dimensional echocardiogram during PTSMA. 1.5 ml Sonovue® is injected into the targeted septal branch under continuous monitoring of 2D echo. The targeted myocardium is shown as an opacification of echo contrast in the myocardium. For further explanation, see text.
*Panel B.* Two-dimensional echocardiogram after PTSMA. Observe the myocardial thinning and the site of infarction after PTSMA. This has probably caused remodeling of the left ventricle. Also, systolic anterior motion is absent.



septal area could be clearly seen, including the site of mitral septal contact, ethanol was slowly injected through the balloon catheter shaft. If necessary the procedure was repeated until a maximum of 6 ml ethanol was given. Five minutes after ethanol injection the balloon was deflated and coronary arteriography repeated. The LVOT gradients were continuously determined again. If the results were not satisfactory the whole procedure, including contrast echo injection, was repeated. Not only the LVOT gradients, but also the presence of mitral regurgitation as assessed from 2D echo Doppler were taken into account during the procedure.

## RESULTS

### Acute results

In these three patients one septal branch per patient was occluded by injection of 4-6 ml 96% ethanol. There were no complications during the PTSMA procedure. Continuous recording of the LVOT gradient revealed a reduction of the gradient from 120 ± 40 mm Hg to 25 ± 5 mm Hg. During the procedure, AV conduction was prolonged and in two patients complete 3$^{rd}$ degree AV block occurred. However, at the end of the procedure only one patient needed temporary pacing. No patient had AV block up to 48 hours after the procedure. Maximal CK levels were 2100 IU, 2100 IU and 2500 IU, respectively.

In one patient 2nd degree AV block occurred after 48 hours, which resumed after another 24 hours of monitoring. Two patients were sent home on day 3; one patient, who had 2nd degree AV block, was sent home on day 5.

**Follow-up at three months**

All patients were seen in the outpatients' clinic between six weeks and two months by the principal investigator (Dr. ten Cate). All three showed an improvement in validity from NYHA class III to II and I (one and two patients, respectively). All patients showed an improvement in exercise time from seven to ten minutes

## DISCUSSION

Our preliminary results in these three patients confirm studies of others describing larger patient groups and longer follow-up.[3-7] In this respect, although rather preliminary, these results are in agreement with the results obtained by surgical myectomy and valvuloplasty.

PTSMA requires no thoracotomy and, if necessary, the procedure can be repeated on another occasion, if the gradient is not abolished satisfactory. This makes it a highly attractive therapeutic procedure.

As with any new procedure, safety precautions are of outmost importance. Since leakage of ethanol into the left anterior descending or larger branches can cause significant myocardial infarction, we would advise the use of contrast echo to determine the myocardium at risk and to see online whether leakage might occur into the LV cavity during the whole procedure.[7]

We consider it very important to keep the indications for PTSMA similar to those for surgery, namely inadequate medical treatment together with an LVOT gradient of ≥ 50 mm Hg at rest.

The long-term effects of the present therapeutic procedure are favorable.[4-6] However, HOCM is a heterogeneous disease with a heterogeneous clinical presentation and outcome. This means that experience with this technique should be restricted to cardio-thoracic centers experienced to treat patients with HOCM. Ideally, PTSMA should be compared to surgical therapy in a randomized, prospective trial to determine its significance in the treatment of this fascinating disease. Therefore, we agree with a recent Editorial by the group of Spencer who pleaded for a registry of patients with PTSMA to be able to determine undesired side effects.[8]

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# 8

# Intracardiac echocardiography to guide percutaneous transluminal septal myocardial ablation in hypertrophic cardiomyopathy

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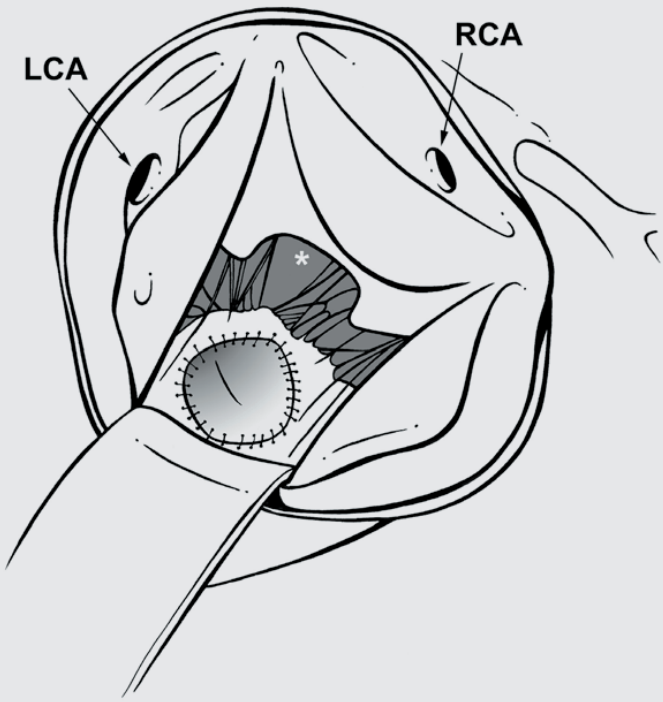
*Submitted for Publication*



## ABSTRACT

**Background:** Transthoracic myocardial contrast echocardiography to guide percutaneous transluminal septal myocardial ablation (PTSMA) is an important additional technique to optimize hemodynamic outcome and to minimize adverse effects during and after the procedure. The use of intracardiac echocardiography has not been previously investigated.

**Methods:** Intracardiac echocardiography was performed in 18 consecutive patients with hypertrophic obstructive cardiomyopathy. The target septal branch was chosen, based on the septal risk-area (SRA) visualized by intracardiac echocardiography after injection of an ultrasound contrast agent into the septal artery. In 12 patients, myocardial infarct size was evaluated by magnetic resonance imaging (MRI), 4 days after PTSMA.

**Results:** The mean interventricular septal width at intracardiac echocardiography was 21 ± 4 mm. During ethanol administration, a backscatter signal enhancement of the SRA was detected, allowing precise determination of its surface area. Using planimetry, the mean surface area of SRA after ethanol injection measured 1.8 ± 0.8 $cm^2$. This area correlated well with the volume of the myocardial infarction on MRI (22 ± 7 cc, r = 0.80). The invasive left ventricular outflow tract (LVOT) gradient was reduced from 74 ± 35 mmHg to 8 ± 16 mmHg ($p<0.0001$) at the end of the procedure. In one patient, a venous dissection occurred during introduction of the intracardiac echocardiography catheter, which did not allow its further use.

**Conclusions:** Intracardiac echocardiography is an accurate technique to monitor ethanol administration during PTSMA. The method is useful to predict the extent of the planned myocardial infarction.

## INTRODUCTION

The presence of a left ventricular outflow tract (LVOT) obstruction is strongly related to symptoms in patients with hypertrophic obstructive cardiomyopathy.[1-3] Percutaneous transluminal septal myocardial ablation (PTSMA) has emerged as an effective treatment modality for these patients, resulting in clinical and hemodynamic improvement comparable to surgery.[4-8] Transthoracic myocardial contrast echocardiography (MCE) has been shown to be of benefit for target vessel selection to guide PTSMA.[9] Furthermore, prevention of retrograde spill of ethanol into the left anterior descending coronary artery as well as misplacement of the myocardial infarction as source of potentially fatal complications were observed with this approach.[10] Intracardiac echocardiography is an invasive tool, recently introduced in our clinical setting, which might have the ability to provide a precise visualization of cardiac and valvular anatomy to guide interventional procedures.[11-13] The aim of the current study was to evaluate the role of intracardiac echocardiography during PTSMA in predicting the extent of the myocardial infarction.

## MATERIAL AND METHODS

### Patient Population

Between September 2003 and February 2005, 19 consecutive patients with hypertrophic obstructive cardiomyopathy underwent PTSMA at the Thoraxcenter. In one patient, the use of intracardiac echocardiography was abolished due to a venous dissection during introduction of the echo-catheter. Patient selection was based on the presence of a LVOT gradient ≥ 50 mm Hg, as documented by transthoracic echocardiography, and persisting symptoms, despite optimal medical treatment. Twelve patients underwent magnetic resonance imaging (MRI), 4 days after the procedure. Our institutional review committee approved the study and all patients gave informed consent.

### Intracardiac Echocardiography Procedure

The Acunav™ –intracardiac probe is a 10F catheter equipped with a linear phased array bifrequency (6-7 MHz) transducer. The catheter has a quadric-directional steerable tip, with a proximal control unit for tip deflection. The insertable length of the catheter is 90 centimetres. Regular two-dimensional echocardiography along with colour Doppler, pulsed and continuous wave Doppler allows comprehensive anatomical and physiological assessment. The probe was interfaced with Sequoia or Cypress platform (Siemens Acuson, Mountainview, California), and the images were digitally

recorded. Bilateral femoral arterial and venous accesses were obtained by a modified Seldinger technique. A 11F venous sheath was placed on the left side to introduce the intracardiac echocardiography probe. A temporary pacemaker lead was positioned in the right ventricle (Bipolar Electrode Catheter, 5F, Arrow, Germany). The tip of the intracardiac echocardiography probe was advanced into the right atrium with the piezo-electric crystal facing the free wall of the right atrium. Next, the probe was gradually deflected towards the atrial septum and advanced into the right ventricle to obtain a long axis of the left ventricle (LV). LVOT and mitral valve were evaluated in echocardiographic secta scan, by Doppler mode. The M-mode of the mitral valve in this plane confirmed the systolic anterior motion and thickness of the interventricular septum (IVS). The probe was locked in this position to view the entire proximal and midseptum for further imaging during myocardial contrast injection and ablation. Coronary angiography was performed in multiple projections to delineate the septal perforator branches. The supposed target vessel artery was identified and cannulated with a 0.014 inch guide wire. A 2.5 x 9 mm over the wire balloon was advanced into the vessel and inflated at 5-6 atmospheres to prevent retrograde flow into the left anterior descending coronary artery. After injection of 1 ml ultrasound contrast agent (Sonovue, Bracco, Milan, Italy) through the balloon catheter shaft, the myocardial area supplied by the vessel (septal risk area, SRA) could be visualized and any leakage form the septal branch or an anomalous distribution could be excluded. PTSMA was performed according to standard protocol [14]. The images obtained during infusion of ethanol revealed the progressive appearance of a sharply demarcated area with increased echo density in the septum within the SRA producing a marked shadowing effect (Figure 1). Measuring the invasive residual LVOT completed the procedure.



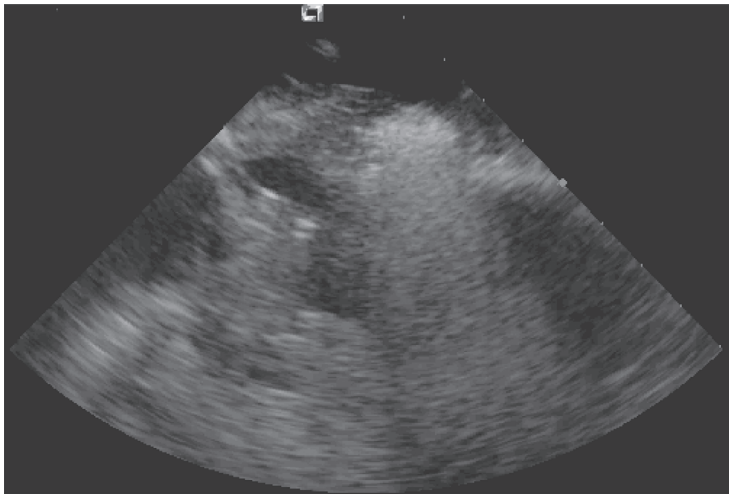


**Figure 1.** Image of the SRA (with ethanol) visualized by intracardiac echocardiography. Note the marked shadowing effect.

**Measurements**

The left ventricular outflow tract (LVOT) gradient was continuously monitored with simultaneous pressure recordings in the LV (6F pigtail catheter) and in the ascending aorta (7F Judkins guiding catheter).

Echocardiographic measurements included maximal septal thickness, septal thickness at the site of treatment, mitral regurgitation (MR) grade, severity of systolic anterior motion (SAM) of the anterior mitral leaflet and LVOT gradient. Septal thickness was measured by intracardiac echocardiography in a long-axis, end-diastolic still-frame of the LV. MR grade was assessed by color-flow Doppler intracardiac echocardiography and graded on a scale from 0 (no regurgitation) to 4 (severe regurgitation). SAM of the anterior mitral leaflet was graded as 0 (absent), 1+ (mild; minimal mitral-septal distance >10 mm during systole), 2+ (moderate; minimal mitral-septal distance ≤10 mm during systole) or 3 (marked; brief or prolonged contact between the anterior mitral leaflet and septum) [15]. The myocardial hyperechoic area developed during alcohol injection (ablated area) was off-line planimetrized.

**MRI protocol**

A clinical 1.5-Tesla MRI scanner with a dedicated cardiac four element phased-array receiver coil was used for imaging (Signa CV/*i*, GE Medical systems, Milwaukee, Wisconsin). Repeated breath-holds and gating to the electrocardiogram were applied to minimize the influence of cardiac and respiratory motion on data collection. The ce-MRI protocol consisted of cine-MRI and DE-imaging.

Left ventricular volumes and wall dimensions were assessed with cine-MRI using a steady-state free-precession technique (FIESTA) with the following imaging parameters: 6-10 seconds per breath-hold per slice (depending on heart rate), 24 phases per slice location, Field of View: 36 x 36 cm; TR 3.4; TE 1.4; flip angle 45 degrees; matrix 160 x 128, bandwidth 83 kHz, 0.75 NEX.) To cover the entire LV, 9 to 12 consecutive slices of 8 mm were planned in short axis view (gap of 2 mm) perpendicular to the horizontal long axis (4-chamber view) of the LV.

Myocardial distribution of DE was studied 10-20 minutes following intravenous administration of Gadolinium-DTPA (0.1 mmol/kg, Magnevist®, Schering). A 2-D T1-weighted inversion recovery gradient-echo sequence with the following imaging parameters was used; FOV: 40 x 32 cm, slice thickness 8 mm gap 2 mm, TR 7.3, TE 1.6, flip angle 20 degrees, TI 180 - 275 ms, matrix 256 x192, 1 NEX, bandwidth 17.9 kHz. The inversion time was adjusted per patient to null the signal of remote myocardium. Slice locations of the DE-images were copied from the cine images. A myocardial segment was judged as non-assessable if the region of DE could not be differentiated clearly from the healthy myocardium (breathing artefacts, erroneous ECG triggering).

### Analysis of MRI

The maximum width of the IVS was measured on cine-images in the LVOT-plane by a physician, who was blinded for the intracardiac echocardiography images. DE-myocardium was clearly differentiated from remote myocardium (nulled signal) with the use of an inversion recovery pulse sequence. Data from one patient had to be excluded since image quality was impaired. The volume of DE was quantified by manually selecting the enhanced regions from the consecutive 2D slices encompassing the LV with dedicated software (Cine, GE, 3.4.0, USA).

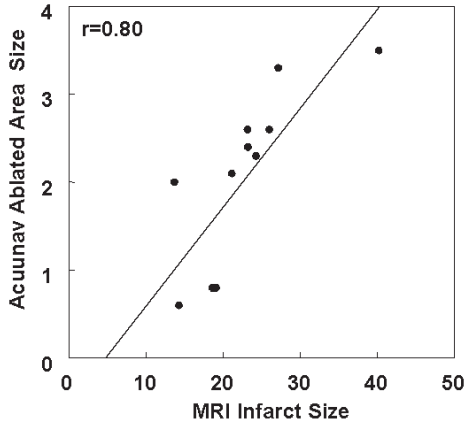





**Figure 2.** Correlation between the surface area ($cm^2$) of the SRA (with ethanol) measured by intracardiac echocardiography and the myocardial infarct size (cc) measured by delay-enhancement MRI.

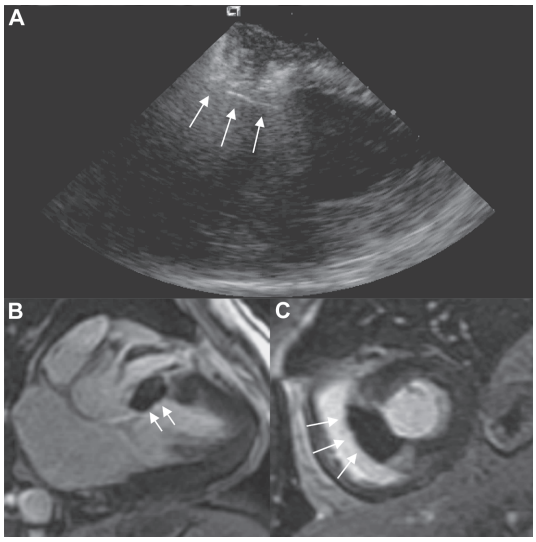



**Figure 3.** SRA (with ethanol) visualized by intracardiac echocardiography and the corresponding infarcted area visualized by MRI (panel B) after ethanol injection in two different septal branches.

## RESULTS

Eighteen patients (mean age 62 ± 13 years; 12 (67%) men) completed the procedure under intracardiac echocardiography guidance. The mean baseline NYHA functional class was 2.5 ± 0.5. All patients were in sinus rhythm.

The maximum width of the IVS measured by intracardiac echocardiography ranged from 15 to 30 mm (mean 21 ± 4 mm), which correlated with the MRI measurements (22 ± 4 mm, r = 0.70). Mean IVS thickness on intracardiac echocardiography at the level of ethanol injection was 20 ± 4 mm. The mean grade of SAM was 2.2 ± 0.9 and a moderate MR was present in 3 patients (17%).

Ethanol dose injected during the procedure was on average 2.1 ± 0.7 ml. Resting LVOT gradient was reduced from 74 ± 35 mmHg to 8 ± 16 mmHg ($p<0.0001$) and, after extra systolic beats, reduced from 130 ± 49 mmHg to 34 ± 33 mmHg ($p<0.0001$). In 1 patient, another, more proximally located septal branch was intubated, since occlusion of the fist selected branch resulted in a moderate proximal localization of the ablated area and with a small reduction in LVOT gradient (20

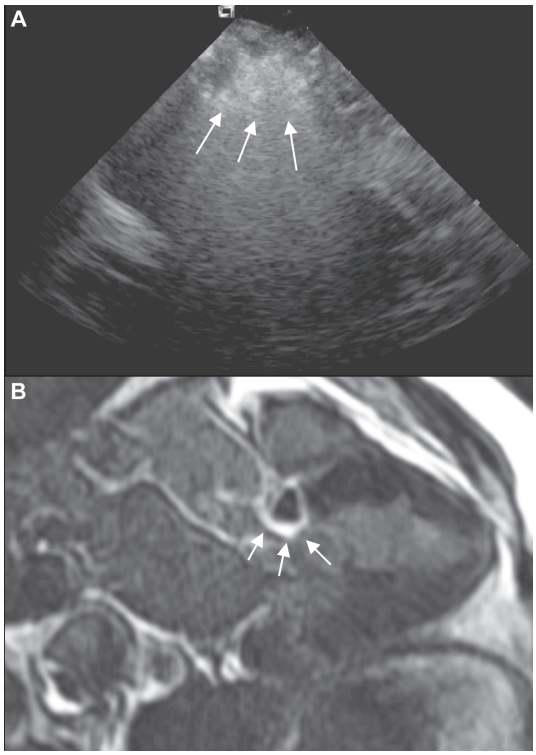



**Figure 4.** Triangular shaped ablated area visualized by intracardiac echocardiography during PTSMA (panel A) and corresponding infarct area visualized by MRI long axis (panel B).

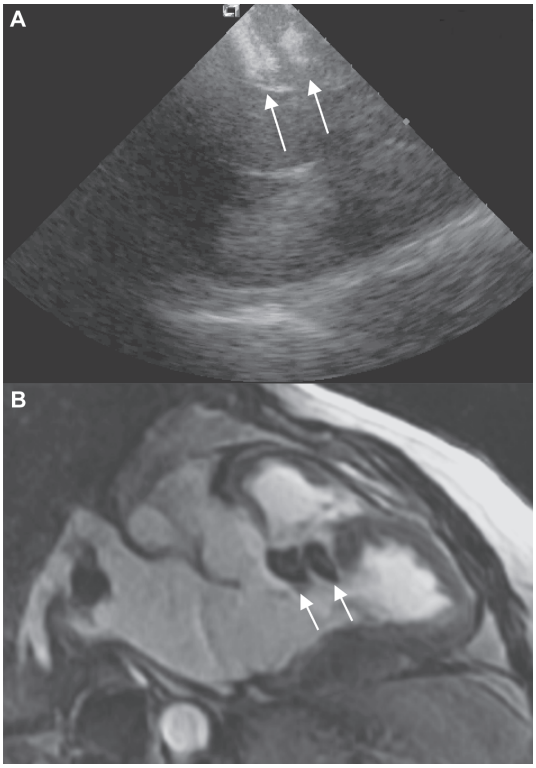





**Figure 5.** Ablated area visualized by intracardiac echocardiography and corresponding infarct area visualized by MRI long axis (panel B) in a patient who underwent PTSMA of two septal branches.

mmHg). The procedure was successful and the immediate reduction of LVOT gradient was higher (50 mmHg). Peak CK-MB and Troponin T was 161 ± 58 IU/L and 2.5 ± 1.1 UI/L, respectively.

The mean ablated area (with ethanol) on planimetry was 1.8 ± 0.8 cm2, which correlated with the MRI-determined infarcted volume (22 ± 7 cc, r = 0.80) (Figure 2, see also figure 3, 4, 5). In 1 patient, introduction of the intracardiac echocardiography catheter induced a venous dissection. The PTSMA procedure in this patient was performed only with transthoracic echocardiography.

## DISCUSSION

The present study demonstrates that intracardiac echocardiography is a accurate imaging technique, which can be used to guide ethanol administration during PTSMA, particularly in the selection of the appropriate septal branch. Also, the surface area of the contrast-enhanced SRA after ethanol injection, as visualized by

intracardiac echocardiography, correlated well with the infarcted size measured by delay-enhancement MRI, 4 days after the intervention.

MCE using transthoracic echocardiography is useful in guiding and monitoring the PTSMA procedure, with a cumulative impact on the interventional strategy reported in about 15-20%. Moreover, it can be helpful in defining the end of the procedure. An appropriate impregnation of the target region has been reported to represent a possible marker to interrupt the procedure, independently of the hemodynamic result since the remodelling process that lately occurs, plays a role in the reduction of the obstruction.[16] During the current procedures, intracardiac echocardiography has been used as a complementary tool to transthoracic MCE. The technique, however, may be managed in a completely autonomous fashion by the interventional team, without the need of constant presence of a standard ultrasound device and an experienced operator during the procedure. The echocardiographic images with intracardiac echocardiography are more easily obtained as compared to transthoracic echocardiography and provide a clear definition of the cardiac structures with a higher image resolution as compared to the transthoracic approach. Furthermore, continuous imaging can be provided during the entire procedure. As compared to transthoracic echocardiography, intracardiac echocardiography can overcome major limitations, including anatomic acoustic barriers (ribs and lungs), obesity, thoracic wall deformity and pulmonary conditions, especially since the patients are examined in a supine position during PTSMA.

## CONCLUSIONS

Intracardiac echocardiography can be used to monitor ethanol administration during PTSMA in hypertrophic obstructive cardiomyopathy patients. The surface area of the echo-enhanced SRA after ethanol injection correlates well to the volume of the myocardial infarction, measured by delay-enhancement MRI. Furthermore, it provides high-quality, continuous imaging of the myocardial segments and valvular structures involved during the PTSMA procedure.

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# 9

# The role of myocardial contrast echocardiography during percutaneous transluminal septal myocardial ablation in predicting the site and size of myocardial infarction

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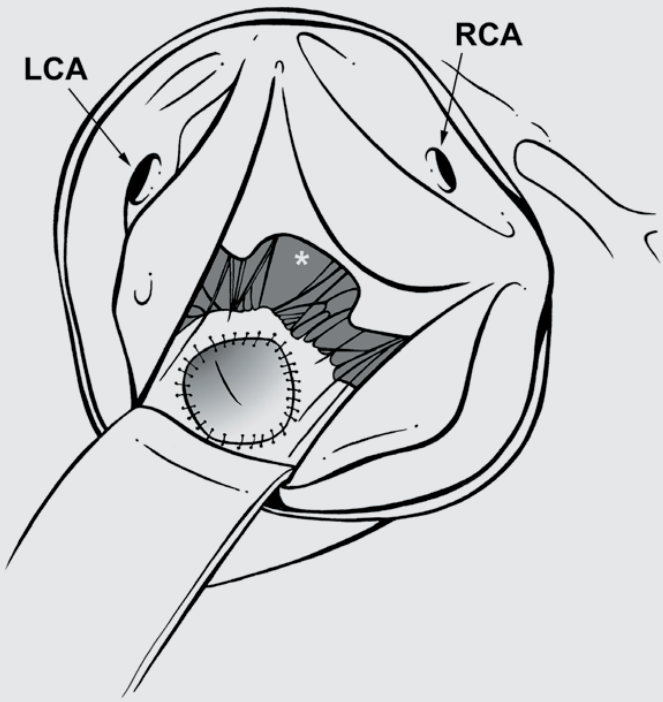
*Submitted for Publication*



## ABSTRACT

**Objectives:** The study was designed to evaluate the value of myocardial contrast echocardiography (MCE) during percutaneous transluminal septal myocardial ablation (PTSMA) in predicting the site and size of ethanol-induced septal myocardial infarction (SMI) as determined by magnetic resonance imaging (MRI).

**Background:** PTSMA entails the induction of a localized SMI with the intention to reduce left ventricular outflow tract obstruction in symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM). Both site and size of SMI are important to optimize hemodynamic results and to maximally preserve left ventricular function after PTSMA. MCE has been introduced as a tool to accurately predict site and size of SMI before definite ethanol injection.

**Methods and Results:** Seventeen consecutive HOCM patients underwent SonoVue® MCE-guided PTSMA and MRI after one month. All patients had SonoVue® opacification of the mid anteroseptal and posteroseptal segments. At follow-up, 91% of these segments showed SMI at MRI. SonoVue® opacification was present in 41% of the basal anteroseptal and posteroseptal segments. Negative and positive predictive values of SonoVue® opacification for basal SMI at MRI were 10% and 86%, respectively. Despite an excellent correlation between total septal surface area at echocardiography and total septal volume at MRI ($R = 0.79$, $P<0.001$), there was a poor correlation between the SonoVue® opacified septal surface and MRI determined final SMI volume ($R = 0.09$, $P = NS$). Injected ethanol volume correlated significantly with post-PTSMA peak CK-MB fraction ($R = 0.73$, $P<0.001$).

**Conclusions:** MCE has an excellent positive predictive value for the desired midseptal site of ethanol-induced SMI. However, SMI frequently extend into more basal septal parts and the correlation between the SonoVue® opacified area and SMI size at follow-up is poor. SMI size depends primarily on injected ethanol volume.

## INTRODUCTION

Percutaneous transluminal septal myocardial ablation (PTSMA) is a catheter-guided procedure to treat patients with hypertrophic obstructive cardiomyopathy (HOCM) and drug refractory symptoms. The procedure entails the induction of a localized septal myocardial infarction (SMI) by infusion of highly concentrated ethanol into one or more septal arteries.[1] In the initial series, a relatively high complication rate was noted, particularly advanced atrio-ventricular heart block.[2-4] Other, less common, complications included extensive myocardial infarction due to retrograde spill of ethanol in the left anterior descending coronary artery or connections from the septal system to right ventricular branches.[5,6]

Myocardial contrast echocardiography (MCE) may be useful in predicting the site and size of the ethanol-induced SMI.[7,8] Correct prediction of SMI site is important because maximal left ventricular outflow tract (LVOT) gradient and systolic anterior motion (SAM) reduction can only be reached when the intervention includes the area of mitral-septal contact.[6,9] Correct prediction of SMI size is important because this area should be as minimal as possible to maximally preserve left ventricular (LV) function and to reduce post-PTSMA atrio-ventricular conduction disturbances and need for permanent pacemaker implantation.[10,11] In the present study, we will focus on the ability of MCE to predict site and size of ethanol-induced SMI, assessed by markers for myocardial necrosis, magnetic resonance imaging (MRI) and transthoracic echocardiography (TTE).

## METHODS

### Patient selection

The study population comprised 17 consecutive HOCM patients with drug-refractory symptoms, who were referred for PTSMA. All subjects demonstrated a dynamic LVOT gradient of ≥ 50 mmHg at rest or on provocation. The hospital's ethical committee approved all PTSMA procedures with informed consent given by the patient.

### PTSMA procedure

Before PTSMA, all patients underwent diagnostic coronary angiography to exclude significant coronary artery disease. PTSMA was performed as previously described.[5] Briefly, a temporary pacemaker lead was positioned in the right ventricle and hemodynamic assessments, including a LVOT gradient, were performed. During the procedure, MCE was used to identify the septal region provided by the selected septal branch. If the relation of this region to the site of mitral-septal contact was judged

satisfactorily, an angioplasty balloon (1.5-2.5 x 10 mm) was inflated in this branch. Then 0.5 ml concentrated ethanol was injected through the balloon catheter shaft in 30 seconds. If the LVOT gradient remained >30 mm Hg, the procedure was repeated in the same or another septal branch, otherwise the balloon was deflated and coronary angiography was repeated in order to confirm discontinuation of the septal branch. The pacemaker lead was left in situ for at least 48 hours after the procedure and the patient was transferred to the clinical department for telemetric observation.

**Echocardiographic analysis**

Before PTSMA and at 6-months follow-up, TTE was performed to evaluate septal thickness at the site of treatment, LVOT gradient, grade of mitral regurgitation and SAM. Septal thickness was measured in the parasternal long-axis view in an end-diastolic still-frame (defined as the last frame before closing of the mitral valve). Peak LVOT gradient was calculated from the colour-guided continuous-wave Doppler velocity using the modified Bernoulli equation. Mitral regurgitation severity was assessed by colour flow Doppler echocardiography and graded on a scale from 0 (no regurgitation) to 4 (severe regurgitation). SAM of the anterior mitral valve leaflet was graded as 0 (absent), 1 (mild; minimal mitral-septal distance >10 mm during systole), 2 (moderate; minimal mitral-septal distance ≤10 mm during systole) or 3 (marked; brief or prolonged contact between the anterior mitral valve leaflet and septum).



**MCE study**

Imaging was performed using a Sonos 5500 system (Philips, Best, The Netherlands) with the S3 transducer. For contrast imaging transmitted frequency was 1.6 MHz and received frequency 3.2 MHz with a mechanical index of 1.6. As a contrast agent, SonoVue® (Bracco, Milan, Italy) was used, a blood pool ultrasound contrast agent based on microbubbles stabilised by a phospholipids shell and filled with sulphur hexafluoride gas with a mean size of 2.5µm.[12] SonoVue®was administered intracoronary as a slow bolus of 1,0 ml. All images were digitally stored and analysed off-line by two observers, blinded to the patients' clinical status. The LV was divided into 16 segments according to the American Society of Echocardiography with the anterior and posterior septum divided into basal, mid and distal segments.[13] The segments were scored positive or negative for SonoVue® opacification. From the apical 4-chamber view, the end-diastolic horizontal cross-sectional total and SonoVue® opacified septal surface area was planimetered.

### Cardiac Magnetic Resonance Imaging

Cardiac MRI was performed at baseline and 1-month after PTSMA with a 1.5 Tesla clinical scanner (Sonata, Siemens) and a four-element phased-array body radiofrequency receiver coil. All images were acquired with ECG gating and during repeated breath-holds of 10 to 15 seconds, depending on heart rate. Cine images were acquired using a segmented steady-state-free precision sequence in three long-axis views and in multiple short-axis views every 10 mm, covering the entire LV from base to apex. At 1-month follow-up, contrast-enhanced MRI was also performed. Contrast-enhanced (CE) images were acquired 15 to 20 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA in the same views as in the cine MRI with a 2D, segmented, inversion-recovery, prepared gradient-echo sequence.[14-16]

### Analysis of CE and cine images

Contrast-to-noise ratio of the hyperenhanced area versus a remote nonenhanced myocardial area was measured on the short-axis slice demonstrating the largest area of hyperenhancement. Contrast-to-noise ratio was calculated using regions of interest and defined as: $(SI_{hyperenhanced} - SI_{remote})$/noise, where SI is signal intensity, and noise is expressed as the SI standard deviation in a background region of interest. Infarct size after PTSMA was measured by manual tracing of the hyperenhanced areas, which were defined as the areas within the septal myocardium with pixel SI values >4 SD of remote, nonenhanced myocardium. Central dark zones within the area of hyperenhancement were included. The center of the infarct area was defined as the center of the hyperenhanced area on the short-axis image with the largest area of hyperenhancement. The interventricular septum was defined as the myocardium between the anterior and posterior junctions of the right ventricle to the LV. Septal myocardial mass was quantified with the MASS software package (MEDIS).

### Statistical analysis

Continuous variables were presented as mean ± standard deviation values and were compared using Student's unpaired t-test. Linear regression analysis was used to analyze the relationship between the various echocardiographic, MRI-determined and PTSMA-related parameters. The Mann-Whitney U test was used to evaluate the correlation between different infarction locations and myocardial infarction size and the volume of ethanol administered. All statistical significance was set at a P value $\leq 0.05$.

## RESULTS

### Baseline and follow-up echocardiographic and clinical data

As seen in Table 1, mean septal thickness, LVOT gradient, mitral regurgitation and SAM grade all significantly decreased. Mean NYHA functional class improved from 2.2 ± 0.4 to 1.4 ± 0.6 (P<0.001). Mean injected ethanol volume was 3.8 ± 1.1 ml, and mean post-PTSMA peak CK-MB fraction was 273 ± 77 IU/L. As seen in Figure 1, injected ethanol volume correlated significantly with post-PTSMA peak CK-MB fraction (R = 0.73, P<0.001).

**Table 1.** Baseline clinical and echocardiographic characteristics of the 17 study patients.

| | Baseline | Follow-up | P-Value |
|---|---|---|---|
| Male gender | 13 (76%) | | |
| Age, years | 44 ± 13 | | |
| NYHA, class | 2.2 ± 0.4 | 1.4 ± 0.6 | <0.001 |
| IVS, mm | 21 ± 3 | 14 ± 3 | <0.001 |
| LVOTG, mmHg | 95 ± 29 | 22 ± 27 | <0.001 |
| MR, grade | 1.4 ± 0.6 | 0.8 ± 0.8 | 0.04 |
| SAM, grade | 2.6 ± 0.6 | 1.5 ± 1.1 | 0.001 |

Abbreviations: NYHA = New York Heart Association. IVS = Interventricular Septum. LVOTG = Left Ventricular Outflow Tract Gradient. MR = Mitral Regurgitation. SAM = Systolic Anterior Motion.



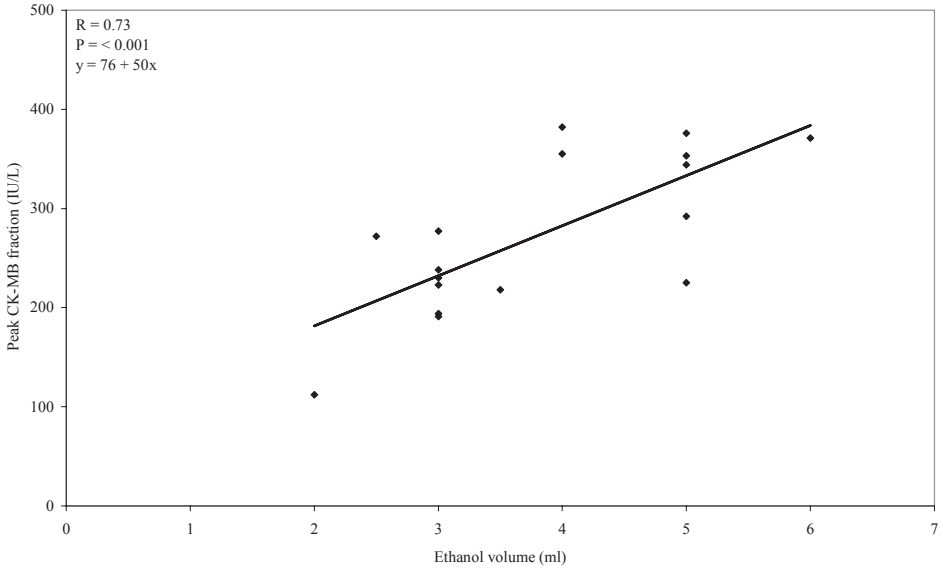



**Figure 1.** Correlation between peak CK-MB fraction and injected ethanol volume.

### Prediction of infarct site with MCE

In Figure 2, the relation between SonoVue® opacified septal segments and SMI site, as determined by TTE and MRI at follow-up, is shown. All patients had SonoVue® opacification of the mid anteroseptal and posteroseptal segments. At follow-up, 85% of these segments showed SMI at TTE and 91% showed SMI at MRI. SonoVue® opacification was present in 41% of the basal anteroseptal and posteroseptal segments. Negative and positive predictive values of SonoVue® opacification for basal septal SMI at TTE were 65% and 43%, respectively. For MRI these values were 10% and 86%, respectively. There were no differences between prediction of SMI for basal anteroseptal and posteroseptal opacified segments.

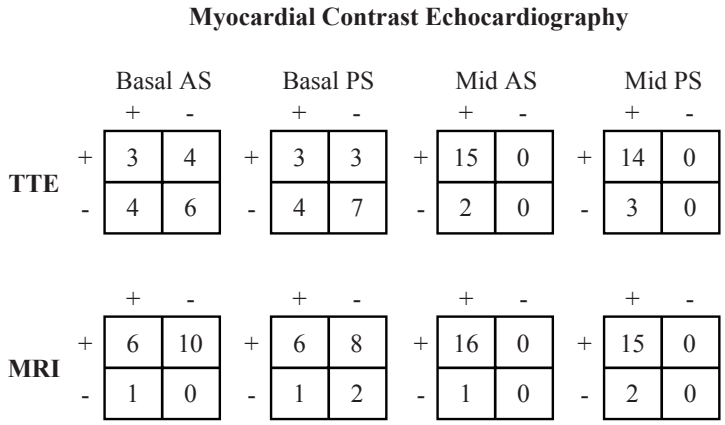



**Figure 2.** Relation between positive or negative echo contrast opacified septal segments (depicted in columns) and the presence or absence of septal myocardial infarction at transthoracic echocardiography (TTE, upper two lanes) and magnetic resonance imaging (MRI, lower two lanes), at follow-up. Abbreviations: AS = Antero-Septal segment. PS = Postero-Septal segment.

### Prediction of infarct size with MCE

Mean horizontal septal cross-sectional surface area at TTE was 15.5 ± 3.8 $cm^2$ (range 11.0 to 23.0 $cm^2$). Mean septal volume at MRI was 84.8 ± 22.1 $cm^3$ (range 40.6 to 127.9 $cm^3$). As seen in Figure 3, total septal surface area at TTE correlated significantly with total septal volume at MRI (R = 0.79, P<0.001). Mean SonoVue® opacified septal surface area was 5.7 ± 2.1 $cm^2$ (range 2.6 to 9.3 $cm^2$) and involved 37.6 ± 15.2% of the total septal surface area. Mean septal volume, as determined by the pre- and post-interventional MRI images, decreased by 11.7 ± 4.8% and mean SMI volume (expressed as percentage of total pre-PTSMA septal volume) was 30.2 ± 11.8%. Total myocardial volume (summation of lost and necrotic muscle volume) decreased by 41.9 ± 14.3%. As seen in Figure 4, SMI volume at MRI correlated significantly to peak CK-MB fraction (R = 0.60, P = 0.017). Non-significant correlations were seen between SonoVue® opacified septal surface area and injected ethanol volume (R = -0.42), peak CK-MB fraction (R = -0.32), and (MRI determined) SMI volume (R = 0.09). As

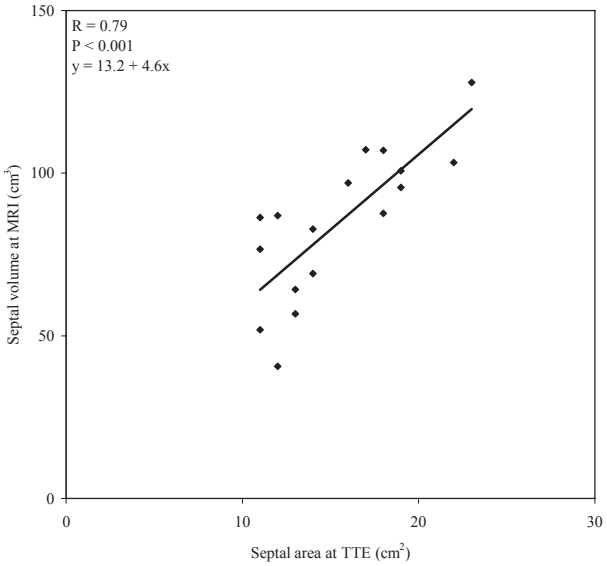



**Figure 3.** Correlation between pre-PTSMA horizontal septal cross-sectional surface area at transthoracic echocardiography (TTE) and septal volume at magnetic resonance imaging (MRI)

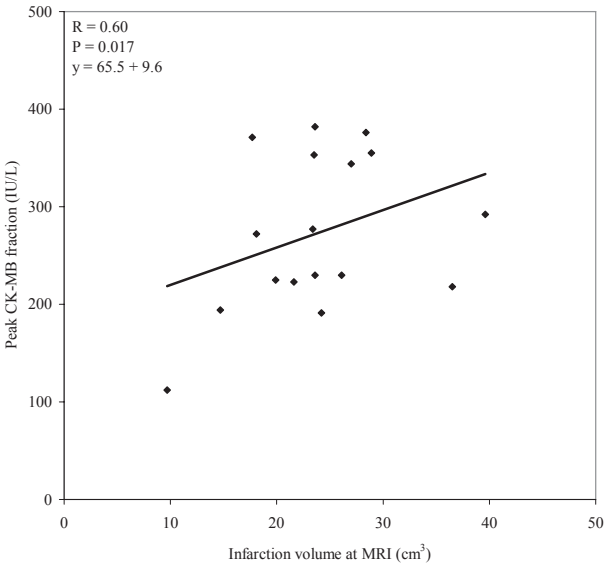



**Figure 4.** Correlation between peak CK-MB fraction and infarction volume at magnetic resonance imaging (MRI).



seen in Figure 5, SMI volume at MRI was only related to SonoVue® opacified septal surface area when this area was corrected for injected ethanol volume (R = 0.56, P = 0.02).

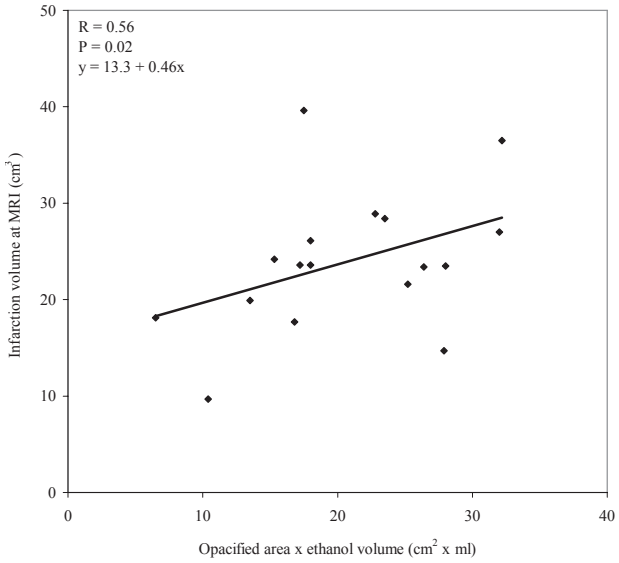



**Figure 5.** Correlation between infarction volume at magnetic resonance imaging (MRI) and SonoVue® opacified septal surface area corrected for injected ethanol volume.

## DISCUSSION

PTSMA is an effective therapy to treat patients with symptomatic HOCM. The procedure mimics surgical septal myectomy to relieve the LVOT gradient in that a septal trough is created after induction of a localized SMI.[3,17] However, due to the anatomic variations of the septal perforator coronary arteries, it is difficult to predict the site and size of the ethanol-induced SMI.[6,9,18] Correct prediction of SMI site is important because maximal LVOT gradient and SAM reduction can only be reached if the intervention includes the area of mitral-septal contact.[9,19-21] Correct prediction of SMI size is important because SMI size should be as small as possible to maximally preserve LV function and to minimize atrio-ventricular conduction abnormalities.[22,23]

Probatory balloon occlusion of the target septal artery has been propagated as a tool to predict the hemodynamic effect of permanent septal occlusion after ethanol injection.[2,24] With this technique, only the acute reduction in LVOT gradient, mainly due to a lesser peak acceleration rate of blood flow proximal to the obstruction, can be assessed.[25] Furthermore, spontaneous variability of the LVOT gradient as well as the influence of various peri-procedural interventions (i.e. use of analgesic agents or need for blood volume correction) on the severity of the LVOT gradient may be underestimated.

Our study is the first that correlates the site and size of the echo contrast-enhanced target septal area to definite SMI site and size, as evidenced by MRI.

### Role of MCE in predicting infarction site

MCE-guided PTSMA was introduced to identify the location of the target septal area in order to predict the site of ethanol-induced SMI. Several authors have demonstrated that, in order to obtain the most effective LVOT gradient reduction, the opacified septal area should entail the area located proximal and distal from the septal-mitral contact site.[4,6,26] Additionally, MCE has a major role in ruling out involvement of segments distant from the septal target area.[6] In our study, the positive predictive value of MCE for the site of ethanol-induced SMI was excellent. However, SMI extended frequently into more basal septal parts. Importantly, the target mid-septal areas were virtually always involved in the infarction area. This is an important finding because the site of SMI seems of greater importance than its definitive size[26,27] Only three SonoVue® opacified mid septal segments (one antero-septal and two postero-septal) did not show SMI with MRI at 1-month follow-up. Two of the 17 patients (12%) had late PTSMA failure (defined as a necessity for re-intervention due to absence of clinical improvement or recurrence of symptoms and a significant LVOT gradient). Only in one of these patients, the mid postero-septal segment did not show SMI at MRI.



### Role of MCE in predicting infarction size

The area of SonoVue® opacification did not correlate to SMI size at follow-up MRI. Methodological problems as the cause for this result seem unlikely since an excellent correlation existed between baseline total echocardiographic septal surface area and MRI septal volume. In addition to this, there was a good correlation between SMI volume at MRI and peak CK-MB fraction. Several factors may account for the poor correlation between the area of SonoVue® opacification and SMI size at follow-up. First, extension of SMI into more basal parts of the septum was poorly predicted by MCE. In fact, in most patients SMI extended into more basal parts of the septum. Second, the target area is a three-dimensional structure whereas the SonoVue® opacified area is a cross-section with only two dimensions. Three-dimensional assessment of SonoVue® opacified volume may provide better predictive results. Finally, and probably most importantly, the SonoVue® opacified area was inversely related to injected ethanol volume. After the starting bolus of ethanol, additional ethanol was injected depending on the LVOT gradient reduction achieved with the previous ethanol dose. In agreement with others, we have described that ethanol volume is a major determinant of SMI size, whether measured with post-PTSMA peak CK-MB fractions or SMI volume at MRI.[4,27,28] Larger ethanol volumes will, until a certain maximum, obviously result in greater SMI volumes. When the SonoVue® opacified area was corrected for ethanol volume (the smallest SMI is expected in small SonoVue® opacified areas with small ethanol volumes whereas the largest

SMI is expected in larger SonoVue® opacified areas with large ethanol volumes) a reasonable correlation with final SMI size was found.

## IMPLICATIONS AND CONCLUSIONS

MCE has an excellent positive predictive value for the desired mid-septal site of ethanol-induced SMI. However, SMI frequently extend into more basal septal parts and the correlation between the SonoVue® opacified area and SMI size at follow-up is poor. SMI size depends primarily on injected ethanol volume.

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# 10

## Prediction of outcome after percutaneous transluminal septal myocardial ablation for hypertrophic cardiomyopathy with clinical, echocardiographic and procedural characteristics

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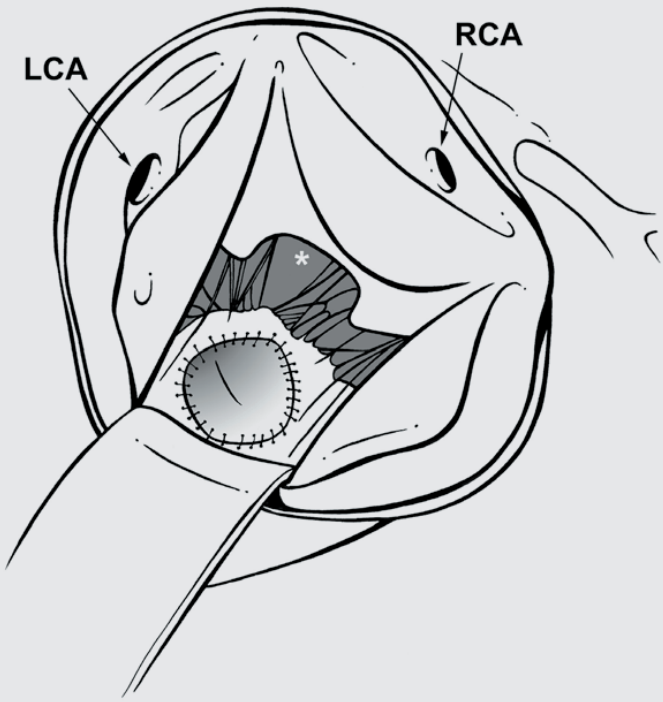
*Submitted for Publication*



## ABSTRACT

**Objectives:** To predict outcome after percutaneous transluminal septal myocardial ablation (PTSMA) in patients with hypertrophic obstructive cardiomyopathy (HOCM).

**Background:** In symptomatic HOCM patients, PTSMA results in hemodynamic and clinical improvement comparable to surgical myectomy. However, the risk for procedure-related complications and need for re-intervention seems higher with PTSMA.

**Methods:** In 131 consecutive HOCM patients (mean age 56 ± 16 years), treated with PTSMA, in-hospital and follow-up complications as well as late PTSMA failure (defined as unsatisfactory clinical outcome and a significant residual outflow tract gradient, necessitating re-intervention) were noted. Baseline hemodynamic, clinical, electrocardiographic and echocardiographic variables were examined as determinants for outcome. Also, the effect of ethanol volume and the role of a learning curve were investigated.

**Results:** PTSMA was successful in 90% of patients. Cardiac events, which were recorded in-hospital or during follow-up, respectively, were noted in 20 patients and included; cardiac death (3 and 1%,resp.), acute myocardial infarction due to ethanol leakage (1 and 0%, resp.), coronary dissection (2 and 0%, resp.), non-fatal cardiac tamponade (1 and 0%, resp.) and permanent pacemaker (5 and 0%, resp.) or ICD (4 and 1%, resp.) implantation. Late PTSMA failure was noticed in 12 patients (10%). All baseline characteristics were comparable between successful and failed patients. Ethanol volume was related to peak CK values ($P<0.0001$) but not to late PTSMA failure or greater need for pacemaker implantation. Late PTSMA failure occurred more frequently in PTSMA procedures performed in the early, less experienced time period ($P<0.0001$).

**Conclusions:** This study confirms that PTSMA is effective to treat HOCM patients at the cost of a relatively high complication rate. Late PTSMA failure could not be predicted by baseline characteristics but could partially be explained by a learning curve effect. This implies that PTSMA procedures should be restricted to experienced centres.

## INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HOCM) is an inheritable disease characterised by asymmetrical septal hypertrophy.[1]. Approximately one-quarter of these patients present with a significant left ventricular outflow tract (LVOT) gradient, which is usually correlated with the degree of complaints.[2] Until recently, septal myectomy was regarded as the gold standard therapy for HOCM patients that remained symptomatic despite optimal medical treatment. During this surgical procedure, a trough within the hypertrophied septum is created by removal of myocardium,[3] which immediately leads to relieve of the LVOT gradient.[4]

Percutaneous transluminal septal myocardial ablation (PTSMA), introduced in 1995, mimics surgical myectomy in that it reduces the LVOT gradient by remodelling the outflow tract.[5] During the procedure, a localized septal myocardial infarction is induced by injection of ethanol into one or more septal branches, which supply that part of the hypertrophied septum believed to produce LVOT obstruction. This results in immediate LVOT gradient reduction due to contractile septal dysfunction followed by gradual diminution of the obstruction later in time, due to septal thinning and further LVOT widening.[6-8] Ethanol should be injected in the myocardial area that is located at or near the point of contact between septum and the anterior mitral valve leaflet.[9,10] The amount of injected ethanol seems related to the final infarct size, as reflected by the rise in creatinine kinase (CK).[11-13] However, the effect of the injected ethanol amount on PTSMA-related complications, as well as on clinical and echocardiographic outcome differs between various studies.[12,14,15]

In the present study, we describe the results of PTSMA, performed at two experienced Dutch centres. We noted the incidence of in-hospital and follow-up events as well as long-term PTSMA failure and compared baseline clinical, echocardiographic and PTSMA characteristics between patients with successful and failed PTSMA.

## METHODS

### Patient selection

The study population comprised 131 consecutive patients with HOCM who underwent PTSMA between 1999 and 2004 at the Thoraxcenter Rotterdam or the Sint Antonius Hospital Nieuwegein. Inclusion criteria in both centers were identical and included persistent symptoms despite optimal medical treatment and a dynamic LVOT gradient ≥ 50 mmHg at rest or on provocation. All patients gave informed consent.

### Echocardiography analysis

Transthoracic echocardiography was performed to evaluate the site of hypertrophy, mitral valve anatomy and LVOT gradient. Septal thickness was measured in the parasternal long-axis view in an end-diastolic still-frame. Peak LVOT gradient was calculated from the color-guided continuous-wave Doppler velocity using the modified Bernoulli equation. Mitral regurgitation (MR) grade was assessed by colour flow Doppler echocardiography and graded on a scale from 0 (no regurgitation) to 4 (severe regurgitation). Systolic anterior motion (SAM) of the anterior mitral leaflet was graded as 0 (absent), 1+ (mild; minimal mitral-septal distance >10 mm during systole), 2+ (moderate; minimal mitral-septal distance ≤ 10 mm during systole) or 3 (severe; brief or prolonged contact between the anterior mitral leaflet and septum).[16] Left atrial and ventricular dimensions were measured using standard M-mode echocardiography from the parasternal long-axis view.

### Percutaneous transluminal septal myocardial ablation

Before the procedure, all patients underwent diagnostic coronary angiography to exclude significant coronary artery disease. PTSMA was performed with assistance of myocardial contrast echocardiography to identify the septal region provided by the selected septal branch.[17] Imaging was performed using the Sonos 5500 (Philips, Best, The Netherlands) with an S3 transducer. For contrast imaging, transmitted frequency was 1.6 MHz and received frequency 3.2 MHz. Mechanical index was 1.6 and frequency 25 Hz. One milliliter of a contrast agent (SonoVue™, Altana Pharma, Bracco, Italy) was administered intracoronary as a slow bolus to identify the septal myocardial region supplied by this selected septal branch. If the relation of this region to the site of mitral-septal contact was judged satisfactorily, a balloon was inflated in this branch. Then, 0.5 to 1.0 ml concentrated ethanol was slowly injected through the balloon catheter shaft in 30 seconds. If the LVOT gradient remained >30 mm Hg, the procedure was repeated after five minutes in the same septal or another septal branch, otherwise the balloon was deflated, and coronary angiography was repeated in order to confirm discontinuation of the septal branch.

### Follow-up

Follow-up data were collected at the outpatient clinic at the latest visit or before a re-intervention by the same cardiologist in each centre (FTC and JTB, respectively) and included mortality, pacing or defibrillating device implantation, New York Heart association (NYHA) class, and the earlier described echocardiographic characteristics. Failed outcome after PTSMA was defined as necessity for re-intervention due to absence of clinical improvement or recurrence of symptoms and a significant LVOT gradient. To analyze clinical and echocardiographic outcome according to the

injected amount of ethanol, patients were separated in three groups with a low (≤ 2 ml), intermediate (>2 to ≤ 4 ml) or high (>4 ml) amount of injected ethanol, respectively. To analyze the influence of a learning curve in relation to the PTSMA procedure, patients were separated into three groups, according to the experience with PTSMA.

### Statistical analysis

Continuous variables were presented as mean ± standard deviation. The clinical, hemodynamic and echocardiographic results of the three ethanol dose groups were analysed using the repeated measures of analysis of variance (ANOVA) method using the Bonferroni correction. This method was also applied to analyze the influence of a learning curve in relation to the PTSMA procedure. Significance was set at $P<0.05$.

## RESULTS

### Baseline characteristics

Baseline clinical, echocardiographic and PTSMA characteristics of the 131 patients are presented in Table 1 (first column). Mean age of the patients was 56 ± 16 years, mean septal thickness was 19 ± 4 mm and mean LVOT gradient was 83 ± 36 mm Hg. Mean volume of injected ethanol was 2.9 ± 1.3 ml. Mean peak creatinine kinase (CK) was 1,404 ± 685 U/L and mean peak CK-MB fraction was 200 ± 156 U/L.

### In-hospital events

Four patients died in relation to the PTSMA procedure. One patient died in the catheterization laboratory due to refractory ventricular fibrillation after induction of the septal infarction. Three patients died at the first day after the procedure due to unexplained cardiac tamponade (n = 1), cardiac tamponade caused by a pacemaker lead perforation (n = 1) and progressive heart failure (n = 1). One patient underwent successful pericardial drainage for cardiac tamponade that occurred after removal of the pacemaker lead. In one patient a large anterior myocardial infarction was induced due to spill of ethanol in the left anterior descending coronary artery. In two patients, dissection of the left anterior descending coronary artery required implantation of a drug-eluting stent. Six patients required permanent pacemaker implantation for persistent advanced atrioventricular block. In 4 patients a cardiac defibrillator was implanted because of ventricular fibrillation (n = 1) and ventricular tachycardia (n = 3) late after PTSMA.

**Table 1.** Baseline Clinical, Echocardiographic and PTSMA Characteristics.

| | All Patients with PTSMA (n = 131)* | Successful PTSMA (n = 114) | Failed PTSMA (n = 12) |
|---|---|---|---|
| Clinical data | | | |
| Age at therapy, years | 56 ± 16 | 55 ± 16 | 61 ± 14 |
| Male gender | 69 (53%) | 57 (50%) | 6 (50%) |
| NYHA class | 2.7 ± 0.7 | 2.6 ± 0.6 | 2.7 ± 0.7 |
| Echocardiographic data | | | |
| Septal thickness, mm | 19 ± 4 | 19 ± 4 | 19 ± 3 |
| LVOT gradient, mm Hg | 83 ± 36 | 82 ± 37 | 93 ± 29 |
| MR, grade | 1.5 ± 0.9 | 1.4 ± 0.9 | 1.9 ± 1.0 |
| SAM, grade | 2.4 ± 0.9 | 2.4 ± 0.9 | 2.6 ± 0.7 |
| LVOT, mm | 15 ± 4 | 15 ± 4 | 15 ± 3 |
| Left atrium, mm | 49 ± 7 | 49 ± 7 | 49 ± 6 |
| LV-EDD, mm | 42 ± 6 | 42 ± 7 | 43 ± 5 |
| LV-ESD, mm | 24 ± 5 | 24 ± 5 | 23 ± 4 |
| PTSMA data | | | |
| Septal arteries, n | 1.3 ± 0.5 | 1.3 ± 0.5 | 1.2 ± 0.4 |
| Ethanol volume, ml | 2.9 ± 1.3 | 2.9 ± 1.3 | 2.7 ± 1.3 |
| Peak CK, IU/L | 1,404 ± 685 | 1,427 ± 707 | 1,212 ± 476 |
| Peak CK-MB, IU/L | 200 ± 156 | 198 ± 159 | 198 ± 93 |

* = including 4 patients with peri-procedural death and 1 patient with peri-procedural large anterior myocardial infarction who were excluded from further analysis. LV-EDD = Left Ventricular End-Diastolic Diameter. LV-ESD = Left Ventricular End-Systolic Diameter. LVOT = Left Ventricular Outflow Tract. MR = Mitral Regurgitation. NYHA = New York Heart Association functional class. PTSMA = Percutaneous Transluminal Septal Myocardial Ablation. SAM = Systolic Anterior Motion.



### Follow-up events

During a mean follow-up of 17 ± 13 months three additional patients suffered a cardiac event (excluding re-interventions which are described later). In one patient a cardiac defibrillator was implanted 30 months post-PTSMA because of syncope with recorded ventricular tachycardia. Two patients died during follow-up. One patient with known poor pulmonary status died 12 months after PTSMA due to pulmonary failure. A second patient died suddenly 27 months after PTSMA. Total cardiac events are displayed in Table 2.

### Electrocardiographic, echocardiographic and clinical characteristics at follow-up

As seen in Table 3, 126 patients with available baseline and follow-up data were analysed. In this group, hemodynamic parameters (LVOT gradient, MR and SAM grade) and clinical NYHA class all improved significantly (all $P<0.001$). The 5 patients with peri-procedural death or an anterior infarction were excluded from analysis. Baseline clinical and echocardiographic characteristics in this group were not different

**Table 2.** Total Cardiac Events in 131 HOCM Patients Undergoing PTSMA.

| | In-hospital Events | Follow-up Events | Total Events |
|---|---|---|---|
| Cardiac death | 4 (3%) | 1 (1%) | 5 (4%) |
| Acute myocardial infarction | 1 (1%) | 0 (0%) | 1 (1%) |
| Coronary dissection | 2 (2%) | 0 (0%) | 2 (2%) |
| Non-fatal cardiac tamponade | 1 (1%) | 0 (0%) | 1 (1%) |
| Pacemaker implantation | 6 (5%) | 0 (0%) | 6 (5%) |
| Defibrillator implantation | 4 (3%) | 1 (1%) | 5 (4%) |
| Re-intervention* | - | 10 (8%) | 10 (8%) |
| Total events | 18 (14%) | 12 (9%) | 30 (23%) |

* = Seven patients underwent re-PTSMA and three patients underwent surgical myectomy.

**Table 3.** Clinical, Electrocardiographic and Echocardiographic Characteristics at Latest Follow-up.

| | All Patients with PTSMA (n = 126)* | Successful PTSMA (n = 114) | Failed PTSMA (n = 12) |
|---|---|---|---|
| Clinical data | | | |
| Follow up, months | 17 ± 13 | 14 ± 12 | 13 ± 11 |
| Age at therapy, years | 56 ± 16 | 55 ± 16 | 61 ± 14 |
| Male gender | 69 (53%) | 57 (50%) | 6 (50%) |
| NYHA class | 1.3 ± 0.6 | 1.2 ± 0.4 | 2.3 ± 0.9 ‡ |
| Electrocardiographic data | | | |
| Right BBB (%) | 57 (51%) | 51 (52%) | 6 (50%) |
| Echocardiographic data | | | |
| Septal thickness, mm | 14 ± 4 | 14 ± 4 | 16 ± 4 |
| LVOT gradient, mm Hg | 23 ± 24 | 18 ± 16 | 66 ± 36 ‡ |
| MR, grade | 0.6 ± 0.7 | 0.5 ± 0.6 | 1.6 ± 1.1 † |
| SAM, grade | 0.8 ± 1.0 | 0.7 ± 0.9 | 1.8 ± 1.1 † |
| LVOT, mm | 18 ± 5 | 18 ± 4 | 16 ± 3 ‡ |
| Left atrium, mm | 47 ± 7 | 47 ± 7 | 48 ± 7 |
| LV-EDD, mm | 44 ± 7 | 44 ± 7 | 43 ± 8 |
| LV-ESD, mm | 27 ± 9 | 28 ± 9 | 22 ± 5 ‡ |

* = excluding the four patients with peri-procedural death and 1 patient with peri-procedural large anterior myocardial infarction. † = P<0.01. ‡ = P<0.001. Abbreviations see Table 1. BBB = Bundle Branch Block.

from the analysable 126 patients. In these 126 patients, PTSMA was successful in 114 patients (90%) and failed in 12 patients (10%). Seven of these 12 patients underwent re-PTSMA after a mean follow-up of 12 months and three patients underwent surgical myectomy after a mean follow-up of 14 months. Two patients refrained from further invasive intervention. Mean baseline clinical, echocardiographic and PTSMA characteristics (Table 1) and the presence of PTSMA-induced right bundle

branch block (Table 3) did not differ significantly between patients with successful and failed PTSMA. Only age and MR grade at baseline tended to be higher in failed patients (both parameters non-significant). Characteristics after failed PTSMA included a significantly higher mean LVOT gradient, SAM and MR grade, and NYHA class (Table 3).

### Echocardiographic, PTSMA and clinical characteristics in relation to ethanol volume

In Table 4, pre- and post PTSMA echocardiographic and clinical characteristics for patients receiving a low, intermediate or high volume of ethanol are presented. In 118 of the 126 analysable patients (94%) ethanol volumes were available. In 57 patients (48%) a low ethanol volume (1.8 ± 0.3 ml), in 47 patients (40%) an intermediate ethanol volume (3.2 ± 0.5 ml) and in 14 patients (12%) a high ethanol volume (5.5 ± 1.0 ml) was used. Larger volumes of ethanol were used in more hypertrophied septa (P<0.005) and resulted in greater CK and CK-MB peak values (P<0.0001). The decrease in septal thickness was, however, independently of used ethanol volume. There was no significant relation between ethanol volume and baseline LVOT gradient, LVOT gradient reduction or clinical NYHA class at follow-up.



**Table 4.** Procedural, Echocardiographic and Clinical Characteristics in Relation to Injected Ethanol Volume.

| | Ethanol Volume <2ml (n = 57) | Ethanol Volume 2 to 4 ml (n = 47) | Ethanol Volume >4 ml (n = 14) |
|---|---|---|---|
| Ethanol volume, ml | 1.8 ± 0.3 | 3.2 ± 0.5 | 5.5 ± 1.0‡ |
| Atrioventricular block | 3 | 2 | 1 |
| Peak CK, U/L | 1,065 ± 422 | 1,572 ± 685 | 2,154 ± 883‡ |
| Peak CK-MB, U/L | 158 ± 161 | 187 ± 98 | 363 ± 196‡ |
| Septal thickness, mm | | | |
| baseline | 18 ± 4 | 20 ± 4 | 22 ± 4† |
| follow-up | 14 ± 3 | 15 ± 5 | 17 ± 3* |
| delta | 4 ± 4 | 5 ± 5 | 5 ± 4 |
| LVOT gradient, mm Hg | | | |
| baseline | 76 ± 35 | 84 ± 38 | 97 ± 29 |
| follow-up | 23 ± 25 | 22 ± 22 | 23 ± 25 |
| delta | 53 ± 35 | 62 ± 38 | 74 ± 38 |
| NYHA class | | | |
| baseline | 2.7 ± 0.6 | 2.6 ± 0.6 | 2.3 ± 0.5 |
| follow-up | 1.3 ± 0.6 | 1.2 ± 0.6 | 1.4 ± 0.5 |
| delta | 1.4 ± 0.8[2*] | 1.4 ± 0.7 | 0.9 ± 0.7* |

Abbreviations as in Table 1. * = P<0.05. † = P<0.005. ‡ = P<0.0001

### Influence of a PTSMA learning curve

As seen in Table 5, the patients were divided in three groups according to the experience with PTSMA. Ethanol volume, in-hospital complications (cardiac death, acute

**Table 5.** In-Hospital Complications, Pacemaker Necessity and Late PTSMA Failure According to Experience.

| | Early Experience (n = 43) | Intermediate Experience (n = 43) | Late Experience (n = 45) |
|---|---|---|---|
| Ethanol volume, ml | 2.7 ± 1.2 | 3.3 ± 1.3 | 2.5 ± 0.9 |
| In-hospital complications* | 2 (5%) | 3 (7%) | 3 (7%) |
| Pacemaker implantation | 3 (7%) | 2 (5%) | 1 (2%) |
| Late PTSMA failure | 9 (21%) | 1 (2%) | 2 (4%)† |
| Total events | 14 (33%) | 6 (14%) | 6 (13%) |

* = Cardiac death, acute myocardial infarction, coronary dissection or non-fatal cardiac tamponade. † = P<0.0001

myocardial infarction, coronary dissection or non-fatal cardiac tamponade) and the need for pacemaker implantation were comparable over time. However, late PTSMA failure occurred more often in patients who underwent a PTSMA procedure in the early, less experienced time period (P<0.0001).

## DISCUSSION

Invasive therapy for HOCM patients with drug-refractory symptoms aims at acute improvement of hemodynamics and sustained clinical improvement during long-term follow-up. Since 1959, an important number of patients have been treated with surgical myectomy.[18] Due to its invasive character as well as the complication rate, mainly reported in the earlier series,[7,13,19] a continuous search for less invasive therapies with comparable beneficial effects has been undertaken. Atrioventricular sequential pacing was the first non-surgical interventional therapy that claimed a high clinical success rate.[20] However, results of randomized trials in which the pacing mode was alternately turned on and off were disappointing and its general use in HOCM patients was discouraged.[21,22] PTSMA was introduced in 1995 as a novel technique that could mimic septal myectomy.[5] Induction of a local myocardial infarction in the hypertrophied septum at the site of septal-mitral contact results in relieve of the LVOT gradient, reduction in MR and improvement of clinical symptoms.[6,14,23,24] The enthusiasm for PTSMA is reflected by the huge number of so far performed procedures, which probably outnumbers the total number of surgical myectomies performed within the past 45 years.[25] PTSMA has, however, a relatively high complication rate and re-interventions are sometimes necessary.[14] Therefore, optimal selection of HOCM patients who really may benefit from PTSMA is important.

### Occurrence of cardiac events

As summarized in Table 2, the need for permanent pacemaker implantation is the most frequent in-hospital complication after PTSMA, despite careful contrast identification of the target septal branch. However, in accordance to a prior publication from our group[26], our more conservative pacemaker implantation strategy resulted in a significantly lower event rate than that reported in the TASH registry.[23] As described before[17], PTSMA also has fatal and other complications, such as spill of ethanol into the left anterior descending coronary artery, coronary dissection or non-fatal cardiac tamponade. Total in-hospital event rate was 14%. Long-term (17 ± 13 months) follow-up was, apart from the later described late re-interventions, quite benign with only one late death.

### Baseline characteristics as predictors of long-term PTSMA outcome

The vast majority of the 131 studied patients experienced improvement in hemodynamic (reduction in LVOT gradient, MR and SAM grade) and clinical (NYHA class) parameters after PTSMA. Hemodynamic and clinical failure of PTSMA during a follow-up of 17 ± 13 months was noticed in 10% of the patients. In other publications, PTSMA failure was seen in 6 to 29% of all patients.[23,27,28] Unfortunately, none of the studied baseline echocardiographic, clinical and PTSMA related characteristics were useful in determining long-term PTSMA success rate. In a study by Chang *et al.*,[27] LVOT gradient reduction immediately after PTSMA in the catheterization laboratory and peak CK were independent predictors of successful outcome. These investigators could, however, also not identify independent predictors from the baseline clinical or echocardiographic characteristics to select patients that benefit most from PTSMA. In our study peak CK did not predict successful outcome.





### The role of ethanol volume

In our study, the mean volume of injected ethanol was relatively large (2.9 ± 1.3 ml) as compared to other studies.[14,29] Contrary to our expectations, ethanol volume did not change over time. In 1999, a maximal ethanol volume of 4 ml was recommended.[7] At present volumes of 1-2 ml or even less are suggested.[30] Veselka *et al.* reported that clinical and echocardiographic results at 6-months follow-up were comparable for injection of 1 to 2 ml and more than 2.0 ml ethanol.[12] At present, it is still debatable what ethanol volume is preferable. To obtain more insight in the effect of injected ethanol volume we divided our patients in three groups according to this volume. Surprisingly, less ethanol volume in our study did not affect the occurrence of advanced atrioventricular block, nor was it associated with late PTSMA failure. In the TASH registry,[23] mean injected ethanol volume was comparable to our study. The authors reported occurrence of atrioventricular conduction block, neces-

sitating permanent pacing, in 9.6%. In our study, only 5% of the patients needed permanent pacing for advanced atrioventricular conduction block. Ethanol volume has been related to infarct size,[13] which was confirmed in our study. Interestingly, the release of peak CK or CK-MB in relation to the amount of ethanol differs significantly between published studies. In our study CK release was 1,404 IU/L per 2.9 ml ethanol, others reported 1,128 IU/L per 1.8 ml and 1,411 IU/L per 2.4 ml,[14,15] whereas in the TASH registry CK-releases of 483 IU/L per 2.8 ml ethanol were reported.

### The role of a learning curve

It is well known that clinical experience influences the results of a procedure. As seen from results of percutaneous coronary interventions,[31,32] a high-volume load for operators and institutions is associated with better procedural outcome. The importance of a learning curve for PTSMA is confirmed in our study since a high incidence of late PTSMA failure was noted in the first group of patients, whereas this number significantly reduced with growing experience. At a volume of approximately 20 treated patients per center per year, late PTSMA failure is currently 4%, which is not different from that in other experienced centers.[23,27] Surprisingly, we did not notice a relation between PTSMA experience and need for pacemaker implantation.

## CONCLUSIONS AND CLINICAL IMPLICATIONS

The present study confirms that PTSMA is an effective method to treat patients with drug-refractory, symptomatic HOCM at the cost of a relatively high complication rate. During follow-up late hemodynamic and clinical failure of PTSMA was noticed in 10% of the patients. PTSMA failure could not be predicted by baseline clinical, electrocardiographic, echocardiographic or PTSMA related characteristics but may partially be explained by a learning curve effect. This implies that PTSMA procedures should be restricted to a limited number of experienced centres.

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# 11

## Percutaneous versus surgical treatment in patients with hypertrophic obstructive cardiomyopathy and an enlarged anterior mitral leaflet

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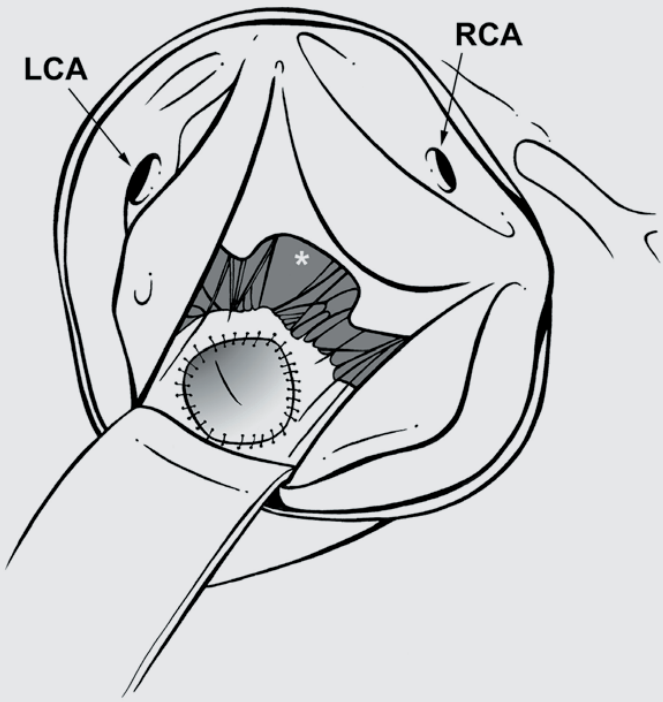
*Circulation 2005;112:482-488*



## ABSTRACT

**Background:** To compare percutaneous transluminal septal myocardial ablation (PTSMA) versus septal myectomy combined with mitral leaflet extension (MLE) in symptomatic hypertrophic obstructive cardiomyopathy (HOCM) patients with an enlarged anterior mitral valve leaflet (AMVL). Both PTSMA and myectomy reduce septal thickness and left ventricular outflow tract (LVOT) gradient. However, an uncorrected enlarged AMVL may predispose to residual systolic anterior motion (SAM) after successful standard myectomy or PTSMA. Myectomy with MLE previously demonstrated superior hemodynamic results compared to standard myectomy but its relative value to PTSMA is unknown.

**Methods and Results:** Twenty-nine patients (44 ± 12 years) underwent myectomy with MLE and 43 (52 ± 17 years) PTSMA. Mitral leaflet area was similar in both groups (16.7 ± 3.4 vs. 15.9 ± 2.7 $cm^2$, respectively). After PTSMA two patients died, four needed a re-intervention and four a permanent pacemaker for complete heart block. After surgery only one patient needed a re-intervention. At one-year follow-up, LVOT gradients did not differ between surgical and PTSMA patients (17 ± 14 vs. 23 ± 19 mm Hg, respectively). Pre-interventional mitral regurgitation grade was more severe in the surgical group but with myectomy MLE the residual grade was similar as compared to PTSMA. Mean SAM grade decreased significantly more after surgery (2.9 ± 0.3 to 0.5 ± 0.7 vs. 2.8 ± 0.5 to 1.3 ± 0.9 grade, $P<0.05$).

**Conclusions.** PTSMA in these selected HOCM patients had more peri-procedural complications and necessity for re-interventions. Hemodynamic results (SAM grade and reduction in mitral regurgitation) were better in surgical patients.

## INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HOCM) is characterised by asymmetrical septal hypertrophy [1] that causes a left ventricular outflow tract (LVOT) gradient. The severity of the LVOT gradient is usually correlated with the degree of complaints.[2] In patients who remain symptomatic despite optimal medical treatment, several invasive therapeutical modalities have been introduced. Septal myectomy, a surgical technique developed by Morrow[3], is regarded as the standard approach to reduce septal thickness and LVOT gradient. This technique proved to be safe with excellent hemodynamic results.[4-7] Percutaneous transluminal septal myocardial ablation (PTSMA) is a non-surgical technique to reduce septal thickness.[8] During this procedure, ethanol is injected into one or more septal branches of the left anterior descending coronary artery (LAD) resulting in a local myocardial infarction with contractile septal dysfunction followed by septal thinning, LVOT widening and eventual LVOT gradient reduction.[9-11]

The mitral valve apparatus frequently demonstrates anomalies in HOCM, for instance increased mitral leaflet area, length and laxity as well as anterior displacement of the papillary muscles.[12-15] All these abnormalities may predispose to residual SAM after successful myectomy. To avoid persistence of LVOT gradient as well as mitral regurgitation (MR), we developed mitral leaflet extension (MLE) in addition to myectomy.[16] Previously, we reported beneficial effects of this novel technique compared to standard myectomy.[16] Currently, it is not known whether PTSMA is equally effective in these selected patients. In this report, we present hemodynamic and clinical 1-year outcome in HOCM patients with an enlarged anterior mitral valve leaflet (AMVL) who underwent PTSMA or myectomy in combination with MLE.

## METHODS

### Patient selection

The study population comprised 72 patients with symptomatic HOCM despite optimal medical treatment. All subjects demonstrated a dynamic LVOT gradient of at least 50 mmHg at rest or on provocation and a mitral leaflet area >12 $cm^2$. Between 1986 and 1999, 29 patients underwent surgical septal myectomy in combination with MLE. After august 1999, 43 consecutive patients underwent PTSMA. Our institutional review committee approved the study and all patients gave informed consent.

### Echocardiographic analysis

Transthoracic echocardiography was routinely performed to evaluate the site of hypertrophy, mitral valve anatomy and LVOT gradient. Mitral valve opening area was measured in the parasternal short-axis view by tracing the innermost margins of the mitral valve at the point of maximal opening. Mitral leaflet area was calculated with a previously validated formula (4.64 + 2.17 x mitral valve opening area).[17] Follow-up measurements included septal thickness at the site of treatment, LVOT gradient, MR grade, severity of SAM and left atrial and ventricular dimensions. Septal thickness was measured in the parasternal long-axis view in an end-diastolic still-frame. Peak LVOT gradient was calculated from the color-guided continuous-wave Doppler velocity using the modified Bernoulli equation. MR severity was assessed by color flow Doppler echocardiography and graded on a scale from 0 (no regurgitation) to 4 (severe regurgitation). SAM of the AMVL was graded as 0 (absent), 1+ (mild; minimal mitral-septal distance >10 mm during systole), 2+ (moderate; minimal mitral-septal distance ≤ 10 mm during systole) or 3 (marked; brief or prolonged contact between the AMVL and septum).[18] Dimensions of the left atrium and left ventricle (LV) were

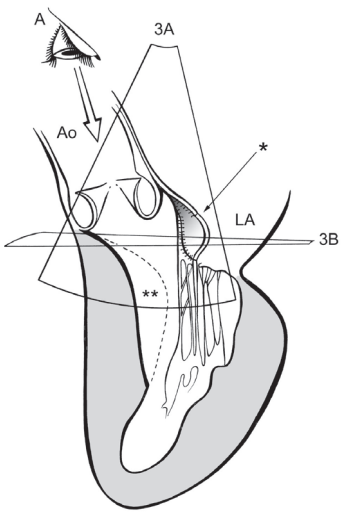



**Figure 1.** Schematic long-axis cross-sectional view of the left ventricle.[35]
The patch extension of the anterior mitral leaflet is indicated by the asterisk. The surgeons' view (point A) is orientated towards the hypertrophied septum and the anterior mitral leaflet. The two sectional planes (3A and 3B) indicate the echocardiographic cross-sections of the still-frames, which are shown in figure 3 (panel A and B, respectively). The double asterisk indicates the site of the septal myectomy.
Ao = Ascending Aorta. LA = Left Atrium.

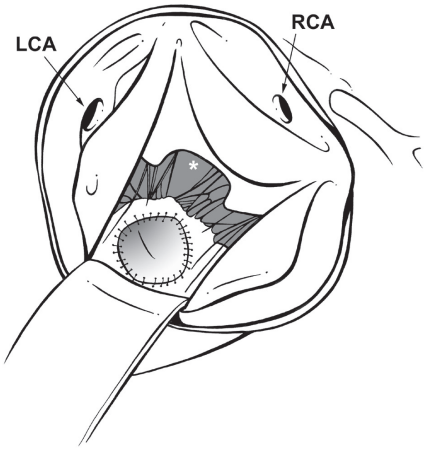



**Figure 2.** The surgeons' view.
The surgeon looks through an oblique incision in the ascending aorta on the hypertrophied septum and the anterior mitral leaflet. The pericardial patch, inserted in the anterior mitral leaflet is clearly seen. The asterisk indicates the myectomy trough. The ostia of both the left (LCA) and right (RCA) coronary arteries are indicated for orientation purposes.

measured using standard M-mode echocardiography from the parasternal long-axis view. In the apical 2 and 4 chamber views, the end-systolic and end-diastolic still-frames were manually traced to assess the left ventricular ejection fractions.[19]

### Surgical myectomy in combination with MLE

Cardiac surgery was performed using standard techniques of cardiopulmonary bypass with moderate hypothermia and myocardial preservation. After aortotomy, the septum was partially resected to the left of an imaginary line through the nadir of the right coronary cusp using a locally designed modified electrocutting technique. If myectomy had been completed, the surgeon performed MLE (Figure 1).[16] An autologous pericardial patch is placed across the bending point of the mitral valve where SAM is maximal to stiffen the buckling AMVL (Figure 2). The patch extends the width but not the length of the AMVL, which shifts the centrally attached chordae laterally. As a result, the chordae are stretched and erected which will enhance leaflet coaptation. Finally, because force produced by blood flow against the leaflet is proportional to its area, the increased leaflet will be pressed posterior with a decrease in SAM and MR. Postoperative results were assessed by transesophageal and epicardial echocardiography immediately after weaning from bypass (Figure 3). There were no suboptimal results that required reinstitution of bypass.

### PTSMA

The right and left femoral arteries were cannulated using standard techniques. A temporary pacemaker lead (Temporary Pacing Electrode Catheter, 5F, Bard, USA which was later replaced by a Bipolar Electrode Catheter, 5F, Arrow, Germany) was positioned in the right ventricle. Simultaneous measurement of the pressures in

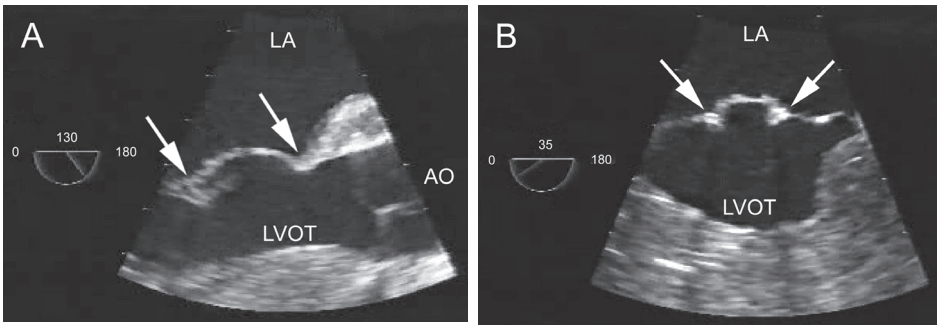



**Figure 3.** Effects of the extension patch.

Esophageal multiplane echocardiography after surgery. Panel A: Long-axis view of the LVOT at 130 degrees shows the "spinnaker sail" effect of the patch (between arrows), which moves the leaflet tissue away from the septum. Panel B: At 35 degrees, the patch is seen in cross-section. The patch causes a lateral displacement of the secondary chordae.

Ao = Ascending Aorta. LA = Left Atrium. LVOT = Left Ventricular Outflow Tract.

the LV (6F pigtail catheter) and in the ascending aorta (7F Judkins guiding catheter) allowed continuous monitoring of the LVOT gradient. Baseline hemodynamic data, including LVOT gradient at rest and at provocation using the Valsalva manoeuvre, were measured. After identification of the septal branches of the LAD, a 1.5-2.5 x 10 mm balloon was introduced over a 0.014-inch guide wire and positioned into the first septal branch. If the position of the balloon was considered satisfactory, the guide wire was removed and the balloon inflated. Subsequently, 1 ml of echocontrast agent (Levovist, Schering AG Berlin) was injected through the balloon catheter shaft. With echocardiography, the myocardial territory supplied by this septal branch was identified and retrograde spill of contrast into the LAD or the right ventricle was excluded. If satisfying images were obtained, 1 to 5 ml of concentrated ethanol (at a rate of 0.5 ml / 30 seconds) was injected through the balloon catheter shaft under close electrocardiographic surveillance. After five minutes, the balloon was deflated and coronary angiography was repeated in order to confirm the patency of the LAD and to confirm discontinuation of the septal branch. If the LVOT gradient remained >30 mmHg, which was observed in seven patients, the result was regarded as suboptimal. Subsequently, the procedure was repeated in the same septal branch if the myocardial territory supplied by this branch was relatively large. Otherwise, other septal coronary vessels were judged on usefulness. After the procedure, the pacemaker lead was left in situ for at least 48 hours and the patient was transferred to the clinical department for telemetric observation.



**Follow-up**

One-year follow-up data included mortality, NYHA class, medication and the earlier described echocardiographic variables (septal thickness, LVOT gradient, MR, SAM grade and left atrial and ventricular dimensions). The clinical status was assessed by one cardiologist (FJtC) and therefore not subject to interobserver variability. We performed a MEDLINE search (1995 towards the present) on studies in English language. Using the search terms "hypertrophic cardiomyopathy" in combination with "septal ablation" or "myectomy", we found 158 and 276 manuscripts, respectively. Based on the abstracts, we selected three articles that compared septal ablation versus septal myectomy.[20-22]

**Statistical analysis**

Continuous variables were presented as mean ± standard deviation values and were compared using Student's unpaired t-test. Categorical variables were presented as counts and percentages and compared with the chi-square test, or when appropriate, with Fisher's exact test.

## RESULTS

### Baseline clinical characteristics

Baseline clinical characteristics of the patients treated by surgery or PTSMA only differed with respect to age (Table 1). PTSMA patients were older at time of intervention ($P<0.05$).

### Baseline echocardiographic measurements

Mean septal thickness, LVOT gradient and mitral leaflet area in the surgical group matched that in the PTSMA group. Only, MR grade was higher in the surgical group. All patients demonstrated typical SAM of the AMVL.

### Clinical outcome

Pre-interventional and post-interventional data at 1-year follow-up are presented in Table 1.

### Outcome after surgery

There were no deaths associated with surgery. Three months after surgery, a patient was hospitalised with shortness of breath. Echocardiography demonstrated severe

**Table 1.** Clinical and Echocardiographic Data at Baseline and at One-Year Follow-up

| | Pre-procedure | | One-year follow-up | |
|---|---|---|---|---|
| | Myectomy (n = 29) | PTSMA (n = 43) | Myectomy (n = 29) | PTSMA (n = 41) |
| Clinical data | | | | |
| Mean age, years | 44 ± 12* | 52 ± 17 | | |
| NYHA class | 2.8 ± 0.4 | 2.4 ± 0.5 | 1.3 ± 0.4† | 1.5 ± 0.7† |
| Number of drugs& | 1.5 ± 0.7 | 1.5 ± 0.9 | 0.8 ± 0.9 | 0.9 ± 0.8 |
| Echocardiographic data | | | | |
| Septal thickness, mm | 23 ± 4 | 21 ± 4 | 17 ± 2† | 16 ± 4† |
| LVOT gradient, mm Hg | 100 ± 20 | 101 ± 34 | 17 ± 14† | 23 ± 19† |
| Mitral regurgitation grade | 2.1 ± 1.1* | 1.5 ± 0.8 | 0.6 ± 0.6† | 0.8 ± 0.8† |
| SAM grade | 2.9 ± 0.3 | 2.8 ± 0.5 | 0.5 ± 0.7*,† | 1.3 ± 0.9† |
| Left atrium, mm | 47 ± 9 | 47 ± 7 | 46 ± 11 | 45 ± 6 |
| LV-EDD, mm | 43 ± 5 | 43 ± 6 | 44 ± 8 | 44 ± 8 |
| LV-ESD, mm | 27 ± 5 | 25 ± 5 | 28 ± 7 | 30 ± 8† |
| LV-EF, % | 72 ± 6 | 71 ± 5 | 70 ± 8 | 69 ± 7 |
| MLA, $cm^2$ | 16.7 ± 3.4 | 15.9 ± 2.7 | | |

N = Number of Patients. NYHA = New York Heart Association functional class. LVOT = Left Ventricular Outflow Tract. SAM = Systolic Anterior Motion. LV-EDD = Left Ventricular End-diastolic Diameter. LV-ESD = Left Ventricular End-systolic Diameter. LV-EF = Left Ventricular Ejection Fraction. MLA = Mitral valve Leaflet Area. * = $P<0.05$ versus PTSMA; † = $P<0.05$ versus baseline value; & = Beta-blocker and/or calcium antagonist.

MR at the site of the patch due to dehiscence. After surgical correction the patients clinical course was further uncomplicated. Mean NYHA class in the surgical group improved from 2.8 ± 0.4 to 1.3 ± 0.4 (P<0.05) at follow-up.

**Outcome after PTSMA**

Two patients died in the PTSMA group. One patient died during the procedure due to refractory ventricular fibrillation after induction of the infarction. The other patient died after the procedure due to cardiac tamponade caused by right ventricular perforation by a pacemaker lead. Since then, we changed the type of pacemaker lead to avoid this complications. Five other patients were successfully resuscitated for ventricular fibrillation within 24 hours after the intervention. One patient with late recurrence of ventricular fibrillation and another patient with late occurrence of non-sustained ventricular tachycardia were treated with an implantable cardioverter defibrillator. Four patients underwent permanent pacemaker implantation because of complete atrioventricular heart block after the procedure. In one patient a large anterior myocardial infarction (maximal creatine kinase 4,700 U/L) was induced due to spill of ethanol in the LAD. Four patients underwent repeat PTSMA after a mean follow-up period of 10 months for recurrence of complaints and significant LVOT gradient. Mean NYHA class in PTSMA patients improved from 2.4 ± 0.5 to 1.5 ± 0.7 (P<0.05) at follow-up.



**Echocardiographic follow-up data**

As seen in Table 1, decrease in septal thickness and LVOT gradient at 1-year follow-up were comparable in both groups. Mean residual MR after surgery did not differ from that in the PTSMA group. However, post-surgical MR decreased at least two grades in 75% of surgical patients whereas this improvement was reached in only 10% of the PTSMA patients (P<0.0001). Mean SAM grade decreased significantly more after surgery (P<0.001). In both groups, mean left ventricular end-diastolic dimensions did not change. Left ventricular end-systolic dimension remained unchanged after surgery whereas it significantly increased after PTSMA (P<0.05). In both groups, left ventricular ejection fractions remained preserved at follow-up.

## DISCUSSION

Both surgical septal myectomy and PTSMA were developed to reduce septal hypertrophy and to relieve LVOT gradient in patients with HOCM. Some of these patients also demonstrate structural anomalies of the mitral valve apparatus that are, however, not corrected with either intervention. This may predispose to residual SAM,

suboptimal alleviation of LVOT gradient and residual MR. Surgical implantation of a mitral valve prosthesis is not attractive due to the risks of thrombo-embolism and bleeding related to the need for anticoagulation therapy.[23] One alternative that preserves native valve tissue is mitral valve plication.[24] In our center, myectomy in combination with MLE is used in patients with an enlarged AMVL. Previously, we reported superior hemodynamic results as compared to myectomy alone[16] and sustained hemodynamic improvement during long-term follow-up.[7] In the present study, we compared this modified surgical procedure with PTSMA in patients with an enlarged AMVL. We observed more peri-procedural complications and necessity for re-interventions in PTSMA patients. Also, hemodynamic results (reduction in SAM and MR grade) were better in surgical patients.

**Comparison of echocardiographic parameters after PTSMA and surgery in other studies**

As summarized in Table 2, three earlier published studies compared the hemodynamic effects and clinical outcome of PTSMA versus septal myectomy.[20-22]

*LVOT gradient*. Acute LVOT gradient reduction after PTSMA happens mainly due to a lesser peak acceleration rate of blood flow proximal to the obstruction.[25] This may be caused by inhomogeneity in LV contraction due to ischemic septal dysfunction[26] and/or conduction abnormalities due to ischemia-induced bundle branch block.[27] Obviously, myectomy results in immediate septal thinning, LVOT widening and gradient reduction. In the long-term follow-up, maximal gradient reduction after PTSMA is achieved due to LVOT remodelling resulting in widening of the LVOT. That short-term LVOT gradient reduction may indeed be better with surgery was shown in the three-months follow-up study of Qin *et al.*[21] Retrospective analysis of our data at three months also showed a significant better reduction in LVOT gradient with myectomy (16 ± 11 mmHg vs. 27 ± 22 mmHg after PTSMA, $P<0.05$). At 1-year follow-up, however, there were no significant differences between surgery and PTSMA in our study and the studies by Nagueh *et al.*[20] and Firoozi *et al.*[22] Notably, all studies demonstrated a tendency toward a better reduction with surgery. At present, it is not known whether the timing of maximal LVOT reduction after an intervention is important in reducing morbidity and mortality. The small mean differences in alleviation of the LVOT gradient between surgery and PTSMA may be of importance because the severity of LVOT gradient is an independent risk factor for functional deterioration.[28] After PTSMA, a residual LVOT gradient in the catheterization laboratory was an independent predictor of adverse outcome at later follow-up in a study by Chang *et al.*[29] After myectomy, it was an independent predictor of mortality at prolonged follow-up in a study by Mohr *et al.*[30]

**Table 2.** Comparison of Published Studies Comparing Surgical Myectomy with PTSMA

| Author | Intervention | Nr. of patients | Follow-up | NYHA class III/IV (%) or mean class | | LVOTG (mm Hg) | | MR mean grade, I/II (%), mean volume (ml) | | SAM grade | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Present study | Myectomy | 29 | 12 months | 2.8 ± 0.4 | 1.3 ± 0.4† | 100 ± 20 | 17 ± 14† | 2.1 ± 1.1 | 0.6 ± 0.6† | 2.9 ± 0.3 | 0.5 ± 0.7†,* |
| | PTSMA | 43 | | 2.4 ± 0.5 | 1.5 ± 0.7† | 101 ± 34 | 23 ± 19† | 1.5 ± 0.8 | 0.8 ± 0.8† | 2.8 ± 0.5 | 1.3 ± 0.9† |
| Nagueh [20] | Myectomy | 41 | 12 months | 78% | 2%† | 78 ± 30 | 4 ± 7† | 83% | 51%† | NA | NA |
| | PTSMA | 41 | | 90% | 0%† | 76 ± 23 | 8 ± 15† | 88% | 29%† | NA | NA |
| Qin [21] | Myectomy | 26 | 3 months | 3.3 ± 0.5 | 1.5 ± 0.7† | 62 ± 43 | 11 ± 6† | 28 ± 12 | 8 ± 5† | 1.1 ± 0.6 | 0.6 ± 0.5† |
| | PTSMA | 25 | | 3.5 ± 0.5 | 1.9 ± 0.7† | 64 ± 39 | 24 ± 19† | 23 ± 12 | 9 ± 3† | 1.4 ± 1.1 | 0.6 ± 0.8† |
| Firoozi [22] | Myectomy | 24 | 12 months | 2.4 ± 0.6 | 1.5 ± 0.7† | 83 ± 23 | 17 ± 12† | NA | NA | NA | NA |
| | PTSMA | 20 | | 2.3 ± 0.5 | 1.7 ±0.8† | 91 ± 18 | 21 ± 12† | NA | NA | NA | NA |

**Table 2.** Comparison of Published Studies Comparing Surgical Myectomy with PTSMA, continued

| Author | Intervention | IVS (mm) | | LV-EDD (mm) | | LV-ESD (mm) | | LA-EDD (mm) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Present study | Myectomy | 23 ± 4 | 17 ± 2† | 43 ± 5 | 44 ± 8 | 27 ± 5 | 28 ± 7 | 47 ± 9 | 46 ± 11 |
| | PTSMA | 21 ± 4 | 16 ± 4† | 43 ± 6 | 44 ± 8 | 25 ± 5 | 30 ± 8† | 47 ± 7 | 45 ± 6 |
| Nagueh [20] | Myectomy | 22 ± 7 | 13 ± 6† | 42 ± 6 | 45 ± 5† | 23 ± 5 | 28 ± 6† | NA | NA |
| | PTSMA | 23 ± 6 | 12 ± 3† | 43 ± 5 | 47 ± 5† | 21 ± 5 | 25 ± 4† | NA | NA |
| Qin [21] | Myectomy | 24 ± 6 | 17 ± 2† | 44 ± 7 | 45 ± 6 | NA | NA | 50 ± 7 | 47 ± 7 |
| | PTSMA | 23 ± 4 | 19 ± 4† | 40 ± 8 | 44 ± 8 | NA | NA | 47 ± 8 | 46 ± 8 |
| Firoozi [22] | Myectomy | 20 ± 6 | 17 ± 5† | 40 ± 7 | 41 ± 6 | 20 ± 6 | 23 ± 7 | 48 ± 8 | 45 ± 8 |
| | PTSMA | 20 ± 3 | 16 ± 3† | 42 ± 4 | 44 ± 6 | 23 ± 5 | 26 ± 5† | 47 ± 8 | 44 ± 9 |

NYHA = New York Heart Association functional class. LVOTG = LVOT Gradient. MR = Mitral Regurgitation grade. NA = Not Available. SAM = Systolic Anterior Motion. IVS = Interventricular Septal Thickness. LV-EDD = Left Ventricular End-Diastolic Dimension. LV-ESD = Left Ventricular End-Systolic Dimension. LA-EDD = Left Atrium End-Diastolic Dimension. * = P<0.05 versus PTSMA; † = P<0.05 versus baseline value.



*SAM of the anterior mitral valve leaflet*. In the study by Qin *et al.*[21], MR as well as SAM of the AMVL reduced equally after surgery and PTSMA. Also in the study by Nagueh *et al.*[20], who only reported on MR, an equal reduction was achieved with both treatment modalities. Interestingly, Qin *et al.*[21] described two patients with an elongated AMVL who did not benefit from PTSMA. In contrast to this observation, Flores-Ramirez *et al.*[25] reported that PTSMA could indeed be effective in HOCM patients with redundant mitral leaflet valves. They stated that, after successful PTSMA, the streamlines of flow are straightened and ejection velocity proximal to the LVOT decreases. Consequently, the drag forces that pull the AMVL into the LVOT will diminish which results in decreased SAM. In the long-term, however, LVOT widening may be of more importance compared to changes in LV ejection dynamics. In the present study, we noticed a greater reduction in SAM after surgery as compared to PTSMA. This result favours the hypothesis that MLE has additional advantages over PTSMA for patients with an enlarged AMVL.[7,16,31] These advantages include: (1) stiffening of the central part of the buckling AMVL to prevent SAM by insertion of a

pericardial patch,[14,32-34] (2) erection of the lax chordae attached to central portions of the AMVL through lateral shift caused by enlargement of the horizontal width of the anterior leaflet,[31] (3) maintenance of valve tethering due to an enlarged leaflet area once the streamlines of flow are straightened after septal myectomy[31] and (4) enhanced reduction in MR provided by greater leaflet area. The observation that the pre-interventional higher grade of MR in the surgical group was abolished to the same extent as after PTSMA, confirms the observation that a larger leaflet contact area reduces MR for any given degree of SAM.[17]

### Comparison of clinical parameters after PTSMA and surgery

Both our and prior studies reported no difference in mean post-interventional NYHA classification between PTSMA and surgery.

### Complications and re-interventions after PTSMA and surgery.

As summarized in Table 3, more complications were noticed after PTSMA. The need for permanent pacemaker implantation, as noticed in other studies occurred more often after PTSMA, despite careful contrast identification of the target septal branch. This difference in incidence may be caused by induced transmural myocardial infarction as opposite to well-controlled, more precise myectomy. As seen in our study, PTSMA has also some relatively unique complications such as spill of ethanol into the LAD and ventricular fibrillation due to induced myocardial ischemia. Also more re-interventions were needed after PTSMA. In contrast to other studies,[25] we could not find a relation between re-interventions, the amount of ethanol used or peak creatine kinase values.

**Table 3.** Reported Complications after Myectomy or PTSMA.

| Author | Intervention | Nr. of patients | Death | Acute MI | Ventricular fibrillation | Permanent pacing | Automatic ICD | Re-intervention |
|---|---|---|---|---|---|---|---|---|
| Present study | Myectomy | 29 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%)‡ |
| | PTSMA | 43 | 2 (5%) | 1 (2%) | 6 (14%) | 4 (9%) | 2 (5%) | 4 (9%) |
| Nagueh [20] | Myectomy | 41 | 0 (0%) | | | 1 (2%) | 4 (10%) | |
| | PTSMA | 41 | 1 (2%) | | | 9 (22%) | 1 (2%) | |
| Qin [21] | Myectomy | 26 | 0 (0%) | | | 2 (8%) | | 0 (0%) |
| | PTSMA | 25 | 0 (0%) | | | 6 (24%) | | 6 (24%) |
| Firoozi [22] | Myectomy | 24 | 1 (4%) | | | 1 (4%) | | |
| | PTSMA | 20 | 1 (4%) | | | 3 (15%) | | |

MI = Myocardial Infarction. ICD = Internal Cardiac Defibrillator. ‡ = Re-intervention because of patch dehiscence.

## STUDY LIMITATIONS

This study was not a randomized trial but an analysis of two cohorts treated with a surgical and percutaneous therapy. The present results may not be generalized since all patients were selected by mitral leaflet area. Furthermore, the groups were dissimilar in respect of age and severity of MR. The choice of treatment, however, was not influenced by these parameters because after 1999 all patients were treated with PTSMA. It is unlikely that the advanced age in this group would have influenced the differences in hemodynamic outcome as compared to surgery. As described by Chang *et al.*[29], age was not a predictor of outcome after PTSMA. It is not clear whether the lesser degree of MR in the PTSMA group influences the outcome in this study but in real clinical practice it seems likely that patients with more severe MR are referred to surgery.

## IMPLICATIONS AND CONCLUSIONS

Both myectomy and PTSMA are effective therapies to diminish the LVOT gradient by reduction in septal thickness. After myectomy, maximal gradient reduction is achieved immediately. As mentioned above, the gradient reduction after PTSMA seems to follow a biphasic course and the maximal reduction is achieved somewhat later in time. In HOCM patients with an enlarged AMVL, myectomy in combination with MLE offers the aforementioned additional effects to further reduce SAM. In the present study we found more peri-procedural complications and necessity for re-interventions in PTSMA patients. Whether the immediate LVOT gradient reduction with the combined surgical approach will result in a better clinical outcome versus PTSMA during a longer follow-up period is unknown and merits further research.

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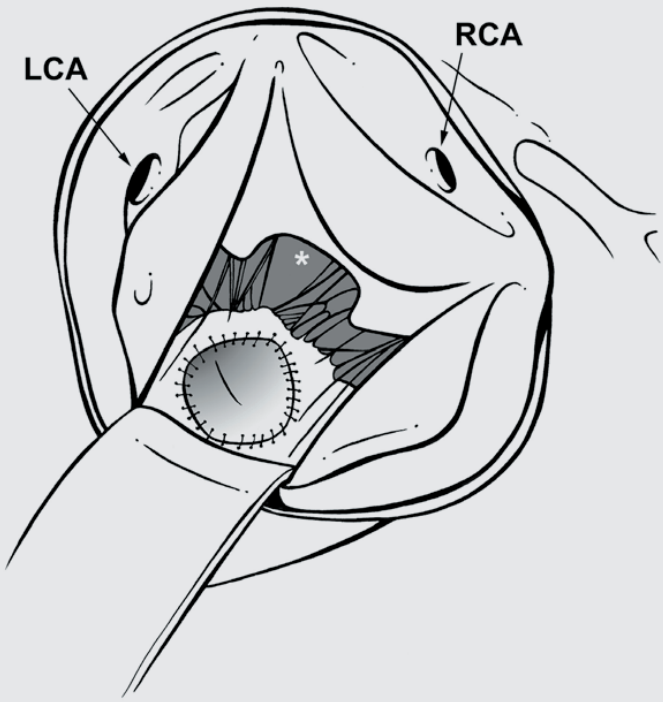
## Summary



Hypertrophic cardiomyopathy (HCM) is an intriguing disease due to its heterogeneity in genetic, morphologic, and clinical spectrum. The insights in the prognosis and natural history of HCM have evolved tremendously over the past 40 years. The first studies, which contained data derived from hospital-based populations, depicted a poor prognosis for HCM patients, in particular due to the high incidence of sudden cardiac death (SCD). More recent studies derived from community-based (or non-referral) centers suggest a more benign clinical course with an annual mortality of <1%. Another important finding is that most HCM patients remain a lifetime without symptoms.

Approximately one-quarter of all HCM patients demonstrate a significant (≥ 50 mm Hg) left ventricular outflow tract (LVOT) obstruction. This type is referred to as hypertrophic *obstructive* cardiomyopathy (HOCM). The severity of the obstruction is usually related to the degree of complaints. In patients, who remain severely symptomatic despite optimal medical treatment, and in whom a significant LVOT gradient can be demonstrated at echocardiography, either surgical septal myectomy or percutaneous transluminal septal myocardial ablation (PTSMA) is indicated. At present, surgery is still regarded as gold standard.

The first part of the current thesis provides an update on prognosis and natural history of HCM. The second part depicts the results of surgery and PTSMA. In this part, the two therapies are compared to provide better insight in their advantages and disadvantages.

## CLINICAL INSIGHTS

The data concerning the natural history of HCM as described in this thesis were mainly derived from 225 consecutive patients, who were studied between 1970 and 1999 at the HCM outpatient clinic of the Erasmus Medical Center Rotterdam. Follow-up of this population revealed an annual cardiac mortality and an annual mortality due to SCD of 0.8% and 0.6%, respectively, which is in agreement with the findings in other, community-based HCM populations. Another important finding was that LVOT obstruction was an independent predictor for clinical deterioration during follow-up for every increase of 10 mm Hg. Also, the presence of syncope was an independent predictor for SCD. Since SCD remains one of the most devastating components of the natural history, it is important to estimate the risk for sudden death. Due to the relative low mortality rates in HCM populations, the identification of risk markers for SCD, however, remains problematic. Besides, it would be most convenient in daily practice to estimate the risk of SCD according to non-invasive markers, which are easy to obtain. Therefore, Elliott *et al.* (J Am Coll Cardiol 2000;36:2212-8)

analyzed six-year-SCD-free survival rates in a group of 368 HCM patients according to five predefined risk markers, including nonsustained ventricular tachycardia, syncope, blood pressure response during exercise, family history of sudden death and left ventricular wall thickness. The study demonstrated that the presence of two or more risk markers substantially increased the risk for SCD as compared to the presence of one or no risk marker. At multivariate analysis, increasing maximal left ventricular wall thickness and the presence of syncope in combination with a positive family history increased the risk for SCD.

## INVASIVE TREATMENT

The therapeutic choice of a HCM patient depends mainly on the presence of symptoms, an outflow tract obstruction, and risk factors for SCD.

The majority of symptomatic HOCM patients are successfully treated with a beta-blocker, a calcium antagonist or a combination of both medications.

In patients with (a) serious risk factor(s) for SCD or those with a previously aborted cardiac arrest, an automatic implantable cardioverter-defibrillator (ICD) has proven an effective treatment to prevent SCD. Implantation of an ICD for secondary prevention (following cardiac arrest) or primary prevention (according to the risk factors) resulted annually in appropriate device intervention at 11% and 5%, respectively.



The standard therapy to treat HCM patients with persisting cardiac symptoms, despite optimal medical treatment, and a dynamic outflow tract gradient ≥ 50 mm Hg is surgical septal myectomy. In the past 15 years, two alternatives to surgery have been proposed. First, chronic dual-chamber pacing was introduced as a relatively small intervention to reduce symptoms and LVOT obstruction. In randomized trials, however, clinical improvement could not be attributed to the presence or absence of cardiac pacing, suggesting a placebo effect. Since then, this therapy has been practically abandoned. Second, PTSMA has been introduced in 1995. The enthusiasm for this procedure can be perceived from the number of procedures so far performed, which outnumbers the number of surgical procedures performed over the past 40 years.

Both surgery and PTSMA are regarded as effective methods to improve hemodynamic status and clinical condition in symptomatic HOCM patients. The results of the surgical and the PTSMA procedures, performed at the EMC Rotterdam have been compared. Two remarkable findings, which are in agreement with the existing knowledge, were made. First, hemodynamic improvement was more marked after surgery. Second, PTSMA is burdened with more peri-procedural complications and necessity for re-interventions. At present, surgery will be advised for young, severe-

ly symptomatic patients and for subjects with additional anatomic alterations of the mitral valve apparatus. A prospective, randomized trial would certainly put the choice for one of these therapies in better perspective. Such a trial, however, may be hampered due to the small number of patients necessitating invasive intervention.

## FUTURE PERSPECTIVES

HCM is a disease characterized by an autosomal-dominant inheritance, with incomplete penetrance. The prevalence of the disease in the general population is 0.2%. At present, more than 400 mutations have been identified located in 11 disease-causing genes. Ten of these genes encode for proteins of the cardiac sarcomere (Table 1).

It is intriguing to question oneself whether the growing genetic interest and experience in the field of HCM is of clinical benefit to the patient. Does a known genotype implicate the possibility to offer advanced clinical care to the patient? Does a specific genotype require a specific therapy and, more importantly, does it offer a clear insight in the risk for SCD? Does the current knowledge allows to draw conclusions concerning the genotype-phenotype correlations?

Genetic screening and an indisputable, DNA-based diagnosis of HCM would clearly offer advantages to specific family members of HCM patients. Certain members, in whom the diagnosis may not be established using conventional techniques, would be offered clarity on the presence or absence of the disease instead of the insecurity that accompanies regular echocardiographic screening. The use of genetic screening, however, is limited due to the inability to locate the disease-causing mutation, which is the case in a substantial part of the HCM population. The limitations of

**Table 1.** Eleven HCM-disease genes, 10 of them encoding cardiac sarcomeric proteins.

| Gene | Encoding protein | Locus |
|---|---|---|
| MYH 7 | β-Myosin Heavy Chain | 14q12 |
| MYBPC3 | Myosin Binding Protein C | 11p11.2 |
| MYL 2 | Regulatory Myosin Light Chain | 12q23-q24.3 |
| MYL 3 | Essential Myosin Light Chain | 3p21.3-p21.2 |
| ACTC | α Actin | 15q11-q14 |
| TPM1 | α-Tropomyosin | 15q22.1 |
| TNNT2 | Troponin T | 1q32 |
| TNNI3 | Troponin I | 19q13.4 |
| TTN | Titin | 2q24.3 |
| MYH6 | α-Myosin Heavy Chain | 14q12 |
| PRKAG2 | Protein Kinase A (γ-subunit) | 7q36 |

**Table 2.** Relative frequency of genotypes as identified in two large cohorts of unrelated HCM patients as well as in a Dutch population.

| | Richard *et al.** (n = 197) | Van Driest *et al.*† (n = 389) | Rotterdam‡ (n = 228) |
|---|---|---|---|
| Genotype + | 124 (63%) | 147 (38%) | 109 (47.8%) |
| MYBPC3 | 52 (26%) | 63 (16.2%) | 86 (37.7%) |
| MYH7 | 50 (25%) | 54 (13.8%) | 14 (6.1%) |
| TNNT2 | 8 (4%) | 6 (1.5%) | 3 (1.3%) |
| TNNI3 | 8 (4%) | 4 (1.0%) | 2 (0.9%) |
| MYL2 | 5 (2.5%) | 7 (1.8%) | 3 (1.3%) |
| TPM1 | - | 2 (0.5%) | - |
| MYL3 | 1 (<0.5%) | - | - |
| ACTC | - | 1 (0.3%) | - |
| >1 mutation | 6 (3%) | 10 (2.6%) | - |
| No mutation | 73 (37%) | 242 (62.1%) | 119 (52.2%) |

Genotype + = Number of patients with an identified mutation.

* = Richard *et al.* Circulation 2003. † = Van Driest *et al.* J Am Coll Cardiol 2004. ‡ = unpublished data.

genetic screening and genotype-phenotype correlations as well as the difficulties to use genotyping as a tool in risk stratification have been described in two studies, which were performed in centers from Europe (Richard *et al.*, France) and the USA (Van Driest *et al.*, Minnesota), respectively. In both centers, blood from many unrelated HCM patients was systematically screened for all protein encoding exons of the known HCM-causing genes. The goal was to estimate the frequency by which each of the disease genes are mutated and, furthermore, to propose a systematic strategy for genetic screening in clinical practice. Also, genotype-phenotype correlations were analyzed for each disease-causing gene. The results of both studies were fairly comparative except for the number of patients with an identifiable mutation. In the French study, 63% of the patients could be genotyped compared to only 38% of the American population. As seen in Table 2, the majority of the disease-causing mutations were localized in two major genes; first, the MYBPC3 gene in 26% and 16% of the patients, respectively, and second, the MYH7 gene in 25% and 14% of the patients, respectively. Mutations of thin filament genes (i.e. the genes encoding for the proteins Troponin T, Troponin I, α-Tropomyosin, and α Actin) accounted for only 8% and 4.6% respectively, which is less than previously assumed (~20%). Furthermore, the identified genotypes were correlated to the (familiar) phenotypes. Correlations were performed for several disease genes:

*MYBPC3:*

Richard *et al.* found a benign or intermediate prognosis in 90% of the families carrying a mutation in the MYBPC3 gene. In the study by Van Driest *et al.*, families harboring a MYBPC3 gene mutation were not statistically different from families with any

of the other mutations according to several parameters, including age at diagnosis, frequency of surgery or need for implantation of an ICD and the degree and distribution of hypertrophy.

*MYH7:*

In the study by Richard *et al.*, MYH7 gene mutations were most prevalent (45%) in families with a malignant prognosis (defined as ≥ 2 documented major cardiac events including sudden death, heart failure death, stroke death, heart transplantation, or resuscitated death related to HCM, each occurring before the age of 60 years). In the study by Van Driest *et al.*, 15% of the HCM population harbored a MYH7 gene mutation. This group had a younger age at diagnosis, a higher frequency of family history in a first-degree relative and demonstrated more hypertrophy as compared to the group without a MYH7 gene mutation.

*TNNT2, TNNI3, TPM1, ACTC (thin filament genes):*

In the study by Richard *et al.*, families with a TNNT2 or TNNI3 mutation were equally associated with a benign or malignant prognosis. This gene, however, was mutated in only 16 out of 197 HCM patients. Comparatively, in only 18 out of the 389 patients in the study by Van Driest *et al*. the thin filament gene was mutated. This small group was statistically indifferent from the remainder of the cohort according to the aforementioned parameters.

*Exceptions:*

Approximately 3% of the patients harbored more than one mutation, located in one or two different genes. This genotype was clearly associated with a severe phenotype.

Patients, in whom no mutations could be identified, were characterized by an older age at diagnosis and less ventricular myocardial hypertrophy.

As a conclusion, disease-causing mutations, analyzed in a large population of unrelated HCM patients, are most frequently located in the MYBPC3 or the MYH7 gene. As seen in Table 2, these two genes are also most frequently mutated in the Dutch population, analyzed at the EMCR (unpublished data). Previous studies, based on screening of a small number of patients from relatively large families, reported a higher frequency of mutations in the TNNT2 gene. This HCM-gene is usually associated with a phenotype including mild or absent hypertrophy and a high risk of SCD. The difference with the French and the American study may be related to the method of recruitment. Patients in the studies by Richard and Van Driest were selected on the basis of proven left ventricular hypertrophy as demonstrated at

echocardiography. The authors suggest that systematic screening of HCM patients should start with the MYBPC3 and the MYH7 gene. Since it has been demonstrated that the presence of multiple mutations in one patient is strongly related to a malignant phenotype, screening should not be stopped after the identification of a single mutation, especially in families with an adverse phenotype, but should be continued on the same gene and at least on the 2 major genes.

The huge variation in HCM genotype and phenotype make it practically very difficult to propose a genotype-phenotype correlation that is useful to the medical specialist in daily practice. Also, the role of genetic and environmental modifiers has not yet been elucidated. Currently, the practical role of genetics is limited to mutational analysis in patients with proven or suspected HCM. In case a mutation is identified in a proband, screening may be offered to his family members. This allows an unequivocal diagnosis of HCM in suspected cases, bypassing regular clinical follow-up.

All data, acquired for clinical or research purposes, should concisely be gathered and combined to the familiar phenotypes in the benefit of ongoing research. In future, this would allow us to use the genotype-phenotype correlation as a tool for risk stratification for SCD or as indicator to choose a certain therapy. With the rapid progressions in molecular genetics, the next futuristic step might be the implementation of genetic engineering, in which the disease gene could be modulated in order to reduce or reverse the progression of left ventricular hypertrophy.

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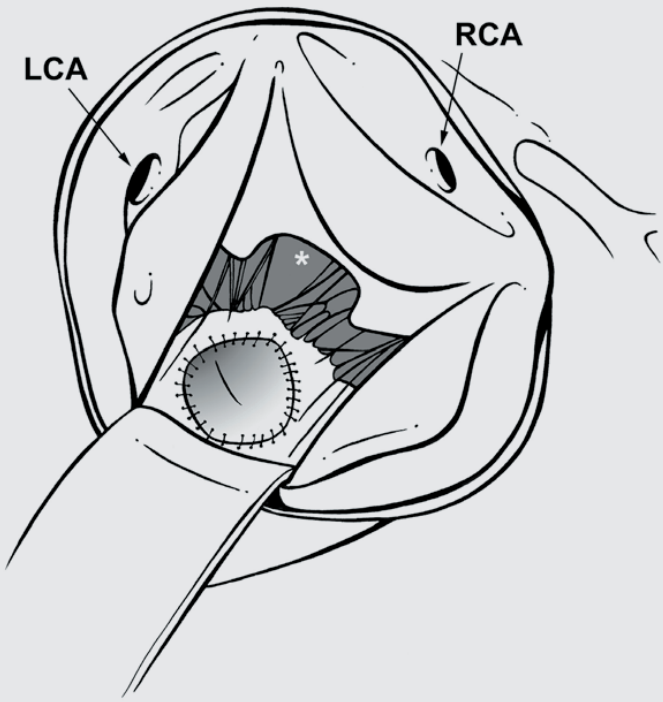
## Samenvatting



Hypertrofische cardiomyopathie (HCM) is een intrigerend ziektebeeld met heterogeniteit in het genetisch, morfologisch en klinisch spectrum. In de afgelopen 40 jaar, is het inzicht in de prognose en het natuurlijk beloop van de ziekte enorm toegenomen. De eerste observationele studies, welke waren gebaseerd op gegevens van naar tertiaire ziekenhuizen verwezen patiënten, suggereerden nog dat de ziekte een slechte prognose had en met name gekenmerkt zou worden door een hoge incidentie van plotse hartdood. De recente studies, waarvan de gegevens zijn gebaseerd op patiënten afkomstig uit niet-tertiaire centra, suggereren daarentegen dat het klinische beloop juist mild is. Deze studies berekenen de jaarlijkse cardiale mortaliteit op minder dan 1%. Een andere opmerkelijke bevinding is dat het merendeel van de HCM-patiënten bij leven helemaal geen klachten ervaart.

Bij ongeveer een kwart van alle HCM-patiënten wordt met Doppler echocardiografie een linker ventrikel (LV) uitstroombaan-obstructie van ≥ 50 mm Hg aangetoond. In dat geval spreekt men van hypertrofische *obstructieve* cardiomyopathie (HOCM). De hoogte van de gradiënt zou samen hangen met de ernst van de klachten. Indien een HOCM patiënt met maximale medicamenteuze therapie symptomatisch blijft en echocardiografisch een uitstroombaan-obstructie van ≥ 50 mm Hg houdt, wordt of chirurgische septale myectomie of percutane transluminale septale myocard ablatie (PTSMA) voorgesteld. Van deze twee methoden, wordt chirurgie nog steeds als de gouden standaard gezien.

Dit proefschrift geeft in het eerste gedeelte de huidige inzichten in prognose en natuurlijk beloop van de ziekte weer. Daarnaast beschrijft het in het tweede gedeelte enerzijds de resultaten van de chirurgische ingreep en anderzijds van PTSMA. Ook wordt in dit gedeelte bekeken of de ene techniek is te prevaleren boven de andere door beide behandelingsmethoden met elkaar te vergelijken.

## KLINISCHE INZICHTEN

De gegevens over het natuurlijk beloop van HCM, welke in het voorliggende proefschrift worden beschreven, zijn gebaseerd op een populatie van 225 opeenvolgende HCM-patiënten, welke tussen 1970 and 1999 aan het Erasmus Medisch Centrum Rotterdam op een speciale HCM-polikliniek werden vervolgd. De jaarlijkse mortaliteit in het vervolgonderzoek van deze groep ten gevolge van een plotse hartdood of een andere cardiale oorzaak werd berekend op respectievelijk 0.6% en 0.8%. Deze bevindingen zijn in overeenstemming met de resultaten van andere, niet-tertiaire centra. Een andere belangrijke observatie betrof de linker ventrikel uitstroombaanobstructie, welke een onafhankelijke voorspeller voor klinische verslechtering bleek te zijn. Tenslotte bleken patiënten die anamnestisch een collaps hadden ervaren,

een verhoogde kans te hebben op plotse hartdood. Aangezien deze plotse dood een van de meest tragische complicaties van de ziekte is, is inschatting van het risico op plots overlijden van groot belang. Door de relatief lage mortaliteitcijfers in HCM-populaties, blijft het echter gecompliceerd om meerdere risicofactoren voor het optreden van plotse cardiale dood te identificeren. Daarbij zou het in de dagelijkse praktijk effectief zijn om risicomarkers te gebruiken welke aan de hand van niet-invasieve methoden te bepalen zijn. Met dit doel voor ogen hebben Elliott *et al.* (J Am Coll Cardiol 2000;36:2212-8) een groep van 368 HCM-patiënten langere tijd vervolgd. De auteurs bestudeerden of de kans op plotse hartdood kon worden ingeschat aan de hand van vijf, vooraf gedefinieerde risicofactoren, te weten kamertachycardieën, collaps, inspanningsgerelateerde bloeddrukdaling, positieve familieanamnese (het voorkomen van plotse cardiale dood bij familieleden) en/of de ernst van LV hypertrofie. De studie toonde aan dat de kans op vóórkomen van plotse hartdood bij patiënten met twee of meer risicofactoren duidelijk hoger was dan bij patiënten met 1 of nul risicofactoren. Met multivariate analyse kwamen de ernst van LV hypertrofie en de combinatie van collaps en positieve familie anamnese als voorspellende risicofactoren voor het optreden van plotse hartdood naar voren.



## INVASIEVE BEHANDELING

De therapie van keuze bij de behandeling van een HCM-patiënt wordt voornamelijk bepaald door het klachtenpatroon, de ernst van LV uitstroombaan-obstructie en de aanwezigheid van risicofactoren voor plotse hartdood.

Symptomatische HOCM patiënten (oftewel degenen met klachten en een uitstroombaan-obstructie van ≥ 50 mm Hg) kunnen veelal succesvol worden behandeld met een bêta-blokkeerder, een calcium-antagonist of een combinatie van beide medicijnen.

Bij patiënten met (een) zwaarwegende risicofactor(en) voor plotse hartdood en bij degenen die succesvol werden gereanimeerd na een hartstilstand, is de implantatie van een automatische implanteerbare defibrillator (ICD) inmiddels een bewezen, effectieve behandeling gebleken ter preventie van plotse hartdood. Van de patiënten die een ICD geïmplanteerd kregen als secundaire preventie maatregel (dwz. na een succesvolle reanimatie) of als primaire preventie maatregel (dwz. gebaseerd op risicofactoren), ontving respectievelijk 11% en 5% jaarlijks een terechte shock.

Bij patiënten met persisterende klachten onder optimale medicamenteuze therapie met daarbij een LV uitstroombaan-obstructie van ≥ 50 mm Hg wordt gekozen voor een invasieve therapie, waarbij de huidige standaard chirurgische septale

myectomie is. In de afgelopen 15 jaar zijn er twee alternatieven voor chirurgie ontwikkeld. Het eerste alternatief was implantatie van een pacemaker. Deze relatief kleine ingreep zou de symptomen van de patiënt verminderen en de ernst van de LV uitstroombaan-obstructie reduceren. De klinische verbetering van de patiënten kon in gerandomiseerd onderzoek echter niet worden gerelateerd aan de werking van de pacemaker. Hieruit werd geconcludeerd dat het therapeutisch effect grotendeels op een placebo-effect moest berusten en in de huidige praktijk wordt deze vorm van therapie dan ook nauwelijks meer toegepast. Het tweede alternatief, PTSMA, werd in 1995 geïntroduceerd. Het enthousiasme voor deze nieuwe techniek is af te lezen aan het aantal tot nu toe verrichte procedures. In de afgelopen 10 jaar zijn er namelijk meer PTSMA procedures uitgevoerd dan dat er septale myectomieprocedures in de afgelopen 40 jaar zijn verricht.

Uit ons onderzoek blijkt dat de hemodynamische toestand en de klinische conditie bij het merendeel van de patiënten zowel na chirurgie als PTSMA verbetert. De resultaten van de twee groepen patiënten die in het EMCR werden behandeld met behulp van chirurgie of PTSMA worden in dit proefschrift met elkaar vergeleken. In deze vergelijkende studie worden twee opvallende bevindingen gedaan welke in overeenstemming zijn met de bestaande literatuur. Ten eerste lijkt de verbetering van de hemodynamiek na chirurgie meer uitgesproken. Ten tweede lijkt er een grotere kans te bestaan op proceduregerelateerde complicaties en noodzaak tot re-interventie na PTSMA. Hoewel er nog veel onduidelijkheden zijn, met name omtrent PTSMA, wordt geadviseerd om jonge, ernstig symptomatische patiënten te opereren evenals HOCM patiënten met anatomische afwijkingen van het mitralisklepapparaat, een combinatie die bij dit ziektebeeld frequent wordt gezien. Een prospectief, gerandomiseerd onderzoek zou meer duidelijkheid kunnen geven welke van de twee behandelingen de voorkeur verdient. De opzet van een dergelijke studie wordt echter bemoeilijkt door het beperkte aantal patiënten dat jaarlijks voor behandeling in aanmerking komt.

## TOEKOMSTPERSPECTIEF

HCM wordt gekenmerkt door een autosomaal-dominant overervingspatroon met incomplete penetrantie. De prevalentie van de ziekte in de algemene populatie wordt geschat op 0.2%. Op dit moment zijn er meer dan 400 mutaties geïdentificeerd welke zijn gelokaliseerd op één van de 11 bekende HCM-genen. Tien van deze genen coderen voor een op een sarcomeer (= segment van een fibril van het hart) gelegen eiwit(zie Tabel 1).

**Tabel 1.** Overzicht van 11 HCM-genen, waarvan 10 coderen voor een sarcomeereiwit.

| Gen | Coderend eiwit | Locus |
|---|---|---|
| MYH 7 | β-Myosin Heavy Chain | 14q12 |
| MYBPC3 | Myosin Binding Protein C | 11p11.2 |
| MYL 2 | Regulatory Myosin Light Chain | 12q23-q24.3 |
| MYL 3 | Essential Myosin Light Chain | 3p21.3-p21.2 |
| ACTC | α-Actin | 15q11-q14 |
| TPM1 | α-Tropomyosin | 15q22.1 |
| TNNT2 | Troponin T | 1q32 |
| TNNI3 | Troponin I | 19q13.4 |
| TTN | Titin | 2q24.3 |
| MYH6 | α-Myosin Heavy Chain | 14q12 |
| PRKAG2 | Protein Kinase A (γ-subunit) | 7q36 |

Een intrigerende vraag is of de groeiende kennis van, en de wetenschappelijke interesse voor dit vakgebied ook daadwerkelijk klinische voordelen biedt aan de HCM-patiënt. Kan men de patiënt bij wie het genotype is geïdentificeerd betere en meer geavanceerde zorg bieden? Dient de behandeling afgestemd te worden op het genotype en, nog belangrijker, geeft het genotype een duidelijker inzicht in de kans op plotse hartdood? Laat het huidige kennisniveau het toe een genotype aan een gedefinieerd fenotype te koppelen? Deze vragen zullen binnen diverse centra verschillend beantwoord worden. Het is duidelijk dat genetische screening en de onomstotelijke, op DNA gebaseerde, diagnose van de ziekte HCM grote voordelen kan bieden aan bepaalde familieleden van de proband (= de persoon die het uitgangspunt vormt bij stamboomonderzoek). Deze bloedverwanten, bij wie de ziekte met behulp van de huidige diagnostische middelen niet kan worden aangetoond cq. uitgesloten, kunnen mogelijk zekerheid krijgen omtrent de diagnose met behulp van DNA diagnostiek. Deze methode is echter niet altijd toepasbaar. In een aanzienlijk deel van de HCM-populatie kan namelijk geen mutatie worden geïdentificeerd. Er zijn studies van twee centra, één in Europa (Richard *et al.*, Frankrijk) en één in de Verenigde Staten (Van Driest *et al.*, Minnesota) waarin de beperkingen van genetisch screenen en van genotype-fenotype duidelijk worden geschetst. Zij beschrijven ook de onvolkomenheden in het gebruik van een genotype als risicofactor. In beide centra werd een grote groep, niet-familiair gerelateerde HCM-patiënten genetisch gescreend. In het bloed van de patiënten werden alle voor eiwitten coderende exons op de bekende, "HCM-veroorzakende"genen geanalyseerd. De opzet van de studies was om de bekende HCM-genen systematisch te screenen met als doel een goede strategie te bepalen voor het genotyperen van HCM-patiënten in de dagelijkse praktijk. Daarnaast werd getracht een verband te leggen tussen genotype en fenotype. De resultaten van beide studies stemden redelijk overeen. Er was

**Tabel 2.** Verdeling van mutatiefrequentie van de 11 bekende HCM-genen in twee populaties met niet familiair-gerelateerde HCM-patiënten.

| | Richard *et al.** (n = 197) | Van Driest *et al.*† (n = 389) | Rotterdam‡ (n = 228) |
|---|---|---|---|
| Genotype + | 124 (63%) | 147 (38%) | 109 (47.8%) |
| MYBPC3 | 52 (26%) | 63 (16.2%) | 86 (37.7%) |
| MYH7 | 50 (25%) | 54 (13.8%) | 14 (6.1%) |
| TNNT2 | 8 (4%) | 6 (1.5%) | 3 (1.3%) |
| TNNI3 | 8 (4%) | 4 (1.0%) | 2 (0.9%) |
| MYL2 | 5 (2.5%) | 7 (1.8%) | 3 (1.3%) |
| TPM1 | - | 2 (0.5%) | |
| MYL3 | 1 (<0.5%) | - | |
| ACTC | - | 1 (0.3%) | |
| >1 mutatie | 6 (3%) | 10 (2.6%) | |
| Geen mutatie | 73 (37%) | 242 (62.1%) | 119 (52.2%) |

Genotype + = Aantal patiënten met een geïdentificeerde mutatie.

* = Richard *et al.* Circulation 2003. † = Van Driest *et al.* J Am Coll Cardiol 2004. ‡ = niet gepubliceerde data.

alleen een groot verschil in het aantal patiënten bij wie een mutatie kon worden geïdentificeerd, namelijk in 63% van de Franse en slechts 38% van de Amerikaanse patiënten.

Het merendeel van de geïdentificeerde mutaties werd gelokaliseerd op twee HCM-genen (Tabel 2), te weten het MYBPC3 gen (26% en 16% van de patiënten, respectievelijk) en het MYH7 gen (25% en 14% van de patiënten, respectievelijk). Het dunne filament gen (= het gen dat codeert voor het sarcomeereiwit Troponine T, Troponine I, α-Tropomyosine, of α Actine) was slechts bij respectievelijk 8% en 4.6% van de patiënten gemuteerd hetgeen beduidend minder is dan de beschreven ~20% uit eerdere studies. In de twee studies werd ook het geïdentificeerde genotype gecorreleerd met het bijbehorende (familiare) fenotypen. De volgende relaties werden gevonden:

*MYBPC3 gen:*

In de studie van Richard *et al.* bleek 90% van de families met een mutatie op het MYBPC3 gen een benigne of intermediaire prognose te vertonen. In de studie van Van Driest *et al.*, bleken families met een mutatie op dit gen niet te onderscheiden van families met een mutatie op een ander HCM-gen zover het betreft de leeftijd waarop de diagnose werd gesteld, de noodzaak tot chirurgie of implantatie van een ICD of de ernst cq. verdeling van de hypertrofie.

*MYH7 gen*

In de studie van Richard *et al.* bleken MYH7 genmutaties aanwezig te zijn in 45% van de families met een slechte prognose (gedefinieerd als ≥ 2 gedocumenteerde

belangrijke cardiale events, te weten plotse hartdood, dood door hartfalen of CVA of harttransplantatie optredend beneden de leeftijd van 60 jaar). Bij Van Driest *et al.* werd een MYH7 genmutatie bij 15% van de 389 patiënten geïdentificeerd. Deze patiënten waren gemiddeld jonger op het moment van diagnose, vertoonden echocardiografisch meer hypertrofie en vermeldden frequenter een positieve familieanamnese bij een eerstegraads verwant in vergelijking met patiënten zonder MYH7 genmutatie.

*TNNT2, TNNI3, TPM1, ACTC (dunne filament genen):*

In de studie van Richard *et al.*, bleek de verdeling tussen een slechte en een goede prognose bij families met een TNNT2 of TNNI3 genmutatie gelijk te zijn. Dit gen toonde echter bij slechts 16 van de 197 HCM-patiënten een mutatie. Ook in de studie van Van Driest *et al.* werd bij slechts 18 van de 389 patiënten een mutatie op een dun filament gen gevonden. Er waren geen statische verschillen tussen deze groep en de rest van het cohort met betrekking tot de eerder genoemde parameters.

*Uitzonderingssituaties:*

In ~3% van de populatie werden meerdere mutaties per patiënt geïdentificeerd. De mutaties konden gelokaliseerd zijn op hetzelfde of op twee verschillende genen. In zowel de Franse als de Amerikaanse studie bleek een dergelijk genotype duidelijk geassocieerd te zijn met een maligne (= ongunstig) fenotype. Patiënten bij wie geen mutatie kon worden geïdentificeerd, werden gemiddeld pas op oudere leeftijd gediagnostiseerd en vertoonden echocardiografisch minder hypertrofie.



Concluderend lijken de HCM-veroorzakende mutaties het meest frequent gelegen te zijn op het MYBPC3 en het MYH7 gen indien men grote populaties met niet familiair-gerelateerde HCM-patiënten zou screenen. In tabel 2 is af te lezen dat mutaties ook in de Rotterdamse situatie het meest frequent op deze twee genen werden aangetroffen (niet gepubliceerde data). In eerdere studies, waarin meerdere personen binnen enkele grote HCM-families werden gescreend, lag de mutatiefrequentie in het TNNT2 gen juist hoog. Een mutatie op dit gen wordt geassocieerd met een fenotype waarbij weinig tot geen hypertrofie kan worden aangetoond en een sterk verhoogd risico op plotse hartdood. Een verklaring voor dit verschil met de Franse en Amerikaanse studie kan worden gevonden in de wijze van rekrutering. De patiënten in de studie van Richard en Van Driest werden namelijk alleen geïncludeerd indien de diagnose HCM, gebaseerd op echocardiografisch aantoonbare hypertrofie van de LV, zeker was.

De suggestie van beide studies is om bij een systematische screening in de praktijk te beginnen met het MYBPC3 en het MYH7 gen. Aangezien de aanwezigheid

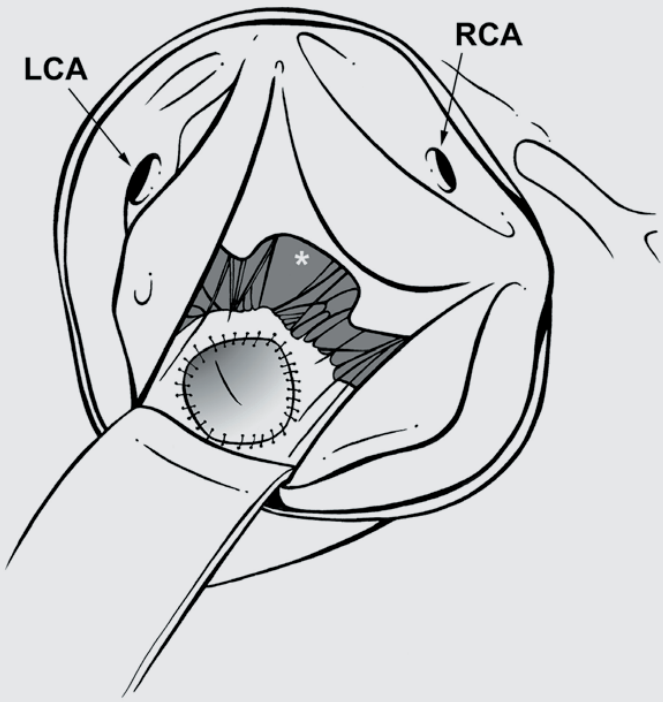
van multipele mutaties in één patiënt echter duidelijk is gerelateerd met een maligne fenotype, dient screening niet te worden gestopt na de identificatie van een mutatie maar, met name in families met een slechte prognose, voortgezet op de rest van het gen en tenminste op de twee belangrijkste genen.

Door de enorme variatie in genotype en fenotype, is het in de praktijk erg moeilijk om de koppeling tussen deze twee, de zgn. genotype-fenotype correlatie, goed te definiëren. Ook is het nog onduidelijk of verschillen in omgevingsfactoren ("environmental modifiers") invloed kunnen hebben op een fenotype. Wat betreft de praktische toepasbaarheid, beperkt de rol van genetische screening zich vooralsnog tot de identificatie van genmutaties bij patiënten met een bewezen HCM of bij hen die van de ziekte verdacht worden. Indien een genmutatie bij een proband wordt geïdentificeerd bestaat de mogelijk om ook de familieleden screening aan te bieden. Hiermee kan hen zekerheid worden geboden omtrent de aanwezigheid van een HCM-gen en een langdurige, poliklinische follow-up worden bespaard.

Alle genetische gegevens, verkregen uit klinisch of wetenschappelijk oogpunt, dienen nu, meer dan ooit, nauwkeurig te worden gedocumenteerd en gecorreleerd met het familiaire fenotype. Alleen op deze manier kan de genotype-fenotype correlatie in de toekomst gebruikt gaan worden als risicomarker voor bijvoorbeeld plotse hartdood of als houvast bij de keuze voor een bepaalde therapie. Een toekomstvisie met genetische manipulatie, waarbij het HCM-gen gemodificeerd wordt en de ontwikkeling van hypertrofie kan worden beperkt of voorkomen, lijkt gezien de huidige snelle ontwikkelingen in de moleculaire genetica niet ondenkbaar.

# D

## Dankwoord



Aan het einde van een proefschrift komt het moeilijkste gedeelte. Op een beperkte hoeveelheid papier een poging wagen alle mensen te bedanken die de 10 jaar werken en promoveren in het Erasmus Medisch Centrum (toen nog "Dijkzigt") mogelijk hebben gemaakt. De kans dat iemand niet wordt vernoemd is aanwezig maar in dat geval is de dank voor de prettige samenwerking niet minder.

Allereerst gaat mijn dank uit naar Dr. F.J. ten Cate. Beste Folkert, vanaf mijn sollicitatie gesprek in 1995 tot aan het afronden van mijn specialisatie en promotie, ben jij betrokken geweest bij mijn klinische en wetenschappelijke vorming. Jouw brede kennis van de hypertrofische cardiomyopathie en de durf om aan nieuwe therapieën te beginnen voordat anderen dat deden hebben geleid tot de kern van dit boekje. De vele klinische uren werk waar een groot deel van dit boekje op gebaseerd is, liggen in jouw handen.

Mijn dank gaat uit naar mijn promotor, Prof. Dr. M.L. Simoons. Beste Maarten, het tot stand komen van dit proefschrift is een voorbeeld van jouw idee dat niets onmogelijk is. Het verlengen van mijn "AGNIO"-arbeidscontracten en de aanmoedigingen om het schrijven vol te houden hebben allemaal bijgedragen aan het volbrengen van dit proefschrift.

De overige leden van de promotiecommissie, Prof. Dr. Cees Visser, Prof. Dr. Ben Oostra, Prof. Dr. Wim van der Giessen en Prof. Dr. Nico de Jong wil ik bedanken voor hun bereidwilligheid dit proefschrift te beoordelen. I would like to thank Prof. Elliott, who is such an experienced and honoured person in the field of hypertrophic cardiomyopathy, for his interest in the present thesis and his presence at the defence.

Mijn dank aan Dr. M.J. Kofflard. Beste Marcel, met name in de eerste jaren heb je mij geholpen met de wetenschappelijke bezigheden zoals data verzamelen, analyseren en het schrijven van artikelen. Daarnaast heb ik van jou geleerd dat promotie onderzoek meerdere kanten heeft en dat communicatie voor een goede samenwerking belangrijk is. Dat samenwerking tot mooie resultaten kan leiden blijkt wel uit het "review" verhaal dat met trots voorin het boekje prijkt.

Mijn paranimfen, Marco en Ruud, wil ik danken voor de steun bij de voorbereiding van deze dag. Marco, nadat we elkaar een tijdje uit het oog hebben verloren, zijn we elkaar weer tegen gekomen "in het circuit" waarbij uiteraard de verhalen over de goede tijden met jouw en Alex naar boven kwamen. Dat jij vandaag als paranimf wilt optreden, verheugt me. Ook in de nabije toekomst hoop ik contact te houden, hoewel dit gezien de afstand meer telefonisch zal zijn. Op naar het volgende (jouw) boekje. Ruud, ik ben trots dat jij mij vandaag als paranimf wil bijstaan. Het is zeker niet de eerste keer dat je me helpt. Als middelbare scholier, als student, als co-assistent en als arts stond ik meerdere malen bij je op de stoep, met of zonder mijn "bontjas". Belangrijkste boodschap voor vandaag, als je aanwijzingen en tips aan mij

doorspeelt, doe dit dan niet al te cryptisch. Ik los dat soort puzzels namelijk niet zo snel op als jij dat doet.

Mijn co-auteurs wil ik danken voor de hulp bij het tot stand komen van de verschillende publicaties.

Dr. M.L. Geleijnse. Beste Marcel, we begonnen als collega's "arts-assistent" in Dijkzigt waar ik je als eerste leerde kenner als de bezitter van een waanzinige cabrio. Daarna zorgde jij voor een vrolijke noot in een voor mij moeilijk jaar. Jouw aanbod om mee te helpen met het "chirurgie versus percutaan" verhaal was een essentieel begin om het laatste voorbereidingsjaar van dit boekje in te luidden. Daarnaast is "het laten beleggen en eten van een goed stokbroodje" een belangrijk leermoment geweest om te beseffen dat er meer is dan alleen wetenschap.

Mijn dank aan Dr. van Herwerden. Beste Lex, jij hebt letterlijk het werk achter de schermen verricht waaraan een zeer belangrijk deel van dit boekje is ontleend. Ik heb altijd met veel bewondering jouw unieke chirurgische technieken om de HOCM patiënten te behandelen, bestudeerd en bekeken. De manier waarop jij je vak uitoefent verdient respect.

Prof. Dr. P. Serruys. Beste Patrick, de gedrevenheid om nieuwe technieken te ontdekken en te introduceren binnen het Thoraxcentrum, heeft het mogelijk gemaakt dat Folkert samen met jouw afdeling de PTSMA behandeling in Rotterdam heeft geïntroduceerd en verder ontwikkeld. Jouw commentaar op het "myectomie versus PTSMA" verhaal ("… deserves Circulation.") hangt nog steeds ingelijst aan de muur. Daarnaast zal ik de prachtige "Acunav"-beelden niet vergeten.



Beste Willem van Dockum en Jurriën ten Berg, de samenwerking met jullie kwam in het latere (PTSMA) gedeelte van het boekje tot stand. Hoewel we samenwerking al heel lang in gedachten hadden (Nice, 1999, uit mijn hoofd) ben ik blij dat de HCM-patiënten en de behandelmethoden nu wel konden worden samengevoegd. Hoewel wetenschap altijd gecombineerd moest worden met een drukke baan, hebben we een aantal mooie manuscripten geschreven die ongetwijfeld tot mooie publicaties zullen leiden.

Beste Wim Vletter, jouw aandeel is van onmisbare waarde geweest. De schitterende echobeelden hebben de uren analyseren een stuk vergemakkelijkt.

Mijn dank gaat uit naar de vele collega's in het Erasmus MC waarmee ik in de afgelopen jaren erg prettig heb samengewerkt. Mijn dank aan jullie voor de support om het schrijven naast de klinische rondes vol te houden. De gezellige "klets"-momenten met de andere assistenten in "onze" kamer hebben hier zeker aan bijgedragen. Daarnaast verpleging op afdeling en IC, Corry en de "poli"-dames (ook echo en ritmeanalyse zal ik niet vergeten), Angela Peterse voor de gezellige en serieuze gesprekken, Ron van Domburg voor de "statistische begeleiding" en promotietips, Yvonne Hoedemaekers voor de genetische adviezen, Adrie, Rob en Mark van de

computergroep voor de eerste hulp bij soft- en/of hardware problemen, Miranda en Willeke voor de hulp bij de afronding van het boekje, Rene Frowijn, Jan Tuin, Jurgen Ligthart en Frits Wilbrink voor de hulp bij de creatie van de mooie foto's; dank jullie hartelijk.

Ik wil ook mijn voormalige collega's uit het Ikazia danken voor die onvergetelijke twee jaar. Wil, ik heb bewondering voor jouw eindeloze geduld om te luisteren en uiteraard voor de bufferfunctie tussen "ons" en de "bazen". Dr. Rob Ouwendijk, bedankt voor het geduld mij te blijven accepteren tijdens de vele assistentenvergaderingen. De bijzondere telefonische onderwijssessies met Dr. Rini Baggen (telefoon in de koffiehouder!) zal ik ook niet snel vergeten. Adrienne, Martijn, Ben, Liesbeth, Maaike, Ram en Marcel; met z'n allen kom je de tijd door, met of zonder examens. Zonder elkaar had ik het nog zo net niet geweten.

Dank aan mijn collega's in Zevenaar voor het geduld om te wachten op mijn komst aangezien ik eerst het boekje naar de drukker moest brengen en op zoek moest gaan naar een ander huis. Op naar een goede en gezellige samenwerking.

Als laatste komen de voor mij belangrijkste personen die eigenlijk als eerste genoemd moeten worden, familie en vrienden.

Lieve Marianne en Ab. Jullie hebben dit voor mij mogelijk gemaakt. Zonder jullie steun, hulp en liefde was al dit moois nooit van de grond gekomen. Pap, telkens zorgde jij er voor dat alles weer voor elkaar kwam. Waar ik ook heen moest voor school, waar ik ook ging wonen. De eindeloze ritten door de polder en over de Veluwe, "effe" 300 km op een dag, ik mis het best. Mam, jouw constante hulp bij het overhoren van mijn huiswerk, het oplossen van mijn problemen, jouw duwtjes in de rug als ik ze nodig had; ze zullen altijd in mijn geheugen gegrift staan. Hoewel jij er op deze dag niet bij zult zijn, kijk je met me mee, zoals we hebben afgesproken. Pap en Henny, jullie wens ik alle goeds toe in de toekomst.

Toos en Karel, jullie hebben een belangrijke bijdrage geleverd aan mijn gelukkige jeugd. Toos, met dit boekje in de hand hebben we een moment om net weer wat sterker aan elkaar te denken dan dat we gewoonlijk al doen. Karel heeft ook zo zijn eigen plek om rustig mee te genieten. Ik hoor hem zeggen; "Wat een uitzicht, joh".

Mijn schoonmoeder ben ik door de loop van de jaren altijd dankbaar geweest. Was het niet dankzij de gastvrijheid gedurende meerdere weken dat ik mijn propedeuse jaar alsnog ben doorgekomen; alles tegen de vergoeding van een stuk echte "Staphorster" kaas. De vele uren die we bij jou hebben doorgebracht "op de Stille" zijn er bij elkaar waarschijnlijk meer dan op de Meppelweg.

Carla en Gerard, wat heerlijk dat ondanks de drukte van alle zaken jullie er altijd zijn als het nodig is. Nu kunnen jullie even gezellig op de koffie komen op weg naar Frankfurt.

Ruud en Marion, bij jullie begon de studie. Dit was volgens mij ook de eerste keer dat ik, uitgebreid de krant lezend, eerder wakker was dan Marion. Juist ja, ik had mijn bed nog niet gezien die nacht. Ik hoop dat we in Zevenaar net zo'n mooi huis gaan treffen als dat van jullie.

Greet en Dick, jullie zijn in de afgelopen paar jaar wel een heel bijzondere rol in ons leven gaan spelen. Wie had dat verwacht op het moment dat we hier gingen wonen. De laatste tijd hebben we veel gezelligheid met elkaar en de kinderen gehad. In het begin echter zou ons gezin wel eens gestrand kunnen zijn als we al jullie hulp niet hadden gehad. Hulp op lastige momenten, gezellig aanschuiven als onze magen knorden, een gezellig dagje Brabant; het heeft ons er doorheen gesleept. Het was altijd belangeloos en gemeend.

Joost, Jeroen en Seraphim. We zijn alle vier op weg om de toekomst meer vastigheid te geven. Geen rommelige studentenkamer meer maar gewoon een huis, kids en een auto (of twee) voor de deur. Het feit dat we na regelmatige radiostiltes weer gewoon doorkletsen bij een onverwacht telefoontje zegt denkt ik genoeg over onze vriendschap. Daar komt geen boekje tussen.

Joke en Cor, jullie zijn ook een belangrijk deel van ons leven gaan uitmaken. Het plezier dat Laurens en Casper bij hun oppasmoeder hebben is groot. Het plezier dat dat ons geeft is niet te beschrijven. Ik zal ze voor ik naar bed ga na de nachtdienst echter geen gedag meer komen zeggen.

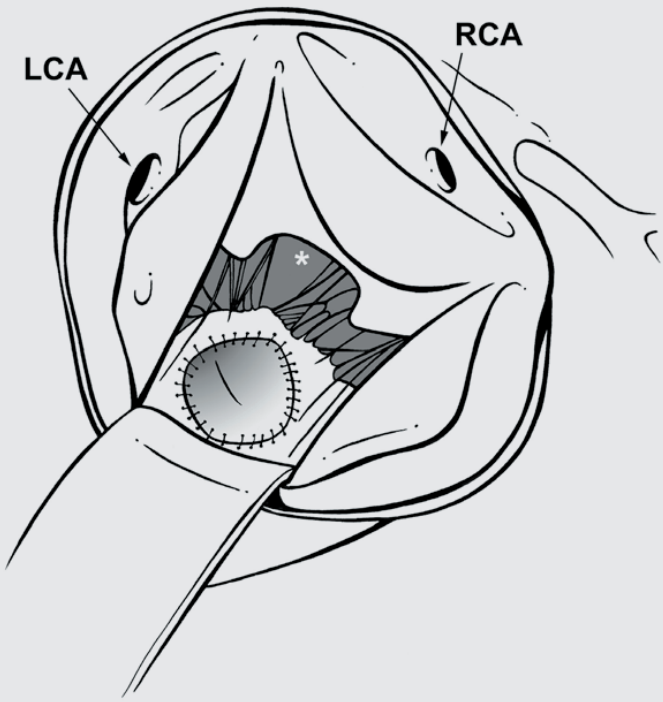


Lieve Natasja, daar staan we dan. Bijna 17 jaar later, allebei de opleiding afgerond, promotie bijna achter de rug. We zullen zien wat de toekomst gaat brengen voor ons.

Laurens en Casper, Casper en Laurens. Drie jaar. Een bijzondere tweeling. Jullie zijn het mooiste geschenk in mijn leven, voor altijd.

# cv

## Curriculum Vitae



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He graduated in 1988 at the Gymnasium Celeanum in Zwolle: VWO-B certificate.
From 1988 to 1992, he studied medicine at the Erasmus University Rotterdam. Within this period, he worked as fellow student-trainee at the department of Cardio-Biochemistry (1992-1994, Dr. J.W. de Jong). In 1996 he obtained his medical degree and started as a resident cardio-pulmonary surgery in Breda. From 1996, he worked at the Erasmus Medical Center Rotterdam as a resident cardiology and as research-fellow at the hypertrophic cardiomyopathy outpatient clinic (Dr. F.J. ten Cate). As part of the training in cardiology, he studied internal medicine from November 2000 to November 2002 at the Ikazia Hospital in Rotterdam (Dr. R.J.Th. Ouwendijk). Thereafter, he started the speciality training cardiology at the Department of Cardiology, Thoraxcenter, EMC Rotterdam (Prof. dr. Roelandt and from 2003 Prof. dr. M.L. Simoons). He was registered as a cardiologist on November 1, 2005. He will start as a cardiologist in the Alysis zorggroep, Ziekenhuis Zevenaar.

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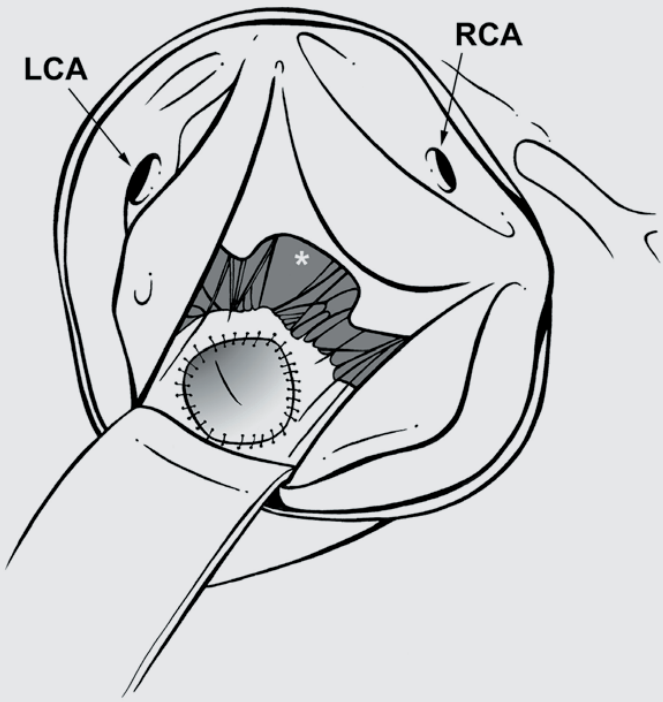
## List of publications



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Ik wil de Jacques H. de Jong Stichting hartelijk danken voor haar bijdrage in de drukkosten van dit proefschrift.

The financial support of the following companies is gratefully acknowledged:
Altana Pharma
Boston Scientific Europe
Novartis Pharma B.V.
Merck Sharp & Dohme B.V.
Menarini Farma Nederland
Pfizer
Merck B.V.
Philips Nederland B.V.
Sanofi Aventis
Bristol-Myers Squibb
AstraZeneca