EVALUATION OF ALCOHOL SEPTAL ABLATION IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

BY MAGNETIC RESONANCE IMAGING
Evaluation of Alcohol Septal Ablation in Obstructive Hypertrophic Cardiomyopathy by Magnetic Resonance Imaging

Willem G. van Dockum
Evaluation of Alcohol Septal Ablation in Obstructive Hypertrophic Cardiomyopathy by Magnetic Resonance Imaging

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan de Vrije Universiteit Amsterdam, op gezag van de rector magnificus prof.dr. L.M. Bouter, in het openbaar te verdedigen ten overstaan van de promotiecommissie van de faculteit der Geneeskunde op donderdag 5 juni 2008 om 15.45 uur in de aula van de universiteit, De Boelelaan 1105

door

Willem George van Dockum

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J Am Coll Cardiol 2004;43:27-34

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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
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<tr>
<td>AS</td>
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<tr>
<td>ASA</td>
<td>Alcohol Septal Ablation</td>
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<tr>
<td>CK</td>
<td>Creatine Kinase</td>
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<tr>
<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
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<tr>
<td>DTPA</td>
<td>diethylene-triamine pentaacetic acid</td>
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<tr>
<td>H(O)CM</td>
<td>Hypertrophic (Obstructive) Cardiomyopathy</td>
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<tr>
<td>ICD</td>
<td>Implantable Cardioverter-Defibrillator</td>
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<td>IVS</td>
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<tr>
<td>LAD</td>
<td>Left Coronary Artery</td>
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<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
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<tr>
<td>LGE</td>
<td>Late Gadolinium Enhancement</td>
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<tr>
<td>LV</td>
<td>Left Ventricle or Left Ventricular</td>
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<td>LVOT</td>
<td>Left Ventricular Outflow Tract</td>
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<td>LVOTG</td>
<td>Left Ventricular Outflow Tract Gradient</td>
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<td>LVUB</td>
<td>Linker Ventrikel Uitstroom Baan</td>
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<tr>
<td>MCE</td>
<td>Myocardial Contrast Echocardiography</td>
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<td>MHC</td>
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<td>MRI</td>
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<tr>
<td>RBBB</td>
<td>Right Bundle Branch Block</td>
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<tr>
<td>RV</td>
<td>Right Ventricle</td>
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</tr>
<tr>
<td>SAM</td>
<td>Systolic Anterior Motion</td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>Signal Intensity or Shortening Index</td>
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<tr>
<td>SMI</td>
<td>Septal Myocardial Infarction</td>
<td></td>
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<tr>
<td>TR</td>
<td>Temporal Resolution</td>
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<tr>
<td>TTE</td>
<td>TransThoracic Echocardiography</td>
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General Introduction and Outline of Thesis

Willem G. van Dockum
GENERAL INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex disease with diverse genetic, morphological, functional, and clinical manifestations. Hypertrophy, the hallmark of this disease, usually develops after puberty. Although in most patients, hypertrophy is initially restricted to the septum, it often progresses with age to involve the whole left ventricle. The septal hypertrophy causes left ventricular outflow tract (LVOT) obstruction which subsequently results in anterior motion of the mitral valve leaflets during systole (SAM) and mid-systolic septal contact with the hypertrophied septum which is an important pathophysiological component of HCM. The SAM results in incomplete leaflet coaptation and the onset of eccentric mitral regurgitation, typically directed posterior into the left atrium. Obstruction of LVOT further enhances the development of hypertrophy, resulting in angina, dyspnea, syncope, and sudden death. Approximately one-third of all HCM patients demonstrate a substantial (≥ 30 mmHg) LVOT obstruction under resting (basal) conditions, which has been shown to be an independent predictor of progressive heart failure symptoms and cardiovascular mortality. In patients with hypertrophic obstructive cardiomyopathy (HOCM) with refractory symptoms despite optimal medication (beta-blocker, calcium antagonist or disopyramide) surgical and nonsurgical procedures have been developed.

Septal myectomy, a surgical technique first performed by Cleland, is regarded as the standard approach to reduce LVOT obstruction. During the classic myectomy (the Morrow procedure), the surgeon excises a small rectangular segment of the thickened basal interventricular septum by a trans-aortic root approach. Surgery has proven to immediately reduce or eliminate the obstruction in most individuals, with a long-lasting effect. Since its introduction five decades ago, modifications to the surgical resection have been developed to additionally correct structural anomalies of the mitral valve apparatus which are frequently encountered in HOCM patients. Typical HCM related deformation of the mitral valve apparatus includes an increased mitral valve area, length and laxity as well as anterior displacement of the papillary muscles. Recently, septal...
myectomy combined with mitral leaflet extension in symptomatic HOCM patients revealed to be more effective compared to standard myectomy in reducing residual systolic anterior motion (SAM), and subsequently decreasing suboptimally diminished LVOT gradient and residual mitral regurgitation. Major complications of surgery include complete heart block, ventricular septal defect, severe aortic insufficiency, and death. The reported postoperative mortality resulting from this operation varies from 1% in young patients to 17% in patients older then 65 years, especially in the presence of coronary artery disease or other concomitant surgical procedures. Recently, dual-chamber pacing with optimization A-V delay has been reported to yield a substantial decrease in the LVOT gradient and symptomatic improvement. However, randomized studies suggest that a placebo effect may play an important role in the short-term symptomatic improvement.

The idea of inducing a septal myocardial infarct by catheter techniques was suggested by the observations that systolic and diastolic myocardial function of selected areas of the left ventricle can be suppressed by balloon occlusion of the supplying artery during coronary angioplasty, and that intracavitary pressure gradients in HOCM decrease significantly when the first septal artery is temporarily occluded by an angioplasty balloon catheter. Transcatheter ablation of the septum with ethanol infusion in the proximal septal branches of the left anterior descending coronary artery was first performed by Sigwart in 1994. As a result, an artificial myocardial infarction was induced, leading to septal scarring and thinning of the ventricular septum, and consequently, widening of the LVOT diameter causing a decrease of the pressure gradient, and symptomatic improvement. In most patients a marked immediate decrease in LVOT gradient is observed after alcohol septal ablation (ASA), probably due to myocardial stunning. Ultimate gradient reduction occurs several weeks after the procedure; the remodeling of the basal septal myocardium incurred by scarring and thinning of the interventricular septum requires some time, leading to widening of the LVOT area. Myocardial contrast echocardiography (MCE) was introduced as part of the procedure to guide the selection of the appropriate septal branch supplying the critical
septal segment (i.e., the point of systolic septal mitral valve contact and maximal flow acceleration), and to identify inappropriate sites for ethanol injection such as a septal branch supplying myocardium too close to the apex, papillary muscle, inferoposterior left ventricle (LV), or right ventricle. In contrast to septal myectomy, which is usually complicated by induction of left bundle branch block (LBBB), ASA may often result in right bundle branch block (RBBB). Major complications of ASA include complete heart block, coronary artery dissection or retrograde ethanol leakage, which may result in occlusion or abrupt coronary no-flow, and subsequent death. In the early days of ASA, the incidence of complete heart block necessitating permanent pacemaker implantation was more than 30%. By reduction of the amount and the injection-speed of ethanol used during the procedure, the incidence of complete heart block necessitating permanent pacemaker implantation has fallen to <10%, which still is higher compared to septal myectomy (≈5%). Nowadays, the procedure related mortality (≈1% to 2%) is comparable with septal myectomy.

Previous echocardiographic studies have described the effects of ASA, but has limited capabilities to accurately quantify myocardial infarct size and exact location at follow-up. In patients with ischemic heart disease, late Gadolinium enhanced (LGE) cardiac magnetic resonance (CMR) imaging accurately delineates infarcted, irreversibly damaged myocardium, both in the (sub-)acute and in the chronic phases. The high spatial resolution of CMR allows detailed evaluation of the cardiac anatomy, and in combination with the ability of tissue characterization using LGE imaging, makes it the best imaging modality to evaluate the artificially induced myocardial infarction by ASA. Also, cine imaging allows accurate assessment of global left ventricular (LV) function and myocardial mass, with a reproducibility accurate enough to detect small changes in global and regional mass. Furthermore, CMR tissue tagging with three-dimensional (3D)-strain analysis is a refined method to quantify regional myocardial function. Finally, CMR phase-contrast velocity measurements allows non-invasive quantification of coronary blood flow.
OUTLINE OF THESIS

The aim of this thesis was to investigate in patients with HOCM the effects of alcohol septal ablation (ASA; synonym PTSMA = percutaneous transluminal septal myocardial ablation) with respect to anatomy, global and regional cardiac LV function, and left anterior descending (LAD) coronary flow. For this purpose, multiple CMR techniques were used (cine-imaging, LGE CMR, myocardial tissue tagging in conjunction with strain analysis, and coronary flow measurements) before and after ASA in patients with HOCM, recruited from The St Antonius Hospital in Nieuwegein and the Academic Hospital of Rotterdam.

Chapter 2
In this chapter, the pathophysiology and clinical management of HCM is reviewed. The etiology, the pathologic features, the different diagnostic tools, the genetics of the disease, its clinical course and therapeutic interventions are discussed.

Chapter 3
In this study we evaluated the infarction induced by ASA in symptomatic patients with HOCM using LGE CMR. We report the extent and the localization of the ethanol-induced LGE myocardial infarct size and its correlation with peri-procedural infarct related parameters.

Chapter 4
ASA reduces LVOT pressure gradient in patients with HOCM, leading to LV remodeling. Early LV remodeling was demonstrated one month after ASA. Using CMR at follow-up, the early to mid-term changes and modulating factors of the remodeling process are described. The potential mechanisms and implications of these changes of regional LV mass are discussed.
Chapter 5
In a subgroup of patients studied in the previous chapter, myocardial tagging was used to calculate systolic 3D myocardial strain values at baseline and at six months follow-up. These strain values were used to calculate the shortening index (SI), a robust parameter for myocardial contraction. Maximum end-systolic (ES) SI and systolic SI-rate were quantified in 3 circumferential segments: septum, adjacent and remote (lateral) myocardium. Using the CMR tissue tagging and three-dimensional (3D) strain analysis we measured the effects of ethanol-induced myocardial infarcts on regional myocardial function.

Chapter 6
CMR flow mapping enables a non-invasive quantification of coronary blood flow. In patients with HOCM after ASA both LVOT gradient reduction and myocardial scarring are expected to influence left anterior descending (LAD) coronary blood flow. In this study, the effects of ASA on coronary blood flow were evaluated in HOCM patients using CMR coronary flow measurements. Furthermore, the determinants of LAD coronary flow changes after ASA were explored.

Chapter 7
Most HOCM patients develop RBBB after ASA. However, it is currently unknown whether infarct characteristics differ between patients with and without RBBB, and to what extent they influence LV pressure gradient reduction and reverse remodeling. We have studied consecutive HOCM patients using CMR and electrocardiography at baseline, and 1 and 6 months after ASA. Infarct characteristics (e.g. infarct size and location, early to mid-term effects on LV function) were compared in patients with and without procedure related RBBB.
Chapter 8

MCE has been introduced as a tool to accurately predict location and size of the septal infarct before definite ethanol injection. Both location and size of the induced myocardial septal infarct are important for optimizing hemodynamic results and maximally preserve left ventricular function after ASA. The study was designed to evaluate the value of MCE during ASA in predicting the location and size of ethanol-induced septal myocardial infarction as determined by CMR.
REFERENCES


Hypertrophic Cardiomyopathy: A Genetic Cardiac Disease

W.G. van Dockum
P.A.F.M. Doevendans
A.A.M. Wilde
A.C. van Rossum

(Ned Tijdschr Geneeskd. 2002;146:705-712)
ABSTRACT

The hallmark of hypertrophic cardiomyopathy (HCM) is (generally asymmetrical) hypertrophy of a non-dilated left ventricle in the absence of another cardiac or systemic disease that could cause left ventricular hypertrophy. It is a genetic disease of the heart with a heterogeneous expression and a wide diversity of morphologic, functional, and clinical features. This review will discuss the etiology, pathology, diagnosis, and genetics of the disease, its clinical course and possible therapeutic interventions.
Hypertrophic cardiomyopathy (HCM) is a disease of the cardiac muscle showing characteristic (generally asymmetrical) hypertrophy of a non-dilated left ventricle in the absence of other cardiac or systemic disease that could cause left ventricular hypertrophy. The muscle cells are not only hypertrophied, but also arranged in a disorganized pattern (a feature known as myocardial disarray). The hypertrophy leads to hemodynamic deterioration as a consequence of diastolic dysfunction of the left ventricle followed eventually by systolic dysfunction.

Sudden heart death, often exercise-related, is the most extreme complication of the disease and occurs mainly in young adults. The disease has intrigued physicians since its clinical recognition almost fifty years ago, though little was known about it for many years. Many studies of the disease have however been published of recent years, including some by Dutch cardiologists. HCM usually shows an autosomal dominant inheritance pattern. Eleven genes causally related to HCM are currently known, several mutations being possible in each of these genes.

ETIOLOGY

The prevalence of HCM in the general population is about 0.2%. HCM is a monogenetic cardiac disease with a heterogeneous expression and a wide diversity of morphologic, functional, and clinical features. It shows an autosomal dominant inheritance pattern in more than 80% of the cases in which hypertension is ruled out. The etiology is as yet undefined in the remaining 20% of patients: in these cases, the disease could possibly also be genetic, caused by mutations in genes which have not yet been recognized.

The genes known to be involved in HCM encode for components of a large protein complex (sarcomere) that is responsible for the contraction of the cardiac muscle. The normal gene produces a protein of a certain composition and function within the sarcomere complex. The mutated gene, from the other parent, produces the same protein but now with an abnormal composition and hence an abnormal function. This abnormal protein has a dominant-negative effect on the normal proteins. The extent of this
The genes in question code for β-myosin heavy-chain (β-MHC), cardiac troponin-T, α-tropomyosin, myosin-binding protein C, myosin regulatory light chain, myosin essential light chain, troponin-I, α-cardiac actin, titin, α-myosin heavy chain and protein kinase A, among others. The cardiac hypertrophy is produced either by a compensatory mechanism due to suboptimal intracellular contraction, or by a hypercontractile state.\textsuperscript{15,16}

**PATHOLOGY AND PATHOPHYSIOLOGY**

The macroscopic findings are increased myocardial mass, and a reduction in the size of the ventricular cavities. The left ventricle (LV) usually shows more hypertrophy than the right ventricle. This hypertrophy leads to diastolic dysfunction with high ventricular end-diastolic pressures, and hence to hypertrophy and dilatation of the atria. Concomitant mitral regurgitation can aggravate the atrial dilatation. It is characteristic of the condition that the amount and extent of the left ventricular hypertrophy can show considerable variation. Most patients feature disproportionate involvement of the interventricular septum (asymmetrical septal hypertrophy) and of the anterolateral left ventricular wall compared with the LV lateral free wall. Approximately 25% of the patients manifest obstruction of the left ventricular outflow tract (LVOT), a condition known as hypertrophic obstructive cardiomyopathy. Concentric LV hypertrophy, characterized by symmetrical thickening of the left ventricle, is less common. Another variant, apical hypertrophy, has only been found in Japan.\textsuperscript{17}

Characteristic microscopic findings are hypertrophy of the cardiomyocytes and a haphazard arrangement of the heart muscle cells (known as ‘myocardial disarray’). Nearly all patients with HCM manifest myocardial disarray, covering more than 5% of the myocardium. Persons without HCM show this disarray in less than 1% of the overall myocardial wall.

Myocardial fibrosis, caused by excessive growth of the collagen network, is another common pathologic feature of hypertrophic cardiomyopathy.\textsuperscript{18} In addition, 80% of HCM
patients show abnormal intramyocardial coronary arteries, most frequently in the interventricular septum. Reduction in the size of the lumen and thickening of the wall of these arteries lead to abnormal flow patterns in epicardial coronary arteries and a reduction in the microcirculation reserve.19,20

**DIAGNOSIS**

Most HCM patients do not have any symptoms in the early stages of the disease. The condition is often diagnosed by the chance observation of a heart murmur or abnormal results in a routine ECG, because they survived a collapse due to an abnormal heart rhythm or when family screening was performed after the sudden death of a family member at a young age.

**Figure 1.** Electrocardiogram of a 16-year-old boy with hypertrophic obstructive cardiomyopathy. The electrocardiogram shows a sinus rhythm (frequency 51 beats per minute), right cardiac axis deviation, left atrial dilatation (biphasic P peak in V1 lead), a widened QRS complex with left bundle block configuration, abnormal repolarization and abnormal Q waves in lead I and aVL.
Physical examination
The findings on physical examination can vary widely, from a complete lack of symptoms to marked symptoms characteristic of this condition. The typical auscultatory sign in HCM patients with LVOT obstruction is a rough crescendo-decrescendo ejection sound, which is best heard at the level of the fourth left intercostal space. It can be elicited or augmented by a Valsalva maneuver – unlike aortic valve stenosis, where the systolic sound is not influenced by this maneuver. In addition, a holosystolic leakage sound due to mitral valve insufficiency can also be heard at the apex (see Echocardiography below).

Electrocardiography
The most common electrocardiographic abnormalities in HCM patients are signs of left ventricular hypertrophy with or without ST-segment changes, abnormal Q-waves, T-wave inversion, interventricular conduction defects, and signs of right or left atrial enlargement. An example of an abnormal ECG in a patient with hypertrophic obstructive cardiomyopathy (HOCM) – a variant of HCM – is shown in Figure 1. In some families known or suspected to be affected with HCM, an abnormal ECG is a sensitive marker for the presence of mutation carriers. An abnormal electrocardiogram in a relative of a patient with genetically proven HCM may be the only clinical expression of the disease (see Table 1).

Echocardiography
2D-echocardiography in combination with Doppler sonography is an important diagnostic technique in patients with suspected HCM, allowing good images to be obtained of the abnormal (often asymmetrical) myocardial hypertrophy and permitting close study of the anatomy and movement of the mitral valve. Abnormal systolic anterior motion (SAM) of the anterior leaflet of the mitral valve towards the interventricular septum is observed in a subgroup of HCM patients (see Figure 2). This phenomenon is caused by hemodynamic changes in the outflow tract narrowed by the septal hypertrophy, and leads to a further increase in the obstruction.
Figure 2. B-mode (a) and M-mode (b) echocardiogram: a parasternal long-axis scan of a HCM patient with left ventricular outflow tract (LVOT) obstruction and systolic anterior motion (SAM) of the anterior leaflet of the mitral valve. This HCM patient shows manifest asymmetrical thickening of the interventricular septum (IVS), with a septum thickness of 25 mm. The LVOT obstruction is caused by a combination of septal hypertrophy and SAM of the mitral valve. The left atrium is dilated.
Echocardiography can also be used to assess the diastolic function of the LV. The myocardial hypertrophy interferes with the relaxation of the left chamber, as a result of which the passive (early) filling phase of the LV does not proceed so readily. The contribution of the late diastolic filling due to the atrial contraction will then increase to compensate for this. Moreover, HCM patients who experience atrial fibrillation without atrial contraction can suffer serious hemodynamic problems, possibly leading to heart failure or shock.

Despite all these possibilities offered by echocardiography, it may happen that some carriers of the gene defect for HCM have no echocardiographic signs of the disease.\textsuperscript{24}

**Cardiac Magnetic Resonance imaging**

Cardiac Magnetic Resonance (CMR) imaging is a non-invasive technique that makes it easy to determine the location and thickness of the hypertrophied myocardium in HCM patients, since the ventricular myocardial tissue is clearly visible between the pericardial fat (which gives a high signal intensity) and the ventricular cavity (which gives a low one); see *Figure 3-a*. Gradient echo techniques (known as cine CMR imaging) make it possible to obtain moving pictures that can be used to assess cardiac function. Quantitative calculations of the LV end-diastolic and end-systolic volumes, the stroke volume, ejection fraction and LV mass can be performed in this way. In addition to these global LV function parameters, specific CMR techniques also permit assessment of regional systolic wall motion and diastolic function parameters.\textsuperscript{25}

Cine CMR can be used to visualize the turbulent blood flow associated with valve defects. If mitral-valve insufficiency is present, the regurgitation volume can be calculated. This technique offers an alternative to echocardiography for demonstration of SAM of the anterior leaflet of the mitral valve, and of LVOT obstruction.

CMR myocardial tagging is a technique that allows the intramural deformation (strain) and torsion of the wall of the heart to be determined with the aid of non-invasively applied magnetic marker lines.\textsuperscript{26} Previous CMR tagging studies in patients with overt
phenotypic HCM have demonstrated abnormal movement patterns in the hypertrophic myocardial regions.\textsuperscript{27-29}

\begin{figure}
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\includegraphics[width=\textwidth]{figure3.png}
\caption{CMR scans of a 31-year-old patient with asymmetrical septal hypertrophy. Black-blood scans: long-axis scan on the left (a) and short-axis scan on the right (b). The asymmetrical interventricular septal hypertrophy is clearly visible. Short-axis cine scans of the same patient: an end-diastolic scan (c) may be seen on the left, and an end-systolic scan (d) on the right.}
\end{figure}
RISK STRATIFICATION AND EARLY IDENTIFICATION

Early identification of genetically affected relatives in whom the phenotypic expression of hypertrophy has not yet become apparent (i.e. who have "pre-clinical HCM") may be useful in risk stratification and choice of lifestyle and management strategies. These include intensive follow-up, pharmacological intervention (whereby sympathicomimetic drugs should be avoided), and the avoidance of intensive training or competitive sports. New clinical criteria for the diagnosis of HCM in adult members of affected families have been proposed on this basis: for example, slight left ventricular hypertrophy or discrete ECG abnormalities may be taken as pointing in this direction.24

So far, mutations associated with HCM have been detected in 11 different genes. As a result of the autosomal dominant inheritance pattern, there is a 50% a-priori chance that first-degree relatives will carry the mutation. Some of the mutations are associated with an impaired prognosis, even though they only cause mild LV hypertrophy. The family anamnese can indicate a genetic predisposition to reduced expectation of life and sudden heart death. Genotyping can reveal ‘malign’ mutations e.g. in β-MHC protein. Troponin T mutations are also almost always associated with an increased risk (up to 50%) of sudden heart death at a relatively low age.30-32 Modifier genes are also known to influence the clinical expression of the disease. An important modifier gene in HCM is that for angiotensin-1 converting enzyme (ACE). Expression of the ACE genotype in HCM patients has been shown to be associated with more extensive LV hypertrophy.33, 34

Since troponin T mutations are often associated with mild or even subclinical hypertrophy; genotyping would seem to be of particular clinical importance in these families. The identification of genetic carriers of HCM in small families is difficult, however, especially if only few individuals are affected. A few medical centers in the Netherlands have active screening programs for certain mutations (e.g. troponin T and β-MHC), but only in selected families.35-37 In fact, such screening is only justified from a medical ethics perspective if preventive measures exist or the health of people found to have the condition can be improved. If preclinical or presymptomatic screening does take place, it should be performed by a multidisciplinary team including clinical and molecular geneticists, cardiologists and social workers.
HCM: a genetic cardiac disease

Table 1. Diagnostic characteristics of HCM patients.

Hypertrophic cardiomyopathy is inherited in an autosomal dominant pattern; in other words, first-degree relatives of a HCM patient have a 50% chance of having the disease. The likelihood that electrocardiographic or echocardiographic signs in a family with a known history of HCM represent the expression of the disease is much higher than when these signs are found in the absence of such a family history.21-23

<table>
<thead>
<tr>
<th>Electrocardiography</th>
<th>Echocardiography</th>
<th>Cardiac Magnetic Resonance Imaging</th>
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<tbody>
<tr>
<td>LVH + abnormal repolarization</td>
<td>LV wall thickness ≥ 15 mm</td>
<td>LV wall thickness ≥ 15 mm</td>
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<td>T-wave inversion</td>
<td>SAM</td>
<td>SAM</td>
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<tr>
<td>Abnormal Q-waves</td>
<td>Dilated LA and/or RA</td>
<td>Dilated LA and/or RA</td>
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<tr>
<td>Complete BBB or (minor) interventricular conduction defect (in LV leads)</td>
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<td>signs of left- or right atrium dilatation</td>
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Family members suspect if:

- see above
- repolarization changes in LV-leads
- Deep S-wave in V2 lead

Family members suspect if:

- LV wall thickness between 13 and 15 mm
- Moderate SAM (no septal-leaflet contact)
- Redundant MV leaflets

Family members suspect if:

- LV wall thickness between 13 and 15 mm
- Prominent papillary muscles in LV and/or RV?
- Increased myocardial mass?
- Abnormal intramural deformation determined using CMR tagging?

Abbreviations: LVH = left ventricular hypertrophy; BBB = bundle branch block; SAM = systolic anterior motion of the anterior leaflet of the mitral valve; LA = left atrium; RA = right atrium; LV = left ventricle, RV = right ventricle; ? = under research
CLINICAL COURSE, PROGNOSIS AND THERAPY

The clinical course of HCM varies widely, from a complete lack of symptoms to severe heart failure, arrhythmia, or sudden heart death. Patients who die of this condition at a young age are generally the victims of sudden heart death, whereas death due to heart failure or a cerebrovascular accident associated with atrial fibrillation is found more often in older patients.

The main complaints, dyspnea, syncope, and exertional angina, can be caused by three different pathophysiological processes. Firstly, diastolic dysfunction can produce symptoms by elevating the left ventricular end-diastolic pressure and reducing the left ventricular filling. Secondly, LVOT obstruction can lead to similar complaints by elevating the systolic and diastolic left ventricular filling pressures. Thirdly, myocardial ischemia can compromise left ventricular systolic and diastolic function to give a reduction in cardiac output, hypotension and elevation of the left ventricular end-diastolic pressure.

Therapeutic strategies may involve the use of suitable pharmacological products (in particular β-blockers and calcium antagonists) to improve diastolic filling and possibly reduce myocardial ischemia in symptomatic patients. The range of drugs used to treat non-obstructive hypertrophic cardiomyopathy with impaired systolic and diastolic left ventricular function can be extended to include angiotensin-converting enzyme (ACE) inhibitors and diuretics.

Surgical myectomy (the Morrow procedure) or the recently introduced percutaneous transluminal alcohol septal ablation (ASA) may be indicated in patients with severe LVOT obstruction. The latter technique uses selective intracoronary infusion of alcohol via a percutaneous transluminal route to achieve reduction of the septal myocardium. Dual-chamber pacing may be a therapeutic alternative for HCM patients over 70 years of age. Atioventricular synchronous pacing reduces LVOT obstruction and gives rapid symptomatic relief. No objective improvement in cardiac performance has been seen in the long term, however.

Use of an implantable cardioverter-defibrillator (ICD) may be indicated in patients with life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia with
syncope and/or low blood pressure). This device currently also has a role to play in the primary prevention of sudden death in high-risk patients (e.g. those with a family history of such complaints and/or with actual extreme hypertrophy).

CONCLUDING REMARKS

Genotyping is the only completely reliable method available at present for the early detection of patients with a predisposition to hypertrophic cardiomyopathy. Current practice in the Netherlands is to apply such screening only to families with a known history of HCM associated with a reduced life expectancy, where clear health benefits are to be expected from the screening. Other diagnostic tools such as electrocardiography and echocardiography can be used in families where genotyping has not been performed, to screen for carriers of the disease carriers; it may be noted that in such cases, ECG findings may be abnormal even if there are no echocardiographic signs of HCM.

Research on proven carriers of the HCM gene, funded jointly by the Dutch Heart Foundation and the Working Group on Inheritable Heart Disease of the Interuniversity Cardiac Institute of the Netherlands, has recently been started to investigate whether cardiac CMR can be used for early detection of phenotypic expression of the disease. Such early identification of mild phenotypic signs of HCM using non-invasive imaging techniques could make an important contribution to the diagnosis and management of the disease and improved understanding of its pathophysiology.

ACKNOWLEDGEMENT

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REFERENCES


HCM: a genetic cardiac disease


Myocardial Infarction after Alcohol Septal Ablation in Hypertrophic Obstructive Cardiomyopathy: Evaluation by Late Gadolinium Enhancement Cardiac Magnetic Resonance Imaging

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ABSTRACT

Objectives
The aim of this study was to evaluate myocardial infarction induced by percutaneous alcohol septal ablation (ASA) in symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) using late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging.

Background
LGE CMR delineates the extent of myocardial infarction in coronary artery disease, but its role in ethanol-induced infarction has not been established.

Methods
Cine and LGE CMR were performed before and 1 month after ASA in 24 patients. Size and location of the induced infarction were related to left ventricular (LV) mass reduction, enzyme release, volume of ethanol administered, LV outflow tract gradient reduction, and coronary ablation site.

Results
One month after ASA, regional hyperenhancement was visualized in the basal interventricular septum in all patients. Mean infarction size was 20 ± 9 g, corresponding to 10 ± 5% and 31 ± 16% of total LV and septal mass, respectively. Total LV mass decreased from 219 ± 64 to 205 ± 64 g (P < 0.01), and septal mass from 76 ± 25 to 68 ± 22 g (P < 0.01). Total LV mass reduction exceeded septal mass reduction (P < 0.01). Infarction size correlated with peak creatine phosphokinase-MB (β = 0.67, P < 0.01), volume of ethanol administered (β = 0.47, P = 0.02), total LV and septal mass reduction (β = 0.50, P = 0.02; β = 0.73, P < 0.01), and gradient reduction (β = 0.63, P < 0.01). Seven patients with exclusively right-sided septal infarction had smaller infarction size and less gradient reduction than remaining patients with left-sided or transmural infarction (P < 0.01). In five of these, ASA was performed distal in the target artery.

Conclusion
LGE CMR allowed detailed evaluation of size and location of septal myocardial infarction induced by ASA. Infarction size correlated well with clinical indexes of infarct size.
Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease characterized by myocardial hypertrophy in the absence of any other systemic or cardiac disease, with predominant involvement of the interventricular septum (IVS). Approximately 25% of the patients have a dynamic left ventricular outflow tract (LVOT) obstruction caused by a narrowed LVOT and abnormal systolic anterior motion of the mitral valve.

Treatment strategies in patients with hypertrophic obstructive cardiomyopathy (HOCM) who remain symptomatic despite optimal medication (beta-adrenergic blocking agents, verapamil and disopyramide) include surgical (septal myotomy-myectomy) and nonsurgical procedures such as dual-chamber pacing and percutaneous septal myocardial ablation (ASA). ASA is a recently developed procedure, which consists of artificially inducing a localized myocardial infarct by ethanol infusion into septal branches of the left anterior descending coronary artery (LAD). Scarring and thinning of the IVS results in widening of the LVOT, a decrease of the pressure gradient, and symptomatic improvement.

The final outcome after ASA is thought to depend on size and location of the inflicted infarction. Infarcts that are too small or are located outside the target area may not achieve the necessary reduction in LVOT gradient. Large infarcts may cause potentially hazardous conduction abnormalities or ventricular arrhythmias. Echocardiography with intracoronary contrast-injection is commonly used during the procedure to guide the selection of the appropriate septal branch, but this technique does not allow visualization of the infarction site at follow-up. Myocardial perfusion defects by single-photon emission computed tomographic myocardial scintigraphy at 6 weeks after ASA correlated with the target area for ablation defined by contrast echocardiography. However, the spatial resolution of this technique is not sufficient to allow transmural evaluation.

In patients with ischemic heart disease late gadolinium enhancement cardiac magnetic resonance imaging (LGE CMR) accurately delineates infarcted, irreversibly damaged myocardium, both in the (sub-)acute and in the chronic phase. The high spatial resolution of LGE CMR would allow detailed evaluation of the ethanol-induced infarction. Contrary to contrast-echocardiography, LGE CMR cannot be used during the
ablation procedure, but it may provide important feedback by accurately delineating the ultimate size and location of the infarction. Although LGE CMR is capable of visualizing ASA-related infarction, its exact significance still needs to be established.\textsuperscript{18}

The purpose of the study was to evaluate myocardial infarction size and location induced by ASA in patients with HOCM using LGE CMR, and correlate the findings to procedural and infarct related parameters, and early clinical outcome.

METHODS

Patients
The study protocol was approved by the Committee on Research Involving Human Subjects and the Medical Ethics Committee of the VU University Medical Center Amsterdam. Eligible for CMR were all patients with HOCM who were scheduled for ASA. The indication for ASA was based on a significant LVOT gradient as documented by echocardiography and New York Heart Association (NYHA) functional class II-IV despite medical treatment. Exclusion criteria were any absolute or relative contra-indication to CMR (e.g. pacemaker, claustrophobia), atrial fibrillation, or failure to give informed consent. Twenty-eight patients were initially enrolled. Four patients were excluded from the final analysis: 3 required pacemaker-implantation during or after ASA, and 1 declined to return for the follow-up examination. The baseline characteristics of the remaining 24 patients are listed in Table 1.

Echocardiography
Baseline echocardiographic measurements of interventricular septum (IVS) and posterior wall thickness, LV end-diastolic and left atrial end-systolic dimensions are listed in Table 1. The LVOT pressure gradient was documented by Doppler echocardiography at baseline and 1 month after ASA. A pressure gradient $\geq 50$ mmHg at rest was considered to be significant. Three patients had a resting gradient $< 50$ mmHg, and provocation was applied both at baseline and follow-up using dobutamine-echocardiography and the
Valsalva maneuver in 2 and 1 patients, respectively. An increase of the pressure gradient during provocation to \( \geq 50 \text{ mmHg} \) was considered significant.

### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients ((n=24))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>(52 \pm 15)</td>
</tr>
<tr>
<td>Men / women</td>
<td>(11 / 13)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>(2.9 \pm 0.4)</td>
</tr>
<tr>
<td>II / III / IV</td>
<td>(3 / 20 / 1)</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
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<tr>
<td>dyspnea</td>
<td>(22)</td>
</tr>
<tr>
<td>angina</td>
<td>(9)</td>
</tr>
<tr>
<td>syncope</td>
<td>(6)</td>
</tr>
<tr>
<td>Family history: HCM / sudden death</td>
<td>(14 / 7)</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
</tr>
<tr>
<td>beta-blockers</td>
<td>(16)</td>
</tr>
<tr>
<td>calcium-antagonists</td>
<td>(12)</td>
</tr>
<tr>
<td>diuretics</td>
<td>(2)</td>
</tr>
<tr>
<td>Echocardiographic parameters at baseline:</td>
<td></td>
</tr>
<tr>
<td>LVOT gradient, mmHg</td>
<td>(87 \pm 22)</td>
</tr>
<tr>
<td>IVS thickness, cm</td>
<td>(2.1 \pm 0.4)</td>
</tr>
<tr>
<td>posterior wall thickness, cm</td>
<td>(1.3 \pm 0.2)</td>
</tr>
<tr>
<td>LV EDD, cm</td>
<td>(4.5 \pm 0.5)</td>
</tr>
<tr>
<td>LA ESD, cm</td>
<td>(4.9 \pm 0.4)</td>
</tr>
</tbody>
</table>

Values expressed as mean \(\pm\) SD. Abbreviations: NYHA = New York Heart Association; HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; LV = left ventricular; LVOT = left ventricular outflow tract; LV EDD = left ventricular end-diastolic diameter; LA ESD = left atrial endsystolic diameter.

**ASA procedure**

All patients underwent ASA in one of two major referral centers in the Netherlands (Thoraxcenter Erasmus Medical Center, Rotterdam 16 patients; St. Antonius Hospital, Nieuwegein 8 patients).
Using a standard Judkins technique an A6F pacemaker lead was placed in the right ventricle, an A6F pigtail catheter was positioned into the left ventricle and an A7F Judkins guiding catheter in the ascending aorta. The LVOT pressure gradient was continuously monitored throughout the whole procedure. After initial angiography for localizing the origin of the septal perforating arteries, a 1.5-2.5 x 10 mm balloon catheter was introduced over a 0.014 inch guide wire into the target perforator artery and inflated. Contrast (Levovist, Schering AG, Berlin, Germany) was then injected through the balloon catheter shaft during simultaneous registration of transthoracic 2D echo to determine the part of the myocardium supplied by the targeted septal artery. If no leakage of contrast occurred into the LV cavity, ethanol was slowly (1 mL/min) injected up to a maximum of 5 mL. Five minutes after ethanol injection the balloon was deflated and coronary arteriography repeated. A successful procedure was defined as the reduction in LVOT pressure gradient of ≥ 50% of baseline. If the results were not satisfactory the whole procedure, including echo-contrast injection, was repeated in another septal branch.

The total volume of ethanol injected into perforating arteries of the LAD during the procedure was documented. Plasma creatine phosphokinase (CK) and CK-MB fraction levels were determined before and every 6 hours after the procedure during a 24-hour period.

**CMR Imaging**

CMR was performed 11 ± 11 days before and 32 ± 9 days after ASA on a 1.5 Tesla clinical scanner (Sonata, Siemens, Erlangen, Germany), using a 4-element phased-array body RF receiver coil.

All images were acquired with ECG gating and during repeated breath-holds of 10 to 15 seconds depending on heart rate. After localizing scouts, cine images were acquired using a segmented steady-state free precession sequence in three long-axis views (2-, 3-, and 4-chamber view) and in multiple short-axis views every 10 mm, covering the whole left ventricle from base to apex. Scan parameters were: temporal resolution 34 ms, TR 3.0 ms, TE 1.5 ms, typical voxel size 1.4x1.8x5 mm³.
LGE images were acquired 15-20 min after intravenous administration of 0.2 mmol/kg gadolinium-DTPA in the same views used in cine CMR, using a 2D segmented inversion-recovery prepared gradient-echo sequence (TE 4.4 ms, TR 9.8 ms, inversion time 250-300 ms, typical voxel size 1.3×1.6×5 mm³).¹⁹,²⁰ LGE images were acquired in all patients at follow-up CMR. As small patchy areas of hyperenhancement were noted in the IVS outside the infarcted region, LGE imaging was added to the baseline protocol in patients 11 to 24.

Data analysis
LGE images, cine images and catheterization data were analyzed separately, and all observers were blinded to the results of the other investigations.

Analysis of LGE images
Contrast-to-noise ratio of the hyperenhanced area versus a remote non-enhanced 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: \((S_I^{\text{hyperenhanced}} - S_I^{\text{remote}}) / \text{noise}\), where \(S_I\) is signal intensity, and noise is expressed as the \(S_I\) standard deviation in a background region of interest.

Myocardial infarction size after ASA was measured by manual tracing of the hyperenhanced areas. The hyperenhanced area was defined as the area within the septal myocardium with pixel SI values > 4SD of remote, non-enhanced myocardium. Central dark zones within the area of hyperenhancement were included.

Analysis of cine images
Left ventricular parameters, including end-diastolic volume, end-systolic volume, ejection fraction, total and septal myocardial mass, and maximum end-diastolic IVS thickness at the infarct site and posterior wall thickness were quantified using the MASS software package (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders were outlined manually in end-diastolic and end-systolic frames of all short-axis slices. Papillary muscles were included in the assessment of LV mass. The IVS was defined as the myocardium between the anterior and posterior junctions of the right to the LV.
**Analysis of coronary arteriograms**  All coronary arteriograms were analyzed and scored in consensus by two experienced interventional cardiologists (JMB, JV), who were blinded to the CMR results. The number of septal perforating arteries, the target artery, and the ablation site within the target artery were registered.

**Statistical analysis**
Results are expressed as mean ± SD. Paired *t* tests were used to evaluate the changes of LV mass and volumes after ASA. Linear regression analysis was used to analyze the relationship between myocardial infarction size (outcome variable) and cardiac enzymes, the volume of ethanol administered during the ablation procedure, total LV and septal mass reduction and LVOT gradient reduction. The analyses were adjusted for age and the results are presented as age-adjusted standardized regression coefficients (*β*), which can be interpreted as partial correlation coefficients. The Mann-Whitney test was used to evaluate the correlation between different infarction locations and myocardial infarction size, the volume of ethanol administered and LVOT gradient reduction. All statistical analyses were performed with SPSS (version 11.0), and significance was set at a probability value ≤ 0.05.

**RESULTS**

Mean volume of ethanol injected was 3.3 ± 1.7 mL, and mean peak CK and CK-MB release was 1592 ± 775 U/l and 198 ± 84 U/l, respectively. One month after ASA, mean LVOT pressure gradient decreased from 87 ± 22 mmHg to 23 ± 29 mmHg (*P* < 0.01) and mean NYHA class improved significantly from 2.9 ± 0.3 to 1.7 ± 0.6 (*P* < 0.01). During the follow-up period, none of the patients experienced syncope, and there were no documented ventricular arrhythmias.

**LGE CMR at baseline**
In 14 patients contrast-enhanced imaging was performed before ASA. In 10 patients
small patchy areas of hyperenhanced myocardium were observed in the IVS, located centrally in the ventricular wall and predominantly at the junctions of the right and left ventricular free wall. The number of focal areas of hyperenhancement per patient was 4 ± 1.5, representing an average mass of 0.5 ± 0.4 g per area. The contrast-to-noise ratio of these areas was 7 ± 4. Figure 1A shows an example of focal contrast-enhancement in a patient before ASA.

Figure 1A. Contrast-enhanced short axis images before (A) and after ASA (B) in a patient with HOCM. Before ASA, a slightly enhanced myocardial region is apparent in the anterobasal wall of the IVS (A). After ASA, the ethanol-induced infarction can be seen as a clearly demarcated area of hyperenhancement (B).

LGE CMR post ASA – infarct size
At follow-up, a clearly demarcated area of hyperenhancement was visualized in the basal part of the IVS in all patients. No patient had evidence of infarction-related hyperenhancement outside the target area. The contrast-to-noise ratio of hyperenhanced areas was 26 ± 7. Mean myocardial infarction size was 20 ± 9 g (range 5 - 41 g), involving 10 ± 5% of the post-ablation total LV mass and 31 ± 16% of the septal myocardial mass. Figure 1B and Figure 2 show examples of ethanol-induced infarctions.
Figure 2. Late gadolinium enhancement images 20 minutes after intravascular administration of gadolinium-DTPA in two patients with hypertrophic obstructive cardiomyopathy one month after alcohol septal ablation. (A, B) Three-chamber view and short-axis view in a patient with transmural septal infarction. (C, D) Comparable views in a patient with myocardial infarction located exclusively on the right ventricular side of the interventricular septum.

Changes in LV mass and volumes
End-diastolic IVS thickness measured at the site of infarction decreased from 2.1 ± 0.4 cm at baseline to 1.6 ± 0.5 cm at follow-up ($P < 0.01$). Total LV myocardial mass decreased significantly from 219 ± 64 g at baseline to 205 ± 64 g after ASA ($P < 0.001$).
Septal myocardial mass decreased from 76 ± 25 g pre-ASA to 68 ± 22 g post-ASA ($P < 0.01$). The reduction in total LV mass was larger than that in septal mass only ($P < 0.01$).

Table 2. Cine CMR and clinical parameters before and 1 month after ASA.

<table>
<thead>
<tr>
<th>Cine CMR parameters</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS thickness at infarct site [cm]</td>
<td>2.1 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>LV PW thickness [cm]</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic volume [mL]</td>
<td>153 ± 41</td>
<td>154 ± 38</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic volume [mL]</td>
<td>47 ± 14</td>
<td>53 ± 17</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>LV ejection fraction [%]</td>
<td>69 ± 5</td>
<td>67 ± 5</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>Total LV mass [g]</td>
<td>219 ± 64</td>
<td>205 ± 64</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Septal mass [g]</td>
<td>76 ± 25</td>
<td>68 ± 22</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>$P$-value</th>
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<tr>
<td>NYHA functional class</td>
<td>2.9 ± 0.4</td>
<td>1.7 ± 0.6</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>LVOT gradient, mmHg</td>
<td>87 ± 22</td>
<td>23 ± 29</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. NS = statistically not significant. Abbreviations: IVS = interventricular septum; LV = left ventricular; PW = posterior wall; NYHA = New York Heart Association; LVOT = left ventricular outflow tract.

The reduction in remote myocardial mass (i.e. excluding the septal mass) was statistically significant ($P < 0.01$). At follow-up, LV end-diastolic volumes were unchanged (153 ± 41 mL vs. 154 ± 38 mL). A significant increase of LV end-systolic volumes was observed (47 ± 14 mL vs. 53 ± 17 mL; $P = 0.03$), with a concurrent decrease in LV ejection fraction (69 ± 5% vs. 67 ± 5%; $P = 0.01$). Changes of LV parameters are summarized in Table 2.
**Correlation between infarct size and other parameters**

Linear regression analysis showed significant associations between myocardial infarction size and both peak CK and CK-MB after ASA. The age-adjusted standardized regression coefficients ($\beta$) were 0.53 ($P = 0.01$) and 0.67 ($P < 0.01$), respectively (Figure 3). Myocardial infarction size also correlated with the volume of ethanol administered ($\beta = 0.47$, $P = 0.02$; Figure 4), total and septal mass reduction ($\beta = 0.50$, $p = 0.02$; $\beta = 0.73$, $P < 0.01$, respectively), and the reduction in the LVOT pressure gradient measured by Doppler echocardiography ($\beta = 0.63$, $P < 0.01$; Figure 3).

**LGE CMR post ASA – infarct location**

The area of hyperenhancement was located exclusively on the right ventricular side of the IVS in seven patients, exclusively on the left ventricular side of the IVS in two patients, and extended transmurally throughout the IVS in 15 patients. Examples of a patient with transmural extent and a patient with exclusively right-sided location of septal infarction are shown in Figure 2.

In the seven patients with exclusively right-sided hyperenhancement infarct size, septal mass reduction, and reduction in LVOT gradient were smaller ($10 \pm 4$ g vs. $23 \pm 8$ g; $2.5 \pm 1.3$ g vs. $9.4 \pm 4.0$; and $30 \pm 28$ mmHg vs. $78 \pm 22$ mmHg; all $P < 0.01$). The volume of ethanol infused during the ablation procedure tended to be lower ($2.6 \pm 1.2$ mL versus $3.6 \pm 1.8$ mL, $P = 0.19$). In these patients mean NYHA functional class improved from $3.1 \pm 0.4$ to $2.3 \pm 0.5$, and in the transmurally infarcted patients from $2.8 \pm 0.4$ to $1.4 \pm 0.5$. The two patients without symptomatic improvement had a right-sided location of the septal infarction without reduction in the LVOT gradient. The infarction size of these two patients was $7.3$ g and $10.2$ g, respectively.

**Correlation between infarct location and coronary ablation site**

The average number of septal perforating arteries per patient was $3.6 \pm 0.8$ (range 2-6). The target artery was the first, second, and third perforator in 13, 11, and 2 patients
respectively. In two patients ethanol infusion was repeated after 20 minutes in a second artery, because of insufficient gradient reduction after the first ethanol infusion.

In the 15 patients with transmural infarction and the two patients with left-sided infarction of the IVS, ASA was performed proximal to the first bifurcation of the target artery. In the seven patients with exclusively right-sided hyperenhancement of the IVS, ASA was performed distal to the first bifurcation of the target artery in four and more distal than usual in a target artery without side branches in 1.

DISCUSSION

Our findings demonstrate that LGE CMR allows the detailed evaluation of the ASA-induced myocardial infarction in symptomatic patients with HOCM. The quantified infarction size was significantly correlated to cardiac enzyme release, volume of ethanol administered, total LV and septal mass reduction, and LVOT pressure gradient reduction. Also, patients with an exclusively right-sided location of the infarction within the IVS had significantly smaller infarction size and less gradient reduction.

Mechanism of hyperenhancement

After coronary artery occlusion, the extracellular contrast agent gadolinium-DTPA accumulates in infarcted regions of the myocardium that are necrotic and irreversibly damaged. In (sub-)acute infarction, this is the result of altered wash-in and wash-out characteristics and an increased volume of distribution caused by myocyte membrane disruption. The mechanism of contrast agent accumulation in ASA-induced infarctions may be similar, due to the direct toxic, osmotic, and thrombotic effects of ethanol spreading throughout the myocardial tissue. Since our data were acquired one month after ASA, at a time when the infarcted myocardium is likely to have entered the chronic phase, other mechanisms like passive diffusion of the contrast agent within enlarged interstitial compartments of the collagen matrix in fibrous scar may have played a role. This mechanism may also explain the presence of patchy focal areas of hyperenhancement that we found in the majority of patients that underwent contrast-
Figure 3. Correlation of myocardial infarction size and peak CK-MB, reduction in septal mass, and the reduction in the LVOT pressure gradient after alcohol septal ablation. The age-adjusted standardized regression coefficient ($\beta$) and the significance ($P$-value) are given.
enhanced CMR before ASA. Choudhury et al. recently reported the presence of multiple foci of patchy hyperenhancement in the majority of a group of asymptomatic patients with HCM. They found that these areas were predominantly located in the middle third of the ventricular wall, at the junction of the septum and RV free wall, which is similar to our findings. The clinical significance of these areas is unknown, but they may act as a substrate for the development of ventricular arrhythmias.

**Figure 4.** Correlation of the volume of ethanol (mL) injected and myocardial infarction size (g) after alcohol septal ablation. The age-adjusted standardized regression coefficient ($\beta$) and the significance ($P$-value) are given.

**Size and location of myocardial infarction**

The range of myocardial infarction size was large (5-41g). Factors that may influence infarction size include differences in septal coronary anatomy, position of the inflated balloon within the target artery during ethanol infusion, and volume of ethanol administered.

In seven patients infarction was located exclusively on the right ventricular side of the septum. These patients had smaller infarction size, less reduction in LVOT gradient, and two patients reported no symptomatic improvement. In contrast to patients with transmural or exclusively left-sided septal infarction, balloon position during ethanol
infusion was frequently distal to a bifurcation. Currently available autopsy data of septal coronary anatomy do not provide a conclusive explanation for the differences in location of the ablation injury.\textsuperscript{26} Our findings suggest that an exclusively right-sided septal infarction may be related to the ablation site.

**Effect of ASA on LV mass and volumes**

Previous echocardiographic studies have demonstrated a significant reduction in LV mass 1 year after ASA. This was not only due to thinning of septal myocardium, but also to a decrease of wall thickness throughout the LV circumference.\textsuperscript{27,28} The accuracy and reproducibility of CMR enabled us to detect small changes in LV and septal mass as early as 1 month after ASA.\textsuperscript{29} In our study, the reduction in total LV mass significantly exceeded the reduction in septal mass, and the reduction in remote myocardial mass proved statistically significant. This may be explained by the reduction in LVOT obstruction that may have caused early regression of (secondary) LV hypertrophy by decreasing LV pressure and wall stress. An alternative explanation could be that ethanol infusion induced infarcts in other parts of the left ventricular wall, by distributing through the capillary network. However, we found no evidence of induced myocardial infarction outside the target area, despite the very sensitive nature of LGE CMR to visualize discrete micro-injury.\textsuperscript{30} The septal infarction caused wall thinning and loss of regional wall thickening, which led to a small but significant increase in LV ESV. LV EDV was unchanged, and as a result, EF slightly decreased. Although the changes were only small, they illustrate again the effects of ethanol-induced infarction. Further study is necessary to evaluate the long term effects of ASA on LV mass and volumes.

**LIMITATIONS**

The total number of patients in our study group was limited. Three patients (11% of the initial study group) could not undergo follow-up CMR because a procedure-related AV-block necessitated pacemaker-implantation. Infarct size according to peak CK-MB in
these three patients was similar to the study group (148 ± 29 vs. 198 ± 84 U/l, \( P = \text{NS} \)), suggesting that infarct location may be an important factor for the development of conduction abnormalities.

The foci of patchy hyperenhancement that were demonstrated in patients with HOCM may have interfered with determination of the infarction size. Generally, they would have caused an overestimation of the infarction size, by overlap of pre-existing foci and ethanol-induced infarction. However, it is unlikely that these areas have significantly influenced our results, since the size was small relative to the procedure-related infarction size.

**Clinical implications**

At present the optimal size and location of the myocardial infarction with respect to clinical outcome is not known. Theoretically, the objective is to abolish the LVOT gradient by inducing an infarction in the basal septum with the smallest possible amount of myocardial damage, located at the site of maximal mitral-septal contact. A catheter position proximal in the target septal perforator artery may increase the success rate of ASA, but should be weighted against the possible risks of proximal balloon inflation, such as injury inflicted on the left anterior descending artery or the potential of slippage of the inflated balloon with retrograde ethanol leakage.

During ASA, temporary balloon inflation and selective coronary myocardial contrast-echocardiography are used to probe the risk area.\(^{14,22}\) Although contrast-echocardiography is helpful in selecting the target location of ablation and septal branch, it does not allow transmural evaluation of the myocardium, and may therefore not be able to reliably predict the adverse occurrence of right-sided septal infarction. Additional studies are needed to explore the relation between the area at risk as estimated by contrast-echocardiography and the ultimate size and location of the inflicted septal infarction.

In conclusion, we found that LGE CMR was an excellent technique for the quantitative evaluation of septal myocardial infarction induced by ASA. The correlation between size and location of the infarction and early outcome provides important feedback and may
help to optimize this promising therapeutic option in patients with hypertrophic obstructive cardiomyopathy.

ACKNOWLEDGMENTS

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REFERENCES


Early Onset and Progression of Left Ventricular Remodeling after Alcohol Septal Ablation in Hypertrophic Obstructive Cardiomyopathy

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ABSTRACT

Background
Alcohol septal ablation (ASA) reduces left ventricular outflow tract (LVOT) pressure gradient in patients with hypertrophic obstructive cardiomyopathy (HOCM), which leads to left ventricular remodeling. We sought to describe the early to midterm changes and modulating factors of the remodeling process using cardiac magnetic resonance imaging (CMR).

Methods and Results
CMR was performed at baseline and 1 and 6 months after ASA in 29 patients with HOCM (age 52 ± 16 years). Late gadolinium enhancement CMR showed no infarct-related hyperenhancement outside the target septal area. Septal mass decreased from 75 ± 23 g at baseline to 68 ± 22 g and 58 ± 19 g (P < 0.001) at 1- and 6-month follow-up, respectively. Remote, non-septal mass decreased from 141 ± 41 g to 132 ± 40 g and 111 ± 27 g (P < 0.001), respectively. Analysis of temporal trends revealed that septal mass reduction was positively associated with LGE infarct size and transmural or left-sided septal infarct location at both 1 and 6 months. Remote mass reduction was associated with infarct location at 6 months but not with LGE infarct size. By linear regression analysis, percentage remote mass reduction correlated significantly with LVOT gradient reduction at 6-month follow-up (P = 0.03).

Conclusion
Left ventricular remodeling after ASA occurs early and progresses on midterm follow-up, modulated by CMR infarct size and location. Remote mass reduction is associated with infarct location and correlates with reduction of the LVOT pressure gradient. Thus, myocardial hypertrophy in HOCM is, at least in part, afterload dependent and reversible and is not exclusively caused by the genetic disorder.
In symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM), alcohol septal ablation (ASA) has been shown an attractive alternative to surgical myectomy. During the ASA procedure, a chemical infarction is artificially induced, which results in regional thinning of the interventricular septum, an increase in outflow tract diameter, and a decrease in pressure gradient and subsequent symptomatic improvement. Some studies have also shown a regression of remote hypertrophy after successful reduction of the outflow tract gradient. This may contribute to symptom relief by improving diastolic function. However, reports have not been conclusive, which may be explained in part by the fact that echocardiographic calculations of left ventricular (LV) mass use geometric assumptions that may not be valid in patients with large differences in regional wall thickness. Cardiac MRI (CMR) allows direct mass calculations and has shown high reproducibility in detecting small changes in global and regional mass. Using CMR, we recently showed significant reductions in septal and nonseptal, remote myocardial mass 1 month after septal ablation. A progressive reduction in remote mass beyond the early phase would provide strong evidence for the suggested relation between relief of outflow tract gradient and LV remodeling. The aim of this study was therefore to evaluate changes and potential modulating factors of these changes in LV remodeling during the first 6 months after ASA.

METHODS

Patients
The study protocol was approved by the Committee on Research Involving Human Subjects and the Medical Ethics Committee of the VU University Medical Center, Amsterdam. Consecutive patients with HOCM scheduled to undergo ASA in 1 of 2 referral centers in the Netherlands were candidates for the study. The indication for ASA was based on a significant LV outflow tract (LVOT) gradient as documented by Doppler echocardiography (≥ 50 mmHg), and New York Heart Association (NYHA) functional
class II, III, or IV despite medical treatment. All patients had basal septal hypertrophy with systolic anterior motion of the anterior mitral valve leaflet.

The ASA procedure was described previously. Exclusion criteria were any absolute or relative contra-indication to CMR (e.g. pacemaker, claustrophobia), atrial fibrillation, or failure to give informed consent. Thirty-three consecutive patients were initially enrolled. Four patients were excluded from the final analysis: 3 required pacemaker implantation because of development of complete atrioventricular block after ASA, and 1 declined to return for the follow-up examinations. The remaining 29 patients formed the final study group. Four patients had resting gradients < 50 mmHg, which increased to ≥ 50 mm Hg with provocation with the Valsalva maneuver. A successful ablation procedure was defined as > 50% gradient reduction at 1 month compared to baseline. The baseline characteristics of these patients are listed in Table 1.

**Table 1. Patient characteristics (n=29).**

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 16 (16 / 13)</td>
</tr>
<tr>
<td>NYHA functional class (II / III / IV)</td>
<td>3.0 ± 0.4 (3 / 24 / 2)</td>
</tr>
<tr>
<td>Dyspnea / angina / syncope</td>
<td>29 / 13 / 5</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
</tr>
<tr>
<td>β-blockers / calcium antagonists</td>
<td>19 / 16</td>
</tr>
<tr>
<td>Antiarrhythmic drugs / diuretics</td>
<td>5 / 2</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. Abbreviations: NYHA = New York Heart Association.

**CMR**

CMR was performed at baseline and 1 and 6 months after ASA with a 1.5-T clinical scanner (Sonata, Siemens, Erlangen, Germany), and a 4-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 with a segmented steady state, free precession, gradient-echo sequence in 3
long-axis views (2-, 3-, and 4-chamber view) and in multiple short-axis views every 10 mm, which covered the entire LV from base to apex. At 1-month follow-up, late gadolinium enhancement (LGE) CMR was also performed. LGE images were acquired 15 to 20 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA in the same views as in cine CMR, with a 2D, segmented, inversion-recovery, prepared gradient-echo sequence.\textsuperscript{16-18}

**CMR analysis**

*Analysis of late gadolinium enhanced images*  Contrast-to-noise ratio of the hyperenhanced area versus a remote non-enhanced myocardial area was measured on the short-axis slice that demonstrated the largest area of hyperenhancement. Contrast-to-noise ratio was calculated with regions of interest and was defined as \(\frac{\text{SI}_{\text{hyperenhanced}} - \text{SI}_{\text{remote}}}{\text{noise}}\), where SI is signal intensity and noise is expressed as the SI standard deviation in a background region of interest.

Infarct size after ASA was measured by manual tracing of the hyperenhanced area, which was defined as the area within the septal myocardium with pixel SI values > 4SD of remote, non-enhanced myocardium.\textsuperscript{15} 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.

*Analysis of cine images*  For all patients, CMR scans were placed in random order after the identity markers were removed. Interventricular septal (IVS) wall thickness at the infarct site was measured at end diastole in the short-axis view that included the center of the infarct. The slice position and measurement site was copied from the contrast image to the corresponding cine view of the 1-month study and subsequently to the baseline and 6-month studies. Wall thickness at the septal, anterior, lateral, and inferior wall, and LV end-diastolic and end-systolic dimensions were all determined in the midventricular short-axis view (level of papillary muscles). Left atrial dimension was measured at end-systole in the 3- and 4-chamber views. LV end-diastolic volume, end-systolic volume, ejection fraction, and total and septal myocardial mass were quantified.
with the MASS software package (Medis, Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders were outlined manually in end-diastolic and end-systolic frames of all short axis slices. Papillary muscles were included in the assessment of left ventricular mass. The IVS was defined as the myocardium between the anterior and posterior junctions of the right ventricle to the LV. Remote, nonseptal LV mass was calculated as LV total mass – IVS mass.

**Statistical analysis**

Results are expressed as mean ± SD. Longitudinal data analysis was performed with generalized estimating equations (GEE’s) for serial measurements to evaluate the changes in LV wall thickness, LV end-diastolic and end-systolic dimensions, left atrial dimension, LV volumes and LV myocardial mass after ASA. In the GEE modeling, time was added as a categorical variable indicated by dummies. In addition to the crude development over time, the influence of certain modulating variables (eg. age, LVOT pressure gradient before ablation, infarct location, and infarct size measured by late gadolinium enhancement CMR and cardiac enzyme release) was investigated. First, the particular variables were added one at the time to the GEE models to investigate whether the intercept of the development was influenced, i.e., whether the variables are stand-alone factors that affected the trend. Second, the interactions between the particular variables and time (i.e., the 2-time dummy variables) were added to the models to investigate whether the development over time was different for the different levels of the modulating variables. All GEE analysis were performed with STATA version 7. Linear regression analysis was used to analyze the relationship between LVOT gradient reduction and remote mass reduction. Reproducibility measurements of the acquisition and the intraobserver and interobserver variability (expressed as intraclass coefficients) were calculated in 10 consecutive patients by 2 independent observers. All statistical analyses were performed with SPSS version 11.0, and significance was set at a probability value $\leq 0.05$. 
RESULTS

Mean age was 52 ± 16 years (range 18 to 71 years), 13 of the 29 patients were female. All but one were receiving one or more drugs (β-blocker \([n=19]\), calcium-channel blockers \([n=16]\) or antiarrhythmic drugs \([n=5]\)). After ASA, the use of medications was reduced markedly (only 10 patients were still taking β-blockers, and 5 of these were receiving half the dosage compared with baseline; only 7 patients were still taking calcium-channel blockers). During the ablation procedure, ethanol was injected in 1 septal artery in 27 patients, and 2 septal arteries were ablated in 2 patients. The mean volume of ethanol injected per artery was 3.2 ± 1.5 mL. Before ASA, 25 patients had a resting LVOT pressure gradient ≥ 50 mmHg (87 ± 19 mmHg; range 52 to 120 mm Hg), and 4 had provocable gradients (68 ± 24 mm Hg; range 50 to 100 mmHg). The mean dynamic pressure gradient decreased from 85 ± 21 mm Hg to 21 ± 27 mm Hg at 1 month after septal ablation therapy \((P < 0.01)\). Four patients had unsuccessful gradient reduction. NYHA functional class improved significantly; at baseline, 3 patients were in NYHA class II, 24 were in class III, and 2 were in class IV. At 1-month follow-up, 13 patients were without symptoms, 12 were in NYHA class II, and 4 were in class III. Three patients were lost for the 6-month follow-up examination: 1 underwent a redo-procedure for recurrent symptoms and significant resting gradient, 1 underwent pacemaker implantation due to late development of complete atrioventricular block after ASA, and 1 had a car accident with multiple bone fractures that made the CMR examination impossible.

Infarct size and location

The mean peak creatine kinase (CK) and CK-MB release were 1612 ± 707 U/L (range 381-3366 U/L) and 217 ± 95 U/L (range 55-371 U/L), respectively. At 1-month follow-up, a clearly demarcated area of hyperenhancement was visualized in the basal part of the IVS in all patients (Figure 1). Mean myocardial infarct size was 20 ± 9 g (range 5 - 42 g) and involved 11 ± 5% of the total LV mass and 32 ± 16% of the septal myocardial
Figure 1. Example of cine and late gadolinium enhancement (LGE) cardiac magnetic resonance images in a patient with HOCM at baseline and at 1 and 6 months after ASA. Distribution of hypertrophy is demonstrated in end-diastolic basal short-axis (SA) view and 3- and 4-chamber views. Thinning of basal interventricular septum is evident, as well as widening of LVOT. Second row demonstrates hyperenhancement in basal septum, which reflects ethanol-induced myocardial infarction 1 month after ASA. FU = follow-up; LGE = late gadolinium enhancement; chview = chamber view.
mass at one month after ASA. As we previously reported, the infarct extended transmural throughout the IVS in 20 patients, was located exclusively on the LV side of the IVS in 2 patients, and was located exclusively on the right ventricular side of the IVS in 7 patients. No patient had evidence of infarct-related hyperenhancement outside the target area.

**Changes in LV wall thickness and dimensions**

End-diastolic IVS thickness measured at the infarct site decreased from 2.1 ± 0.4 cm at baseline to 1.4 ± 0.4 cm at 1 month and 1.0 ± 0.4 cm at 6 months. Anterior, lateral and inferior wall thickness at the mid-LV level also progressively decreased at 1 and 6 months after ASA. Whereas LV end-diastolic dimensions remained unchanged, end-systolic dimensions increased during follow-up. Furthermore, left atrial end-systolic dimensions in both three- and four-chamber views decreased significantly (Table 2).

Longitudinal data analysis of the influence of modulating variables revealed that none influenced the intercept of the development. However, the following modulators affected development over time of the 2D parameters. (1) A larger decrease in IVS wall thickness was associated with a larger contrast-enhanced infarct size ($P < 0.01$ at 1 and 6 months, respectively), higher levels of CK ($P < 0.01$ and $P = 0.06$, respectively) and CK-MB release ($P = 0.03$ and $P = 0.08$, respectively), and transmural or left-sided septal infarct location ($P < 0.01$ at 1 and 6 months, respectively). (2) The decrease of remote myocardial wall thickness was not significantly influenced by any of the variables. (3) A larger increase of LV end-systolic dimension was associated with larger LGE infarct size at 1-month follow-up only ($P = 0.04$). (4) A larger decrease of left atrial dimension was associated with larger contrast-enhanced infarct size ($P = 0.03$) and with transmural or left-sided septal infarct location ($P = 0.03$).

**Changes in LV mass, volumes, and function**

Changes in 3D LV parameters are summarized in Table 3. LV end-diastolic volumes remained unchanged at follow-up, whereas end-systolic volumes increased
significantly. Consequently, there was a small decrease in LV ejection fraction at 1 and 6 months. Total LV myocardial mass decreased from 216 ± 62 g at baseline to 200 ± 60 g

### Table 2. Cardiac dimensions at baseline and after ASA.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month FU</th>
<th>6 months FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter</td>
<td>47.8 ± 5.3</td>
<td>47.8 ± 5.8</td>
<td>47.5 ± 5.7</td>
</tr>
<tr>
<td>LV end-systolic diameter</td>
<td>25.8 ± 4.0</td>
<td>29.3 ± 6.0*</td>
<td>28.8 ± 5.7*</td>
</tr>
<tr>
<td>LA end-systolic diameter (3 chv)</td>
<td>50.9 ± 6.5</td>
<td>46.2 ± 6.8*</td>
<td>45.7 ± 7.2*</td>
</tr>
<tr>
<td>LA end-systolic diameter (4 chv)</td>
<td>59.2 ± 7.4</td>
<td>54.5 ± 6.3*</td>
<td>52.4 ± 5.8*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. *P < 0.01 vs. baseline.

(-8%) at 1 month and 170 ± 45 g (-21%) at 6 months, respectively. Septal myocardial mass decreased from 75 ± 23 g to 68 ± 22 g (-10%) at 1 month and to 58 ± 19 g (-23%) at 6 months. Non-septal mass decreased from 141 ± 41 g at baseline to 132 ± 40 g (-6%) at 1 month and to 111 ± 27 g (-21%) at 6 months’ follow-up. The relative reduction of septal and non-septal myocardial mass is shown in Figure 2.

Also with respect to these 3D parameters, the intercept of the development was not influenced by the modulating variables. Time-dependent trends were as follows: (1) A larger decrease of septal mass was associated with a larger contrast-enhanced infarct size (P<0.01 at 1 and 6 months, respectively), higher levels of CK (P = 0.05 at 1 month and P < 0.01 at 6 months) and CK-MB (P = 0.17 at 1 month and P = 0.03 at 6 months),

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and transmural or left-sided septal location ($P < 0.01$ at 1 and 6 months, respectively).

(2) A larger decrease of remote mass was associated with transmural or left-sided septal infarct location ($P = 0.12$ at 1 month, and $P < 0.01$ at 6 months), but not with contrast-enhanced septal infarct size.

Reproducibility measurements of image acquisition and intraobserver and interobserver variability were performed in 10 consecutive patients by two independent observers. intraclass coefficients of reproducibility and of intraobserver and interobserver variability ranged between 0.98 and 0.99 for end-diastolic volume, end-systolic volume, ejection fraction and myocardial mass, respectively.

Table 3. LV volumes and mass at baseline and after ASA.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-month Follow-Up</th>
<th>6-month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume [mL]</td>
<td>170 ± 42</td>
<td>167 ± 41</td>
<td>169 ± 39</td>
</tr>
<tr>
<td>LV end-systolic volume [mL]</td>
<td>54 ± 16</td>
<td>57 ± 18*</td>
<td>59 ± 17†</td>
</tr>
<tr>
<td>Stroke volume [mL]</td>
<td>116 ± 29</td>
<td>110 ± 25*</td>
<td>110 ± 25</td>
</tr>
<tr>
<td>LV ejection fraction [%]</td>
<td>69 ± 5</td>
<td>67 ± 5†</td>
<td>66 ± 4†</td>
</tr>
<tr>
<td>Total LV mass [g]</td>
<td>216 ± 62</td>
<td>200 ± 60†</td>
<td>170 ± 45†</td>
</tr>
<tr>
<td>Septal mass [g]</td>
<td>75 ± 23</td>
<td>68 ± 22†</td>
<td>58 ± 19†</td>
</tr>
<tr>
<td>Non-septal mass [g]</td>
<td>141 ± 41</td>
<td>132 ± 40†</td>
<td>111 ± 27†</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. *$P < 0.05$ vs baseline, †$P < 0.01$ vs baseline.

**Correlation between regional mass reduction and gradient reduction**

Linear regression analysis showed a significant association between percent reduction of remote mass and LVOT pressure gradient reduction at 6-month follow-up ($r = 0.44$, $P = 0.03$; *Figure 3*). No correlation was found between percent reduction of septal mass and LVOT gradient reduction ($r = 0.31$, $P = 0.12$).
DISCUSSION

Quantitative analysis without geometrical assumptions revealed a significant early and progressive LV remodeling with reduction in septal and remote myocardial mass throughout the 6-month follow-up period. Whereas diastolic volumes remained unchanged, systolic volumes increased, and left atrial dimensions decreased. CMR-derived infarct size and location were found to modulate the early temporal changes of the parameters that reflect the LV remodeling process. Whereas reduction in septal mass was associated with infarct size and location, reduction in remote mass was associated with infarct location and not with infarct size and correlated significantly with reduction of the LVOT tract gradient. Because absence of hyperenhancement outside the target septal area excluded alcohol-induced injury on remote myocardium, remote myocardial remodeling may be attributed to the reduction in outflow tract gradient and the concomitant decrease in LV wall stress. The association with infarct location became apparent at 6 months only, which reflects a more gradual process of remodeling than in the IVS, where the association is immediately apparent at 1 month and remains at 6 months because of the directly inflicted infarct. Also, the reversibility of the remote myocardial mass implies that hypertrophy in HOCM is not caused exclusively by the genetic disorder but is induced, at least in part, secondary to the dynamic obstruction of the outflow tract.

Changes in septal and remote myocardial mass after ASA

The genetic disorder in HOCM leads to a primary molecular abnormality. Expression of mutant sarcomeric proteins (contractile units) leads to a decrease in generation of force, which results in impaired cardiac myocyte contractility and increased cardiac myocyte stress.21 In the subset of patients with LVOT obstruction, increased LV pressure and wall stress induces secondary hypertrophy that may be (partly) reversible after elimination of the LVOT obstruction.9,22 Previous echocardiographic studies have shown ambiguous results with respect to reduction of LV posterior wall thickness.7-11,23-26 Tomographic techniques such as electron-beam computed tomography and CMR may be more
LV remodeling after ASA in HOCM

accurate and reproducible than echocardiographic measurements and LV mass calculations. Electron-beam computed tomography showed septal mass reduction 1 week after ASA, and found reduced remote mass at 4 to 6 months of follow-up. The results of the present study using CMR are in line with these observations and additionally revealed factors associated with the remodeling process over time. Not surprisingly, septal wall thickness and septal mass demonstrated immediate and progressive reduction associated with the alcohol-induced infarct size and location at 1 and 6 months. Reduction of remote wall thickness, however, although significant at 1 and 6 months, was not associated with infarct size and location at any time, whereas reduction of the mass did show an association with infarct location at 6 months. 2D measurements of wall thickness performed regionally probably are less precise than 3D mass calculation of the entire remote myocardium in revealing the association with the gradual process of remote remodeling over time.

Figure 2. Percent changes in septal and remote LV myocardial mass after ASA at 1- and 6-month follow-up.
The early onset of regression of remote hypertrophy may be explained by an immediate reduction in the expression of cardiac growth factors. Nagueh et al.\textsuperscript{22} found decreased expression of myocardial tumor necrosis factor-$\alpha$ in patients with HOCM 6 weeks after relief of the LVOT obstruction by ASA. The decreased cardiac levels of tumor necrosis factor-$\alpha$ were accompanied by a reduction in myocyte size and in the amount of interstitial collagen.

The causative relation between regression of remote hypertrophy and reduction in outflow tract gradient is supported by the correlation that reached statistical significance at 6-month follow-up. The relation between septal mass reduction and outflow tract gradient reduction was not significant. Septal mass reduction is the result of the chemically induced infarction and subsequent scar formation, a direct process that is not secondary to the reduction in LVOT gradient. This is supported by the positive time-dependent interactions of septal mass reduction with contrast-enhanced infarct size: a larger reduction in septal myocardial mass was associated with larger contrast-enhanced infarcts. In contrast, the change in remote mass was not associated with contrast-enhanced infarct size but only with transmural or left-sided septal location.

**Changes in dimensions and volumes after ASA**

Previous studies have generally found significant increases in both end-systolic and end-diastolic dimensions.\textsuperscript{9,27} We found a significant increase in end-systolic dimension and a small but significant increase in LV end-systolic volume at 6-month follow-up. These changes may be explained by septal thinning and reduced thickening as a result of the ethanol-induced infarction. LV end-diastolic dimension and volume remained unchanged at both follow-up CMR scans. As a result, there was a small decrease in LV ejection fraction at 6 months.

Left atrial dimensions decreased after ASA, larger decreases being associated with larger contrast-enhanced infarcts. The decrease is likely to reflect the effect of the ASA procedure on improving diastolic function.

A general limitation of the study is the difficulty in obtaining blinded measurements, because effects of treatment by ASA are often clearly visible for the experienced CMR
observer, which thus introduces observer bias in judgment of post-ablation wall thickness. In the present study, we did not measure the increase in LVOT area, which has been shown to have a close relationship with the decrease in septal wall thickness.\textsuperscript{28}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Correlation between reduction in remote myocardial mass and LVOT gradient reduction at 6-month follow-up.}
\end{figure}

These measurements, however, require imaging of the LVOT in multiple orientations, with addition of flow quantification acquisitions, which is time consuming. In our imaging protocol, we gave priority to the addition of acquisitions of delayed imaging after gadolinium. Furthermore, only left atrial dimensions were measured, which are likely to be less accurate than volume determinations. However, our primary aim was not to measure the effects of ASA on left atrial volumes, and consequently, the CMR protocol did not include full coverage for measuring left atrial volume. We merely
sought to provide circumstantial evidence in support of improvement of diastolic function. Moreover, dimensions may be more meaningful to clinicians than left atrial volumes.

In summary, we used CMR to evaluate left ventricular remodeling after ASA in symptomatic patients with HOCM. LV remodeling occurred early and progressed on mid-term follow-up, modulated by infarct size and location. Regression of non-septal, remote myocardial mass was significantly associated with infarct location and correlated with the reduction in LVOT pressure gradient at 6-month follow-up. Our findings support the theory that myocardial hypertrophy in patients with HOCM is, at least in part, afterload dependent and reversible and thus is not caused exclusively by the genetic disorder.

ACKNOWLEDGMENTS

This study was supported by grant 99.203 from the Netherlands Heart Foundation and the Interuniversity Cardiology Institute of the Netherlands.
REFERENCES


Septal Ablation in Hypertrophic Obstructive Cardiomyopathy Improves Systolic Myocardial Function in the Lateral (Free) Wall

A follow-up study using CMR tissue tagging and 3D strain analysis

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J.P.A. Kuijer
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(Eur Heart J 2006;27:2833-2839)
ABSTRACT

Aims
Alcohol septal ablation (ASA) has been successful in the treatment of symptomatic hypertrophic obstructive cardiomyopathy (HOCM). The aim of this study is to evaluate the effects of ethanol-induced myocardial infarcts on regional myocardial function using cardiac magnetic resonance (CMR) tissue tagging and 3-dimensional (3D) strain analysis.

Methods and Results
In nine patients (age 49 ± 19 years) who underwent ASA, CMR was performed prior to and 6 months after the procedure. Regional myocardial mass was evaluated using cine imaging. Myocardial tagging was used to calculate systolic 3D myocardial strain values. These strain values were used to calculate the shortening index (SI), a robust parameter for myocardial contraction. Maximum end-systolic (ES) SI and systolic SI rate were quantified in three circumferential segments: septum, adjacent and remote (lateral) myocardium. Compared with baseline, septal and non-septal mass decreased at follow-up (from 72 ± 27 g to 59 ± 21 g; \( P = 0.008 \) and from 131 ± 34 g to 109 ± 30 g; \( P = 0.008 \), respectively). In the septum, maximum ES SI and SI rate remained unchanged after ASA. In adjacent myocardium, ES SI remained unchanged, whereas SI rate improved (from \(-56.5 \pm 21.1 \% \text{s} \) to \(-70.0 \pm 16.7 \% \text{s} \); \( P = 0.02 \)). Both ES SI and SI rate improved significantly in remote myocardium (from \(-16.9 \pm 2.8 \% \) to \(-18.8 \pm 3.2 \% \); \( P = 0.02 \), and from \(-70.3 \pm 9.2 \% \text{s} \) to \(-86.1 \pm 15.0 \% \text{s} \); \( P = 0.01 \), respectively).

Conclusion
Reduction of left ventricular (LV) outflow tract obstruction in symptomatic HOCM is associated with a significant reduction in myocardial mass and improvement of intramural systolic function in the lateral (remote) wall, indicating reversed LV remodeling.
Recently, alcohol septal ablation (ASA) has been successfully introduced to treat symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM). Ablation by ethanol infusion into septal branches of the left anterior descending coronary artery (LAD) results in an artificially induced septal myocardial infarction with regional myocardial wall thinning, a decrease of the pressure gradient and left ventricular (LV) wall stress, and subsequently a relief of symptoms.

Using cardiac magnetic resonance (CMR) imaging, we have demonstrated that both septal and non-septal (remote) myocardial mass reduction can be found as early as 1 month after ASA in patients with HOCM, and mass reduction continues afterwards. The reduction in remote LV mass supports the theory that myocardial hypertrophy in HOCM is not exclusively caused by the genetic disorder, but is also afterload-dependent and reversible. Few studies report on the effects of afterload reduction on regional myocardial function in these patients. The reduction of the Tei index, an echocardiographic Doppler parameter reflecting both systolic and diastolic LV functions, was found, suggesting improved myocardial performance. Echocardiographic strain rate imaging has shown reduced systolic function in the peri-infarct septal zone and preserved systolic function in the remote non-ischemic septal zone directly after ASA.

CMR tissue tagging with three-dimensional (3D)-strain analysis is an established method for quantification of regional myocardial function. When the technique is used in patients with myocardial infarction because of coronary artery disease, differences in function between infarcted and non-infarcted (remote) regions can be detected accurately. These regional differences in function are thought to play a role in post-infarct remodeling. However, it is unknown to what extent a therapeutic and artificially induced infarction affects regional function in patients with obstructive cardiomyopathy with an associated pre-existent abnormal structure of the myocardium. On the one hand, the ethanol-induced infarction may cause a further decline in regional myocardial function and trigger an adverse remodeling process. On the other hand, beneficial effects due to the reduction of the pressure gradient might counterbalance deleterious effects from ASA.
The purpose of this study is to determine the effect of ASA on regional myocardial function. Three-dimensional myocardial strain was quantified in nine patients with symptomatic HOCM before and 6 months after successful ASA.

METHODS

Patients
The study protocol was approved by the Committee on Research Involving Human Subjects and by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands. Consecutive patients with HOCM scheduled for ASA and eligible for CMR imaging were studied. Exclusion criteria were any absolute or relative contraindication to MR imaging (e.g. pacemaker and claustrophobia), atrial fibrillation (AF), or failure to give informed consent. The indication for ASA was based on a significant LV outflow tract (LVOT) pressure gradient as documented by echocardiography and symptoms [New York Heart Association (NYHA) functional class II-IV], despite medical treatment. The septal ablation procedure has been described previously.10

One patient was excluded for enrolment because of AF. In total, 19 consecutive patients underwent 3D CMR myocardial tagging in addition to a standard CMR imaging protocol that included volume and mass measurements and late gadolinium enhancement (LGE) imaging. Four patients were lost to 6 months follow-up: three required pacemaker implantation because of the development of complete atrioventricular block (in one patient, 3 months after the procedure) and one declined to return for the follow-up examination. Two patients with recurrent symptoms were excluded from the final analysis because no successful gradient reduction (>50%) was achieved after septal ablation procedure. One of these patients underwent a redo procedure, and the other underwent a surgical myectomy in combination with mitral leaflet extension because the patient had an enlarged anterior mitral valve leaflet with residual systolic anterior motion and severe mitral regurgitation. In four patients, strain
analysis was not possible because of poor image quality: in one patient, breath-holding was inadequate, one patient developed claustrophobia during the follow-up CMR, one patient had motion artifacts on FU CMR, and in one patient, tag lines faded very quickly. Results of the standard CMR protocol in a larger group (29 patients) have been published elsewhere.11 This article reports the results of the subgroup that underwent CMR tagging.

**Echocardiography**

The LVOT pressure gradient was documented by Doppler echocardiography. In symptomatic patients, a pressure gradient ≥ 50 mmHg at rest was considered to be significant. One patient with a resting gradient < 50 mmHg was symptomatic. In this patient, provocation was applied using the Valsalva maneuver, resulting in a pressure gradient of ≥ 50 mmHg.

**CMR image acquisition**

CMR was performed prior to and 6 months after ASA on a 1.5 T clinical scanner (Sonata, Siemens, Erlangen, Germany), using a four-element phased-array receiver coil. All images were acquired with ECG gating and during repeated single breath-holds of 10 to 15 seconds depending on heart rate.

Cine images were acquired using a segmented steady-state free precession gradient-echo sequence in three long-axis views (2-, 3-, and 4-chamber view) and in multiple short-axis views every 10 mm, covering the entire LV from base to apex.

LGE images were acquired 15-20 minutes after intravenous administration of 0.2 mmol/kg gadolinium-diethylene-triamine pentaacetic acid (DTPA) in the same views used in cine CMR, using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence.19 The LGE images were acquired in five patients at baseline and in all patients at follow-up CMR and were used to make sure that the ablation procedure was successful and that the infarct region was limited to the septum.10

CMR tissue tagging using spatial modulation of magnetization15,16 was applied to create markers (tags) non-invasively within the myocardium for the calculation of myocardial strain. Five to six parallel LV short-axis- and three long-axis-tagged images
were acquired by a spoiled gradient echo sequence. A temporal resolution of 30 ms was achieved by application of a view-sharing technique.

**CMR image analysis**

*Analysis of cine images (global ventricular function)*  Global LV function parameters, including end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and total and septal myocardial mass, were quantified using the MASS software package (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders were traced manually in end-diastolic and end-systolic frames of all short-axis slices. Papillary muscles were included in the assessment of LV mass. The septum was defined as the myocardium between the anterior and posterior junctions of the right ventricle (RV) to the LV.

*Analysis of tagged images (regional myocardial function)*  The short-axis- and long-axis-tagged images were processed using a dedicated software package (SPAMMVU, University of Pennsylvania, PA, USA). After combining the short-axis and long-axis myocardial motion, tetrahedrons (of myocardium) were created and the 3D strain values of these tetrahedrons were calculated. The normal strains were expressed in a cardiac coordinate system defined by the radial, circumferential and longitudinal directions. The strain components were computed with respect to these three directions.

The radial strain is defined as the relative change in the length of a radial line segment and expressed in per cent value. Positive radial strains represent the local contribution to wall thickening. Negative values for radial strain imply local wall thinning. Circumferential and longitudinal strains were defined similar to the radial strain, quantifying the change in length in the circumferential and longitudinal directions, respectively. Negative circumferential and longitudinal strains represent local shortening. From each strain parameter, peak values were determined and expressed as ‘maximum systolic strain’.

Systolic strain rate was defined as the slope of the strain curve averaged from five time frames (from 90 to 210 ms after the QRS interval), reflecting myocardial deformation over time.
The circumferential-longitudinal shear strain gives the change in the angle between the circumferential and longitudinal line segments. This circumferential-longitudinal shear angle can be interpreted as the local contribution to global LV torsion.

The shortening index (SI) reflects the geometric mean of fractional one-dimensional shortening within the circumferential-longitudinal plane. The SI is negative for muscle shortening and directionally insensitive within the plane. SI turns out to be a robust parameter to quantify myocardial contraction.\(^{22}\)

Strain values were averaged from base to apex, and strain parameters were calculated in six circumferential segments; anterior, antero-lateral, postero-lateral, inferior, infero-septal and antero-septal. The infero- and antero-septal segments were considered to be target area for the ethanol-induced myocardial infarction. The anterior and inferior segments were considered as ‘adjacent’ myocardium and the antero- and postero-lateral segments as ‘remote’ area.

**Statistical analysis**

Results are expressed as mean ± SD. Non-parametric testing (Wilcoxon signed rank test) was used to evaluate changes in LV volumes, in global and regional myocardial mass, and in segmental strain values before and 6 months after ASA. All tests were two-sided and the data were aggregated on the patient level. Linear regression analysis was used to analyze the relationship between percentage of remote mass reduction and improvement of the SI.

All statistical analyses were performed with SPSS version 11.0, and significance was set at a value of \(P \leq 0.05\).
Table 1. Cardiac dimensions and mass at baseline and after ASA.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Δ-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS thickness at infarct site [mm]</td>
<td>19.9 ± 2.6</td>
<td>9.8 ± 2.6</td>
<td>10.1 ± 5.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Wall thickness at mid LV level [mm]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal wall</td>
<td>17.3 ± 5.5</td>
<td>15.3 ± 5.8</td>
<td>2.0 ± 1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Anterior wall</td>
<td>9.8 ± 3.8</td>
<td>8.8 ± 3.8</td>
<td>1.0 ± 0.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Lateral wall</td>
<td>7.3 ± 1.1</td>
<td>6.3 ± 1.0</td>
<td>1.0 ± 0.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>9.9 ± 4.0</td>
<td>9.1 ± 3.9</td>
<td>0.8 ± 0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>LV end-diastolic volume [mL]</td>
<td>160 ± 42</td>
<td>160 ± 36</td>
<td>0.4 ± 16</td>
<td>0.86</td>
</tr>
<tr>
<td>LV end-systolic volume [mL]</td>
<td>51 ± 16</td>
<td>55 ± 18</td>
<td>-3.7 ± 9</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke volume [mL]</td>
<td>109 ± 26</td>
<td>104 ± 21</td>
<td>4.8 ± 14</td>
<td>0.34</td>
</tr>
<tr>
<td>LV ejection fraction [%]</td>
<td>68 ± 3</td>
<td>66 ± 5</td>
<td>2.2 ± 5</td>
<td>0.33</td>
</tr>
<tr>
<td>Total LV mass [g]</td>
<td>203 ± 59</td>
<td>168 ± 50</td>
<td>34.9 ± 16</td>
<td>0.008</td>
</tr>
<tr>
<td>Septal mass [g]</td>
<td>72 ± 27</td>
<td>59 ± 21</td>
<td>13.1 ± 7</td>
<td>0.008</td>
</tr>
<tr>
<td>Non-septal mass [g]</td>
<td>131 ± 34</td>
<td>109 ± 30</td>
<td>21.8 ± 11</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. Δ, actual changes from baseline at 6-month follow-up. Abbreviations: LV = left ventricular.
Table 2. Maximum systolic strains in septal, adjacent, and remote myocardium before and 6 months after ASA in HOCM.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Δ-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septum (antero- and inferoseptal wall)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch (Err)</td>
<td>10.3 ± 5.9</td>
<td>9.9 ± 5.0</td>
<td>0.4 ± 5.9</td>
<td>0.722</td>
</tr>
<tr>
<td>Circumferential shortening (Ecc)</td>
<td>-10.8 ± 3.6</td>
<td>-11.0 ± 3.0</td>
<td>0.2 ± 1.3</td>
<td>0.672</td>
</tr>
<tr>
<td>Longitudinal shortening (Ell)</td>
<td>-7.6 ± 4.4</td>
<td>-8.7 ± 3.8</td>
<td>1.1 ± 2.5</td>
<td>0.172</td>
</tr>
<tr>
<td>Torsion (Acl) [degrees]</td>
<td>7.4 ± 3.1</td>
<td>7.0 ± 3.4</td>
<td>0.4 ± 1.6</td>
<td>0.594</td>
</tr>
<tr>
<td>SI</td>
<td>-9.7 ± 4.2</td>
<td>-10.2 ± 3.5</td>
<td>0.5 ± 1.8</td>
<td>0.587</td>
</tr>
<tr>
<td><strong>Adjacent (anterior and inferior wall)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch (Err)</td>
<td>15.0 ± 5.4</td>
<td>18.0 ± 4.2</td>
<td>3.0 ± 2.8</td>
<td>0.021</td>
</tr>
<tr>
<td>Circumferential shortening (Ecc)</td>
<td>-15.6 ± 5.5</td>
<td>-16.4 ± 4.1</td>
<td>0.8 ± 2.9</td>
<td>0.528</td>
</tr>
<tr>
<td>Longitudinal shortening (Ell)</td>
<td>-8.0 ± 4.0</td>
<td>-10.6 ± 3.9</td>
<td>2.6 ± 1.8</td>
<td>0.011</td>
</tr>
<tr>
<td>Torsion (Acl) [degrees]</td>
<td>8.2 ± 2.8</td>
<td>8.4 ± 2.1</td>
<td>0.2 ± 1.9</td>
<td>0.767</td>
</tr>
<tr>
<td>SI</td>
<td>-12.1 ± 4.4</td>
<td>-13.6 ± 3.7</td>
<td>1.4 ± 2.3</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>Remote (antero- and inferolateral wall)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch (Err)</td>
<td>25.5 ± 4.6</td>
<td>27.9 ± 5.6</td>
<td>2.4 ± 4.4</td>
<td>0.137</td>
</tr>
<tr>
<td>Circumferential shortening (Ecc)</td>
<td>-22.1 ± 3.6</td>
<td>-23.5 ± 3.3</td>
<td>1.5 ± 2.0</td>
<td>0.050</td>
</tr>
<tr>
<td>Longitudinal shortening (Ell)</td>
<td>-11.2 ± 3.3</td>
<td>-13.5 ± 4.5</td>
<td>2.3 ± 3.0</td>
<td>0.041</td>
</tr>
<tr>
<td>Torsion (Acl) [degrees]</td>
<td>8.3 ± 2.1</td>
<td>8.8 ± 1.3</td>
<td>0.5 ± 2.5</td>
<td>0.859</td>
</tr>
<tr>
<td>SI</td>
<td>-16.9 ± 2.8</td>
<td>-18.8 ± 3.2</td>
<td>1.8 ± 1.8</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. Δ, actual changes from baseline at 6-month follow-up.
RESULTS

Mean age was 49 ± 19 years (range 18 to 71, 5 males). Nine patients received one or more drugs [beta-blocker (n = 4), calcium-channel blockers (n = 7) or anti-arrhythmic drugs (n = 2)]. After ASA, the dose-regimen in patients using a beta-blocker was continued; in two of the four patients receiving both calcium-channel blockers and beta-blockers pre-ablation, the calcium-channel blockers were discontinued at follow-up. During the ablation procedure, ethanol was injected in one septal artery in all patients. The mean volume of ethanol injected during the ASA procedure was 4.1 ± 1.4 mL (range 2.0 - 5.0 mL). The mean peak CK and CK-MB release were 1881 ± 831 U/L (range 991-3366) and 249 ± 103 U/L (range 100-376), respectively. In five patients, LGE imaging was performed at baseline. In four patients, small patchy areas of hyperenhanced myocardium were observed in the ventricular wall and predominantly at the junctions of the RV and LV free walls. None of the patchy areas were transmural, and no hyperenhanc-

Figure 1. LGE image in a short-axis view. Hyperenhancement in the interventricular septum indicates the procedure-related infarct.
cement was observed in the antero- and postero-lateral segments (remote area). The number of focal areas of hyperenhancement per patient was 4.7 ± 1.0, representing an average mass of 0.5 ± 0.5 g per area. Using LGE imaging after the procedure, none of the patients had evidence of infarct-related hyperenhancement outside the interventricular septum. An example of the infarcted area as imaged by LGE is shown in Figure 1.

The dynamic pressure gradient decreased from 91 ± 15 mmHg to 11 ± 15 mmHg at 6 months after the procedure (P < 0.001). All patients reported subjective improvement of exercise tolerance. The mean NYHA functional class improved significantly from 2.8 ± 0.4 to 1.3 ± 0.5 (P < 0.001) at 6 months of follow-up.

**Global ventricular function**

Regional wall thickness, LV volumes, EF, and mass are summarized in Table 1. The decrease in regional wall thickness in the infarcted, adjacent, and remote myocardium was significant in all three regions. A significant mass reduction was observed both in the target septal myocardium and in the non-septal myocardium (both P = 0.008).

**Regional myocardial function**

*Systolic strain*

*Figure 2* shows an example of end-systolic short-axis tagged images at baseline and 6 months after the septal ablation procedure. *Figure 3* represents a 3D functional display of circumferential shortening (Ecc), computed from five short-axis and three long-axis-tagged views at baseline and at 6 months of follow-up. Three-dimensional strain parameters are listed in Table 2. Before ASA, myocardial function in the target septal area was significantly reduced when compared with the remote myocardium (for SI, –9.7 ± 4.2 versus –16.9 ± 2.8; P = 0.008). After the artificially induced septal infarction, no significant changes of maximum systolic strain were observed in the septum.
Table 3. Maximum systolic strain rate in septal, adjacent, and remote myocardium at baseline and 6 months after ASA in HOCM.

<table>
<thead>
<tr>
<th>Max systolic strain rate (strain/s)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Δ-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antero- and inferoseptal wall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch rate (Err) (strain/s)</td>
<td>46.7 ± 22.4</td>
<td>48.6 ± 17.7</td>
<td>2.0 ± 23.1</td>
<td>0.953</td>
</tr>
<tr>
<td>Circumferential shortening rate (Ecc) (strain/s)</td>
<td>-55.2 ± 19.2</td>
<td>-54.2 ± 11.8</td>
<td>1.0 ± 13.6</td>
<td>0.833</td>
</tr>
<tr>
<td>Longitudinal shortening rate (Ell) (strain/s)</td>
<td>-35.2 ± 17.3</td>
<td>-41.2 ± 19.0</td>
<td>6.0 ± 11.6</td>
<td>0.159</td>
</tr>
<tr>
<td>Torsion rate (Acl) (degrees/s)</td>
<td>33.5 ± 10.8</td>
<td>29.8 ± 12.2</td>
<td>3.7 ± 7.4</td>
<td>0.214</td>
</tr>
<tr>
<td>SI rate (strain/s)</td>
<td>-46.8 ± 19.2</td>
<td>-49.5 ± 14.4</td>
<td>2.7 ± 8.4</td>
<td>0.399</td>
</tr>
<tr>
<td><strong>Anterior and inferior wall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch rate (Err) (strain/s)</td>
<td>62.8 ± 20.2</td>
<td>81.5 ± 10.8</td>
<td>18.7 ± 16.2</td>
<td>0.021</td>
</tr>
<tr>
<td>Circumferential shortening rate (Ecc) (strain/s)</td>
<td>-72.9 ± 25.1</td>
<td>-81.9 ± 15.9</td>
<td>9.0 ± 20.2</td>
<td>0.236</td>
</tr>
<tr>
<td>Longitudinal shortening rate (Ell) (strain/s)</td>
<td>-37.5 ± 17.5</td>
<td>-50.5 ± 17.5</td>
<td>13.0 ± 6.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Torsion rate (Acl) (degrees/s)</td>
<td>35.7 ± 9.9</td>
<td>42.3 ± 8.1</td>
<td>6.6 ± 8.2</td>
<td>0.028</td>
</tr>
<tr>
<td>SI rate (strain/s)</td>
<td>-56.5 ± 21.1</td>
<td>-70.0 ± 16.7</td>
<td>13.5 ± 11.9</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Antero- and inferolateral wall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial stretch rate (Err) (strain/s)</td>
<td>90.5 ± 17.0</td>
<td>111.1 ± 30.3</td>
<td>20.6 ± 26.2</td>
<td>0.049</td>
</tr>
<tr>
<td>Circumferential shortening rate (Ecc) (strain/s)</td>
<td>-91.9 ± 9.3</td>
<td>-102.3 ± 10.8</td>
<td>10.4 ± 11.8</td>
<td>0.034</td>
</tr>
<tr>
<td>Longitudinal shortening rate (Ell) (strain/s)</td>
<td>-42.8 ± 13.0</td>
<td>-62.5 ± 20.5</td>
<td>19.7 ± 15.3</td>
<td>0.012</td>
</tr>
<tr>
<td>Torsion rate (Acl) (degrees/s)</td>
<td>.............34.8 ± 10.0</td>
<td>41.7 ± 6.2</td>
<td>6.9 ± 11.7</td>
<td>0.11</td>
</tr>
<tr>
<td>SI rate (strain/s)</td>
<td>70.3 ± 9.2</td>
<td>-86.1 ± 15.0</td>
<td>15.8 ± 13.9</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. Δ, actual changes from baseline at 6-month follow-up.
In the adjacent myocardium, radial stretch and longitudinal shortening improved significantly ($P = 0.02$ and $P = 0.01$, respectively), whereas circumferential shortening remained unchanged. There was a trend in the improvement of the SI, although it did not reach statistical significance.

In the remote area, significant improvement in myocardial shortening was observed, reflected by the improved SI (from $-16.9 \pm 2.8$ to $-18.8 \pm 3.2$; $P = 0.017$). Circumferential shortening and longitudinal shortening both improved significantly ($P = 0.049$ and $P = 0.041$, respectively), whereas radial stretch remained unchanged.

**Figure 2.** End-systolic short-axis-tagged CMR images in a HOCM patient at baseline (a) and 6 months after ASA (b).

### Systolic strain rates at baseline vs. follow-up

Before ASA, systolic strain rate in the septal target area was significantly lower when compared with that in the adjacent and remote areas (both $P = 0.011$) (Figure 4). Six months after the ablation procedure, systolic strain rates in the infarct area did not change compared with baseline (Table 3). However, in adjacent myocardium, all strain rates except the circumferential shortening strain rate increased. In remote myocardium, strain rates for all strain parameters except for the circumferential-longitudinal shear strain increased at follow-up (Table 3).
Correlation between remote mass reduction and shortening index

Linear regression analysis showed a strong positive correlation (not statistically significant) between per cent reduction of non-septal mass and per cent improvement in SI in remote myocardium at 6 months of follow-up ($r = 0.61$, $P = 0.08$).

![Figure 3. 3D functional display of circumferential shortening ($E_{cc}$), calculated from five short-axis and three long-axis views at baseline (a) and at 6 months after ASA (b).](image)

DISCUSSION

This is the first study that used CMR tissue tagging and 3D-strain analysis to evaluate the effects on regional myocardial function in symptomatic patients with HOCM after ASA. As reported previously, both septal- and non-septal myocardial mass significantly decreased as early as 1 month after septal ablation and progressed on mid-term follow-up.10,11 This reduction in non-septal LV mass supports the concept that myocardial hypertrophy in HOCM is partly afterload-dependent and reversible. Using CMR tissue tagging, we have now demonstrated that ASA improves regional intramural myocardial systolic function in the adjacent and remote myocardium. Both observations support the concept that a reduction of LVOT obstruction in symptomatic HOCM leads to reversed LV remodeling after ASA. The observed positive correlation between the percentage remote
mass reduction and the improvement of remote myocardial contraction supports the hypothesis of a reversed remodeling process, although statistical significance could not be reached, which may be related to the relatively small sample size of the study population.

**Effect of ASA on myocardial mass**

Although HCM is a genetic disorder leading to a primary molecular abnormality resulting in an increase of wall thickness, elimination of the LVOT obstruction will result in a decrease of LV pressure and wall stress and subsequently in a regression of LV hypertrophy. Accordingly, previous echocardiographic studies have demonstrated a significant reduction in LV mass at 1 year after septal ablation. This was not only due to thinning of septal myocardium, but also due to a decrease of wall thickness throughout the LV circumference. Using CMR, we demonstrated that reversed LV remodeling after ASA was associated with septal infarct location and correlated with reduction of the LVOT pressure gradient. On the basis of these findings, it was concluded that myocardial hypertrophy in HOCM is at least in part afterload-dependent and reversible and not exclusively caused by the genetic disorder.

**Effect of ASA on regional myocardial function**

In patients with hypertrophic cardiomyopathy, it has been previously demonstrated that circumferential and longitudinal shortening are decreased in the septal, anterior, and inferior (hypertrophied) myocardial segments, compared with normal subjects. Our 3D-strain data acquired prior to the ablation procedure are in line with these observations.

Compared with baseline, systolic myocardial strains and systolic strain rates in the target septal myocardium did not change after ASA. Prior to intervention, septal systolic deformation was already markedly reduced, and the formation of scar tissue as result of the ethanol-ablation procedure did not lead to further impairment of the regional septal function. In contrast, Abraham et al. found reduced systolic function in the peri-infarct septal zone and preserved systolic function in the non-ischemic septal zone after
Figure 4. Typical example of regional SI strain curves in a HOCM patient pre- and post-ASA.
septal ablation, using strain rate imaging with echocardiography. These findings are not contradictory to the present results because, first, in our study, the strain analysis was calculated for the whole septum without differentiation between infarcted and non-infarcted subregions. Secondly, the difference in outcome is probably also related to the fact that their patient group was studied directly after the septal ablation procedure, at which time myocardial stunning may have played a role. In contrast, our CMR tagging data were acquired 6 months after ASA, and the improvement in function of the non-ischemic septal myocardium may compensate for a loss of function of the infarcted septal tissue.

SI, which incorporates both circumferential- and longitudinal shortening, has been introduced as a robust parameter to quantify myocardial contraction. In the present study, SI tended to increase in the adjacent myocardium and improved significantly in remote myocardium at 6 months of follow-up, thereby demonstrating improved remote myocardial contraction. Similar findings were reported after afterload reduction as a result of valve replacement in patients with aortic stenosis. In that study, normalization of the LV torsion and a significant increase in basal circumferential shortening were observed 12 months after surgical valve replacement. Furthermore, the increase in the circumferential shortening correlated with a decrease in the LV mass index at 1-year follow-up. This also agrees with our finding of a positive correlation between non-septal mass reduction and the percent increase of the SI of remote myocardium at 6-month follow-up.

In a previous echocardiographic study, a decrease of the Tei index was found, a Doppler parameter reflecting both systolic and diastolic LV function, in the mid-term follow-up, indirectly suggesting improvement of myocardial performance. Again, this is in agreement with the results of the current study.

LIMITATIONS

Only a limited number of patients with HOCM were studied, and the results should be interpreted with care. Nevertheless, the 3D-strain data convincingly indicate that...
significant changes in regional myocardial function occur in the non-infarcted (adjacent and remote) myocardial regions after ASA. Furthermore, we have chosen to aggregate the data on the patient level instead of using (for instance) multilevel analysis. This was mainly done because it improves the interpretability of the results.

In view of the limited number of patients, it must be realized that CMR tissue tagging, especially when a four-dimensional (3-D + time) reconstruction of the LV is made, is accompanied by a time-consuming post-processing procedure. The number of tracked points within the LV wall using CMR tissue (line) tagging with a tag-tag distance of 6-7 mm is limited, which, in turn, restricts the transmural coverage of the strain calculations. More recently developed strain imaging techniques, which allow for automated strain analysis, may overcome these limitations in future studies. These methods, however, were not available to us at the start of the study. Furthermore, we confined our measurements to systolic deformation, whereas HCM is also associated with impairment of diastolic function. Further work is needed to study the changes in diastolic function after ASA.

In conclusion, we demonstrated that reduction in remote myocardial mass after ASA was accompanied by a significant improvement of regional systolic myocardial function, supporting a concept of structural and functional reversed LV remodeling.

ACKNOWLEDGMENTS

This study was supported by grant 99.203 from the Netherlands Heart Foundation and the Interuniversity Cardiology Institute of the Netherlands.
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Septal Alcohol Ablation in Hypertrophic Obstructive Cardiomyopathy: Improving Cardiac Function by Generating a Myocardial Scar

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(Eur Heart J 2007;28:1270-1271)
LETTER TO EDITOR

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We read with great interest the article by Van Dockum et al.\textsuperscript{1} on the improvement of systolic myocardial function of the left ventricular (LV) lateral (free) wall in patients with hypertrophic cardiomyopathy (HCM) after alcohol septal ablation (ASA). Using cardiac magnetic resonance (CMR) tissue tagging and three-dimensional strain analysis, the authors found that both maximum end-systolic strain index and systolic strain index rate improved significantly in remote myocardium.

This report shows for the first time that the reduction of the LV outflow tract gradient in symptomatic patients with obstructive HCM treated with ASA is associated with the improvement in intramural systolic function in the lateral wall remote from the ablated area. Although this is an interesting finding, there is a main point to be addressed in relation with the procedure. In Figure 1, there is a clear demonstration of a gross gadolinium late myocardial hyperenhancement in the interventricular septum attributable to the procedure, although there is no report of direct comparison with pre-procedural gadolinium myocardial enhancement in the same patient. It would be very interesting if myocardial hyperenhancement data derived by CMR before and after ASA could be provided by the authors. Such data would be very helpful to estimate the impact of ASA on the development of new fibrosis superimposed on an already existing one.

The most dramatic event in HCM is sudden death attributable to arrhythmogenic substrate owing to cardiac fibrosis. Cell death with subsequent healing and replacement fibrosis induced by ASA eventually leads to an increase in the already existing myocardial fibrosis, creating a substrate more prone to arrhythmic events. In other words, we are trying to improve patient’s symptoms by generating a scar tissue that may be deleterious long life, especially for young subjects. Data on sudden death after ASA are lacking. Therefore, as stated by Maron,\textsuperscript{2} avoidance of septal ablation in young patients is probably prudent, especially if the surgical option is feasible.
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REPLY

We thank Efthimiadis et al. for their comments on our article concerning the improvement of systolic myocardial function in the lateral (free) wall in hypertrophic obstructive cardiomyopathy after alcohol septal ablation (ASA) which was studied using CMR tissue tagging and 3D strain analysis.\(^1\) In previous work we have demonstrated that in symptomatic patients with HOCM, left ventricular remodeling after ASA occurs early and progresses on midterm follow-up, and total left ventricular mass reduction exceeded septal mass reduction.\(^2\) The remote mass reduction was correlated with the LVOT pressure gradient reduction, and thus we concluded that myocardial hypertrophy in HOCM is, at least in part, afterload dependent and reversible and is not exclusively caused by the genetic disorder.

In this article we have studied in a subgroup of patients the regional changes in septal, adjacent and remote systolic myocardial function by calculating the shortening index, a combined strain parameter reflecting myocardial contraction. We have demonstrated for the first time that reduction in symptomatic HOCM patients achieved by ASA not only was associated with a significant reduction in myocardial mass, but also with an improvement of intramural systolic myocardial function in the lateral (remote) wall, supporting the concept of reversed LV remodeling.
Previously, our group has demonstrated that contrast-enhanced CMR allowed detailed evaluation of size and location of septal myocardial infarction induced by ASA, and that the infarction size was correlated with clinical indexes of infarct size. In this study we have demonstrated that contrast-enhanced imaging data derived in approximately 60% of the study-group pre-ASA after administration of gadolinium-DTPA contained only small pre-existing foci of delayed myocardial hyperenhancement, representing myocardial fibrosis and other pathologic changes in the myocardial wall (e.g. disarray, inflammation, edema, myolysis, and necrosis). Compared with these hyperenhanced area-size assessed preablation, the infarct-size induced by ASA was about ten-fold larger. In this respect, the induced myocardial infarct after septal ablation therapy enlarges the already existing arrhythmogenic substrate in HOCM patients. However, an electrophysiology report in high risk patients after ASA have not indicated an increased arrhythmic substrate necessitating higher rates of implanting defibrillators. Although ventricular tachycardia and sudden death have been reported after ASA, these clinical features characterize the natural course hypertrophic cardiomyopathy irrespective of therapeutic LVOT gradient reduction. Further studies are necessary to evaluate the long-term effects of ASA with respect to ventricular arrhythmias and sudden cardiac death. Our goal in the near future must be developing additional tools to identify the high-risk HCM patients, regardless of a potential intervention for LVOT obstruction, in whom defibrillator implantation is justified.

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2. van Dockum WG, Beek AM, ten Cate FJ, ten Berg JM, Bondarenko O, Götte MJW, Twisk JWR, Hofman MBM, Visser CA, van Rossum AC. Early onset and progression of left


Impact of Alcohol Septal Ablation on Left Anterior Descending Coronary Artery Blood Flow in Hypertrophic Obstructive Cardiomyopathy

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ABSTRACT

Objectives
The aim of this study was to evaluate the effects of alcohol septal ablation (ASA) on coronary blood flow in symptomatic hypertrophic obstructive cardiomyopathy (HOCM) using cardiac MR (CMR) coronary flow measurements.

Background
CMR flow mapping enables quantification of coronary blood flow in a noninvasive way. Both left ventricular outflow tract (LVOT) gradient reduction and myocardial scarring after ASA are expected to influence left anterior descending (LAD) coronary blood flow.

Methods
Cine, late gadolinium enhancement (LGE) imaging and breath-hold CMR phase contrast velocity mapping were performed at baseline and 1 and 6 months after ASA in seven patients. Changes of coronary blood flow were related to left ventricular (LV) mass reduction, enzyme release, volume of ethanol administered, LVOT gradient reduction, and LV rate pressure product (LVRPP).

Results
A significant mass reduction was observed both in the target septal myocardium and in the total myocardium (both $P < 0.01$). Mean myocardial infarct size was $23 \pm 12$ g (range 7.3 to 41.6 g). LVRPP decreased from 13268 ± 2212 to 10685 ± 3918 at 1 month ($P = 0.05$) and 9483 ± 2496 mmHg beats/min at 6-months follow-up ($P < 0.01$). LAD coronary blood flow decreased from $100 \pm 37$ mL/min at baseline to $84 \pm 54$ mL/min ($P = 0.09$) at 1 month and $67 \pm 33$ mL/min at 6 months follow-up ($P < 0.01$). A significant correlation was found between the change in LVRPP and LAD coronary flow at one month follow-up ($r = 0.83$, $P = 0.02$). LGE-infarct size tended to modulate the blood flow changes over time ($P = 0.12$); no correlation was observed between enzyme release, volume of ethanol or both septal- and total mass reduction and coronary blood flow.

Conclusion
The reduction in coronary blood flow is primarily associated with diminished LV loading conditions, whereas the induction of metabolically inactive myocardial scar tissue by ASA did not significantly influence the changes in coronary blood flow.
Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease characterized by hypertrophy of the myocardium in the absence of any systemic or other cardiac disease, which predominantly affects the interventricular septum. In approximately one quarter of patients, the disease process of asymmetrical septal hypertrophy is complicated by left ventricular outflow tract (LVOT) obstruction due to bulging of the thickened septum into the outflow tract and abnormal anterior motion of the mitral valve during systole. The inherent augmented loading conditions result in increased basal levels of oxygen utilization and coronary blood flow. Coronary vasodilator reserve in HCM, however, is impaired due to coronary microvascular dysfunction. Consequently, metabolic demand frequently exceeds supply, leading to myocardial ischemia and its related symptoms.

Alcohol septal ablation (ASA) has shown to successfully relieve LVOT obstruction with subsequent relief of symptoms in patients with hypertrophic obstructive cardiomyopathy (HOCM). This is achieved by ethanol infusion into septal branches of the left anterior descending coronary artery (LAD) resulting in an artificially induced septal myocardial infarction with regional myocardial wall thinning and widening of the LVOT. The decrease of the pressure gradient leads to a reduction of the left ventricular (LV) end-diastolic pressure and LV wall stress. Myocardial scarring and reduced metabolic demand caused by diminished loading conditions after ASA are expected to influence LAD blood flow. Data to substantiate this hypothesis, however, are lacking.

Phase-contrast velocity measurements with cardiac magnetic resonance imaging (CMR) allows non-invasive quantification of coronary blood flow. The present study was conducted to serially assess the impact of ASA on LAD resting blood flow using CMR phase-contrast imaging. Furthermore, the determinants of flow changes were explored.
METHODS

Patients
Patients with HOCM scheduled to undergo ASA and eligible for CMR imaging were studied. The indication for ASA was based on a significant left ventricular outflow tract (LVOT) pressure gradient as documented by echocardiography and symptoms (NYHA functional class II-IV), despite medical treatment. Exclusion criteria were any absolute or relative contra-indication to CMR imaging (e.g. pacemaker, claustrophobia), atrial fibrillation, or failure to give informed consent. The septal ablation procedure has been described previously.8 Results of the standard CMR protocol in a larger group have been published elsewhere.8,12

Patients underwent phase-contrast velocity measurements in addition to a standard CMR imaging protocol that included volume and mass measurements and delayed contrast-enhanced imaging prior to ASA and at one and six months after treatment. A total number of 16 patients were included in the study. Due to imaging artifacts and missing follow-up data, 7 patients completed the study protocol and are reported in the current paper. One patient with recurrent symptoms underwent a redo procedure at four months after the initial ASA because no successful gradient reduction was achieved (>50%).

The study protocol was approved by the Committee on Research Involving Human Subjects and the Medical Ethics Committee of the VU University Medical Center, Amsterdam.

Echocardiography
The LVOT pressure gradient was documented by Doppler echocardiography. In symptomatic patients a pressure gradient ≥ 50 mmHg at rest was considered to be significant. One patient was symptomatic with a resting gradient < 50 mmHg. In this patient, provocation was applied using the Valsalva maneuver resulting in a pressure gradient during provocation of ≥ 50 mmHg.
CMR image acquisition

CMR was performed at baseline and 1 and 6 months after ASA on a 1.5 Tesla clinical scanner (Sonata, Siemens, Erlangen, Germany), using a 4-element phased-array receiver coil. Cine- and delayed contrast-enhanced images were acquired with ECG gating and during repeated single breath-holds of 10 to 15 seconds depending on heart rate, coronary phase contrast velocity images were acquired using breath holds of 20 to 30 seconds. Cine images were acquired using a segmented steady-state free precession gradient-echo sequence in three long-axis views (2-, 3-, and 4-chamber view) and in multiple short-axis views every 10 mm, covering the entire left ventricle from base to apex.

Late gadolinium enhancement (LGE) images were acquired 15-20 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA in the same views used in cine CMR, using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence. The LGE images were acquired to determine infarct size and location after the ablation procedure and to make sure that the infarct region was limited to the septum.

Coronal and transversal scout images were acquired to localize the left anterior descending (LAD) artery. Two-dimensional double oblique coronary angiographic sequence was obtained perpendicular to the direction of LAD flow with a breath-hold technique during inspiration. CMR phase contrast velocity measurements were performed in a plane perpendicular to the proximal LAD within one breath-hold (spatial resolution 1.2 x 1.4 x 5.5 mm³). A segmented k-space technique was used to obtain multiple phase-encoding steps (5) for each frame within the cardiac cycle, resulting in an acquisition window of 95 ms. Other imaging parameters included a temporal resolution using echo sharing of 63 ms, a flip angle of 25°, a field of view of 300 x 244 mm², an echo time of 3.6 ms and a scan duration of 20 heart beats. The encoding velocity was set between 40 - 125 cm/s. Heart rate and systemic arterial pressure were monitored during the imaging procedure.
CMR image analysis

Analysis of cine images  Global LV function parameters, including end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), total and septal myocardial mass were quantified using standard software (MASS, Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders were traced manually in end-diastolic and end-systolic frames of all short-axis slices. Papillary muscles were included in the assessment of left ventricular mass. The septum was defined as the myocardium between the anterior and posterior junctions of the right to the left ventricle.

Analysis of contrast-enhanced images  Infarct size after ASA was measured by manual tracing of the hyperenhanced area within the septal myocardium with pixel signal intensity (SI) values > SI of remote, non-enhanced myocardium + 4 SD. Central dark zones within the area of hyperenhancement were included.

Analysis of left anterior descending blood flow  Flow analysis was performed with the standard software (FLOW, Medis Medical Imaging Systems, Leiden, the Netherlands). The contour of the cross-sectioned LAD was visually determined on a magnitude image at mid diastole, the phase of the cardiac cycle in which the highest image quality was obtained. The area of the region of interest was kept constant over the cardiac cycle and repositioned at each time frame on the magnitude image. The averaged velocities were measured within each contour on the corresponding phase contrast image. The velocity of the myocardial motion was obtained by drawing a contour in the myocardial tissue close to the vessel of interest. To correct for cardiac motion the velocity within this contour was subtracted from the flow velocity within the vessel, resulting in a net forward velocity. The product of area and velocity yields instantaneous volumetric blood flow. Plots were made of phasic velocity and volume of blood flow versus time in the cardiac cycle. Because a prospectively triggered electrocardiographic gating technique was used, no measurements could be obtained during the final 50 ms of the cardiac cycle. Data sets were interpolated over the whole cardiac cycle.
Statistical analysis

Results are expressed as mean ± SD. Longitudinal data analysis was performed using generalized estimating equations (GEE) for serial measurements to evaluate the changes in heart rate, systolic (SBP) and diastolic blood pressures (DBP), septal and total LV myocardial mass, LV volumes, LVOT pressure gradient (LVOTG), LV rate pressure product (LVRPP = (SBP + LVOTG) * heart rate) and LAD coronary artery blood volume flow from baseline to 1 and 6 months after ASA. In the GEE-modeling, time was added as a categorical variable indicated by dummies. Besides the crude development over time, the influence of certain modulating variables (e.g. amount of ethanol administered, cardiac enzyme release, infarct size measured by contrast-enhanced CMR, and serial change in the LVRPP) was investigated by adding the particular variables one at the time to the GEE-models in order to investigate whether the ‘intercept’ of the development was influenced. GEE analysis was also used to estimate the correlation between the changes in LAD blood volume flow and the changes in septal and total LV mass, LV volumes, ejection fraction, infarct size measured by contrast-enhanced CMR, and LVRPP. Linear regression analysis was used to analyze the relationship between LAD blood volume flow and the amount of ethanol administered, cardiac enzyme release and infarct size measured with contrast-enhanced CMR. All GEE-analyses were performed with STATA (version 9); linear regression analyses were performed with SPSS version 14.0, and significance was set at a $P$-value ≤ 0.05.

RESULTS

Mean age was 46 ± 12 years (range 32 to 64, 5 males). The mean volume of ethanol injected during the ASA procedure was 2.9 ± 1.2 mL (range 1.5 to 5.0 mL). The mean peak CK and CK-MB release were 1385 ± 410 U/L (range 807 to 1997 U/L) and 207 ± 54 U/L (range 112 to 292 U/L), respectively. All patients were receiving 1 or more drugs (beta-blockers [$n=5$], calcium channel blockers [$n=5$], and antiarrhythmic drugs [$n=1$]), which were kept constant during the follow-up period.
Figure 1. Typical example of an anatomical (A) and corresponding velocity encoding CMR image (B) of the LAD coronary artery at mid-diastole [arrow]. The graph represents the coronary blood flow curve of this patient.
At baseline, LVOT pressure gradient was ≥ 50 mmHg in six patients (87 ± 11 mmHg; range 52 to 100 mmHg), and one had a provocab le gradient (26 mmHg at rest, 80 mmHg after Valsalva maneuver). A gradient reduction of more than 50% was achieved in 6 patients at a follow-up period of 6 months. All except one patient reported subjective improvement of exercise tolerance. The mean NYHA functional class improved significantly from 2.9 ± 0.4 to 1.8 ± 0.9 at 1 month and 1.3 ± 0.7 at 6 months after ASA (P < 0.01 for trend).

Using delayed contrast-enhanced imaging after the procedure, septal infarct was demonstrated in all patients, none of the patients had evidence of infarct-related hyperenhancement outside the interventricular septum. Mean myocardial infarct size was 23 ± 12 g (range 7.3 to 41.6 g).

**Hemodynamic parameters**

Changes in hemodynamic parameters are summarized in Table 1. Compared to baseline, no change was observed in heart rate, systolic and diastolic arterial blood pressure at 1 and 6 months after ASA. The LVOT gradient decreased from 79 ± 25 mmHg to 34 ± 48 mmHg at 1 month to 23 ± 35 mmHg at 6 months after the procedure (P < 0.01). LVRPP decreased from 13268 ± 2212 to 10685 ± 3918 at 1 month (P = 0.05) and 9483 ± 2496 mmHg·beats/min at 6-months follow-up (P < 0.01).

**LV volumes, ejection fraction, regional mass**

CMR derived values of LV volumes, EF, and regional myocardial mass are listed in Table 1. Ejection fraction decreased slightly, but significantly (P < 0.01), owing to a significant increase in LV ESV (P < 0.05) over time after treatment. In addition, a significant mass reduction was observed both in the target septal myocardium and in the total myocardium (both P < 0.01).

**Correlation between changes in LAD blood flow and other parameters**

LAD coronary blood flow decreased from 100 ± 37 mL/min at baseline to 84 ± 54 mL/min at 1 month (P = 0.09) and 67 ± 33 mL/min at 6 months follow-up (P < 0.01;
The following modulators affected development over time: a larger decrease of coronary blood flow was associated with a larger decrease of the LVOT pressure gradient ($P = 0.01$ for trend) and LVRPP ($P < 0.01$ for trend). Figure 2 graphically displays the linear regression analysis between the change in LVRPP and LAD coronary flow at one month follow-up ($r = 0.83$, $P = 0.02$).

Coronary blood flow was not influenced by the amount of ethanol administered during the ASA procedure or cardiac enzyme release, although LGE infarct size tended to modulate the blood flow changes over time ($P = 0.12$). In addition, changes in myocardial mass did not exert influence on the observed flow changes.

Table 1. Basal hemodynamics and CMR derived parameters at baseline and after ASA.

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>1-month Follow-up</th>
<th>6-months Follow-up</th>
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<tr>
<td><strong>Hemodynamic parameters</strong></td>
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<tr>
<td>Heart rate</td>
<td>65 ± 5</td>
<td>65 ± 6</td>
<td>64 ± 6</td>
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<tr>
<td>Systolic blood pressure [mmHg]</td>
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<td>Diastolic blood pressure [mmHg]</td>
<td>74 ± 13</td>
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<td>LV outflow gradient [mmHg]</td>
<td>79 ± 25</td>
<td>34 ± 48*</td>
<td>23 ± 35*</td>
</tr>
<tr>
<td>LVRPP [mmHg·beats / min]</td>
<td>13268 ± 2212</td>
<td>10685 ± 3918§</td>
<td>9483 ± 2496*</td>
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<tr>
<td><strong>CMR derived parameters</strong></td>
<td></td>
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<tr>
<td>LAD blood flow [mL/min]</td>
<td>100 ± 37</td>
<td>84 ± 54</td>
<td>67 ± 33*</td>
</tr>
<tr>
<td>LV end-diastolic volume [mL]</td>
<td>164 ± 46</td>
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<td>Total LV mass [g]</td>
<td>238 ± 81</td>
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<tr>
<td>Septal mass [g]</td>
<td>77 ± 25</td>
<td>69 ± 25*</td>
<td>64 ± 23*</td>
</tr>
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</table>

Values expressed as mean ± SD. *$P < 0.01$ vs baseline, § $P \leq 0.05$ vs. baseline, || $P < 0.01$ vs. 1 month

Abbreviations: LV = left ventricular; RPP = rate pressure product.
DISCUSSION

This is the first study that used CMR coronary flow quantification, using phase-contrast velocity measurements, to evaluate the effects of ASA on coronary blood flow in symptomatic patients with HOCM. Our data revealed a significant reduction of resting LAD coronary artery blood flow during the ensuing months of follow-up. We additionally explored the role of changes in hemodynamics and scar size induced by ablation therapy in relation to the observed changes in coronary blood flow over time.

Figure 2. Serial changes in LAD coronary blood volume flow at baseline and at 1 and 6 months after ASA, $P < 0.01$ for trend.

Resting coronary blood flow is adjusted at the microvascular level in response to varying demand through autoregulation of the coronary microcirculation. As heart rate and LV end-systolic cavity pressure are the major determinants of the energy requirement of the myocardium, these loading conditions primarily dictate the level of basal coronary blood flow. The latter holds true under physiological as well as pathophysiological conditions, such as in patients with HCM. In the present study,
alcohol ablation significantly reduced the hemodynamic loading conditions, i.e. LVRPP. These changes were solely determined by the reduction in LVOT pressure gradient as heart rate and arterial blood pressure were unaffected by the procedure. As hypothesized, the changes in coronary blood flow were directly related to these alterations in loading conditions. These observations are in line with Cannon et al. who elegantly demonstrated a reduction of great cardiac vein flow as well as global myocardial oxidative metabolism 6 months after surgical myectomy in symptomatic HOCM patients. Similar to the present findings, these changes were directly governed by the magnitude of outflow tract pressure gradient relief. More recently, using cardiac positron emission tomography, Jörg-Ciopor et al. revealed a lower perfusion per grams of septal tissue after surgical myectomy compared with medically treated patients. Moreover, Rajappan and co-workers have shown that these physiological flow changes can also be observed after gradient reduction through valve replacement in patients with aortic valve stenosis.

The fundamental approach of alcohol ablation is based on artificially inducing a fairly large myocardial infarct in the hypertrophied myocardial septum. The procedure itself results in obliteration of a septal branch of the LAD. Furthermore, the generated scar is metabolically inactive relative to the previous myocardium subtended by the sacrificed coronary artery. As the current flow measurements were presumably performed proximal to the ablation site of the LAD, just distal to the junction of the left main coronary artery and circumflex, these conditions in theory are expected to influence coronary blood flow. Nonetheless, a clear relationship between LGE-estimated infarct size and changes in coronary blood flow could not be established, although a trend was observed ($P = 0.12$). It therefore appears, that the reduction in coronary blood flow is primarily instigated by altered LV loading conditions as opposed to the induction of metabolically inactive myocardial scar tissue. The lack of impact of scar on coronary blood flow is not well understood and requires further investigation.
Figure 3. Correlation between the changes in LVRPP and LAD coronary blood flow.

Regardless of the underlying mechanisms that are responsible for the observed decrease in coronary blood flow, the observation is important from a pathophysiological point of view. The occurrence of coronary microvascular dysfunction in HCM has been firmly established and shown to be of important prognostic relevance. The reduction in loading conditions by ASA and the concomitant reduction in basal coronary flow could result in enhanced coronary flow reserve, although the effects of ASA on hyperemic flow remain to be elucidated. In other words, relief of resting loading conditions may result in less frequent episodes of ischemia for a given level of exertion, and could explain the reported reduction for anginal symptoms after treatment, and may ultimately contribute to the suggested beneficial effects on prognosis.
LIMITATIONS

Only a limited number of patients with HOCM were studied, and the results should be interpreted with care. Nevertheless, the coronary flow data convincingly indicate significant changes in coronary blood flow in the LAD coronary artery after ASA.

The single breath-hold phase contrast velocity quantification technique used in this study has some limitations. First, it requires a long breath-hold (25-30 s), which is difficult to obtain in every patient. Second, the position of the breath-holding may vary, which can result in a different image position from the originally planned. Third, the technique has a large acquisition window which results in some image blurring because of cardiac motion. Newer techniques such as the use of spiral imaging reduced this acquisition window and will result in a higher accuracy, but this could not be achieved on the system used. The slice thickness (5.5 mm) is not likely to importantly affect the through plane velocity measurement, because the imaged plane was positioned perpendicular to a relative straight segment of the proximal left anterior descending coronary artery. Fourth, the in-plane spatial resolution of the CMR acquisition is limited with respect to the vessel diameter, which is expected to cause variability on the cross-sectional area assessment, and thereby on the volume flow.

In our study, the same methodology was used before and after septal ablation. Attention was given to position the CMR slice-position in an identical position within the left anterior descending coronary artery. Thus, by using each patient as his own control, errors in methodology are expected to remain constant and thus allow valid observation of the impact of the ablation procedure on coronary artery flow.

In conclusion, we demonstrated that the reduction of the LVOT pressure gradient by alcohol septal ablation in symptomatic patients with HOCM was accompanied by a significant decrease in left anterior descending coronary resting blood flow. No significant correlation was found between the artificially induced septal myocardial infarct size and the reduction in coronary blood flow over time. These findings support
the hypothesis that diminished loading conditions after successful relief of the LVOT pressure gradient decreases the oxygen utilization and consequently, coronary blood flow after ASA.

ACKNOWLEDGMENTS

This study was supported by grant 99.203 from the Netherlands Heart Foundation and the Interuniversity Cardiology Institute of the Netherlands.
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Extent of Myocardial Infarction and Reverse Remodeling Assessed by CMR in Patients With and Without Right Bundle Branch Block following ASA for Obstructive HCM

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(Am J Cardiol. 2007;99:563-567)
ABSTRACT

Percutaneous alcohol septal ablation (ASA) is an established technique for the relief of refractory symptoms in patients with obstructive hypertrophic cardiomyopathy. Most subjects develop right bundle branch (RBBB) block after ASA, but it is not known whether these patients have similar infarct characteristics, which may influence left ventricular (LV) pressure gradient reduction and reverse remodeling, compared to those patients without RBBB. Twenty-seven consecutive patients (15 men, 12 women; mean age 62 ± 16 years) were studied with electrocardiography and cardiac magnetic resonance imaging (CMR) at baseline and 1 and 6 months (n=25) after ASA. Infarct size and location were determined at 1 month by late gadolinium enhancement CMR. The 17 subjects who developed RBBB tended to have larger infarcts (CK-MB 251 ± 92 vs. 148 ± 97 U/L, P = 0.03; CMR mass 22.5 ± 9.3 vs. 16.6 ± 8.3 g, P = 0.1) and were more likely to have sustained anterior and inferior septal transmural infarctions (9 of 17 vs. 1 of 10, P = 0.03) than those without RBBB. Those who developed RBBB had greater LV mass reductions at 6 months (46 ± 26 vs. 29 ± 13 g, P = 0.04) despite similar reductions in LV pressure gradients (64 ± 31 vs. 56 ± 32 mmHg). In conclusion, patients who develop RBBB after ASA tend to have more extensive transmural septal infarctions and greater reverse remodeling than those without RBBB.
Percutaneous alcohol septal ablation (ASA) is an established alternative technique to surgical myectomy for the relief of refractory symptoms in patients with hypertrophic obstructive cardiomyopathy (HOCM).\textsuperscript{1-3} ASA is associated with improvement in symptoms\textsuperscript{4,5}, reductions in pressure gradients and left ventricular mass.\textsuperscript{6,7} Both ASA and surgical myectomy are associated with atrioventricular conduction abnormalities.\textsuperscript{3} After ASA, most patients develop right bundle branch block (RBBB),\textsuperscript{8-10} and there is an approximate 10% risk of requiring permanent pacing, particularly if there is pre-existing left bundle branch block.\textsuperscript{3,11} No previous report has investigated the effect of extent and location of the septal myocardial infarction on the development of RBBB and subsequent effects on LV reverse remodeling after ASA. We hypothesized that patients with new RBBB would have larger evidence of transmural septal infarctions and achieve similar reductions in LV mass as those without RBBB after ASA.

METHODS

The inclusion and exclusion criteria for participation in this prospective study have been published in detail,\textsuperscript{12} as well as the main results of reverse remodeling for the whole group.\textsuperscript{13} Patient numbers and main electrocardiographic findings at each time point of the study are outlined in Figure 1. The 2 subjects with preexisting RBBB were excluded from the present results, which therefore include 27 and 25 patients with complete data at 1 and 6 months follow-up, respectively.

Standard 12-lead electrocardiograms were recorded at 25 mm/s and 1 mV/cm on a MAC 1200 machine (GE Medical Systems, Milwaukee, Wisconsin, USA) on the same day as cardiac magnetic resonance (CMR) imaging examinations at baseline and 1 and 6 months after ASA. The PR and QRS intervals were measured automatically to the nearest 2ms by the on board computer. A single investigator (GPM) blinded to the results of the CMR imaging examinations interpreted the electrocardiograms for the presence of conduction abnormalities. CMR imaging was performed using a 1.5 Tesla clinical
scanner (Sonata or Vision, Siemens Medical Systems, Erlangen, Germany). The detailed method has been published previously. Briefly, cine images were acquired using a segmented steady-state free precession gradient-echo sequence in three long-axis views (2-, 3-, and 4-chamber views), and in multiple short-axis views every 10 mm, covering the entire left ventricle from base to apex. Contrast-enhanced images were acquired in all patients at 1 month of follow-up, 15-20 minutes after the intravenous administration of 0.2 mmol/kg gadolinium-diethylene-triamine pentaacetic acid, in the same views used in the cine images, using a 2-dimensional segmented inversion-recovery prepared gradient-echo sequence. Left ventricular mass, septal mass and infarct size were quantified using the MASS software package (Medis Medical Imaging Systems, Leiden, The Netherlands). Interobserver agreement for the presence of abnormal delayed contrast enhancement ($\kappa = 0.76$), interobserver (5 ± 18%) and intra-observer variability (4 ± 7%) for quantification of delayed contrast enhanced mass are excellent for our group. Patients with new RBBB were compared with those without RBBB by unpaired Student’s $t$ tests and by the chi-square test for proportions as appropriate. A $P$ value < 0.05 was considered statistically significant.

**Figure 1:** Inclusion of patients (pts) by electrocardiographic classification. ASA= alcohol septal ablation; FU = follow-up; LBBB = left bundle branch block; PPM = permanent pacemaker.
The protocol conformed to the Declaration of Helsinki, and the medical ethics committee of the VU University Medical Center (Amsterdam, The Netherlands) approved the project. All subjects gave informed consent before participation in the study.

Table 1. Baseline characteristics of patients with and without right bundle branch block.

<table>
<thead>
<tr>
<th></th>
<th>New RBBB (n=17)</th>
<th>No RBBB (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.1 ± 12</td>
<td>48.6 ± 22</td>
</tr>
<tr>
<td>Men/Women</td>
<td>11/6</td>
<td>4/6</td>
</tr>
<tr>
<td>NYHA II/III/IV</td>
<td>3/14/0</td>
<td>0/8/2</td>
</tr>
<tr>
<td>Axis (degree)</td>
<td>24 ± 42</td>
<td>9 ± 41</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>169 ± 24</td>
<td>187 ± 33</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>101 ± 12</td>
<td>99 ± 11</td>
</tr>
<tr>
<td>LVOT PG (mmHg)</td>
<td>85 ± 26</td>
<td>80 ± 18</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>220 ± 55</td>
<td>218 ± 76</td>
</tr>
<tr>
<td>Septal mass (g)</td>
<td>77 ± 24</td>
<td>76 ± 25</td>
</tr>
</tbody>
</table>

LVOT = LV outflow tract; NYHA = New York Heart Association; PG = pressure gradient.

RESULTS

After ASA, there was no change in PR interval (173 ± 34 vs 172 ± 30 ms) or QRS axis (16.6 ± 45 vs 13.2 ± 54°) for the group as a whole, although QRS duration significantly increased (100 ± 12 vs 120 ± 20 ms, \( P < 0.001 \)), with 17 patients developing new permanent RBBB (see Figure 1). Those patients who developed RBBB had similar baseline characteristics (Table 1) and reductions in New York Heart Association functional class and pressure gradients but received more ethanol and tended to have
larger infarct size than those without RBBB (see Table 2). The mean infarct size measured by delayed contrast enhancement was $20.8 \pm 8.9$ g and only the basal and mid interventricular septum were affected. Five infarct sites were purely on the right side of the interventricular septum, and 22 were transmural. Patients with anterior (15 of 20 vs. 2 of 7, $P = 0.03$) and especially anterior and inferior transmural (9 of 10 vs. 8 of 17, $P = 0.03$) infarctions were more likely to develop RBBB (see Figures 2 and 3). Patients with persistent RBBB had greater reductions in LV mass at six months of follow-up than those without RBBB (see Table 2).

DISCUSSION

In the present study, 10% of patients required permanent pacing for complete heart block following ASA, and 17 of 30 patients developed persistent RBBB, which is similar to previous reports.\(^8\)\(^-\)\(^10\) Left bundle branch block rarely develops after ASA, probably because the most basal part of the interventricular septum containing the left bundle is not infarcted, possibly because of joint supply from the right coronary artery. The left bundle then divides into anterior and posterior fascicles that run on the LV endocardial surface of the interventricular septum, which explains why left bundle branch block is very frequent after surgical myectomy.\(^1\)\(^3\) Patients who developed RBBB had similar baseline demographics, reductions in pressure gradients, and NYHA functional classes but tended to have larger infarct sizes compared with those without RBBB. They also received more ethanol at the time of ASA to reduce LV outflow tract pressure gradients. This finding probably reflects on the variation in size of septal perforator arteries among subjects: those patients with larger arteries receive more ethanol, which tends to result in larger and more extensive infarctions. Most patients who had transmural anteroseptal infarctions and almost all those with anterior and inferior transmural septal hyperenhancement (9 of 10) developed RBBB. No single pattern of infarction was completely specific in identifying patients who developed RBBB, which probably reflects variability in the anatomic location of the right bundle branch and it is not
surprising, therefore, that patients with more extensive septal infarctions were more likely to develop RBBB.

**Table 2. Infarct size and effect on reverse remodeling in patients with and without new RBBB after ASA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>New RBBB</th>
<th>No RBBB</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol (mL)</td>
<td>3.7 ± 1.7</td>
<td>2.6 ± 1.0</td>
<td>2.2, 0.01</td>
<td>0.049</td>
</tr>
<tr>
<td>Peak CK</td>
<td>1780 ± 617</td>
<td>1325 ± 891</td>
<td>1179, -270</td>
<td>0.2</td>
</tr>
<tr>
<td>Peak CK-MB</td>
<td>251 ± 92</td>
<td>148 ± 97</td>
<td>12, 193</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA reduction</td>
<td>1.5 ± 0.6</td>
<td>1.3 ± 0.7</td>
<td>0.8, -0.3</td>
<td>NS</td>
</tr>
<tr>
<td>PG reduction (mmHg)</td>
<td>64 ± 31</td>
<td>56 ± 32</td>
<td>36, -19</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 month follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>New RBBB</th>
<th>No RBBB</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal Infarct (g)</td>
<td>22.5 ± 9.3</td>
<td>16.6 ± 8.3</td>
<td>13.0, -1.3</td>
<td>0.10</td>
</tr>
<tr>
<td>LV Mass reduction (g/m²)</td>
<td>18.1 ± 10</td>
<td>13.2 ± 8</td>
<td>11.8, -2.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Septal mass reduction (g/m²)</td>
<td>9.0 ± 6</td>
<td>5.6 ± 4</td>
<td>7.5, -0.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Nonseptal mass reduction (g/m²)</td>
<td>9.6 ± 6</td>
<td>7.6 ± 5.3</td>
<td>6.6, -2.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

6 month follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 16</th>
<th>N=9</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Mass reduction (g/m²)</td>
<td>45.5 ± 26</td>
<td>28.8 ± 13</td>
<td>33, 0.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Septal mass reduction (g/m²)</td>
<td>16.9 ± 9</td>
<td>11.5 ± 5</td>
<td>11.2, -0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Nonseptal mass reduction (g/m²)</td>
<td>28.6 ± 18</td>
<td>17.3 ± 10</td>
<td>23.5, -0.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CI = confidence interval; CK = creatine kinase; other abbreviations as in Table 1.

Surprisingly, patients with RBBB had more evidence of reverse remodeling, with significantly greater reductions in LV mass at 6 months. Although the extent of left ventricular hypertrophy is an important prognostic indicator in HOCM,17 it is unclear whether this greater mass reduction will result in a more favorable prognosis, and any benefit is likely to be offset by an increased requirement for permanent pacing. Even in
Figure 2: Baseline and post-ASA electrocardiograms of a patient who developed RBBB. Top baseline: abnormal T-wave inversion in leads I and aVL and biphasic T wave in V6. Bottom, 1 month after ASA: new RBBB and abnormal T-wave inversion remains in leads I and aVL.
**Figure 3.** CMR images at baseline and 1 and 6 months after ASA in patients with and without RBBB. Diastolic images in 3-chamber (*top rows, A and B*) and basal short-axis (*bottom rows, A and B*) views. *(A)* A patient who developed RBBB; *(B)* a patient who did not develop RBBB. **Left column,** end-diastolic cine images at baseline showing asymmetric septal hypertrophy. **Middle column,** delayed contrast images at 1 month post ASA demonstrating transmural basal infarction (*arrows*). **Bright areas** represent areas of infarction, and **dark regions** within infarcted territory probably represent slow wash in of contrast because of microvascular disruption. **Right column,** end-diastolic cine images at 6 months after ASA showing thinned interventricular septum in area of infarction (*arrows*).
the relatively short follow-up period of this study, 1 of the 17 patients with RBBB developed complete heart block necessitating pacing.

The numbers included in this study were small, but the excellent reproducibility of CMR increases the statistical power of the study to detect small differences in mass.\textsuperscript{19} However, we were unable to subgroup the patterns of delayed contrast enhancement further because of the small sample size, and the results should be regarded as preliminary. Delayed contrast enhancement in HOCM without ASA is well recognized and may have caused the overestimation of infarct size. However, the extent of hyperenhancement seen at baseline in 14 subjects studied was extremely small (0.5 ± 0.4g) compared with infarct size after ASA.\textsuperscript{12}

Patients who develop RBBB after ASA are more likely to have more extensive transmural infarctions and greater reductions in left ventricular mass than those who do not develop RBBB. The prognostic significance of these findings is uncertain.

**ACKNOWLEDGEMENTS**

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REFERENCES


The Role of Myocardial Contrast Echocardiography during Alcohol Septal Ablation in Predicting the Site and Size of Myocardial Infarction

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(submitted)
ABSTRACT

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

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

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.
Percutaneous alcohol septal ablation (ASA) 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.\(^2,^8\) 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-ASA 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 (CMR) and transthoracic echocardiography (TTE).

METHODS

Patient selection
The study population comprised 17 consecutive HOCM patients with drug-refractory symptoms, who were referred for ASA. All subjects demonstrated a dynamic LVOT gradient of \(\geq 50\) mmHg at rest or on provocation. The hospital’s ethical committee approved all ASA procedures with informed consent given by the patient.
ASA procedure
Before ASA, all patients underwent diagnostic coronary angiography to exclude significant coronary artery disease. ASA was performed as previously described. 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 mmHg, 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 ASA 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 color-guided continuous-wave Doppler velocity using the modified Bernoulli equation. Mitral regurgitation severity was assessed by color 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 micro bubbles stabilized by a phospholipids shell and filled with sulphur hexafluoride gas with a mean size of 2.5 μm. SonoVue® was administered intracoronary as a slow bolus of 1.0 mL. All images were digitally stored and analyzed offline 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. 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 CMR was performed at baseline and 1-month after ASA with a 1.5 Tesla clinical scanner (Sonata, Siemens, Erlangen, Germany) 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 CMR was also performed. Late gadolinium enhancement (LGE) 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 CMR with a 2D, segmented, inversion-recovery, prepared gradient-echo sequence.
Analysis of LGE and cine images
Infarct size after ASA was measured by manual tracing of the hyperenhanced areas, which were defined as the areas within the septal myocardium with pixel signal intensity (SI) values > 4 SD of remote, non-enhanced 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 Medical Imaging Systems, Leiden, The Netherlands).

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, CMR-determined and ASA-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 ≤ 0.05.

RESULTS

Baseline and follow-up echocardiographic and clinical TTE
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-ASA peak CK-MB fraction was 273 ± 77 IU/L. As seen in Figure 1, injected ethanol volume correlated significantly with post-ASA peak CK-MB fraction (r = 0.73, P < 0.001).
Table 1. Baseline clinical and echocardiographic characteristics of the 17 study patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44 ± 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>13 (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA, class</td>
<td>2.2 ± 0.4</td>
<td>1.4 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>21 ± 3</td>
<td>14 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOT gradient, mmHg</td>
<td>95 ± 29</td>
<td>22 ± 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR, grade</td>
<td>1.4 ± 0.6</td>
<td>0.8 ± 0.8</td>
<td>0.04</td>
</tr>
<tr>
<td>SAM, grade</td>
<td>2.6 ± 0.6</td>
<td>1.5 ± 1.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: NYHA = New York Heart Association; IVS = Interventricular Septum; LVOT = left ventricular outflow tract; MR = mitral regurgitation; SAM = systolic anterior motion.

Prediction of infarct site with MCE

In Figure 2, the relation between SonoVue® opacified septal segments and SMI site, as determined by TTE and CMR 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 with TTE and 91% showed SMI with CMR. 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 with TTE were 65% and 43%, respectively. For CMR these values were 10% and 86%, respectively. There were no differences between prediction of SMI for basal anteroseptal and posteroseptal opacified segments.

Prediction of infarct size with MCE

Mean horizontal septal cross-sectional surface area with TTE was 15.5 ± 3.8 cm² (range 11.0 to 23.0 cm²). Mean septal volume with CMR was 84.8 ± 22.1 cm³ (range 40.6 to 127.9 cm³). As seen in Figure 3, total septal surface area with TTE correlated
significantly with total septal volume with CMR ($r = 0.79$, $P < 0.001$). Mean SonoVue® opacified septal surface area was $5.7 \pm 2.1 \text{ cm}^2$ (range 2.6 to 9.3 cm²) and involved 37.6 ± 15.2% of the total septal surface area. Mean septal volume, as determined by the pre- and post-interventional CMR images, decreased by 11.7 ± 4.8% and mean SMI volume (expressed as percentage of total pre-ASA 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 with CMR 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 (CMR determined) SMI volume ($r = 0.09$). As seen in Figure 5, SMI volume with CMR 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 1](image.jpg)  
**Figure 1.** Correlation between peak CK-MB fraction and injected ethanol volume.
DISCUSSION

ASA 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 CMR.

**Role of MCE in predicting infarction site**

MCE-guided ASA 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) TTE not show SMI with CMR at 1-month follow-up. Two of the 17 patients (12%) had late ASA 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 TTE not show SMI with CMR.
**Figure 3.** Correlation between pre-ASA horizontal septal cross-sectional surface area with transthoracic echocardiography (TTE) and septal volume with cardiac magnetic resonance imaging (CMR).

**Figure 4.** Correlation between peak CK-MB fraction and infarction volume with cardiac magnetic resonance imaging (CMR).
Role of MCE in predicting infarction size

The area of SonoVue® opacification TTE not correlate to SMI size at follow-up CMR. Methodological problems as the cause for this result seem unlikely since an excellent correlation existed between baseline total echocardiographic septal surface area and CMR septal volume. In addition to this, there was a good correlation between SMI volume with CMR 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®

Figure 5. Correlation between infarction volume with cardiac magnetic resonance imaging (CMR) and SonoVue® opacified septal surface area corrected for injected ethanol volume.
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-ASA peak CK-MB fractions or SMI volume with CMR.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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Summary and Future Perspectives

Willem G. van Dockum
SUMMARY

The initial clinical reports of hypertrophic cardiomyopathy (HCM) describe the subaortic, dynamic left ventricular outflow tract (LVOT) gradient as one of the most recognizable features of the cardiac disease. In hypertrophic obstructive cardiomyopathy (HOCM), a gradient of at least 50 mmHg has historically been the threshold to perform transthoracic surgical interventions in patients with severe refractory symptoms despite optimal medical management. Alcohol septal ablation (ASA) has emerged as an effective alternative treatment modality for these patients, resulting in clinical and hemodynamic improvement comparable to surgery. This percutaneous catheter-based procedure involves ethanol infusion into septal perforating branches of the left anterior descending coronary artery, resulting in a discrete artificially induced septal myocardial infarct. After septal myocardial remodeling, regional myocardial wall thinning leads to relief of the LVOT obstruction and abolition of the pressure gradient, with subsequent improvement of symptoms.

Previous echocardiographic studies have described the effects of ASA, but echocardiography has limited capabilities to accurately quantify myocardial infarct size and its exact location at follow-up, which is necessary to enable further refinement of this new therapeutic technique.

The high spatial resolution of CMR in combination with its capability to assess in detail cardiac anatomy, global and regional myocardial function, blood flow velocities, and tissue characteristics using contrast-enhanced imaging, makes it an optimal imaging modality to evaluate the effects of ASA. In this thesis, the effects of ASA therapy performed in symptomatic patients with HOCM are described with respect to anatomy, global and regional cardiac function and mass, and coronary blood flow using cardiac magnetic resonance imaging (CMR). For this purpose, multiple techniques including cine-imaging, late gadolinium enhancement (LGE) CMR, myocardial tissue tagging in conjunction with strain analysis, and coronary flow measurements were applied.
Chapter 2
The hallmark of hypertrophic cardiomyopathy (HCM) is a, generally asymmetrical,
distributed, hypertrophy of a non-dilated left ventricle in the absence of another cardiac
or systemic disease that may cause left ventricular hypertrophy. It is a genetic disease of
the heart with a heterogeneous expression and a great diversity of morphologic,
functional and clinical features. In this review the aetiology, the genetic background,
pathologic features, and pathophysiology of the disease discussed, as well as different
diagnostic tools and therapeutic possibilities.

Chapter 3
Infarct size and location induced by ASA were evaluated 1 month after the procedure in
24 patients with symptomatic HOCM using LGE CMR. At baseline, we found patchy areas
of hyperenhanced myocardium in the septum, located centrally in the ventricular wall
and predominantly at the insertion points of the right ventricular free wall into the
septum. Probably these areas reflect replacement fibrosis, due to ischemic injury,
resulting from a mismatch between the hypertrophied myocardium and capillary
density. One month after ASA, LGE CMR allowed detailed evaluation of size and location
of septal infarction induced by ASA. Infarct size correlated with peak CK-MB, volume of
ethanol administered, total left ventricular (LV) and septal mass reduction, and LVOT
gradient reduction. Two different patterns of infarction were observed: patients with
transmural extent of the infarction with larger infarct size and LVOT gradient reduction,
and a second group with exclusively right-sided location of septal infarction. After
analyzing the procedural coronary angiograms, it was shown that in the transmural
infarct group the ablation was performed more proximal in the target artery compared to
the right sided infarction group. Importantly, the right sided infarction group had
substantial less LVOT gradient reduction, which has clinical consequences. This is
important feed-back for the interventional cardiologist performing the ASA procedure.
Chapter 4
LV remodeling was evaluated using CMR imaging in 29 patients with symptomatic HOCM at one and six months after ASA. No evidence of procedure related infarction outside the target septal area was found. Progressive, significant reductions in septal and remote non-septal myocardial mass were found at 1 and 6 months after ablation. Regression of remote hypertrophy at 6 months follow-up correlated significantly with the reduction in outflow tract pressure gradient. Our findings thus support the theory that hypertrophy in patients with HOCM is partly afterload dependent and reversible, and not exclusively caused by the genetic disorder.

Chapter 5
Regional myocardial mass and systolic three-dimensional strain and shear strain were calculated in 9 symptomatic HOCM patients at baseline and at 6 months follow-up using CMR cine imaging and myocardial tagging. Both septal and non-septal mass decreased significantly, whereas the shortening index (SI) and SI-rate improved significantly in the remote myocardium 6 months after the procedure. ASA results in reversed LV remodeling characterized by a decrease in extent of remote LV hypertrophy with an increased SI and strain rate.

Chapter 6
In this chapter, the effects of ASA on coronary blood flow in symptomatic HOCM patients are reported. Using CMR coronary flow measurements, a progressive, significant decrease of resting LAD coronary blood flow was observed. The coronary blood flow reduction correlated with a decreased left ventricular rate pressure product (LVRPP) at one month follow-up. However, infarct size only tended to modulate the blood flow changes over time; no correlation was observed between enzyme release, volume of ethanol, both septal- and total mass reduction, and coronary blood flow. These observations indicate that the reduction in coronary blood flow is primarily associated with diminished LV loading conditions, whereas the induction of metabolically inactive
myocardial scar tissue by ASA does not significantly influence the changes in coronary blood flow.

Chapter 7
The value of ECG changes following ASA in 33 HOCM patients were studied in predicting reductions in LV mass at 1 and 6 months after ASA compared to baseline. ECG voltages and voltage-duration products were assessed as predictors of changes of LV mass. However, estimation of mass reductions following ASA is not feasible by ECG voltages alone, and should be performed by a reliable imaging technique. Patients developing RBBB are more likely to have sustained both anterior and inferior septal transmural infarction compared to those that do not develop RBBB.

Chapter 8
In this study, the value of myocardial contrast echocardiography (MCE) during percutaneous ASA was investigated in predicting the location and size of ethanol-induced septal myocardial infarction (SMI) compared with LGE CMR determined myocardial infarction after the procedure. Seventeen consecutive HOCM patients underwent MCE-guided ASA and CMR after one month. All patients had opacification of the mid anteroseptal and posterior septal segments. Despite an excellent correlation between total septal surface area at echocardiography and total septal volume at CMR, no correlation was found between the opacified septal surface and CMR derived final SMI volume. Injected ethanol volume correlated significantly with post-ASA peak CK-MB fraction. SMI size depends primarily on injected ethanol volume.
FUTURE PERSPECTIVES

Determination of the characteristics of the induced myocardial infarction and the effects on LV anatomy and cardiac function using CMR imaging has proven to yield valuable insight into the effects of ASA on LV geometry and function. Since the introduction of nonsurgical alcohol septal ablation in 1994 as an alternative therapy to surgical myectomy, the procedure has evolved considerably. Modifications of the ASA procedure such as introduction of selective coronary myocardial contrast-echocardiography to probe the risk area, and reductions of the amount and injection-speed of ethanol have importantly reduced the complications of this procedure, including the incidence of complete heart block necessitating permanent pacemaker implantation. The application of peri-procedural contrast-echocardiography in our study group, probably caused our patients to remain free of remote ASA-induced myocardial infarctions, the latter having occasionally been reported in the early days of ASA. Our study revealed that proximal infusion of ethanol into the target artery resulted in a more transmural extent of the infarct with larger infarct size, and subsequent larger LVOT gradient reduction and relief of symptoms, compared to a second group with exclusively right-sided location of septal infarction. This is important feedback for the interventional cardiologist to optimize this promising therapeutic option in HOCM patients.

With the introduction of ASA, a theoretical concern emerged that the alcohol-induced infarction might introduce of a potential arrhythmogenic substrate in patients who are already at risk to develop ventricular tachycardia (VT) and/or ventricular fibrillation. However, an electrophysiological study in high-risk patients after ASA did not demonstrate increased arrhythmogenicity requiring implantation of defibrillators. Although ventricular tachycardia and sudden death have been reported after ASA, it may reflect the natural course of hypertrophic cardiomyopathy irrespective of therapeutic LVOT gradient reduction. In addition, the potential increased risk of ventricular tachycardia by ASA is probably counterbalanced by a beneficial of reducing the of significant LVOT gradient, which by itself has an increased risk of VT.
In our study group, approximately 10% of the treated patients necessitated pacemaker implantation due to procedure-related complete atrioventricular block. Bolus injection of alcohol, injection in more than one septal artery, and probably infarct location, are independent predictors of complete heart block. Recently, an alternative strategy inducing septal myocardial infarction by coil embolization has been introduced in order to avoid the direct alcohol toxicity upon the conductive tissue. Interestingly, no severe ventricular arrhythmias and complete heart block were observed during or after the procedure. Infarct size as assessed by peak CK-release and contrast-enhanced CMR were lower using coils than alcohol. However, a considerable residual resting LVOT gradient (35 ± 29 mmHg) was observed at 6 months follow-up, compared to the reported residual resting gradient of 10 to 20 mmHg after ASA. Therefore, the effects of coil embolization versus the effects of ASA and/or surgical myectomy on hemodynamics and symptomatic relief should be further investigated in a randomized, double blinded study.

REFERENCES


Samenvatting en Toekomst Perspectieven

Willem G. van Dockum
SAMENVATTING

"Evaluatie van alcohol septum ablatie in obstructieve hypertrofische cardiomyopathie met behulp van magnetische resonantie imaging"

Linker ventrikel uitstroombaan (LVUB) obstructie, aanwezig bij een aanzienlijk deel van de patiënten met hypertrofische cardiomyopathie (HCM), is vanaf de eerste beschrijvingen een zeer opvallend klinisch kenmerk van het ziektebeeld. Bij symptomatische HCM patiënten die ondanks optimale medicamenteuze therapie een ernstige LVUB obstructie (≥ 50 mmHg) hebben, is chirurgische septale myectomie de primair aangewezen behandeling om de obstructie en symptomen te reduceren. Recent is een niet-chirurgische behandelingstechniek als alternatief ontwikkeld, de percutane alcohol septum ablatie (ASA). De symptoom- en gradiënt reductie verkregen met een geslaagde ASA of chirurgische behandeling is min of meer vergelijkbaar.

Bij de ASA procedure wordt bewust een klein hartinfarct gemaakt door middels hartkatheterisatie een paar milliliter alcohol in een zijtak van de linker kransslagader te injecteren. Dit veroorzaakt een infarct in het gedeelte van het septum dat de LVUB obstructie veroorzaakt. Wanneer dit infarct geneest, ontstaat er een litteken met inkrimpen cq. dunner worden van het septum ter plaatse, waardoor de LVUB weer goed doorgankelijk wordt, de obstructie afneemt en daarna ook de klachten.

In dit proefschrift worden klinische studies beschreven in patiënten met obstructieve HCM, voor en het ondergaan van ASA. Daarbij worden de effecten van de procedure bestudeerd met betrekking tot de linker ventrikel anatomie, globale en regionale functie en massa, en de coronaire bloeddoorstroming. Hiervoor hebben we gebruik gemaakt van een magnetic resonance imaging (MRI) scan, een afbeeldingstechniek waarmee nauwkeurig de linker kamer functie en massa bepaald kan worden. Wanneer MRI wordt
Hoofdstuk 9.2

toegepast met aanvullend een contrastmiddel, kan plaats en grootte van een infarct nauwkeurig worden bepaald. Tenslotte kan met een speciale MRI techniek (‘myocardial tagging’) de vervorming van de hartspier worden gemeten tijdens het samentrekken en tijdens het vullen van het hart. Deze technieken zijn gebruikt bij HCM patiënten met LVUB obstructie om het effect van ASA te onderzoeken op de korte (1 maand) en de middellange termijn (6 maanden).

In hoofdstuk 2 wordt het ziektebeeld HCM beschreven, een hartspierziekte met karakteristieke (meestal asymmetrische) hypertrofie van de hartspier bij afwezigheid van een andere cardiale of systemische ziekte die linkerventrikelpertrofie zou kunnen veroorzaken. HCM is een genetisch overdraagbare hartziekte met een heterogene expressie en een grote diversiteit in morfologische, functionele en klinische kenmerken. Achtereenvolgens worden besproken de etiologie, pathologie, pathofysiologie, diagnostiek, genetica, klinisch beloop en therapeutische mogelijkheden.

In hoofdstuk 3 wordt in 24 symptomatische obstructieve HCM patiënten de grootte en de locatie van het door ASA veroorzaakte hartinfarct gemeten met contrast MRI. De grootte van het infarct bedroeg gemiddeld 10% van de totale massa van de linker kamer wand en 30% van het septum. De (septale) infarctgrootte bepaald met MRI correleerde met enzymatisch bepaalde infarctgrootte, met de hoeveelheid alcohol die gebruikt was tijdens de procedure én met de totale en septale myocardiale massareductie als gevolg van de ASA. Er konden 2 infarctvormen worden onderscheiden: 1. infarcten waarbij zowel de linker als de rechter helft van het septum betrokken was en 2. infarcten die alleen in de rechterhelft van het septum geïsoleerd waren. De eerstgenoemde vorm gaf het beste resultaat: meer afname van de LVUB obstructie en meer klachtenvermindering. Om een verklaring te vinden voor de verschillende lokalisaties van de septale infarcten hebben we de coronairangiografieën van de septale alcohol ablatie procedures in detail beoordeeld. Daaruit bleek dat bij rechtszijdig van het septum gelegen infarcten de alcohol meer distaal in de septale takken was geïnfundeerd.
Met MRI zagen we na 6 maanden dat verdere afname van de hartspierverdikking had plaatsgevonden: niet alleen van het septum – waar het infarct was aangebracht – maar ook van de rest van de hartwand (*hoofdstuk 4*). Daaruit blijkt dat de verdikking van de hartwand niet alleen door erfelijke factoren wordt bepaald, maar dat er ook een omkeerbare component is die samenhangt met drukafname in de hartwand als gevolg van de ASA. Verder konden we op de contrast-MRI beelden van vóór de ASA kleine gebieden met contrast-aankleuring in het midden van het septum aantonen. Waarschijnlijk bevindt zich in deze haarden bindweefsel dat ontstaan is als gevolg van eerder opgetreden hartspierschade. Steeds vaker blijkt dat dit soort haarden van contrast-aankleuring vóórkomen bij patiënten met hartspierziekten, die niet het gevolg zijn van hartinfarcten (en niet alleen bij HCM). Deze haarden onderscheiden zich van de contrast-aankleuring van een ‘gewoon’ hartinfarct doordat ze zich midden in de wand bevinden en niet zoals bij een hartinfarct zich verspreiden vanuit de binnenlaag van de hartwand.

In negen symptomatische HOCM-patiënten is de regionale myocardiale massa en 3D systolische deformatie berekend voor en 6 maanden na de procedure met behulp van cine imaging en myocardiale tagging (*hoofdstuk 5*). Na ASA was er sprake van zowel septale als niet-septale massareductie, en er werd een geringe afname van functie van het septum gezien met daartegenover een functieverbetering van het niet-septale gedeelte van de hartspierwand. Hieruit blijkt dat de drukafname als gevolg van de ablatie procedure gepaard gaat met remodelering van de hartspier met een afname van de hartspiermassa en met een verbeterde contractiepatroon van het niet-septale deel van de linker hartkamer.

Vervolgens hebben we in een subgroep van de HCM-patiënten die een ASA hebben ondergaan de doorbloeding van de linker kransslagader geanalyseerd (*hoofdstuk 6*). Het bloedvolume dat per minuut door de kransslagader stroomt neemt af na de ASA en correleert met de afname van de LVUB obstructie. De grootte van het door de ingreep veroorzaakte hartinfarct heeft een minder sterk effect op de doorbloeding van de
Hoofdstuk 9.2

kranslagader; er werd geen relatie gevonden tussen de doorbloedingafname en de hoogte van de gemeten hartenzymen, de hoeveelheid gebruikte alcohol, en de septale en totale myocardiale massa afname. Deze bevindingen geven aan dat de afname van de doorbloeding van de linker kranslagader met name is gerelateerd aan de drukafname in de linker kamer, en dat het metabool inactieve septale hartinfarct hierbij een minder belangrijke rol speelt.

In hoofdstuk 7 wordt onderzocht of veranderingen op het elektrocardiogram (hartfilmpje) kunnen voorspellen hoe groot de afname van hartspierverdikking is op 1 en 6 maanden na ASA. Een aantal elektrocardiografische criteria zijn gebruikt als voorspellers van de myocardiale massa. Het bleek echter niet goed mogelijk om met behulp van deze criteria na ASA een schatting van de massareductie te maken, bepaling van de afname van de hartspierverdikking is alleen mogelijk met een betrouwbare imaging techniek zoals MRI. Daarnaast werd gevonden dat patiënten die na de ASA een geleidingsvertraging op het hartfilmpje hebben verkregen (zogenaamd rechterbundeltak blok) een uitgebreider hartinfarct hebben dat de gehele dikte van het septum beslaat.

In hoofdstuk 8 hebben we onderzocht of met behulp van contrast echocardiografie verricht tijdens de ASA procedure de uiteindelijke locatie en grootte van het hartinfarct voorspeld kunnen worden en of deze vergelijkbaar zijn met locatie en grootte van contrast-MRI na de procedure. Er blijkt een goede relatie te bestaan tussen het met contrast-echocardiografie berekende septum-oppervlak en het septale volume zoals berekend met MRI; er is echter geen relatie tussen het echocardiografisch berekende infarctoppervlak en de met contrast MRI berekende infarctgrootte.
TOEKOMST PERSPECTIEVEN

Cardiale MRI heeft bewezen een waardevolle techniek te zijn om de karakteristieken van het door ASA geïnduceerde hartinfarct in beeld te brengen, en levert ook de mogelijkheid om de effecten van ASA op LV geometrie en functie nauwkeurig te bestuderen. Sinds de invoering in 1994 van de niet-chirurgische septale alcohol ablatie als een alternatief voor chirurgische myectomie, heeft eerstgenoemde procedure zich sterk ontwikkeld. Veranderingen rond de ASA procedure zoals de invoering van selectieve coronaire myocardiale contrast-echocardiografie om het risico gebied vast te stellen, en de toepassing van een kleinere dosering en lagere injectiesnelheid van de alcohol, hebben de complicaties van deze procedure in belangrijke mate vermindert. Met name de noodzaak voor permanente pacemaker implantatie als gevolg van het optreden van een compleet atrioventriculair (AV-) hartblok na de procedure, is aanzienlijk afgenomen. Het gebruik van contrast-echocardiografie tijdens de procedure zoals dat is toegepast is onze studie groep heeft er waarschijnlijk toe bijgedragen dat onze patiënten geen ‘remote’ myocard infarct ontwikkelden ten gevolge van ASA, zoals in de begindagen van ASA wel eens werd beschreven. Onze studie toonde aan dat infusie van ethanol proximaal in de juiste septale coronair arterie resulteerde in een groter infarctgebied met meer transmurale uitbreiding, in een grotere afname van de LVUB gradiënt, en in een afname van symptomen ten opzichte van een tweede studie groep die een uitsluitend rechtszijdig gelokaliseerd septaal infarct doormaakte. Dit is belangrijke informatie voor de interventie cardioloog die de ASA procedure verricht, omdat daarmee deze veelbelovende therapeutische optie in HOCM patiënten geoptimaliseerd kan worden.

Al direct vanaf de introductie van ASA heeft men bezorgdheid geuit over het aanbrengen van een potentieel aritmogeen substraat als gevolg van het induceren van een myocard infarct in patiënten die op zich al een verhoogd risico hebben op het ontwikkelen van een ventriculaire tachycardie of ventrikelfibrilleren. Echter, een elektrofysiologische studie in hoog risico patiënten na ASA liet geen toename zien van aritmieën waarvoor
pacemaker implantatie noodzakelijk was.¹ Alhoewel ventriculaire tachycardie en plotselinge hartdood beschreven zijn na ASA, kan dit ook een weerspiegeling zijn van het natuurlijke beloop van hypertrofische cardiomyopathie, onafhankelijk van de therapeutische afname van de LVUB gradiënt. Tegenover het mogelijk toegenomen risico op kamertachycardiëen na ASA door de introductie van een aritmogeen substraat, staat een afname van het risico op kamertachycardiëen als gevolg van een significante gradiëntreductie.²

In onze studie groep was in ongeveer 10% een permanente pacemakerimplantatie noodzakelijk als gevolg van het ontstaan van een aan de procedure gerelateerd compleet AV-blok. Onafhankelijke voorspellers voor het ontstaan van een compleet AV-blok zijn bolus injectie van alcohol, injectie in meer dan 1 septale arterie, en waarschijnlijk ook de infarct lokalisatie. Recent is een nieuwe methode geïntroduceerd waarbij in plaats van alcohol een zogenaamd coil, een soort plug, in de septale arterie wordt geplaatst, waardoor de directe toxiciteit van alcohol op het geleidingssysteem wordt vermeden.³ Een belangrijk resultaat van deze eerste studie met septale coiling is dat géén van de HOCM patiënten kamertachycardiëen of een compleet AV-blok ontwikkelde na de procedure. Zowel de enzymatisch gemeten infarctgrootte als de infarctgrootte gemeten met cardiale MRI waren kleiner dan met ASA. Echter in vergelijking met de septale alcohol ablatie was er op 6 maanden na coiling nog een aanzienlijke LVUB gradiënt in rust aanwezig (35 mmHg versus 10-20 mmHg). De effecten van ASA en septale coiling met betrekking tot verbetering van hemodynamiek en symptomatiek dienen met elkaar en met name ook op de langere termijn te worden vergeleken in een gerandomiseerde dubbel geblindeerde studie, alvorens septale coiling als standaard methode in de kliniek te implementeren.
LITERATUUR


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CURRICULUM VITAE

LIST OF PUBLICATIONS


