Hypertrophic Cardiomyopathy - The Case for Alcohol Ablation Therapy

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ABSTRACT

Hypertrophic Cardiomyopathy (HCM) is a genetic disease caused by a variety of mutations in proteins, mostly but not exclusively, of the cardiac sarcomere. It is characterized by hypertrophy of the left ventricle (LV), often with obstruction of the LV outflow tract (LVOT), in the absence of another cause, such as hypertension or aortic stenosis, capable of producing the degree of hypertrophy observed. It presents with markedly variable morphologic and hemodynamic abnormalities and clinical manifestations. The present review will briefly summarize the genetics, pathophysiology, clinical features and management of this disease and will mainly deal with the non-surgical reduction of septal hypertrophy by means of transcoronary alcohol septal ablation.

GENETIC SUBSTRATE

HCM is inherited as an autosomal dominant trait and it constitutes the most common genetic cardiovascular disease, affecting about 0.2% of the general population [1]. Eleven mutations involving sarcomeric genes have been identified so far, the most common being beta myosin heavy chain and myosin-binding protein C. Moreover, there are several different mutations in each gene, the total number exceeding 400 [2]. Additionally, two non-sarcomeric protein mutations affecting cardiac metabolism, have been identified with a phenotype similar to HCM [3]. The progress in molecular genetics have permitted the detection of mutated genes, thus providing a genetic diagnosis even in asymptomatic relatives of patients with HCM, allowing better counseling as well as recognition of a greater number of affected individuals.

PATHOLOGY, PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The mutations in contractile protein genes appear to be directly affecting sarcomere function, leading to the characterization of HCM as a “disease of the sarcomere”. The hypertrophy of the LV is a consequence of sarcomeric dysfunction. Myocyte disarray with loss of parallel arrangement, abnormal intercellular connections and variation between individual myocytes constitute the major histopathologic findings. The macroscopic result is a usually asymmetric LV hypertrophy, involving the septum more than the free walls. There is a substantial diversity regarding the distribution and
magnitude of LV hypertrophy even between close relatives. The right ventricle is involved in 30% of cases. Frequently, an abnormal mitral valve with elongation of leaflets or anomalous insertion of the papillary muscles may also be present [4].

In patients with HCM, the left ventricle exhibits a hyperdynamic systolic function maintaining a small cavity. LVOT obstruction occurs in 30-50%, causing a gradient between the LVOT and the aorta, sometimes at rest and sometimes only with drugs or maneuvers. The main mechanism involves a systolic anterior motion (SAM) of the mitral leaflets due to a suctioning effect that pulls them towards the hypertrophied septum (i.e. a Venturi effect) [1]. The resulting mitral regurgitation is usually mild to moderate and eccentric. On the contrary, when primary mitral valve disease exists, the direction of the regurgitant jet is usually central and of varying magnitude.

Diastolic function is also affected in 80% of patients, with a prolonged rapid filling phase and an increased atrial contribution, showing impaired LV relaxation. It constitutes a major cause of symptoms of dyspnea and exercise limitation both in obstructive and non-obstructive HCM [2].

Many patients with HCM are asymptomatic and are often diagnosed during family screening. When symptoms do develop, they are usually one or more of the following: Dyspnea on exertion and occasionally orthopnea or paroxysmal nocturnal dyspnea, chest pain, presyncope and syncope, palpitations and fatigue [5]. The degree of obstruction is not predictably correlated with symptoms. Some patients with severe LV outflow tract obstruction remain asymptomatic for many years, while cardiac arrest or sudden death may be the initial presentation of the disease, thus underscoring the importance of family screening. Syncope may be due to conduction diseases, paroxysmal arrhythmias or abnormal vascular responses such as inappropriate vasodilatation in non-exercising muscles and reflex dilatation of venous beds triggered by LV baroreceptors [1]. Myocardial ischemia may be due to increased oxygen demand due to hypertrophy, thickening and narrowing of small intramural vessels and systolic compression of larger perforator and epicardial vessels. The most common arrhythmia in patients with HCM is paroxysmal or chronic atrial fibrillation (AF), both symptom-compromising and increasing risk of embolic events [6]. Other arrhythmias include ventricular ectopic beats and non-sustained VT in ambulatory ECG.

**Natural History and Prognosis**

The clinical course of HCM is quite variable and it may run asymptomatic for the majority of patients over long periods of time. The annual mortality rate is roughly 1% per year and is somewhat higher in children [1,4]. Those patients who have symptoms upon presentation have a greater annual rate of cardiac death (0.9 versus 1.9 percent, p<0.05) and sudden death (1.4 versus 0.1 percent, p<0.05), compared to asymptomatic patients [7]. A small proportion of patients with HCM eventually progress to a stage, with reduced LV systolic function with dilation and wall thinning, resembling the morphologic and functional features of dilated cardiomyopathy, called “end-stage” or “burned out” HCM [8].

**Management**

A. **Prevention of Sudden Cardiac Death**

Patients with HCM are prone to both atrial and ventricular arrhythmias, the incidence of which increases with age. However the majority of these are not life-threatening. Ventricular tachycardia and fibrillation can cause sudden cardiac death (SCD), most commonly during adolescence and young adulthood. It should be noted that many of these patients were totally asymptomatic and sudden cardiac death was the first manifestation of the disease. Moreover, HCM is the most common cause of death among young athletes [9].

The major risk factors for SCD are a prior cardiac arrest or sustained VT, a family history of HCM-related death, syncope especially during exertion, a hypotensive response to exercise, multiple episodes of non-sustained VT in ambulatory Holter monitoring, massive LV hypertrophy (>30 mm), presence of an LV apical aneurysm and the end-stage disease with LV systolic dysfunction [10]. Certain mutations such as, beta myosin heavy chain and troponin T, are also associated with premature death more than others [11].

The implantation of a cardioverter-defibrillator (ICD) is the preferred therapy for HCM patients at high-risk of SCD, both for secondary (i.e. implantation after cardiac arrest) and primary prevention, in patients with one or more high risk factors [12]. The role of antiarrhythmic drugs is limited to patients with an ICD who experience frequent episodes, or as an alternative to an ICD, in high-risk patients who are not candidates for or choose not to have an ICD.

B. **Medical Treatment**

For heart failure symptoms due to diastolic dysfunction or LVOT obstruction, beta-blockers have been extensively used with excellent results both in obstructive and non-obstructive HCM, since they block catecholamines, thereby reducing LVOT gradient and improving diastolic filling time and relaxation. Verapamil may also provide symptomatic benefit for similar reasons but a number of patients with elevated venous pulmonary pressures may experience pulmonary edema and SCD [2]. Disopyramide has also been proven effective, especially in combination with beta-blockers owing to its negative inotropic effects and no evidence of proarrhythmia in these patients [13]. When atrial fibrillation complicates the clinical course of HCM it requires aggressive interven-
tion with anticoagulation, attempts to restore sinus rhythm, both pharmacological and electrical, and consideration of catheter ablation of the pulmonary veins and the surgical maze procedure [2].

NON-MEDICAL TREATMENT
Pharmacologic therapy is the first-line treatment for symptomatic patients with LVOT obstruction. For those patients that prove to be refractory to medical therapy, surgical myectomy, dual-chamber pacing and, more recently, ethanol ablation of the hypertrophied septum, have all been tried with variable results. It has been estimated that these approaches are required in approximately 5% of all patients with HCM and up to 30% in tertiary referral centers [1,14].

1. Dual Chamber Pacing
Dual chamber pacing has been used in the past as an alternative to surgery, but studies have not shown objective evidence of gradient reduction and improvement of exercise capacity [1,4]. It is now primarily performed in patients undergoing ICD implantation, as well as selected older patients (more than 65 years of age), or those with other indications for pacing. The rationale behind dual-chamber pacing is that, by initiating the signal in the right ventricular apex, it alters the sequential contraction of the basal septum, thus reducing the gradient.

2. Surgical myectomy
Surgery for HCM has been a well-established therapeutic option for over 40 years. The Morrow procedure involves the resection of a small portion of the basal interventricular septum (2 to 11 gm) and has shown excellent results in reducing LVOT gradient, improving symptoms and reducing mitral regurgitation, but also in reducing mortality risk in severely symptomatic patients with obstructive HCM [15]. Although earlier reports mentioned a mortality rate of 4%-6% [16,17], more recent studies report mortality rates of less than 2% [15,18]. The surgical results are much improved due to better anesthesia, myocardial protection during cardio-pulmonary bypass, and the use of intra-operative transesophageal echocardiography [19]. The latter permits a thorough evaluation of the surgical result upon the interventricular septum and, if required, the mitral valve, before the patient leaves the operating room.

Complications of surgical myectomy include ventricular septal defect due to excessive removal of cardiac muscle, aortic regurgitation due to the transaortic approach and LBBB or complete heart block requiring a permanent pacemaker [20-22].

3. Alcohol Septal Ablation (ASA)
Non-surgical reduction therapy (NSRT), or alcohol septal ablation (ASA), or transcoronary ablation for septal hypertrophy (TASH), or percutaneous transluminal septal myocardial ablation (PTSMA), are all equivalent terms, referring to the creation of an iatrogenic septal infarct via alcohol injection in a perforating septal branch of the left anterior descending artery (LAD). Since it was first introduced in 1995 [23] it has been used as a therapeutic option alternative to surgery. The initial concept was conceived after recognizing that spontaneous anterior myocardial infarctions in HCM patients resulted in reducing the LVOT gradient. Nowadays more than 3500 patients have undergone the procedure [24].

The appropriate selection criteria for patients’ suitability for alcohol septal ablation (ASA) are described in the ACC/ESC Expert Consensus Document on hypertrophic cardiomyopathy (see Table 1). It is important to note that for asymptomatic or slightly symptomatic patients, given their relatively low risk of sudden cardiac death if they don’t possess any high risk factors, probably aggressive intervention is not justified although there are not enough data to address the question, [25]. Another important issue is the approach to patients with obstruction and one or more high risk factors. For this subgroup of patients it would be reasonable to implant an ICD and reevaluate the effect of sequential AV pacing on LVOT gradient and then, if still symptomatic, consider alcohol septal ablation or surgery [1].

The main parts of the procedure are as follows: After the insertion of a temporary pacemaker in the right ventricular apex, for the possibility of complete heart block, a left heart catheterization is performed, starting with a multipurpose catheter to measure the LV gradient by a pull-back method [26]. This is followed by coronary angiography to identify the septal perforator branches of the LAD. An over-the-wire balloon catheter is introduced and inflated into those branches and contrast medium is injected into the balloon catheter lumen. Contrast echocardiography is then performed in order to identify the area supplied by the specific branch and thus select the most suitable for infarction. The use of echocardiography also ensures that the contrast goes only to the septum, close to the point of its contact with the mitral valve, and not elsewhere such as the papillary muscles, the LV free wall or the right ventricle. A small amount of absolute ethanol (usually 1-3 ml) is then injected very slowly and the inflation is maintained for a few minutes. Subsequently, a new angiography is done to ensure LAD patency and the occlusion of the target branch. Finally, the intraventricular gradient is remeasured to assess the acute effect of the procedure. It should be noted that the LVOT gradient in the acute phase is reduced, probably due to a stunning effect, and in the next few days gradually increases, possibly due to edema, until it finally falls over a period of weeks, due to scar formation [24]. This has been called a ‘triphasic’ response.

The main complications arising from alcohol septal ablation are summarized in Table 2 [27]. The in-hospital death may range from 1% to 4% but in specialized centers may be
TABLE 1. Indications for ASA

<table>
<thead>
<tr>
<th>Indications</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Symptoms, functional class III to IV</td>
<td></td>
</tr>
<tr>
<td>Severe side effects of medical treatment</td>
<td></td>
</tr>
<tr>
<td>LVOT pressure gradient (maximum gradient) &gt;30(50) mmHg</td>
<td></td>
</tr>
<tr>
<td>Provokable LVOT pressure gradient (maximum gradient) &gt;50(100) mmHg</td>
<td></td>
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<tr>
<td>Systolic anterior motion related obstruction</td>
<td></td>
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<tr>
<td>Mid-cavity obstruction</td>
<td></td>
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<tr>
<td>Septal thickness &gt;15(18) mm</td>
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<tr>
<td>Suitable septal branch</td>
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TABLE 2. Periprocedural complications of alcohol septal ablation

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Early mortality (within 30-days)</td>
<td>1.5% (0-5%)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>2.2%</td>
</tr>
<tr>
<td>LAD dissection</td>
<td>1.8%</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0.6%</td>
</tr>
<tr>
<td>Complete heart block requiring pacing</td>
<td>10.5%</td>
</tr>
<tr>
<td>Need for repeat ASA</td>
<td>6.6%</td>
</tr>
<tr>
<td>Need for surgical myectomy</td>
<td>1.9%</td>
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dangerous complications include LAD dissection, periprocedural ventricular arrhythmias including fibrillation and pericardial effusion, but they are not often reported and can be dealt with successfully.

The concern about the possibility of long-term ventricular arrhythmias due to myocardial scaring has also been raised [37]. The in-hospital malignant arrhythmias can be probably attributed to ischemia, but there have been reports of ventricular tachycardias in follow-up [38,39]. Nevertheless, the reduction of LVOT gradient and the subsequent regression in LV hypertrophy, due to ASA may also exert an antiarrhythmic effect [26]. A study of ventricular arrhythmias in patients already having an ICD did not show increased episodes [40].

The beneficial effects of ASA have been well documented over the last decade. It appears that septal ablation reduces LVOT gradient, increases exercise capacity and peak oxygen consumption and reduces NYHA class [41,42]. There is also a favorable effect on LV regional asynchrony, which accounts for the acute improvement in LV relaxation, as shown by tissue Doppler imaging [43]. The long-term benefits derive from the localized septal infarction and the subsequent scar formation, which results in an increase in LVOT diameter and a decrease in LV mass and the extent of hypertrophy. Such a therapeutic remodeling of the left ventricle results in the observed clinical benefits [44,45]. A reduction in nonseptal mass over time after ethanol septal ablation has been observed that may indicate that a degree of myocardial hypertrophy in HCM is in part afterload-dependent, due to the excessive septal hypertrophy, and is not entirely due to the genetic defect [44,45]. There is also a beneficial effect on mitral regurgitation [30,42]. Several studies have documented the beneficial effects of alcohol septal ablation on the left ventricular diastolic properties [46,47]. A shortening of isovolumic relaxation time and transmural early diastolic propagation velocity have been attributed to an improved relaxation profile of the left ventricle [47]. A great part of the observed benefit is due to the continuous regression of LV hypertrophy as shown by Mazur et al [44]. Finally, an improvement in the Tei Doppler index was shown in mid-term follow-up of patients who had undergone ASA [48].

Nevertheless, weaknesses of the procedure began to emerge shortly after its introduction in clinical practice. Younger patients with greater thickness in the interventricular septum were found to have a lesser degree of LVOT gradient reduction after septal ablation [49]. Similar, unsatisfactory results were reported by Faber et al [50]. Moreover, in a substantial number of cases, a suitable branch for alcohol infusion may not be found [51,52]. This would obviate the need for patient referral for surgical treatment.

As regards the comparison of alcohol ablation therapy with surgical myectomy, it should be noted that there are no randomized controlled trials. Such a trial would enlighten the medical community regarding the appropriate selection.
of patients for each method. The practical problems that arise make such a possibility quite distant [53]. The different morphologic effects of the two procedures were shown in a recent prospective study of 48 patients using cardiac magnetic resonance (CMR). While myectomy resulted in a discrete area of resected tissue in the anterior septum, alcohol ablation caused tissue necrosis more inferiorly and extending into the right septal side at the midventricular level, thereby producing a more variable effect [54].

With respect to the clinical outcomes both methods have proven efficacy. In a report from the Cleveland clinic, the authors concluded that both interventricular septal thickness and LVOT gradient were reduced and NYHA class was significantly improved in patients with obstructive HCM [30]. A similar study showed similar hemodynamic and functional improvements at one year in patients with a resting LVOT gradient at least 40 mmHg, who were severely limited by dyspnea or angina or had recurrent limiting presyncope or syncope [31]. A more recent study comparing outcomes after ablation or myectomy showed significantly lower postintervention LV outflow gradients at rest and with provocation in the myectomy group accompanied by reduced systolic anterior motion of the mitral valve and improved NYHA class [55].

CONCLUSION

Both surgical myectomy and alcohol septal ablation are effective treatments for highly symptomatic patients with HOCM. Due to the lack of randomized controlled trials for direct comparison, physicians need to consider the advantages of each one when selecting patients for septal reduction therapy. Advantages of the ablation technique include the avoidance of a major surgical procedure, the lack of post-operative pain and need for transfusion, the shorter hospital stay and the low incidence of atrial fibrillation [24]. Advantages of the surgical technique are the immediate and permanent relief of outflow gradient, the less need for a permanent pacemaker, the fact that coexisting mitral and coronary artery disease can be dealt with at the same time and the proven long-term efficacy. For the ablation procedure such long-term data are lacking [56] and moreover the question of the possible arrhythmic risk due to scar formation remains unanswered. As noted by Maron et al., although there is an increasing enthusiasm for the ablation procedure among interventional cardiologists, we should remember that surgery is the most effective and long-lasting treatment for alleviating symptoms of obstructive HCM and therefore it should be regarded as the primary treatment option for drug-refractory symptomatic patients [29].

REFERENCES

49. Seggewiss H, Faber L, Gleichmann U, Horstkotte D. Age relat-


