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# Old and new therapeutic solutions in the treatment of hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a genetic disease of the myocardium that is relatively common in the general population, with an autosomal dominant inheritance as a genetic basis. Clinical and natural history pathways can be very different among patients with HCM. Treatment strategies have made very important advances in the last two decades, especially reducing cases of sudden death through effective risk stratification and the use of implantable defibrillators. Heart failure has become the predominant cause of morbidity and mortality in patients with HCM, being responsible for as many as 60% of disease-related deaths. HCM is most often characterized by the presence of left ventricular outflow tract (LVOT) obstruction, and this obstruction is the most frequent cause of impaired exercise tolerance in HCM and a strong independent predictor of heart failure progression and mortality. The different treatment strategies of LVOT obstruction in HCM are discussed below: surgical, invasive, and the more recent pharmacological.

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the myocardium that is relatively common in the general population. Indeed, studies based on echocardiography have shown a prevalence of 1:500 persons,[1] and a higher prevalence (1:200) is described when both clinical and genetic diagnoses are considered.[2] HCM is caused by mutations in sarcomeric genes. Approximately 1400 causative mutations have been identified in 12 sarcomeric genes, of which more than 70% involve the myosin-beta heavy chain gene (MYH7) and the cardiac myosin-binding protein C gene (MYBPC3).[1] HCM is inherited in an autosomal dominant pattern with incomplete penetrance. Alongside this genetic heterogeneity, patients with HCM can have different types of clinical presentation, natural history, and prognosis[3]: (i) patients at high risk of sudden death, without symptoms of heart failure, (ii) patients with progressive symptoms of heart failure, (iii) patients who develop left ventricular systolic dysfunction or apical aneurysms, and (iv) patients experiencing atrial fibrillation with high risk of thromboembolism and stroke.

The various pharmacological and non-pharmacological management strategies (defibrillators, surgical myectomy, alcoholic ablation, and cardiac transplantation) developed in the last two decades have modified the natural history of the disease, above all by reducing sudden death through a more accurate selection of patients with an indication for cardioverter defibrillator implantation in primary prevention.[3]

As a result, heart failure has become the predominant cause of morbidity and mortality in patients with HCM, being responsible for as many as 60% of disease-related deaths.

Left ventricular outflow tract (LVOT) obstruction is the most frequent cause of decreased exercise tolerance in HCM and a strong independent predictor of heart failure progression and mortality four-fold greater than in patients without obstruction.[3–5] HCM is essentially an obstructive disease with 70% of patients presenting with a gradient in the LVOT either at rest or with provocation.[6]

Treatment of obstructive HCM therefore represents a critical step in the management of patients with HCM, with the potential to significantly impact the mortality and morbidity of this disease.

## Non-pharmacological treatment of obstructive HCM (septal reduction therapy)

Transaortic septal myectomy [septal myectomy (SM)] is the most effective treatment to abolish the outflow tract

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gradient and improve long-term quality of life.[2] It is likely, although we do not have any randomized studies in this regard that myectomy surgery also improves the survival of patients with LVOT obstruction.[7]

Over the years, SM surgery has known procedural implementations compared to the classic Morrow procedure introduced in the 1960s which involved the removal of a portion of the basal septum at the point of contact with the mitral valve. Currently, a more extensive myectomy is performed as well as corrective operations on the mitral valve (plication of the leaflets) and on the subvalvular mitral apparatus (chordae and papillary muscles). Italian surgery has the merit of having introduced and developed the 'chordal cutting' technique which allows, through the cutting of thickened and retracted mitral valve secondary chordae, to move in systole the mitral apparatus and the coaptation point of the leaflets away from the LVOT and to move it towards the posterior wall of the left ventricle, thus tackling an important mechanism by which the obstruction is generated.[8]

### Patients in NYHA Classes III and IV

In the latest 2020 AHA/ACC Guidelines, SM performed at expert centres has a Class I indication in patients with severely symptomatic LVOT obstruction despite optimal medical therapy.[2] However, this indication of the American Guidelines has appeared limiting to many experts.

### Patients in NYHA Class II

It had already been proposed for some time to intervene on the obstruction in the LVOT without waiting for the progression of symptoms to NYHA Classes III and IV.[5,9] SM improves haemodynamic parameters by reducing intraventricular pressures, mitral regurgitation, and pressure in the left atrium, all factors leading to atrial dilation and development of atrial fibrillation (an important prognostic factor). Furthermore, early intervention offers the patient the opportunity to enjoy a longer life span without disabling or limiting symptoms. In a recent analysis by the Cleveland Clinic, patients operated in NYHA Class II, for drug intolerance or for reduced exercise capacity and quality of life, showed a better event-free survival (death or appropriate defibrillator intervention) compared to patients operated in NYHA Classes III and IV, as for Class I indication according to the 2020 AHA/ACC Guidelines.[10] Therefore, the current approach is to properly evaluate the symptoms of the patient with important obstruction of the LVOT and in NYHA Class II, also by means of the cardiopulmonary test and possibly indicate the SM intervention to be performed at an experienced centre.

### The cardiac surgery in HCM experienced centres

The need for an expert centre, with a high volume of interventions in obstructive HCM, is always underlined by the guidelines produced in the last 20 years. An interesting analysis of over 6000 myectomies performed in US hospitals from 2003 to 2011 showed that 60% of hospitals had performed fewer than 10 operations in the period of observation and that dividing hospitals by tertiles of increasing activity, in-hospital mortality was respectively 15.6, 9.6, and 3.8% ($P < 0.01$) with longer length of stay and higher costs.[11] An unacceptable excess of mortality, considering that in the centres of excellence with surgeon expert in the complex anatomy of the outflow tract of the left ventricle, operative mortality ranged from 0.3 to 1.1%.[12] The problem of establishing the minimum number of operations/years to ensure safety and efficacy remains open.[3]

### Few cardiac surgeons are experienced in myectomy surgery

At present, there are an inadequate number of cardiac surgeons experienced in SM surgery compared to the population of patients with the obstructive form of HCM who could benefit from this intervention. This critical issue has been denounced and shared by the most experienced cardiac surgeons in HCM at an international level.[13]

In conclusion: SM has been shown to be an effective therapy by improving short- and long-term symptoms in 90% of patients, male or female, with the obstructive form of HCM, allowing longevity no different from that of the general population, and potentially reducing the risk of sudden death with a safety among the best in the field of open heart surgery (operative mortality around 0.5%,[3] when performed in experienced centres).

### Alcohol septal ablation (ASA: alcohol septal ablation)

The other non-pharmacological option of septal reduction therapy (SRT) is alcoholic septal ablation in which septal thickness reduction is achieved through a well-localized myocardial infarction and a subsequent replacement scar. In general terms, this procedure appears to have the same short-term outcomes as SM in terms of mortality but more frequent use of pacemaker implantation for advanced atrioventricular block and less extent and stability in reduction of the LVOT gradient.

Randomized trials comparing SM and ASA are lacking. However, a recent study compared the long-term mortality of 585 patients undergoing ASA and that of 3275 patients undergoing SM, at 3 different HCM specialized centres. Mortality from all causes at 10 years was 26.1% in the ASA group and 8.2% in the SM group, also irrespective of age, sex, and comorbidities (hazard ratio: 1.68; $P < 0.001$).[14]

In the recent AHA/ACC guidelines of 2020, the ASA has a Class I indication 'when surgery is contraindicated, or the risk is deemed unacceptable due to the presence of severe comorbidities or advanced age' and must be performed in experienced centres. Here comes the problem of the need to operate in centres with experience in HCM and in the interventional procedure. The analysis on the volume of activity and the prognosis was also applied to ASA and showed that with increasing tertiles of activity, both mortality is reduced (2.3, 0.8, and 0.6%, respectively; $P = 0.02$) and morbidity (6.2, 7.6, 2.4%, respectively; $P < 0.001$).[11] It must also be considered that ASA is not indicated in children.

## Pharmacological treatment of hypertrophic obstructive cardiomyopathy

If surgery currently remains the treatment of symptomatic obstructive HCM innovative treatment strategies are

emerging in the pharmacological treatment of LVOT obstruction. Historically, American and European guidelines both recommend medical therapy for patients with the obstructive form of the disease and symptoms that worsen daily routine and/or quality of life.[2,15] The drugs to be used are the negative inotropic ones: beta blockers (first choice), verapamil (not to be administered in the presence of high gradients in the LVOT), and disopyramide (almost always associated with a beta blocker). These drugs, used in standard doses, do not have the power to significantly reduce the basal gradient even if beta blockers can attenuate the gradients that develop during physical exercise. When symptoms and exercise capacity limitations become refractory to maximal medical therapy, it becomes necessary to resort to the non-pharmacological treatment represented by SM, or ASA in selected individuals.[2,15] However, the landscape of pharmacological treatment of obstruction now presents new options.

## Myosin inhibitors

The myosin–actin interaction presents the fundamental unit capable of generating force in the sarcomere; the conformation of the myosin is fundamental in determining the number of interaction sites with actin and therefore the total force that will be developed. In HCM, the excess of active bridges between myosin and actin contributes significantly to the hyperdynamic behaviour of the left ventricle and impaired myocardial relaxation. Through inhibition of myosin ATPase, cardiac myosin inhibitors reduce the number of myosin/actin active sites and potentially reduce the hyperdynamic state of the left ventricle that greatly contributes to generating the outflow tract gradient during systole.[16]

Two myosin inhibitors are currently under clinical evaluation: mavacamten and aficamten.

The first clinical study on patients with obstructive HCM was the EXPLORER-HCM study published in August 2020 in the Lancet.[17] In this study, 251 patients were randomized to mavacamten or placebo and followed up for 30 weeks. Treatment with mavacamten achieved the primary end point (improvement of cardiopulmonary exercise tolerance or NYHA class improvement) in 37% of treated patients, compared to 17% of placebo patients. As regards the secondary end points, treated patients more frequently showed a reduction in the outflow gradient (<30 mmHg peak) and an improvement in the subjective perception of well-being through the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS).[17] A subsequent echocardiographic substudy showed in detail the reduction of mitral SAM and the gradient in the outflow tract as well as an improvement in diastolic function indices.[18]

In the VALOR-HCM study, 112 patients with a peak LVOT gradient >50 mmHg and NYHA functional Classes III and IV, eligible for non-pharmacological SRT therapy, were randomized to mavacamten (5–15 mg) or placebo. The primary end point was to assess how many of these patients still met SRT eligibility criteria after treatment. After 16 weeks, 76.8% of patients on placebo remained eligible for SRT according to guidelines, while only 17.9% of patients on mavacamten met the established criteria for SRT.[19]

Mavacamten was also tested in patients with non-obstructive HCM, with the rationale that this drug, by altering the contractile mechanics of the cardiomyocyte, could have favourable effects on the pathophysiology of the disease and therefore improve symptoms. The MAVERICK-HCM multicentre trial randomized 59 patients to mavacamten (2 different doses) and placebo. After 16 weeks of treatment, the drug was well tolerated by the patients, and a significant reduction of NT-proBNP was observed in the treated group.[20]

The MAVA-LTE study is an ongoing study with a 5-year extension that includes 231 of 244 patients who completed Phase 3 treatment of the EXPLORER-HCM trial. The study was designed to evaluate the efficacy, safety, and optimal dosage of the drug in the long term.[21]

Aficamten is a new myosin inhibitor being studied for use in patients with symptomatic obstructive HCM. It has distinctive features including a shorter half-life than mavacamten, reversibility of drug effect within 24 h of drug discontinuation, a dose–response ratio that allows for a broad therapeutic window, and a lack of significant drug–drug interactions.[15]

At present, the Phase 2 study REDWOOD-HCM,[22] randomized 2:1 to aficamten (two different doses) or placebo, has been published. The study, with a duration of 10 weeks, showed a reduction of the gradient in LVOT both at baseline and after Valsalva manoeuver and a significant reduction of NT-proBNP, in the majority of patients. In this study, response in terms of (subjective) improvement in symptoms was observed in 43% of patients treated with the lowest dose and 64% of patients with the highest dose of the drug.

The Phase 3 SEQUOIA-HCM study will include cardiopulmonary testing to evaluate the efficacy of aficamten after 24 weeks of treatment.

There is no doubt that the use of these drugs can represent an innovative approach in the pharmacological treatment of HCM, by intervening on one of the pathophysiological aspects of the disease, i.e. the contractility. However, some, not secondary, points remain to be clarified: (i) the experimental studies of these drugs have been performed on mice with mutations on cardiac myosin, while the clinical studies have only a percentage of patients genetically tested for mutations on myosin; (ii) all the studies were conducted on relatively small cohorts and, with short follow-up, this last representing a major limitation if we consider that the population to which these therapies should be targeted include essentially young subjects or young adults; and (iii) the impact of these drugs on the reduction of contractility and ejection fraction (although dose-dependent and reversible with drug suspension) suggests great caution for long-term treatment.

Further studies, prolonged follow-up and use in patients with pathogenic mutations on myosin and pre-clinical phenotype, will clarify whether these drugs represent a disease modifying therapy in HCM.

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## Data availability

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