Hypertrophic obstructive cardiomyopathy surgery. Which surgery for which patients?

An echocardiography, cardiac magnetic resonance and surgical techniques study.

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LIST OF ABBREVIATIONS

HOCM = hypertrophic obstructive cardiomyopathy

SAM = systolic anterior motion

LVOT = left ventricle outflow tract

SMS = subaortic membrane stenosis

PM = papillary muscles

AML= anterior mitral leaflet

PML= posterior mitral leaflet
SYNOPSIS

Transaortic septal myectomy is currently considered the most appropriate treatment for the majority of patients with obstructive hypertrophic cardiomyopathy and severe symptoms unresponsive to medical therapy. Surgical results, although vastly improved in recent years, are nevertheless limited to relatively few centers with extensive experience and particular interest in the management of hypertrophic obstructive cardiomyopathy. Both the traditional myectomy (Morrow procedure) with about a 3-cm long resection or extended myectomy (a resection of about 7 cm) are currently used. The transaortic approach remains the primary method of exposure. Virtual abolition of the LV outflow gradient and mitral regurgitation is usually accomplished by muscular resection resulting in physical enlargement of the outflow tract and by interruption of the mitral valve SAM, which is usually responsible for the outflow gradient.

Mitral valve abnormalities were not part of modern pathological and clinical descriptions of hypertrophic cardiomyopathy in the 1950s, which focused on left ventricular hypertrophy and myocyte fiber disarray. Although systolic anterior motion of the mitral valve was discovered as the cause of left ventricular hypertrophy
outflow tract obstruction in the M-mode echocardiography era, in the 1990s structural abnormalities of the mitral valve became appreciated as contributing to systolic anterior motion pathophysiology. Hypertrophic cardiomyopathy mitral malformations have been identified at all levels. They occur in the leaflets, usually elongating them, and also in the submitral apparatus, with a wide array of malformations of the papillary muscles and chordae, that can be detected by transthoracic and transesophageal echocardiography and by cardiac magnetic resonance. Because they participate fundamentally in the predisposition to systolic anterior motion, they have increasingly been repaired surgically.

In order to assess the results (hospital mortality, improvement in clinical and echocardiographic parameters) of the hypertrophic obstructive cardiomyopathy surgical treatment, all patients requiring surgery among the centers included in the study group will be prospectively collected and recruited from the Italian Registry of Cardiac Surgery.
STATE OF THE ART and PRELIMINARY DATA

The transaortic surgical septal myectomy [1] is the most commonly used technique to treat HOCM, and is associated with low operative morbidity and mortality and reduction of the outflow gradients [2, 3]. In the modern era, the role of the mitral valve in the pathophysiology of HOCM has been addressed [4-7]. Initially, the left ventricle outflow tract (LVOT) obstruction was thought to be the result of a Venturi effect produced by the septal hypertrophy involving the mitral valve [8]. More recently, a “drag” [9] rather than “suck” [8] mechanism was proposed: the flow acceleration around the hypertrophied septum pushes the anterior mitral leaflet (AML) into the LVOT causing systolic anterior motion (SAM). Noteworthy, subvalvular mitral valve apparatus malformations causing SAM–related LVOT obstruction can even occur in patient with no or moderate septal hypertrophy [7]. These include leaflets elongation and a wide array of malformations of the papillary muscles (PM) and chordae [9] that can be detected by echocardiography and by cardiac magnetic resonance [10, 11].

The role of mitral valve in the pathogenesis of LVOT has been emphasize by few centers [4-6, 13, 14] worldwide.
The 0.4% (17/3695 patients) of the composite operative mortality after septal myectomy from 5 major high-volume Centers in North America highlights the role of dedicated HOCM units [14]. In Europe [13], the review of 124 consecutive patients with heart failure symptoms due to HOCM undergoing extended left ventricular septal myectomy revealed a low (<1%) early operative mortality, and a reduction in outflow tract gradients and SAM-mediated mitral regurgitation. Abnormal PM morphology are reported in HOCM. PM displacement, bifid PM [19], hypertrophy, anterior fusion, and inward orientation, has been frequently observed in patients with LVOT obstruction [7, 9, 11, 20]. An anterior and basilar displacement of the base of the anterolateral PM and abnormal muscular connections with the anterolateral wall, inserting into or near the A1 scallop of the mitral valve, are the most common pathoanatomic findings [7]. Bifid and hypermobile PM increase the obstruction even without significant basal septal hypertrophy [19], and PM hypertrophy occurs in more than half of patients with HOCM [21]. The relief of PM fusion and anomalous chordae tendinae resection (false cordae), in addition to an extended septal myectomy, improve surgical outcomes [22] and, reduce the risk of reoperation [23].

In a series of 124 consecutive patients [13], the resection of fibrous–muscular attachments between PM and ventricular septum or free wall was performed in all
cases to relieve the LVOT obstruction. Thickened and retracted secondary chordae that insert beyond the free margin and rough zone of the AML may contribute to obstructive pathophysiology, lifting and tenting the AML anteriorly toward the LVOT [6], and predisposing to SAM [7]. Their role in obstruction, especially in the relative thin septum, have been recently demonstrated by Ferrazzi [6]. The anomalous chordae resection (a median of 3, range 1-8) associated with a shallow myectomy in 39 patients (with a ventricular septal thickness ≤19 mm) showed better clinical and hemodynamic results compared the control group (only myomectomy, 29 patients). Noteworthy, the conventional surgery jeopardized the repair of the mitral valve and increased the need for prosthetic rings, compared to the transaortic chordal cutting. During a 23±2 months of follow-up, 1/39 patients showed mitral regurgitation ≥3.

One third of patients with hypertrophic cardiomyopathy present a primary increase in mitral leaflet length [10] and this is even more pronounced in HOCM [7], where the protruding leaflets increase the risk of SAM. Patients with HOCM presents usually an AML greater than 30 mm [25]. Thus, surgical correction could be reasonable. The outcomes after the horizontal plication, aiming at shortening and stiffening the AML, in addition to the myectomy and PM release, the so called resect-plicate-release strategy, have been extensively reported in 252 patients with HOCM [7, 25]. The
elegant algorithm guiding this surgical strategy, that shows a 0.4% of both operative mortality and early reoperation and 0.6% of pacemaker implantation, is reported by Sherrid [7]. Vriesendorp reported the benefit of AML extension in addition to myectomy in 98 patients with HOCM [4], with an average AML length of 34 mm. The procedure stiffens the midportion of the AML and is carried out through the transaortic approach. No hospital mortality was reported and during the long-term follow-up (8±6 years), the patients experienced significant symptomatic and hemodynamic improvement. The rate of pacemaker implantation, need for reoperation for patch dehiscence, and residual obstruction were 4%, 2% and 1%, respectively. Three patients underwent further mitral valve replacement during the follow-up. Isolated elongation of the PML can push anteriorly the coaptation with AML causing SAM, mitral-septal contact, and LVOT obstruction [7, 9]. Dulguerov [5] reported a three-step procedure (transaortic septal resection, transmitral septal resection through the AML that is detached and reconstructed using autologous pericardial patch, and PML resection followed by rigid mitral valve annuloplasty) to treat 16 patients with HOCM and more than 20 mm PML in length. This elegant procedure aims at 1) completing and extending the septum resection up to the ventricular apex through the mitral valve, and 2) moving posteriorly the coaptation
plane of the mitral valve, away from the septum, increasing the AML area and restricting the PML motion (with PML resection and annuloplasty). The excellent mid-term surgical results, although a high rate of pacemaker implants (18%) occurring at the beginning of the experience, clearly address the role of the PML in the pathogenesis of LVOT obstruction.
AIM and END-POINTS OF THE PROJECT

Primary aim. To evaluate the results of the surgical treatment for HOCM in term of survival and changes in clinical and echocardiographic parameters. Primary end-points: 1) Survival: 30-day survival (yes/no) and in-hospital survival (yes/no); 2) Clinical: change of NYHA as difference between pre-surgery and 3-months and 1-year follow-up test; 3) Echocardiography: change of LVOT gradient, septum thickness, and residual mitral regurgitation as differences between pre-surgery and 3-months and 1-year follow-up tests.

Secondary aims. To assess the role of the mitral valve (leaflet, chordae and papillary muscles, PM) in the LVOT obstruction and the long term survival. Secondary end-points. 1) mitral valve surgery (yes/no): any procedures involving the mitral valve and sub-valvular apparatus; 2) survival (yes/no) at last follow-up.
INCLUSION CRITERIA

All patients requiring HOCM surgery among the cardiothoracic centers involved in the trial during the study period.
STUDY DESIGN

Observational, prospective, multicenter.

All demographic, preoperative, intraoperative and postoperative variables will be analysed. Surgical techniques will be recorded. Follow-up information (survival, NYHA, LVOT gradient, major adverse cardiac and cerebrovascular event) will be gathering routinely by outpatient clinic, telephone calls or the treating general physician. Preoperative and follow-up image findings (transthoracic, transesophageal and stress echocardiograms and magnetic resonance) will be recorded. Patient consents will be obtained before the operation. Other preoperative echocardiographic and MRI parameters: anterior and posterior mitral leaflet length, mitral valve coaptation depth, mitral valve secondary cordae length, cardiac mass, transverse LV outflow tract diameter and the ratio of the transverse LV outflow tract diameter to AML length.
SAMPLE SIZE

Previous studies [14, 24, 27, 28] show values of 30-day survival post-surgical treatment for HOCM from 0.1% to 4%. Because the most relevant result is around 0.1% [14], we assume this proportion as the null hypothesis of the sample size calculation.

In order to achieve a power of 90% to detect a real difference of 3.9% in 30-day survival, a sample size of 96 patients is required. This calculation was estimated using the one-sided binomial exact test with a significant level of 5% [29, 30].
STATISTICAL ANALYSIS

The comparison between NYHA, LVOT gradient, septum thickness and residual mitral regurgitation before and after surgery will be assessed by paired T-test. In order to assess the 30-day and hospital survival the percentage and interval confidence (CI 95%) will be evaluated.

In order to assess the long term survival the Kaplan-Meier estimate will be applied.

Data management and all statistical analysis will be performed using SAS version 9.4 and all p-values <0.05 will be considered statistically significant.
RESEARCH AGENDA

Research will be divided into the following phases:

October-November 2016: 1. EACTS project presentation
                        2. SICCH project presentation and approval

January-May 2017:      1. Institutional IRRB and EC approval:
                        2. Database set

June 2017-December 2019: 1. Patients recruitment and data collection

November 2020:          1. Manuscript draft
                        2. SICCH presentation.
COSTS

PI time: 40 hours/month

Overall co-investigators time: 25 hours/month
REFERENCES


SIGNATURE and DATE

November 7, 2016