Surgical Myectomy for Hypertrophic Obstructive Cardiomyopathy:

The Cut That Heals

Running title: Williams et al.; Myectomy: The cut that heals

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Hypertrophic cardiomyopathy (HCM) has been one of the most interesting and controversial disorders in cardiovascular medicine. Although initial descriptions of the pathology of hypertrophic cardiomyopathy (HCM) were published over a century ago, it was not until the surgical and pathological observations of Brock and Teare respectively that this cardiac entity came to attention in the modern era. HCM is a primary disorder of the myocardium characterized by myocyte hypertrophy and fibre disarray, myocardial fibrosis, and abnormal coronary intramural microvasculature. Although HCM is characterized by tremendous diversity in terms of phenotypic expression, genetic substrate, and clinical presentation, left ventricular outflow tract (LVOT) obstruction is an integral component of the disease, occurring in up to 70% of patients either at rest or with provocation.

Concepts and consequences of left ventricular outflow tract obstruction

Dynamic LVOT obstruction has long been recognized as a clinical feature of HCM, but the pathophysiology and clinical significance of intraventricular pressure gradients sparked much controversy and debate. While initially thought to result from early excessive and rapid ejection from a hypercontractile left ventricle (LV) as opposed to true mechanical impedance to blood flow, this hypothesis was later refuted by Wigle and colleagues, who demonstrated a prolonged LV ejection time in the presence of such intraventricular pressure gradients. The pathophysiology of LVOT obstruction is now widely accepted to be due to an eject-obstruct-leak concept, driven by Venturi and drag forces of the anterior mitral valve leaflet. Echocardiographic and cardiac magnetic resonance (CMR) studies have documented that reduction in LVOT cross-sectional area is due to morphologic features such as narrowing of the LVOT by septal hypertrophy, intrinsic abnormalities of the mitral valve leaflets, anterior displacement of the mitral apparatus, and anterior malposition of the papillary muscles, either alone or in
combination. Rapid LV ejection through a narrowed outflow tract results in the anterior mitral leaflet being subjected to Venturi and/or drag forces distal to the site of coaptation with the posterior mitral leaflet. These forces draw and then continue to push the anterior leaflet towards the septum, resulting in the development of a sharp anterior and superior angulation of the leaflet and mitral leaflet-septal contact in early to mid-systole (SAM). The resulting distortion of the mitral valve leaflets results in malcoaptation and an interleaflet gap, giving rise to the posteriorly-directed jet of mitral regurgitation that is typically seen in most patients with LVOT obstruction (Figure 1).

Outflow tract obstruction imposes a hemodynamic load on the LV, resulting in a complex interplay of diastolic dysfunction, elevated LV end-diastolic pressure, mitral regurgitation, and myocardial ischemia. Clinically, LVOT obstruction causes symptoms of dyspnea, ischemic chest pain, presyncope, or syncope with exertion. Obstruction is typically dynamic in nature, depending on inotropic and chronotropic state, loading conditions and systemic vascular resistance. While resting LVOT obstruction (defined as a peak instantaneous LVOT gradient ≥ 30mmHg) is present in around 25-30% of patients with HCM, a further third or more have evidence of latent LVOT obstruction (<30mmHg at rest and ≥30mmHg with provocation) with physiologic manoeuvres such as the Valsalva manoeuvre or exercise testing1.

The importance of identifying LVOTO lies in its adverse impact on morbidity and mortality. In a large multicenter study, resting LVOTO was associated not only with a higher likelihood of death due to HCM, but also with progression to NYHA Class III or IV symptoms or death due to heart failure or stroke3.

Medical Therapy for symptomatic obstructive HCM

While some individuals with LVOT gradients ≥ 50mmHg are asymptomatic, most present with
Symptoms necessitating therapy. Beta-blockers remain the cornerstone of therapy, and via their negative inotropic and chronotropic effect reduce obstruction and improve diastolic filling. In patients intolerant of beta-blockers, Verapamil may result in symptomatic improvement. However, calcium channel blockers should be used cautiously in patients with severe LVOT obstruction and elevated pulmonary artery wedge pressures due to the risk of precipitating pulmonary edema. Since the first introduction of Disopyramide by investigators in our institution\(^4\) numerous reports have attested to its safety and efficacy as a second-line agent in patients resistant to therapy with beta or calcium-channel blockers\(^5\). The addition of Disopyramide in these patients, via its negative inotropic effect, may result in significant symptomatic improvement, as demonstrated in large series from Toronto\(^6\) and New York\(^7\). Disopyramide is used less frequently in the United States than in Canada and Europe, partly due to guideline recommendations of commencing Disopyramide in an in-patient setting with ECG monitoring for QT prolongation\(^8\). However, in our practice we have commenced Disopyramide therapy in several hundred outpatients without any apparent major cardiac events or deaths. Several studies have demonstrated that approximately two-thirds of patients can be managed with medical therapy with amelioration of symptoms and \(>50\%\) reduction in the LVOT gradient\(^5,7\). In addition, Ball and colleagues have demonstrated that the long-term survival of patients treated conservatively with medical therapy is much better than previously thought. In their large cohort of 649 patients they showed that those patients who demonstrate both a significant improvement in symptoms and reduction in resting LVOT gradient have a similar overall and HCM-related survival to patients treated by an invasive septal reduction strategy\(^6\).

**Interventional therapy for HOCM**

Despite the efficacy and safety of medical therapy, a significant proportion of patients require
interventional strategies for relief of LVOT obstruction. Given the potential complications of invasive therapies, it is important that patients fulfil clinical, anatomic and hemodynamic criteria to determine suitability for a particular procedure. The ACCF/AHA 2011 guidelines recommend that septal reduction therapy only be performed by experienced operators in the context of a comprehensive clinical HCM program, for patients with severe symptoms refractory to maximally tolerated medical therapy with a resting or provokable LVOT gradient ≥ 50mmHg, and septal hypertrophy of sufficient thickness to perform the procedure safely and effectively.

Alcohol septal ablation (ASA), when performed in experienced centers, provides a suitable alternative for those patients of advanced age or with significant co-morbidities that increase surgical risk, or to avoid surgery. Infarction of the territory supplied by the obliterated septal perforator(s) leads to regression of subaortic hypertrophy with scar formation over a 6-12 month period. Myectomy surgery is generally preferred when septal hypertrophy is excessive, or concomitant surgery on the coronary arteries or mitral valve apparatus is required.

Dual-chamber pacing while a potential therapeutic option, has shown only a modest benefit in randomised controlled trials. Its primary use is in patients over the age of 65 years or those who have an independent indication for pacemaker implantation (or ICD) or an unacceptably high risk for surgical myectomy or alcohol septal ablation.

**Surgical myectomy for HOCM**

Brock’s initial report of muscular hypertrophy of the LVOT led to the concept that surgical division or myotomy of septal muscle bundles would lead to relief of obstruction via interruption of the “sphincter-like” muscular contraction ring. W.P. Cleland first performed a myectomy in November 1958 via the transapical approach in London, England. In early case reports a reduction in LVOT gradients was observed in most patients, but in-hospital mortality was high...
and obstruction persisted in some patients. Thereafter surgical intervention (first in the form of myotomy and subsequently myectomy) was pioneered by Morrow (National Institutes of Health), Kirklin (Mayo Clinic), and Bigelow and Williams (Toronto General Hospital). The classic myectomy (Morrow operation or trough myectomy) involved resection of only a small amount of muscle from the proximal interventricular septum, thereby increasing the cross-sectional area of the LVOT. More recently, surgeons have employed an “extended myectomy”, whereby muscular resection is wider and extends more distally beyond the point of SAM-septal contact towards the base of the anterolateral papillary muscle, allowing more complete abolition of SAM and LVOT obstruction. Newer surgical approaches have been described which include resection of septal muscle in addition to mitral valve plication and papillary muscle manipulation.

In this issue of Circulation, Desai et al\textsuperscript{10} describe a consecutive 11 year experience of 699 patients who underwent septal myectomy at the Cleveland Clinic for obstructive HCM between January 1997 -December 2007. This series is similar to reports from other HCM centers of excellence (both in terms of patient population and results), except for the exclusion of patients labelled as having hypertensive heart disease and concomitant LVOT obstruction and patients with LV systolic dysfunction. In addition, the pre-operative use of Disopyramide in the current series was only 7%, a rate significantly lower than our experience in Toronto\textsuperscript{6,11} but in keeping with the prevalence of Disopyramide use in other centers in the United States\textsuperscript{12,13}. In this series concomitant surgical procedures included mitral valve repair/replacement (23%), coronary bypass grafting (9%), combined mitral and coronary surgery (3%), surgical MAZE or pulmonary vein isolation (11%), and left atrial appendage ligation/exclusion (14%). Concomitant mitral surgery was more common in patients with a septal thickness < 2cm (41%) compared with those
with a septal thickness > 2cm (25%). Over a mean follow-up period of 6.2 years, the authors demonstrate a low event rate (using a composite endpoint of all death, appropriate AICD discharges, resuscitated sudden death, documented stroke, and onset of congestive heart failure requiring inpatient hospitalization) at 30 days (0.7%) and at 1 year (2.8%). In addition, the hard event rate (death, appropriate AICD discharge, or revival from sudden death) were also low at 30 days (0%) and 1 year (1.5%). An excellent hemodynamic and symptomatic response to surgery is reported, with post-operative resting and provocable LVOT gradients of < 30mmHg in 98% of patients and < 50mmHg in 84% respectively, in association with NYHA class I or II symptoms in 96% of cases. Nonsustained VT was noted in 71 patients during follow-up, with sustained VT in a further 3 patients. Redo surgery was performed in 3.4% of cases for residual LVOT obstruction (80% of reoperations were mitral valve replacement). After multivariate analysis predictors of poor outcome after myectomy included advanced age and persistence of post-operative atrial fibrillation, while concomitant surgical procedures predicted composite events only on univariate analysis. Increasing age has previously been shown to be related to outcome in several surgical series, including those from Toronto\textsuperscript{11} and New York\textsuperscript{13}. Similarly the need for concomitant surgical procedures as opposed to isolated myectomy is a well-established risk factor for adverse outcomes\textsuperscript{11,13}. Woo et al have previous demonstrated an association between pre-operative atrial fibrillation and poor outcome, but this is the first study to relate residual post-operative atrial fibrillation with both composite and hard events.

The current paper adds to a substantial body of literature demonstrating the efficacy of surgical myectomy, which can be performed in experienced high-volume centers with not only low morbidity and mortality, but also excellent long-term symptomatic improvement, excellent hemodynamics and low sudden death rates. With greater expertise in surgical technique there has
been a clear reduction in operative mortality and improved long-term survival since the initial published series in the 1980’s and 1990’s, as demonstrated in Table 1. In addition, concomitant surgical procedures are performed more frequently, likely due to operating on older patients with significant co-morbidities. Although ASA has emerged as an effective invasive approach for the relief of LVOT obstruction, surgery offers the advantage of immediate and greater reductions in LVOT gradients, with low peri-operative mortality and morbidity and excellent long-term survival. While concern remains over the long-term arrhythmic risk associated with the creation of an area of myocardial infarction after ASA in patients already at risk of life-threatening arrhythmias, many reports have suggested that these concerns are unfounded. However, several series have raised concerns regarding long-term outcome. Ten Cate et al demonstrated an annual event rate (cardiac death, aborted cardiac arrest, and/or appropriate AICD discharge) of 4.4% following ASA. Similarly, data from the Massachusetts General Hospital suggests a 5% annual event rate for VT/VF after ASA. These event rates clearly exceed those of surgical myectomy, although differences exist between patient groups in terms of age and comorbidities that limit direct comparison. However, the long-term survival after ASA remains to be determined, given the length of follow-up in most studies is relatively short compared with the gold standard of surgical myectomy.

**Does myectomy confer additional benefits?**

While several studies have demonstrated the safety and efficacy of medical therapy in patients with obstructive HCM, with a similar overall and HCM-related survival to those patients treated by an invasive septal reduction strategy, there remains a clear benefit for myectomy in those patients who remain in NYHA class III or IV despite optimal medical therapy.

Left atrial dilatation, a marker of adverse cardiovascular outcomes including atrial
fibrillation (AF), stroke, sudden death and heart failure-related mortality, has been shown to be subject to beneficial reverse remodelling after myectomy, with a significant reduction in left atrial volume index. Incidence of AF after myectomy (excluding the initial period) is not widely reported, but in the present study by Desai et al the prevalence of AF decreased from 26% preoperatively to 20% post-operatively. In the study by Woo et al, 54% of patients with evidence of pre-operative AF went on to have further episodes of AF after surgery. In addition, AF occurred in 21% of patients without a prior history of AF after myectomy. Whether the beneficial effects of myectomy on left atrial reverse remodelling will translate into a concomitant reduction in AF has yet to be determined, but conceptually this would be expected.

In contrast to the potential arrhythmia risk associated with ASA, which has been demonstrated in short-term follow-up to be around 10%, myectomy carries no increased risk of arrhythmia due to the lack of creation of intramyocardial scarring. In fact many series have reported a low risk of sudden cardiac death or appropriate AICD discharges after myectomy. Myectomy itself appears to alter the natural history of HCM, conferring an excellent survival benefit and near-normal life expectancy. Not only is there a marked reduction in the incidence of appropriate AICD discharges and risk of sudden cardiac death after myectomy when compared with patients treated medically, but also a reduction in recurrent syncope and increased survival in the surgically-managed group. This is likely particularly true in patients with marked pre-operative symptoms.

Conclusion and Summary

Patients with symptomatic obstructive HCM who have failed medical therapy require an invasive interventional therapy to restore them to long term health. Regardless of the procedure chosen, operator and institutional experience are crucial to successful outcomes and low peri-procedural
morbidity and mortality. Given the substantial learning curve associated with invasive procedures for HCM, these should be performed in centers with adequate procedural volumes to ensure good early and long term results. While controversy still exists as to what intervention is best, Desai et al have provided important additional evidence highlighting that surgical myectomy remains the gold standard by which other procedures need to be compared to. The results for myectomy are unmatched for early efficacy, low procedural mortality and morbidity and the ability to perform concomitant coronary and valve surgery that is required in about 1/3rd of referred patients. Desai et al have further confirmed the sustained excellent long term benefit, but also the risks of post myectomy atrial fibrillation, which remains a major management challenge. Surgical myectomy is truly the cut that heals and the achievable outstanding early and late outcomes should be an impetus to create more centers of surgical excellence around the world.

Conflict of Interest Disclosures: None.

References:


5. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ.


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<th>Study</th>
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<th>Patients enrolled</th>
<th>Concomitant procedures</th>
<th>Follow-up</th>
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<th>30-day mortality</th>
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**Figure Legend:**

**Figure 1.** Mechanism of dynamic outflow tract obstruction. The upper cartoon shows a schematic representation of the mitral leaflets at A: Onset of systole; B: Early systole; C: Mid-systole; Note the elongated mitral leaflets which are drawn into the LVOT during early systole with mid-systolic prolonged SAM-septal contact, malcoaptation of the mitral leaflets and the resultant posteriorly-directed jet of mitral regurgitation. The lower images show mid-esophageal transesophageal images with (right) and without (left) color flow imaging. The extensive mitral leaflet malcoaptation is shown by the yellow triangles, resulting in a wide jet of posterior directed mitral regurgitation. (Figure reproduced from The Practice of Clinical Echocardiography 4th Edition 2012, Catherine Otto, Chapter 27 Page 524, with permission from Elsevier). (Panels A to C originally from Grigg LE, Wigle ED, Williams WG, Daniel LB and Rakowski H. Transesophageal Doppler echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance in intraoperative decision making. J Am Coll Cardiol. 1992; 20(1):42-52. Reproduced with permission from Elsevier).
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