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Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: past, present and future

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Fifty years ago, the first modern reports of what we now recognise as hypertrophic cardiomyopathy (HCM) were written by a surgeon, Sir Russell Brock,¹ and a pathologist, Donald Teare.² These classic papers stimulated an intense and sometimes controversial field of study, focused in large part on the characterisation of left ventricular outflow tract obstruction. Detailed invasive haemodynamic investigations highlighted the extraordinary dynamic nature of this new form of outflow obstruction, and numerous surgical therapies were proposed and abandoned. The introduction of echocardiography allowed investigators to determine the mechanism for obstruction—an adverse interaction between a hypertrophied septum and abnormal movement of the mitral valve towards the septum—but also showed that obstruction was not a universal feature of the disease. The focus of this article is to review the historical controversies surrounding left ventricular outflow tract obstruction in hypertrophic cardiomyopathy, and to discuss the modern approach to its assessment and treatment.

PRESENCE AND PREVALENCE OF OBSTRUCTION

As is the case with many disease processes, initial clinical reports suggested that hypertrophic cardiomyopathy was a rare disorder that was nearly always associated with the need for surgery to relieve obstruction or death at a young age.^{1–3} In the late 1950s, master clinicians (see Coats and Hollman⁴) elucidated the dynamic nature of the muscular, rather than valvular, outflow tract obstruction utilising bedside manoeuvres.⁵ Thus, physical signs of outflow obstruction, responsive to manipulation of ventricular preload and afterload, in the absence of radiographic evidence of aortic valve calcification, were the key to pre-mortem diagnosis. In the years that followed, pharmacological manipulations during invasive haemodynamic assessment furthered the understanding of the physiological determinants of obstruction, and suggested options for its treatment (table 1).^{6–10}

In spite of this work, the very existence of impedance to left ventricular ejection was vigorously contended in the early 1960s.^{11–13} The subject was considered of such importance that it was the subject of a debate at the annual scientific sessions of the American Heart Association in 1963 with no other concurrent sessions, and again two decades later.¹⁴ Neither the auscultatory findings nor the invasive haemodynamic measurements were in question. Rather, it was the mechanism by which

the measured pressure gradients were generated and their clinical significance that were contested. Some investigators suggested that the apparent difference in pressure between the left ventricle (LV) and the aorta was an artefact caused by rapid ejection, complete systolic emptying and cavity obliteration.^{11–15} Other researchers acknowledged that flow acceleration due to systolic obliteration of the LV cavity could result in this errant impression of “obstruction”, but pointed to studies demonstrating identical pressures in the LV apex and LV inflow with a pressure drop in the outflow tract as evidence that some patients did have true obstruction to LV ejection.^{13–16} The debate was seemingly settled when studies carried out with the new imaging modality, echocardiography, demonstrated that many patients have true obstruction at the outflow tract with an open, rather than obliterated LV cavity.^{17–20}

The lessons learnt from this debate are still relevant to modern-day practice. During the echocardiographic evaluation of patients with hypertrophic cardiomyopathy, isolated systolic cavity obliteration must be excluded, and systolic anterior motion of the mitral valve (see below), with an open LV cavity must be demonstrated before concluding that a measured pressure gradient represents true obstruction. This is important therapeutically as septal myectomy or septal alcohol ablation would not be expected to have benefit for patients with complete emptying of the left ventricle in the absence of left ventricular outflow tract obstruction.

Whether true obstruction was common or rather the exception furthered the debate over its importance. The use of echocardiography from the late 1960s onwards demonstrated that hypertrophic cardiomyopathy (HCM) was more common than originally appreciated,^{21–22} but also suggested that most patients did not have evidence of outflow tract obstruction under resting conditions. However, it was also appreciated that outflow tract obstruction could be provoked during physical effort or with simple bedside manoeuvres (table 1).^{7–23–24} The frequency of this latent form of obstruction has been investigated in several studies (including one by Shah *et al*²⁵). Collectively, they suggest that up to 70% of HCM patients referred for clinical assessment have either resting or easily provokable obstructive physiology.²⁶ The implications of this observation are not trivial. The majority of HCM patients experience their symptoms with physical effort, but standard haemodynamic assessments in the

Table 1 Clinical modulators of dynamic left ventricular outflow tract obstruction

Obstruction augmented	Obstruction diminished
Decrease preload	Increase preload
Short filling period (fast heart rate)	Long filling period
Hypovolaemia/dehydration/diuretics	Volume repletion
Valsalva	Leg raise
Squat-to-stand	Stand-to-squat
Warm environment	Cool environment
Postprandial state	
Decrease afterload	Increase afterload
Vasodilators	Vasoconstrictors
Increase contractility	Decrease contractility
Positive inotropes	Negative inotropes

echocardiographic or invasive laboratories are performed with the patient at rest in a lying position, conditions that minimise the obstruction. Thus, when latent obstruction is suspected clinically, provocation manoeuvres such as upright exercise, Valsalva or pharmacological challenge should always be employed. Here again, documentation of not only the observed gradients but also the systolic anterior motion of the mitral valve and a non-obiterated cavity are required to confirm latent obstruction.

MECHANISM OF OBSTRUCTION

Theories on the cause of dynamic obstruction to left ventricular outflow in hypertrophic cardiomyopathy have evolved in parallel with the technologies available to clinical investigators. Initial descriptions, derived from surgical reports, suggested that a muscular ring or sphincter contracted during ventricular systole to constrict the diameter of the outflow tract.^{27–29} Indeed, the original myotomy procedure was inspired by the operative approach to pyloric stenosis. While abnormal positioning of the mitral valve and its support structures was evident from very early studies, M-mode echocardiography revealed that approximation of the anterior mitral leaflet to the basal ventricular septum in systole rather than a muscular ring is the mechanism by which the outflow tract is dynamically narrowed.¹⁷ Early hydrodynamic theories regarding the mechanism of systolic anterior motion (SAM) of the anterior mitral leaflet favoured the Venturi effect, whereby the accelerating high velocity blood flow in the outflow tract results in a suction force that pulls the mitral valve leaflet anteriorly.³⁰ Studies performed in the past two decades suggest a more complex mechanism that involves an interaction between the shape of the interventricular septum, abnormal mitral valve anatomy and altered flow vectors in the LV cavity (fig 1).^{19–31} SAM of the mitral valve leaflet often begins before the aortic valve has opened (when Venturi effects are negligible), suggesting that the position of the mitral valve leaflets in relation to the LV outflow tract is a major determinant of obstruction, rather than a secondary phenomenon that exacerbates the obstruction.^{18–19–31} In some patients anterior displacement of the papillary muscles results in a more anterior coaptation point. Together with an enlargement or elongation of one or more cusps of the anterior mitral leaflet, this results in a sail-like configuration of the valve. As systolic flow in the LV cavity courses first posteriorly in the mid-ventricle around the bulging septum and then anteriorly towards the outflow tract, flow vectors run across, rather than parallel to, the closed mitral valve, with the result that it is “pushed” into the outflow tract. Drag forces, similar to that of a hydrofoil, are also implicated in

this process. Thus, thoughts on SAM have moved from that of an important secondary phenomenon caused by suction to a mechanism initiated by blood flow pushing the valve into the outflow tract.

In most patients, SAM of the mitral valve causes a variable degree of mitral regurgitation. In the absence of other anatomical mitral valve abnormalities, SAM-mediated mitral regurgitation should have a posteriorly directed jet and the severity of regurgitation in individual patients should mirror the severity of obstruction. Mitral regurgitant jets that are central or anteriorly directed should raise the suspicion of intrinsic structural mitral valve abnormalities (prolapse, flail, perforation, etc), a finding that can have a bearing on therapy options, particularly if the intrinsic valve disease is clinically significant.

CLINICAL IMPORTANCE OF OBSTRUCTION

It has been recognised since the very first descriptions of hypertrophic cardiomyopathy that dynamic left ventricular outflow tract (LVOT) obstruction can cause symptoms. Syncope and pre-syncope result from reduced stroke volume; increased intra-cavitary pressure causes angina by exacerbating microvascular ischaemia secondary to increased myocardial mass and microcirculatory abnormalities^{32–33}; and mitral regurgitation caused by SAM of the mitral valve and load-dependent diastolic dysfunction contributes to exertional dyspnoea. All of these features are exacerbated by effort-related increases in contractility and decreases in systemic vascular resistance, which promote acute worsening of outflow tract obstruction. And yet, resting gradients do not correlate well with objectively determined functional limitation in cross-sectional analyses, probably because the dynamic nature of obstruction weakens the relation between resting gradients observed in the laboratory and activity-related obstruction experienced by patients in daily life; however, in longitudinal studies, progression to severe functional limitation (New York Heart Association Class (NYHAC) III–IV) occurs more commonly in untreated patients with resting obstruction than in non-obstructive patients.³⁴

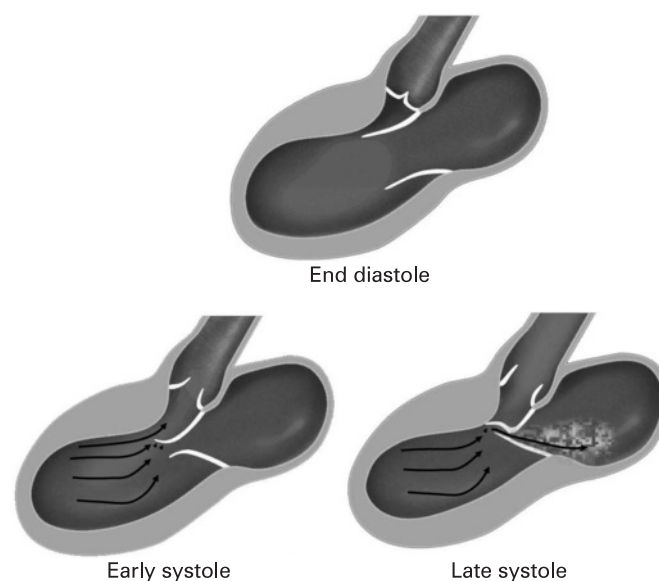


Figure 1 Depiction of the modern concepts of the mechanism of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. In early systole (bottom left), abnormal flow around the hypertrophied septum pushes the mitral valve into the outflow tract and results in obstruction and mitral valve regurgitation (bottom right).

After many decades of research it is only recently that an association between obstruction and survival has been demonstrated.³⁵ Specifically, patients with obstruction have worse overall survival, HCM-related survival and survival free from sudden cardiac death than HCM patients without obstruction.^{34,36} The interaction between obstruction and sudden cardiac death is explored elsewhere in this issue (see Elliott and Spirito³⁷). The excellent long-term survival following surgical septal myectomy provides indirect evidence to support the relation between obstruction and outcome.^{38,39}

TREATMENT OF OBSTRUCTION

During the five-decade history of HCM, many therapies to reduce or eliminate outflow tract obstruction have been proposed (table 2).

Brock's initial paper, however, cautioned that surgery was difficult and perhaps even dangerous.¹ Indeed, the operative mortality reported in the early surgical series led to appropriate caution about the utility of surgical relief of obstruction. Even in the modern era with markedly improved surgical outcomes, it is still important to recognise that relief of symptoms is the primary goal of treatment and that most patients can be treated successfully with medications alone.

Pharmacological therapy

The recognition that outflow tract obstruction, dependent on contractility and loading conditions, could be manipulated with drugs^{7,8,10} led to the widespread use of β -adrenergic antagonists as standard first-line therapy in obstructive HCM.^{7,8,10,40,41} These agents decrease catecholamine mediated increases in ventricular contractility and heart rate and, by blunting the effort-related increase in heart rate, help to preserve the duration of diastolic filling and thereby maintain ventricular preload. The calcium channel blocking agents, verapamil⁴²⁻⁴⁴ and diltiazem, were also found to be useful, working via similar negative inotropic and negative chronotropic properties, as well as having some specific effects on diastolic function.⁴⁵ Another drug that decreases contractility and heart rate, the class 1A anti-arrhythmic agent, disopyramide, offers a safe and effective choice for continued medical therapy in obstructive HCM.^{46,47} While β -adrenergic antagonists have major impact on blunting the catecholamine and effort-related augmentation of obstruction, disopyramide may derive its efficacy from a preferential decrease in resting gradient.

In the modern management of HCM, it is also very important to avoid medications and environmental factors that may

augment the obstruction. For example, patients should be counselled to avoid vasodilators such as dihydropyridine calcium channel blockers, α -adrenergic antagonists, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Similarly, high-dose diuretics should be avoided and the importance of maintaining hydration should be emphasised. Recreational activities such as saunas, whirlpools or consumption of alcoholic beverages can be problematic for some patients.

Dual-chamber pacing

Despite the excellent results achieved with drug therapy, some patients remain symptomatic. For this reason, there has been continued innovation in surgical and other invasive therapies. In the 1990s, there was considerable interest in the potential role of dual chamber pacing as a treatment for obstructive symptoms. This was based on the hypothesis that optimised atrioventricular timing, maximised ventricular preload and septal dyssynergy might result in remodelling of the left ventricular outflow tract. Initial case reports and single-centre experiences suggested real promise for this technique.^{48,49} However, subsequent multicentre randomised trials produced less promising results, revealing a significant placebo effect and lack of sustained improvement.^{50,51} While a small cohort of patients did appear to benefit, the magnitude of the treatment effect was much less than that afforded with surgical septal myectomy⁵² and there were no variables that identified responders.⁵³ Thus, utilisation of the pacemaker for symptom relief in patients with LVOT obstruction is confined to individuals who have a independent indication for placement of a pacemaker (or implantable defibrillator), or an extremely high risk for surgical or catheter-based therapy.

Mitral valve replacement

The recognition that altered mitral valve anatomy and function are integral to the development of outflow tract obstruction soon led to the evaluation of mitral valve replacement, with or without concomitant myectomy, as a method to eliminate obstruction. However, mitral valve replacement requires life-long anticoagulation and repeat cardiac operations to replace the mitral valve prostheses as they began to fail, a particular problem in young patients. Accordingly, mitral valve replacement for the sole purpose of reducing outflow tract obstruction is not currently recommended. Mitral valve repair is utilised in selected patients undergoing surgical myectomy, where there are co-existent primary mitral valve structural abnormalities, such as a flail segment or mitral prolapse, causing haemodynamically significant regurgitation independent of systolic anterior motion of the valve.

Evolution of surgical myectomy

The primary indication for operation in HCM is the relief of symptoms due to obstruction that are refractory to pharmacological therapy. The myectomy procedure has evolved during the 50-year history,⁵⁴ but the trans-aortic approach developed by Morrow remains the most commonly used technique. The classic Morrow procedure utilised two parallel longitudinal incisions in the basal septum below the aortic valve that were joined distally. Excision of the tissue left behind a trough in the septum that reduced SAM of the mitral valve, reduced obstruction and improved symptoms.²⁸ Recognition of the importance of flow vectors around the hypertrophied septum have led to modification of technique to ensure that the septal incisions extend well beyond the point of mitral valve septal

Table 2 Therapies to relieve outflow tract obstruction

Myectomy	
Trans-aortic	1958
Trans-ventricular	1961
Trans-atrial	1963
Trans-right ventricle	1967
Transplant	1968
Mitral valve replacement	1970
Aortoventriculoplasty	1975
Apicoaortic conduit	1976
Dual-chamber pacing	1992
Percutaneous alcohol septal ablation	1994
Pharmacological	
β -adrenergic antagonists	1962
Calcium entry blockers	1976
Disopyramide	1982

contact. Indeed, many surgeons extend the excision down to the base of the papillary muscles and laterally to increase the width of the trough (wider at the apical portion of the resection).⁵⁵ These modifications, as well as improved cardio-protection, have transformed surgical myectomy from a potentially high-risk procedure (upwards of 10% in some reports), to one of the lowest-risk cardiac procedures now performed. The operative mortality is now less than 1% in centres with experienced HCM-focused clinicians and surgeons, with near or complete durable abolition of the LVOT obstruction.^{38 56 57} The need for repeat myectomy (2% of cases at the Mayo Clinic) is very low.⁵⁸ While the beneficial effect of myectomy on symptoms has been proved for decades,^{28 59–61} its impact on long-term survival is still debated. Recent observational data report no adverse long-term effects, and suggest a possible survival benefit with myectomy.^{38 57} Overall survival among patients who have undergone myectomy is equivalent to the age-matched and gender-matched general population and the annualised HCM-related event rate of 0.5% per year, is much lower than that observed in obstructive patients managed without operation.³⁸ The sudden cardiac death rate and rate of appropriate implantable cardioverter-defibrillator discharge following myectomy is also very low and nearly 20 times lower than would be expected based on the risk factor profile of these patients.^{38 39}

It is important to note that the reported results of surgical intervention are derived from patients with severe lifestyle-limiting drug-refractory symptoms. There are no data to suggest that myectomy or other invasive procedures should be offered to patients who have minimal or no symptoms. Patients can be counselled that if they do have drug-refractory symptoms, surgical myectomy offers very high success rates (>90%), with low procedure-related morbidity (2–3%) and mortality (<1%) and excellent long-term outcomes such that they can lead a more satisfactory quality of life.

Percutaneous septal ablation

In 1994, a new percutaneous catheter-based technique for reducing left ventricular outflow tract gradients was proposed.⁶² The aim was to infuse alcohol into the septal perforator artery supplying the basal interventricular septum in order to cause a localised, tactically placed myocardial infarction. Following an acute decrease in systolic thickening of the treated portion of the septum, scarring and thinning in the target area resulted in a long-term reduction in outflow gradient. Recognition of the variable blood supply of the basal septum led to modification of the technique to include selective intracoronary injection of echocardiographic contrast agents to ensure that only the septum adjacent to the mitral valve-septal contact point is targeted.^{63 64} Owing to the decreasing numbers of cardiac surgeons with adequate expertise to perform myectomy, and the perception that the percutaneous procedure was not as technically demanding, the new technique has been rapidly embraced by interventional cardiologists around the world. Reports suggest that when performed by experienced operators, the short-term and intermediate-term improvements in haemodynamics and gradient are good.^{65 66} Over the decade from 1995–2005, nearly two dozen series involving more than 1000 patients were reported. The technical success rate, defined by intraprocedural decreases in gradient, ranged from of 75–80%. Among those with technical success, short-term gradient and symptom reduction approached that observed with myectomy. The complications rates, largely driven by complete heart block, ranged from 9–38%; however, this was reduced significantly

after the introduction of contrast echocardiography. Procedure-related mortality rates ranged from 0–4% (average 1.9%). Four retrospective observational studies have compared septal ablation to myectomy.^{67–70} The results show comparable symptom and gradient relief among those patients in whom the procedures were feasible, but higher non-fatal complications (permanent pacemakers and resuscitated cardiac arrests) in patients treated with alcohol ablation. Procedure-related mortality was 0.9% in myectomy patients and 1.3% in the ablation patients. There are few robust long-term outcomes data but a German registry⁷¹ reports post-ablation mortality at 3–6 months of 2.5%. The most experienced centre in the United States reported an annual mortality of approximately 2% per year,⁶⁶ while in Canada mortality was 4% at 10 years.⁷⁰ The most recent data suggest that, while outcomes are generally good with septal ablation, they may not be as good as those observed with myectomy, particularly in younger patients (age <65) where the rate of death or recurrent symptoms was approximately doubled in comparison with myectomy patients.⁷²

THE PRESENT AND FUTURE OF OBSTRUCTION

The consensus document on the management of HCM in 2003⁷³ recommends that the management of outflow tract obstruction should be focused on the relief of lifestyle-limiting symptoms only. Negative inotropic and chronotropic medications (β -adrenergic antagonists, verapamil, diltiazem and disopyramide) should be the first-line therapy. If patients remain symptomatic, or if the medications impart intolerable side effects, then surgical myectomy can be offered as a highly efficacious and safe procedure with the knowledge that postoperative outcomes are excellent in experienced centres. Percutaneous septal ablation is a potential alternative to operation for patients with appropriate coronary anatomy and other co-morbidities thought to elevate surgical risk.

There have been multiple editorials on the relative merits of the percutaneous technique and surgical myectomy. While randomised trials have been suggested, none has been conducted, in part because of the very large number of patients who would need to be recruited.⁷⁴ However, a first step in comparing therapies would be to agree upon appropriate definitions of success (table 3). This would give cardiologists and patients the ability to better understand the relative strengths and weaknesses of the various treatment options.

It has been common to report technical success rates for procedures (that is, the percentage of referred patients who actually had the procedure performed), but given that the main goal of therapy in obstructive HCM is to relieve symptoms, one of the key metrics in any comparison is the change in functional class or the proportion of patients rendered minimally symptomatic. Patient safety must be paramount and interventions

Table 3 Proposed definitions of success for invasive treatment of left ventricular outflow tract obstruction

Category	Metric	Goal
Symptoms	NYHA Class	<Class III
Safety	Significant procedural complications	<5%
	Procedure-related mortality	<1%
Survival	Long-term disease-related mortality	<1% per year
	Repeat procedure rate	<5%
Haemodynamic	Final gradient	<20 mm Hg

should have low procedure-related mortality and non-fatal complication rates. As a minimum, the procedure should be associated with a neutral effect on survival. Haemodynamic definitions of success are complex for obstructive HCM. The very nature of the dynamic obstruction and the potential for residual latent obstruction make it difficult to define a target for residual gradients but, given that half of patients with resting gradients less than 30 mm Hg can have easily provokable obstruction,²⁵ the lower the residual gradient the better. Once symptoms, safety, survival and haemodynamics are consistently and routinely reported, then other procedure-specific differentiators can be considered in context.

CONCLUSION

Left ventricular outflow tract obstruction was a predominant feature of HCM in the initial descriptions of the disease five decades ago and remains an important management issue to this day. In most patients obstruction can be managed with lifestyle advice and drug therapy. In the minority who require more invasive treatment, symptom relief can be achieved at low risk, when patients are assessed and managed in expert centres.

Much has been learned and argued over the past 50 years regarding obstruction in hypertrophic cardiomyopathy. For the future, the opportunity to diagnose HCM at a preclinical stage may allow the application of strategies to prevent the development of hypertrophy, obstruction and their consequences. This will require collaboration, and open-minded discussion between HCM centres worldwide, with the common goal of serving our patients' needs.

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