Midventricular Obstruction and Clinical Decision-Making in Obstructive Hypertrophic Cardiomyopathy

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Abstract
The presence of intraventricular obstruction is a powerful predictor of outcome in patients with hypertrophic cardiomyopathy (HCM) and, when associated with severe, drug-refractory symptoms, should be managed aggressively. Resting left ventricular outflow obstruction is found in approximately 20% of the patients, classically occurs at the subaortic level, and is associated with mitral valve systolic anterior motion (SAM). In a minority of patients, however, the impedance to flow occurs at midventricular level, unrelated to SAM. Symptomatic midventricular obstruction represents a clinical challenge, and its treatment is not standardized. In these patients, both surgical myectomy and alcohol septal ablation (ASA) are technically feasible. A rational approach to the management of these patients depends on accurate characterization of the pathophysiology, coupled with comparison of the results of different management strategies. To illustrate these points, the details of a patient who first underwent percutaneous ASA and subsequently required redo surgical treatment are described here, with special emphasis on the implications to the management of midventricular obstruction, as well as to the more global issue of obstructive HCM.

Klinischer Behandlungspfad bei hypertrophischer obstruktiver Kardiomyopathie

Zusammenfassung

Introduction
In patients with hypertrophic cardiomyopathy (HCM), dynamic left ventricular (LV) outflow tract obstruction, a classic pathophysiologial feature of the disease, is associated with an increased risk of clinical deterioration and cardiovascular mortality [1–4]. Under resting conditions LV outflow obstruction is found in approximately 20% of HCM patients [1]. In an additional proportion of patients, close to 40%, a gradient ≥ 50 mmHg can be elicited with physiological provocation (exercise) [5]. LV outflow obstruction classically occurs at the subaortic level, mainly due to mitral valve systolic anterior motion (SAM) causing mid-systolic septal contact [1, 2]. SAM is produced by a drag effect in the presence of high-velocity LV ejection, and is largely responsible for concomitant mitral regurgitation due to incomplete leaflet apposition [6, 7]. In a minority of HCM patients, however, the impedance to flow occurs at the midventricular level, unrelated to SAM, and is predominantly caused by marked septal hypertrophy coming into contact with a hypercontractile antero-
lateral LV wall, often with the interposition of the anterolateral papillary muscle [1, 4], and hypertrophic longitudinal muscle bands on the posterolateral wall of the LV.

Midventricular obstruction represents a clinical challenge when associated with severe symptoms, and its treatment is not standardized. In an attempt to clarify this issue, we present a case of midventricular obstruction, and discuss the implications for management in HCM patients.

**Case Presentation**

A young woman was diagnosed with HCM at the age of 27, and was referred to our institution for evaluation. She complained of mild dyspnea on effort (New York Heart Association [NYHA] functional class II), and frequent palpitations. The family history was unremarkable. Genetic analysis showed an R869H missense mutation on MYH7 gene. On examination, she had a 3/6 grade ejection murmur in the subaortic area, which increased with the Valsalva maneuver. The echocardiogram showed very marked asymmetric hypertrophy of the LV, with a maximum septal thickness of 34 mm measured at the midventricular level. At this point, there was systolic septal contact with the anterolateral wall, with sphincter-like cavity obliteration creating two distinct (basal and apical) chambers (Figure 1). There was no SAM of the mitral valve. Doppler examination showed midventricular obstruction with a peak systolic gradient of 40 mmHg. There was no obstruction of the LV outflow, nor significant mitral regurgitation. She was started on β-blockers (nadolol 80 mg/day) and followed regularly.

In the following years she developed worsening of her congestive symptoms (to NYHA class III) despite progressive increase of nadolol dosage (to 160 mg/day). Furthermore, she experienced several dizzy spells and one syncopal episode on effort. Repeated Holter ECG monitorings showed brief runs of non-sustained ventricular tachycardia. A treadmill exercise test showed marked reduction in functional capacity, and an abnormal blood pressure response (early drop in systolic blood pressure of 25 mmHg). Therefore, at the age of 31, she received an implantable cardioverter defibrillator (ICD) and a few months later she underwent percutaneous alcohol septal ablation (ASA) for relief of midventricular obstruction. An echocardiogram before ASA showed a midventricular peak systolic gradient of 54 mmHg, which was reduced to 22 mmHg after the procedure, and remained < 20 mmHg in the following months (Figure 2). The patient’s symptoms improved dramatically, and she resumed a normal lifestyle. No further syncopal episodes occurred, and there were no ICD interventions.

5 years later, however, she complained of recurring dyspnea on effort, and her symptoms rapidly returned to “exactly like they were before ASA”. An echocardiogram again showed marked intracavitary LV obstruction at the midventricular level, with a peak gradient of 66 mmHg (Figure 3a). At this stage, she was offered surgery, which she readily accepted in order to regain the symptomatic improvement experienced after ASA, which had been progressively lost. She therefore underwent operation performed through a transaortic approach combined with a “fishmouth” incision of the LV apex, in order to achieve full relief of the midventricular, sphincter-like obstruction. This resulted in the complete abolition of the midventricular gradient, with a significant increase in LV cavity size at this level (Figure 3b). The patient, now aged 36, experienced dramatic improvement of her symptoms. She remains virtually free of congestive symptoms and functional limitation, and is back to her presymptomatic lifestyle. Subsequent follow-up echocardiograms have confirmed the absence of dynamic gradients within the LV, and preserved systolic function.
Pathophysiology and Clinical Consequences of Intraventricular Obstruction

Dynamic LV outflow obstruction has attracted the interest of clinicians involved in HCM since the early descriptions of the disease. Only recently, however, has outflow obstruction been identified as a major prognostic indicator in patients with HCM. In a multicenter study coauthored by our group [2], patients with a gradient ≥ 30 mmHg in resting conditions incurred an almost fourfold independent increase in HCM-related mortality or progressive clinical deterioration to severe congestive symptoms, compared to nonobstructive patients. Among patients with obstruction, the outcome was more severe in the presence of symptoms, or when atrial fibrillation was present [8]. Subsequent studies have reported consistent findings [3].

Of note, none of these reports have specifically addressed the issue of midventricular obstruction, due to its relative rarity and unique pathophysiology [9]. For clinical purposes, however, it seems reasonable to expand to this peculiar HCM subgroup the conclusions derived from the large studies based on the classic, SAM-related form of intraventricular obstruction. Therefore, an indication for invasive septal reduction therapies should be considered when midventricular obstruction is associated with severe, drug-refractory symptoms.

The Issue of Sudden Death

LV outflow tract obstruction at rest is associated with an increased risk of sudden cardiac death [2, 10]. Specifically, the relative risk of sudden death associated with LV outflow obstruction is about twofold that of nonobstructive patients. This finding is presumably due to increased hemodynamic and electric instability in patients with obstructive HCM, as a result of elevated intraventricular pressures and subendocardial ischemia occurring in the context of diffuse microvascular dysfunction [11]. It is noteworthy, however, that while doubling of relative risk for sudden death in obstructive patients may seem substantial, the absolute increase in risk is actually small, due to the low event rates observed in HCM cohorts (0.3–1% per year) [12]. In addition, the intracavitary LV gradients in HCM patients are classically dynamic, and may change considerably (or even disappear) depending on medical or invasive management, LV loading conditions and systolic function [1–5]. As a consequence, the positive predictive value and reliability of a resting gradient ≥ 30 mmHg are too low to guide any clinical decision for primary prevention of sudden death in HCM patients, particularly with regard to ICD implantation. Thus, as in the clinical case described, ICDs should only be implanted in obstructive patients when warranted based on the established risk factors outlined in the existing guidelines, which include prior cardiac arrest or sustained ventricular tachycardia, malignant family history, unexplained syncope, repetitive nonsustained ventricular tachycardia, abnormal blood pressure response during exercise, and extreme LV hypertrophy [4].

Therapeutic Options for Obstructive HCM

In symptomatic patients with LV outflow obstruction, β-blocking agents and/or verapamil may improve congestive symptoms and functional limitation, although there is no evidence that these agents have a consistent effect on the intraventricular gradient [4]. Disopyramide, a class IA antiarrhythmic drug with negative inotropic properties, has also been reported to improve symptoms by reducing the degree of ob-

93x503 to 370x756

[Image 93x503 to 370x756]

Obstruction, particularly when combined with β-blockers [6]. However, medical therapy is rarely capable of achieving adequate and long-lasting control of obstruction-related symptoms [4, 13]. In patients with marked LV outflow tract obstruction (peak instantaneous gradient ≥ 50 mmHg at rest or with exercise) and heart failure symptoms refractory to maximum tolerated medical therapy, invasive relief of the intraventricular gradient should be considered [1–4, 13].

For several decades, surgical septal myectomy has been the only established invasive treatment for obstructive HCM [4, 13–17]. Surgical myectomy is associated with very low complications rates at experienced centers, and has been shown to substantially and permanently abolish the LV outflow gradient and mitral regurgitation due to SAM in most patients [4, 13]. A successful myectomy is classically followed by dramatic long-term improvement in symptoms, and confers enhanced survival and protection from disease progression [4, 13–17]. In one recent study, patients with surgical myectomy showed a life expectancy comparable to that of the general population, with a 98% cardiovascular survival at 5 years and 95% at 10 years [15]. Furthermore, myectomy patients showed better long-term overall survival, and a reduced risk for sudden unexpected death, compared to obstructive patients who were treated medically [15].

The percutaneous technique of ASA procedure has been introduced only a decade ago, but has rapidly experienced increasing popularity, because it is less invasive and more accessible outside HCM referral centers [18–21]. At present, ASA is the most prevalent invasive treatment for obstructive HCM, and is performed in such striking volumes as to suggest that lower symptom and gradient thresholds may have been employed for referral, compared to surgery [13]. ASA achieves its hemodynamic and clinical effects by means of a localized ethanol-induced myocardial infarction, aimed at the septal area of contact with SAM. In the process, a residual intramyocardial scar is created that has raised concerns due to its potential role in triggering life-threatening arrhythmias [13].

The acute effects of ASA on the gradient are generally less striking than surgery. In the course of several months, however, ASA induces progressive remodeling of the outflow tract, ultimately reducing SAM and relieving symptoms in most patients [19–21]. Nevertheless, some of the available, nonrandomized comparative analyses suggest that gradient reduction by ASA is somewhat less consistent and complete than with surgical myectomy [22–25]. Since the long-term safety of ASA remains to be established, the current American College of Cardiology/European Society of Cardiology (ACC/ESC) guidelines support the view that surgical septal myectomy should represent the gold standard treatment for drug-refractory patients with obstructive HCM, particularly in the young, while ASA should be considered an important complementary treatment option to be preferred in those patients who are elderly, have increased operative risk, do not have access to expert surgical centers, or reject operation [4].

Recurrence of Obstruction Following Septal Reduction Therapies

There is paucity of information regarding the recurrence of intraventricular obstruction following myectomy or ASA. In surgically treated patients, recurrences of the gradient requiring redo procedures are generally reported as rare. In a recent study from the Mayo Clinic, only 13 of 610 consecutive myectomies (2%) were repeat procedures performed in patients who required a novel operation due to recurrent obstruction [26]. Mechanisms of recurrence included limited myectomy at initial operation, midventricular obstruction and anomalies of papillary muscles. The authors suggest that the need for reoperation may be reduced with modern surgical techniques that include...

Detection of site of obstruction and additional features (mitral regurgitation, LA dilatation, apical aneurysm, MV abnormalities)

Drug-refractory symptoms and gradient persistence

β-blockers ± disopyramide

Obstructive HCM

Exercise echocardiography

Obstructive HCM

Tailored myectomy

Clinical follow-up

Alcohol septal ablation

Symptom improvement and gradient abolition

Genotyping and risk profile assessment

Figure 4. Flow chart illustrating the recommended management strategy in hypertrophic cardiomyopathy (HCM).


a more extended resection of the midventricular septum, relief of papillary muscle anomalies, and routine use of intraoperative transesophageal echocardiography [26]. Conversely, even in the most expert hands, about 20% of ASA patients require repeated procedures (redo ASA or myectomy) due to inadequate reduction or recurrence of the gradient, and persistent symptoms [4, 23–25]. In these patients, recurrence is generally related to massive hypertrophy, mitral subvalvular abnormalities, and, especially in the young, very redundant mitral leaflets that continue to generate SAM despite remodeling of the outflow tract [13]. Patients with recurrence of the gradient following alcohol ablation represent a clinical challenge, and their management is not mentioned in the current ACC/ESC guidelines. In our experience, extended tailored surgical myectomy and correction of the mitral valve and subvalvular apparatus abnormalities, with restoration of the functional anatomy of the LV outflow tract, is to be preferred to a repeat ASA, and represents the most prudent choice in these patients [22]. In patients with midventricular obstruction, the risk of recurrence may be even higher than in the classic form of outflow obstruction [26]. Therefore, surgery should be considered the first choice in patients such as the young woman described in this paper. A flow chart illustrating a contemporary approach to HCM, derived from the guidelines and our own clinical practice, is shown in Figure 4.

Conclusion

The presence of intraventricular obstruction is a powerful predictor of outcome in HCM patients and, when associated with severe, drug-refractory symptoms, should be managed invasively. Effective septal reduction therapies include surgical myectomy and ASA: both techniques are feasible also in the rare HCM patients with severe midventricular obstruction, although such feature represents a greater technical challenge compared to classic SAM-related obstruction. In our experience, surgery offers the best chance of permanent gradient and symptom relief, and should be the preferred option in obstructive young HCM patients, especially when atypical pathophysiological features contribute to the obstruction.

References


