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Narrative Review

Modern Perspectives on Hypertrophic Cardiomyopathy—No One Size Fits All

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Abstract

Despite substantial advances in the management of hypertrophic cardiomyopathy, advanced heart failure remains a major cause of morbidity in this patient population. This narrative review presents the case of a patient with hypertrophic obstructive cardiomyopathy who underwent alcohol septal ablation to frame a discussion of modern therapies for hypertrophic cardiomyopathy. The current treatment landscape includes medications, both old and new, and surgical and procedural interventions to relieve mechanical obstruction. Several promising new modalities for relieving obstruction are in the nascent stages of development.

Keywords: Cardiomyopathy, hypertrophic; ablation techniques; radiosurgery

Introduction

The mortality rate in patients with hypertrophic cardiomyopathy (HCM) has decreased to 0.5% per year because of advances in treating HCM, including novel drug therapies, interventions to reduce left ventricular (LV) obstruction, and implantable cardiac devices.[1] Advanced heart failure (HF), however, remains a substantial cause of morbidity in this patient population. In a study of 2,447 patients with HCM, more than half of the cohort developed advanced, refractory HF symptoms (New York Heart Association [NYHA] class III or IV) during a mean follow-up period of 13 years.[2] Pharmacologic therapy with negative inotropic agents (eg, β-adrenergic blockers, calcium channel blockers, disopyramide) is the first-line therapy for patients with symptomatic hypertrophic obstructive cardiomyopathy (HOCM), which typically results from LV outflow tract (LVOT) obstruction.[3] Recent studies have shown that cardiac myosin inhibitors such as mavacamten and aficamten are also effective therapies for patients with HOCM.[4] In 2 randomized, controlled clinical trials, mavacamten improved functional outcomes and reduced the proportion of patients who met the criteria for septal reduction therapy.[5,6] Although many patients initially respond to pharmacologic therapy, drug-refractory disease requiring procedural intervention remains common.[3,7]

Per current American College of Cardiology/American Heart Association guidelines, patients who have HOCM with NYHA class III or IV symptoms refractory to medication and high LVOT gradients (>50 mm Hg) at rest or with provocation are candidates for invasive therapy with either transaortic septal myectomy or transcatheter alcohol septal ablation (ASA).[8] Surgical myectomy is considered the standard of care for procedural intervention in patients with HOCM; in high-volume centers, it is safe (<1% operative mortality, similar to that of patients with nonobstructive HCM) and effective (>90% success in achieving NYHA class I or II with minimal residual LVOT obstruction).[9-11] Alcohol septal ablation is a less invasive alternative to surgical myectomy, associated with shorter hospital stays, and successful in more than 80% of cases.[12] Data directly comparing septal myectomy and

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ASA are limited. In a study of 3,859 patients, ASA was associated with greater all-cause mortality than surgical myectomy, independent of age, sex, and known comorbidities; however, the difference in mortality may have been influenced by unmeasured confounding factors, highlighting the importance of patient selection and patient preference.[12,13] This narrative review presents an illustrative case of HCM, with an overview of the current and emerging minimally invasive treatment strategies for HCM.

Case Presentation

A 61-year-old man with a history of hyperlipidemia was seen by a gastroenterologist and diagnosed with achalasia. During the workup, a prominent systolic murmur was noted in the right upper sternal border. The patient was referred to a cardiology center for preoperative risk evaluation before a planned esophagomyotomy. During the consultation, the patient mentioned recently experiencing substantial dyspnea on minimal exertion. He had no history of syncope or family history of cardiovascular conditions, including sudden cardiac death. An echocardiogram showed asymmetric septal hypertrophy of 1.9 cm, with an LVOT obstruction exceeding 130 mm Hg with Valsalva maneuver. The patient was started on metoprolol tartrate; up-titration was limited by bradycardia and hypotension. Despite this treatment, he continued to have severe symptoms on minimal exertion (NYHA class III), and echocardiography showed persistently elevated LVOT gradients.

The patient was counseled extensively on treatment options, including the addition of a cardiac myosin inhibitor and cardiac intervention. Because he preferred to avoid taking a novel drug and was strongly opposed to open heart surgery, despite its potential benefits, the patient decided to proceed with ASA and was taken to the cardiac catheterization laboratory.

A pigtail catheter was placed in the left ventricle via a left radial approach, and a 6F Cordis XB (Cordis) guide catheter was placed in the ascending aorta via a right femoral arterial approach. A 5F balloon-tipped pacing catheter was placed in the right ventricle through the right jugular vein as a safety measure in case of bradyarrhythmia during alcohol ablation. The preintervention baseline peak LV-aortic gradient was approximately 100 mm Hg and exceeded 170 mm Hg with Valsalva maneuver and after premature ventricular contractions (Fig. 1).

Key Points

- Medical advances have drastically reduced mortality in patients with HCM, but HF remains a major cause of morbidity. Most current treatments are aimed at relieving the symptoms of heart failure.
- Although surgical myectomy remains the gold standard for relieving mechanical obstruction in HCOM, ASA stands as a safe and effective alternative in appropriate patients.
- The future of HCM treatment may include other minimally invasive or noninvasive techniques that are currently being developed.

Abbreviations and Acronyms

ASA	alcohol septal ablation
HCM	hypertrophic cardiomyopathy
HF	heart failure
HOCM	hypertrophic obstructive cardiomyopathy
LV	left ventricular
LVOT	left ventricular outflow tract
NYHA	New York Heart Association
RFA	radiofrequency ablation
SBRT	stereotactic body radiation therapy
SESAME	Septal Scoring Along the Midline Endocardium

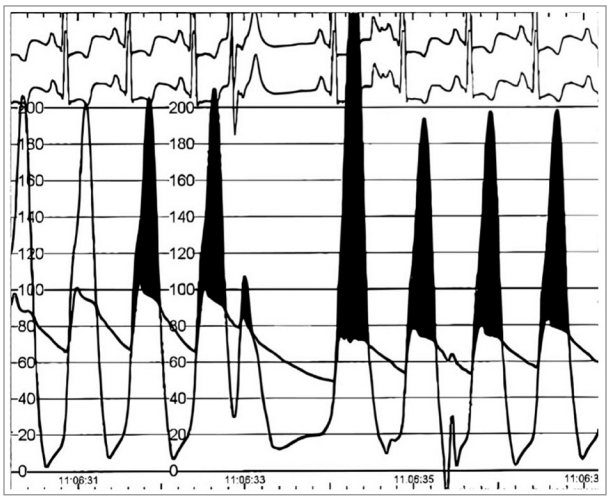

Fig. 1 Intraoperative hemodynamic pressure tracing of LV-aortic gradient before alcohol septal ablation is shown. The concurrent measurement of aortic and LV pressures shows a systolic LV pressure approximately 100 mm Hg higher than the aortic pressure secondary to LV outflow obstruction. After a premature ventricular contraction and the ensuing compensatory sinus pause, the LV-aortic gradient increases to greater than 170 mm Hg, a phenomenon known as the Brockenbrough-Braunwald-Morrow sign.

LV, left ventricular.

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Angiograms of the left coronary system showed 2 prominent proximal septal perforating arteries, designated as septal artery 1 and septal artery 2. The second septal artery had an early bifurcation and was subdesignated as septal artery 2a and septal artery 2b. The proximal left anterior descending artery was wired with a 0.014-inch Boston Scientific Choice floppy guide wire. The wire was difficult to maneuver into the first septal artery and was exchanged for a 0.014-inch Abbott Fielder FC wire (Asahi Intecc USA, Inc), which selectively entered the septal branches. A Boston Scientific 1.5-mm × 8-mm over-the-wire Emerge balloon was advanced into the first septal artery over the wire and inflated to 6 atm of pressure. Then, the vessel was selectively infused with agitated saline under visualization with transthoracic echocardiography. After the vascular territory was confirmed to be confined to the proximal interventricular septum, alcohol-selective infusion with 1 mL alcohol (absolute) was performed over 2 minutes, and balloon inflation was extended to 5 minutes. A subsequent angiogram confirmed occlusion of the first septal artery.

A transthoracic echocardiogram showed residual outflow tract gradient. The decision was made to perform alcohol ablation of the second septal artery. Given the early bifurcation of the second septal vessel, each branch of the artery was selectively engaged, and ASA was performed sequentially by using the same equipment and technique as described in the previous paragraph. A final angiogram showed successful flow arrest in the first septal artery and septal artery 2a and partial occlusion of septal artery 2b (Fig. 2).

After ablation, the LV-aortic gradient was less than 10 mm Hg (Fig. 3). The patient was admitted to the coronary care unit for observation and pain control. High-sensitivity troponin peaked at 26,756,000 μg/L. The patient was discharged 3 days later, after an uncomplicated course, with no evidence of bradyarrhythmia.

After 4 weeks, the patient was seen for follow-up in the clinic, where he reported complete resolution of symptoms. A postoperative echocardiogram showed a residual gradient of 20 mm Hg at rest and 40 mm Hg after Valsalva maneuver. Even though his pressure gradient across the LVOT substantially improved, it did not fully resolve. The lack of complete response may have been related to the presence of a prominent accessory papillary muscle or marked elongation of his anterior mitral leaflet causing persistent systolic anterior motion, as was seen on his follow-up echocardiogram. This finding was despite an adequately sized transmural scar in his intraventricular septum, confirmed by magnetic resonance imaging, which included the point of septal contact of the mitral valve. The patient is now in a clinical situation like that of a sizable proportion of patients in that he might require an additional drug or a procedural intervention in the future.

Currently Available Invasive Therapies

At experienced centers, more than 90% of patients who undergo septal myectomy are relieved of LVOT obstruction and have a low operative mortality rate.[12] Outside of experienced centers, though, worse outcomes are observed, likely because of the technical expertise required to perform the operation and the need for an experienced multidisciplinary team to evaluate these patients' complex cases. In a study of septal myectomy that spanned from 2003 to 2011, Kim and colleagues[14] reported a 15.6% surgical mortality rate at centers in the lowest tertile of procedural volume, whereas mortality was at 3.8% in centers in the highest tertile.

Alcohol septal ablation was first described in 1995 as an alternative to septal myectomy for the treatment of medication-refractory, severe HOCM.[8] Alcohol septal ablation has a periprocedural mortality rate of 1% to 2% and is less operator dependent than surgical myectomy.[14] Over the past 25 years, ASA has become more widely available than surgery and is a less invasive option, with a shorter hospital stay.[12] Because procedural success with ASA has no standard definition and because the following value has been the historical benchmark for surgical myectomy, surgeons generally consider a residual LVOT gradient less than 10 mm Hg an indicator of success. By this definition, ASA is successful in approximately 80% of cases. Furthermore, when patients are properly selected, 1 or more appropriate septal perforator arteries are available, and standards for proper technical performance are met, the clinical efficacy of ASA may nearly match that of surgical myectomy.[15]

In a 2012 study of 177 patients treated with ASA, 79% survived to a median follow-up of 5.7 years, comparable with the expected survival for the general population and the survival of the age-matched and sex-matched cohort of patients treated with surgical myectomy.[16] Vriesendorp and colleagues[17] reported a similar 10-year survival rate in patients treated with ASA (82%) and myectomy (85%) (log-rank $P = .50$); after ASA, the rate of sudden cardiac death remained low (1.0% per year).

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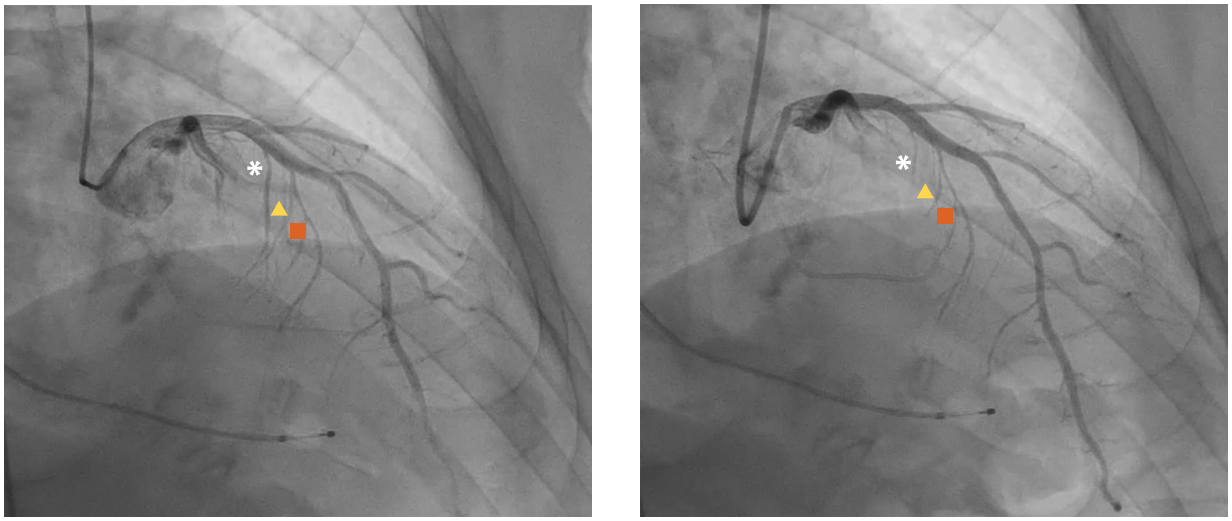

Fig. 2 Selective coronary angiograms show the effects of alcohol septal ablation on the left anterior descending and septal perforator arteries. Images were obtained in a right anterior oblique projection (**A**) before and (**B**) after alcohol septal ablation. There is interval occlusion of septal perforator 1 (asterisk), septal perforator 2A (triangle), and partial occlusion of septal perforator 2B (square).

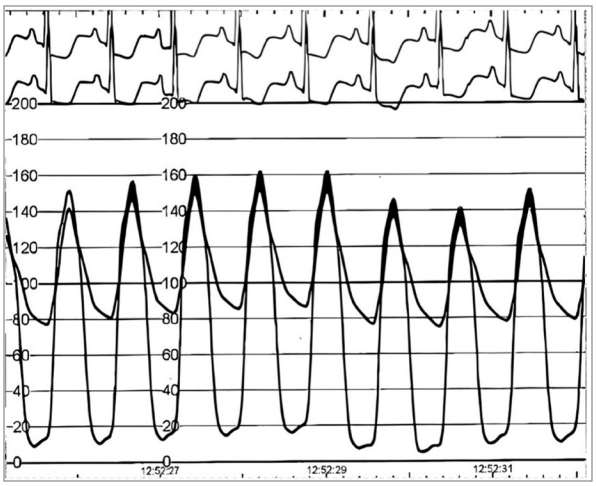

Fig. 3 Intraoperative hemodynamic pressure tracing after alcohol septal ablation of 2 prominent septal arteries shows the left ventricular–aortic gradient was improved to less than 10 mm Hg.

A recent meta-analysis comparing the efficacy of ASA and myectomy revealed no difference in long-term or short-term all-cause mortality, cardiovascular mortality, sudden cardiac death, or stroke rates between patients undergoing ASA vs myectomy.[18] Alcohol septal ablation was associated with fewer periprocedural complications but with higher rates of reintervention and pacemaker dependency, whereas myectomy resulted in a slightly greater reduction in LVOT gradient and clinical symptoms.

Despite the comparable efficacy of ASA and septal myectomy, a higher rate of recurrent symptoms has been observed in younger patients, who may poorly tolerate incomplete relief of LVOT gradients.[19] Additional procedural risks include pacemaker dependency, coronary dissection or perforation, anterior myocardial infarction, and ventricular arrhythmia resulting from myocardial ischemia and scarring.[8,12] The concept of inducing a targeted myocardial infarction is central to the efficacy of ASA; guidance with echocardiographic and saline contrast and meticulous alcohol injection helps limit the myocardial infarction's size to the minimum necessary LV mass.[15] The damaged myocardium subsequently undergoes remodeling over the next 3 to 6 months, reducing LVOT gradients and clinical symptoms.[16]

Surgical and catheter-based treatment options for HCM have been available for more than 25 years; however, outcome surveillance and quality assurance lag behind those of other procedures. Two such operations are transcatheter aortic valve implantation and transcatheter edge-to-edge repair of the mitral valve. National coverage determinations for these procedures are governed by the mandated use of multidisciplinary heart valve teams, participation in national registries, and reporting of procedural and 1-year outcomes. These requirements have provided insight into commercial practice patterns, clinical outcomes, health care economics, and areas needing further study while fostering collaboration across surgical and medical specialties.[20,21] If the practice

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of ASA required participation in national registry reporting and similar use of multidisciplinary heart teams, the field could establish standard definitions of procedural success, optimize outcome reporting, and facilitate optimal multidisciplinary collaboration to improve patient care.

Emerging Treatment Options

Although existing pharmacotherapies are effective for treating symptomatic HCM, emerging drugs have also shown promise.[22] Mavacamten, a reversible inhibitor of cardiac myosin adenosine triphosphatase, was shown to decrease hypercontractility, improve functional capacity, and reduce the need for septal reduction therapy, at least in the short term. Mavacamten gained US Food and Drug Administration approval in April 2022 for patients with HOCM and NYHA class II or III symptoms. This decision was based on the results of the VALOR-HCM and EXPLORER-HCM trials, which demonstrated significantly reduced LVOT gradients (at rest and with Valsalva maneuver), improved NYHA functional class, and improved peak oxygen consumption.[5,6]

Other cardiac myosin inhibitors, ion channel inhibitors, and angiotensin II receptor blockers are actively under investigation.[22] Aficamten, a next-in-class selective cardiac myosin inhibitor, has been shown in a phase II trial to reduce LVOT gradients at rest and with Valsalva maneuver and to improve NYHA functional class with good tolerability.[23] The angiotensin receptor blocker valsartan, when tested in patients with early sarcomeric HCM, slowed the progressive loss of tissue Doppler diastolic velocities and LV end-diastolic volumes but did not significantly slow the progression of LV hypertrophy.[24]

Currently, no medical therapy has been shown to reduce HCM progression. Long-term data are awaited for the cardiac myosin inhibitor class.

Patients whose HCM remains drug refractory and who are not eligible for septal myectomy or ASA could potentially benefit from novel techniques that appear to address the limitations of existing treatments. Percutaneous septal radiofrequency ablation (RFA) employs electroanatomic mapping systems to target specific areas of the myocardium and reduce the rate of complications and the subsequent need for postprocedural pacemaker placement.[25,26] In 2011, septal RFA was first described in a series of 19 inoperable patients and resulted in a significantly reduced resting LVOT gradient.[27] In 2022, a trial of septal RFA in 200 patients with drug-refractory HCM, an LVOT gradient greater than 50 mm Hg, and NYHA class II or higher symptoms associated septal RFA with a reduction in LVOT gradient from 79 mm Hg to 14 mm Hg and showed that 96% of patients had NYHA class I to II symptoms at follow-up.[25] In addition, an ongoing open-label trial of noninvasive stereotactic body radiation therapy (SBRT) is examining the primary outcome measure of safety and the secondary outcomes of major adverse cardiovascular events, coronary artery patency, conduction disturbance, LVOT gradient, functional class, LV ejection fraction, and exercise capacity.[26]

In addition, a transcatheter myotomy procedure known as Septal Scoring Along the Midline Endocardium (SESAME) was developed based on old surgical myotomy techniques. In the SESAME procedure, before septal myectomy, circumferential myofibers are splayed apart to reduce septal encroachment and relieve LVOT obstruction. With the use of coronary guiding catheters and guidewires to mechanically enter the basal interventricular septum, the local myocardium is lacerated with electrosurgical tools to create a myotomy.[28] Preclinical data in pigs showed improved LVOT area without formation of ventricular septal defects, conduction blocks, or injury to nearby coronary arteries.[29] Additional clinical experience with this procedure and trial data supporting its use are needed to characterize the use of SESAME in the invasive treatment of HCM.

Finally, SBRT was first described in the 1990s and has become a well-established treatment in oncology.[30] A 2017 study showed that SBRT was also effective in treating cardiology patients with refractory ventricular tachycardia, which opened the possibility of applying SBRT to other forms of heart disease.[31] In 2023, in a first of its kind study, septal RFA with SBRT was used to treat 5 patients with drug-refractory HOCM and NYHA class III or IV symptoms who were ineligible for surgery or ASA. The patients' NYHA class symptoms and 6-minute walking distance improved substantially.[32] Although the reduction in LVOT gradient (from 88 mm Hg to 52 mm Hg at rest) in this study was not as robust as that observed with ASA or septal myectomy, the absence of any serious adverse effects or complications during a 12-month follow-up underline the safety and feasibility of SBRT as a treatment option for patients with HOCM. The risks associated with SBRT, such as atrioventricular conduction disturbance and radiation-induced noncardiac injuries, were minimized

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by multidisciplinary evaluation and the 3-dimensional reconstruction of computed tomographic images, electrophysiologic mapping, and pre-evaluation of the effects of variable radiation doses in an animal laboratory.

Final Thoughts

First-line HOCM management involves pharmacologic therapy with negative inotropic agents, including cardiac myosin inhibitors. When NYHA class III or IV symptoms persist and LVOT gradients remain greater than 50 mm Hg, the current guidelines support the use of transaortic septal myectomy or transcatheter ASA. Data from randomized clinical trials directly comparing septal myectomy with ASA are limited; therefore, procedure choice should be based on a combination of anatomic characteristics and patient preferences. Other treatments in the nascent stages of application include septal RFA, SESAME, and—perhaps the most innovative—noninvasive SBRT. Further investigation is warranted to explore these procedures' efficacy, safety, and comparability with surgical myectomy.

Although surgical myectomy remains the standard of care for the mechanical relief of LVOT obstruction, ASA is a less invasive alternative with similar efficacy in appropriately selected patients. The possibility remains that a substantial proportion of patients with incomplete relief of obstruction with ASA are poor anatomic candidates for this operation. In patients with appropriate LV septum and coronary anatomy (and confirmatory scans showing that the target septal branch perfuses the area of septal contact against the anterior mitral valve leaflet), ASA may have similar efficacy to septal myectomy. Meticulously selecting patients, ensuring the competency of the entire care team, and sharing decision-making are key to achieving optimal results.

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