Symptomatic Obstructive Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a common, yet challenging condition for clinical management. The majority of these patients have evidence of left ventricular outflow tract (LVOT) obstruction that may be asymptomatic or associated with debilitating symptoms of heart failure. In this report, we discuss the clinical presentation, appropriate evaluation, and management of a patient with symptomatic obstructive HCM.

Case Presentation
A 65-year-old woman presents to the ambulatory clinic for evaluation and management of dyspnea. The patient has a lifelong history of a murmur but was never limited in her activities until ≈8 months ago. Her symptoms consist of dyspnea that occurs when climbing a flight of stairs and while gardening. These activities can also precipitate light-headedness, although she has never had frank syncope. The patient’s medical history is significant for medically treated hypertension (metoprolol succinate, 100 mg/d); there is no history of coronary or peripheral atherosclerosis. She also has a 42-year-old son, who was recently diagnosed with obstructive HCM during a routine medical examination.

On physical examination, the patient is relatively small in stature (5’7”; 55 kg). Her blood pressure is 120/70 mm Hg with a heart rate of 60 bpm. Her lungs are clear to auscultation. The jugular venous pulse is normal. Carotid upstroke is brisk and not bifid. Her left ventricular apex is localized and slightly sustained (1+). No murmur is present at rest. However, with squat-to-stand maneuver, there is a 2/6 systolic ejection murmur heard best at the left lower sternal border. The remainder of the physical examination is unremarkable. An ECG demonstrates normal sinus rhythm and voltage criteria for left ventricular hypertrophy. A chest radiograph is normal.

The patient undergoes a transthoracic echocardiogram (Figure 1). Left ventricular size is normal, and systolic function is preserved (ejection fraction, 65%). There is moderate myocardial hypertrophy localized to the ventricular septum (maximal thickness, 18 mm). Trivial mitral regurgitation is present without systolic anterior motion. Two-dimensional (2D) imaging and Doppler interrogation of the LVOT demonstrate no significant gradient at rest or during Valsalva strain. The left atrium is slightly dilated (volume index, 29 mL/m²). Remainder of the echocardiogram is unremarkable.

Discussion

Dr Sorajja: Does this patient have HCM? And, how do you differentiate HCM from hypertensive heart disease?

Dr Ommen: I think this patient does have HCM. As to how you differentiate hypertensive heart disease from HCM, this differentiation almost does not matter. Such differentiation is only helpful in recommendations about the potential for inheritance and need for family screening. Otherwise, you are going to treat the pathophysiology the same. In this case, it is unusual for hypertension to cause asymmetrical hypertrophy, especially ≤18 mm.

Dr Nishimura: I would agree entirely with Dr Ommen. I do feel that the degree of hypertrophy is out of proportion to what you would find with hypertension. Usually, as Dr Ommen stated, hypertension alone would be associated with concentric hypertrophy and the thickness typically is <15 mm.

Dr Ommen: If the patient has had uncontrolled, long-standing hypertension, then you could have more latitude in terms of severity of hypertrophy, especially if they have coexistent renal disease or another cause that might contribute to hypertrophy.

Dr Sorajja: The patient has no evidence of LVOT obstruction on her echocardiogram. Does HCM explain her symptoms?

Dr Nishimura: In patients with HCM and symptoms, the major focus of the evaluation is to determine whether there is a resting or provokable obstruction. About one third of patients have resting outflow tract obstruction, but another one-third will not have any at rest and will only develop obstruction with provocation or during exercise. The onus is on the clinician to search for the presence of obstruction in a symptomatic patient, as this a treatable therapeutic target in terms of the medical and surgical options. In the absence of outflow tract obstruction, diastolic dysfunction from her HCM may explain her symptoms of dyspnea.1–3

Dr Sorajja: How do you evaluate for suspected LVOT obstruction in a patient with HCM?

Dr Ommen: You would start that with your physical examination, and do maneuvers with the patient. In this case, there was no murmur at rest but with the squat-to-stand maneuver, suggesting there is provokable outflow tract obstruction. Other important bedside maneuvers would include Valsalva strain, although this can be challenging for some patients to do adequately in terms of achieving the necessary reduction in preload. Quite often, I will exercise patients in the hallway...
and listen for a provocation murmur. If a provocable murmur during these maneuvers fits with the way she relays her symptoms, then the next step is to search and formally document the presence of outflow tract obstruction. We have practice algorithms when this is necessary.4

Our echo laboratory starts with a standard 2D and Doppler transthoracic echocardiogram. If there is a gradient across the LVOT of ≥50 mm Hg, no provocation is necessary. Otherwise, imaging is done with the Valsalva maneuver. If there continues to be no significant gradient, a nurse is called to administer amyl nitrite and we again look for provocable obstruction. It is important not to do just the continuous wave Doppler, but also the 2D to show systolic anterior motion of the mitral valve with color. This helps to ensure that we are getting the right signal, which needs to be differentiated from mitral regurgitation.

Dr Sorajja: At this point, our patient did not have evidence of significant obstruction on her transthoracic study. However, she had severe symptoms and some physical findings suspicious for provokable obstruction. She, therefore, was referred for an invasive hemodynamic study. Dr Nishimura, can you talk about the technical approach to performing these invasive studies at the Mayo Clinic?

Dr Nishimura: First of all, the search for obstruction in suspected patients can be done noninvasively, typically with provocation in the laboratory using Valsalva strain or amyl nitrate inhalation or with exercise on a using a standard treadmill protocol. The invasive approach can be undertaken in a symptomatic patient suspected of obstruction after an inconclusive echocardiogram.

It is important to note that cardiac catheterization for HCM can be misleading because of the potential for catheter entrapment in small, hyperdynamic ventricles. One should not use a single end-hole catheter, which can easily get entrapped from any approach. It is also important not to use a pigtail catheter because of the multiple side holes on the shaft that prevents an accurate assessment of the outflow tract gradient. At Mayo, we use the technique first put forth by Doug Wigle, who advocated a transseptal approach in which a catheter is placed across the atrial septum, through the mitral valve, and into the left ventricular inflow area, where there is no chance of entrapment. The left ventricular pressure is measured, and a 5 or 6 Fr catheter is used for simultaneous ascending aortic pressure, so that one can then accurately determine the true gradient across the LVOT. With the side arm of the transseptal catheter, one can also get simultaneous left atrial pressure. The transseptal technique is important but should only be done by highly trained operators.

If there is an LVOT gradient >50 mm Hg, there is no need for any type of provocation. If, as in this case, there is no significant gradient at rest, then you need to do more provocative maneuvers. You can look at the beat after a premature ventricular contraction, which is an easy methodology to provoke obstruction. One needs to be sure that there is not only an increased gradient but a true Brockenbrough phenomenon in which the aortic pulse pressure also decreases with an accentuation of the spike-and-dome pattern. The Valsalva strain maneuver is more difficult to perform in the catheterization laboratory because the change in preload will alter the position of the catheters within the ventricle. In those patients in whom we are not able to get either a resting gradient or one after a premature ventricular contraction, we will give isoproterenol.

Dr Sorajja: What about dobutamine, and why do you prefer isoproterenol?

Dr Nishimura: Dobutamine, at a higher dosage, has an α-effect, and this effect will increase afterload and you might not be able to generate a gradient. Isoproterenol, however, simulates exercise with the β-2 property causing vasodilatation, as well as the β-1 property that increases contractility and heart rate. We feel that isoproterenol is the best drug to
simulate exercise and determine the presence of clinically significant obstruction. There are no data on specificity of the isoproterenol response, but there are studies that have shown symptom relief with septal reduction therapy in those with gradients provoked by isoproterenol.5

Dr Sorajja: And do you always do a simultaneous echocardiography during these studies?

Dr Nishimura: You have to do a simultaneous echo because you want to know where the level of the obstruction is if a gradient is found. In true dynamic outflow tract obstruction, you need to see simultaneous systolic anterior motion of the mitral valve.

Dr Sorajja: Let us discuss her medical therapy. Do you think this medical therapy was appropriate for what you suspect may be causing her symptoms?

Dr Nishimura: It is important that negative inotropes are the cornerstone of therapy for obstructive HCM. Although vasodilators and diuretics are commonly used in patients with hypertension, these agents will exacerbate dynamic obstruction in HCM even when used in small doses. β-Blockers are effective for resting or latent obstruction. Verapamil can also be used, but one should be careful with severe resting obstruction, and some clinicians will only start these agents under close observation in hospital in patients with high gradients because of the potential to decrease afterload and exacerbate obstruction. Disopyramide is also an option, although several patients have tachyphylaxis and also cannot tolerate the anticholinergic side effects. Some clinicians have used pyridostigmine successfully to enable tolerance of the anticholinergic side effects of disopyramide.

Dr Ommen: You could add verapamil or disopyramide to her β-blocker to see if those might have benefit. With a heart rate of 60 bpm, the 100-mg dose of metoprolol is probably adequate for the patient and there is not much room to add other agents although disopyramide sometimes is tolerated in patients with resting bradycardia. If she were on a vasodilator, such as an angiotensin-converting enzyme-inhibitor, it would be important to take it away as we have seen great benefit in doing so in several patients. If her medication options have been exhausted and we cannot control her symptoms, then a more definitive approach, such as surgical myectomy or catheter-based ablation, are options for her. These options also may be needed if we cannot control her blood pressure without drugs that are contraindicated because of her obstruction, such as a vasodilator.

Dr Sorajja: It was clear that this patient had severe, drug-refractory symptoms, and there was strong suspicion that these symptoms were because of obstructive HCM. An invasive hemodynamic study with isoproterenol provocation was recommended as the next step in her evaluation. Before the patient was brought to the cath laboratory, there was a discussion about the options of surgical myectomy and alcohol septal ablation. Tell us about the important points of this discussion.

Dr Nishimura: There are data from our institution and several other HCM centers that demonstrate symptom relief in 90% to 95% of patients with surgical myectomy. It is important to note these data come from specialized centers where there are surgeons with the experience necessary to perform the procedure properly. In these patients who have successful myectomy, the long-term outcome is excellent, with survival similar to that of the general population. The risk of the procedure also is low, usually ≤1% in these highly experienced centers.6

Septal ablation is also a good option in experienced hands. Success rates are slightly lower; usually ≈80% to 85% patients have hemodynamic relief close to what is achieved with surgery. The major reason for this difference is the lack of an appropriate septal artery, which must target the area of the systolic anterior motion of the mitral valve-septal contact. The major risk of alcohol septal ablation is complete heart block requiring a permanent pacemaker, occurring in ≈10% to 15% of patients but is much higher if there is an underlying left bundle-branch block. The risk of the procedure itself is in experienced hands is quite low, <2% to 3%, but there is always the potential for complications such as coronary dissection, tamponade, large myocardial infarction, or ventricular fibrillation. The long-term adverse outcome of severe ventricular arrhythmias is a potential in every patient, but, in experienced hands, there is probably not a statistically significant increase with ablation in comparison with that achieved with a myectomy.7-11

Dr Ommen: We do not have randomized trials comparing the 2 therapies and probably never will because of the large number of patients needed for such a study.12 Based on observational data, surgical myectomy generally is favored for all patients as a class IIa indication according to latest HCM guidelines and as in this case. Septal ablation would be a class IIb recommendation, except in patients at high risk for surgery, where it is IIa. These differences are primarily based on the longer experience with surgical myectomy and the more predictable response with surgery compared with ablation. The short-term risks are greater for ablation, and some of these patients do require repeat procedures or crossover to surgery.

Dr Sorajja: Are there certain clinical variables that you use to help select patients for alcohol septal ablation or for surgical myectomy?

Dr Ommen: There are some, but we talk to each patient about all of the procedures in detail. Elderly age, frailty, and comorbidity tip the balance toward ablation rather than surgery. Ablation generally should be avoided in those who are relatively younger because of the absence of long-term data in these patients, especially those <40 years. The presence of underlying left bundle-branch block or a wide QRS markedly increases the risk of pacemaker dependence, as high as 50%, and would lead to consideration of myectomy. More severe pathology, such as severe hypertrophy or high resting gradients, is more likely to be safely and completely treated with surgery. There are no clear cut-offs, but a reasonable consideration is surgery for those with wall thickness of >24 mm. In an article, a gradient of <100 mmHg was associated with optimal outcome with ablation. If the hypertrophy is mild, one has to be certain that dynamic LVOT obstruction is secondary to the hypertrophy and not to abnormalities of the mitral apparatus. Concomitant disease, in terms of the potential need for other procedures such as bypass grafting or other valve therapy, is also a consideration. Patient preference plays an important role. It is their choice in the end as long as you discuss each of the procedures with them in detail and the therapy anatomically can be done.
Dr Sorajja: What special considerations are there in terms of anatomic eligibility?

Dr Ommen: Patients who have concomitant mitral valve disease or other pathology, such as anomalous papillary insertion and long anterior leaflets that need to be addressed, are candidates for operation and not for the catheter-only approach. The typical mitral regurgitation because of systolic anterior motion of the mitral valve from dynamic obstruction is directed posteriorly. In these patients, with either ablation or surgical myectomy, the mitral valve regurgitation will be addressed with appropriate treatment of the septum. If there is a central or an anterior jet of mitral regurgitation, the implication is a structurally abnormal mitral valve. Further testing, such as transesophageal echocardiography, is important in those instances, particularly if one is considering ablation and leaving the mitral valve alone. One wants to be sure that you are not going to leave the patient with significant, symptomatic mitral regurgitation after having done a procedure.

Dr Nishimura: The typical myectomy is the transaortic approach. So, if in fact there is a moderate degree of aortic regurgitation, surgery will make it worse and that would be one of the relative contraindications to performing the myectomy. However, if it is severe aortic regurgitation, you probably are best off replacing the aortic valve with a proper myectomy and not doing an ablation.

Dr Ommen: If there is moderate or severe aortic regurgitation in someone whom you think has HCM, it is also important to be sure there is no fixed subaortic stenosis. Significant aortic regurgitation is not a common finding in patients with HCM, but it is common with a fixed subaortic

Figure 2. Hemodynamic study with isoproterenol. At rest (left), there was no significant left ventricular outflow tract gradient (10 mm Hg). With isoproterenol (2 μg/min), a left ventricular outflow tract gradient of 121 mm Hg developed. Simultaneous echocardiography demonstrated systolic anterior motion of the mitral valve (Figure 3). Ao indicates ascending aorta; LA, left atrium; and LV, left ventricle.

Figure 3. Transthoracic echocardiogram during isoproterenol study. Top, Magnified, apical 4-chamber view in at end-diastole. Middle, End-systolic frame demonstrating systolic anterior motion of the mitral valve (arrowhead). Bottom, Color imaging demonstrating flow acceleration at the site of systolic anterior motion of the mitral valve. LA, left atrium; LV, left ventricle; and RV, right ventricle.
stenosis. With fixed subaortic stenosis, it is a surgical correction that is needed.

Dr Sorajja: And what about dual-chamber pacing for symptomatic obstructive hypertrophy, a therapy that you have had a lot of experience with?

Dr Nishimura: Dual-chamber pacing is a great placebo intervention. Initially, there was great enthusiasm that pacing the right ventricle and causing dyssynchronous contraction of the septum would decrease the obstruction and the outflow tract gradient. However, we found in randomized trials that the majority of patients felt better irrespective of whether they were paced. After 6 to 12 months, probably <20% to 25% of patients actually got a true benefit from dual-chamber pacing. It may be reasonable to attempt pacing in patients who already have dual-chamber devices in place for other indications, but the effect is much less certain than with ablation and myectomy.

Dr Sorajja: The clinician discussed the need for an invasive hemodynamic study and the options of medical therapy, surgical myectomy, and ablation in detail with the patient. In this discussion, the patient chooses to have septal ablation performed during the same catheterization procedure if dynamic LVOT obstruction is found.

The resting hemodynamic study demonstrates an LVOT gradient of 10 mm Hg and a left atrial pressure of 19 mm Hg. With isoproterenol infusion (2 μg/min), there is an LVOT gradient of 121 mm Hg (Figure 2). Simultaneous echocardiography during isoproterenol infusion demonstrates systolic anterior motion of the mitral valve with complete septal contact, and moderately to severe, posteriorly directed mitral regurgitation (Figure 3). A temporary pacemaker is implanted via her right internal jugular vein. Septal ablation is then performed with instillation of 1.7 mL of alcohol down her first septal perforator artery (Figure 4). Immediately after the procedure, the provable LVOT gradient decreased to <10 mm Hg. There are no complications, including no heart block.

If a patient requires a pacemaker after septal ablation, do you implant a defibrillator? Would you recommend placement of internal cardioverter defibrillator as prophylaxis against sudden cardiac death regardless of the need for a pacemaker in these patients?

Dr Ommen: It depends on the patient’s underlying risk factors for sudden death. Without conventional HCM risk factors (ie, massive hypertrophy, family history of sudden death because of HCM, nonsustained ventricular tachycardia, abnormal blood pressure response to exercise, and unexplained syncope), there is not a need to implant a defibrillator solely because the patient has had a septal ablation. For a patient with risk factors who has septal ablation, one may consider a defibrillator if a pacemaker is required after the procedure or if the patient and clinician were undecided about the need for a device based on the patient’s risk profile.1

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Figure 4. Alcohol septal ablation. Top left, Coronary angiography demonstrates a candidate septal perforator artery (arrow). Middle left and Bottom left, Contrast injection down a branch of the first septal artery demonstrates enhancement of the ventricular septum near the site of systolic anterior motion of the mitral valve (arrow). Top right, After instillation of 1.7 mL of alcohol, there is obliteration of the branch of the first septal artery. Bottom right, After ablation, there is no significant left ventricular outflow tract gradient at rest or after a premature ventricular contraction beat (<10 mm Hg). Ao indicates ascending aorta; LA, left atrium; and LV, left ventricle.
Dr Sorajja: It is clear that septal ablation can be performed using conventional catheterization equipment in many laboratories. The most recent HCM guidelines have put forth the importance of specialized centers for the care of these patients. Does septal ablation need to be performed in a tertiary center?

Dr Nishimura: Absolutely. It is also essential that the patient is well informed about all of the potential options, medical, and surgical. In this case, the patient consented to having alcohol ablation in the event that obstruction was found, and it is important that this discussion occurred before coming to the laboratory and not on an ad hoc basis.

Dr Ommen: Yes. There is good evidence that success rates increase and complications decrease by operator and institutional experience. The evaluation, care, and delivery of these therapies should be in the context of a comprehensive program that addresses all aspects of HCM, not just the ability to deliver alcohol down an artery. There are data that suggest a minimum number of cases, ≈50, are needed to achieve optimal clinical success, but the most important aspect is to be evaluated and treated in a center of expertise. The center should have a deep understanding of the pathophysiology, genetics, and the hemodynamics; an echo and MRI laboratory skilled in imaging these patients; and the ability to counsel patients on their risk for sudden cardiac death. Examining the anatomy of the outflow tract and mitral valve can be challenging because of morphological variable as we discussed, the anatomy of the outflow tract and mitral valve can be challenging because of morphological variable as we discussed, and the evaluation often requires being seen in a specialized center. These elements are crucial to the success of treating patients with HCM.

Dr Nishimura: And if there is any equipoise in a set of therapeutic options after you do shared decision making with the patient, it is in the patient’s best interest to go to a center that offers all therapeutic options, including surgery, and not just a single procedure.1

Clinical Outcome

Significant improvement in her symptoms occurs after septal ablation, with only mild dyspnea occurring during heavy exertional activities. These residual symptoms have been attributed to underlying diastolic dysfunction from her HCM. The patient continues to do well 4 years after her septal ablation.
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