Circulation Cardiovascular Case Series

Still a Kid at Heart
Hypertrophic Cardiomyopathy in the Elderly

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Forward

Information about a real patient is presented in stages (boldface type) to an expert clinician (Dr Michael A. Fifer), who responds to the information, sharing his reasoning with the reader (regular type). A Discussion by the authors follows.

A 76-year-old man with a history of hypertrophic obstructive cardiomyopathy (HOCM), hypertension, dyslipidemia, and obstructive sleep apnea presents with dyspnea on exertion. This symptom has progressed slowly over the past year, to the point that he now has dyspnea on climbing 1 flight of stairs. The patient denies orthopnea, paroxysmal nocturnal dyspnea, edema, chest discomfort, palpitations, lightheadedness, and syncope. His medications are metoprolol, verapamil, disopyramide, rosuvastatin, and omeprazole. He is a retired electrician, is married with 3 adult children, and lives in Florida and Massachusetts, each for half the year. He has a history of heavy tobacco use but quit smoking more than 30 years ago. His family history is notable only for diabetes mellitus and stroke in his father; there are no family members with heart failure, hypertrophic cardiomyopathy (HCM), or sudden cardiac death (SCD).

Dr Michael A. Fifer: This patient’s presenting complaint is progressive dyspnea on exertion, for which he has possibly contributory comorbidities, namely, obstructive sleep apnea and hypertension. The history of HCM is particularly relevant because dyspnea is a common initial manifestation of the disease.1 Dyspnea may occur in HCM as a result of a variety of mechanisms, including diastolic heart failure due to myocardial hypertrophy and fibrosis, left ventricular outflow tract (LVOT) obstruction, and associated mitral regurgitation (MR). Although the correlation between symptoms and the magnitude of the LVOT gradient is weak,2 dyspnea is usually relieved by septal reduction therapy. In this patient, any or all of these factors might contribute to progressive dyspnea on exertion. More information regarding how the diagnosis of HOCM was made and how the condition has been managed since it was diagnosed would help determine whether it is primarily responsible for the worsening dyspnea.

The diagnosis of HOCM was made 10 years before the current presentation. He presented then with exertional chest pain and dyspnea. An echocardiogram showed asymmetrical septal hypertrophy and a resting LVOT gradient. The diagnosis was confirmed by left-sided heart catheterization, which revealed an LVOT gradient that increased to 90 mm Hg with the Valsalva maneuver. Holter monitoring did not demonstrate ventricular tachycardia. The patient had substantial improvement in symptoms after undergoing medical therapy, which consisted of sustained-release metoprolol titrated up to 200 mg daily and sustained-release verapamil 120 mg daily. With the reappearance of dyspnea 1 year before the current presentation, disopyramide was added to the medical regimen, again with an initially favorable response.

Dr Michael A. Fifer: Although HCM is classically diagnosed in young patients, the disease has a wide age spectrum and may have its onset in middle age or in the elderly. Compared with younger patients, individuals with late-onset disease tend to have milder hypertrophy3 and may have comorbidities, such as hypertension and aortic stenosis (AS), that cause or contribute to left ventricular hypertrophy (LVH) by means of pressure overload. Isolated upper septal hypertrophy (USH) is fairly common in elderly patients, especially with those with hypertension, and may be difficult to distinguish from genetic HCM.4

The mainstays of pharmacological management of symptoms due to HOCM are β-blockers and nondihydropyridine calcium channel blockers (usually verapamil).5 In many cases, such as this one, there is added benefit from disopyramide, which shares with β-blockers and calcium channel blockers a negative inotropic action.6 This patient has been managed with simultaneous administration of all 3 types of negative inotropic agents.

On physical examination, he appears well, with no increased work of breathing at rest. Pulse is 51 bpm and regular, blood pressure 140/70 mm Hg in both arms, and respiratory rate is 18 breaths/min with oxygen saturation...
98% on room air. Jugular venous pressure is 7 cm H₂O with a normal contour. Carotid upstrokes are not delayed, and a bisferious pulse is not appreciable. Lungs are clear to auscultation. The point of maximal impulse is sustained and not displaced. He has a normal S₁ and S₂, with an S₃ and a harsh, crescendo-decrescendo systolic murmur at the base, radiating to the carotid arteries. There is a second, holosystolic murmur at the lower left sternal border and apex that radiates to the axilla and increases in intensity with the Valsalva maneuver. His abdomen is benign, without organomegaly, pulsatile mass, or bruit. His pulses are normal, without bruits, and there is no edema.

Complete blood count, electrolytes, and renal blood tests are normal. The ECG (Figure 1) shows sinus rhythm, left atrial enlargement, left-axis deviation consistent with left anterior fascicular block, and left ventricular hypertrophy with associated repolarization abnormalities. Chest radiography shows no signs of cardiac or pulmonary disease. Pulmonary function testing demonstrates normal forced vital capacity and forced expiratory volume in 1 second.

Dr Michael A. Fifer: This patient has 2 systolic murmurs. The murmur of HOCM is generally best heard at the lower left sternal border. With the Valsalva maneuver, there is decreased venous return to the right and, a few beats later, left side of the heart. With the decrease in left ventricular (LV) size, the septum and mitral valve are in closer apposition, the gradient increases, and the murmur intensifies. The maneuver must be performed with the patient supine (to avoid syncope). Because LVOT obstruction is usually associated with MR, there is often a systolic murmur at the apex and in the axilla as well. This part of the patient’s examination is consistent with HOCM.

The murmur of HOCM generally does not radiate to the neck. The presence in this patient of a crescendo-decrescendo systolic murmur at the base, radiating to the carotid arteries, suggests some degree of turbulence owing to thickening or stenosis of the aortic valve. The presence of normal carotid upstrokes suggests that the degree of AS is not severe.

There are no overt signs of heart failure or other diagnoses that would account for the patient’s worsening dyspnea. The ECG confirms the presence of LVH but does not distinguish among HCM, hypertension, and AS as the principal cause. To delineate whether AS is present in addition to HOCM, I would recommend transthoracic echocardiography as the next step.

An echocardiogram shows a hyperdynamic, small LV (35 mm at end diastole at the base) with ejection fraction 81% (online-only Data Supplement Figure 1). There is asymmetrical septal hypertrophy (septal thickness 17 mm, posterior wall thickness 12 mm; Figure 2). There is a late-peaking LVOT gradient of 129 mm Hg, which increases to 185 mm Hg with the Valsalva maneuver (Figure 3). There is moderate to severe posterolaterally directed MR due to systolic anterior motion (SAM) of the mitral valve (Figure 4); there are no abnormalities intrinsic to the mitral valve. The aortic valve is tricuspid, with thickening and calcification of the leaflets resulting in restricted aortic leaflet opening, consistent with valvular AS. Peak aortic valve gradient is 44 mm Hg (Figure 5), mean gradient is 27 mm Hg, and valve area is 1.4 cm² by planimetry. The continuity equation for aortic valve area was not used because of the high...
velocity in the LVOT. There is left atrial enlargement. The right ventricle is normal.

Dr Michael A. Fifer: The echocardiogram confirms the presence of all of the features of HOCM, namely, asymmetrical septal hypertrophy, SAM, an LVOT gradient, and MR. The most important new information is the grading of AS, which is moderate. Distinguishing the LVOT gradient from the aortic valve gradient on echocardiography can be challenging. M-mode abnormalities associated with dynamic LVOT obstruction include SAM of the mitral valve and midsystolic closure of the aortic valve. SAM can also be identified with 2-dimensional echocardiography, and its presence is indirect evidence of LVOT obstruction. The mechanism of SAM is complex. The Venturi theory, based on increased flow velocity in a narrowed outflow tract, is contributory but not fully explanatory. Other factors, such as anterior and inward displacement of the papillary muscles, anterior displacement of the mitral leaflets, and elongation of the mitral leaflets, also contribute to the development of SAM.7

Interrogation of the LVOT with Doppler provides the opportunity for quantitation of the degree of obstruction. Color flow Doppler typically demonstrates acceleration and aliasing of blood flow as it approaches the LVOT. Pulsed Doppler can localize high ejection velocities to the LVOT; with severe obstruction, however, the velocity exceeds the Nyquist limit, so that aliasing occurs. Continuous-wave Doppler can accurately quantitate high-velocity flow but cannot identify the location of the obstruction (ie, LVOT versus aortic valve). The shape of the outflow velocity profile, however, can be used to correctly identify LVOT gradients. The velocity profile of AS is symmetrical and parabolic. That of HOCM generally peaks relatively late in systole, producing an asymmetrical, “dagger-shaped” profile. In patients with 2 separate causes of outflow obstruction, continuous-wave Doppler demonstrates superimposed but distinctly different ejection envelopes, which suggests the presence of dual pathology.

It is also important to distinguish the gradient associated with dynamic LVOT obstruction from that between LV and left atrium associated with MR. Evaluation of the timing of the onset of blood flow can be helpful in making this distinction. MR is a holosystolic phenomenon, so that regurgitant flow begins earlier in systole than does that of LV ejection.

The next step for this patient should be cardiac catheterization. Right-sided heart catheterization will be useful for the determination of pulmonary artery and “pulmonary capillary wedge” pressures, as well as for exclusion of a right ventricular outflow tract gradient. Left-sided heart catheterization will be important for the further distinction between AS and HOCM. Coronary artery anatomy should be documented to exclude concomitant coronary artery disease and to delineate the septal anatomy to determine whether alcohol septal ablation is a therapeutic option.
The patient undergoes cardiac catheterization. Right atrial pressure is 8 mm Hg, right ventricular pressure is 35/10 mm Hg, pulmonary artery pressure is 35/15 mm Hg, and pulmonary capillary wedge pressure is 15 mm Hg. Left-sided heart catheterization with an end-hole catheter shows an LV apex pressure of 160/21 mm Hg, LVOT pressure of 141/21 mm Hg, and ascending aortic pressure of 126/65 mm Hg. Thus, resting peak-to-peak gradients are 19 mm Hg within the LV cavity and 15 mm Hg at the level of the aortic valve. A Brockenbrough sign (a decrease in systemic arterial pulse pressure after a ventricular premature beat) is present (Figure 6), and the LVOT gradient increases to 105 mm Hg with the Valsalva maneuver (Figure 7), both of which are consistent with dynamic LVOT obstruction. The aortic valve is moderately calcified. There is minimal coronary atherosclerosis, with a septal perforator branch of the left anterior descending coronary artery suitable for alcohol septal ablation.

Dr Michael A. Fifer: The left-sided heart catheterization confirms the presence of dynamic LVOT obstruction, although the resting gradient is markedly less than that seen on echocardiography. This type of variability is common, because the gradient of HOCM, unlike that of AS, may vary from day to day, presumably because of variations in volume status and other changes in loading conditions.8

In a patient with refractory symptoms and a low (<50 mm Hg) resting LVOT gradient, it is important to measure the gradient provoked by Valsalva maneuver or exercise. Both forms of septal reduction therapy (septal myectomy and alcohol septal ablation) are appropriate in patients with provable obstruction in addition to those with resting obstruction.

Both hypertension and AS regularly produce pressure-overload hypertrophy. An occasional patient with AS or hypertension has “HOCM physiology,” with SAM, an LVOT gradient, and MR in the absence of familial HCM. In such patients, LVH is usually symmetrical. The patient presented here has asymmetrical septal hypertrophy and had LVH before the appearance of AS, which suggests the presence of HCM; his hypertension may also be a contributing factor.

There is considerable practice variation (and some controversy9,10) in the triage of HOCM patients with refractory symptoms to septal myectomy or septal ablation. One condition for the performance of septal ablation is the absence of an independent condition for which cardiac surgery is indicated. In this patient, AS is not (yet) severe, but the likelihood that he will
require aortic valve replacement within several years tips the balance toward surgery in preference to septal ablation.

The patient undergoes septal myectomy and aortic valve replacement with a 25-mm bovine pericardial bioprosthesis. The myectomy is extended as far into the ventricle as possible. Pathology of the hypertrophied septum is notable for myocyte disarray, interstitial fibrosis, and arterial hyperplasia consistent with HCM (Figure 8).

Dr Michael A. Fifer: Although the presence of myocyte disarray is neither fully sensitive nor fully specific for HCM, its presence in this patient supports the diagnosis. Septal myectomy performed by skilled surgeons at high-volume centers results in abolition of the LVOT gradient and relief of symptoms in ≈90% of patients. After myectomy (as after septal ablation), there is regression of LVH in areas remote to the septum, which implies the presence of pressure-overload hypertrophy (even in patients without hypertension or AS) superimposed on that intrinsic to HCM. Mortality in high-volume centers for patients undergoing “pure” myectomy is <3%. Complications peculiar to septal myectomy include ventricular septal defect (1%) and complete heart block (3% to 10%).

Figure 7. Increase in gradient between left ventricular apex and femoral artery during the Valsalva maneuver.

Figure 8. Histopathology of the myocardium obtained during myectomy. A and B, Myocyte disarray; C, endocardial fibrosis; and D, arteriolar hyperplasia. All of these findings are consistent with, although not specific for, hypertrophic cardiomyopathy.
Recovery time, measured in months and highly dependent on the age of the patient, is similar to that for other cardiac operations. Although the incidence of SCD is low after septal myectomy, there are no data that indicate that postoperative risk factors for SCD differ from those in the general HCM population; it is therefore prudent to apply current recommendations to continual SCD risk stratification after surgery.11

Postoperatively, the patient has had complete resolution of dyspnea on exertion. Interestingly, the patient’s 51-year-old son has dyspnea and palpitations and has been found to have asymmetrical septal hypertrophy on echocardiography, which confirms the presence of genetic HCM in the family.

Dr Michael A. Fifer: First-degree relatives of patients with HCM should undergo screening for the disease. Phenotypic screening consists of an ECG and echocardiography at 12- to 18-month intervals during the teenage years and 5-year intervals in adulthood. Alternatively, genotypic screening may be performed, as considered in the Discussion.

Discussion
In a young HCM patient with a family history of the disease, the condition is usually demonstrably genetic. The yield of genotyping is particularly high if the myocardial thickness is maximal in the mid as opposed to the upper septum.12 In an elderly patient without a family history of HCM, the yield of genetic testing is much lower.13 In a community-based cohort from the Framingham Heart Study, 3% of all adults had unexplained LVH; of these, a little more than one sixth had a sarcomeric protein gene mutation.14

A possible explanation for the decreased yield of genetic testing in the elderly is that late-onset HCM is a more heterogeneous disease. The lack of certainty that such patients have genetic HCM has led to alternative terminology such as sigmoid septum, USH, or (in the many such elderly patients with concomitant hypertension) hypertensive cardiomyopathy.15,16

A characteristic feature of some cases of late-onset disease is increased angulation of the aorta with respect to the long axis of the LV. This may reflect a “functional” age-related change in cardiac shape that results in an upper septal bulge (sigmoid septum) and narrowing of the outflow tract.17 In subjects with USH, echocardiographic indexes of diastolic function are similar to those in patients with pressure-overload hypertrophy due to AS and intermediate between those in normal subjects and those with HCM.18 USH has not, however, been associated with the pathological features of genetic HCM such as myocyte disarray.19

Among patients with demonstrably genetic HCM, certain mutations predispose to later-onset disease. On average, patients with cardiac myosin-binding protein C mutations present later than those with β-myosin heavy chain or troponin T mutations.20 Late-onset HCM has also been linked recently to less common mutations in the troponin I and α-myosin heavy chain genes.13

The distinction between genetic HCM and related diagnoses such as sigmoid septum or USH is of some importance, because the natural history and implications for family screening differ among the conditions. Compared with younger patients, patients with late-onset LVH tend to have milder hypertrophy that is more localized to the anterior interventricular septum. Hypertension is more frequent as well, but its role in triggering the development of hypertrophy is unclear.

In addition to milder hypertrophy, late-onset disease is associated with a better overall prognosis. This was illustrated in a review of 277 outpatients who were followed up for 8 years.21 The annual mortality compared with the general population was increased substantially in those identified during childhood (1.3% versus 0.1%) but not in those identified in adulthood (2.2% versus 1.9%). Some mutations associated with late-onset disease, however, do not have a benign course. In a longitudinal study of 39 individuals with late-onset HCM due to a cardiac myosin-binding protein C gene mutation, 7 had manifestations of end-stage HCM (LV systolic dysfunction, cavity dilation, and irreversible heart failure).22

The management of HCM consists of 4 components: activity limitation with avoidance of volume depletion; risk stratification for and prevention of SCD; symptom control; and family screening. Guidelines have been put forward for participation in recreational sports.23 Accepted risk factors for SCD are unexplained syncope; family history of SCD due to HCM or occurring with no other explanation before 50 years of age; extreme (>30 mm) LVH; ventricular tachycardia, as detected by Holter monitoring; and an abnormal blood pressure response to exercise. Young and middle-aged patients at risk of SCD are usually offered an implantable cardioverter-defibrillator. The risk of SCD may be lower in elderly patients with HCM, but there is uncertainty with regard to how to adapt the conventional risk factors to this population.

Management options for symptoms in HCM are medical therapy consisting of β-blockers, nondihydropyridine calcium channel blockers, and disopyramide, alone or in combination; septal myectomy24; alcohol septal ablation25; and pacing with short AV delay. The latter strategy has not withstood the test of randomized, controlled trials but may be effective in a minority of patients. It is generally reserved for patients who have a dual-chamber pacemaker or implantable cardioverter-defibrillator for another indication. For patients with HCM without resting or provocable obstruction, standard therapy for symptoms consists of 180-blockers and calcium channel blockers. An algorithm for the management of symptoms in HCM is shown in Figure 9.

Elderly patients with LVH very often have concomitant hypertension, which may in fact be a contributing or even the major cause of hypertrophy. Many antihypertensive medications are relatively contraindicated in HCM, particularly if LVOT obstruction is present. Diuretics are relatively contraindicated by adverse effects of volume depletion, whereas vasodilators may produce hypotension, especially in the presence of LVOT obstruction. β-Blockade is the mainstay of therapy. When other drugs are required, they must be used with caution.

Family screening may be performed with a phenotypic (as described above) or genotypic strategy. Commercial genotyping is now routinely available. It is expensive, and insurance coverage for the test is variable. If a causative mutation is identified in a proband, genetic screening of relatives is relatively inexpensive. Relatives without the mutation do not require...
phenotyping testing. If no causative mutation is found, family
counseling may be an option, but further evaluation to identify
the underlying cause is recommended.

Thus, it is crucial to consider the patient's age, presenting 
symptoms, and family history when deciding on the 
management approach. Early intervention, such as 
medication or septal ablation, may be necessary to 
manage symptoms and prevent complications. Further 
research is needed to better understand the natural 
history and genetic factors of HCM in the elderly.

Disclosures

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