Hypertrophic cardiomyopathy is a fascinating disease entity in which hypertrophy of the myocardium occurs, primarily as a result of mutations of genes encoding the cardiac sarcomere.1–3 Our knowledge of patients with this unique disease of the heart muscle has advanced significantly. Once thought to be a rare malignant disease with a high risk of sudden death, population studies have revealed hypertrophic cardiomyopathy to be a more common disease with a benign outlook in the majority of affected patients.4 Hypertrophic cardiomyopathy is now recognized to comprise a wide spectrum of disease processes, with varying genetics, anatomy, clinical presentation, and prognosis. The dynamic left ventricular outflow tract obstruction that was initially the hallmark of hypertrophic cardiomyopathy continues to be a source of controversy.

The pathophysiology of hypertrophic cardiomyopathy is complex and still not completely understood. The first description of hypertrophic cardiomyopathy came in 1957 when Sir Russell Brock5 found a functional subvalvular obstruction in patients undergoing aortic valvotomy for clinically suspected valvular aortic stenosis. In 1958, Teare6 described the cardiac anatomy of 8 young patients who died suddenly with severe asymmetric left ventricular hypertrophy with bizarre muscle bundle orientation. In the 1960s, Braunwald et al7 defined a specific disease process in which asymmetric septal hypertrophy, myofibril disarray, and dynamic outflow tract obstruction were found. Thus, the early focus of hypertrophic cardiomyopathy was on this dynamic obstruction; the response of the obstruction to changes in preload, afterload, and contractility formed the basis for diagnosis.

With the advent of echocardiography, which allowed direct visualization of the hypertrophied myocardium, it became apparent that obstruction was not necessary for the diagnosis of hypertrophic cardiomyopathy. The entire relationship of obstruction to hypertrophic cardiomyopathy was subsequently questioned. Some thought that hypertrophic cardiomyopathy was primarily a disease of diastole, with obstruction playing little role in the pathophysiology of symptoms.8–10 Others proposed that the gradients obtained were not due to true obstruction but rather were an artifact of catheter entrapment.11 It has now become clear, however, that left ventricular outflow tract obstruction does play a major role in the pathophysiology of a subgroup of patients with hypertrophic cardiomyopathy. It may be present at rest, provokable (mild at rest but significant with provocation), or latent (not present at rest but evident with provocation). Although altered diastolic filling is evident in all patients with hypertrophic cardiomyopathy, it is the high contraction load imposed by the obstruction that significantly worsens ventricular filling and relaxation (Figure). Other mechanisms by which obstruction produces symptoms are limitation of cardiac output, increased myocardial oxygen demand, and decreased coronary perfusion pressure. In addition, obstruction is associated with distortion of the mitral valve apparatus, resulting in secondary mitral regurgitation, further elevating left atrial pressure, and contributing substantially to severe symptoms of dyspnea.

The mechanism by which obstruction is produced is complex. It was initially thought that the obstruction was the result of the hypertrophied septum projecting into the left ventricular outflow tract, causing a Venturi effect that would “suck” the mitral valve leaflets into the left ventricular outflow tract.12 Through intricate flow studies in the left ventricular cavity, it has been shown that obstruction can be secondary to an anterior displacement of the mitral valve apparatus coupled with accelerated flow around the septal hypertrophy, which produces a drag force to “push” the mitral leaflets into the outflow tract.13 Irrespective of the mechanism, we now know that obstruction plays a major role in this disease. The presence of obstruction portends a poorer prognosis as compared with nonobstructive hypertrophic cardiomyopathy.14 It is mainly patients with hypertrophic cardiomyopathy and obstruction for whom we have adequate treatment options. Medical therapy with high doses of β-blocker, calcium channel blocker, or disopyramide is effective in relieving symptoms in patients with documented obstruction, but these agents are relatively ineffective in patients without obstruction. In patients who remain severely symptomatic despite optimal medical therapy, septal reduction procedures can be performed. Septal myectomy is the “gold standard” of treatment and can completely abolish the gradient and improve symptoms in >90% to 95% of patients with low complication rates.2 Septal ablation, in which alcohol is injected through a percutaneous approach to cause a localized myocardial infarction, is a relatively new alternative to septal myectomy.15 Although initial studies have shown this to be effective in relieving symptoms and gradient in selected patients, long-term follow-up is required to determine the ultimate role of this treatment modality.
For these reasons, options for treatment are based on the presence of significant left ventricular outflow tract obstruction. In the past, obstruction was thought to be present in only 30% of patients with hypertrophic cardiomyopathy, and fewer than 5% would be candidates for septal reduction therapy. In this issue of Circulation, Maron et al have shown that resting obstruction (>50 mm Hg) was present in one third of their patients, but severe dynamic outflow tract obstruction was found in more than two thirds of patients when provoked by exercise and assessed by Doppler echocardiography. The dynamic nature of the obstruction was able to be brought out by the changes in contractility and afterload during exercise and was felt to be the cause of exertional symptoms in these patients. This correlates with the 70% of patients shown to have severe obstruction at our institution.

This study has important clinical implications. In patients with hypertrophic cardiomyopathy and severe symptoms, it is important to consider the possibility of labile or latent obstruction as the cause of the symptoms, even in patients who do not have a gradient at rest. Evaluation of symptomatic patients who have mild or no resting gradients (<50 mm Hg) should always include provocative maneuvers to determine whether a severe obstruction can be provoked. The findings of obstruction, either at rest or during provocation, can then be used to target therapy.

Doppler echocardiographic findings of a late-peaking, high-velocity signal from the left ventricular outflow tract have been considered to be an accurate method for measurement of the severity of left ventricular outflow tract obstruction. The modified Bernoulli equation can be applied to the peak velocity to determine the left ventricular outflow tract gradient. Maron et al have extended the use of Doppler echocardiography to measure provoked outflow gradients immediately after exercise. Their study is important because it shows that provocative gradients must be pursued in symptomatic patients with hypertrophic cardiomyopathy and the absence of severe resting obstruction. However, caution must be exercised when extending their findings to all patients with hypertrophic cardiomyopathy in all centers.

Doppler echocardiography requires skill and expertise to measure the outflow tract obstruction. Exercise is certainly the most physiological mechanism to provoke obstruction, but the rapid labored respiratory movements at peak exercise may interfere with the Doppler interrogation. Mitral regurgitation can also result in a high flow velocity in the same direction as the outflow tract obstruction, frequently contaminating the outflow signal. Differentiation of the mitral regurgitation signal from the outflow tract signal is more difficult after exercise. Cavity obliteration may occur in the mid-ventricular region and cause an increased velocity not due to true obstruction but rather due to the high velocity caused by a small hyperdynamic cavity, as has been shown to occur with dobutamine stimulation. A number of patients who had misleading Doppler information, suggesting a significant dynamic outflow tract gradient when no obstruction existed at rest or with provocation, have been referred to others and to us for septal reduction therapy.

It is therefore essential in all of these studies to assure that true obstruction is present during any type of provocation, as well as with exercise. The simple auscultatory finding of a loud systolic murmur appearing with provocation, whether during exercise or during simple maneuvers at the time of physical examination, is good confirmatory evidence of true obstruction. True outflow tract obstruction must be accompanied by demonstrable systolic anterior motion of the mitral valve, necessitating meticulous 2-dimensional echocardiographic imaging concurrent with the Doppler interrogation. In select cases in which it is still unclear as to whether a provokable obstruction is present, we and others have performed cardiac catheterization with isoproterenol infusion via a transseptal approach that avoids catheter entrapment artifact. LA indicates left atrium; LV, left ventricle; Ao, central aortic pressure.
vers with careful demonstration of systolic anterior motion of the mitral valve may identify patients with labile or latent obstruction who would benefit from treatment. However, we should not confine our approach to only the identification and treatment of obstruction. It is necessary to determine if other pathophysiological problems are present, such as intrinsic mitral valve disease, fixed subaortic obstruction, mid-ventricular obstruction, or apical involvement, as the presence of these coexistent lesions may have important implications for therapy. It also must be emphasized that sudden death may occur unrelated to obstruction and all patients with hypertrophic cardiomyopathy must also undergo risk stratification for sudden death. Family screening and genetic counseling should be part of the evaluation of any patient with hypertrophic cardiomyopathy. Although the new data by Maron et al.\textsuperscript{16} push us to search for obstruction, a complete understanding of this complex disease is always of utmost importance to provide the optimal care for these patients.

Disclosures

None.

References


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