Hypertrophic cardiomyopathy: a 1987 viewpoint

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HYPERTROPHIC CARDIOMYOPATHY (HCM) is characterized by symmetric or asymmetric hypertrophy of the left and/or right ventricle (table 1). It is a primary disorder of heart muscle in which the site and extent of the hypertrophic process are important in determining the disease manifestations.1

Ventricular (asymmetric) septal hypertrophy is the commonest form of HCM (table 1) and is characterized by abnormalities of systolic and diastolic function as well as rhythm disturbances. Systole is characterized by the presence or absence of an intraventricular pressure gradient, which when present may be persistent (gradient at rest), labile (spontaneously variable), or latent (provocable).1,2 Diastole is characterized by abnormalities of ventricular relaxation3 and passive chamber stiffness.4 Patients with extensive hypertrophy are more likely to manifest the abnormalities of systolic and diastolic function, as well as being more prone to atrial and ventricular arrhythmias and sudden death.1

During the almost three decades that HCM has been recognized as a clinical entity with regard to the significant morbidity and mortality, our knowledge and understanding of the diastolic and rhythm abnormalities have advanced in a fairly orderly, if perhaps modest, fashion. Such is not the case, however, with interpretation of the significance of the systolic intraventricular pressure differences. Most investigators accept that the characteristic pressure gradient, caused by prolonged mitral leaflet–septal contact, represents obstruction to left ventricular outflow and offer these patients surgical relief of the obstruction if they are unresponsive to medical therapy.1,2,5,6 However, there is a small cadre of investigators7–9 who believe there is no hemodynamic evidence of obstruction to outflow and suggest that the intraventricular pressure differences are the result of excessively rapid early systolic ejection with resultant cavity obliteration7 or elimination.8

It is the purpose of this commentary to discuss two aspects of HCM: (1) to review the evidence for and against obstruction to left ventricular outflow in obstructive HCM and (2) to emphasize and contrast the important differences between ventricular relaxation and passive chamber stiffness in regulating ventricular diastolic filling.

Systole

Evidence for obstruction to left ventricular outflow (the obstructive viewpoint)

Types of intraventricular pressure differences in HCM. Before considering the significance of intraventricular pressure differences in HCM, it is necessary to appreciate that there are four different types of systolic pressure difference that may be encountered in this condition.1 A small early systolic impulse gradient across the aortic valve is a normal phenomenon that results from early systolic flow acceleration; this gradient is often greater than normal in HCM because of the rapid ejection in early systole but does not extend beyond mid-systole.9 The pressure gradient in midventricular obstruction occurs at the level of the papillary muscles and not in the left ventricular outflow tract at the site of mitral leaflet–septal contact as in obstructive HCM (muscular or hypertrophic subaortic stenosis). These two types of pressure difference may be readily recognized.1 The third type of pressure gradient that may be encountered in HCM is the obstructive subaortic pressure gradient caused by mitral leaflet–septal contact (figures 1, left, and 2). The phenomenon of cavity obliteration may produce the fourth type of systolic pressure difference in HCM (figure 1, right).

In the presence of an obstructive subaortic pressure gradient in HCM, all intraventricular pressures proximal to the obstruction are elevated, including the left ventricular inflow tract pressure1,10 (figure 1, left). In the case of an intraventricular pressure difference

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*In an attempt to limit the number of references, the author has referred to a recent review article (ref. 1) for much of the work coming from the Toronto General Hospital, and to a lesser extent in summarizing the literature.
TABLE 1
Types of hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Type of involvement</th>
<th>Approximate incidence&lt;sup&gt;A&lt;/sup&gt; (%)</th>
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<tr>
<td>Left ventricular involvement</td>
<td></td>
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<tr>
<td>Asymmetric hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal hypertrophy</td>
<td>90</td>
</tr>
<tr>
<td>Midventricular hypertrophy</td>
<td>1</td>
</tr>
<tr>
<td>Apical hypertrophy</td>
<td>3</td>
</tr>
<tr>
<td>Posteroseptal and/or lateral wall hypertrophy</td>
<td>1</td>
</tr>
<tr>
<td>Symmetric (concentric) hypertrophy</td>
<td>5</td>
</tr>
<tr>
<td>Right ventricular involvement</td>
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<sup>A</sup>At the Toronto General Hospital. The incidence of the different types of hypertrophic cardiomyopathy varies considerably between different centers.

caused by cavity obliteration, the systolic pressure is elevated in the area of cavity obliteration, whereas all other intraventricular pressures, including the left ventricular inflow tract pressure, are low and equal to the outflow tract and aortic systolic pressures<sup>1, 10</sup> (figure 1, right). It is of the utmost importance to distinguish between an obstructive and an obliterative intraventricular pressure difference in HCM by use of the inflow tract pressure concept (figure 1) and the many other characteristic differentiating features of these two types of intraventricular pressure difference. This distinction is crucial in determining the presence or absence of obstruction to left ventricular outflow in HCM and hence in determining the appropriateness of medical and/or surgical therapy.

Mechanism of the obstructive subaortic pressure gradient caused by mitral leaflet–septal contact. In 1971 we suggested that a Venturi mechanism was the cause of systolic anterior motion of the anterior mitral leaflet and that subsequent mitral leaflet–septal contact resulted in the obstruction to left ventricular outflow and the concomitant mitral regurgitation<sup>11</sup> (figure 2). At that time it was reasoned that rapid early nonobstructed systolic ejection, through an outflow tract narrowed by subaortic septal hypertrophy, would draw the anterior mitral leaflet toward the septum by Venturi forces, caused by the high-velocity ejection jet passing closer to the mitral leaflets than is normal<sup>11</sup> (figure 2, left).

Evidence in support of the Venturi mechanism being the cause of systolic anterior motion of the mitral leaflets.

(1) HCM patients with obstructive pressure gradients generally have a greater degree of subaortic septal hypertrophy and a narrower left ventricular outflow tract at the onset of systole than do patients without

FIGURE 1. The left ventricular inflow tract pressure concept.<sup>10</sup> Left, In obstructive HCM, because the obstruction to left ventricular outflow (arrow) is caused by anterior mitral leaflet–ventricular septal contact, the intraventricular pressure distal to the stenosis (and proximal to the aortic valve) is low (+), whereas all ventricular pressures proximal to the stenosis, including the one just inside the mitral valve (the inflow tract pressure), are elevated (+ +). Right, When an intraventricular pressure difference is recorded because of catheter entrapment by the myocardium in an area of cavity obliteration, the elevated ventricular pressure is recorded only in the area of cavity obliteration (+ +). The intraventricular systolic pressure in all other areas of the left ventricular cavity, including that in the inflow tract just inside the mitral valve, is low (+) and equal to the aortic systolic pressure. Thus the inflow tract pressure is elevated in obstructive HCM but not in cavity obliteration. There are now more than 20 characteristic differences between these two types of intraventricular pressure difference.<sup>1, 10</sup> The three areas of the left ventricle represented by the + signs in each of these diagrams are, from above downward, the outflow tract just below the aortic valve (subaortic region), the inflow tract just inside the mitral valve, and the left ventricular apex. AO = aorta; LA = left atrium; LV = left ventricle.

FIGURE 2. Left, Mechanism of mitral leaflet systolic anterior motion in early systole in obstructive HCM. The ventricular septal hypertrophy causes a narrow outflow tract, as a result of which the ejection velocity is rapid and the path of ejection (dashed line) is closer to the mitral leaflets than is normal. These hydrodynamic and anatomic features in obstructive HCM result in Venturi forces (three short oblique arrows in the outflow tract) drawing the anterior (upper two arrows) and/or posterior (lower arrow) mitral leaflet(s) toward the septum (systolic anterior motion). Subsequent mitral leaflet–septal contact results in obstruction to left ventricular outflow and the concomitant mitral regurgitation, as

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seen on the right. In obstructive HCM with posterior leaflet systolic anterior motion, the posterior leaflet is either longer than the anterior leaflet (see diagram) or the mitral annulus is tilted so that the posterior leaflet extends further into the left ventricular cavity than the anterior leaflet. AO = aorta; LA = left atrium; MV = mitral valve; LV = left ventricle. Right, By mid-systole, anterior mitral leaflet–septal contact is well established, causing marked narrowing in the left ventricular outflow tract with obstruction to outflow. Proximal to the level of mitral leaflet–septal contact, the converging lines indicate the acceleration of the jet just proximal to the obstruction, as well as the narrowing of the jet width that occurs, presumably caused by mitral leaflet systolic anterior motion.12 Distal to the obstruction, the arrow and diverging lines indicate the high velocity flow that emanates from the site of mitral leaflet–septal contact, which is directed posterolaterally at a considerable angle from the normal path of aortic outflow.16, 17, 35 In late systole, although forward flow continues into the outflow tract12, 16, 17, 35 and aorta, 18, 20, 21, 26–28 the volume of flow is much less (smaller aortic arrow) than in early nonobstructive systole (left). The right upper oblique arrow arising from the mitral valve orifice indicates the occurrence of mitral regurgitation. A = the integrated Doppler flow signal in the ascending aorta in obstructive HCM27, 28 (flow toward the transducer); B, C, and D = the Doppler flow velocity signals that can be recorded from the apex of the left ventricle in obstructive HCM by means of pulsed and/or continuous-wave Doppler12, 16, 34 (flow away from the transducer); B = the high outflow tract velocities that emanate from the site of mitral leaflet–septal contact and that correspond closely to the simultaneously measured pressure gradients1, 16; C = the presence of mitral regurgitation; D = the late systolic velocity peak that can be recorded in the apical region of the left ventricle. Although this diagram (right) depicts systolic events after mitral leaflet–septal contact in obstructive HCM, A, B, C, and D represent flow/velocity signals throughout systole (see text).

obstructive pressure gradients, setting the stage for the Venturi mechanism to be operative.1

(2) Early systolic ejection in obstructive HCM is rapid and unobstructed before the onset of the pressure gradient1, 2 (figure 2, left) and the velocity of ejection accelerates just before the onset of mitral leaflet systolic anterior motion.12

(3) To test the hypothesis that mitral leaflet systolic anterior motion was caused by Venturi forces, Bellhouse and Bellhouse13 built a model of the left ventricle to resemble dynamic subaortic stenosis and were able to demonstrate mitral leaflet systolic anterior motion when the ejection velocities were rapid enough, as well as close enough, to the mitral leaflets.

(4) Widening of the outflow tract by surgery (ventriculomyectomy) (figure 3) or increased preload (transfusion) reduces or abolishes mitral leaflet systolic anterior motion because the rapid early systolic ejection path is no longer in close proximity to the mitral leaflets. Surgical widening of the lateral half of the left ventricular outflow tract will abolish systolic anterior motion of the lateral half of the anterior mitral leaflet, whereas systolic anterior motion remains in the medial half of the leaflet where the outflow tract remains narrow.1

(5) Any maneuver that changes the velocity of early systolic ejection will alter the degree of systolic anterior motion and hence the severity of the pressure gradient and mitral regurgitation.1 Thus increased contractility (positive inotropes) or decreased afterload (vasodilators) increase this velocity and hence the severity of mitral leaflet systolic anterior motion, the pressure gradient, and mitral regurgitation. Decreased contractility (negative inotropes) and increased afterload (vasopressors) have the opposite effect by decreasing early systolic ejection velocity.

(6) The Venturi mechanism can also explain the occurrence of dynamic subaortic stenosis caused by
mitral leaflet systolic anterior motion in hypovolemia, hyperkinetic states, tissue mitral valve protheses, mitral annular calcification, and Carpentier ring valvuloplasty. In each of these instances the left ventricular outflow tract is narrowed, setting the stage for the Venturi mechanism to be operative. Elongated mitral leaflets and/or mitral leaflets displaced anteriorly by abnormally placed papillary muscles would be more subject to Venturi effects during early systolic ejection. The Venturi mechanism can also explain systolic anterior motion of the posterior mitral leaflet (figure 2, left).

(7) Mitral leaflet systolic anterior motion has been attributed to contraction of malaligned papillary muscles or to posterior wall hyperkinesis or cavity obliteration. If any of these contraction mechanisms were responsible for systolic anterior motion and mitral leaflet–septal contact, then maximal systolic anterior motion (mitral leaflet–septal contact) should remain until the end of contraction, i.e., until end-systole. Mitral leaflet–septal contact, however, ends about three-quarters of the way through systole, making these contraction mechanisms unlikely, if not untenable. In addition, the rate of development of mitral leaflet systolic anterior motion is three times the rate of inward movement of the posterior wall of the left ventricle, and mitral leaflet–septal contact occurs over 200 msec before maximal inward movement of the posterior wall. These considerations would render it impossible for a hyperkinetic posterior wall, whether associated with cavity obliteration or not, from having any part to play in the genesis of mitral leaflet systolic anterior motion.

(8) Although there is considerable evidence to support the Venturi mechanism initiating mitral leaflet systolic anterior motion, it is presently unclear whether mitral leaflet–septal contact is maintained by continuing Venturi forces and/or by the left ventricular systolic pressure proximal to the site of obstruction.

Evidence that mitral leaflet–septal contact is the cause of the obstructive subaortic pressure gradient and mitral regurgitation

(1) HCM patients with severe systolic anterior motion with early and prolonged mitral leaflet–septal contact have obstructive pressure gradients, whereas patients with moderate, mild, or no systolic anterior motion do not.

(2) Combined hemodynamic-echocardiographic and hemodynamic-cineangiographic studies reveal that the onset of the obstructive pressure gradient (defined as the peak of the aortic percussion wave) begins just before or simultaneously with the onset of echo-cardiographic or cineangiographic mitral leaflet–septal contact. The mitral leaflet strikes the septum with considerable force, as is evidenced by the septal fibrous plaque, the fibrous thickening of the surface of the mitral leaflet that strikes the septum, and the occasional occurrence of an audible sound at the onset of mitral leaflet–septal contact.

(3) A number of characteristic features of obstructive HCM occur in close time proximity to the onset of mitral leaflet–septal contact: the peak of the aortic percussion wave, the onset of flow deceleration in the ascending aorta, the point of inflection on the rising left ventricular pressure tracing and on the continuous-wave Doppler recording from the outflow tract, and the onset of partial aortic valve closure. This combination of near-simultaneous events strongly suggests a sudden alteration of systolic hemodynamics, i.e., the onset of obstruction.

(4) The time of onset in systole of mitral leaflet–septal contact determines the magnitude of the obstructive pressure gradient, the degree of prolongation of the left ventricular ejection time, and the percentage of stroke volume that is ejected in the presence of the obstruction. Thus, early (and prolonged) mitral leaflet–septal contact is associated with a high pressure gradient, marked prolongation of left ventricular ejection time and a large percentage of left ventricular stroke volume is ejected against the obstruction. In contrast, mitral leaflet–septal contact of late onset (and short duration) is associated with a small pressure gradient and mild prolongation of left ventricular ejection time, and only a small percentage of left ventricular stroke volume is ejected against the obstruction. If mitral leaflet–septal contact occurs after 55% of the systolic ejection period, no pressure gradient develops.

(5) Recently reported high pulsed repetition frequency (PRF) pulsed Doppler, as well as continuous-wave and color Doppler studies provide important new confirmatory evidence that the site of the obstruction, and hence the origin of the pressure gradient, in obstructive HCM is at the level of mitral leaflet–septal contact (figure 2, right). High PRF and continuous-wave Doppler techniques permit accurate measurement of the peak flow velocity across a stenotic orifice, allowing calculation of the pressure gradient by the modified Bernoulli equation (PG = 4 × peak velocity²). Both high PRF pulsed Doppler and sequential continuous-wave and color Doppler studies in obstructive HCM localize the origin of the high outflow tract velocities to the site of mitral leaflet–septal contact (B in figure 2, right). When pressure gradi
ents are derived from these peak flow velocities across the outflow tract, there is a highly significant correlation with the simultaneously measured hemodynamic pressure gradients, whether recorded in the catheterization laboratory or intraoperatively. This close correlation between the flow velocity measured by pulsed or continuous-wave Doppler and the simultaneously measured pressure gradient represents strong confirmatory evidence of the obstructive nature of the left ventricular outflow tract pressure gradient in HCM. These same strong correlations between flow velocity and pressure are present in valvular aortic stenosis.

Color Doppler studies demonstrate two other important features in obstructive HCM: (a) acceleration of the jet, just proximal to the obstruction, i.e., mitral leaflet–septal contact (in valvular aortic stenosis the jet accelerates just proximal to the valve), and (b) significant systolic narrowing of the jet at the level of mitral leaflet–septal contact, presumably caused by mitral leaflet systolic anterior motion (figure 2, right).

(6) Mitral regurgitation, believed to be caused by mitral leaflet systolic anterior motion, has been shown by indicator dilution technique to invariably accompany an obstructive pressure gradient, although Doppler and cineangiographic studies do not always detect it. In the absence of an independent mitral valve abnormality, the degree of mitral regurgitation in the individual case is directly related to the severity of the obstruction (and hence the severity of mitral leaflet–septal contact). Although mitral regurgitation may be detected by cineangiographic or Doppler techniques at the onset of systole, both cineangiographic and color Doppler studies reveal that the major portion of mitral regurgitation occurs in the last half of systole and is a major determinant of the end-systolic size of the left ventricle. In obstructive HCM, both color Doppler and cineangiographic studies reveal rapid, unobstructed, early systolic ejection into the aorta, the onset of mitral leaflet–septal contact and the obstruction, followed by predominantly late systolic mitral regurgitation (eject/obstruct/leak) (figure 2).

Significance of the obstructive pressure gradient in HCM.

Percentage of stroke volume ejected in the presence of the pressure gradient. It is recognized that there is rapid, nonobstructed, early systolic ejection in obstructive HCM (figure 2, left). If this were not the case, there would be no Venturi effect to cause mitral leaflet systolic anterior motion. The question to be answered here is: What percentage of left ventricular stroke volume leaves the left ventricle after the onset of mitral leaflet–septal contact and the pressure gradient? This matter has been studied by no fewer than five different investigative techniques, and the results are similar. The percentage of cineangiographic emptying or echocardiographic minor diameter shortening after the onset of mitral leaflet–septal contact, or the percentage of nuclear angiographic emptying after the onset of the pressure gradient, varies between 47% and 73%. These three studies reflect total left ventricular emptying, i.e., both forward flow and mitral regurgitation. Two other studies have indicated that the percentage of forward flow into the aorta after the onset of the pressure gradient or mitral leaflet–septal contact varies between 40% and 70% of forward stroke volume when measured by Doppler or intraoperative electromagnetic flow techniques. Thus five different investigative techniques have demonstrated that a significant percentage of left ventricular emptying occurs after the onset of the obstruction to left ventricular outflow. We have provided evidence that the time of onset of mitral leaflet–septal contact determines not only the magnitude of the pressure gradient and the degree of prolongation of left ventricular ejection time but also the percentage of stroke volume that is ejected against the obstruction. This systolic overload of the left ventricle accounts for other characteristic features of obstructive HCM (see below).

Prolongation of left ventricular ejection time. One of the most characteristic features of any form of obstruction to left ventricular outflow is prolongation of the left ventricular ejection time. In obstructive HCM, left ventricular ejection time is prolonged in direct relation to the magnitude of the pressure gradient and both are related to the time of onset of mitral leaflet–septal contact during systole. Interventions that decrease the pressure gradient (increased afterload, decreased contractility, successful surgery) also decrease the ejection time as would be expected with relief of obstruction to outflow. Conversely, interventions that increase the pressure gradient (decreased afterload, increased contractility) result in prolongation of left ventricular ejection time, as would be expected with increased obstruction to outflow. The prolongation of ejection time in HCM patients with obstructive pressure gradients is even more impressive when it is recalled that all of these patients also have mitral regurgitation, which of itself would tend to shorten the ejection time. The prolongation of ejection time in obstructive HCM has now been demonstrated by clinical phonocardiographic, echocardiographic, hemodynamic, and Doppler techniques.

Evidence of slowed ejection with the onset of the pressure gradient. It has often been stated that the
supranormal ejection rate and high ejection fraction in obstructive HCM are incompatible with obstruction. It must be appreciated, however, that up to 40% of patients with critical valvular aortic stenosis also have supranormal ejection rates. In addition, in obstructive HCM, once the obstruction commences the major part of mitral regurgitation also begins to occur, providing the left ventricle with an alternative path of emptying. In spite of this late systolic mitral regurgitation contributing to left ventricular emptying after the onset of the obstruction, two recent studies have shown an abrupt mid-systolic slowing of left ventricular emptying and velocity of inward wall movement in obstructive HCM. These results are very much in agreement with a number of studies of ascending aortic flow that reveal an abrupt systolic deceleration of aortic flow in early systole, followed by a reduced but definite amount of flow in late systole (A in figure 2, right).

Myocardial ischemia associated with obstructive pressure gradients. In patients with obstructive HCM, large pressure gradients are associated with increased myocardial oxygen consumption and metabolic evidence of myocardial ischemia during pacing. Surgical abolition of the pressure gradient results in a marked reduction in myocardial oxygen consumption and alleviation or abolition of the myocardial ischemia. The significance of these findings is enhanced when it is realized that impaired relaxation in diastole may also cause myocardial ischemia in HCM (figures 4 and 5).

Symptoms related to the presence of obstruction to left ventricular outflow. It is recognized that HCM patients with and without obstruction may have similar symptoms and this has been cited as evidence against the obstruction having any clinical significance. Recently, however, we have analyzed the symptomatic state of a large number of HCM patients with and without obstruction and have found that those with obstructive pressure gradients have a significantly higher incidence of class III to IV NYHA symptoms as well as a significantly higher overall incidence of angina and dyspnea. Patients with obstructive pressure gradients also have a significantly higher incidence of grade III-IV/VI apical systolic murmurs and reversed splitting of the second heart sound. These facts provide evidence that the obstructive pressure gradients in HCM are not only of hemodynamic and metabolic significance but also of profound clinical significance and are in keeping with the dramatic clinical benefits derived from a successful ventriculomyectomy operation (figure 3).

The nonobstructive viewpoint. The foundation for the nonobstructive viewpoint in HCM revolves around the phenomenon of cavity obliteration (elimination), the interpretation of the nature of intraventricular pressure differences, as well as the interpretation of ascending aortic velocity flow curves.

Intraventricular pressure differences associated with cavity obliteration. Gauer and Henry and Martin et al. first

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**FIGURE 4.** Diagram indicating the mechanisms by which relaxation is impaired and chamber stiffness increased in HCM. Increased restoring forces may result in exaggerated changes in shape during isovolumic relaxation, whereas the degree of ventricular interaction may be decreased by the extent of septal hypertrophy. See text. (Reproduced with permission from Prog Cardiovasc Dis 28: 1–83, 1985.)

**FIGURE 5.** Coronary filling in HCM is believed to be adversely affected by septal perforator artery compression, small-vessel disease, the extent of hypertrophy, decreased perfusion pressure, decreased coronary flow reserve, and impaired relaxation. This diagram indicates a vicious cycle, relating decreased coronary filling and myocardial ischemia to impaired left ventricular relaxation in HCM. Decreased coronary filling during early diastole will impair relaxation by the decreased load (1), as well as by producing myocardial ischemia (2), which in turn decreases inactivation (3) and increases nonuniformity (4), both of which act to slow the rate of relaxation (5 and 6). Decreased inactivation also decreases load dependency (7), which would further impair relaxation (8). Finally, impaired relaxation itself would reduce coronary filling (9) during early diastole, and this would complete the vicious cycle by further reducing the coronary filling (relaxation) load (1) and producing more myocardial ischemia (2). (Reproduced with permission from Prog Cardiovasc Dis 28: 1–83, 1985.)
described the occurrence of intraventricular pressure differences in association with cavity obliteration during the study of experimental hemorrhagic shock, especially if catecholamines were administered. These authors attributed the elevated ventricular systolic pressures recorded in the obliterated apical region of the left ventricle, as well as the occurrence of subendocardial hemorrhages in the same location, to systolic apposition of the ventricular walls, with continued isometric contraction in the obliterated apex of the ventricle.

In the mid-1960s, Criley et al. documented the occurrence of similar intraventricular pressure differences in HCM patients with apical cavity obliteration. As was the case with Gauer and Henry and Martin and associates, these authors indicated that the elevated left ventricular systolic pressure was the result of "the catheter tip being completely enfolded or engulfed in contracting muscle" or alternatively was caused by "isometric contraction on a catheter in an emptied region of the hypertrophied ventricle." Thus the conclusions of these investigators were similar if not identical; that is, in cavity obliteration the high intraventricular pressure occurred as the result of the catheter tip being enfolded, engulfed, or entrapped by isometrically contracting myocardium in an area of the left ventricle that became obliterated early in systole. In support of this contention, catheters recording the elevated ventricular systolic pressures have been shown to be outside of the angiographic silhouette of the ventricle, i.e. they were recording pressures from the sites of cavity obliteration.

This nonobstructive view of the nature of intraventricular pressure differences in HCM in the mid-1960s caused considerable confusion and consternation in the cardiologic community and threw doubt on the practice of operating on patients with obstructive HCM. However, within a year of the first expression of this nonobstructive viewpoint, methods were described that enabled investigators to clearly distinguish between an obstructive subaortic pressure gradient and the intraventricular pressure difference encountered in apical cavity obliteration. These methods included use of the left ventricular inflow tract pressure concept (figure 1), the demonstration that left ventricular ejection time was prolonged in obstructive HCM but not in cavity obliteration, and the fact that catheters recording elevated ventricular pressures were inside the left ventricular silhouette in obstructive HCM but were outside the systolic angiographic silhouette when recording elevated pressures in cavity obliteration. Subsequently, many other methods to distinguish between these two types of intraventricular pressure difference have been described. Recently Grose et al., using simultaneous hemodynamic and cineangiographic techniques, confirmed the distinctive differences between these two types of intraventricular pressure difference. In the presence of an intraventricular pressure difference caused by cavity obliteration, the apical obliteration occurred early in systole before the peak pressure difference, the apical catheter recording the high pressure was outside of the systolic angiographic silhouette, there was no evidence of mitral leaflet–septal contact, and the inflow tract pressure was low and equal to aortic pressure (figure 1, right). In contrast, in the presence of an obstructive pressure gradient in HCM, the inflow tract pressure was elevated (figure 1, left), there was cineangiographic evidence of mitral leaflet–septal contact that coincided with the onset of the pressure gradient, and the peak pressure gradient occurred well before any end-systolic emptying that would be partially related to late systolic mitral regurgitation.

It is important to appreciate that cavity obliteration (or elimination) is not a diagnosis but rather a nonspecific manifestation of ventricular emptying that is most commonly associated with left ventricular hypertrophy. It is best appreciated in HCM because of the extent of hypertrophy but also occurs in left ventricular hypertrophy due to other causes, provided that ventricular function is preserved. The degree to which cavity obliteration occurs in left ventricular hypertrophy varies with the degree of hypertrophy, left ventricular systolic function, and whether or not there is obstruction to left ventricular outflow or mitral regurgitation. Cavity obliteration may be mild, moderate, or severe and may occur early or late in systole, depending on the four variables that determine its degree. An intraventricular pressure difference occurs in cavity obliteration when a catheter is purposely or inadvertently advanced to the area of obliteration, where it may become enfolded or entrapped by the contracting myocardium. However, an intraventricular pressure difference is not recorded in the presence of cavity obliteration where the catheter remains in the nonobliterated part of the ventricular cavity.

Since the distinction between an obstructive pressure gradient caused by mitral leaflet–septal contact and the intraventricular pressure difference caused by cavity obliteration was made, the proposed mechanism of generation of the intraventricular pressure difference in cavity obliteration has been changed significantly. Proponents of the nonobstructive view-
point\textsuperscript{4, 33} no longer refer to the catheter recording the elevated ventricular pressure being “enfolded” or “engulfed” by isometrically contracting myocardium in an area of cavity obliteration,\textsuperscript{32} but rather they suggest that the elevated systolic pressure is generated by the rapidly contracting apex of the left ventricle and that this elevated pressure is somehow not transmitted to the relatively noncontractile body and outflow tract.\textsuperscript{7, 33} If this suggestion is correct, then high PRF Doppler velocity tracings recorded at the level that separates the obliterating apex from the noncontractile basal region of the left ventricle should reveal velocities that correspond in time and magnitude to the measured intraventricular pressure difference. But such is not the case. Pulsed Doppler recordings from this area reveal minimal velocities in early and mid-systole and a peak velocity at end-systole that rarely exceeds 2 m/sec (gradient 16 mm Hg)\textsuperscript{12, 34} (D in figure 2, right). An obliteratorive intraventricular pressure difference often begins early in systole, is well developed by mid-systole, and is declining by end-systole. Thus it would seem unlikely that the intraventricular pressure difference in cavity obliteration is caused by the generation of a pressure difference between the rapidly contracting apex and the noncontractile base of the left ventricle. Based on current evidence, the intraventricular pressure difference in cavity obliteration is more likely to be caused by the apical catheter being enfolded,\textsuperscript{32} engulfed,\textsuperscript{32} or entrapped\textsuperscript{10} by the surrounding myocardium, as originally suggested. The elevated pressure recorded in these circumstances may well reflect intramyocardial tissue pressure.\textsuperscript{10}

The term “catheter entrapment” was used “to describe the situation wherein cardiac muscle enfolds a catheter situated in a portion of the left ventricular cavity that is emptied of its contents in systole (obliterated).”\textsuperscript{10} The words enfold,\textsuperscript{32} engulf,\textsuperscript{32} and entrap\textsuperscript{10} have similar, if not identical, meaning and yet some authors have chosen to regard the elevated pressures recorded by an entrapped catheter to be an artifact\textsuperscript{1, 33} in that atypical ventricular pressure wave forms are sometimes recorded.\textsuperscript{10} It would seem more likely that the degree of catheter entrapment by cavity obliteration and/or the type of catheter used would determine whether or not unusual wave forms are noted in the elevated ventricular pressures recorded under these circumstances.

Aortic flow studies in HCM. Studies with catheter-mounted velocity flow probes have demonstrated abbreviated early systolic flow with little or no late systolic flow in both obstructive and nonobstructive HCM.\textsuperscript{9} Proponents of the nonobstructive view in HCM have often cited these studies as proof of the nonobstructive nature of the pressure gradients in HCM, i.e., the ventricle empties more rapidly than normal whether a pressure gradient is present or not.\textsuperscript{7-9}

However, four other techniques of measuring ascending aortic velocity-flow have reported quite different results in HCM.\textsuperscript{18, 20, 21, 26-28} Thus the pressure differential,\textsuperscript{26} intraoperative electromagnetic,\textsuperscript{21} Doppler,\textsuperscript{18, 20} and 16-gated Doppler–two-dimensional echocardiographic\textsuperscript{27, 28} techniques have revealed essentially normal ascending aortic flow profiles in nonobstructive HCM, whereas in obstructive HCM there is a sudden deceleration of aortic flow in early systole, virtually coincident with the onset of the obstruction (A in figure 2, right). During the remainder of systole, a reduced but definite amount of forward aortic flow is recorded.\textsuperscript{18, 20, 26-28} The recently reported 16-gated Doppler–two-dimensional echocardiographic observations are particularly important to note in that this technique samples flow across the whole of the ascending aorta.\textsuperscript{27, 28} These studies reveal that forward aortic flow is not abbreviated in either obstructive or nonobstructive HCM, nor is it uniform in obstructive HCM in that forward flow close to the posterior wall may cease before end-systole, while it continues throughout systole in the more anterior parts of the ascending aorta.\textsuperscript{27, 28} Other authors have also observed nonuniform aortic flow in obstructive HCM.\textsuperscript{12, 35} It is important to appreciate that to convert a velocity signal, recorded from a single aortic site, to instantaneous aortic flow, the velocity should be uniform over the entire cross-section of the aorta (blunt waveform). It seems reasonable to assume a blunt ascending aortic velocity waveform in nonobstructive HCM and also in early systole in obstructive HCM (figure 2, left). However, once mitral leaflet–septal contact occurs in obstructive HCM, with the development of eccentrically directed high-velocity jets in the left ventricular outflow tract (figure 2, right), both multigated\textsuperscript{27, 28} and continuous-wave\textsuperscript{12, 35} Doppler studies indicate that ascending aortic velocity and flow become nonuniform and are not blunt. These observations dictate extreme caution in the interpretation of aortic velocity-flow measurements when they are recorded from a single aortic site by any technique. Recordings near the posterior aortic wall could be particularly misleading in that abbreviated systolic flow could be recorded.\textsuperscript{27, 28}

The integrated nonobstructive viewpoint. An integrated nonobstructive “perspective” has resulted from combining angiographic and catheter-mounted aortic velocity flow studies.\textsuperscript{7} The authors concluded that obstruction “is rarely, if ever present” in HCM and
described systole as being divided into three phases. Phase 1 is characterized by a rapid or supranormal early systolic ejection (no difference from the obstructive viewpoint).

Phase 2 is characterized by the development of an intraventricular pressure difference between the rapidly contracting apex and the poorly contracting basal region of the left ventricle. During this phase there is a decline in aortic flow to zero or near zero (i.e., ejection ceases) and mitral leaflet–septal contact is described as occurring halfway through this phase, near the nadir of the aortic flow signal (i.e., not much forward flow occurs after mitral leaflet–septal contact). Mitral leaflet–septal contact is attributed to obliteration of the subvalvular left ventricular cavity, that is, it is related to cavity obliteration.

Phase 3 is characterized by "virtually no aortic outflow and the left ventricle is essentially isovolumetric." Let us now examine the basis for this nonobstructive viewpoint, while keeping in mind that its proponents make no attempt to distinguish between an obstructive subaortic pressure gradient caused by mitral leaflet–septal contact from an intraventricular pressure difference caused by cavity obliteration.

Is there a pressure difference generated between the rapidly contracting apex of the left ventricle and the poorly contracting basal part of this chamber? High PRF pulsed Doppler recordings from the junction between the rapidly contracting apex of the left ventricle and the relatively noncontractile basal part of this chamber (D in figure 2, right) do not correspond in time or magnitude to either an oblitative intraventricular pressure difference (figure 1, right) or to what we have defined as an obstructive intraventricular pressure gradient caused by mitral leaflet–septal contact (figures 1, left, and 2, right). In the absence of evidence to suggest that an intraventricular pressure difference is developed between these rapidly and poorly contracting areas of the left ventricle, one is led to conclude that the intraventricular pressure differences reported by those holding the nonobstructive viewpoint must either be obstructive subaortic pressure gradients caused by mitral leaflet–septal contact (for which there are corresponding high velocities in the outflow tract; B in figure 2, right) or are intraventricular pressure differences caused by cavity obliteration with actual entrapment or enfolding of the catheter recording the elevated pressure by left ventricular myocardium.

Does left ventricular ejection cease at the end of phase 2, and is phase 3 isovolumetric as proposed in the nonobstructive viewpoint? Studies of the velocity–flow profiles in the ascending aorta, and left ventricular outflow tract downstream from the site of obstruction (mitral leaflet–septal contact) (A and B in figure 2, right) reveal continued forward ejection from the left ventricle throughout all of systole. In addition, cineangiographic and color Doppler studies reveal that the mitral regurgitation associated with the outflow obstruction occurs principally in the last half of systole and is a major determinant of the end-systolic size of the left ventricle. Thus in obstructive HCM there is a large volume of evidence to indicate that the left ventricle is not isovolumetric during the last half of systole, but rather it continues to empty into both the aorta and left atrium.

Are mitral leaflet systolic anterior motion and septal contact caused by cavity obliteration and hence a relatively late event as proposed in the nonobstructive viewpoint? We have provided evidence that mitral leaflet systolic anterior motion is caused by Venturi forces on these leaflets that result from the rapid, nonobstructed, early systolic ejection (figure 2, left). In keeping with this belief, systolic anterior motion may begin as early as 6% of the systolic ejection period and mitral leaflet–septal contact may occur as early as 15% of this period. Even in cavity obliteration, the left ventricle is not emptied this early. We have also demonstrated clearly that mitral leaflet–septal contact cannot be related to posterior wall hyperkinesis or cavity obliteration in that there is no correlation between the development of mitral leaflet systolic anterior motion and posterior wall movement or cavity obliteration.

Does a significant percentage of left ventricular ejection occur after the onset of mitral leaflet–septal contact and the pressure gradient? The nonobstructive viewpoint suggests that mitral leaflet–septal contact occurs at a time when the left ventricle has almost emptied itself of its contents. However, we have indicated that no fewer than five different methods of investigation have shown that from 40% to 70% of left ventricular emptying occurs after the onset of mitral leaflet–septal contact and the pressure gradient.

Is the prolonged left ventricular ejection time caused by obstruction to left ventricular outflow or by impaired relaxation? Several proponents of the nonobstructive viewpoint have suggested that the prolonged left ventricular ejection time is related to impaired left ventricular relaxation. However, a prolonged left ventricular ejection time is found only in patients with obstructive pressure gradients, and the degree of prolongation is directly related to the magnitude of the pressure gradient. Impaired relaxation in
nonobstructive HCM has not been demonstrated to result in a prolonged ejection time.¹

**Can obstructive pressure gradients occur in HCM in the absence of cavity obliteration?** The nonobstructive viewpoint suggests that cavity obliteration is the cause of intraventricular pressure differences in HCM. However, large obstructive pressure gradients (> 100 mm Hg) have been described in the absence of cavity obliteration (ejection fraction 50%).¹ It would be difficult to ascribe the pressure gradient to cavity obliteration in such circumstances when there is none.

**In obstructive HCM, is the postextrasystolic beat decrease in aortic pulse pressure explained on an obstructive or nonobstructive basis?** A number of nonobstructive mechanisms have been advanced to explain this phenomenon.⁷ In obstructive HCM, both echocardiography and cineangiography reveal that in the postextrasystolic beat, mitral leaflet–septal contact occurs earlier in systole and is more prolonged than in sinus beats.¹ As would be predicted from this fact,¹ the pressure gradient is greater,³⁶ the left ventricular ejection time more prolonged,¹² and a greater degree of mitral regurgitation occurs.¹ Continuous-wave Doppler¹²,¹⁶ studies of postextrasystolic beats in obstructive HCM reveal higher outflow tract velocities (emanating from the site of mitral leaflet–septal contact) than in sinus beats, and these correlate closely with the simultaneously measured higher hemodynamic pressure gradient.¹⁶ This constellation of facts would appear to provide incontrovertible evidence of increased obstruction in the postextrasystolic beat in obstructive HCM, as originally proposed by Brockenbrough et al.³⁶

As a result of the foregoing analysis of the obstructive vs the nonobstructive viewpoint in obstructive HCM (muscular or hypertrophic subaortic stenosis), one can only conclude that true obstruction to left ventricular outflow does exist and is caused by prolonged mitral leaflet–septal contact. Recent pulsed,¹,¹² continuous-wave,¹²,¹⁶,³⁵ multigated,²⁷,²⁸ and color¹⁶,¹⁷ Doppler studies only reinforce this conclusion, which was previously based on clinical,¹,²,²¹,²³ phonocardiographic,²,²³ echocardiographic,¹,¹⁸ hemodynamic,²,¹⁰,¹¹,²¹,²² and cineangiographic¹,¹⁵,²¹ evidence. Appropriate care must continue to be exercised in distinguishing the obstructive subaortic pressure gradient in obstructive HCM from the intraventricular pressure difference encountered in cavity obliteration or in midventricular obstruction.¹,¹⁰ Fortunately there are now clinical¹,² as well as echocardiographic and Doppler* criteria that permit clear distinction between obstructive and nonobstructive HCM without resorting to invasive studies. The latter should be reserved for diagnostic problems and/or when surgery is being considered.

To deny the presence of obstruction to left ventricular outflow in obstructive HCM is to deny these patients appropriate medical and/or surgical therapy.

**Diastole**

Although the major focus of this commentary is on systolic events in HCM, it would be wrong not to comment on the impaired diastolic filling in this condition in that in some cases, as stated in 1962, the hypertrophic process “may disable a patient more from poor ventricular filling in diastole, than from obstruction to outflow of blood in systole.”²³ In the early 1960s, investigators²,²³ spoke of decreased compliance of the ventricles in HCM at a time when the process of ventricular relaxation was not fully appreciated, nor could it be measured. In the past quarter century, this state of affairs has changed drastically for two reasons. First, the “triple control of relaxation” by load, inactivation, and nonuniformity has begun to be appreciated, largely as the result of work by Brutsaert et al.³ Second, just as modern cardiologic technology has helped to unravel the “apparent” mysteries of systole, so many of the same techniques have permitted investigators to derive indexes of active relaxation that have advanced our knowledge and understanding of this process, particularly in HCM. It is as though modern cardiologic technology and HCM were “meant for each other” in that these technologies have added to our understanding of HCM probably more than of any other form of heart disease.

Diastolic dysfunction in HCM is mainly related to impaired relaxation and/or increased chamber stiffness, although other factors may be important (figure 4).

**Impaired relaxation.** There is evidence that all three factors (load, inactivation, and nonuniformity) that control ventricular relaxation are altered in HCM¹,³ (figure 4). The subaortic stenosis may act as a contraction load,¹ whereas the principle relaxation loads (coronary and ventricular filling) are reduced.¹,³ All of these load changes would impair relaxation.³ Impaired inactivation of the biochemical processes responsible for contraction, by primary or ischemia-induced calcium overload, would not only reduce the rate of relaxation directly but would render the myocardium insensitive to the already reduced principle relaxation loads³ (figure 4) (double-edged sword effect of impaired in-
activation). Finally, there is abundant evidence of non-uniformity of load and inactivation in space and time.3 Thus, in HCM all three factors (load, inactivation, and nonuniformity) that control relaxation are altered in a way that relaxation would be impaired.1,3 The adverse effect of impaired relaxation on coronary filling and myocardial ischemia is shown in figure 5.

Calcium-entry blockers may improve relaxation in HCM by favorably altering the contraction and relaxation loads, by enhancing the inactivation process, or by lessening the degree of nonuniformity. Although calcium-entry blockers usually result in clinical benefit, the vasodilatory properties may worsen the outflow tract obstruction and the negative inotropic properties may cause heart failure in patients with compromised left ventricular systolic function. Care must be exercised to ensure that benefit and not harm result from the use of these agents in patients with HCM.

**Increased chamber stiffness.** Chamber stiffness (dp/dv) (the inverse of chamber compliance [dv/dp]) is directly related to myocardial stiffness and mass and inversely related to chamber volume.4 In HCM there is an increase in myocardial stiffness and mass and a decrease in chamber volume, all three factors acting to increase chamber stiffness (decrease compliance) (figure 4).

**Impaired relaxation vs increased chamber stiffness.** Impaired relaxation of the left ventricle results in a decrease in the rate and volume, as well as a prolongation, of rapid filling, a shortening or abolition of diastasis, and exaggerated atrial systolic filling (to compensate for reduced rapid filling).37 In patients with grossly impaired relaxation, the fourth heart sound is frequently the loudest ventricular filling sound, in keeping with exaggerated atrial systolic filling of the ventricle. In contrast, in patients with increased chamber stiffness and with resultant "restriction" of diastolic filling, rapid filling rates may be increased and be accompanied by a loud third heart sound, whereas atrial systolic filling of the ventricle is normal or reduced.1 Thus impaired relaxation and increased chamber stiffness result in sharply contrasting ventricular diastolic filling patterns that may be distinguished by a number of investigative techniques or in some circumstances by clinical examination according to which ventricular filling sound is the loudest.

It is important to appreciate, however, that both types of diastolic dysfunction are often present to a variable degree in any given patient with HCM (figure 4), as in other types of heart disease. This only adds to the complexity of analysis of diastolic function by any of the currently available techniques. Indeed, when impaired relaxation is the dominant diastolic fault, as it often appears to be in HCM, it may be difficult if not impossible to assess passive chamber stiffness, in that severe abnormalities in relaxation may have an impact on all four phases of diastole.1

HCM patients with significant impairment of relaxation would be expected to suffer particularly adverse consequences from tachyarrhythmias such as atrial fibrillation in that relaxation would be further impaired by the shortened diastole, and the loss of enhanced atrial systolic filling of the ventricle would remove the most important mechanism by which the heart compensates for impaired relaxation. Such patients often develop pulmonary edema, angina, or syncope with the onset of atrial fibrillation. On the other hand, the onset of atrial fibrillation in patients with increased chamber stiffness would not be expected to lead to drastic clinical deterioration in that rapid filling would be little affected by the shortened diastole, and the loss of atrial systole should not be of great consequence because with "restriction" of diastolic filling atrial systole contributes only a normal or reduced amount to the end-diastolic volume.

**Conclusion**

HCM is a diverse disease entity in which the presence and severity of the various clinical and pathophysiologic abnormalities appear related to the site and extent of the hypertrophic process. Recent evidence confirms that mitral leaflet-septal contact is the cause of the obstructive subaortic pressure gradient. The time of onset of mitral leaflet-septal contact not only determines the magnitude of the pressure gradient but also the degree of prolongation of left ventricular ejection time, the percentage of stroke volume that is obstructed, and the degree of mitral regurgitation. Diastolic filling is compromised by impairment of ventricular relaxation and increased passive chamber stiffness. Rational medical and/or surgical therapy is now available for most of the pathophysiologic abnormalities of HCM. Although modern cardiologic technology has helped to unravel many of the real, as well as the "apparent" mysteries of HCM, much is still to be learned about this fascinating but no longer so perplexing disorder.

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