Has ‘obstruction’ hindered our understanding of hypertrophic cardiomyopathy?

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The ill and unfit choice of words wonderfully obstructs the understanding. — Sir Francis Bacon

The presence of an outflow tract pressure gradient in patients with hypertrophic cardiomyopathy (HCM) has been equated with an obstruction deemed primarily responsible for significant morbidity and mortality. Over 40 names containing variations of the words obstruction or stenosis have been applied to this disease. So strong was the belief in the presence and primacy of obstruction in the early 1960s that angiocardiograms and surgical observations were perceived to demonstrate a muscular sphincter or “contraction ring” that later proved to be mythical. We believe that hindered or impeded outflow is rarely, if ever, present in HCM and that the equation gradient = obstruction has wonderfully obstructed the understanding of this disease process for nearly 3 decades. The bases for our questioning the primacy of obstruction and suggesting that impaired diastolic function and life-threatening arrhythmias are of more significance in HCM will be developed in this article. Since it was the outflow tract pressure gradient that initially led to the assumption that an obstruction was present, mechanisms responsible for the development of pressure gradients will first be discussed.

Pressure gradients. At least four different mechanisms capable of producing physiologic or pathologic outflow tract pressure gradients have been characterized. The left ventricular and aortic pressure, aortic flow, and left ventricular volumetric events associated with these gradients will be depicted.

Impulse gradients (figure 1) are instantaneous pressure differences between the left ventricle and aorta that occur in normal hearts and are generated in early systole during the time when peak flow acceleration (dQ/dT) and velocity are achieved. After peak flow there is a deceleration with reversal of the early systolic pressure gradient so that the aortic pressure exceeds left ventricle pressure and the rate of outflow declines. Impulse gradients are related to flow acceleration in early systole as left ventricle pressure rapidly increases and aortic pressure lags behind. They are of greater magnitude in high flow states such as during exercise or after a premature ventricular contraction.

The normal ventricle ejects approximately 60% of its stroke volume in the first half of systole, and the ventricular volumetric curve has achieved an asymptote at the time of aortic valve closure. In the following two figures, these normal contours for aortic flow and left ventricular volume are reproduced in open lines and circles for comparison with the contours in the disease states depicted.

Discrete obstructive pressure gradients (figure 2) across localized regions of stenosis, as in aortic stenosis, are associated with a reduction in the rate of ejection and ventricular emptying. There is a diminished rate of rise (dP/dT) of the pressure pulse distal to the stenosis. The orifice size calculated by hydrodynamic formulation remains constant over a wide range of flow. An inverse relationship has been demonstrated between the magnitude of the pressure gradient in aortic stenosis and the rate of ventricular emptying—the more severe the gradient, the more retarded the rate of emptying. Peak flow and velocity occur later than normal and flow is distributed almost symmetrically (58%/42%) over the entire ejection period, which is longer than normal. Thus, both the systolic ejection period (measured from the onset of aortic pressure rise to the dicrotic notch) and the ejection time (duration of aortic outflow) are prolonged. Aortic valve closure occurs shortly after the onset of retrograde aortic flow, which results from relaxation of the left ventricle and the development of an adequate negative pressure gradient and negative dP/dT. The ventricle both empties and fills more slowly than the normal ventricle (solid dots vs open circles), and augmented atrial transport function (prominent increase in left ventricular volume with the "a" wave) is evident.

Dynamic gradients (figure 3) between the body and outflow tract of the left ventricle are recorded at rest or after provocation in some patients with HCM. Pressure gradients with similar waveform appearance (brisk
PERSPECTIVE

FIGURE 1. Impulse gradient in a normal ventricle. Left ventricular (LV) and aortic (Ao) pressure, aortic flow, and ventricular volumetric relationships are displayed. Vertical solid lines indicate aortic valve opening (AVO) and aortic valve closure (AVC), and encompass the systolic ejection period. Dashed lines indicate the midpoint of systole and mitral valve opening (MVO). a = atrial contribution to ventricular filling.

Aortic upstroke, mid and late systolic gradient) can also be induced in normal or hypertrophied ventricles subjected to inotropic, hypervolemic, or vasodilator provocations. \(^5\) Calculations of outflow orifice area based on hydrodynamic formulae suggest progressive constriction during systole, and perturbations that increase the magnitude of the gradient result in marked decreases in calculated orifice size. \(^1\) The pressure and flow relationships \(^1\) \(^,\) \(^7\) \(^,\) \(^8\) associated with dynamic gradients in a patient with HCM can be divided into three time periods, which are designated in figure 3 by encircled numbers and are referred to throughout this article as phases 1 to 3.

In phase 1, the body, outflow tract (dashed line), and aortic pressures rise while peak flow acceleration and velocity are enhanced and achieved earlier than in the outflow tract of the normal left ventricle. As a consequence, there is a larger impulse gradient than in a normal ventricle and the emptying slope of the left ventricle volumetric plot is correspondingly steeper (solid dots vs open circles). \(^1\) \(^,\) \(^8\) \(^,\) \(^9\)

Phase 2 is characterized by a divergence of the pressure in the body of the left ventricle from that in the outflow tract and aorta. There is a decline in aortic flow to zero or near zero. The pressure gradient reaches its maximum during this phase, as the ventricular pressure reaches a midsystolic peak and the outflow tract and aortic pressures a midsystolic trough. \(^1\) \(^,\) \(^7\) \(^,\) \(^9\) Left ventricular ejection ends as the ventricle achieves a small volume and a supernormal ejection fraction. \(^8\) \(^,\) \(^10\)

In phase 3 there is virtually no aortic outflow \(^1\) \(^,\) \(^7\) \(^,\) \(^11\) and the ventricle is essentially isovolumetric. \(^8\) \(^,\) \(^10\) There is a persistent but declining pressure gradient as the ventricular pressure falls, while there is a secondary rise in outflow tract and aortic pressures. The pressures in the ventricular body and outflow tract then equalize as they decline below the aortic pressure. Complete aortic valve closure and the aortic dicrotic notch occur after a negative gradient and an adequate negative dP/dT have developed between the outflow tract and aorta to initiate retrograde aortic flow. The systolic ejection period is prolonged, while ejection time measured from the flow signal is short. \(^1\) \(^,\) \(^7\) \(^,\) \(^10\) As in aortic stenosis, passive ventricular filling is impeded in HCM, reflecting decreased distensibility, and augmented atrial transport function is required to achieve an adequate end-diastolic volume.

FIGURE 2. Discrete obstructive gradient in aortic stenosis. The format is similar to that of figure 1. Normal contours for aortic flow and instantaneous volume curves are depicted in open lines and circles for comparison. Abbreviations are as in figure 1.

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Catheter entrapment (figure 4) results in an artificially high pressure when the catheter is embedded in the ventricular wall during systole and records intramyocardial and not intracavitary pressure. The recording illustrated in figure 4 was made during advancement of a retrograde left ventricular catheter. The pressure waveform demonstrates a mid and late systolic “pressure gradient” with a delay in the decline of pressure, so that the ventricular downstroke follows the central aortic dicrotic notch. The entrapped catheter does not eject blood nor permit blood sampling through its lumen during systole.

Obstructive vs nonobstructive interpretations of dynamic pressure gradients. Two diametrically opposite interpretations of dynamic pressure gradients have been put forth: midsystolic obstruction and excessively rapid and complete elimination of left ventricular cavitary contents. Advocates of the obstruction theory have postulated that the outflow tract is widely patent during phase 1, progressively impedes outflow during phase 2 as ejection occurs in the face of a pressure gradient, and is totally obstructed during phase 3. In the first decade after the discovery of HCM this contention was supported by intraoperative central aortic flowmeter recordings demonstrating cessation of flow in midsystole, angiocardiograms that were thought to show “a long area of subvalvular narrowing,” and intraoperative findings of a “forceful contraction of the outflow tract on the examining finger.” Surgical interruption of the septal aspect of the contraction ring by myotomy/myectomy was devised as an operation analogous to resection of pyloric stenosis. The relief of the gradient and concurrent symptomatic improvement have been considered further confirmation of the obstructive nature of the pressure gradient.

When the long area of angio graphic subvalvular narrowing was acknowledged to be a result of the diastolic excursion of the anterior mitral leaflet and the presence of a contraction ring could not be corroborated by angiography, the site of obstruction was translocated to the systolic apposition of the anterior mitral leaflet and the interventricular septum. This new zone of obstruction appeared as a subtle horizontal lucent line on angiocardiograms and as systolic anterior motion (SAM) on echocardiograms. Despite this translocation of the presumed obstruction, myotomy-myectomy designed to interrupt the “contraction ring” has re-
mained the most commonly performed surgical procedure for this condition.

It has been postulated that SAM is a result of a Venturi phenomenon, in which the high outflow velocity in the narrowed left ventricle draws the anterior leaflet forward against the septum. The temporal and quantitative relationship between SAM-septal contact (SSC, figure 3) and the interventricular pressure gradient, as well as the presence of flow during the development of the pressure gradient, are used to support the contention that the mitral valve imposes a significant impediment to outflow.11, 12, 15

A nonobstructive explanation of the dynamic pressure gradient is that the ventricle rapidly ejects during phase 1, decreases its rate of ejection while achieving its minimal residual volume (“dead space”) during phase 2, and is isovolumetric with a sustained isometric contraction during phase 3.4, 5, 10, 13 This phenomenon has been termed cavity obliteration or cavity elimination. The paradox of a pressure gradient without obstruction was elucidated by Gauer and Henry in studies during hemorrhagic shock and during application of negative gravitational force in animals. They recorded dynamic gradients (as shown in figure 3) and demonstrated that continued isometric contraction after the ventricle had emptied the pathologically small intracavitary contents produced a high pressure in the obliterated cavity. This phenomenon could also account for the sensation of a contraction ring when the surgeon’s exploring finger enters the obliterating cavity.13

The Gauer phenomenon can be studied in a hydrodynamic model of the left ventricle and aorta that is anatomically incapable of outflow obstruction, as described by White et al. The contractile force, aortic resistance, and ventricular filling can be controlled independently, and dynamic intracavitary gradients can be readily generated by perturbations that match those that provoke gradients in experimental animals and patients with HCM. For example, if the systolic ventricular pressure is held constant and the aortic resistance is reduced, there is a rapid aortic upstroke, a mid-systolic trough, and a mid and late systolic gradient similar to the three phases in figure 3. The ventricle rapidly eliminates its contents as the gradient is developing in phases 1 and 2, and is isovolumetric during phase 3. White et al. noted “as the cavity becomes smaller, the body and the outflow tract of the ventricle become progressively isolated from one another and a pressure difference develops between these two areas. These two regions are not separated by an obstruction, but by the tightly opposed walls of an essentially emp-ty ventricle below.” It is important to emphasize that the pressure gradient develops during ejection as the ventricle progressively isolates the obliterating body from the noncontractile outflow tract, which is in free communication with the aorta beyond, and shares its lower pressure.

Hemodynamic and cineangiographic studies of the ventricle in the presence of dynamic pressure gradients in patients with HCM, normal subjects undergoing the Valsalva maneuver and inotropic stimuli, and animals with intraventricular gradients induced with isoproterenol reveal cavitory obliteration compatible with Gauer’s phenomenon. These studies have demonstrated the development of the peak pressure gradient during rapid obliteration of the ventricle, phase 2. When the left ventricular ejection fractions of patients with HCM are grouped according to hemodynamic subsets, patients with resting gradients have the highest ejection fractions, those with inducible gradients intermediate ejection fractions, and those without resting or inducible gradients the lowest ejection fractions. In patients with HCM studied with and without an intracavitary gradient, the left ventricle empties more rapidly and the ejection fraction increases when the gradient is induced or augmented. Thus, the imposition of a pressure gradient is associated with enhanced left ventricular emptying (both rate and degree) and belies the concept of impeded or obstructed outflow. If an obstruction were responsible for the gradient, it would be expected to retard emptying when present.

Since some degree of mitral regurgitation, which might represent a low resistance alternate pathway for left ventricular ejection, is usually present in patients with HCM it has been argued that the rapidity of emptying is a result of mitral regurgitation. However, this hyperdynamic emptying pattern is also seen when trivial or no mitral regurgitation is present.

Although there are important differences in the genesis of dynamic gradients due to cavity obliteration and the artifactual high pressures recorded from catheters embedded or entrapped in the left ventricular wall, these two phenomena have unfortunately been confused and equated.

Echocardiography in HCM. The relationship between SAM-septal contact and dynamic pressure gradients need not be cause and effect; both may be the result of rapid and complete left ventricular emptying. In support of this alternative, the rate of emptying of the left ventricle is enhanced (and therefore not impeded) during the presence of the gradient and SAM.

Patients with resting pressure gradients in excess of
90 mm Hg studied in our laboratory by angiography and two-dimensional echocardiography were found by both techniques to have cavitary obliteration. Figure 5 diagrammatically depicts the typical echocardiographic findings in these patients. Two-dimensional parasternal long-axis (top) and short-axis (middle and bottom) images are related to the M mode images at the level of the mitral valve (center of middle row) and body of the ventricle (center of bottom row). The posterior mitral leaflet (black area) originates from the mitral anulus and occupies roughly two-thirds of the circumference of the mitral sleeve while the anterior leaflet (white area) has no annular attachment and is in continuity with the posterior wall of the aorta.

In diastole, the mitral sleeve is confined by the walls of the inflow region of the left ventricle, so that the anterior leaflet impacts on the interventricular septum and the posterior leaflet on the left ventricular posterior and lateral walls. During systole vigorous systolic constriction of the anulus and circumferential contraction of the ventricular walls causes the posterior leaflet to engulf the anterior leaflet, and the sleeve is corrugated like a folded umbrella. Because of the lateral divergence of the ultrasound beam (dashed lines) the digitated peaks and valleys of the puckered leaflets are superimposed to yield a laminated multilayer SAM on the one-dimensional M mode image (center). The distal mitral apparatus has a hockey-stick configuration (top right) or crossed-swords appearance on apical four-chamber views (not shown) because folds of the posterior leaflet often project anterior to the anterior leaflet. In systolic long- and short-axis views (top and bottom right), obliteration of the submitral cavity is seen.

The onset of SAM-septal contact occurs at the midpoint of phase 2, near the nadir of the radially declining aortic flow signal and as the ventricle has nearly achieved its dead space (SSC, figure 3). If SAM-septal contact was due to the Venturi phenomenon, the decline to zero velocity in the outflow tract would not be expected to sustain the anterior displacement of the mitral valve throughout the remainder of systole. The relationship of SAM-septal contact to a small left ventricular volume and its appearance with rapid and complete emptying of the ventricle are consistent with the view that the mitral valve becomes distorted as the left ventricle empties convulsively up to the level of the mitral apparatus, as depicted in figure 5.

The aortic valve may partially “preclose” in mid-systole when outflow diminishes, but complete closure (and the second heart sound) does not occur until ventricular relaxation permits retrograde aortic root flow.

Is obstruction necessary to explain the clinical picture of HCM? There are many observations that are not in concert with the presence of an important or clinically relevant impediment to left ventricular outflow in HCM. Natural history studies demonstrate the lack of correlation between the presence and magnitude of an outflow tract gradient and symptoms or mortality. In a study of a group of 126 patients in which 10 cardiac deaths were reported, seven deaths occurred in 49 patients with insignificant gradients (0 to 30 mm Hg), and none occurred in 34 patients with gradients over 90 mm Hg. Thus, the presence of a pressure
gradient is not predictive of cardiogenic death. More recent studies have demonstrated that the appearance of ventricular tachyarrhythmias on ambulatory electrocardiographic monitoring is predictive of sudden death.20

The morphologic hallmark of the disease process is inordinate hypertrophy, which is not dependent on the presence of a pressure gradient. The triad of symptoms (angina, syncope, and dyspnea) can be attributed to the consequences of pathologic hypertrophy, since these symptoms are frequently present in patients with HCM but without pressure gradients. The hypertrophied muscle has the potential for myocardial supply/demand imbalance, which can readily explain the triad on the bases of ischemia, arrhythmias, and diminished ventricular distensibility. Medications (e.g., β-adrenergic receptor- or calcium channel-blocking drugs) that do not consistently alter the pressure gradient but that decrease myocardial oxygen consumption and/or improve ventricular distensibility have been demonstrated to ameliorate symptoms.21

While the results of operative intervention suggested a link between relief of symptoms and reduction of the pressure gradient, the aforementioned natural history studies do not support any consistent relationship between symptoms and pressure gradients.18 19 21 This lack of correlation would suggest that the symptomatic benefits imparted by operative intervention may not be directly related to the reduction of the pressure gradient, but to other factors (pericardotomy, decreased contractility, enlargement of cavity size, cardiac derangement, etc.). Despite the reported symptomatic benefits, septal myotomy-myectomy carries a substantial morbidity and mortality and has little if any impact on the occurrence of sudden death.22

The cardiovascular physical findings in HCM can be explained by cavity obliteration/elimination. The arterial “spike and dome” represents the rapid ejection of blood in phase 1 followed by a reflected wave from the peripheral reflecting sites. The prolongation of the systolic ejection period results from delayed closure of the aortic valve. This delay in aortic valve closure and the late systolic wave in the apical impulse result from the sustained contraction and delayed rate of relaxation16 in the body of the left ventricle in phase 3. The aortic valve does not close fully (and cause the dicrotic notch) until relaxation of the left ventricle results in a negative gradient across the valve and initiates retrograde aortic flow.

The Brockenbrough-Braunwald-Morrow phenomenon,1 the failure of the postextrasystolic arterial pulse pressure to rise, has been attributed to increased obstruction. Since the rapidity and degree of emptying are enhanced rather than retarded in the beat with a gradient,1 9 10 three nonobstructive mechanisms can be invoked for the attenuation of the arterial pulse pressure: (1) reduced diastolic left ventricular compliance preventing increased filling during the postextrasystolic pause, (2) an emptier, more compliant aortic bed as a result of enhanced runoff time, and (3) increased mitral regurgitation due to earlier and more profound distortion of the mitral apparatus in the inotropically stimulated ventricle.

The characteristic mid–late systolic murmur of HCM is considered a cardinal manifestation of an outflow tract stenosis, but is often present in the absence of a gradient. Unlike aortic stenosis, the magnitude of the murmur fails to track consistently with the magnitude of the gradient.23 The murmur is best heard at the apex and lower sternal border and is rarely transmitted to the base and carotid arteries, unlike murmurs generated in the outflow tract. A mid–late systolic murmur is recorded in the left atrium by intracardiac phonocardiography, while a typical “ejection murmur,” peaking in early systole, is recorded during phase 1 in the aortic root.9 The response of the murmur to postural maneuvers is similar to that of the murmur of mitral prolapse (increased intensity on standing, decreased with squatting) because both HCM and mitral prolapse have a significant ventriculovalvular disproportion in which the ventricle is too small to support the mitral valve in a competent subannular position in mid and late systole. Each of these observations support the contention that the principal murmur is caused by mitral regurgitation through the distorted mitral valve.

Summary and conclusions. HCM is a disorder associated with significant morbidity and mortality and a propensity to cause sudden, often unexpected death. The similarity to the symptom complex of aortic stenosis and the presence of a pressure gradient justified the initial assumption that obstruction was of prime importance in HCM and that relief of obstruction was the focal point of rational therapy. However, it is our belief that the dogma of obstruction has impeded progress in and obscured the understanding of HCM and interpretation of its manifestations. The purpose of this article is to call attention to significant discrepancies in the obstructive concept that have been reinforced as new techniques emerged that have allowed further study of the disease.

Since neither the presence of a gradient nor SAM can be justifiably equated with the presence of an obstruction, it is proposed that the appellation “obstruction” be reserved for those cases in which the rate of
outflow or the rate or degree of ventricular emptying are demonstrably impeded, as in aortic stenosis.

Therapy with β-adrenergic–receptor and calcium channel–blocking agents have shown promise for alleviating symptoms and possibly prolonging life without systematically or predictably affecting the pressure gradient, probably because of their beneficial effects on ventricular relaxation and diastolic filling. Antiarrhythmic therapy has been effective in reducing mortality. Ideally, prevention or regression of the pathologic hypertrophy should be the major focus of future therapeutic interventions in hypertrophic cardiomyopathy.

References

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