The Mechanism of the Intraventricular Pressure Gradient in Idiopathic Hypertrophic Subaortic Stenosis

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The INTRAVENTRICULAR pressure gradients that are recorded in patients with idiopathic hypertrophic subaortic stenosis (IHSS) differ in many respects from those observed in patients with the various discrete forms of obstruction to left ventricular outflow. Thus, it is now generally recognized that the magnitude of the pressure gradient measured in the resting state may bear little relation to the severity of the patient's symptoms, and that in some patients, variations in the magnitude of the pressure gradient occur in the course of a single hemodynamic study, or at sequential cardiac catheterizations. The finding that in patients with IHSS approximately 80% of the stroke volume is ejected during the first half of left ventricular systole led Hernandez and co-workers to consider the possibility that no obstruction to left ventricular outflow occurs in this disease. These investigators suggested that little or no orthograde flow might emanate from the area of high pressure and that the elevated systolic pressure might exist only within trabeculations in the wall of the empty ventricle. Burchell, on the basis of angiocardiographic observations, also raised the possibility that in some patients with IHSS the small apical portion of the left ventricle might act as a "self-obstructing diverticulum," although like many other observers, he considered the basic obstructive lesion to lie in the left ventricular outflow tract. Recently, Criley and associates, on the basis of cineangiographic and hemodynamic studies, have supported the theory that no obstruction to left ventricular outflow exists in IHSS and have questioned the rationale of operations designed to relieve obstructions in patients with this disease.

The hypothesis that muscular hypertrophy of the left ventricular outflow tract results in systolic obstruction to ejection in patients with IHSS has been developed in a number of laboratories since the initial clinical description of this entity by Brock, in 1957. A considerable body of clinical, angiographic, hemodynamic, and anatomic information has now accumulated, much of which appears consistent with this theory, and a detailed review of these studies has been presented recently. It would appear of considerable importance from both theoretical and therapeutic points of view to consider carefully the problem of whether or not obstruction to outflow exists in IHSS, particularly since a number of recent reports have described the application of operations designed to relieve left ventricular outflow tract obstruction in patients with IHSS; many of these operative methods, as well as earlier surgical results, have been reviewed recently.

It is the purpose of the present report to examine in detail the possibility that "cavity obliteration" rather than obstruction is responsible for the pressure gradient in patients with IHSS. Pertinent anatomic, clinical, and hemodynamic findings in this disease are reviewed, and the results of recent angiographic and hemodynamic studies related to this problem are presented. Finally, a view of the dynamics of left ventricular contraction in IHSS has been developed which perhaps can relate many of the observations that presently appear to be discordant.
INTRAVENTRICULAR PRESSURE GRADIENT

Anatomic Considerations

Observations at Operation

Sixteen patients with IHSS have been operated upon in this clinic; when the surgeon's finger was inserted through the aortic valve into the outflow tract of the empty, beating left ventricle, an area of hypertrophy that gripped the finger during systole could invariably be felt. It should be emphasized that this constriction was localized to the outflow tract and that obstruction was not appreciated in the main cavity or apex of the left ventricle, the sites at which constriction would be most pronounced if cavity obliteration without obstruction existed. Similarly, Bentall and associates\textsuperscript{15} have described hypertrophied septal muscle 2 to 3 cm below the aortic valve in the majority of the 12 patients in their series, and others have observed marked septal hypertrophy, often with focal thickening of the endocardium over the area of hypertrophy.\textsuperscript{11, 19} Julian and associates\textsuperscript{16} recently described the anatomic findings, as viewed through wide apical left ventriculotomies, in five patients with IHSS; a small subaortic channel was always visualized, and the aortic valve was obscured by bulging of the interventricular septum and the "posterior, mural portion of the conus." In one patient diffuse apical hypertrophy was associated with a narrowed fibrous area adjacent to the mitral annulus, and in the remaining four patients, an obstructing band of hypertrophic muscle was noted, which was usually covered partially by white fibrous tissue. Kirklin and Ellis\textsuperscript{20} have described an "obstructing muscular mass," and Trimble and co-workers\textsuperscript{12} observed a visible and palpable protruding "bar" of muscle 1 to 2 cm below the aortic valve. When this band was sectioned, the latter authors described systolic retraction of the cut ends of the band, with consequent abolition of a sphincter-like action of the deep constrictor muscle. Morrow and associates,\textsuperscript{9} similarly, have likened the effects of ventriculotomy in patients with IHSS to those achieved by pyloromyotomy in patients with hypertrophic pyloric stenosis.

Observations at Necropsy

The dynamic observations made at operation are consistent with a recent description of the pathological anatomy of IHSS by Edwards:\textsuperscript{21} "In this condition, the primary cause of obstruction appears to be protrusion of an abnormal mass of myocardium into the channel of the left ventricular outflow tract." Since the report of asymmetric hypertrophy of the interventricular septum by Teare in 1958,\textsuperscript{22} a number of other descriptions of the gross pathological anatomy in IHSS have also been published; these reports have been reviewed elsewhere.\textsuperscript{6, 23} In a few specimens, diffuse left ventricular hypertrophy was observed, although whether or not these patients actually exhibited an intraventricular pressure gradient during life is not clear. In the majority of specimens, however, there was anatomic evidence that the left ventricular outflow tract was compromised by nodular hypertrophy of the ventricular septum, which could be likened to a tumor obstructing left ventricular ejection.\textsuperscript{2, 23}

Hemodynamic Considerations

Observations at Cardiac Catheterization

Pressures in Left Ventricular Inflow Tract

The inflow tract of the left ventricle, that is, the area just downstream to the mitral valve, never empties completely in patients with IHSS (figs. 1, and 7 to 9). Since Criley and associates\textsuperscript{7} concluded that elevated left ventricular systolic pressure develops only in portions of the left ventricular cavity which become essentially obliterated during systole, it was of critical importance to determine the magnitude of the systolic pressure in the inflow tract relative to that in apical portions of the left ventricular cavity. If true obstruction in the left ventricular outflow tract is responsible for the systolic pressure gradient, then the systolic pressure should be elevated in the inflow tract; if cavity obliteration is responsible for the pressure difference, then the systolic pressure in the inflow tract should be equal to that in the aorta (fig. 2). The analysis of pressure tracings recorded as a catheter is withdrawn across the mitral valve.
Lateral views from biplane selective left ventricular (LV) angiocardiograms in two patients with IHSS. LA indicates the region of the left atrium. Panels A and B show diastole and systole, respectively, in one patient; panels C and D, diastole and systole in the other patient. Note that the region of the left ventricular inflow tract, just anterior to the mitral valve, is not obliterated during systole. In addition, no mitral regurgitation was evident in either study.

from the left ventricle should allow clarification of this important issue. This measurement is complicated, however, by the fact that the transseptal catheters ordinarily employed for this maneuver have numerous side holes, which may record left ventricular and left atrial pressures simultaneously during the withdrawal, thereby artifactually lowering the left ventricular systolic pressure. This problem was overcome by passing a PE no.
50 catheter, which has an end hole only, through the transseptal catheter, or by passing an end-hole catheter from the left ventricle into the left atrium by the retrograde arterial approach; in addition, several patients had PE no. 50 end-hole catheters introduced into the left ventricle through the mitral valve by the transbronchial route.

Eleven patients with IHSS and intraventricular pressure gradients were studied by the methods described, and in every patient the systolic pressure in the left ventricular inflow tract exceeded the aortic systolic pressure, and this zone of elevated pressure was shown clearly to extend from the ventricular apex to the leaflets of the mitral valve (fig. 3). Indeed, in several patients the catheter tip traversed the mitral valve during midsystole, and the elevated systolic pressure pulse in the left ventricle changed abruptly to or from a left atrial contour (fig. 3A and D). On one occasion, a catheter passed from the left ventricular outflow tract directly across the mitral valve and into the left atrium; this occurrence

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**Circulation, Volume XXXIV, October 1966**
Simultaneous left ventricular (LV) and brachial arterial (B.A.) pressures recorded while passing an end-hole catheter across the mitral valve in four patients. Panel A: As the catheter is withdrawn across the mitral valve, the elevated LV systolic pressure falls abruptly in mid-systole (vertical arrow) when the catheter tip enters the left atrium. Panel B: The catheter is withdrawn from the ventricle into the left atrium (LA), and an elevated LV pressure is recorded up to the moment the catheter traverses the mitral valve. The alteration in LV systolic pressure is the result of bigeminal ventricular extrasystoles (ECG, upper tracing). Panel C: The catheter tip initially lies in the LV outflow tract, where systolic pressure equals that in the brachial artery. On further withdrawal of the catheter, the tip enters a high pressure zone in the LV cavity, just prior to crossing the mitral valve into the LA. Panel D: The catheter is advanced from LA into LV in early systole; note the immediate pressure change in midsystole to an elevated systolic LV pressure.

is not surprising, since the anterior leaflet of the mitral valve provides one border of the left ventricular outflow tract (fig. 2), and it would be possible to traverse the leading edge of the leaflet during a single diastolic interval. In the same patient, when the catheter was withdrawn from the high-pressure area, it entered the left atrium directly. In other patients, when the catheter was withdrawn from the left ventricular outflow tract to the left atrium, it traversed a high-pressure zone (fig. 3C). These findings, together with the angiographic evidence that the inflow tract is never obliterated during systole (figs. 1, and 7 to 9) strongly support the concept that a true zone of obstruction must exist downstream to the inflow tract, that is, in the left ventricular outflow tract.

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Postextrasystolic Contractions

In patients with IHSS, the contraction following an extrasystole is often associated with a reduction in the stroke volume and brachial arterial flow and a decrease in the systemic arterial pulse pressure. In contrast, in the normal heart, postextrasystolic potentiation results in more complete ventricular emptying which produces an increase in the stroke volume and the pulse pressure during the contraction following the extrasystole. In IHSS, postextrasystolic potentiation also occurs, as evidenced by the increased systolic ventricular pressure during the postextrasystolic beat. Therefore, if cavity obliteration were responsible for the systolic pressure gradient in this disease, more complete emptying of nonobliterated portions of the cavity should provide an increase in stroke volume and pulse pressure rather than the decrease that is generally observed with IHSS. Supporting this reasoning are recent findings in experimental animals. In these studies elevated left ventricular systolic pressures were produced in the normal ventricle of the dog by bleeding or by administration of positive inotropic agents, or by both. Under these conditions, in which the elevated intraventricular pressures may well be due to cavity obliteration, the pulse pressure during the postextrasystolic beat increased normally.

Increased mitral regurgitation could accompany the postextrasystolic beat and contribute to the fall in forward stroke volume observed in patients with IHSS. By itself, however, mitral regurgitation provides an unlikely explanation for the fall in forward stroke volume, since patients with severe isolated mitral regurgitation from other causes exhibit a normal increase in the arterial pulse pressure during a postextrasystolic beat. Moreover, while an elevated ventricular systolic pressure everywhere within the left ventricular cavity during the contraction following an extrasystole could enhance mitral regurgitation if, as postulated by Criley and co-workers, the elevated pressure exists only in portions of the left ventricle which are essentially obliterated during systole, then there would be no reason for increased mitral regurgitation alone to be responsible for a fall in stroke volume. It seems more reasonable to conclude, therefore, that in patients with IHSS the increased force of contraction following the extrasystole, together with a reduction in the distending pressure in the left ventricular outflow tract consequent to lowered aortic pressure, produces further narrowing of the outflow tract; this, in turn, results in increased obstruction to ejection, increased left ventricular systolic pressure, and a diminution in the stroke volume. This increased obstruction and the higher systolic pressure within the main left ventricular cavity could well be directly responsible for increased mitral regurgitation during the postextrasystolic beat, but whether or not such an augmentation of mitral regurgitation contributes to the fall in stroke volume during the postextrasystolic beat remains to be established.

The Valsalva Maneuver and Nitroglycerin

The primary hemodynamic effect of the Valsalva maneuver is to impede the inflow of blood into the thorax, thereby producing a progressive reduction in the stroke volume. In the patients with IHSS, as intrathoracic pressure is elevated, a progressive increase in the magnitude of the intraventricular pressure gradient commences immediately (fig. 4). If cavity obliteration rather than true obstruction is to explain the pressure gradient in IHSS, it would be necessary to postulate that during this maneuver an immediate increase in left ventricular contractile force takes place in essentially empty portions of the ventricular cavity. That such an immediate increase in contractility could occur during the Valsalva maneuver on a reflex basis is most unlikely, since reflex increases in heart rate and peripheral vascular resistance commence only toward the end of the maneuver. It is postulated, therefore, that a decrease in venous return, such as that induced by the Valsalva maneuver, does not result in "more profound systolic cavity obliteration," but that the progressive mechanical limitation of
inflow and the accompanying reduction in arterial pressure\(^5\) result in progressively closer apposition of the walls of the left ventricular outflow tract, thereby increasing the severity of obstruction. Similar considerations apply to nitroglycerin, the administration of which also augments the pressure gradient in IHSS but decreases the gradient in patients with valvular aortic stenosis.\(^{30,33}\) This drug has no known direct effect on the myocardium, but it dilates systemic veins\(^34\) and reduces venous return to the heart; hence it decreases the dimensions of the normal left ventricle\(^35\) and presumably the size of the outflow tract in patients with IHSS.

**Intraoperative Studies**

Pierce and associates,\(^24\) using an electromagnetic flow transducer positioned around the aortic root in patients with IHSS, prior to operative correction of the lesion, confirmed the finding of Hernandez and associates\(^1\) that a large fraction of the stroke volume is ejected during the first half of left ventricular systole (average, 78\%). In addition, simultaneous recordings of left ventricular and aortic pressures and aortic blood flow showed that while rapid ejection occurred during very early systole, when the pressure gradient was absent or relatively small, a significant pressure gradient then developed rapidly and reached a peak during the second half of systole; a progressive reduction in the flow and the calculated instantaneous outflow orifice area occurred during this period. In addition, a phase was always observed late in systole when a pressure gradient persisted while little or no orthograde flow was apparent. Examples of these tracings, recorded at a paper speed of 200 mm/sec to permit precise definition of the time course of the events, are reproduced in figure 5. In patient B.W. (panel A), in whom the heart rate was slow, the lack of an appreciable pressure gradient in early systole is evident, and the late phase of left ventricular contraction, in which a pressure gradient existed without forward flow, is also apparent; similar phenomena were observed in patient J.T. (panel C). However, in both patients a relatively large proportion of the stroke volume (67 and 70\%, respectively) was ejected during the phase of contraction in which a significant

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**Figure 4**

*Effect of Valsalva maneuver on the left ventricular (L.V.) and brachial arterial (B.A.) pressures in a patient with IHSS and a minimal pressure gradient prior to the maneuver. There is an early, progressive increase in the pressure gradient following the initiation of the Valsalva maneuver (arrow).*

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pressure gradient existed. Furthermore, although the period of left ventricular contraction at the end of systole during which no flow occurred was lengthened when the pressure gradient was augmented by isoproterenol infusion (panel B), the fraction of the total stroke volume that was ejected during the time a pressure gradient existed was also increased (from 67 to 80%). This finding of early nonobstructive and late nonejecting phases of left ventricular contraction obviously requires modification of previous concepts concerning calculation of the area of the left ventricular outflow orifice by standard hydraulic formulae; it seems clear that for the most precise definition of the effective orifice size, the instantaneous relations between the pressure gradient and forward ejection rate throughout systole should be utilized.

The possibility was considered that in the intraoperative studies the high left ventricular pressures were recorded from isolated pockets within the ventricular wall. However, the catheters used for recording these ventricular pressures were inserted through the ventricular apex under direct vision and were advanced well into the left ventricular cavity, a method which has been shown in experimental animals to avoid measurement of artifactually elevated left ventricular systolic pressures. In addition, pressures have been measured simultaneously at the time of operation through several catheters placed in different areas of the left ventricular cavity proximal to the outflow tract; pressure gradients of the same magnitude were found to exist in all of these areas (fig. 6). Since approximately 70% of the stroke volume is ejected while a pressure gradient is present (fig. 5), if cavity obliteration were to explain the presence of the pressure gradient in four widely separated portions of the left ventricle, most of the stroke volume would have had to originate from a site other than that containing the catheters. It does not seem possible that 70% of the stroke volume could have originated from the small portion of the

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Figure 5

Simultaneous recordings of aortic (Ao) blood flow with left ventricular (L.V.) and aortic pressure pulses at the time of operation in two patients with IHSS. Panel A: Early, rapid ejection (indicated by diagonally hatched area) occurs in the absence of a L.V. to aortic pressure gradient. With the onset of the pressure gradient (stippled area), aortic flow declines; in late systole, a pressure gradient exists (vertically hatched area) when no forward flow is evident. 67% of the LV stroke volume is ejected during the period when the pressure gradient exists. Panel B: Tracings in the same patient following the administration of Isuprel (isoproterenol). The duration of the late nonejecting phase of systole is increased, but the fraction of the stroke volume that is ejected while the pressure gradient is recorded (stippled area) is also increased. Panel C: Recordings in another patient in the control state, showing similar phases of contraction; 70% of the LV stroke volume is ejected while a L.V. to aortic pressure gradient is recorded.

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left ventricular cavity comprising the outflow tract.

In this connection, the concept that an elevated systolic pressure can develop in an obliterated ventricular cavity or intertrabecular recess is supported by several studies in normal dogs in which positive inotropic agents or reduced venous return, or both, were associated with intraventricular pressure gradients. In one of these experimental studies, when a catheter was inserted through the ventricular apex, no intraventricular pressure gradient could be demonstrated as the catheter was withdrawn from the aorta through, and out of, the ventricular apex; however, pressures exceeding those in the aorta could be recorded simultaneously through other catheters inserted into the left ventricle by the transseptal or retrograde arterial routes. The contrasting observations in IHSS, made both at cardiac catheterization and at operation, indicate that an elevated left ventricular systolic pressure exists everywhere within the main left ventricular cavity, as described above, and suggest that the mechanism producing the intraventricular pressure difference in normal animals is basically different from that responsible for the pressure gradient in patients with IHSS.

Hemodynamic investigations carried out in other laboratories also support the concept that obstruction to left ventricular outflow exists in IHSS. Gorlin and associates in a recent review of their extensive studies in such patients, indicated that the pressure gradient occurs across the muscular outflow tract and that the degree of stenosis is variable, being dependent upon initial left ventricular volume, the inotropic state of the myocardium, and the afterload. Widge has placed emphasis on the distending pressure in the left ventricular outflow tract as a major determinant of the magnitude of the pressure gradient. It was concluded that all of the hemodynamic responses to various pharmacological agents in IHSS could be explained by the relative effects of distending pressure, intracavitary blood volume, and the contractile state of the myocardium on the dimensions of the left ventricular outflow tract and, therefore, on the severity of true obstruction to left ventricular ejection. Likewise, Goodwin, Shah, and their co-workers have...
stressed the importance of changes in venous return and myocardial contractility in altering the size of the left ventricular outflow tract, and thereby modifying the severity of obstruction. Whalen and associates have also pointed out the dynamic nature of the obstruction.

Angiographic Observations

In the hemodynamic and cineangiographic studies carried out by Criley and co-workers in patients with IHSS, the catheter tip was always situated in small recesses between trabeculae carneae or in the ventricular apex at the time an elevated systolic pressure was measured, and by midsystole the intertrabecular recesses and apical portions of the ventricle were always obliterated. We also have observed an elevated systolic pressure when the catheter tip is positioned deep within the left ventricular cavity in patients with IHSS, and, indeed, such a pressure can sometimes be recorded when a catheter tip is wedged in an intertrabecular recess in patients who do not have IHSS. However, if the theory is valid that outflow obstruction does not exist and the high pressure is developed only within essentially obliterated portions of the ventricle, then the converse of the findings by Criley and associates must also be true; that is, no pressure gradient should be observed when the catheter tip is maintained intentionally in the pool of contrast material contained within the ventricular cavity during systole.

In order to test this hypothesis, it was of importance to correlate hemodynamic and angiographic events during systole. Angiographic studies were therefore performed in 17 patients with IHSS in whom pressure was recorded in the body of the left ventricle.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7**

Biplane angiographic films, with the simultaneously recorded left ventricular (L.V. Press) and radial arterial (R.A. Press) pressures in two patients with IHSS. The timing of each angiographic exposure is marked by the interruption of the beam lying below the ECG. The moments of exposure of the anteroposterior and lateral films of 2 beats (A and B) are indicated by the brackets and the arrows. The films were exposed while the peak pressure gradient was being recorded (beats A and B), and the tip of the L.V. pressure monitoring catheter lies freely within the pool of contrast material in the L.V. chamber (arrows on roentgenograms).
Figure 8

Angiograms showing obstruction in a patient with IHSS. Films were obtained during selective left ventricular angiography and were exposed in the frontal and lateral projections. During systole (panels A and B), when open aortic valve leaflets could be identified, marked narrowing of the left ventricular outflow tract is apparent at the region of the mitral valve (dotted semicircular lines and arrows, panels A and B). In the frontal plane (panel A) a linear radiolucent
through a catheter introduced by the retrograde arterial route. In seven patients the injection of contrast material was made into the left atrium through a catheter positioned by means of transeptal puncture, and left ventricular pressure was recorded continuously; in 10 other patients, pressure was measured in the left ventricle immediately after injection of contrast material through the retrograde catheter. In 11 of these 17 patients, biplane angiograms were exposed at 6 frames per second, and the time of exposure of each film was recorded directly on the arterial and left ventricular pressure tracings. In the other six patients, cineangiograms were performed sequentially in two projections, and the left ventricular and brachial arterial pressure tracings were recorded directly on the cine film by means of the Cinetrace system. In 11 patients it was possible to demonstrate clearly that the tip of the catheter lay within the pool of contrast material in the left ventricular cavity at the precise moment that a pressure gradient between the left ventricle and the systemic artery was being recorded (fig. 7); in the other six patients no conclusions could be drawn from the studies, either because of inadequate visualization of the ventricular chamber or inappropriate timing of film exposures in relation to the cardiac cycle. Thus, although Criley and associates have shown quite properly that a pressure gradient can be recorded when a catheter tip lies in an obliterated portion of the left ventricular cavity, we have observed that a gradient can also be demonstrated when the catheter tip lies freely within a nonobliterated portion of the left ventricular cavity. The latter finding indicates that obstruction exists downstream to the tip of the catheter, in the outflow tract of the left ventricle.

The fact that few of the published biplane angiograms show severe narrowing of the outflow tract has been cited as evidence that true obstruction to outflow does not exist; moreover, as we have pointed out previously, several published angiograms from this and other clinics, which were purported to show obstruction, were exposed in early diastole when the open anterior leaflet of the mitral valve forms one aspect of the narrowed area. Several factors may be responsible for the low frequency with which an area of obstruction can be identified. Since the pressure gradient develops progressively during systole, it is perhaps not surprising that the instant of maximum obstruction is not often demonstrated on films taken at 4 or 6 exposures per second. In addition, although the cineangiograms of Criley and associates failed to show evidence of outflow tract constriction, the published films were exposed in the right anterior oblique projection which, in our experience, is least likely to reveal a narrowed area. The anterior leaflet of the mitral valve forming one plane of the left ventricular outflow tract, and recent analyses of casts made from the ventricular chambers of the normal dog arrested in systole indicate that the muscle of the left ventricular outflow tract envelops this leaflet; moreover, the narrowest dimension of the outflow tract is best visualized when the cast is viewed in the left anterior oblique position from a somewhat cephalad direction, an angiographic projection seldom used (fig. 2). Finally, in some patients, biplane angiograms do reveal an area of narrowing. During systole, and when open aortic leaflets can be identified, marked narrowing of the left ventricular outflow tract is apparent (figs. 8 and 9). It has been noted that in the frontal plane (figs. 8A and 9A), a linear radiolucent area corresponds to the site of obstruction localized fluoroscopically and hemodynamically by withdrawal pressure tracings (fig. 10). The position of the site of pressure drop and the shape of the area of obstruction suggest that this area is formed by hypertrophied

area (arrows) corresponds with the site of obstruction localized fluoroscopically at the time of withdrawal pressure recordings (see fig. 10). During diastole (panels C and D), the radiolucent area associated with the anterior leaflet of the mitral valve is more readily identified. Ao. = aorta; L.V. = left ventricle; L.A. = left atrium.

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Figure 9

Angiograms showing obstruction in a patient with familial IHSS. Films were obtained during selective left ventricular angiography, and in the frontal and lateral projections. During systole (panels A and B) a linear area of narrowing is apparent (arrows), which lies at the point where the hypertrophied septum impinges on the closed anterior leaflet of the mitral valve. Films exposed in diastole (panels C and D) also reveal the site of the mitral valve leaflet.

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Localization of the site of intraventricular pressure change in the left ventricle of a patient with IHSS. Panels A and B show sequential cine frames in the frontal projection, the position of the tip of the pressure-monitoring catheter being indicated by arrows as it is withdrawn from the high pressure portion of the left ventricle (A) to the low pressure portion (B). The Cinetrace (white tracing, lower right, in each cine frame) shows the corresponding L.V. pressure at the end of each tracing; at position B the catheter has just traversed the site of obstruction and is positioned in the outflow tract. Panel C shows an angiographic film exposed during systole in the frontal projection in the same patient in which contrast substance was injected into the left atrium. The catheter positions corresponding to those in panels A and B (see location of rib, dotted lines) are indicated. The site of the pressure change occurs at the position of the mitral valve. Panel D shows the L.V. and brachial (B.A.) pressure pulses recorded simultaneously with the angiographic exposure shown in panel C. The time of exposure, in midsystole, is indicated by the bracket.

Clinical Considerations

Analysis of Symptoms and Signs

Considerable difficulty in the evaluation of patients with IHSS has resulted from the vari-
ability of the hemodynamic findings in a given patient and from the fact that the occurrence of dyspnea, angina, and syncope may bear little or no relation to the magnitude of the intraventricular pressure gradient measured in the resting state at cardiac catheterization.\textsuperscript{8, 47} It should be emphasized that hemodynamic measurements have generally been carried out with the patient in the supine position, in which gravity does not influence venous return, hence ventricular filling, and in which sympathetic augmentation of ventricular contractility is presumably less pronounced than in the erect position. Of interest in this regard are recent observations indicating that when patients with IHSS are tilted upright the intraventricular pressure gradient is augmented, while the cardiac index is reduced.\textsuperscript{48} It seems possible, therefore, that if the intraventricular pressure gradient could be measured during activity in the erect position, the posture in which symptoms usually occur, a closer correlation might be found between the magnitude of the pressure gradient and the clinical picture.

The similarity in the incidence of angina and syncope observed in IHSS and that occurring in severe valvular aortic stenosis is striking. In particular, the relatively frequent occurrence of syncope, together with its disappearance following operations designed to relieve obstruction in patients with IHSS (as described below), suggests that the measured intraventricular pressure gradient reflects mechanical obstruction to left ventricular ejection.

It has been suggested that the systolic murmur associated with IHSS has many of the characteristics of a regurgitant murmur rather than an ejection murmur, and in two patients studied by intracardiac phonocardiography, the murmurs were recorded best in the left atrium and to a lesser extent in the left ventricle and aorta.\textsuperscript{7} However, many patients with IHSS who have a holosystolic murmur at the apex which radiates to the axilla also have a systolic ejection murmur heard best along the left sternal border; the intensity of the ejection murmur is roughly proportional to the magnitude of the pressure gradient.\textsuperscript{6} Moreover, the intensity of the ejection murmur is augmented by interventions which increase the intraventricular pressure gradient, such as the Valsalva maneuver or assumption of the upright posture; also, other intracardiac phonocardiographic studies have shown the ejection murmur to be loudest in the left ventricular outflow tract.\textsuperscript{44, 49} Finally, mitral regurgitation cannot be detected by angiography in approximately 50% of patients with IHSS (fig. 1),\textsuperscript{6} these patients nevertheless have prominent ejection murmurs and sometimes thrills, an observation incompatible with the possibility that the systolic murmur is produced only by mitral regurgitation.

Approximately one third of the 64 patients with IHSS recently analyzed exhibited paradoxical splitting of the second heart sound.\textsuperscript{6} In this group, the intraventricular pressure gradients were significantly higher than in those patients whose second heart sounds were normally split; moreover, in 60% of the patients with abnormal splitting, a systolic thrill was associated with the murmur. These findings do not appear consistent either with the possibility that the murmur and thrill in patients with IHSS are due solely to mitral regurgitation, or with the concept that the pressure gradient is due to rapid ejection and early obliteration of the ventricular cavity, since both of these conditions would tend to shorten rather than lengthen the duration of left ventricular ejection.

**Results of Operative Treatment**

Ventriculotomy, with or without resection of a portion of the hypertrophied left ventricular septum, as described in detail elsewhere,\textsuperscript{9} has been carried out in 16 patients in this clinic. Prior to operation all patients had large systolic pressure gradients and were markedly symptomatic. All of the 15 surviving patients have experienced significant clinical improvement. Preoperatively 10 patients had angina pectoris, and this was completely relieved in nine. Ten patients had experienced multiple syncopal episodes before operation; none has had syncope postoperatively.
Twelve patients, who have been followed for 1 to 6 years, have undergone left heart catheterization postoperatively. The systolic pressure gradients measured in the basal state were lower than the preoperative ones in all 12 patients; eight patients had no residual pressure gradient, while four had gradients between 10 and 44 mm Hg.

Most of the recent operative results reported from other clinics also indicate that the great majority of patients with IHSS have benefited strikingly from ventriculomyotomy or myectomy or both, and when postoperative cardiac catheterizations have been performed, the pressure gradients have almost always been abolished or greatly reduced. Thus, when the 12 patients from this clinic are added to those reported by Kittle, Trimble, Frye, Bentall, Julian, and their respective collaborators, the pressure gradient has been abolished, or reduced to less than 25 mm Hg in 28 of the 33 patients studied both before and after operation.

Several mechanisms, other than relief of obstruction, might be postulated to be responsible for these postoperative results. It might be suggested that hemodynamic improvement could be merely a reflection of the variability of the gradient that has been observed in individual patients. While it is appreciated that fluctuations in the gradient do occur spontaneously in patients with IHSS, the likelihood that these operative results represent a random change are extremely remote, and the directional change in the pressure gradient that occurred in the 28 patients described herein is highly significant statistically (P < 0.003). Another possible factor in clinical improvement following operation could be a decrease in the severity of pre-existing mitral regurgitation. While relief of obstruction could diminish coexisting mitral regurgitation and thereby play a role in alleviating clinical symptoms in some patients, a possibility suggested by Bentall and coworkers, this mechanism does not provide a general explanation for the hemodynamic results of operation since, as has already been pointed out, mitral regurgitation is present prior to operation in only about half of the patients. Thus, the clinical and hemodynamic results of operative treatment tend to support strongly the hypothesis that obstruction to outflow plays an important role in the pathophysiology of IHSS.

Discussion, Conclusions, and Summary

The present report has examined the anatomic, hemodynamic, angiographic, and clinical features of IHSS in particular relation to possible mechanisms responsible for the intraventricular pressure gradient that occurs in this disease. It is concluded that the evidence strongly favors the concept that the pressure gradient is associated with mechanical obstruction to left ventricular ejection and that cavity obliteration does not adequately explain either the location of the gradient or its modification by various interventions.

The major points favoring the existence of true obstruction to ejection may be summarized as follows: anatomic observations at necropsy and at operation have revealed "bars," "bands," or "tumors" of hypertrophic muscle which appear to obstruct the left ventricular outflow tract; in addition, it has been observed at operation that an incision into these hypertrophied areas of the interventricular septum immediately abolishes a sphincter-like action of the ventricular outflow tract. Hemodynamic observations, made at the time of operation in patients with IHSS, have shown that approximately 70% of the stroke volume is ejected during the time a pressure gradient exists and that the elevated left ventricular systolic pressure exists within the cavity of the left ventricle at all sites proximal to the outflow tract. Moreover, at cardiac catheterization, when the catheter tip was deliberately positioned in the inflow tract, an elevated systolic pressure was recorded while simultaneous biplane angiography revealed the catheter tip to be lying free within this area of the ventricular cavity, an area which did not become obliterated even in late systole. Obstruction rather than cavity obliteration, therefore, must have been responsible for this pressure gradient.
Angiograms were presented showing that in some instances a site of obstruction during systole can be visualized, lying in the outflow tract where the hypertrophied interventricular septum meets the anterior leaflet of the mitral valve. The fact that this area cannot be seen in some patients may be related to the oblique plane of this region, to the encirclement of the anterior leaflet of the mitral valve by the outflow tract, and to the relatively brief duration of the period of severe obstruction.

In this connection, it is pertinent to discuss the findings in a patient referred to the National Heart Institute by the Department of the Army for consideration of therapy. This patient had been studied previously, and was among those described in the recent report by Criley and co-workers. Angiograms performed in this laboratory showed systolic obstruction in the region of the anterior leaflet of the mitral valve (fig. 11), and a pullback pressure tracing across the mitral valve from the left ventricle into the left atrium revealed a high systolic pressure to exist in the inflow tract (fig. 3D); a zone of low pressure in the body of the ventricle could not be identified. Thus, it seems clear that the patients described by Criley and associates do not have anatomic and hemodynamic features basically different from those patients presented in the present study.

Finally, in summarizing the evidence favoring the existence of obstruction, clinical observations, such as the presence of a systolic murmur in patients without demonstrable mitral regurgitation, and the relief of angina and syncope by operations designed to relieve outflow tract obstruction should be mentioned. In addition, the marked reduction or elimination of the pressure gradient by these operations further supports the concept that obstruction plays a significant role in this disease.

Equally important to an understanding of the mechanism behind the intraventricular pressure gradient in IHSS is a consideration of the brachial arterial pressure pulse has been transposed to correspond with the L.V. pressure pulse.

**Figure 11**

Angiographic visualization of the site of obstruction in a patient with IHSS. The lower panel shows an angiographic film, in the lateral projection, obtained during a selective left ventricular angigram in which the timing of each radiographic exposure was recorded simultaneously with the left ventricular and brachial arterial pressure pulses (upper panel). The film shown was exposed in late systole (as indicated by the bracket in the lower panel), at a time when a large pressure gradient was recorded. Above the tip of the transseptal catheter (arrow) which recorded the elevated L.V. pressure, a linear radiolucent area in the inferior portion of the L.V. outflow tract is noted. The radiolucent zone is interrupted anteriorly by the tip of the retrograde arterial catheter lying within the outflow tract. The outline of the LV chamber, indicated by the dashed line, shows the hypertrophied ventricular septum projecting toward and presumably impinging upon the anterior leaflet of the mitral valve, resulting in the radiolucent zone corresponding to the level of obstruction in the outflow tract.
of whether or not the concept of systolic obliteration of portions of the left ventricular cavity can explain all of the angiographic and hemodynamic features of IHSS, as suggested by Criley and co-workers. In the present study it was concluded that several phenomena could not be adequately explained by this mechanism. First, as Criley and associates have shown in diagrammatic form, their theory requires that a low left ventricular systolic pressure, equal to that in the aorta, be present in the main ventricular cavity. This was not the case in any of our studies (figs. 3 and 7). Likewise it is difficult to see how the reduction in the stroke volume and arterial pulse pressure during the contraction following an extrasystole and the effects of the Valsalva maneuver can be accounted for by this theory. Moreover, as discussed above, recent studies in animals strongly imply that the mechanism behind the intraventricular pressure difference that can be induced in the normal ventricle of the dog is basically different from that existing in patients with IHSS. Thus it seems clear, as pointed out by Criley and co-workers, that these experimentally induced elevations of intraventricular pressure do not represent true obstruction to flow. Therefore, according to conventional hemodynamic usage, these pressure differences should not be termed "pressure gradients;" the term "intraventricular pressure differences" perhaps better describes their nature, and this terminology also might be preferable in referring to elevated pressures measured in empty portions of the ventricular cavity in patients with IHSS. Criley and his collaborators have made a most important contribution in pointing out that pressure is elevated in essentially empty portions of the left ventricle in patients with IHSS and have stimulated renewed interest in the hemodynamic mechanisms associated with this disease; however, the hemodynamic significance of this finding in patients with IHSS remains to be established. On the other hand, it can be stated with assurance that obstruction to outflow, of greater or lesser severity, does exist in patients with IHSS in whom an elevated systolic pressure is present in nonobliterated portions of the left ventricular cavity.

Our current view of the dynamics of left ventricular contraction in IHSS may be outlined, then, as follows. Following the onset of left ventricular contraction, isometric pressure development and early ventricular ejection appear to proceed at a more rapid rate than in the normal subject, and approximately 30% of the forward stroke volume is ejected while there is no significant pressure gradient. This phase of systole is responsible for the sharp upstroke of the arterial pressure pulse. Subsequently, the hypertrophied interventricular septum approaches the anterior surface of the closed mitral valve, and the intraventricular pressure at all points in the cavity below this site begins to exceed that in the outflow tract. The pressure gradient from the body of the ventricle to the outflow tract then increases progressively as further narrowing of this region occurs, and ortho-grade flow consequently diminishes, the remaining 70% of the stroke volume being ejected during this phase. Finally, in late systole, obstruction in the outflow tract becomes essentially complete, and elevated pressure persists in both obliterated and in nonobliterated portions of the ventricle, at a time when forward flow cannot be detected. In addition to obstruction to left ventricular emptying, the reduced compliance of the thickened ventricular wall in IHSS also interferes with left ventricular filling and accordingly, ventricular end-diastolic volume may be reduced despite an elevated left ventricular diastolic pressure. The relative importance of such impedance to left ventricular filling during diastole, and the obstruction to outflow during systole, undoubtedly varies among individual patients.

A number of unanswered questions concerning the dynamics of left ventricular contraction in IHSS await solution. The importance of the elevated ventricular systolic pressure in producing or magnifying mitral regurgitation and the precise role of more rapid and more extensive shortening of the minor ventricular circumference in causing the obstruction, as
detailed by Klein and co-workers,51 await further quantitative studies. It has not yet been possible to measure precisely at cardiac catheterization the severity of obstruction during ejection and during the late phase of systole in the individual patient, since measurements of instantaneous orthograde flow and intracavitary left ventricular pressure are required. Likewise, the clinical importance in each patient of the late systolic phase of contraction, in which obstruction appears to be complete, remains to be determined. Finally, the precise mechanisms by which operative resection or myotomy affect certain other features of left ventricular contraction have not yet been completely elucidated. In addition to the important effects of relieving the obstruction, it is possible that the impedance to ventricular filling is also diminished and that the interruption of circumferential muscle fibers proximal to the site of obstruction reduces the extent and speed of fiber shortening in the wall surrounding the main cavity; an increase in end-systolic volume would then be anticipated, a change further favoring relief of muscular obstruction.

Because of the generalized nature of the myocardial disorder in IHSS, operative intervention has been recommended to relatively few patients, and only to those with severe symptoms. The considerations developed herein strongly favor a significant role for obstruction in the pathophysiology and symptomatology of IHSS, and the operations designed to relieve obstruction have been shown to result in distinct clinical and hemodynamic improvement. Therefore, while it is hoped that an effective means of nonoperative treatment will become available, at the present time it does not appear that current concepts concerning operation should be revised on the assumption that obstruction to outflow does not exist.

References


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L'Interet de la Verite

In general it is better for scientific people to avoid controversy, particularly of the unpleasant kind that involves questions of priority. Joseph Barcroft once remarked, in a comment on a complaint by X that Y had been stealing his work:

"X should have been proud that Y thought his work worth stealing."

And the only time I ever saw W. B. Hardy really angry was when he heard a remark by Z, that he (Z) could not admit people freely into his laboratory because they might pilfer his ideas. The complete negation of the scientific spirit, Hardy called it. All his life Hardy continued to dig out and expose new ideas; if others took them up and exploited them, that was splendid, it left him free to go on finding new ones.

Honest criticism too can be welcome. One should be proud if other people find one's work worth criticizing; but on condition that criticism does not merge into misrepresentation, as too often it does in politics (or antivivisection). Then it must be answered, otherwise it gets rapidly into reviews and text-books where it may remain, to confuse non-specialists, for a generation.—ARCHIBALD VIVIAN HILL: Trails and Trials in Physiology. Baltimore, The Williams & Wilkins Co., 1965, p. 363.
The Mechanism of the Intraventricular Pressure Gradient in Idiopathic Hypertrophic Subaortic Stenosis

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Circulation. 1966;34:558-578
doi: 10.1161/01.CIR.34.4.558

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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