Pressure Gradients without Obstruction

A New Concept of “Hypertrophic Subaortic Stenosis”

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Robert I. White, Jr., M.D., and Richard S. Ross, M.D.

Obstruction to left ventricular outflow has been considered a characteristic and functionally important feature of "hypertrophic subaortic stenosis." The presence of obstruction has been inferred from the finding of a pressure gradient within the left ventricle during catheterization of the left heart in certain patients with idiopathic left ventricular hypertrophy. Indeed, the disease was not recognized as a clinical entity until after the advent of left heart catheterization techniques. Infrequent descriptions of massive hypertrophy with virtual obliteration of the left ventricular cavity in autopsy reports dating back to 1907,1 lend some support to the concept of muscular obstruction.

A number of observations render the functional importance of obstruction less clear in "hypertrophic subaortic stenosis" than in discrete forms of aortic stenosis. 1. There is no correlation between the size of the left ventricular gradient ("severity of the obstruction") and the functional status of the patient.2 2. The pressure gradient is quite variable and often absent during the course of a left heart catheterization study or on repeated studies. 3. No obstruction is found at operation or at autopsy in some patients with large pressure gradients.

The generally accepted theory holds that, during systole, the walls of the left ventricle come together and form a stenotic area within the ventricular cavity and that the pressure gradient is produced by this circumferential obstruction (fig. 1A). The development of this "functional obstruction" is dependent upon the contractile force of the left ventricle and the amount of venous return.2-4 An intervention which increases the force of left ventricular contraction (inotropic drugs, post-ectopic beats, etc.) or which diminishes venous return to the left ventricle (nitroglycerin, hemorrhage, etc.) increases the left ventricular pressure gradient. Conversely, increasing the ventricular afterload by vasoconstriction or aortic clamping and increasing the venous return by transfusion diminish the pressure gradient. The unusual arterial pressure contour—an initial spike of short duration followed by a rapid fall to near diastolic pressure—has been attributed to unimpaired early systolic ejection followed by progressively severe obstruction. Calculations of effective outflow orifice size throughout the systolic cycle, based on flow meter and pressure data obtained at operation, have indicated progressive constriction terminating in total obstruction in late systole.2

Cardiac lesions characterized by obstruction can be demonstrated by contrast radiography, and there is usually a good correlation between the degree of narrowing and the pressure gradients measured. However, a significant narrowing of the outflow tract was not seen by left ventricular cineangiography in the seven patients with left ventricular pressure gradients studied in our laboratory (table 1). This paradox prompted a review of the published angiocardiograms of patients with "hypertrophic subaortic stenosis."5-9

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Supported in part by U. S. Public Health Service Research Grant HE-05584 CV from the National Heart Institute, by Clinical Center Grant FR-34 from The Division of General Medical Sciences, and by a Public Health Service Research Career Program Award K3-HE-3795 from the National Heart Institute.

Dr. Lewis is a Research Fellow of The Heart Association of Maryland.

Dr. White is a Research Fellow supported by U. S. Public Health Service Training Grant STI-HE-5159.
In analyzing the figures for evidence of systolic obstruction, it was important to ascertain that the exposure was made in **systole**.

A dramatic conical or hour-glass narrowing of the left ventricular contrast silhouette takes place in a normal ventricle in **diastole**, due to the inflow of nonopaque blood from the left atrium (fig. 2). The anteromedial leaflet of the mitral valve swings across the left ventricular outflow tract, and may meet the interventricular septum, especially if there is asymmetric hypertrophy of the latter. Serial film angiograms taken at six exposures per second must be carefully examined to avoid confusion of end-systole with early di-

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**Figure 1A**

Diagram of a hypothetical right anterior oblique angiogram demonstrating obstruction in the left ventricle. The diastolic contour of the left ventricular cavity is indicated by light gray shading, and the systolic contour in darker cross-hatching. The myocardium in diastole is represented by the stippled area. The extreme narrowing of the outflow tract is based on the assumption that the pressure gradient is due to obstruction. L.A., left atrium; Ao., aorta; high, high pressure area in left ventricle; low, low pressure area in left ventricle.

**Figure 1B**

Diagram demonstrating “cavity obliteration.” Diastolic and systolic contours of the left ventricular cavity are depicted as in figure 1A. A catheter lying in the regions emptied during systole—the apex or the intertrabecular spaces—would record a high ventricular pressure. Mitral incompetence is indicated by the shaded area in the left atrium.

**Figure 2**

Diagram of an early diastolic frame from a lateral left ventricular angiogram demonstrating “pseudo-obstruction” of the left ventricle. The mitral valve is open and the anterior leaflet has swung across the outflow tract of the left ventricle as nonopaque blood enters from the left atrium. If this diastolic frame were confused with systole, the apparent narrowing of the outflow tract produced by the open mitral valve on one side and septal hypertrophy on the other might be interpreted as muscular subaortic stenosis. This “pseudo-obstruction” is best seen in lateral and left anterior oblique views. The closed aortic valve establishes the correct timing of the event to diastole.
Table 1

Clinical and Hemodynamic Data from Seven Patients with Idiopathic Hypertrophic Subaortic Stenosis without Demonstrable Outflow Obstruction by Cineangiocardiography

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, race, sex</th>
<th>Signs &amp; symptoms</th>
<th>Duration, yr.</th>
<th>Physical findings</th>
<th>ECG</th>
<th>Chest x-ray</th>
<th>Rest.</th>
<th>Maximum gradient, mm. Hg</th>
<th>Isop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.E.</td>
<td>43 W M</td>
<td>Murmur</td>
<td>11</td>
<td>Double apical impulse</td>
<td>LVH</td>
<td>LV+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOE</td>
<td>8</td>
<td>S-4</td>
<td>S-T ↓ in</td>
<td>CT 44%</td>
<td>51</td>
<td>96</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td>8</td>
<td>Apical holo SM</td>
<td>V₃₋₆</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Murmur</td>
<td>14</td>
<td>LV lift</td>
<td>LVH</td>
<td>LV+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.F.</td>
<td>42 W F</td>
<td>Syncope</td>
<td>14</td>
<td>S-3 &amp; S-4</td>
<td>QS II, III</td>
<td>CT 52%</td>
<td>27</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td>14</td>
<td>Apical late SM</td>
<td>aV₆</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>DOE</td>
<td>2</td>
<td>LV lift</td>
<td>LBBB</td>
<td>LV+</td>
<td></td>
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</tr>
<tr>
<td>P.W.</td>
<td>58 W M</td>
<td>Murmur</td>
<td>2</td>
<td>S-4</td>
<td>CT 48%</td>
<td>48</td>
<td>63</td>
<td>111</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>DOE</td>
<td>8</td>
<td>Double apical impulse</td>
<td>Q in I,</td>
<td>LV+</td>
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<tr>
<td>R.E.</td>
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<td>Pain</td>
<td>8</td>
<td>S-3 &amp; S-4</td>
<td>aV₆, &amp;</td>
<td>CT 48%</td>
<td>50</td>
<td>66</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Murmur</td>
<td>4</td>
<td>Apical late SM</td>
<td>V₄₋₆</td>
<td></td>
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<tr>
<td>J.M.</td>
<td>18 W M</td>
<td>Asympt.</td>
<td></td>
<td>LV lift</td>
<td>LVH</td>
<td>LV+</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Murmur</td>
<td>14</td>
<td>Apical ejection SM</td>
<td>CT 50%</td>
<td>75</td>
<td></td>
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<tr>
<td>D.R.</td>
<td>27 W M</td>
<td>Murmur</td>
<td>18</td>
<td>S-4</td>
<td>Inv. T in</td>
<td>CT 48%</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>DOE</td>
<td>4</td>
<td>Double apical impulse</td>
<td>LVH</td>
<td>LA+</td>
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<tr>
<td></td>
<td></td>
<td>Pain</td>
<td>4</td>
<td>Apical thrill</td>
<td>LVH</td>
<td>LV+</td>
<td></td>
<td>110</td>
<td>135</td>
</tr>
<tr>
<td>L.L.</td>
<td>33 N F</td>
<td>Murmur</td>
<td>11</td>
<td>Double apical impulse</td>
<td>LAH</td>
<td>CT 55%</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: DOE, dyspnea on exertion; SM, systolic murmur; LV, left ventricle; LVH, left ventricular hypertrophy; LV+, left ventricular enlargement; LA+, left atrial enlargement; LBBB, left bundle-branch block; REST., resting gradient between left ventricle and systemic artery; VALS., gradient during Valsalva maneuver; p ECT., gradient in postectopic beat; ISOP., gradient during infusion of isoproterenol; CT, cardiothoracic ratio.
astole, events which may be separated by as little as 0.1 second.

Diastolic “pseudo-obstruction” produced by the open mitral valve was identified by the finding of a closed aortic valve in many of the published angiocardiograms, and these cases were excluded from consideration. There was no clear-cut demonstration of significant narrowing in the majority of the remaining published pictures. The aortic diameter was used for reference, and most of the “obstructions” demonstrated were about three quarters of the diameter of the aorta or larger, a degree of narrowing incapable of producing a significant pressure gradient at the low flow rates known to be present after midsystole. In no case was a left ventriculogram demonstrating the predicted total obstruction seen.

In an attempt to elucidate the reason for the lack of correlation between the hemodynamic and angiographic data, studies were performed on six dogs in which pressure gradients of 72 to 146 mm. Hg within the left ventricle were produced by isoproterenol infusions,10 as described by Krasnow et al.11 Left ventricular cineangiograms obtained during the control state and during the isoproterenol infusions revealed a marked increase in the rapidity and degree of the left ventricular emptying after the inotropic agent. In each instance, the recording tip of the catheter measuring high ventricular pressure was completely outside the contrast silhouette of the left ventricular cavity during the latter half of each systolic cycle. The catheter tip was completely enfolded in contracting muscle, although free in the cavity during diastole. Cinefluorographic catheter withdrawals indicated that the high pressure portion of the ventricle was invariably at the apex, an area devoid of contrast material by mid-systole in each of the animals. Significant contraction of the outflow tract did not occur.

These cineangiographic findings were identical to those reported by Martin12 in dogs in which pressure gradients were induced by hemorrhagic shock. Isometric contraction in mid-to-late systole by an empty portion of the left ventricle, rather than outflow obstruction, was clearly responsible for the pressure gradient in both experiments.

The left ventricular cineangiograms of the seven patients with left ventricular pressure gradients without demonstrable angiographic obstruction were reexamined to determine if a mechanism similar to that operative in the dog experiments could be responsible for the apparent obstruction. Cinefluorographic catheter withdrawals were carefully matched with the angiographic contour of the left ventricle to determine the site of pressure change. In each case, the catheter proved to be in a small recess between trabeculae carneae, or at the apex at the time the high pressure was recorded, and the fall in pressure occurred as the catheter entered the central cavity of the left ventricle (figs. 1B and 3). The intertrabecular recesses and the apical portions of the left ventricle were obliterated by midsystole. In one patient, a 5-cm. length of catheter was enfolded by the muscle of the empty apical portion of the left ventricle (fig. 3C). In the cineangiograms obtained in this patient with a gradient of 133 mm. Hg, the only remaining contrast material in end-systole was in the subvalvular area. The rest of the ventricle was unequivocally empty. Many of the published angiograms which do not demonstrate obstructions are quite compatible with “complete emptying” as seen in our cineangiograms.

Systolic obliteration of portions of the left ventricular cavity provides an explanation for the pressure gradient in “hypertrophic subaortic stenosis,” which is compatible with all of the hemodynamic and angiographic observations that have been made. Patients with this disease eject a normal stroke volume more rapidly than normal–75 to 80 per cent of the stroke in the first half of systole13—and have a normal or smaller than normal end-systolic volume. These observations are quite incompatible with significant obstruction, but fit well with cavity obliteration. Isoproterenol augments the rate and degree of emptying, and would be expected to increase the force of isometric contraction in mid and late systole. Decreases in venous return permit small-
Diagram of superimposed systolic and diastolic frames of a left ventricular cineangiogram from a patient with a 133-mm. Hg systolic pressure gradient in the left ventricle. Note extremely small systolic ventricular size (dark cross-hatching) and absence of obstruction at any site in the left ventricle. The retrograde catheter was free in the left ventricular cavity during diastole (light gray shading), but completely enfolded by myocardium during systole. The transseptal catheter was in an intertrabecular recess. Both ventricular catheters recorded equally high ventricular pressures. The retrograde catheter was slowly withdrawn during the cineangiogram, and a fall in pressure was noted as the catheter entered the area representing systolic chamber size on the diagram. It is important to note that the catheters were not penetrating the myocardium during systole, but were completely enfolded by contracting muscle.

Systolic frame from the same patient's (fig. 3A) cineangiogram demonstrating the retrograde catheter outside the systolic cavity of the left ventricle. The diastolic silhouette is indicated by dotted lines.

er left ventricular volumes and more profound systolic cavity obliteration.

The murmur in patients with “hypertrophic subaortic stenosis” is best heard at the left sternal border or apex, is well transmitted to the axilla, and is rarely well transmitted to the carotid area. Although late systolic in onset, it has many of the characteristics of a regurgitant murmur rather than an ejection murmur.3

Mitral regurgitation was present on left ventriculography in all seven of the patients with “hypertrophic subaortic stenosis” studied in our laboratory, and was increased by isoproterenol infusions in the three patients receiving the drug. In the two patients studied by intracardiac phonocardiography, the murmur was recorded best in the left atrium and to a lesser extent in the left ventricle and aorta. The late systolic onset of the murmur suggests competence of the mitral valve in early systole followed by regurgitation, perhaps caused by the abnormally aligned papillary muscles in the small end-systolic cavity.6 It is also possible that the mitral valve is structurally abnormal in these patients, as postulated by several investigators.14, 15

It is not known whether cavity obliteration will explain the presence of a pressure gradient in all cases of “hypertrophic subaortic

Circulation, Volume XXXII, December 1965
stenosis.” The theory furnishes an alternative to obstruction, however, and fits well with the evanescent nature of the gradient and the observation frequently made at operation or autopsy that no obstruction exists. In the instances in which a sphincter-like muscle grips the surgeon’s exploring finger, it is entirely possible that the finger, like the catheter, is experiencing isometric contraction by an empty portion of the ventricle.

Further careful studies must be made in patients with “hypertrophic subaortic stenosis” to assess the significance of the pressure gradient. Intelligent medical and surgical management requires a clear understanding of the role of obstruction in the pathogenesis. It is clear that there is morbidity, that the cardiac muscle is abnormal in structure and function, and that patients occasionally succumb to the disease. It is not clear that “relief of obstruction” is the treatment of choice.

**Summary and Conclusions**

Significant outflow tract obstruction was not seen by left ventricular cineangiocardiography in seven patients with “hypertrophic subaortic stenosis.”

Catheter withdrawals through the left ventricle, recorded cinefluorographically, localized the high pressure areas to portions of the left ventricle which emptied completely in early systole. Sustained systolic contraction in empty portions of the left ventricle provides an explanation for the pressure gradients in these patients.

Isoproterenol infusions increased the rate and degree of left ventricular emptying, obliterating portions of the cavity earlier and increasing the pressure gradient.

The mechanism of gradient production without obstruction was similar to the phenomenon observed in dogs receiving isoproterenol infusions.

The cardiac muscle in these patients is abnormally thick and the left ventricle empties more rapidly than normal; therefore a “hypertrophic hyperkinetic cardiomyopathy” is present.

The nonobstructive nature of the disease in these patients necessitates revision of therapeutic considerations in patients with pressure gradients within the left ventricle.

**Acknowledgment**

The authors wish to thank Robert B. Dickerson, Colonel, M.C., Robert C. Jones, Lieutenant Colonel, M.C., and Richard J. McCarty, Captain, M.C. of Walter Reed Army General Hospital, and Sander H. Mendelson, Captain, M.C. of Fort Belvoir, Virginia, for referring two of the patients in this study.

**References**


*In order to avoid an overly lengthy bibliography, only selected specific references were quoted. In the preparation of this report, however, extensive use was made of the monograph on Idiopathic Hypertrophic Subaortic Stenosis (reference 2) and the bibliography containing 191 references was extremely useful.
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All the structures contributing to the passage of blood into the lungs had now been described, but it took more than 150 years to understand exactly the nature of the exchange which took place within the lungs between air and circulating blood. The question had been begging for solution since Empedocles. The correct answer had to wait for progress in physics and chemistry, and for successive and often combined inquiries, experiments, and discoveries. This was the achievement of the English scientists, Boyle, Hooke, Lower, and later, Priestly, and of Lavoisier, the founder of respiratory physiology.—André Cournand, M.D. Circulation of the Blood. Edited by Alfred P. Fishman, M.D., and Dickinson W. Richards, M.D. New York, Oxford University Press, 1964, p. 29.
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Circulation. 1965;32:881-887
doi: 10.1161/01.CIR.32.6.881
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

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