The Clinical, Hemodynamic, and Pathologic Diagnosis of Muscular Subvalvular Aortic Stenosis

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STENOSIS of the outflow tract of the left ventricle is a disease of serious and often fatal consequence. The form of obstruction varies, but most commonly it is a discrete ridge of fibrous tissue that projects into the left ventricle completely encircling the outflow tract. In some instances this fibrous ridge may be accompanied by bulging and hypertrophy of the underlying interventricular septum. Recently, several authors have reported muscular hypertrophy of the septum and left ventricle alone as a cause of subvalvular aortic stenosis. They suggest that during systolic contraction this thickened muscle comes together, narrowing the outflow area and impeding ventricular ejection.

In 1958 Teare reported postmortem findings in eight relatively young people who had what he termed "asymmetrical cardiac hypertrophy." In each instance there was diffuse hypertrophy of the interven- tricular septum and anterior left ventricle. Shortly thereafter, Brock described six cases of hypertrophy of the left ventricle and upper muscular septum with resultant functional obstruction to left ventricular outflow. Bercu and associates added a similar case in which a systolic gradient existed between the left ventricle and aorta and at necropsy only hypertrophy of the musculature of the outflow tract was evident.

In early 1960 Brent and associates described a number of patients with this same entity. They emphasized the familial incidence of the disease, since all of their six pa-

tients having proved muscular subaortic stenosis were members of only two families. Brachfeld and Gorlin reviewed the subject of subaortic stenosis and reported two cases with predominantly muscular obstruction. Goodwin and associates suggested the name "obstructive myocardiopathy," stating that this massive muscular hypertrophy could obstruct the inflow and outflow of blood in both the right and left ventricles. Most recently, Braunwald and co-workers presented a study of 14 patients who had a condition that the authors called "idiopathic hypertrophic subaortic stenosis." Their recognition of the similarities in the previous cases, coupled with their own experience, enabled them to elucidate this entity.

Recently, we have reviewed all the cases at the Mayo Clinic in which a diagnosis of subaortic stenosis was made either at operation or at necropsy. This is a report of those cases in which diffuse muscular thickening of the interventricular septum and wall of the left ventricle resulted in obstruction of left ventricular outflow.

Materials and Methods

Eight cases of proved muscular subvalvular aortic stenosis have been reviewed. In three cases necropsy was performed, while in five cases the diagnosis was established at operation. The clinical evaluation includes data on the patient's history, physical examination, electrocardiogram, roentgenograms, and cardiac catheterization. In view of the difficulty of recognizing obstruction of left ventricular outflow of this "functional" muscular variety, both the thickness of the left ventricle and the width of the interventricular septum were measured in the necropsy specimens. The entire muscular septum was cut in a vertical section beginning at the commissure of the right and posterior coronary cusps. A point 1.5 cm. down from the junction of the muscular and membranous septum was arbitrarily selected, and here the width of the septum was measured. The left ventricular mes-
urement was taken at a point of average thickness as suggested by Saphir. The septal width was then divided by the thickness of the left ventricle in an attempt to establish a ratio between the two.

A control series of 50 hypertrophied hearts and 20 apparently normal hearts were evaluated similarly. These hearts were selected in consecutive order at necropsy.

Sections for microscopie study were taken from the area of obstruction and from a similar area in the control group. These sections were prepared with hematoxylin and eosin and elastic van Gieson stains.

Results

Clinical

General Data. Six patients were males and two were females. Their ages were as follows: 17, 20, 23, 35, 36, 37, 47, and 59 years.

History. None had a history of rheumatic fever. A murmur was first noted at ages 6, 12, 14, 20, 29, 36, 39, and 47 years, respectively. Similarly, symptoms began at ages 12, 19, 21, 30, 34, 36, 44, and 46 years. Six patients had a history suggestive of angina. All eight patients had dyspnea on exertion, and two had a history compatible with frank congestive heart failure. One died suddenly at home (59 years of age), while two men, 35 and 36 years of age, died after operation. A review of the family histories revealed heart disease in two instances: The mother of the 17-year-old boy had died suddenly at 51 years of age of a heart condition of undetermined nature. Similarly, the mother of the 20-year-old girl had died unexpectedly at 39 years of age of heart disease and diabetes.

Physical Findings. All eight patients had a systolic murmur described as grade 3 or 4 (basis of 1 to 4) and harsh, although in three instances a higher pitched component to the murmur was audible. In seven, the murmur was heard best at the fourth to fifth left intercostal spaces and in one it was heard equally well at the right second interspace and along the left sternal border. The murmur in seven patients was heard well in the aortic area, but in only five was it heard over the vessels of the neck. No patient had a diastolic murmur. The aortic second sound was decreased in one and was normal in seven. Seven patients had a palpable thrill—in six it was in the fourth left interspace and in one, at the suprasternal notch. Blood pressure was normal in all eight. A narrow splitting of the second sound, heard in three instances, was loudest in the right second interspace. Change in the width of the splitting was not detectable during phases of respiration, nor did a phonocardiogram taken in one case disclose any alteration in the width with breathing. An apical third heart sound was audible in three cases. In one patient the phonocardiogram confirmed the presence of this sound and in addition disclosed a fourth heart sound (fig. 1). Atrial fibrillation oc-

Figure 1

Phonocardiogram (case 6). Note character of the murmur, the third and fourth heart sounds, and the bisferious character of the carotid pulse tracing.
curred periodically in the 59-year-old man, but no others demonstrated any irregularities in rhythm.

Electrocardiogram. In seven of the eight patients the electrocardiograms were interpreted as left ventricular hypertrophy of the pressure overload type. One disclosed a left bundle-branch block. Left atrial enlargement was noted in two.

Roentgenogram. Posteroanterior and oblique views of the thorax disclosed evidence of left ventricular enlargement in all cases. Left atrial enlargement was present in three cases (fig. 2). In no patient was there x-ray evidence of a calcified aortic valve or dilatation of the ascending aorta (fig. 3).

Cardiac Catheterization. This procedure was carried out in seven instances. In only three cases, however, were left ventricular withdrawal tracings obtained. Each withdrawal tracing demonstrated a zone of reduced systolic pressure in the outflow area of the left ventricle (fig. 4). Systolic gradients across the region of the aortic valve in the seven cases varied from 64 to 135 mm. In every instance an anacrotic notch was evident on the ascending limb of the left ventricular pressure curve. In six of the seven cases the aortic curve showed a rapid upsweep of the percussion wave (less than 0.13 second) with a delayed or bisferious form and a good dicrotic notch (fig. 5). In the seventh instance central arterial pulse tracings were not recorded. Ventricular end diastolic pressures were elevated in five of the seven cases. The highest was 29 mm. and the lowest, 18 mm. Equivocally elevated pulmonary artery pressures were noted in the two instances in which they were recorded. Left atrial contraction waves also were noted in these two cases. In five cases a single extrasystole and compensatory pause could be demonstrated. The systemic arterial tracings in each of these revealed that the beat that followed the compensatory pause had a smaller pulse pressure than the control values for that patient (fig. 6).

In one patient an angiocardiogram displayed an area of narrowing in the outflow tract of the left ventricle. This narrowing appeared to increase during ventricular systole (fig. 7).

Pathologic Findings

Five patients were treated surgically and specific measurements of the septum and left ventricle were not obtained. All five had gross muscular hypertrophy of the upper muscular septum with obstruction to the left ventricular outflow tract. In addition, the left ventricle in each patient was greatly thickened.

At necropsy the hearts of three men who died at ages 59, 35, and 36 years weighed 720, 780, and 930 Gm., respectively; the normal weight in each case would have been 262, 214, and 382 Gm.* The left ventricles measured 1.8, 1.7, and 2.0 cm. while the right ventricles measured 0.5, 0.5, and 0.6 cm. Septal hypertrophy subjectively was graded as 4 (basis of 1 to 4) in all cases. In one case (59-year-old man) the upper septum bulged signifi-

*Normal weights were determined with reference to age and weight of patient.

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Figure 3


cantly so that it formed a ledge at the junction of the muscular and membranous septa (fig. 8). In the other two cases the upper septum showed diffuse thickening but with less bulging of the superior edge. In the three cases the thickness 1.5 cm. from the junction of the muscular and membranous septa was 2.8, 3.0, and 3.1 cm. The ratio of the septal width to the left ventricular thickness in these three cases was 1.55, 1.76, and 1.55 (figs. 9 and 10). The heart of the older man (case 8) disclosed evidence of healed endocarditis of the mitral valve.

Subvalvular sclerosis, grade 3, was noted in each of the three patients; however, no fibrous ridge was evident. Coronary artery sclerosis was grade 1 in two cases and grade 2 in the third case. There were no associated anomalies. In one case there was microscopic evidence of a minimal increase in connective tissue within the muscular septum. Each showed a thickened hyalinized endocardial surface and the cardiac muscle appeared normal (fig. 11).

Control Group

All 20 normal hearts weighed between 240 and 460 Gm. Each was within normal limits with respect to the weight and age of the patient. The thickness of the left ventricle varied between 1.0 and 1.5 cm., the average being 1.3 cm. The septal width 1.5 cm. down from the junction of the muscular and membranous septa measured from 1.0 to 1.4 cm. with an average of 1.2 cm. The ratio of the septal width to the left ventricular thickness was calculated in each case with the average ratio being 0.95 (fig. 9).

The weights of the 50 hypertrophied hearts ranged from 500 to 1,122 Gm. The thickness of the left ventricle varied between 1.1 and 2.0 cm., the average being 1.7 cm. The mean width of the upper muscular septum was 1.65 cm., with a range of 1.0 to 3.0 cm. The average ratio of the septal width to the thickness of the left ventricle was 0.98. This ratio exceeded 1.25 in a single instance, that of a 38-year-old man with a calcified stenotic aortic valve that was thought to be bicuspid. The septum was grossly thickened with a small left ventricular cavity. The septum measured 3.0 cm. and the left ventricle 2.0 cm. with a ratio of 1.5. Microscopic sections of the upper interventricular septum were interpreted as normal in both the control and the hypertrophied group.

Discussion

Symptoms and Signs

Muscular obstruction of the left ventricle has become increasingly important as a potentially operable form of heart disease. Most
commonly, the symptoms are dyspnea and angina, although lightheadedness and palpitations have been reported with some frequency. Congestive heart failure may occur and sudden death is not uncommon. Often one may elicit a family history of heart disease. In this series symptoms became evident between the second and fifth decades, although younger patients with this disease have been reported.10,12 A harsh, "diamond-shaped" murmur, much like that heard in aortic valve stenosis, is invariably present along the lower left sternal border. The murmur may have a higher pitched component, and clinically, mitral insufficiency is frequently suspected. Transmission of the murmur to the vessels of the neck occurred in more than half of the cases in this study, although other authors have suggested that this is uncommon.12 A systolic thrill is felt oftenest along the left sternal border, but it may be detected in the suprasternal notch.

The second sound in the aortic area is usually of normal intensity. The absence of an ejection click in all of these cases supports the recent observations of Hancock15 that this phenomenon does not occur in muscular obstruction. Paradoxical splitting of the second sound would be expected and was present with some frequency in one series.12 Although a split second sound was noted in several of these cases, there was no detectable change in the width of the splitting during phases of respiration. It should be re-emphasized that paradoxical splitting may be obscured if the sound of pulmonic valve closure is masked by the prolonged systolic murmur.12 Our experience as well as that of Braunwald and co-workers12 suggested that a diastolic murmur would make the diagnosis of muscular outflow obstruction unlikely. Apical third and fourth heart sounds may be heard, but phonocardiography should be employed to detect sounds that are clinically inaudible. Atrial fibrillation, although rare, does occur. There were no patients in our series with elevated blood
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pressure or other diseases that might have predisposed to cardiac hypertrophy.

Roentgenograms and Electrocardiograms

The absence of aortic valvular calcification and poststenotic dilatation of the ascending aorta have been used previously as diagnostic aids to distinguish valvular from subvalvular aortic stenosis.2, 16, 17 The younger age of some patients with diffuse muscular obstruction makes the absence of calcium in the aortic valve a less significant guide. A normal appearing ascending aorta, however, is of great diagnostic help. Advanced left ventricular hypertrophy is a constant x-ray finding, and frequently left atrial enlargement is suspected. Similarly, the electrocardiogram discloses an enlarged left ventricle and not uncommonly it suggests left atrial hypertrophy.

Anomalous atrioventricular excitation, although reported in one series,12 was not found in any of our preceding cases. The experience of other authors, in addition to our experience in one case mentioned herein, indicates that angiocardiography is a reliable method of demonstrating the region of obstruction.12

Hemodynamics

The diagnosis of muscular subvalvular obstruction can be confirmed accurately by cardiac catheterization. The most reliable criterion is the presence of a zone of reduced systolic pressure in the infundibulum of the left ventricle (table 1). As the catheter is withdrawn across the narrowed outflow area the systolic pressure drops, but the diastolic pressure remains unchanged. When the aortic valve is traversed, the diastolic pressure rises but systolic levels remain unaltered. This phenomenon also has been described in patients with proved fibrous subaortic stenosis. Not uncommonly, a small gradient also may occur between the right ventricle and the pulmonary artery.

Consistently, in this series, a notch appeared on the ascending limb of the left ventricular pressure tracing. The exact mechanism for this phenomenon is not clear. It may be that blood is ejected at the inception of systolic contraction, as it is in the normal heart. However, with the approximation of the hypertrophied septum and left ventricle, an obstruction develops. This causes a momentary delay in ejection until greater systolic force can overcome the obstruction. This brief pause creates the left ventricular anacrotic notch. Braunwald and associates12 expressed the opinion that this anacrotic notch may signify a delayed onset of contraction of the sphincteric outflow tract.

Unlike the prolonged ascent of the central arterial pulse in aortic stenosis, patients with muscular obstruction demonstrate a rapid systolic upstroke. Commonly, the aortic curve has a secondary peak or what Brachfeld and Gorlin2 called a "tidal wave" form. The sharp systolic upsweep and the initial peak occur with early systolic contraction. Obstruction (with the resulting trough) follows and then the delayed ejection of blood occurs causing the secondary or tidal form.

After an extrasystole and a compensatory pause, five patients in this study exhibited a compensatory beat which in each case had a smaller pulse pressure than the control values for that patient. This is in contradistinction to the normal heart, in which one would anticipate a larger pulse pressure in the compensatory beat. Brockenbrough and Braunwald18 considered this phenomenon to be diagnostic of muscular subvalvular aortic obstruction. They postulated that the greater contractile

Figure 5
Cardiac catheterization tracings showing anacrotic notch on left ventricular pressure tracing and biferious aortic pulse (case 1).
Cardiac catheterization tracings showing small compensatory beat after extrasystole (case 6).

Table 1

Hemodynamic Data*

<table>
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<tr>
<th>Case</th>
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<th>Right ventricle</th>
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*One patient, a 59-year-old man, was not catheterized (case 8).

force of the compensatory beat forces the thickened musculature ever closer together. The severity of the outflow obstruction increases and the left ventricular stroke volume is reduced.

Pulsus alternans, an elevated pulmonary artery pressure, and left atrial contraction waves are findings that may occur with varying frequency and degree. Elevated end diastolic pressures in the left ventricle occurred fairly consistently in many of these cases, and may have been, as Braunwald and co-workers[12] suggested, the result of decreased compliance of the left ventricle.

Three patients (only one of whom is included in this study) did not demonstrate a left ventricular-aortic gradient at the time of surgical exploration. Preoperatively each had a significant gradient as well as other characteristic clinical and laboratory evidence of muscular subvalvular obstruction. In one case surgical correction was deferred, but at a later date this patient was examined at the National Heart Institute* where surgical exploration revealed diffuse muscular obstruction. The second patient, who had a clinical diag-

*National Institutes of Health, Bethesda, Maryland.

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nosis of mitral insufficiency, was operated on at the clinic. A systolic gradient of 70 mm. had been demonstrated across the region of the aortic valve, but none was evident at the time of operation. The surgical approach through the interatrial septum revealed a normal appearing subvalvular valve with a mild degree of regurgitation. In retrospect, the classic catheterization findings coupled with persistent symptoms and signs after operation suggest that the primary lesion was actually muscular subaortic obstruction. The third patient was found to have a consistent preoperative gradient of 100 mm. However, this could not be confirmed at operation. Exposure through a left ventricular incision revealed typical muscular subvalvular stenosis.

The reason for the disappearance of the gradient remains elusive. Condon and Lee described a patient with tetralogy of Fallot with infundibular pulmonic stenosis whose obstruction appeared to be relieved by cyclopropane anesthesia. It may be that when the patient is under anesthesia there is a reduction in cardiac output and in the force of systolic contraction. As a result the septum and left ventricle may not become so tightly approximated and the "functional" obstruction may diminish or disappear entirely.

Braunwald and associates noted the association of mitral insufficiency in 11 of the 12 cases of hypertrophic subaortic stenosis. They also found evidence suggesting mitral stenosis in one instance. The mitral valve did not show evidence of disease and this fact was attributed to distortion of the orifice secondary to myocardial hypertrophy. Goodwin and associates also considered infow obstruction to both ventricles as a manifestation of this disease. Mitral regurgitation was not significant in any of our surgical cases. At necropsy, endocarditis of the mitral valves was detected in one case; in the other two cases the mitral valves appeared normal. An angiocardiogram done in one patient showed a small reflux of contrast media through the mitral orifice into a dilated left atrium. As mentioned previously, one patient was operated on for mitral insufficiency and at a later date was recognized as having muscular subvalvular stenosis. These latter three cases support the premise that mitral valvular dysfunction may coexist with muscular outflow obstruction. However, a consistent, so-called functional regurgitation or stenosis was not apparent.

Pathologic Findings

The large size of the hearts on surgical examination and at necropsy further confirms the seriousness of this disease. The septum in the cases measured was at least one and a half times as thick as the left ventricle, a proportion far beyond that in the normal and hypertrophic hearts of the control group. The
Figure 9
Muscular subvalvular aortic stenosis (case 4). Note marked increase in width of ventricular septum in contrast to that of normal heart on right. Ruler lies at point of measurement 1.5 cm. from junction of muscular and membranous septa.

Figure 10
Muscular subvalvular aortic stenosis (case 5). Septal width after sectioning measured 3.1 cm.

average ratio of septal width to left ventricular thickness was 1.0, and in only a single instance did it exceed 1.25. This unusual thickness occurred coincidentally in a patient with a stenotic bicuspid aortic valve. In the event that this man had had a successful repair of his aortic valve, a significant residual obstruction probably would have developed.

These measurements indicate that knowledge of the relative width of the muscular septum and left ventricle helps significantly in establishing the diagnosis of muscular subvalvular obstruction. If the septal-ventricular ratio at necropsy exceeds 1.3, the presence of obstruction to left ventricular ejection prior to death should be suspected.

Some anatomic variation was observed in the three hearts evaluated at necropsy. In each case the muscular interventricular septum was diffusely thickened and subvalvular endocardial sclerosis was advanced. In one instance, however, the superior aspect of the septum formed a shelf that created the impression of greater apparent bulging of the upper septum into the outflow area. This latter case seems analogous to the concentric hypertrophy of the left ventricular outflow tract described by Brock and appears similar to one of the cases photographed in the series reported by Brent and associates.

Microscopic descriptions of hearts with diffuse muscular obstruction are few. Teare noted alterations in the arrangement of bundles of muscular fibers with variation in size and separation of some by clefts lined with endothelium. Walther and co-workers reported the cases of three young siblings having what appeared to be this same disease. On microscopic examination they noted hypertrophy of individual muscle fibers and areas of focal scarring. Brent and associates found hypertrophy of individual muscle fibers but not the increase in connective tissue described by the others. Only one of the preceding three cases examined microscopically demonstrated any significant abnormality as compared with the control group. In that one case the increase in connective tissue was minimal.
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Etiologic Findings

The cause of muscular subvalvular aortic obstruction remains a subject for conjecture. In none of the cases presented herein was there evidence to suggest that prenatal or postnatal factors were contributory. In the absence of any significant microscopic alteration, inflammation also would not seem a probable cause. The early sudden death from heart disease of the mothers of two patients further confirms suggestions previously made in the literature that this may be a familial disease.7, 9, 10, 12 However, the absence of any familial incidence in the other six cases detracts from this hypothesis.

Braunwald and associates12 similarly described patients with and without significant family histories. In addition, they reported that murmurs had been heard shortly after birth in three patients; they classified these cases as congenital in origin. Although not included in the preceding series, we also have studied three patients in whom this disease was noted at birth.20 Clinical studies in two revealed combined subvalvular aortic and infundibular pulmonic stenosis. The third was a stillborn infant. Anatomic evidence of biventricular obstruction of outflow was confirmed in all three—two at necropsy and one at surgical exploration. In each case there was hypertrophy of both ventricles with an enlarged crista supraventricularis and a greatly thickened muscular septum. In the two cases in which specific measurements were obtained the septal-left ventricular ratios were greater than 2. These cases may represent a variant or simply a greater degree of the disease process that produces the muscular obstruction of left ventricle we have described.

It would be an assumption to state that the gross thickening of the septum in these patients represents only cardiac hypertrophy of overwork. The asymmetric distribution of the muscle suggests that the primary abnormality actually may be developmental in origin. Perhaps for reasons unapparent, an abnormal amount of muscle becomes incorporated into the intraventricular ridge as it forms during the second gestational month. As a result, the fully developed septum is unusually wide, and with the obstruction that develops there is secondary myocardial hypertrophy.

Although familial and developmental factors appear to be implicated, present information is not sufficient to draw any positive conclusions as to etiology.

Summary

Muscular obstruction to left ventricular outflow is a rare but serious occurrence. Eight cases in which this disease was anatomically proved are presented. The commonest symptoms are angina, dyspnea, and palpitations. Not uncommonly a family history of heart disease may be elicited. A systolic murmur along the left sternal border is the most characteristic physical finding, but a normal aortic second sound, the presence of third and fourth heart sounds, splitting of the second sound, and the absence of a diastolic murmur are all helpful clinical guides. Withdrawal pressures from the left ventricle reveal a characteristic infundibular pressure zone. Other hemodynamic findings include an anacrotic notch on the left ventricular pressure tracing, a rapidly ascending bisferious aortic pulse and a small compensatory beat after extrasystoles.

Necropsy specimens reveal a grossly thickened interventricular septum as compared with normal and hypertrophied control hearts. Microscopic alterations are minimal. The etiology remains obscure but familial and developmental factors, either or both, appear to be implicated.

Acknowledgment

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References


3. Walsh, B. J., Connerty, H. V., and White,


It has often been said that, to make discoveries, one must be ignorant. This opinion, mistaken in itself, nevertheless conceals a truth. It means that it is better to know nothing than to keep in mind fixed ideas based on theories whose confirmation we constantly seek, neglecting meanwhile everything that fails to agree with them. Nothing could be worse than this state of mind; it is the very opposite of inventiveness. Indeed a discovery is generally an unforeseen relation not included in theory, for otherwise it would be foreseen.—CLAUDE BERNARD. An Introduction to the Study of Experimental Medicine. New York, The MacMillan Company, 1927, p. 37.
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