Muscular Subaortic Stenosis

The Direct Relation Between the Intraventricular Pressure Difference and the Left Ventricular Ejection Time

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SUMMARY

Left ventricular ejection time was correlated with the intraventricular pressure gradient in 35 cases of muscular subaortic stenosis in which simultaneous aortic and left ventricular pressure recordings were available. Ejection times were corrected for heart rate by dividing them by the square root of the cycle length. There was a direct relation between the degree of prolongation of the ejection time and the magnitude of the pressure gradient whether the latter varied spontaneously or followed surgical or pharmacological intervention. The only exceptions occurred in three of nine cases during stimulation of the gradient with isoproterenol.

In contrast, when an intraventricular pressure difference resulted from catheter entrapment in left ventricular myocardium in patients with nonobstructive cardiomyopathy, there was an inverse relation between ejection time and pressure difference, whether the latter varied spontaneously or following pharmacological intervention.

These studies provide further evidence that (1) two types of intraventricular pressure difference may be encountered within the left ventricle of man, and (2) the pressure difference in muscular subaortic stenosis results from obstruction to the left ventricular outflow.

Additional Indexing Words:
Catheter entrapment  Pharmacology of muscular subaortic stenosis  Isoproterenol
Amyl nitrite  Angiotensin  Norepinephrine

A difference in pressure within the left ventricle of man has characteristically been associated with muscular (or fibrous) subaortic stenosis, wherein the ventricular systolic pressure proximal to the stenosis exceeds that recorded distal to the stenosis. Within the past several years a number of reports1–10 have drawn attention to the fact that an intraventricular pressure difference may also be encountered when an intracardiac catheter becomes entrapped,5,6 enfolded, or embedded7 in cardiac muscle in systole and thereby records elevated left ventricular systolic pressure. Earlier reports record examples of this same phenomenon.11–15 Such catheter entrapment is most likely to occur when the left ventricular apex is emptied (obliterated) in early systole1–3,5,6 but may occur when a catheter is advanced to other portions of the left ventricular wall in such a manner that it is enfolded by cardiac muscle in systole.4,5,8,10 The suggestion has been made that the intraventricular pressure difference in muscular subaortic stenosis may not be the result of obstruction to left ventricular outflow, but rather of catheter entrapment.5,6

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MUSCULAR SUBAORTIC STENOSIS

In previous communications as to the nature of intraventricular pressure differences recorded in the left ventricle of man and dogs, Ross and associates\textsuperscript{16} and ourselves\textsuperscript{9, 10} have provided evidence that the measurement of the initial inflow tract pressure provided a means of differentiating an intraventricular pressure difference due to muscular subaortic stenosis from that due to catheter entrapment. In muscular subaortic stenosis, all ventricular pressures proximal to the stenosis including the pressure just inside the mitral valve (the initial inflow tract pressure\textsuperscript{9, 10}) were elevated above the outflow tract or aortic systolic pressure. In the intraventricular pressure difference due to catheter entrapment by cardiac muscle in man\textsuperscript{9, 10} and dogs,\textsuperscript{4, 7} the initial inflow tract pressure was not elevated but was precisely equal to outflow tract systolic pressure. Only the entrapped catheter recorded elevated left ventricular systolic pressure, which may reflect the high subendocardial intramyocardial tissue pressure.\textsuperscript{9, 10} Use of the initial inflow tract pressure measurement plus ancillary observations\textsuperscript{9, 10} has made it possible thus far prospectively to distinguish an intraventricular pressure difference due to muscular subaortic stenosis from that due to catheter entrapment. This method does not, however, allow us to ascertain retrospectively whether cases of muscular subaortic stenosis previously studied\textsuperscript{17, 18} and operated upon\textsuperscript{19, 20} did in fact have obstruction to left ventricular outflow.

Prolonged left ventricular ejection time has been a recognized feature of valvular aortic stenosis for more than 40 years.\textsuperscript{21-31} Similarly, there is prolongation of left ventricular ejection time in both fibrous and muscular subaortic stenosis.\textsuperscript{22, 25, 26, 29, 32} The prolonged left ventricular ejection time in muscular subaortic stenosis is, in itself, supportive evidence that the intraventricular pressure difference is due to an obstruction to left ventricular outflow.

It appeared important, however, to ascertain whether the degree of prolongation of left ventricular systole bore any relation to the magnitude of the intraventricular pressure difference in muscular subaortic stenosis and whether there was a relation between the ejection time and pressure difference when the latter varied spontaneously or varied after surgical or pharmacological intervention. This report describes such a study in the series of patients diagnosed as having muscular subaortic stenosis in this laboratory over the past 6 years.\textsuperscript{17, 18} In addition, the relation of left ventricular ejection time to the magnitude of the intraventricular pressure difference due to catheter entrapment is analyzed.

Methods

All patients diagnosed as having muscular subaortic stenosis in this laboratory by clinical and hemodynamic methods were reviewed. Thirty-five of these patients, for whom simultaneous left ventricular and aortic pressure recordings were available and in whom the aortic dicrotic notch was clearly defined, were studied further. In each of these patients the left ventricular ejection time was measured from the onset of the aortic pressure rise to the dicrotic notch. Each ejection time was corrected for heart rate by dividing it by the square root of the cycle length. The reported ejection time corrected for heart rate is the mean of three such determinations in each case. The corresponding linear left ventricular-aortic systolic pressure difference was measured. In several of these patients in whom this pressure difference varied with respiration,\textsuperscript{33} multiple corrected ejection times were correlated with the spontaneously changing magnitude of the pressure gradient.

Twelve of these patients inhaled amyl nitrite\textsuperscript{34} during the hemodynamic investigation; isoproterenol\textsuperscript{35} was infused into nine patients, angiotensin\textsuperscript{36, 37} into seven, and norepinephrine\textsuperscript{38-39} into two. Before and during each of these pharmacological interventions, corrected left ventricular ejection time was again correlated with the magnitude of the pressure gradient.

Similarly, preoperative and postoperative corrected left ventricular ejection times and pressure gradients in 10 patients undergoing ventriculomotomy\textsuperscript{10, 20} were assessed. Three other patients have been studied postoperatively,\textsuperscript{20} but the preoperative hemodynamic studies were carried out elsewhere.

In addition to these studies in patients diagnosed as having muscular subaortic stenosis, similar studies were carried out in five patients with nonobstructive cardiomyopathy in whom an intraventricular pressure difference due to catheter entrapment was recorded.\textsuperscript{9, 10} The relation of
The relation between left ventricular ejection time corrected for heart rate (E.T.c.) and the left ventricular (LV)-aortic systolic pressure difference in 35 cases of muscular subaortic stenosis. With increasing magnitude of the pressure gradient there is progressive prolongation of ejection time as would be expected with an obstruction to left ventricular outflow.

The relationship between corrected left ventricular ejection time (E.T.c.) and left ventricular (LV)-aortic systolic pressure difference in a patient with muscular subaortic stenosis (M.S.S., circles) and in a patient in whom there was an intraventricular pressure difference due to catheter entrapment (squares). In both patients the pressure difference varied spontaneously with respiration. With increasing magnitude of the pressure difference in muscular subaortic stenosis there is progressive prolongation of the ejection time (direct relationship) whereas when the pressure difference due to catheter entrapment increased, there is shortening of the ejection time (an inverse relationship) (see text).

Results

In muscular subaortic stenosis the degree of prolongation of left ventricular ejection time was directly related to the magnitude of the intraventricular pressure difference (fig. 1). When this pressure difference varied spontaneously during respiration in any one case, the linear correlation between the ejection time and the pressure difference was even more striking (fig. 2, top). In contrast to this state of affairs in muscular subaortic stenosis, when an intraventricular pressure difference due to catheter entrapment varied with respiration in a patient with nonobstructive cardiomyopathy, there was an inverse relationship between the ejection time and the magnitude of the pressure difference (fig. 2, bottom). This latter relation might be expected in these circumstances, because the shorter ejection time would reflect more rapid ventricular emptying which would result in greater catheter entrapment and the recording of higher pressure by this catheter.

Inhalation of amyl nitrite in patients with muscular subaortic stenosis invariably resulted in an increase in the pressure gradient and a prolongation of left ventricular ejection time (fig. 3). When a transseptal left ventricular
catheter was positioned against the left ventricular wall in three of the patients with nonobstructive cardiomyopathy, the inhalation of amyl nitrite resulted in the appearance of an intraventricular pressure difference that was associated with a shortened left ventricular ejection time (fig. 3). This type of elevated left ventricular pressure was believed to have resulted from catheter entrapment by cardiac muscle as the result of enhanced ventricular emptying due to the amyl nitrite-induced vasodilatation.

Infusion of angiotensin or norepinephrine into patients with muscular subaortic stenosis

**Figure 3**

The relation between corrected left ventricular ejection time (E.T.c.) and the left ventricular (LV)-aortic systolic pressure difference in 12 patients with muscular subaortic stenosis before (solid circles) and after (open circles) amyl nitrite inhalation. In every case there was prolongation of ejection time associated with an increase in the magnitude of the pressure difference. The two patients showing the least prolongation of ejection time failed to develop a significant increase in heart rate suggesting an incomplete response to the drug.

In three patients with nonobstructive cardiomyopathy there was no intraventricular pressure difference when the transseptal catheter was in contact with the left ventricular wall (solid squares). When these patients developed an intraventricular pressure difference due to catheter entrapment following amyl nitrite inhalation (open squares) the left ventricular ejection time shortened in each instance (see text).

**Figure 4**

The relation between the corrected left ventricular ejection time (E.T.c.) and left ventricular (LV)-aortic systolic pressure difference (increasing from right to left on the abscissa) in patients with muscular subaortic stenosis (M.S.S.) before (solid circles) and after (open circles) the infusion of angiotensin (solid line) and norepinephrine (dashed line). These same relationships are shown for three patients with an intraventricular pressure difference due to catheter entrapment before (solid squares) and after (open squares) infusion of angiotensin (solid line) and norepinephrine (dashed line). In muscular subaortic stenosis the infusion of these two drugs shortened ejection time while reducing or abolishing the intraventricular pressure difference, whereas these drug infusions prolonged ejection time and had a variable effect on the intraventricular pressure difference due to catheter entrapment (see text).
The relation between corrected left ventricular ejection time (E.T.c.) and left ventricular (LV)-aortic systolic pressure difference (increasing from right to left on the abscissa) in 10 patients with muscular subaortic stenosis before (solid circles) and after (open circles) undergoing the ventriculotomy operation. When the pressure gradient was reduced or abolished surgically, there was a concomitant reduction in left ventricular ejection time (see text).

Invariably reduced or abolished the pressure gradient and shortened left ventricular ejection time (fig. 4). In the presence of an intraventricular pressure difference due to catheter entrapment, the infusion of angiotensin into one patient abolished the pressure difference and prolonged the ejection time. Norepinephrine infusion in two such patients prolonged the ejection time in both instances.

The relation between corrected left ventricular ejection time (E.T.c.) and left ventricular (LV)-aortic systolic pressure difference in nine cases of muscular subaortic stenosis (M.S.S.) before (solid circles) and after (open circles) infusion of isoproterenol. The same relationships in two cases with an intraventricular pressure difference due to catheter entrapment are shown before (solid squares) and after (open squares) isoproterenol infusion. Of the nine patients with muscular subaortic stenosis, when the pressure gradient increased during isoproterenol infusion, the ejection time was prolonged in six, essentially unchanged in one (B) and shortened in two (A and C). The unchanged or shortened ejection times in the isoproterenol-induced increase in the pressure gradient in cases A, B, and C were the only instances in this study in which there was not a direct relationship between ejection time and pressure gradient. Table I, however, demonstrates that in cases A, B, and C the direct relationship between ejection time and pressure gradient was maintained during all other pharmacological interventions in these three cases. An isoproterenol-induced intraventricular pressure difference due to catheter entrapment was associated with a shortened ejection time.
Table 1
Pharmacological Interventions in Cases A, B, and C (Fig. 6)

<table>
<thead>
<tr>
<th>Case</th>
<th>Intervention</th>
<th>L.V. pressure gradient (mm Hg)</th>
<th>E.T.c. (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Control</td>
<td>84</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol</td>
<td>131</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Angiotensin</td>
<td>100</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Amyl nitrite</td>
<td>76</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101</td>
<td>0.45</td>
</tr>
<tr>
<td>B</td>
<td>Control</td>
<td>65</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Angiotensin</td>
<td>22</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>84</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>0</td>
<td>0.34</td>
</tr>
<tr>
<td>C</td>
<td>(8/25/64)</td>
<td>65</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Angiotensin</td>
<td>5</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>55</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Amyl nitrite</td>
<td>91</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>50</td>
<td>0.344</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol</td>
<td>77</td>
<td>0.345</td>
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<tr>
<td>C</td>
<td>(11/7/63)</td>
<td>45</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol</td>
<td>75</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Control</td>
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<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>0</td>
<td>0.29</td>
</tr>
</tbody>
</table>

The data in this table from three patients with muscular subaortic stenosis marked A, B, and C in figure 6 indicate that in each case there was a direct relationship between the left ventricular ejection time (E.T.c.) and the magnitude of the intraventricular pressure gradient with all pharmacological interventions except during isoproterenol infusion. The order in which the various pharmacological agents were administered is numbered. Control measurements were made prior to each intervention. Case B was studied on two occasions. (See fig. 6 and text.)

while decreasing the pressure difference in one and increasing it in the other (fig. 4).

In the 10 patients with muscular subaortic stenosis undergoing ventriculomyotomy the surgical abolition (eight patients) or reduction (two patients) of the pressure gradient produced an invariable and dramatic reduction in left ventricular ejection time (fig. 5). Thus in muscular subaortic stenosis there was a direct relation between left ventricular ejection time and pressure gradient (fig. 1) whether the latter varied spontaneously (fig. 2) or as a result of pharmacological (figs. 3 and 4) or surgical (fig. 5) intervention.

Figure 6 plots the relation between left ventricular ejection time and intraventricular pressure difference during isoproterenol infusion in nine patients with muscular subaortic stenosis and in two patients with an intraventricular pressure difference due to catheter entrapment. In the latter two instances the ejection time shortened as the pressure difference increased, whereas in six of nine patients with muscular subaortic stenosis the ejection time became markedly prolonged as the pressure gradient increased. One patient with muscular subaortic stenosis (B, fig. 6) showed essentially no change in ejection time when the gradient was increased during isoproterenol infusion and two patients (A and C, fig. 6) showed a definite decrease in ejection time with an isoproterenol-induced increase in the pressure gradient. Because patients A, B, and C (fig. 6), during isoproterenol infusion, were the only patients with muscular subaortic stenosis, who did not have a direct relation between left ventricular ejection time and pressure gradient, the reactions of these patients to the other pharmacological agents were reviewed. Table 1 demonstrates that during variation of the pressure gradient in cases A, B, and C (fig. 6) by pharmacological agents other than isoproterenol, there was a direct relation between ejection time and pressure gradient.

Discussion

These studies indicate that in muscular subaortic stenosis the left ventricular ejection time was prolonged in direct relation to the magnitude of the intraventricular pressure difference and this direct relation persisted when the pressure difference varied spontaneously or as the result of surgical or pharmacological intervention. The only exception to this direct relation was encountered in three of nine patients with muscular subaortic stenosis to whom isoproterenol was administered. In these three patients, during administration of other pharmacological agents to increase (amyl nitrite) or decrease (angiotensin, norepinephrine) the pressure difference, a direct
relation between ejection time and pressure difference was observed. The fact that this direct relationship between ejection time and pressure difference was preserved during other pharmacological interventions leads us to conclude that these three patients do not differ from the other patients with muscular subaortic stenosis, but rather that the shortened ejection time during isoproterenol infusion was in some way related to the complex cardiovascular actions of isoproterenol.9

In two of these three patients (A and B, fig. 6) the careful assessment of the initial left ventricular inflow tract pressure revealed that this pressure was elevated above the aortic systolic pressure, a characteristic of muscular subaortic stenosis.9, 10 The inflow tract pressure was not assessed in case C (fig. 6). Cohn and Hancock10 have previously observed that an amyl nitrite-induced increase in the pressure difference in muscular subaortic stenosis was associated with a greater increase in left ventricular ejection time than was the case with an isoproterenol-induced increase in this pressure difference.

The fact that prolongation of left ventricular ejection time was directly related to the magnitude of the intraventricular pressure difference in muscular subaortic stenosis was believed to provide strong evidence that the pressure difference recorded in this condition resulted from an obstruction to left ventricular outflow. The generally inverse relation between the left ventricular ejection time and the magnitude of the intraventricular pressure difference due to catheter entrapment in cardiac muscle enhanced this belief. Thus, in this study the left ventricular ejection time was shortened when the intraventricular pressure difference due to catheter entrapment increased spontaneously or during administration of amyl nitrite or isoproterenol. The enhanced pressure difference in these circumstances was believed to result from exaggerated early systolic emptying of the left ventricle with resultant increased entrapment of the catheter by the myocardium. The infusion of angiotensin or norepinephrine prolonged the ejection time in nonobstructive cardiomyopathy, but shortened it in muscular subaortic stenosis. In one of the two patients with nonobstructive cardiomyopathy receiving norepinephrine, the intraventricular pressure difference due to catheter entrapment decreased but in the second it increased. This variable result is believed to be explicable on the basis of the opposing effects of norepinephrine on this type of intraventricular pressure difference. Thus, the positive inotropic effect would accentuate ventricular emptying and favor catheter entrapment, whereas the vasoconstrictive effect would retard ventricular emptying and make catheter entrapment less likely to occur. Depending on which effect was predominant, an intraventricular pressure difference due to catheter entrapment could be increased or decreased. Evidence previously presented supported the belief that the norepinephrine-induced intraventricular pressure difference due to catheter entrapment in dogs resulted from the dominance of the positive inotropic over the vasoconstrictive properties of this drug.7 In muscular subaortic stenosis, on the other hand, the abolition of the intraventricular pressure difference by norepinephrine or angiotensin was considered related to the vasoconstrictive properties of these drugs.56-38

The invariable reduction in left ventricular ejection time that accompanied the reduction or abolition of the pressure gradient following ventriculotomy is important evidence supporting the obstructive nature of muscular subaortic stenosis. This postoperative reduction in ejection time and pressure gradient occurred whether or not the ventriculotomy incision produced a ventricular conduction defect.41 Proponents of the view that the intraventricular pressure difference in muscular subaortic stenosis may result from catheter entrapment have suggested that the surgical abolition of this pressure difference may result from a retarded and less complete emptying of the ventricle, making catheter entrapment less likely.6 The shortened postoperative ejection time in muscular subaortic stenosis is a strong argument against this nonobstructive reasoning.
The results of this study have provided evidence of the obstructive nature of muscular subaortic stenosis and also have permitted a retrospective review of the cases that we have investigated and treated prior to knowing that an intraventricular pressure difference may result from catheter entrapment in muscle, as well as from muscular subaortic stenosis. This retrospective study of our case material, demonstrating the direct relationship between ejection time and pressure gradient, leads us to conclude that patients diagnosed as having muscular subaortic stenosis in this laboratory have truly had an obstruction to left ventricular outflow. This statement is enhanced by the fact that eight of the patients with muscular subaortic stenosis showing a direct relationship between ejection time and pressure gradient have also had an elevated initial left ventricular inflow tract pressure.

In the course of this review we came upon one case in which an intraventricular pressure difference followed amyl nitrite inhalation but in which there was no such pressure difference at rest. The ejection time in this case shortened with the development of the pressure difference and we concluded that the pressure difference in this case was most likely due to catheter entrapment in cardiac muscle.

Mitral insufficiency is known to shorten left ventricular ejection time. This observation made the prolonged ejection time in muscular subaortic stenosis even more notable since mitral insufficiency was an almost invariable accompaniment of this form of obstruction to left ventricular outflow, and in any one case the severity of the mitral leak was directly related to the magnitude of the pressure gradient.

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