The Effect of Nitroglycerin on Left Ventricular Wall Tension in Fixed Orifice Aortic Stenosis

By Joseph G. Perloff, M.D., James A. Ronan, Jr., M.D., and Antonio C. de Leon, Jr., M.D.

SYMPTOMS of myocardial ischemia occur in patients with either acquired or congenital aortic stenosis.1-8 The presence of normal coronary arteries in many of these subjects suggests that the cause of the cardiac pain relates to left ventricular outflow obstruction and not to coronary artery disease.1, 2, 5, 8 Opinion differs regarding the symptomatic response of the chest pain to nitroglycerin,9, 10 and the drug's mode of action in this clinical context is unclear. Increased left ventricular wall tension—a principal determinant of myocardial oxygen consumption (qO₂)11—may contribute to the occurrence of aortic stenotic angina. Nitroglycerin has been shown to diminish left ventricular work12, 13 and to decrease ventricular dimensions in man.14 These pharmacologic effects should reduce myocardial oxygen requirements.11, 14 Whether the drug has similar effects in the presence of fixed obstruction to left ventricular outflow has not been examined in detail. This investigation was accordingly undertaken to study the influence of sublingual nitroglycerin on left ventricular wall tension in patients in whom fixed orifice aortic stenosis was the sole hemodynamic fault.

Materials and Methods

Studies were conducted on eight patients (table 1), six male and two female, ranging in age from 16 to 63 years. Six had rheumatic valvular aortic stenosis and two were congenital (one valvular and one discrete subvalvar). All patients had typical clinical features of uncomplicated aortic stenosis. Five experienced angina, six had exertional dyspnea, four had syncopal episodes, and one was asymptomatic. The degrees of obstruction ranged from mild to severe. For purposes of comparison, data were obtained from one patient (case 9) with muscular subaortic stenosis.

The diagnoses of fixed orifice obstruction were

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<tr>
<td><strong>Clinical Information</strong></td>
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<td>Case</td>
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based upon the hemodynamic criteria of Brockenbrough et al. In six instances the diagnoses were further confirmed at open operation. Left heart catheterizations were performed by the percutaneous transseptal technic and cardiac outputs were determined by the dye-dilution method. The dose of sublingual nitroglycerin was 0.4 mg. in four patients and 0.6 mg. in four. Pressures in the brachial artery and left ventricle were recorded continuously before and after the drug was given. Observations were made for 10 to 30 minutes following administration of the drug. Immediately before the drug was given, cardiac outputs were done by left ventricular injection of indocyanine green dye. The outputs were repeated at intervals which appeared to represent periods of significant hemodynamic response. The following variables were measured: brachial arterial pressure, heart rate, left ventricular peak and mean systolic pressures, left ventricular end-diastolic pressure, peak and mean systolic gradients, cardiac index, aortic valve area, left ventricular stroke and minute work, and systolic ejection period. The tension-time index per beat in mm. Hg seconds was calculated by multiplying the left ventricular systolic mean pressure by the duration of systole. The tension-time index per minute was the product of the tension-time index per beat and the heart rate.

Statistical analyses: The data were evaluated by applying Student's t test with use of paired sample analyses rather than the differences between the control and experimental means.17

Results

Patients 1 through 7 formed a homogeneous group with similar directional changes in the measured variables (table 2). However, in patient 8 (surgically proven congenital valvular stenosis) the hemodynamic response to nitroglycerin differed markedly and was in fact similar to the response described in muscular subaortic stenosis as illustrated in case 9.

Patients 1 through 7

Systemic arterial pressure. The brachial arterial systolic pressure fell without exception with an average decline of 15 per cent \((p < 0.01)\). The diastolic pressure decreased by an average of 8 per cent \((p < 0.05)\).

Left ventricular systolic pressure. An average decline of 8 per cent in left ventricular peak systolic pressure was not significant \((p < 0.1)\) although notable individual varia-

tions occurred. In case 3 the systolic pressure rose slightly and at no point fell below control levels. In cases 6 and 7 the systolic pressures declined by 42 and 28 mm. Hg, respectively, but during the course of the observations each rose above control levels by 16 and 12 mm. Hg. On the other hand, left ventricular mean systolic pressure significantly and uniformly decreased (average 13 per cent, \(p < 0.01\)) irrespective of the directional change in peak pressure (fig. 1).

Transvalvular gradient. The average change
Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>BA</th>
<th>L.V. mm. Hg</th>
<th>Gradient, mm. Hg</th>
<th>C.I., L./min./M.²</th>
<th>Str. vol. index, ml./M.²</th>
<th>Valve area, cm.²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm. Hg</td>
<td>Peak</td>
<td>systolic</td>
<td>EDP</td>
<td>Peak</td>
<td>Mean</td>
</tr>
<tr>
<td>Cont.</td>
<td>118/68</td>
<td>212</td>
<td>20</td>
<td>94</td>
<td>67</td>
<td>2.32</td>
</tr>
<tr>
<td>1 NTG</td>
<td>106/71</td>
<td>198</td>
<td>12</td>
<td>92</td>
<td>62</td>
<td>2.04</td>
</tr>
<tr>
<td>Cont.</td>
<td>104/72</td>
<td>186</td>
<td>14</td>
<td>82</td>
<td>54</td>
<td>2.94</td>
</tr>
<tr>
<td>2 NTG</td>
<td>84/60</td>
<td>167</td>
<td>5</td>
<td>83</td>
<td>55</td>
<td>2.75</td>
</tr>
<tr>
<td>78/58</td>
<td>183</td>
<td>4</td>
<td>104</td>
<td>60</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>189</td>
<td>9</td>
<td>81</td>
<td>46</td>
<td>2.97</td>
</tr>
<tr>
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<td>88/64</td>
<td>202</td>
<td>10</td>
<td>114</td>
<td>56</td>
<td>2.55</td>
</tr>
<tr>
<td>Cont.</td>
<td>134/84</td>
<td>240</td>
<td>8</td>
<td>106</td>
<td>72</td>
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</tr>
<tr>
<td>4 NTG</td>
<td>112/80</td>
<td>186</td>
<td>5</td>
<td>74</td>
<td>41</td>
<td>2.0</td>
</tr>
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<td>198</td>
<td>19</td>
<td>89</td>
<td>65</td>
<td>1.6</td>
</tr>
<tr>
<td>5 NTG</td>
<td>98/57</td>
<td>189</td>
<td>14</td>
<td>91</td>
<td>59</td>
<td>1.7</td>
</tr>
<tr>
<td>Cont.</td>
<td>135/60</td>
<td>219</td>
<td>14</td>
<td>84</td>
<td>61</td>
<td>3.7</td>
</tr>
<tr>
<td>6 NTG</td>
<td>106/54</td>
<td>235</td>
<td>7</td>
<td>129</td>
<td>76</td>
<td>—</td>
</tr>
<tr>
<td>111/59</td>
<td>177</td>
<td>7</td>
<td>66</td>
<td>39</td>
<td>3.4</td>
<td>37.8</td>
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<tr>
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<td>106/67</td>
<td>253</td>
<td>20</td>
<td>147</td>
<td>90</td>
<td>—</td>
</tr>
<tr>
<td>7 NTG</td>
<td>100/62</td>
<td>225</td>
<td>8</td>
<td>125</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>97/68</td>
<td>265</td>
<td>8</td>
<td>168</td>
<td>97</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cont.</td>
<td>116/69</td>
<td>213</td>
<td>15</td>
<td>97</td>
<td>65</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Aver.

NTG 99/63 194 9 95 56 2.4 25.08 0.58

% Change —15/-8 —8 —40 NIL —14 —11 —17 —9

p Value <0.01/<0.05 <0.1 <0.02 <0.9 <0.3 <0.1 >0.02 <0.1

Cont. 131/84 178 8 47 42 2.9 36.25 0.9

8 NTG 125/86 246 6 121 62 — — —

Cont. 136/88 160 4 24 20 2.6 41.27 1.9

9 NTG 92/74 246 20 154 96 — — —

Cont. 136/82 206 8 70 63 2.4 24.0 0.7

in peak gradient was nil although individual variations occurred. In cases 1, 4, and 5 the peak gradients remained unaltered or persistently fell. In cases 2 and 3 the gradients rose 22 and 33 mm. Hg, respectively, above control levels. In cases 6 and 7, the gradients declined 18 and 22 mm. Hg, respectively, but during the course of observation each rose above control levels by 45 and 21 mm. Hg. The average decline in mean systolic gradient was 14 per cent but the change was not significant (p < 0.3). In cases 1, 4, 5, and 7 the mean gradient remained essentially unchanged or persistently fell. In cases 2 and 3 there were rises of 6 to 10 mm. Hg above control levels. In case 6 the mean gradient rose 15 mm. Hg but during the course of observation it declined 18 mm. Hg below the control.

Left ventricular diastolic pressure. The left ventricular end-diastolic pressure declined an average of 40 per cent (p < 0.02) with no significant alteration in case 3 (fig. 2).

Cardiac output. There was a slight decrease in cardiac index in each patient, but there was no change in case 5 with a critically low

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control output. The average decrease of 11 per cent was, however, not significant ($p < 0.1$). The decline in cardiac index together with the increase in heart rate resulted in an average decline of 17 per cent in stroke volume index ($p > 0.02$).

Aortic orifice size. There was no significant change in calculated aortic valve areas.

Left ventricular work. A uniform decline in actual left ventricular stroke work occurred, with an average decrease of 26 per cent ($p < 0.05$). The effective stroke work declined similarly (average 27 per cent, $p < 0.02$) except in case 5 with no change. The actual and effective left ventricular minute work fell, except in case 5 with severe stenosis and a critically low control cardiac output.

Heart rate. The heart rate either remained constant or increased by an average of 7 per cent ($p > 0.05$).

Duration of systole. The systolic ejection period decreased in each case with an average decline of 21 per cent ($p < 0.01$, fig. 3).

Tension-time index. The uniform decrease in both systolic ejection period and left ventricular mean systolic pressure resulted in a
significant decrease in tension-time index per beat (−21 per cent, \( p < 0.001 \)) and per minute (−25 per cent, \( p < 0.01 \)) with no individual exceptions (figs. 4 and 5). The tension-time index diminished even in patients 2, 3, 6, and 7, in whom left ventricular peak sys-

tolic pressures or peak-mean gradients had increased.

Patient 8 was a 16-year-old boy with hemodynamic criteria of fixed orifice aortic stenosis. At open operation (Dr. Charles A. Huf-nagel) the aortic valve was functionally bi-
cuspid; the commissures between the left and right coronary cusps were completely fused. There was moderate fusion of the commis-
sures between the left and noncoronary and between the right and noncoronary cusps causing moderate obstruction. Observations of the subvalvular area were made but there was no evidence of discrete subvalvular ob-
struction. During the preoperative diagnostic studies, this patient responded to nitroglycerin with marked increases in left ventricular peak and mean systolic pressures, parallel increases in the duration of systole and in the peak-
mean systolic gradients, and considerable in-
creases in tension-time index per beat and per minute (table 2). These changes were similar in direction and magnitude to those.

In cases 1 through 7 the left ventricular end-diastolic pressure declined (average fall 40 per cent, \( p < 0.02 \)). In case 8 the left ventricular end-diastolic pressure also declined, even though responses of other measured variables in this case resembled the directional changes seen in muscular subaortic stenosis (case 9).
Occurrence of pain in patients with aortic stenosis but with normal coronary arteries suggests that symptoms of myocardial ischemia relate to the left ventricular outflow obstruction per se and not to coronary artery disease.\textsuperscript{1, 2, 5, 8} Angina is generally considered a reflection of disparities between myocardial oxygen requirements on the one hand and myocardial oxygen availability on the other.\textsuperscript{19} It therefore follows that lesions such as aortic stenosis, which cause

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{In cases 1 through 7 the tension-time index per beat diminished (average decrease 21 per cent, \(p < 0.001\)). In case 8 the tension-time index increased as it did in case 9, with muscular subaortic stenosis.}
\end{figure}

observed in patient 9, the 33-year-old man with classic muscular subaortic stenosis.

\section*{Discussion}
Cardiac pain is an established symptom in both congenital and acquired fixed orifice aortic stenosis.\textsuperscript{1–8} The type of pain may resemble angina pectoris\textsuperscript{9} although departures from the characteristic descriptions of angina are common.\textsuperscript{10} In cases 1 through 7 the tension-time index per minute decreased (average fall 25 per cent, \(p < 0.01\)). In case 8 the tension-time index rose as it did in case 9, with muscular subaortic stenosis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{In cases 1 through 7 the tension-time index per minute decreased (average fall 25 per cent, \(p < 0.01\)). In case 8 the tension-time index rose as it did in case 9, with muscular subaortic stenosis.}
\end{figure}
substantial increases in myocardial oxygen needs, may in their own right seriously challenge the capacity of the coronary bed to provide these increments in oxygen requirements. Investigators beginning with Starling and Visscher have been interested in defining factors that influence myocardial need for oxygen. In 1937, Contratto and Levine postulated that oxygen consumption depends upon cardiac work and that cardiac work is increased in aortic stenosis. In human subjects, a direct relationship between the pressure work of the heart and myocardial oxygen requirements has been described. Sarnoff and his collaborators, in more detailed studies, concluded that "in any given functional state of the beating heart, the mean systolic pressure times the duration of systole is the principal, if not the sole determinant, of myocardial oxygen utilization." In aortic stenosis, both the left ventricular systolic mean pressure and the duration of systole are characteristically prolonged. The product of these two variables, the tension-time index, must then necessarily rise, so that aortic stenosis should be accompanied by an increase in myocardial oxygen requirements. Furthermore, it is reasonable to infer that the severer the obstruction is, the greater the tension-time index, the greater the \( q_{O_2} \), the less favorable the margin between oxygen need and oxygen availability, and the more likely the occurrence of cardiac pain. Coexisting coronary artery disease, by hindering oxygen delivery, presents an added handicap. Exercise, by increasing the heart rate as well as the left ventricular systolic mean pressure, increases the tension-time index both per minute and per beat and hence poses an additional burden. However, because of the occasional occurrence of angina in patients with mild aortic stenosis and normal coronary arteries, an alternate explanation relating inadequate coronary flow to the sucking effect of the aortic jet has been proposed. Nevertheless, drugs that diminish the tension-time index without significantly reducing coronary blood flow should favorably influence the myocardial oxygen balance in aortic stenosis.

The effect of nitrites on decreasing cardiac work was suggested by Sir Lauder Brunton in 1897. The importance of this pharmacologic property of nitroglycerin has been subsequently affirmed and more recently has been emphasized as a major contribution to the relief of angina. In aortic stenosis, nitroglycerin has been reported to decrease left ventricular minute work and to decrease left ventricular peak systolic pressure. These observations were limited and further details relating to ventricular wall tension were not provided.

In this study (table 2, cases 1 through 7) nitroglycerin caused left ventricular stroke and minute work to diminish, except in case 5 (with a critically reduced control cardiac index), in which these directional changes were slight. More significant, however, was the consistent effect of nitroglycerin on tension-time index. In each of these seven patients tension-time index both per beat and per minute materially decreased (table 2, figs. 4 and 5). This decrease was due to a uniform fall in left ventricular systolic mean pressure (fig. 1) as well as to a uniform shortening of the duration of systole (fig. 3). There was a decline in tension-time index per minute despite moderate accelerations of heart rate (table 2). It appeared, therefore, that nitroglycerin administered under the conditions of these studies caused a significant decrease in left ventricular wall tension and should accordingly cause a decline in left ventricular oxygen requirements. This favorable response should apply unless the drug-induced fall in systemic blood pressure results in a disproportionate decrease in coronary perfusion. Gorlin and co-workers have indicated that when nitroglycerin was given to patients with increased left ventricular work, the coronary flow either remained unchanged or decreased. However, the magnitude of the decline was small. In the dog, nitroglycerin does not reduce coronary blood flow during its hypotensive effect on arterial pressure because it concurrently dilates the coronary arteries.

Left ventricular systolic size has been considered an important variable in determining
transmural tension because, according to the law of Laplace, wall tension varies directly with the square of the radius of a theoretically spherical ventricle. Cineradiographic methods that permit direct measurements of radiopaque tantalum clips on the surface of the ventricles have shown that nitroglycerin reduces left ventricular systolic and diastolic size in human subjects. Indirect evidence of a decrease in heart size has been inferred from the fall in diastolic filling pressure of both ventricles as well as from the decline in venous return. Furthermore, in patients with idiopathic hypertrophic subaortic stenosis, reduction in left ventricular systolic size is considered the mechanism by which nitroglycerin augments the degree of obstruction. Although the slight decrease in cardiac output following nitroglycerin in aortic stenosis (table 2) may reflect a decline in venous return, it is not clear whether changes of such small order exert a significant effect on ventricular dimensions. In this study (table 2, cases 1 through 7) nitroglycerin tended to decrease the left ventricular diastolic filling pressure, particularly when it was initially elevated (fig. 2). If a reduction in left ventricular systolic size were to accompany this decline in filling pressure, it would then follow that nitroglycerin could diminish wall tension by its effect on left ventricular dimensions as well as by its effect on tension-time index.

In muscular subaortic stenosis, nitroglycerin augments the gradient by increasing left ventricular systolic pressure while systemic systolic pressure falls. On the other hand, in fixed orifice aortic stenosis a decline in left ventricular systolic pressure has been reported to accompany the fall in systemic pressure so that no rise in peak transvalvular gradient occurs. It was of interest, therefore, that in four patients (table 2, cases 2, 3, 6, and 7) the peak systolic gradients rose 21 to 45 mm. Hg above control levels, either because left ventricular systolic pressure temporarily increased or because it failed to decline in parallel with brachial systolic pressure. One observation deserves separate comment because the response to nitroglycerin deviated so markedly from the relatively uniform results obtained in cases 1 through 7. The patient was a 16-year-old boy with surgically proven congenital valvular aortic stenosis operated upon because of progressive left ventricular hypertrophy even though the calculated orifice size was 0.9 cm. (table 2). During the preoperative diagnostic study, the peak transvalvular gradient rose from 47 to 121 mm. Hg after nitroglycerin. There were persistent substantial increases in left ventricular peak and mean systolic pressures (fig. 1), in mean systolic gradient, and in tension-time index both per beat and per minute (figs. 4 and 5). In addition, the Valsalva maneuver augmented the gradient by 66 mm. Hg. These changes were similar in direction and magnitude to those induced by nitroglycerin in muscular subaortic stenosis. Hemodynamic data from a 33-year-old man (case 9) with muscular subaortic stenosis are listed for comparison (table 2, figs. 1-5). Significantly, however, the brachial arterial pulse pressure following premature beats remained unchanged or rose in case 8, but consistently declined in case 9. These responses are considered diagnostic of fixed orifice and muscular subaortic stenosis, respectively. Attention has been called to secondary subvalvular hypertrophy in some patients with discrete aortic stenosis and one such patient had hemodynamic features of muscular subaortic stenosis following surgical relief of the fixed obstruction. In case 8, the hemodynamic response to nitroglycerin may have been determined by the presence of secondary hypertrophic subaortic stenosis in a patient with congenital valvular obstruction.

The observed nitroglycerin-induced reduction in tension-time index and the inferred reduction in left ventricular dimensions should cause myocardial oxygen needs to decrease in fixed orifice aortic stenosis and should thus favorably influence the balance between oxygen availability and oxygen requirements. Since chest pain did not occur during our observations, direct inferences regarding the action of nitroglycerin on aortic stenotic angina cannot be drawn, although the influence
should be beneficial if the effect of the drug on myocardial oxygen requirements during anginal attacks were similar to its effect during asymptomatic intervals. This conclusion is consistent with impressions that nitroglycerin relieves the cardiac pain of both aortic stenosis and coronary artery disease. However, others have indicated that aortic stenotic angina is not characteristically modified by nitroglycerin. Should the drug succeed in reducing myocardial oxygen requirements to a level commensurate with oxygen availability, a salutory symptomatic result might ensue. On the other hand, it is possible that this optimal level cannot be uniformly achieved despite significant reduction in oxygen needs. Furthermore, an occasional patient—perhaps one with secondary hypertrophic subaortic stenosis (case 8)—may experience an increase in left ventricular wall tension, which should oppose a beneficial symptomatic effect.

**Summary**

Symptoms of myocardial ischemia occur in aortic stenosis in the absence of coronary artery disease. Increased left ventricular wall tension, a principal determinant of myocardial oxygen requirements, may contribute to these symptoms. This investigation was undertaken during the course of transseptal left heart catheterization in order to study the effect of nitroglycerin on left ventricular wall tension in eight patients with fixed orifice aortic stenosis. In seven of the subjects, nitroglycerin significantly reduced tension-time index per beat and per minute. In addition, left ventricular size may have diminished as a consequence of lower diastolic filling pressure. In view of the relationship between wall tension and myocardial oxygen consumption, these effects should favorably influence the balance between oxygen availability and oxygen requirements in patients with fixed obstruction to left ventricular outflow. The eighth patient experienced an appreciable increase in tension-time index, suggesting secondary hypertrophic subaortic stenosis.

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**References**

12. **Gorlin, R., Brachfeld, N., MacLeod, C., and Bopp, P.:** Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. Circulation 19: 705, 1959.

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The Scientific Revolution

The whole of modern thought is steeped in science; it has made its way into the works of our best poets, and even the mere man of letters, who affects to ignore and despise science, is unconsciously impregnated with her spirit, and indebted for his best products to her methods. I believe that the greatest intellectual revolution mankind has yet seen is now slowly taking place by her agency. She is teaching the world that the ultimate court of appeal is observation and experiment, and not authority; she is teaching it to estimate the value of evidence; she is creating a firm and living faith in the existence of immutable moral and physical laws, perfect obedience to which is the highest possible aim of an intelligent being.—T. H. Huxley (Collected Essays, VIII, Discourses, Biological and Geological. London, 1893-94, p. 226).
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