Haemodynamic Effects of Nitroglycerin in Patients with Mitral Valvular Disease

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Nitrites are widely used for the treatment of angina pectoris, but their mechanism of action is still not clear. Animal experiments have shown that nitrites dilate arteries, arterioles, capillaries, and veins (for a review: see Charlier, 1961). Most workers feel that nitroglycerin acts by dilating coronary vessels, though such an effect has been difficult to show in patients with coronary heart disease. Moreover, Gorlin et al. (1959), Weiss, Wilkins, and Haynes (1937), Wilkins, Haynes, and Weiss (1937), and Johnsson, Henning, and Åblad (1965) have shown that the most important circulatory effect of nitrites in man is probably a dilatation of peripheral veins, which may lead to a fall in central blood volume and a reduction of the work of the heart. Others, e.g. Christensson, Karlefors, and Westling (1965), maintain that this may be a sufficient explanation for the relief of anginal pain, since they found a reduced stroke volume after nitroglycerin, particularly when the drug was given during anginal pain provoked by sitting exercise. However, these findings were not confirmed by Hoeschen et al. (1966): they found increased cardiac output and stroke volume when nitroglycerin was given to patients with angina pectoris under experimental conditions which appear similar to those of Christensson et al. (1965). It has also been observed by O. Müller (1963, personal communication), Arborelius et al. (1968), and Najmi et al. (1967) that nitroglycerin may prevent anginal pain during supine exercise without a reduction of cardiac output, but with reduced pressures in the lesser circulation. Variations in the patients and the experimental methods may possibly explain the different results, but nevertheless these findings and those of Hoeschen et al. (1966) appear to cast doubt on the theory that nitroglycerin acts only by reducing the work of the heart.

New light on the haemodynamic consequences of coronary insufficiency was obtained by Müller and Rørvik (1958). They found that anginal pain was associated with increased pressures in the left atrium and the pulmonary artery. After nitroglycerin the pressures were quickly lowered to normal. The effects of nitroglycerin and related substances on other conditions with raised pressures in the pulmonary circulation have also been studied. Thus, reduction of pressures in the pulmonary artery and the left atrium has been obtained in patients with left ventricular failure due to hypertension, and in patients with mitral valvular disease (Johnson, Gross, and Hale, 1957; Johnson, Fairley, and Carter, 1959; Fremont, 1961; Kleinerman et al., 1964).

The present report contains further observations on the action of nitroglycerin in patients with mitral valvular disease, with particular reference to the effects during exercise. The investigation was initiated by the favourable clinical effects obtained by nitroglycerin in patients with symptoms of imminent pulmonary oedema in connexion with catheterization.

SUBJECTS AND METHODS

Observations were made on 26 patients with mitral valvular disease, judged to be predominantly stenosis, who underwent a routine pre-operative assessment.

Right heart catheterization was carried out in the supine position, after premedication with a small dose of barbiturate; the examination was performed in the morning and the patients were not given breakfast.

A double-lumen catheter was used for simultaneous recording of pressures in the pulmonary artery and in the wedge position (PCV pressure). A polyethylene
Nitroglycerin in Mitral Disease

TABLE I

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Heart rate (beats/min.)</th>
<th>Cardiac output (l/min.)</th>
<th>Stroke volume (ml.)</th>
<th>PCV</th>
<th>Pulm. art.</th>
<th>Brach. art.</th>
<th>Oxygen consumption (ml/min.)</th>
<th>Art. ven. oxygen diff. (ml/l)</th>
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<td>B 127</td>
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<td>B 100</td>
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<td>89</td>
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<tr>
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<td>104</td>
<td>B 104</td>
<td>7.4</td>
<td>71</td>
<td>15</td>
<td>29</td>
<td>13</td>
<td>82</td>
<td>135</td>
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PCV = Pulmonary artery wedge pressure.
BSP = Bromsulphalein.
S, D, M = Systolic, diastolic, and mean pressure, respectively.

In order to evaluate the possible spontaneous changes in the haemodynamic conditions during continuous exercise, duplicate determinations were made in a series of patients with mitral valvular disease (Gustafson, 1966). The interval between the two determinations was about 5 minutes. The results in 14 patients with sinus rhythm are given in Table II.

RESULTS

The predominant haemodynamic effect of nitroglycerin during exercise was the reduction of both pulmonary and PCV pressures (Tables I and II). The reduction of systemic arterial pressure was also statistically significant. Cardiac output was slightly decreased in those patients to whom nitroglycerin was given in comparison with the patients to whom it was not given. The stroke volume was more reduced since the heart rate increased after nitroglycerin. The arteriovenous oxygen difference increased slightly.

A difference in the behaviour of the cardiac output and stroke volume became apparent if the patients were divided in two groups, according to the level of the PCV pressure after nitroglycerin. In the 6 patients with the lowest PCV pressures after nitroglycerin (average value 12 mm. Hg against 25 mm. Hg before the drug), cardiac output decreased by 1.3 l/min. and stroke volume by 17 ml., on the average. In the remaining 6 patients PCV pressures fell from 33 to 25 mm. Hg. In this group...
The authors will be pleased to send them to anyone who is interested.

The haemodynamic changes after nitroglycerin at rest were in principle the same as those described above during exercise.*

In 7 patients, who had respiratory distress and objective signs of imminent pulmonary oedema at rest or during exercise, the symptoms disappeared quickly after nitroglycerin, in pace with the reduction of PCV pressure.

**DISCUSSION**

The effects of nitroglycerin in the present series of patients with mitral valvular disease were in the main confined to a reduction of pulmonary arterial and PCV pressures. The calculated pulmonary vascular resistance was reduced more than the systemic vascular resistance. These observations are in accordance with those reported by Dresdale *et al.* (1963) regarding the effect of isosorbide dinitrate on the haemodynamics in patients with mitral stenosis.

One possible mode of action of nitroglycerin in mitral stenosis is on the peripheral veins (capacitance vessels), thereby reducing the blood flow into the lesser circulation, with a consequent drop in pulmonary and left atrial pressure. It is also possible that nitroglycerin reduces the tone in the pulmonary veins; this would also decrease the left atrial pressure. The latter mechanism would fit in with the reports of disturbed ventilation, decreased compliance, and increased pulmonary blood volume (Dresdale *et al.*, 1963; Kleinerman *et al.*, 1964; Ferrer *et al.*, 1966).

It seems likely that the pressure gradient over the mitral valve was reasonably well maintained in those patients in whom nitroglycerin caused a moderate fall in PCV pressure. Left ventricular diastolic pressure would thus decrease in parallel with the left atrial pressure. With a more pronounced effect, stroke volume and cardiac output also fell, indicating a reduction in effective pressure gradient, possible because of approaching a "minimal" left ventricular diastolic pressure.

We would like to suggest that the mechanism of action of nitroglycerin is the same in mitral valvular disease and in coronary heart disease. The different results as regards cardiac output and stroke volume obtained by O. Müller (1963, personal communication), Christansson *et al.* (1965), Hoeschen *et al.* (1966), Arborelius *et al.* (1968), and Najmi *et al.* (1967) should, in our opinion, be regarded as quantitatively rather than qualitatively different.

In this connexion, the important problem of a generally increased venous tone in patients with manifest or imminent cardiac failure should be discussed. It is even possible that the increase in venous tone in certain patients is more pronounced in the pulmonary veins. Raphael and Steiner (1966) have shown that the motor activity of the pulmonary veins is changed in patients with mitral stenosis. It is well known that an increase in venous tone caused by sympathetic stimulation can bring about pulmonary oedema in such patients, as well as in patients with latent left ventricular failure from any cause. In such patients the administra-

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**TABLE II**

**SUMMARY OF HAEMODYNAMIC EFFECTS OF NITROGLYCERIN DURING EXERCISE IN PATIENTS WITH MITRAL VALVULAR DISEASE (SINUS RHYTHM)**

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Nitroglycerin group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean initial</td>
<td>No. of observations</td>
</tr>
<tr>
<td>Heart rate (beats/min.)</td>
<td>101</td>
<td>14</td>
</tr>
<tr>
<td>Cardiac output (l./min.)</td>
<td>8·35</td>
<td>14</td>
</tr>
<tr>
<td>BSP (mm Hg)</td>
<td>85·2</td>
<td>14</td>
</tr>
<tr>
<td>Stroke volume (ml.)</td>
<td>19·6</td>
<td>14</td>
</tr>
<tr>
<td>Mean pressure (mm Hg)</td>
<td>30·1</td>
<td>14</td>
</tr>
<tr>
<td>PCV (ml./min.)</td>
<td>671</td>
<td>14</td>
</tr>
<tr>
<td>Oxygen uptake (ml./min.)</td>
<td>80·1</td>
<td>14</td>
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</tbody>
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Nitroglycerin in Mitral Disease


Gorlin, R., Brachfeld, N., MacLeod, C., and Bopp, P. (1959). Effects of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. Circulation, 18, 705.


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