Hemodynamic Effects of Nitroglycerin in Patients with Angina Pectoris Studied by an Atrial Pacing Method

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SUMMARY

The hemodynamic effects of nitroglycerin on 20 patients with coronary arterial disease were assessed by using atrial pacing to invoke angina pectoris. This new technique also permitted study of the hemodynamics during pain without the interference of the effects of muscular exercise on the heart affected by coronary artery disease.

The pain threshold of each patient was determined by successive pacing runs and the effects of nitroglycerin were evaluated both before and during the pacing up to the level of pain. With regard to the circulatory status at pain an abnormally elevated pulmonary venous "wedge" pressure was an infrequent phenomenon. This difference from the data of studies in which muscular exercise is used is briefly discussed.

Sublingual nitroglycerin decreased aortic, pulmonary arterial, right atrial, and pulmonary capillary venous pressures. Stroke volume and cardiac output were reduced and this reduction was accompanied by a compensatory rise in heart rate. Tension-time index was reduced and during pacing at identical rates never reached the level at which angina pectoris was experienced before nitroglycerin. End-diastolic heart size as estimated from conventional chest roentgenograms was reduced by nitroglycerin at every pacing step in all six patients studied by this method. The conclusions were that at all heart rates studied nitroglycerin (a) decreased atrial pressures, (b) decreased heart size, (c) caused peripheral vasodilatation, and (d) allowed the heart to be driven at a higher rate without production of anginal pain. These hemodynamic changes reflect a decreased oxygen requirement of the heart and are consistent with the pain-relieving properties of nitroglycerin.

Additional Indexing Words:
Angina threshold Cardiac work Coronary artery disease Heart size
Supraventricular tachycardia Triggered x-rays

DESPITE THE FACT that muscular exercise is the most physiological situation triggering pain in patients with angina pectoris, its use in hemodynamic studies has led to controversial views about both the hemodynamics of angina pectoris and the hemodynamic effects of nitroglycerin in this condition.1-11 The differences in opinion mostly concern left ventricular function and are based on the inability to separate the hemodynamic effects of exercise on the heart affected by coronary artery disease from the effects of ischemia at the moment of pain. A few observations exist on the hemodynamic effects of ischemia during spontaneous attacks of pain,1, 6, 10, 12, 13 but no systematic investigation has been carried out.

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A recently developed technique that uses atrial pacing in the resting patient will produce cardiac pain in patients who had previously had angina pectoris. This safe and repeatable procedure gave an accurate pain threshold in terms of the tension-time index, which varied by less than 5% in 10 of 13 (77%) patients in whom angina was produced repeatedly by this method. The present report describes the hemodynamic effects of nitroglycerin in patients with angina pectoris produced by this technique.

Methods

Twenty male patients with typical angina pectoris have been studied. The age range was 41 to 73 years (mean, 55 years). Patients with signs of heart failure, other types of heart disease, hypertension, or pulmonary disease were excluded. Selective coronary cineangiography performed in three patients provided an anatomic basis for the clinical diagnosis in these.

The studies were performed in the morning. The patients had had their usual breakfast and were not premedicated. The supine position was used. The procedure, which we have previously described in detail, consisted of passing either a double-lumen catheter directly into an arm vein and placing the tip in the pulmonary capillary wedge position or passing a fine nylon tube percutaneously into the pulmonary artery, by use of the flow-guided principle. A polythene tube was placed percutaneously into the aortic arch, and a bipolar pacing electrode catheter with or without a lumen was inserted into the right atrium. Pacing with an external battery-powered pacemaker unit began 5 to 10 beats/min above the resting heart rate and proceeded in increments of 5 to 10 beats/min until pain occurred or until pacing became unsatisfactory because of intermittent atrial capture. This procedure was performed three times with a 10-min control period between the pacing runs. After the last control run nitroglycerin (0.6 mg) was administered sublingually and the pacing run was repeated 5 min after the nitroglycerin tablet had dissolved.

Pressures were measured before pacing and after 45 sec of each pacing step by means of Consolidated Electronics strain-gauge transducers (Type 4-326-L212) and recording on a Sanborn-964 four-channel direct writer. The mean pressures were obtained by electrical integration. The zero level for pressure reference was at the mid-chest.

Cardiac output was measured before pacing and at 60 to 90 sec, at pacing rates of 110, 130, and 150/min and also when pain occurred. Five milligrams of indocyanine green was injected into the pulmonary artery, and arterial blood was withdrawn by a Kipp and Zonen constant rate pump through a Gilford densitometer feeding a Honeywell recorder.

End-diastolic x-rays were taken during pacing utilizing an ECG-triggering device (J. Norman and K. Jefferson, personal communication, 1967). Exposures were made during continuous respiration at the end of inspiration to avoid a Valsalva maneuver. The uncorrected frontal plane heart area was calculated in square centimeters according to Jonsell.

The following hemodynamic indices were derived: tension-time index as the product of mean aortic ejection pressure, ejection time, and heart rate; total peripheral resistance by dividing the pressure drop across the pulmonary vascular bed by cardiac output; and left ventricular work and stroke work as the product of the flow and mean aortic pressure multiplied by 13.6/1,000.

The statistical significance of the difference of the means before and after nitroglycerin was determined by the Student's t-test and paired comparison.

Results

Hemodynamic data were obtained in 16 patients. Thirteen of these had pain during the study and three did not. These are treated as separate groups. The individual unpaced data before and after nitroglycerin of the group with pain during the study are shown in figure 1. The individual values before and after nitroglycerin during pacing at the rate which initially provoked pain are shown in figure 2. Table 1 summarizes the mean values for the whole group that had pain during the study. The data of the group without pain are shown in table 2. End-diastolic x-rays were obtained in six patients in four of whom this was the only study made.

Hemodynamics Without Pacing

After nitroglycerin the heart rate was increased \((P<0.001)\) and the stroke volume decreased \((P<0.001)\). The net effect was a decrease in cardiac output \((P<0.05)\) accompanied by a significant decrease in all the pressures measured. The pressure drop in systemic and pulmonary circulations was not accompanied by an increase in the respective
resistances. Both left ventricular work ($P < 0.001$) and stroke work ($P < 0.001$) decreased, but tension-time index remained unchanged. All these changes were also present in the small separate group of patients listed in table 2.

**Hemodynamics During Pacing**

Thirteen of the 16 patients had pain provoked by atrial pacing before nitroglycerin, but only three of the patients had pain when paced following nitroglycerin. In one subject the heart rate at which pain occurred was almost identical before and after nitroglycerin, but in the other two patients faster rates were required to produce pain after nitroglycerin. In the remaining 10 subjects, we were unable to produce pain after nitroglycerin despite pacing at rates considerably faster than those provoking pain before the drug (table 3).

The rate at which pain was provoked before nitroglycerin was used for the hemodynamic comparison following the drug. Values before and after nitroglycerin, therefore, refer to identical rates in any one patient, but these rates differ from patient to patient.

At identical paced rates (table 1) there were no significant changes in stroke volume or cardiac output after nitroglycerin. Nitroglycerin reduced both aortic ($P < 0.001$) and pulmonary arterial pressures ($P < 0.001$). The same was true for the pulmonary capillary venous pressure ($P < 0.05$) and there was a similar trend in right atrial pressure.

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**Figure 1**

Individual data for the whole group with pain during study without pacing before and after nitroglycerin. Abbreviations used in all figures: $HR =$ heart rate; $SV =$ stroke volume; $CO =$ cardiac output; $TPR =$ total peripheral resistance; $PVR =$ pulmonary vascular resistance; $LVW =$ left ventricular work; $LVSW =$ left ventricular stroke work; $TTI =$ tension-time index; $PBA =$ mean brachial artery pressure; $PRA =$ right atrial pressure; $PPC =$ mean pulmonary artery pressure; and $P_{PCV} =$ mean pulmonary capillary (venous) wedge pressure.
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Figure 2

*Individual data for the whole group during pacing. The initial points refer to the values at the onset of anginal pain before nitroglycerin. The final points refer to the values at identical paced heart rates after nitroglycerin without pain. Symbols as in figure 1.*

Before nitroglycerin the pulmonary capillary venous (wedge) pressure either remained constantly low, slowly increased during pacing, or rose rapidly at the moment of pain. On three occasions during 19 pre-nitroglycerin pacing runs at which satisfactory pulmonary capillary venous pressure tracings were obtained, the mean pressure exceeded 12 mm Hg. In one additional patient, in whom this pressure was not obtained, the pulmonary arterial pressure rose precipitously at pain. After nitroglycerin the pulmonary capillary venous pressure was above 12 mm Hg at the end of pacing in one patient who did not have pain.

Total peripheral resistance was reduced by nitroglycerin (P < 0.02), but a 20% drop in the pulmonary vascular resistance was not statistically significant. Left ventricular work (P < 0.05) and left ventricular stroke work (P < 0.02) were reduced and a significant decrease occurred in the tension-time index (P < 0.001). The changes were in general similar in the group without pain (table 2).

End-diastolic frontal plane heart area was reduced after nitroglycerin in all the six patients in whom it was obtained. Two typical examples are shown in figure 3.

**Discussion**

The present technique of atrial pacing induces a slowly rising tension-time index as the heart rate and aortic pressure increase. In most patients with angina pectoris pain occurs at a certain level of tension-time index and can be produced repeatedly by resuming the pacing procedure.14 This level can
be regarded as the point at which the myocardial oxygen supply is exceeded by demand. Since studies of the effect of nitroglycerin on the coronary circulation in patients with coronary arterial disease have not consistently shown increased coronary blood flow,\(^{17,18}\) attention has been directed to other effects of the drug. The present data show that after nitroglycerin the tension-time index was lower at every pacing step (figure 4). Moreover, the heart area and presumably the ventricular volume were smaller after nitroglycerin, and this occurrence would theoretically reduce the oxygen requirements of the heart by decreasing the tension in the ventricular wall according to the equation of Laplace. Our data support the view that nitroglycerin reduces myocardial oxygen demands at any given heart rate, both by its action in lowering systemic arterial pressure and by its effect on heart size. The changes in heart area agree with earlier observations in healthy men.\(^{19,20}\)

Cardiac output, stroke volume, and aortic pressure were reduced after nitroglycerin, the last presumably being responsible for the observed tachycardia. The present data also suggest peripheral arteriolar vasodilatation since there was no increase of peripheral resistance as the cardiac output fell. Similarity between the effect of nitroglycerin and that of lower limb venous tourniquets has been previously pointed out.\(^2\)

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**Table 1**

*Mean Hemodynamic Data Without Pacing and During Pacing of the Thirteen Patients Who Had Pain During Pacing*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Preparing</th>
<th></th>
<th>At the level of pain*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ±SD</td>
<td>P</td>
<td>Mean ±SD</td>
<td>P</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>13</td>
<td>A 74.8 10.8 0.001</td>
<td>B 116.3 17.3 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>7</td>
<td>A 70.3 21.7 0.001</td>
<td>B 47.4 19.8 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>7</td>
<td>A 5.6 1.7 0.05</td>
<td>B 5.3 1.8 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>10</td>
<td>A 14.5 3.5 0.01</td>
<td>B 17.7 6.6 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>7</td>
<td>A 7.3 3.1 0.02</td>
<td>B 11.6 5.6 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>3</td>
<td>A 2.3 0.3 0.05</td>
<td>B 2.3 0.6 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>13</td>
<td>A 97.9 8.1 0.001</td>
<td>B 106.4 13.1 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
<td>7</td>
<td>A 19.1 6.4 ns</td>
<td>B 22.6 7.4 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (units)</td>
<td>5</td>
<td>A 1.03 0.47 ns</td>
<td>B 0.79 0.45 ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular work (kpm/min)</td>
<td>7</td>
<td>A 7.1 1.6 0.001</td>
<td>B 7.3 1.7 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular stroke work (gcm/beat)</td>
<td>7</td>
<td>A 90.7 19.4 0.001</td>
<td>B 63.6 23.0 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-time index (mm Hg sec/min)</td>
<td>13</td>
<td>A 2550 367 ns</td>
<td>B 3225 506 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Refers to the pacing rate at which patients had angina before nitroglycerin.

Abbreviations: N = number of paired observations; ns = not significant; A = before nitroglycerin; and B = after nitroglycerin.
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Table 2

Hemodynamic Effects of Nitroglycerin in Patients Without Pain During Pacing

<table>
<thead>
<tr>
<th></th>
<th>Mean Prepacing</th>
<th>Range</th>
<th>At max. pacing rate</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>A 78.7</td>
<td>64-94</td>
<td>131.3</td>
<td>119</td>
<td>145</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>B 86.7</td>
<td>83-100</td>
<td>133.3</td>
<td>120</td>
<td>150</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>A 66.0</td>
<td>50.0-87.5</td>
<td>39.3</td>
<td>22-50</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>A 5.4</td>
<td>3.5-7.1</td>
<td>5.1</td>
<td>3.3-6.5</td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>A 93.2</td>
<td>84-103</td>
<td>99.8</td>
<td>90-107</td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
<td>A 19.5</td>
<td>11.2-30.0</td>
<td>21.8</td>
<td>15.4-31.0</td>
<td></td>
</tr>
<tr>
<td>Left ventricular work (kpm/min)</td>
<td>A 6.6</td>
<td>4.1-8.2</td>
<td>7.2</td>
<td>4.7-8.8</td>
<td></td>
</tr>
<tr>
<td>Stroke work (g-m/beat) (mm Hg sec/min)</td>
<td>A 2388</td>
<td>1851-3093</td>
<td>3247</td>
<td>2094-3857</td>
<td></td>
</tr>
<tr>
<td>Tension-time index</td>
<td>B 9.3</td>
<td>9.0-10.0</td>
<td>11.0</td>
<td>11.0-13.0</td>
<td>8.0-15.0</td>
</tr>
</tbody>
</table>

Abbreviations: A = before nitroglycerin; B = after nitroglycerin.

Table 3

Maximum Pacing Rates Before and After Nitroglycerin in the Sixteen Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximum pacing rate before nitroglycerin (beats/min)</th>
<th>Maximum pacing rate after nitroglycerin (beats/min)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>130</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>116</td>
<td>150</td>
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<tr>
<td>4</td>
<td>130</td>
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<td>5</td>
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<tr>
<td>6</td>
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<td>17</td>
<td>135</td>
<td>147</td>
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<tr>
<td>18</td>
<td>138</td>
<td>156</td>
</tr>
<tr>
<td>19</td>
<td>143</td>
<td>158</td>
</tr>
</tbody>
</table>

Figure 3

Changes in frontal plane heart area in two patients from triggered x-rays as the heart rate was increased. Open symbols = before nitroglycerin; filled symbols = after nitroglycerin. In case 14 nitroglycerin was given during pacing at 113 beats/min. In case 17 nitroglycerin was given when the heart was not being paced and a separate pacing run was then performed.

Since the original description by Müller and Rørvik it has been repeatedly pointed out that angina pectoris is associated with elevated left ventricular end-diastolic pressure although Cohen and associates were unable to show this, and abnormally high pulmonary capillary venous pressures occurred only in 13 of 36 patients in the
series of Malmborg. Closer inspection of the data of studies in which muscular exercise has been used to precipitate angina and in which the results are amenable to a time-sequence analysis shows that left ventricular end-diastolic pressure or pulmonary capillary venous pressure has been elevated during the exercise prior to the onset of pain and might represent the response of an abnormal heart to exercise and not necessarily the effect of anginal pain on left ventricular function. The raised left ventricular end-diastolic pressure during exercise in these patients, often interpreted as left ventricular failure, might be due to a noncompliant ventricle facing the increased inflow produced by muscular exercise. In the present study cardiac output remained relatively steady throughout the pacing confirming earlier findings and thus the left ventricle was not stressed by increased venous return. In these circumstances angina pectoris caused an abnormally raised pulmonary capillary venous or pulmonary arterial pressure in only four patients, although the mean figures for the group showed a small increase both before and after nitroglycerin. It is also worth emphasizing that when a rise occurred during one pacing run up to pain it did not necessarily occur during the other runs in the same patient similarly driven up to pain. To assess the importance of the duration of the angina, one patient was paced to higher heart rates despite pain (fig. 5). The pulmonary capillary venous pressure rose continuously demonstrating the importance of this factor in causing deterioration in left ventricular function. In addition to the hemodynamic effects of muscular exercise, this time factor might confuse the issue as, when exercise is used to produce angina, it is not possible to revert instantly the circulatory changes when pain occurs.

The use of pulmonary capillary wedge pressures at fast heart rates to indicate left ventricular end-diastolic pressures is open to suspicion, since the short diastole tends to produce an unduly elevated wedge pressure. Even if this effect occurred in our patients, it would support our conclusions that left ventricular end-diastolic pressure did not rise above normal limits (12 mm Hg) in the majority of our patients.

In this study, the relief of the hemodynamic load on the left ventricle achieved by reduced systemic blood pressure and blood flow after nitroglycerin leads to decreased oxygen requirements of the heart and can be compared with the situation when angina occurs spontaneously at rest. During muscular exercise the findings after nitroglycerin...
have been somewhat different and controversial and variable changes have been observed in the tension-time index or in its components. A decrease in the heart volume has often been suggested but this parameter was measured in only one study when a decrease was observed after nitroglycerin. In each of the six patients in whom we obtained end-diastolic triggered x-rays, the frontal plane area of the heart decreased after nitroglycerin. This suggests that the heart volume decreased, and it seems likely that the left ventricle participated in this change. If this was so, it would be another factor reducing myocardial oxygen requirements. In the face of lack of definitive and consistent hemodynamic oxygen-saving effects combined with the indisputable pain-relieving properties of nitroglycerin during muscular exercise, it is possible that nitroglycerin may act, in addition to its extracardiac effects, by favorably altering the distribution of myocardial blood flow as suggested by Fam and McGregor.

Conclusions

Hemodynamic studies before and after 0.6 mg of nitroglycerin given sublingually to 16 resting patients with angina pectoris in whom the heart rates were controlled by atrial pacing support the following conclusions:

1. Following nitroglycerin the heart can be driven to much higher rates than before without provoking pain.

2. Nitroglycerin reduces systemic and pulmonary arterial pressures and also reduces right atrial and left atrial (pulmonary capillary wedge) pressures at all heart rates.

3. Nitroglycerin reduces end-diastolic heart size at all heart rates.

References


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Yang Yin

... It is the business of those who study human conduct as embodied in institutions and group action past and present to mediate as best they can between the two camps of visionaries. The vision of one group is seen over its shoulder in an idealized and nonexistent past and the vision of the other is a mirage of unattainable perfectibility in the future. It is at this point that history, the mother of all the social sciences, steps forth from the obscenity into which she is being pushed by her children, to lay a cooling hand upon the brows of contending factions and say, "Why so hot, little man? You and your kind who learned nothing and forgot nothing always lost in the end, and you over there and your kind have attained none of the utopias your leaders prophesied."

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