Influence of Nitroglycerin on Myocardial Metabolism and Hemodynamics during Angina Induced by Atrial Pacing

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SUMMARY

Myocardial lactate extraction, arterial-coronary sinus difference (A-CS) of potassium (K+), hemodynamics, and S-T segments were studied in 15 patients with coronary artery disease who developed angina during atrial pacing. The study consisted of the following periods: control (C1), pacing (P1), recovery (C2), control after nitroglycerin (C\textsubscript{GTN}), second pacing (P2), and recovery. During C1, mean lactate extraction, S-T segments, and left ventricular end-diastolic pressure (LVEDP) were normal, and there was no myocardial K+ loss. During P1 the mean lactate production was -12.0%, mean K+ loss -0.26 mEq/liter, and mean S-T segment depression 1.97 mm, while the average LVEDP remained unchanged, increasing when pacing was discontinued to a mean value of 23.3 mm Hg. These values returned to control levels by the time GTN was administered. After GTN there were significant decreases in mean cardiac index, LVEDP, brachial artery pressure, and left ventricular stroke work. During P2, eight subjects had no pain, five experienced less severe angina, mean lactate production and K+ loss were abolished, S-T segments became less depressed (0.8 mm), and mean LVEDP decreased during pacing, rising only to 11.4 mm Hg when pacing was discontinued. Myocardial lactate production reverted to extraction in two patients and decreased in another two, whereas seven patients showed a decreased K+ loss or uptake. It is concluded that GTN may prevent or reduce pacing-induced angina, as well as improve the electrocardiogram and hemodynamics, and in some patients decrease myocardial anaerobiosis.

Additional Indexing Words: Lactate, Potassium, Sodium, Left ventricular function, S-T segment, Myocardial ischemia

PACING-INDUCED tachycardia is a well-known method of producing angina and hemodynamic and metabolic abnormalities in patients with coronary artery disease (CAD) and reduced coronary reserve.\textsuperscript{1-4} This response to pacing consists of chest pain indistinguishable from that of angina pectoris, S-T-segment depression, abnormalities of the left ventricular end-diastolic pressure (LVEDP), myocardial lactate production, and potassium (K+) loss from the heart.\textsuperscript{3, 4} These effects subside promptly after return to sinus rhythm. Since nitroglycerin (GTN) is known to relieve angina pectoris,\textsuperscript{5-7} it was decided to investigate the effects of this drug on angina induced by atrial pacing. Patients with CAD who developed angina during a period of atrial pacing were studied before...
and after the administration of GTN. The results show that this agent, in addition to relieving chest pain, may improve the hemodynamic, electrocardiographic, and metabolic disturbances observed during myocardial ischemia.

Material and Methods

Fifteen patients with coronary artery disease and a history of exertional chest pain who developed angina during atrial pacing were selected for this study (table 1). All patients were free of cardiomegaly, arrhythmias, and clinical evidence of cardiac failure. None of them was receiving digitalis or diuretics at the time of the study, and none had been treated for arterial hypertension. The patients were brought to the laboratory the day prior to the study so that they would be familiar with the surroundings and the nature of the procedure, and informed consent was obtained.

The subjects were studied in the fasting state without premedication. Under local anesthesia, the brachial artery and two or three veins were isolated in the right antecubital fossa. A no. 9 double-lumen Cournand catheter was positioned in the right heart so that the tip lay in the pulmonary artery. A no. 8 Goodale-Lubin catheter, modified by the incorporation of bipolar electrodes 1.5 and 3.0 cm from the tip, was passed into the midportion of the coronary sinus to permit sampling as well as pacing. In three patients studied by the continuous-sampling technic, a no. 6 Cournand catheter was positioned in the axillary vein for blood infusion. A no. 8 Sones catheter was introduced into the left ventricle from the right brachial artery and a short Teflon catheter was inserted through the arteriotomy into the distal brachial artery for sampling. The left brachial artery was also cannulated with a Teflon catheter using the Seldinger technic.

Hemodynamic and metabolic data were obtained during the study that lasted 68 minutes and consisted of a 10-min control period (C1), a 10-min period of atrial pacing (P1), a 20-min recovery period (C2), a 9-min period following the administration of 0.5 mg of chewable GTN (CGTN), an additional 10-min pacing period (P2), and a final period of recovery.

In the present investigation it was chosen to begin atrial pacing 9 min after GTN, since this was the shortest period of time that would provide adequate stability for the measurement of cardiac output followed by blood sampling for metabolic studies. It has also been previously shown in our laboratory that, in most patients with a depressed ventricular contractility during myocardial ischemia induced by atrial pacing, nitroglycerin could restore the relationship between left ventricular end-diastolic pressure and left ventricular stroke work during pacing and postspacing periods to levels similar to those found in normal subjects and patients with coronary artery disease, when tested 6–10 min after the administration of GTN. Duplicate cardiac-output determinations by the dye-dilution method using indocyanine green were carried out between the fifth and seventh minute of each control and pacing periods and before and after nitroglycerin administration. The electrocardiogram was recorded continuously.

Pressures were obtained at intervals with P23 Db Statham strain gauges from a zero reference level 5 cm below the angle of Louis and recorded over, at least, two respiratory cycles. The mean pressures in the brachial and pulmonary arteries were obtained electronically. Recording speed was normally 25 mm/sec, but a speed of 100 mm/sec at a high sensitivity was used to record LVEDP. The left ventricular stroke-work index (LVSWI) in g·m/m² was calculated using the formula:

\[
\text{LVSWI} = \frac{\text{SI} \times (\text{BAm} - \text{LVEDP}) \times 13.6}{1000}
\]

where SI = stroke index in ml/m², BAm = brachial artery mean pressure in mm Hg, and LVEDP = left ventricular end-diastolic pressure in mm Hg. The modified tension-time index (TTI) was calculated as the product of peak left ventricular systolic pressure and the heart rate. In three patients in whom a continuous blood sampling technic was employed, 400 ml of venous blood was withdrawn slowly into a blood-donor bag containing acid-citrate-dextrose solution 24–48 hours previously for reinfusion during the study. Blood was continuously withdrawn from the coronary sinus and brachial artery at a rate of 2.5 ml/min into tubes placed in a fraction-collector set to change position every minute, so that each tube contained an integrated sample collected over 1 min. In these patients, blood was infused via the axillary vein catheter at a rate comparable to the sampling rate. In the remaining 12 patients two paired samples were obtained from the coronary sinus and brachial artery during the final 2 min of C1, P1, and P2 and one paired sample during the final 2 min of C2, CGTN, and the recovery period.

The collected blood was centrifuged at 5°C; the plasma was removed within 30 min and stored at −35°C. Lactate was determined by the automated enzymatic method of Hochella and Weinhouse and expressed in mg/100 ml of plasma. Myocardial extraction of lactate was calculated as the ratio of the arterial-coronary
Table 1

Resume of Data in a Group of 15 Patients with Pacing-Induced Angina

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Coronary angiography*</th>
<th>Coll circ</th>
<th>Left ventriculography</th>
<th>Lactate production (during atrial pacing)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AD</td>
<td>L</td>
<td>C</td>
<td>R</td>
</tr>
<tr>
<td>H.W.</td>
<td>45</td>
<td>M</td>
<td>Inadequate</td>
<td>Inadequate</td>
<td>75%</td>
<td>Yes</td>
</tr>
<tr>
<td>J.F.</td>
<td>60</td>
<td>M</td>
<td>70%</td>
<td>N</td>
<td>Min</td>
<td>No</td>
</tr>
<tr>
<td>D.C.</td>
<td>46</td>
<td>F</td>
<td>100%</td>
<td>50%</td>
<td>Min</td>
<td>Yes</td>
</tr>
<tr>
<td>G.V.</td>
<td>39</td>
<td>M</td>
<td>100%</td>
<td>90%</td>
<td>50%</td>
<td>Yes</td>
</tr>
<tr>
<td>B.C.</td>
<td>57</td>
<td>M</td>
<td>70%</td>
<td>85%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>J.S.</td>
<td>45</td>
<td>M</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>E.J.</td>
<td>49</td>
<td>M</td>
<td>85%</td>
<td>85%</td>
<td>90%</td>
<td>Yes</td>
</tr>
<tr>
<td>R.S.</td>
<td>42</td>
<td>M</td>
<td>N</td>
<td>85%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>D.D.</td>
<td>41</td>
<td>M</td>
<td>90%</td>
<td>Min</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>B.S.</td>
<td>57</td>
<td>F</td>
<td>100%</td>
<td>Min</td>
<td>Min</td>
<td>Yes</td>
</tr>
<tr>
<td>W.M.</td>
<td>51</td>
<td>M</td>
<td>90%</td>
<td>100%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>H.L.</td>
<td>47</td>
<td>M</td>
<td>50%</td>
<td>75%</td>
<td>85%</td>
<td>No</td>
</tr>
<tr>
<td>G.W.</td>
<td>43</td>
<td>M</td>
<td>N</td>
<td>90%</td>
<td>N</td>
<td>Yes</td>
</tr>
<tr>
<td>G.A.</td>
<td>51</td>
<td>M</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>W.S.</td>
<td>61</td>
<td>M</td>
<td>100%</td>
<td>90%</td>
<td>100%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: L = left coronary artery; R = right coronary artery; AD = anterior descending branch; C = left circumflex branch; GTN = nitroglycerin; N = normal; Coll circ = collateral circulation; Min = minimal.

*The percentages under coronary angiography represent degree of stenosis.
sinus difference to the arterial blood level in
percent \( \left( \frac{A-CS}{A} \times 100 \right) \). Plasma potassium and
sodium were measured by automated flame
photometry using a Technicon Auto-analyzer.

Following completion of the studies, selective
cinecoronary arteriography and left ventriculogra-
phy were carried out in all patients. Each subject
served as his own control, and comparisons
between the different periods were evaluated
using standard Student t test.

Results

As shown in table 1, there were 13 men and
two women in this group, with ages ranging
between 39 and 61 years, with eight subjects
in the fifth decade. All patients developed
angina between the second and sixth minute
of the first pacing period which persisted until
sinus rhythm was restored. Eight of these
patients did not develop angina during the
second pacing period, five experienced less
severe pain, and in two patients nitroglycerin
had no effect on this symptom.

Radiologic (Table 1)

In one patient (H.W.) only the right
coronary artery was adequately visualized and
showed a narrowing of 75%. The main trunk of
the left coronary artery was free of disease in
the other 14 subjects, but a 50% or greater
stenosis was present in the main branches of
the coronary system with the following
distribution: triple-vessel disease in seven
patients, two-vessel disease in three, and one-
vessel disease in four. Collateral circulation
was present in 12 subjects although there was
no correlation with the severity of the disease.
In three patients with no collateral circulation,
two had one-vessel disease and the other had
involvement of both coronary systems. Left
ventriculography revealed areas of akinesis in
three patients and a hypokinetic ventricle in
four others. Left ventriculography in the
remaining eight was normal including the
three subjects without collateral circulation.

Electrocardiographic and Hemodynamic
(Table 2)

During C1, three patients showed S-T
segment depression of 0.5 mm or more, the
average for the group being \(-0.16 \pm 0.47 \text{ mm}\)
(see figs. 2 and 4, below). During P1, the S-T
segments became depressed in all but one
patient, and the average S-T depression for
the group was \(1.97 \pm 1.13 \text{ mm} \) (mean \( \pm \text{sd,}
\ P < 0.001 \)). During C2, the S-T segments were
depressed less than 1.0 mm in all subjects.
After nitroglycerin, the S-T remained un-
changed in 13 patients, became more de-
pressed in one, and improved in another
subject. During P2, S-T segments became more
depressed in only seven patients, the average
value for the entire group being \(-0.8 \pm 1.0 \text{ mm} \)
(\(P < 0.03\)), which was significantly less
than the change observed during P1
(\(P < 0.01\)).

Left Ventricular End-Diastolic Pressure

LVEDP was normal (less than 12 mm Hg)
during C1 in eight patients and averaged
12.5 \(\pm\ 5.7 \text{ mm Hg} \). During P1, LVEDP rose in
four patients, fell in 10, and remained
unchanged in the other patient, averaging
11.3 \(\pm\ 10.9 \text{ mm Hg} \) for the group. Immedi-
ately after cessation of pacing this pressure
rose abnormally in 14 subjects and averaged
23.3 \(\pm\ 8.6 \text{ mm Hg} \), a significant change from
C1 (\(P < 0.001\)). During C2, LVEDP remained
abnormal in seven patients, the mean value
for the group being 12.4 \(\pm\ 5.6 \text{ mm Hg} \).
Nitroglycerin reduced LVEDP to normal in
all subjects, with a mean for the group of
6.0 \(\pm\ 3.8 \text{ mm Hg} \), a value significantly lower
than C2. (\(P < 0.005\)). During pacing after
GTN, the LVEDP remained normal in all but
one patient, with a mean of 4.3 \(\pm\ 4.0 \text{ mm Hg} \),
which was not different from that seen during
C\(\text{GTX}\) but significantly lower than during P1
(\(P < 0.025\)). The postpacing LVEDP aver-
gaged only 11.4 \(\pm\ 6.0 \text{ mm Hg} \), a much lower
value than the mean of 23.3 \(\pm\ 8.6 \text{ mm Hg} \)
observed after cessation of P1 (\(P < 0.001\)).
Close examination of the data revealed that
abnormally high levels of LVEDP still oc-
curred in seven patients during the postpacing
period. Four of these developed angina during
P2, although their values were substantially
lower than during P1.
Table 2

Summary of Metabolic and Hemodynamic Data

<table>
<thead>
<tr>
<th>State</th>
<th>Lactate uptake (%)</th>
<th>K⁺ (A-CS) (mg %)</th>
<th>S-T (mm)</th>
<th>HR (beats/min)</th>
<th>CI (liters/min/m²)</th>
<th>SI (ml/m²)</th>
<th>BAm (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LVSWI (gpm/min/beat)</th>
<th>TTI (mm Hg/min × 10⁻⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>C₁</td>
<td>+20.7</td>
<td>+0.03</td>
<td>-0.16</td>
<td>81</td>
<td>3.06</td>
<td>39</td>
<td>99</td>
<td>12.5</td>
<td>43.9</td>
<td>1098</td>
</tr>
<tr>
<td></td>
<td>±3.7</td>
<td>±0.07</td>
<td>±0.47</td>
<td>11.1</td>
<td>±0.60</td>
<td>±4.8</td>
<td>±14.4</td>
<td>±5.7</td>
<td>±11.5</td>
<td>±192</td>
</tr>
<tr>
<td>P₁</td>
<td>-13.5</td>
<td>-0.26</td>
<td>-1.97</td>
<td>142</td>
<td>3.10</td>
<td>22</td>
<td>118</td>
<td>11.3 (23.3)</td>
<td>31.4</td>
<td>1975</td>
</tr>
<tr>
<td></td>
<td>±28.5</td>
<td>±0.19</td>
<td>±1.13</td>
<td>±10.0</td>
<td>±0.86</td>
<td>±6.0</td>
<td>±16.8</td>
<td>±10.9 (+8.6)</td>
<td>±9.3</td>
<td>±317</td>
</tr>
<tr>
<td>C₂</td>
<td>+14.6</td>
<td>+0.17</td>
<td>-0.10</td>
<td>78</td>
<td>2.84</td>
<td>35</td>
<td>102</td>
<td>12.4</td>
<td>44.5</td>
<td>1112</td>
</tr>
<tr>
<td></td>
<td>±14.6</td>
<td>±0.22</td>
<td>±0.34</td>
<td>±10.3</td>
<td>±0.34</td>
<td>±6.0</td>
<td>±13.6</td>
<td>±5.6</td>
<td>±9.5</td>
<td>±116</td>
</tr>
<tr>
<td>CGTN</td>
<td>+18.3</td>
<td>+0.13</td>
<td>-0.13</td>
<td>84</td>
<td>2.57</td>
<td>31</td>
<td>87</td>
<td>6.0</td>
<td>35.3</td>
<td>1060</td>
</tr>
<tr>
<td>P₂</td>
<td>±12.9</td>
<td>±0.14</td>
<td>±0.44</td>
<td>±9.3</td>
<td>±0.34</td>
<td>±6.4</td>
<td>±22.3</td>
<td>±3.8</td>
<td>±13.5</td>
<td>±203</td>
</tr>
<tr>
<td>P₁ (C₁-P₁)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P₂ (C₂-C₁)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P₃ (C₃-CGTN)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P₄ (CGTN-P₂)</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P₅ (P₁-P₂)</td>
<td>&lt;0.025</td>
<td>&lt;0.005</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.02</td>
<td>&lt;0.025</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: n = number of patients; C₁ = first control period; P₁ and P₂ = pacing periods; C₂ = control period before nitroglycerin; CGTN = control period after nitroglycerin; HR = heart rate; CI = cardiac index; SI = stroke index; BAm = brachial artery mean pressure; LVEDP = left ventricular end-diastolic pressure during pacing (postpacing values in parentheses); LVSWI = left ventricular stroke-work index; TTI = tension-time index. Values are mean ± so.
Other Hemodynamic Data

The mean heart rates during the two control periods were similar (81 ± 11 and 78 ± 10 beats/min), and a nonsignificant increase was seen after nitroglycerin administration (84 ± 9 beats/min). Identical mean heart rates were present during the two pacing periods (142 ± 10 beats/min). Cardiac index, which averaged 3.06 ± 0.60 liters/min/m² during C₁, remained unchanged during P₁, fell to 2.57 ± 0.34 liters/min/m² following GTN administration (P < 0.05), but rose significantly during P₂ (2.92 ± 0.52, P < 0.05). This increase in cardiac index during P₂ is probably related to the decreasing effect of nitroglycerin at this time rather than to pacing itself. Stroke index fell significantly during P₁ (P < 0.001) but returned to normal during C₂. There was a slight fall after GTN administration with a further significant decline during P₂ to a level comparable to that of P₁. The average brachial artery mean pressure rose from 99 ± 14.4 mm Hg to 118 ± 16.8 mm Hg during P₁ (P < 0.005). There was a fall in pressure following GTN administration to 87 ± 22.3 mm Hg (P < 0.05), with a nonsignificant rise to 100 ± 19.9 mm Hg during P₂, although this pressure was significantly lower than during P₁ (P < 0.02). LVSWI fell from 43.9 ± 11.5 to

Values of lactate uptake in the 15 patients throughout the study. For abbreviations see Methods in text.
31.4 ± 9.3 g-m/beat during P₁ (P < 0.01), but returned to 44.5 ± 9.2 g-m/beat. During P₂, LVSWI was 27.2 ± 8.2 g-m/beat, a level similar to P₁. TTI rose consistently during P₁ with a mean change of +83.8 ± 35.9% (P < 0.001) and then returned to normal during C₂. This variable remained unchanged following GTN administration, but it rose significantly during P₂, (+74.3 ± 27.4%, P < 0.001), a level comparable to P₁. There was no significant change in the first derivative of the left ventricular pressure during the study.

**Metabolic (Fig. 1-4)**

*Lactate Metabolism*

During C₁, the average myocardial lactate extraction was +19.0 ± 11.8% with three patients showing an extraction of less than 10%, suggesting myocardial ischemia although no lactate production was observed. At the end of P₁ (before nitroglycerin), 12 patients, including the three mentioned above, showed

![Figure 2](http://circ.ahajournals.org/content/45/5/1050/suppl/figure2)

*Figure 2*

A patient with continuous sampling of blood throughout the study. Before GTN, pacing-induced angina caused marked lactate production, ST-segment depression, and abnormalities of the LVEDP. After GTN, pain was absent during pacing, lactate production did not occur, ST-segment depression was less marked, and the LVEDP was normal.

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abnormal lactate metabolism with a mean extraction of $-13.5 \pm 28.5\%$ ($P < 0.001$). In this latter group, lactate production was seen in 10 subjects (table 1). Before and after GTN administration, the mean lactate extractions were $+14.6 \pm 14.6$ and $+18.3 \pm 12.9\%$, respectively. Four patients had abnormal lactate metabolism before nitroglycerin, and two of them reverted to normal after the drug. An opposite effect was observed in two subjects (G.V. and B.S.) whose lactate extraction became abnormal after GTN. This drug had no effect in another three patients (D.D., H.L., and W.S.) who had borderline lactate uptake throughout the study.

During the second pacing period ($P_2$), the mean lactate extraction was $+1.9 \pm 16.4\%$. This value is still abnormal but significantly different from that seen during $P_1$ ($P = 0.025$), suggesting that despite the variability of the results, myocardial anaerobiosis had decreased in some patients. Improvement of myocardial lactate metabolism was found in four subjects (H.W., G.V., E.J., and G.A.) with reversal to lactate uptake in two (E.J. and G.A.). Of these four patients, three had no angina, and one had less severe pain during the second pacing period. Before nitroglycerin, myocardial lactate production during pacing was shown in 10 patients. After nitroglycerin, this abnormality was observed in seven subjects. The values for lactate uptake during the different experimental periods in all subjects appear in figure 1, and the changes in lactate metabolism, S-T segment, and LVEDP throughout the study are presented in figure 2. No definite correlation could be established between myocardial lactate production and the angiographic abnormalities (table 1).

Figure 3

Changes of lactate uptake and A-CS potassium in nine patients during pacing before and after GTN. Note that before nitroglycerin, six patients had abnormal myocardial lactate metabolism and K+ loss. After GTN, two patients reverted to normal lactate uptake, whereas K+ loss was abolished in three subjects with a positive balance seen in another four.
Electrolyte Balance

The mean A-CS difference of plasma K⁺ during C₁ in 10 patients was +0.03 ± 0.07 mEq/liter. During the latter part of P₁, all patients lost K⁺, this loss being more marked in the second paired samples as reflected in the A-CS difference of −0.26 ± 0.19 mEq/liter (P < 0.001). Before and after GTN, the A-CS difference of K⁺ was +0.17 ± 0.22 mEq/liter and +0.13 ± 0.14 mEq/liter, respectively, but these values were not significantly different from C₁ due to individual variations. During P₂, the average K⁺ balance across the heart for all patients in the two paired samples were +0.10 and +0.02 mEq/liter, with six of 10 patients showing a gain of this cation by the heart in at least one of the two samples. In addition, K⁺ loss was decreased in another two subjects. When the balance of this cation across the heart is compared at the end of P₁ and P₂, the difference is highly significant (P < 0.005, table 2).

In nine patients who had simultaneous lactate and K⁺ determinations, lactate production before GTN was reversed to lactate uptake in two after the administration of this drug, whereas seven subjects showed either decreased K⁺ loss or a positive A-CS difference of this cation across the heart (fig. 3). The mean A-CS differences for Na⁺ were small and uninfluenced by pacing or GTN.
S-T loss, in and NITROGLYCERIN DURING ANGINA

The mean changes in lactate uptake, K+ loss, S-T segments, and LVEDP are presented in figure 4.

Discussion

The results of the present study confirm previous reports that atrial pacing in patients with CAD may induce chest pain, abnormalities of the LVEDP, S-T-segment depression, and changes in myocardial lactate metabolism and K+ balance. The hemodynamic changes observed 6–8 min after the administration of nitroglycerin agree with observations reported previously. The actions of this drug have been extensively investigated in animals and in man revealing the complex action of nitroglycerin at different levels of the circulation. It is known that the basic pharmacologic action of nitrates is a nonspecific relaxation of vascular smooth muscle, accounting for the postural hypotension seen in subjects given sodium nitrite, but this effect is not of equal intensity in all vascular beds. Blood pooling in the splanchnic area has been postulated as the cause of the hypotension but this could not be confirmed by Ferrer et al. who found that nitroglycerin constricted the splanchnic vascular bed but induced vasodilatation of the pulmonary and peripheral areas.

The precise site of action in the peripheral circulation remained obscure until Mason and Braunwald reported that this drug induces vasodilatation of the forearm veins and pooling of blood and that this mechanism could be responsible for decreased venous return and a reduction in cardiac size. This effect and smaller end-diastolic left ventricular volumes have been demonstrated after nitroglycerin administration by other investigators. The hemodynamic and metabolic consequences of a reduction in cardiac volume are a decrease in wall tension and myocardial oxygen requirements. This sequence of events is supported by the finding that relatively small phlebotomies may relieve pacing-induced angina and improve ventricular function, whereas reinfusion of the blood causes the return of angina and a rise in left ventricular end-diastolic pressure. From the theoretic point of view it might be expected that whenever nitroglycerin relieves angina the altered hemodynamics and metabolic effects associated with this syndrome will improve or return to normal. However, in this study, during pacing after nitroglycerin, while eight patients remained free of pain and another five experienced less severe angina, no clear correlation could be established between chest pain and metabolic events. A reduction in myocardial ischemia is suggested by the less marked S-T depression and myocardial K+ loss in most patients during pacing after nitroglycerin. However, under the present experimental conditions, it is not possible to determine whether this effect is due to a decrease in myocardial oxygen requirements or an increase in oxygen delivery to the ischemic areas of the heart.

Abnormal lactate metabolism as an index of myocardial anaerobiosis was not seen in all patients despite the occurrence of angina during pacing before nitroglycerin, as previously reported. After nitroglycerin, although mean lactate production was abolished during pacing, substantial individual variation was observed, with improvement of lactate metabolism in only four of the 10 patients who produced lactate. The complex nature of the disease itself may have contributed to the lack of correlation between pacing-induced angina, electrocardiographic and hemodynamic disturbances, and the abnormal handling of lactate by the heart. Recently, Helfand and coworkers were unable to show improvement of the electrocardiogram or lactate metabolism during pacing-induced angina after nitroglycerin administration, despite prompt relief of the pain. Their results are at variance with those found in the present study, and may be related to the small number of patients or to a different experimental design.

We have previously reported that during pacing-induced angina the human heart loses K+ to a significantly greater degree than during pacing in the absence of myocardial ischemia. In this respect the human heart is
not different from that of other species, in which myocardial ischemia enhances the K⁺ loss induced by tachycardia.²⁹ In the present study there was a marked decrease in myocardial K⁺ loss during pacing after nitroglycerin, and a gain of this cation was seen in some patients despite similar heart rates during both pacing periods. This observation is difficult to explain, and it may be related to the effect of the second pacing period itself, to improvement in myocardial oxygenation, to changes in myocardial contractility, or to a direct effect of this drug on ion movements across the myocardial cell membrane. These points deserve further investigation.

Whether the changes observed in myocardial metabolism during the second pacing period are primary or secondary to the hemodynamic effects of nitroglycerin is difficult to ascertain, although the latter possibility appears more likely. In addition to the peripheral vasodilator effect of the drug there is evidence that nitroglycerin also has a direct action on the coronary blood vessels. It has been reported that during coronary angiography, coronary vasodilatation occurs after sublingual nitroglycerin,³⁶ ³⁷ but this cannot be equated with an increase in myocardial blood flow. Bernstein and co-workers¹⁰ found that sublingual nitroglycerin did not significantly change myocardial blood flow as measured by the ¹³³xeon method in patients with normal or diseased coronary vessels, although early increases have been reported using different methodology.³⁸ When the drug was administered intracoronally in large doses, however, myocardial blood flow always increased in dogs and in man¹⁹ suggesting that the coronary vascular bed is responsive to nitroglycerin.

It has been postulated on the basis of animal²⁰,²¹ and human studies¹⁹ that myocardial blood flow may be redistributed through collateral channels to ischemic areas of the heart. Recently, increased perfusion of ischemic myocardium has been shown after nitroglycerin in patients with coronary artery disease during thoracotomy by the direct subepicardial injection of ¹³³xeon.³⁶ Furthermore, regional improvement of myocardial oxygenation has been demonstrated by the work of Winbury and co-workers²² who recorded simultaneously the oxygen tension in the subepicardial and subendocardial regions of the dog heart in vivo. It was found that nitroglycerin invariably caused an increase in subendocardial PO₂, both in normal animals and in the presence of acute restriction of coronary blood flow. The available evidence supports the postulate that nitroglycerin may improve myocardial ischemia and oxygen delivery by, at least, a dual mechanism which includes peripheral vasodilatation with its hemodynamic consequences and a direct effect on the coronary vascular bed with redistribution of blood flow in the complex coronary system.

It should be kept in mind, however, that nitroglycerin may also have direct effects on the metabolism of the heart and blood vessels, and this metabolic action may be the basis for the clinical, electrocardiographic, and hemodynamic effects. There is evidence that this drug may have adrenergic blocking action on the heart,⁴⁰-⁴³ that it may act as a monoamine oxidase inhibitor in rat heart mitochondria,⁴⁴ that it may inhibit ATPase activity in homogenates of rabbit aorta,⁴⁵ and that it may reduce oxygen uptake by the rabbit aorta in therapeutic concentrations.⁴⁶ Research on the metabolic actions of nitroglycerin has been somewhat neglected in the past. More work is needed in this area, which could increase our understanding of the use of this drug in the treatment of coronary artery disease.

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