A Comparative Study of Nitroglycerin and Propranolol

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SUMMARY
The action of sublingual nitroglycerin (0.6 mg) and intravenous propranolol (0.1 mg/kg) on shortening of right ventricular fibers was investigated in patients with and without coronary artery disease. This was accomplished with a newly devised strain gauge catheter. Hemodynamic parameters and changes in the oxidation-reduction potential of heart muscle were determined. Nitroglycerin results in decrease in shortening and velocity of shortening of ventricular fibers, heart rate, left ventricular end-diastolic and systemic pressure, dp/dt, tension-time index, stroke index, peripheral resistance, and left ventricular minute work in normal and arteriosclerotic subjects. Intravenous propranolol leads to a fall in velocity of shortening of myocardial fibers, heart rate, dp/dt, stroke index, and left ventricular minute work. However, there is an increase in tension-time index and peripheral resistance with no change in systemic pressure. Left ventricular end-diastolic pressure rises significantly in arteriosclerotic patients. The myocardial oxidation-reduction potential increases after nitroglycerin whereas it falls after propranolol in normal and arteriosclerotic patients.

Additional Indexing Words:
Hemodynamics Velocity of fiber shortening Oxidation-reduction potential Lactic-pyruvic acid ratio

For almost a century nitroglycerin has been in use for the relief of angina pectoris. Brunton, who first described the anti-anginal effect of the drug, related it to the fall in arterial blood pressure due to vasodilatation of systemic vessels.

Several possibilities could explain the mechanism of the action of nitroglycerin in the relief of angina pectoris. It has been postulated that it exerts its action primarily through coronary vasodilation. However, a number of reports indicate that nitroglycerin, although increasing total coronary blood flow in normal hearts, fails to do so in the presence of coronary arteriosclerosis. Recently emphasis has been shifted to a primary peripheral action of the drug, resulting in reduction of myocardial oxygen requirements due to decreased work load of the heart. Thus, Mason and Braunwald found that nitroglycerin reduced systemic arterial pressure, elevated forearm blood flow, and decreased forearm vascular resistance. Ferrer and co-workers found no evidence of venous pooling in the splanchic area, although there was vasodilation and pooling of blood in the pulmonary vascular bed. Williams and associates discovered that, possibly as a result of peripheral vasodilation and pooling, ventricular size and intraventricular systolic pressure diminished and both end-diastolic and end-systolic ventricular dimensions decreased. Since these factors determine the degree of myocardial wall tension and since ventricular tension...
is an important determinant of myocardial oxygen consumption,\textsuperscript{19–21} a decline in myocardial tension induced by nitroglycerin could lead to a diminution in myocardial oxygen demands.

A biochemical basis of the pharmacological action of nitroglycerin has not been clearly established. Krantz and co-workers\textsuperscript{22} found that nitroglycerin inhibited ATP-ase activity in rats and postulated that this action was responsible for its vascular effect. Using very large doses of nitroglycerin, Hunter and associates\textsuperscript{23} demonstrated uncoupling of oxidative phosphorylation in liver mitochondria. Experiments by Ogawa and associates\textsuperscript{24} revealed a monoamine oxidase (MAO) inhibitory effect of nitroglycerin on rat heart.

In recent years, a new group of drugs, the beta-adrenergic blocking agents, has been investigated in the prophylactic treatment of angina pectoris.\textsuperscript{25–27} In 1948, Ahlquist\textsuperscript{28} introduced the concept of a dual alpha and beta-adrenergic receptor mechanism to explain contrasting responses to various sympathomimetic amines. Alpha-adrenergic stimulation results in arterial vasoconstriction with little direct effect on the heart, whereas beta-adrenergic activity is responsible for arterial vasodilation and for positive chronotropic and inotropic actions of the heart. The result of beta-adrenergic stimulation on the heart is an increase in myocardial oxygen consumption.\textsuperscript{29, 30} It has been thought that this increase in the oxygen demands of the heart may have a deleterious effect on patients with coronary arteriosclerosis.\textsuperscript{31} Angina pectoris often occurs at times of increased sympathetic activity, namely during exercise and emotional stress. Interruption of sympathetic stimulation may be of benefit in patients with angina of effort.\textsuperscript{32} Recently, experiments have shown that acute myocardial ischemia enhances endogenous catecholamine mobilization and a shift toward anaerobic energy production. These responses of heart muscle to ischemia were delayed and slowed by beta-adrenergic blockade.\textsuperscript{33}

The first specific beta-adrenergic blocking agent, dichloroisoproterenol (DCI), introduced by Powell and Slater\textsuperscript{34} in 1958, was reported to antagonize the positive inotropic and chronotropic actions of cardiac adrenergic stimuli. However, because of intrinsic sympathomimetic activity, DCI was found unsuitable for clinical investigation.\textsuperscript{35} In 1962, Black and Stevenson\textsuperscript{36} introduced pronethalol. This compound was an effective beta-adrenergic blocking agent, almost completely free of intrinsic sympathetic activity. It was reported to be effective in the treatment of angina pectoris,\textsuperscript{25} but it was abandoned because of cancerogenic properties.\textsuperscript{37} Finally in 1964, Black and co-workers\textsuperscript{38} described another analog of isoproterenol, propranolol. This agent is 10 times more potent than pronethalol in its beta-adrenergic blocking properties.\textsuperscript{39} It inhibits the cardiac accelerator responses to sympathetic stimulation,\textsuperscript{39} reduces myocardial blood flow, and increases myocardial resistance to flow.\textsuperscript{40} It also decreases heart rate, cardiac output, mean arterial pressure, and left ventricular minute work in response to exercise.\textsuperscript{41} In addition, propranolol has a direct myocardial depressing action when used in large doses.\textsuperscript{42} As with pronethalol, propranolol has been reported to be effective in the treatment of angina pectoris.\textsuperscript{26, 27}

The present report is a comparative study of the various cardiovascular actions of nitroglycerin and propranolol,\textsuperscript{9} on the measurements of heart rate, left ventricular pressure, and its first derivative, tension-time index, cardiac index, stroke index, and mean systolic ejection rate, peripheral resistance, and left ventricular minute work. In addition to these parameters, the effects of nitroglycerin and propranolol on directly measured myocardial fiber shortening and velocity of shortening are reported. These measurements were recorded in human subjects utilizing a new catheter strain gauge assembly (fig. 1). This device permits continuous monitoring of ventricular fiber shortening before and after administration of pharmacologic agents.
NITROGLYCERIN AND PROPRANOLOL

Figure 1

The strain gauge catheter used to determine directly myocardial fiber shortening. The built-in strain gauges are embedded between the two prongs. The strain gauge bearing stylet is threaded through a no. 8 French catheter. The prongs are lodged through the endocardium into the myocardium through a ventricular cavity.

Finally, the effects of nitroglycerin and propranolol on the oxidation-reduction potential of cardiac muscle are also reported.

Methods

Fifty-seven (57) patients are included in this study. Thirty (30) patients (group I) received nitroglycerin sublingually in a dose of 0.6 mg. Propranolol was administered intravenously in a dose of 0.1 mg/kg over a period of 2 to 4 minutes to 27 patients (group II). Seventeen (17) patients (group Ia) and 19 patients (group IIa) who underwent diagnostic catheterization were found to be free of any significant cardiac disease. The remainder of group I (group Ib, 13 patients) and group II (group IIb, eight patients) had clinical and electrocardiographic evidence of myocardial infarction with or without angina.

All subjects were in the preprandial phase and received no pre-medication. Left and right heart catheterizations with intubation of the coronary sinus were performed. Pressures were obtained through no. 7 Lehman catheters connected to a Statham P23ID strain gauge. These measurements were amplified and recorded on an Electronics for Medicine recorder (Model DR-8). The first derivative of the left ventricular pressure pulse (dp/dt) was recorded by means of a linear R-C differentiating circuit. The tension-time index (TTI) was measured from the planimetrically determined area under the left ventricular pressure curve using simultaneously recorded heart sounds to indicate the onset and termination of ventricular systole. Cardiac output was measured, using indocyanine green as the indicator.

The following formulas were used:

1. Mean systolic ejection rate (ml/sec/m²)

\[
\text{Stroke index (ml/beat/m²) = \frac{\text{Stroke volume (ml/beat)}}{\text{Systolic ejection time (sec/beat)}}}
\]

2. Peripheral resistance (dynes sec cm⁻⁵/m²)

\[
= \frac{\text{Mean aortic pressure (mm Hg)}}{\text{Cardiac index (L/min/m²)}}
\]

3. Left ventricular work (kg-m/min/m²)

\[
= \frac{\text{Mean LVSP (or ASP) (mm Hg) \times 13.6 \times CI}}{1,000}
\]

where 13.6 is the mercury conversion factor.

Direct estimation of changes in shortening and maximal velocity of shortening of myocardial fibers using a newly devised strain gauge catheter was carried out in 4 normal individuals who received nitroglycerin sublingually and in four others to whom propranolol was administered intravenously. Technical and physiological details of this instrument have been described elsewhere. This device consists of a flexible stylet with prongs at its tip, each bearing a strain gauge (fig. 2). It is inserted into a no. 8 thin-walled Lehman catheter. As the catheter moves through the cardiac cavities, the prongs are contained within the catheter. When contact is made with a certain portion of the endocardium, the two prongs are advanced and engaged in the endomyocardium by careful manipulation of the proximal end of the catheter assembly. This procedure is performed under fluoroscopy and an attempt is made to place the prongs in

Figure 2

Proximal of the strain gauge assembly with the location of the two strain gauges (all dimensions in millimeters).

*Abbreviations LVSP (or ASP) = left ventricular (or aortic) pressure; CI = cardiac index (L/min/m²).
a plane perpendicular to the apical endocardium in the frontal plane. The leads from the strain gauge are then connected to a full-bridged circuit and a recorder.*

The dimensions of the strain gauge assembly as well as the spacing of the extended prongs in the free position are shown in figure 2. The figure also shows the position of the gauges. Its frequency response was found to be uniform through the frequency range of 15 to 300 cycles/sec. A straight linear relationship was found between the spacing of the prongs and strain measured by the gauges. There was also a linear relationship between the force necessary to displace the prongs and the strain applied to the gauges. In in vitro experiments, it became evident that the force necessary to displace the prongs was a negligible factor in comparison with the force displayed by the muscle. Therefore, the strain gauge assembly measures shortening and velocity of shortening of myocardial fibers.

A constant pattern with respect to simultaneously recorded cardiac events (electrocardiogram, phonocardiogram, arterial or ventricular pressure tracings) is indicative that the prongs of the strain gauge assembly have remained as originally placed.

It has been shown in this laboratory that the difference in the lactate/pyruvate ratio between coronary vein and arterial blood (Δ Eh) bears a direct relationship to the lactate/pyruvate in the heart muscle itself. Thus, Δ Eh reflects the oxidation-reduction of the myocardium. For the determination of the difference in oxidation-reduction potential between coronary vein and arterial blood (Δ Eh), blood samples were withdrawn simultaneously from the coronary sinus and the left ventricle (or aorta) before and after administration of the drug. From these samples, coronary venous and arterial differences for lactate and pyruvate were determined. Lactate and pyruvate were measured enzymatically using the methods of Hohorst and Bücher and co-workers, respectively. The difference in oxidation-reduction potential between coronary vein and arterial blood (Δ Eh) was calculated by the following equation:

\[
\Delta \text{Eh (mv)} = 30.7 \times \log \frac{L_{a1} \times P_{y2}}{L_{a2} \times P_{y1}}
\]

where 30.7 is a known constant, La1 and Py1 are the concentrations of lactate and pyruvate in arterial blood; La2 and Py2 are the concentrations of lactate and pyruvate in coronary vein blood.

Calculations of Δ Eh must be interpreted with caution and represent at best only average values. Chance and co-workers have shown that sinusoidal and nonsinusoidal oscillations occur in a cell-free system of glycolytic enzymes; of the two, only the sinusoidal form is observed in vivo. However, while caution must be exercised in the evaluation of these data, the magnitude of the changes and their statistical significance following administration of drugs may reflect alterations in the oxygenation of heart muscle.

All determinations were made prior to the administration of the drugs. They were repeated 5 minutes after nitroglycerin and 15 minutes after propranolol.

Results

Hemodynamics

As it may be seen from table 1, after administration of nitroglycerin, the left ventricular systolic pressure decreases by 35% (P < 0.005) in normal individuals and by 21% (P < 0.001) in arteriosclerotic patients. In both groups there are equally significant falls in left ventricular end-diastolic pressure (P < 0.001), mean aortic pressure (P < 0.005), TTI per beat (P < 0.005). The first derivative of the left ventricular pressure (dp/dt) declines in group Ia by 15% (P < 0.025) and in group Ib by 11% (P < 0.02). Although the fall in cardiac index is not significant (P > 0.9) in normal individuals, there is a significant fall in arteriosclerotic patients (P < 0.01). The significant increase in heart rate in both groups (P < 0.001) is associated with a significant decrease in stroke index (group Ia, P < 0.005; group Ib, P < 0.001). The mean systolic ejection rate falls by 37% (P < 0.02) in normal individuals, and by 31% (P < 0.01) in arteriosclerotic patients. There are significant declines in TTI per minute (group Ia, P < 0.02; group Ib, P < 0.001), peripheral resistance (group Ia, P < 0.01; group Ib, P < 0.05) and left ventricular minute work (group Ia, P < 0.025; group Ib, P < 0.01).

Table 2 summarizes the hemodynamic responses of normal and arteriosclerotic patients to propranolol administration. In both groups there is a significant fall in heart rate (P < 0.001), dp/dt (P < 0.005), and cardiac index (P < 0.001). The changes in mean aortic and left ventricular systolic pressures are not

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*Electronics for Medicine (Model DR-8).
### Table 1

#### Hemodynamic Effects of Nitroglycerin

<table>
<thead>
<tr>
<th></th>
<th>Normal individuals</th>
<th></th>
<th>Patients with coronary heart disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean of change</td>
<td>Significance of change</td>
<td>% of change</td>
<td>Mean of change</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>19 ± 8.13</td>
<td>&lt; 0.001</td>
<td>27</td>
<td>15 ± 13.23</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>43 ± 30.76</td>
<td>&lt; 0.005</td>
<td>-35</td>
<td>24 ± 17.11</td>
</tr>
<tr>
<td>(mm Hg) EDP =</td>
<td>5 ± 3.36</td>
<td>&lt; 0.001</td>
<td>-86</td>
<td>7 ± 3.78</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>29 ± 17.80</td>
<td>&lt; 0.005</td>
<td>-38</td>
<td>22 ± 11.63</td>
</tr>
<tr>
<td>TTI/beat (mm Hg sec)</td>
<td>12.51 ± 9.81</td>
<td>&lt; 0.005</td>
<td>-40</td>
<td>8.40 ± 6.07</td>
</tr>
<tr>
<td>TTI/min (mm Hg sec/min)</td>
<td>558 ± 598.84</td>
<td>&lt; 0.02</td>
<td>-26</td>
<td>343 ± 238.33</td>
</tr>
<tr>
<td>dp/dt (mm Hg/sec)</td>
<td>270 ± 260.33</td>
<td>&lt; 0.025</td>
<td>-15</td>
<td>187 ± 206.41</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>0.2 ± 0.64</td>
<td>&gt; 0.9</td>
<td>-12</td>
<td>0.2 ± 0.15</td>
</tr>
<tr>
<td>Stroke index (ml/min/m²)</td>
<td>15 ± 6.41</td>
<td>&lt; 0.005</td>
<td>-33</td>
<td>13 ± 11.02</td>
</tr>
<tr>
<td>MSER (ml/sec/m²)</td>
<td>62 ± 38</td>
<td>&lt; 0.02</td>
<td>-37</td>
<td>48 ± 33.11</td>
</tr>
<tr>
<td>PR (dyne sec cm⁻⁵/m²)</td>
<td>349 ± 244.64</td>
<td>&lt; 0.01</td>
<td>-15</td>
<td>368 ± 339.98</td>
</tr>
<tr>
<td>LVW (kg-m/min/m²)</td>
<td>1.4 ± 1.07</td>
<td>&lt; 0.025</td>
<td>-38</td>
<td>1.69 ± 1.19</td>
</tr>
</tbody>
</table>

Abbreviations: LVP = left ventricular pressure; S = systolic pressure; EDP = end-diastolic pressure; TTI = tension-time index; MSER = mean systolic ejection rate; PR = peripheral resistance; LVW = left ventricular minute work.
### Hemodynamic Effects of Propranolol

<table>
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<th>Patients with coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean of change</td>
<td>Significance of change</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 ± 5.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>1 ± 3.1</td>
<td>&gt; 0.4</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>2 ± 1.25</td>
<td>&gt; 0.6</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>2 ± 4.44</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>TTI/beat (mm Hg sec)</td>
<td>1.23 ± 1.55</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>TTI/min (mm Hg sec/min)</td>
<td>38 ± 109.44</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>dp/dt (mm Hg/sec)</td>
<td>310 ± 253.50</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.0 ± 0.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke index (ml/min/m²)</td>
<td>10 ± 6.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MSER (ml/sec/m²)</td>
<td>39 ± 29.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PR (dyne sec cm⁻⁵/m²)</td>
<td>720 ± 385.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVW (kg·m/min/m²)</td>
<td>1.26 ± 0.73</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: LVP = left ventricular pressure; S = systolic pressure; EDP = end-diastolic pressure; TTI = tension-time index; MSER = mean systolic ejection rate; PR = peripheral resistance; LVW = left ventricular minute work.
Nitroglycerin and Propranolol

Figure 3

Effects of nitroglycerin upon right ventricular fiber shortening. The curves were recorded with a specially devised strain gauge catheter. The electrocardiogram, right ventricular pressure, and phonocardiogram were simultaneously recorded. There is a 37% decrease in myocardial fiber shortening with an associated decrease of 56% in maximal velocity of myocardial fiber shortening (patient R.T.).

Table 3

Effects of Nitroglycerin upon Right Ventricular Fiber Shortening

<table>
<thead>
<tr>
<th>Patient's initials</th>
<th>Age (yr), sex</th>
<th>Change in myocardial fiber (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.T.</td>
<td>28 F</td>
<td>-37</td>
</tr>
<tr>
<td>B.T.</td>
<td>35 M</td>
<td>-24</td>
</tr>
<tr>
<td>L.S.</td>
<td>36 M</td>
<td>-22</td>
</tr>
<tr>
<td>A.W.</td>
<td>45 M</td>
<td>-15</td>
</tr>
<tr>
<td>Average change (%)</td>
<td>-25</td>
<td>-32</td>
</tr>
</tbody>
</table>

Figure 4

Effects of intravenous propranolol upon right ventricular fiber shortening. There is a 19% decrease in myocardial fiber shortening with a concomitant drop of 22% in maximal velocity of myocardial fiber shortening (patient A.B.).

Table 4

Effects of Propranolol on Right Ventricular Fiber Shortening

<table>
<thead>
<tr>
<th>Patient's initials</th>
<th>Age (yr), sex</th>
<th>Change in myocardial fiber (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.B.</td>
<td>35 F</td>
<td>-19</td>
</tr>
<tr>
<td>R.S.</td>
<td>42 M</td>
<td>-16</td>
</tr>
<tr>
<td>T.A.</td>
<td>38 M</td>
<td>-10</td>
</tr>
<tr>
<td>O.B.</td>
<td>45 F</td>
<td>-9</td>
</tr>
<tr>
<td>Average change (%)</td>
<td>-14</td>
<td>-17</td>
</tr>
</tbody>
</table>

(group IIa, P < 0.001; group IIb, P < 0.01). The peripheral resistance increases by 34% (P < 0.001) in normal subjects and by 70% (P < 0.005) in arteriosclerotic patients.

Myocardial Fiber Shortening and Change of Maximal Velocity of Fiber Shortening

Fiber shortening was recorded from the apex of the right ventricle during diagnostic catheterization.

An example of the effect of sublingual nitroglycerin upon shortening of right ventricular fibers is illustrated in figure 3. Administration of the drug results in an average drop of 25% in fiber shortening with an associated average fall of 32% in maximal velocity of ventricular fiber shortening after 5 minutes (table 3).
Intravenous propranolol causes an average decrease of 14% in myocardial fiber shortening after 15 minutes. There is a concomitant average decrease of 17% in maximal velocity of fiber shortening (table 4). Such a response is exemplified in figure 4.

**Oxidation-Reduction Potential of Heart Muscle**

The average baseline $\Delta$ Eh (oxidation-reduction potential of heart muscle as determined indirectly by the difference in lactate/pyruvate ratio between coronary vein and arterial blood expressed in millivolts) is positive in normal subjects and negative in arteriosclerotic patients. The negative values for $\Delta$ Eh in the latter group suggests myocardial hypoxia. Nitroglycerin results in a significant rise in $\Delta$ Eh in both normal ($P < 0.05$) and arteriosclerotic subjects ($P < 0.025$) (fig. 5) indicating improvement in the oxidative metabolism of the heart.

After propranolol, the fall in $\Delta$ Eh is insignificant in the normal group ($P > 0.05$); in contrast, the decrease in the arteriosclerotic group is significant ($P < 0.05$). This latter response suggests that intravenous propranolol results in an impairment of myocardial oxygenation in patients with coronary artery disease (fig. 6).

**Discussion**

Some of the hemodynamic responses to nitroglycerin administration confirm the data reported in the literature (table 1). The decrease in the systemic arterial pressure is the main factor in the observed decrease in tension-time index (TTI), peripheral resistance, and left ventricular minute work.

The drop in left ventricular systolic and end-diastolic pressures and in stroke index may be related to a decrease in ventricular filling as a consequence of peripheral pooling of blood. Ferrer and associates reported pooling of blood in the pulmonary vascular bed. Williams and co-workers demonstrated diminished systolic and end-diastolic dimensions after nitroglycerin and attributed this finding to diminished venous return. According to Laplace's law a decrease in ventricular pressure and dimension contribute toward diminished myocardial wall tension and thus to a decline in oxygen demands of the heart.
Following intravenous administration of propranolol (table 2), the decrease in heart rate, cardiac output, stroke volume, and left ventricular minute work observed in the present study is comparable with the findings of other workers.\textsuperscript{41, 49, 50} There is an increase in peripheral resistance with no significant change in mean aortic and left ventricular systolic pressures in normal and arteriosclerotic subjects.\textsuperscript{50, 51} In contrast, studies by Epstein and associates\textsuperscript{41} demonstrated that cardiac output and mean aortic pressure diminished to the same extent so that peripheral resistance remained essentially unchanged.

After propranolol, the tension-time index per beat rises significantly in both groups. This is due to an increase in the duration of ventricular systole.\textsuperscript{49} As a result of slowing of the heart rate, the tension-time index per minute decreases but this drop is insignificant.

Following nitroglycerin the mean systolic ejection rate falls solely as a function of a decline in stroke index. Propranolol results also in a decrease in stroke index and mean systolic ejection rate. However, the drop in the latter is also due to an increase in systolic ejection time.\textsuperscript{49}

The increase in left ventricular end-diastolic pressure observed after propranolol in this study suggests that the adrenergic nervous system plays an important and supportive role in cardiac function in patients with coronary heart disease. The heart normally responds to exercise by a decrease in its systolic and diastolic diameters.\textsuperscript{52} This response is abolished by beta-adrenergic blockade,\textsuperscript{52, 53} and it is often absent in arteriosclerotic subjects.\textsuperscript{54} The augmented activity of the sympathetic nervous system observed in congestive heart failure may be present in coronary heart disease. In both conditions, a deficit in cardiac catecholamines and an increase in plasma and urinary catecholamines have been reported.\textsuperscript{54–56}

Direct measurements of right ventricular fiber shortening were performed following nitroglycerin and propranolol. This was made possible by a newly developed strain gauge assembly. As seen in table 3, nitroglycerin decreases shortening and velocity of shortening of ventricular fibers. This response may be related to a decrease in end-diastolic fiber length. Williams and associates\textsuperscript{16} reported a 13.3% fall in right ventricular systolic excursions associated with 5% decrease in right ventricular end-diastolic length in normal individuals after nitroglycerin administration. Previous experiments by Hill\textsuperscript{57, 58} have demonstrated that the rate of heat production was proportional to the velocity of muscle shortening. Recently, Sonnenblick and co-workers\textsuperscript{59} using the maximum and mean rates of ventricular ejection and the rate of left ventricular pressure rise (dp/dt) as determinants of velocity of myocardial fiber shortening, showed a good, direct correlation between myocardial oxygen consumption and velocity of contraction. Thus, reduction in oxygen requirements of the heart may be attributed to the decrease in ventricular wall tension and velocity of myocardial fiber shortening after nitroglycerin administration. These factors are also responsible for the observation that the drug improves the oxidative state of the myocardium as reflected by a rise in $\Delta$Eh (the difference in lactate/pyruvate ratio between coronary vein and arterial blood expressed in millivolts).

Intravenous propranolol results also in a decrease in shortening and velocity of shortening of ventricular fibers (table 4). In contrast to nitroglycerin, this decrease is accompanied by an increase in left ventricular end-diastolic pressure and ventricular wall tension (TTI). Our observations are in agreement with those of Murray and associates\textsuperscript{60} who found an increase in left ventricular end-diastolic pressure and left ventricular transmural pressure and a decrease in mean circumferential shortening velocity in anesthetized dogs after propranolol administration. In our study the oxygen-sparing effect due to a decline in velocity of myocardial fiber shortening is offset by the increase in left ventricular wall tension. The result of these different hemodynamic interactions is an impairment of myocardial cellular oxidation as
reflected in a decrease in $\Delta$ Eh in normal as well as in arteriosclerotic subjects.

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References


References

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Myocardial Infarction
Well of Ignorance

A systematic review of our understanding of myocardial infarction and its management produces a startling picture of ignorance. Even the classic formulation that coronary occlusion, thrombotic or otherwise, precedes ischemic necrosis which is responsible for the life threatening manifestations of the disease is now clearly inadequate. We are constrained to admit that we do not understand the cause of myocardial infarction in the sense that we do not usually know what converts coronary artery disease into myocardial infarction.

We do not know the natural course of myocardial infarction with sufficient certainty to judge the effect of even major interventions.

We have little insight into the factors which determine the course of the disease. What are the metabolic determinants of death or survival of the ischemic cell? We really don't know what kills the cell!

... We are very limited in our ability to make a quantitative diagnosis—that is to determine the size of the infarction, the adequacy of the primary and collateral circulation and the state of other body systems which are relevant.

I do not believe that a single order which we write on the chart of the patient with myocardial infarction rests upon as sound a scientific basis as the orders we write in the management of diabetic acidosis or acute infectious disease.

... No one knows when the negative effects of restricted activity may outweigh the advantages.

... Nothing is known of the mechanism of this complication (electromechanical uncoupling as a terminal phenomenon) and to my knowledge treatment has been uniformly unsuccessful.

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BING

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