Hemodynamic Effects of Nitroglycerin, Propranolol, and Their Combination in Coronary Heart Disease

By Leslie Wiener, M.D., Edward M. Dwyer, Jr., M.D., and J. William Cox, M.D., Ph.D.

SUMMARY

The hemodynamic effects of 10 mg of propranolol given intravenously (iv) were studied in 10 patients (group I) with coronary heart disease (CHD). These results were compared with the hemodynamic effects in a similar group of the nine (CHD) patients (group II) who were studied after administration of 0.6 mg of nitroglycerin and then after receiving 10 mg of propranolol iv with a second 0.6-mg dose of nitroglycerin. Measurements were obtained at rest and during exercise: before treatment, after nitroglycerin alone, after propranolol alone, and after nitroglycerin-propranolol in combination. Pretreatment exercise showed a 125% increase in mean pulmonary artery pressure (PAP) to 43 mm Hg and a 163% increase in left ventricular end-diastolic pressure (LVEDP) to 29 mm Hg. Nitroglycerin decreased PAP (−45%) and LVEDP (−66%); as did nitroglycerin-propranolol: PAP (−33%) and LVEDP (−38%). Nitroglycerin reduced tension-time index (TTI) −21%, and increased cardiac index (CI) +17%, heart rate (HR) +10%, left ventricular work index (LVWI) +11%, and left ventricular dp/dt (LV dp/dt) +22%. By contrast, nitroglycerin-propranolol reduced LVWI −14%, LV dp/dt −30%, TTI −15%, and HR −13% but did not significantly alter CI from pretreatment.

Propranolol increased PAP to 40 mm Hg, did not change LVEDP at 29 mm Hg and decreased stroke index (SI) 16%. Nitroglycerin-propranolol diminished PA and LVED pressure and increased SI 14%. Effects of propranolol alone and of nitroglycerin-propranolol on HR, TTI, and LV dp/dt were not significantly different.

Nitroglycerin-propranolol appears to have important advantages over nitroglycerin or propranolol alone. A reduction in HR, TTI, and LV dp/dt, determinants of myocardial oxygen consumption, concurrent with improved left ventricular function, demonstrates a beneficial synergistic hemodynamic action for nitroglycerin combined with propranolol.

Additional Indexing Words: Left ventricular hemodynamics Exercise hemodynamics

Since 1859 nitrates have demonstrated clinical value in the treatment of angina pectoris. Nonetheless, the mechanisms of action of nitroglycerin and chemically related compounds remain a subject of continued controversy. Evidence obtained predominantly by indirect means suggests that the drug's beneficial effect results from reduced cardiac work and coronary vasodilation or both.1-4


The opinions expressed herein are those of the authors and cannot be construed as reflecting the views of the Navy Department or the Naval Service at large.
Evaluations of nitroglycerin's actions directly measured from the left ventricle are limited in scope and are infrequently performed during exercise.

The development of drugs capable of selectively blocking beta sympathetic receptor sites coupled with the well-known aggravating effects of local and circulating catecholamines on the ischemic heart has provided a pharmacological basis for studies in patients with angina pectoris. Presently the evidence for a favorable therapeutic response to beta-adrenergic blockers appears well supported.\textsuperscript{5-7} Amelioration of angina pectoris apparently derives from attenuation of positive chronotropic and inotropic cardiac responses, thereby diminishing myocardial oxygen requirements.\textsuperscript{8} Information describing the effects of propranolol, a beta-adrenergic blocker, on the left ventricle during physical activity is available;\textsuperscript{9, 10} however, comparisons with the actions of nitroglycerin under similar conditions have not been examined.

Studies by McAlpin and co-workers\textsuperscript{10} and Russek,\textsuperscript{11} involving patients with angina pectoris have shown that beta-adrenergic blockade in combination with nitrates is capable of increasing exercise tolerance, delaying the onset of pain, and diminishing ischemic electrocardiographic responses beyond that which could be achieved by either drug independently. The purpose of this investigation is to observe the effects of exercise on left ventricular function in patients with angina pectoris and coronary artery disease proven by angiography and to compare these responses with those following the administration of nitroglycerin, propranolol, and both drugs in combination.

Methods

These studies were performed on 19 male subjects, undergoing diagnostic coronary arteriography. Control determinations at rest and exercise were made prior to drug therapy. Patients were then divided into two groups. Group I (10 patients) was studied after receiving propranolol, 10 mg iv alone. Group II (nine patients) was studied initially, after receiving sublingual nitroglycerin, 0.6 mg, and restudied following administration of propranolol, 10 mg iv, and a second 0.6-mg sublingual dose of nitroglycerin. An additional dose of nitroglycerin was decided upon since a 32-minute interval (vide infra) preceded repeat measurements. Consequently, the pharmacological effects of the initial dose of this short-acting drug were presumed to have been essentially dissipated. The age range was 30 to 59 (mean, 47 years). Patients with symptoms or signs of congestive heart failure, valvular and hypertensive heart disease, or pulmonary disease were excluded. Selective coronary cineangiography demonstrated greater than 50% obstruction of at least one of the three major arteries in all cases.

All patients were brought to the laboratory on the day prior to the study. The procedures were explained, and each subject was exercised in the supine position on a bicycle ergometer. A work load of maximal tolerance was selected which produced angina, dyspnea, or fatigue but permitted 3 minutes of continuous exercise. Subsequent exercise studies were performed at the same work load and duration. All studies were conducted in the fasting state. Premedication consisted of pentobarbital (100 mg p.o.). Under local anesthesia (lidocaine 1%), the right brachial artery and vein were isolated. Right heart catheterization was performed using a no. 8 100-cm Cournand catheter. Retrograde left heart catheterization was performed with a Statham SF-1 catheter manometer. The left brachial artery was cannulated with a no. 18 Teflon needle. Measurements of pulmonary artery pressure, left ventricular pressure and its first derivative, brachial artery pressure, and cardiac output were analyzed at rest and during exercise, beginning 2 minutes after onset. Fifteen minutes following control measurements, patients in group I were given propranolol (10 mg iv) and 15 minutes thereafter, measurements were repeated during rest and exercise.

Group II patients were studied in the following sequence: (1) Fifteen minutes after control measurements, nitroglycerin, 0.6 mg, was administered sublingually. Two minutes later rest values were obtained and were followed immediately by a repeat exercise study. (2) Fifteen minutes after exercise propranolol (10 mg iv) was given, and after another 15-minute waiting period nitroglycerin, 0.6 mg, was again administered sublingually. Two minutes later resting and exercise values were determined.

The hemodynamic changes during control conditions were compared to those obtained after use of propranolol and nitroglycerin alone as well as in combination. Comparisons of control conditions with drug effects were made separately for group I and group II.
Table 1

Summary of Hemodynamic Effects of Nitroglycerin and Propranolol in Patients with Coronary Artery Disease and Angina Pectoris in the Resting State

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 10</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>140 ± 19</td>
<td>132 ± 18</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12 ± 4</td>
<td>13 ± 5</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>14 ± 3</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>LV dp/dt (mm Hg/sec)</td>
<td>1570 ± 320</td>
<td>1273† ± 439</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.7 ± 0.2</td>
<td>2.3† ± 0.5</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>35 ± 4</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>LVWI (kg-m/beat/m²)</td>
<td>4.7 ± 0.5</td>
<td>3.7† ± 0.7</td>
</tr>
<tr>
<td>SWI (kg-m/beat/m²)</td>
<td>61 ± 4</td>
<td>51 ± 3</td>
</tr>
<tr>
<td>MSER (ml/sec/m²)</td>
<td>116 ± 21</td>
<td>101† ± 26</td>
</tr>
<tr>
<td>TTI (mm Hg sec/min)</td>
<td>2755 ± 423</td>
<td>2678 ± 123</td>
</tr>
<tr>
<td>BA pressure (mm Hg)</td>
<td>100 ± 13</td>
<td>116 ± 15</td>
</tr>
</tbody>
</table>

* ±1 Standard error of the mean.
† Statistically significant (P < 0.05) reduction from control values.
‡ Statistically significant (P < 0.05) increase from control values.

Abbreviations: LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; PAP = mean pulmonary artery pressure; LV dp/dt = first derivative of left ventricular pressure pulse; LVWI = left ventricular work index; SWI = stroke work index; MSER = mean systolic ejection rate; TTI = tension-time index; BA pressure = mean brachial artery pressure.
Table 2

Summary of Hemodynamic Effects of Nitroglycerin and Propranolol in Patients with Coronary Artery Disease and Angina Pectoris During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
<td>Control</td>
<td>Nitroglycerin</td>
<td>Propranolol-nitroglycerin</td>
</tr>
<tr>
<td></td>
<td>Mean  ± s.e.</td>
<td>Mean  ± s.e.</td>
<td>Mean ± s.e.</td>
<td>Mean ± s.e.</td>
<td>Mean ± s.e.</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>111 ± 7</td>
<td>103±11</td>
<td>123 ± 9</td>
<td>131 ± 16</td>
<td>107±7</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>172 ± 19</td>
<td>161±20</td>
<td>169 ± 19</td>
<td>151±15</td>
<td>151±15</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>27 ± 8</td>
<td>29±10</td>
<td>30 ± 10</td>
<td>10±3</td>
<td>10±4</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>35 ± 7</td>
<td>40±8</td>
<td>34 ± 9</td>
<td>18±2</td>
<td>21±5</td>
</tr>
<tr>
<td>LV dp/dt (mm Hg/sec)</td>
<td>2618 ± 815</td>
<td>1748±600</td>
<td>2562 ± 832</td>
<td>3297±882</td>
<td>1831±362</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>4.2 ± 6</td>
<td>3.3±1.1</td>
<td>4.4 ± 0.6</td>
<td>4.6 ± 0.9</td>
<td>3.8±0.8</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>37 ± 4</td>
<td>31±9</td>
<td>32 ± 5</td>
<td>35±10</td>
<td>36±8</td>
</tr>
<tr>
<td>LVWI (kg-m/min/m²)</td>
<td>8.0 ± 2</td>
<td>5.7±1.6</td>
<td>8.1 ± 2.1</td>
<td>8.9 ± 2.8</td>
<td>6.9±1.7</td>
</tr>
<tr>
<td>SWI (kg-m/beat/m²)</td>
<td>73 ± 6</td>
<td>55±4</td>
<td>68 ± 5</td>
<td>68±8</td>
<td>64±5</td>
</tr>
<tr>
<td>MSER (ml/sec/m²)</td>
<td>156 ± 31</td>
<td>111±36</td>
<td>139 ± 24</td>
<td>161±40</td>
<td>126±28</td>
</tr>
<tr>
<td>TTI (mm Hg sec/min)</td>
<td>4875 ± 950</td>
<td>4218±810</td>
<td>5254 ± 1130</td>
<td>4323±650</td>
<td>4490±685</td>
</tr>
<tr>
<td>BA pressure (mm Hg)</td>
<td>127 ± 14</td>
<td>120±18</td>
<td>123 ± 13</td>
<td>117±13</td>
<td>110±10</td>
</tr>
</tbody>
</table>

* ±1 Standard error of the mean.
† Statistically significant (P < 0.05) reduction from control values.
‡ Statistically significant (P < 0.05) increase from control values.
Abbreviations: Same abbreviations as in Table 1.
Coronary Heart Disease

Pressures other than those from the left ventricle were measured with a Statham 23 Db strain-gauge transducer. Mean pressures were obtained by electronic filtering. Left ventricular end-diastolic pressure was determined from high amplification pressure tracings. The first derivative of the left ventricular pressure curve was measured using an R/C differentiating circuit.* Cardiac output determinations were made by the dye-dilution technic using indocyanine green (Cardio-Green) as an indicator. The indicator was injected into the pulmonary artery and withdrawn from the brachial artery at a constant flow rate with a Harvard withdrawal-perfusion pump. A Gilford cuvette densitometer was coupled to the input of a Gilford dye-dilution computer. Dye curves and pressures were recorded by an oscillographic photographic recorder (DR-8, Electronics for Medicine) at 25 and 75 mm/sec.

The dye curve was measured by planimetry and the cardiac output was calculated by the standard Hamilton formula. The following formulas were used:

Left ventricular work index (mg·min/m²) = \[
\frac{LVSP - LVEDP \times 1.36 \times CI}{100}
\] (1)

Stroke work index (mg·beat/m²) = \[
\frac{LVSP - LVEDP \times 1.36 \times SI}{100}
\] (2)

Mean systolic ejection rate (ml/sec/m²) = \[
\frac{SI}{SEP}
\] (3)

Tension-time index (g·m/sec/m²) = mean LVSP \times \text{heart rate} \times SEP (4)

where LVSP = left ventricular systolic pressure, LVEDP = left ventricular end-diastolic pressure, CI = cardiac index, SI = stroke index, and SEP = systolic ejection period.

All results were statistically analyzed by Student's t-test.

Figure 1

Summary of the mean rest and exercise effects of nitroglycerin, propranolol, and nitroglycerin-propranolol on: (A) heart rate, (B) left ventricular systolic pressure, (C) left ventricular dp/dt max, (D) left ventricular tension-time index. * (Asterisk) indicates a significant change from control.

*Electronics for Medicine, White Plains, New York.
Results

The data are compiled in tables 1 and 2 and summarized in graphic form in figures 1 and 2.

Hemodynamic Measurements
Before Drug Therapy
(Group I and II Controls)

Resting values were all within normal limits. During exercise, the left ventricular end-diastolic pressure (LVEDP) rose 172% (11 to 30 mm Hg) while the mean pulmonary artery pressure (PAP) increased 125% from 15 to 34 mm Hg. The effects of exercise on left ventricular systolic pressure (LVSP) +25%, left ventricular first derivative (LV dp/dt) +70%, cardiac index (CI) +57%, left ventricular work (LVW), +68% and tension-time index (TTI), +70% were similar to those reported previously by us in angina patients of comparable age and at similar work loads. All changes occurring from rest to exercise were significant \((P<0.01)\). No statistically significant hemodynamic differences at rest or exercise were observed between groups I and II before drug therapy.

Hemodynamic Alterations at Rest and During Exercise Following Administration of Nitroglycerin

Following administration of 0.6 mg of nitroglycerin, the resting heart rate increased from 76 to 94 beats/min \((P<0.05)\), and LV dp/dt rose 20% \((P<0.05)\). LVSP \((-15%)\), LVEDP \((-55%)\), and LVWI \((-29%)\) all demonstrated significant \((P<0.05)\) declines after the drug.

Exercise hemodynamics, under the influence of nitroglycerin, were altered from control exercise values in a manner similar to the alterations seen during rest when nitroglycerin was given. The LV dp/dt reached a higher...
peak value, 3,297 mm Hg/sec \( (P < 0.05) \) than was observed during control exercise (2,562 mm Hg/sec). Concurrently, considerable reductions \( (P < 0.05) \) were found in LVSP \(-11\%\) and LVEDP \(-66\%\). Average heart rate and LVWI were higher than during control exercise; however, the difference was not significant at the 0.05 level.

**Comparison of the Hemodynamic Effect of Propranolol with Control Values and with Nitroglycerin Response**

At rest, the major effect of propranolol was a reduction of LV dp/dt of \(-20\%\), LVWI of \(-21\%\), and the mean systolic ejection rate (MSER) of \(-12\%\); all changes were significant at the 0.05 level. The drug had no significant effect of heart rate, LVSP, or LVEDP.

Exercise measurements following administration of propranolol were compared to control exercise values. After propranolol, average exercise values of LV dp/dt decreased \(-34\%\), LVWI \(-31\%\), and MSER \(-28\% \( (P < 0.05) \). In addition, beta-adrenergic blockade demonstrated a significant decrease of heart rate \(-11\%\) and LVSP \(-7\% \( (P < 0.05) \). The abnormal LVEDP response to exercise was not altered by propranolol. On all functions measured, propranolol exerted a more pronounced effect during exercise than during rest.

Comparison of the effects of nitroglycerin and propranolol with control values at rest demonstrated similar reductions in LVSP, CI, SI, LVWI, SWI, MSER, and TTI. During exercise only LVSP and TTI were reduced by the action of both drugs. An increase in heart rate and LV dp/dt was seen after nitroglycerin at both rest and exercise. By contrast, propranolol reduced heart rate and LV dp/dt. The most pronounced difference between the two drugs was their effect on the LVEDP. Nitroglycerin produced a marked reduction in LVEDP at rest \(-55\% \) and during exercise \(-66\% \( (P < 0.05) \). Propranolol failed to alter LVEDP significantly from the control level.

**Hemodynamic Effects of Nitroglycerin-Propranolol Combination**

The combination of nitroglycerin and propranolol demonstrated several important ac-

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observed vasodilation and pooling of blood in the pulmonary vascular bed. Williams and co-workers\textsuperscript{17} ascribed reductions in end-systolic and diastolic ventricular dimensions as well as intraventricular pressure to the effects of vascular pooling and diminished venous return.

Following nitroglycerin, observations of increased left ventricular dp/dt both at rest and during exercise suggest that the drug may have inotropic properties. Wallace and co-workers\textsuperscript{18} exploring the hemodynamic determinants of the maximal rate of rise of left ventricular pressure under controlled conditions showed that dp/dt max increases directly with increases in left ventricular end-diastolic pressure, mean aortic pressure, aortic diastolic pressure, and heart rate. As a consequence, it is apparent that left ventricular dp/dt max is a complex function, subject to changes not necessarily affecting the intrinsic contractile state. However, an increase in LV dp/dt of 28\%, while aortic pressure (mean and diastolic) and left ventricular end-diastolic pressure diminish and heart rate increases only 15\%, implies inotropic activity. Employing the regression equation derived from Wallace's study, left ventricular dp/dt max as a function of heart rate shows an expected increase of only 13\% at heart rates comparable to our experimental conditions. This increment is less than that resulting from nitroglycerin (+28\%) particularly under conditions of declining ventricular diastolic pressure and aortic pressure. In addition, nitroglycerin was observed to shift the work-to-pressure relationship to the left and superiorly (fig. 2) indicating enhanced left ventricular performance. Similar results were obtained by Arborelius and associates.\textsuperscript{19} These findings imply that the beneficial effects of this drug are not likely the result of reduced external work of the heart as suggested by Christenson and co-workers.\textsuperscript{20} Darby and associates,\textsuperscript{21} measuring myocardial force directly in dogs, have confirmed that nitroglycerin increases contractile force. Because this effect is prevented by sympathectomy, they concluded that the positive inotropic response results from sympathetic reflex activity induced by a fall in arterial pressure. The present study confirms these observations since the increase in left ventricular dp/dt produced by nitroglycerin is prevented by beta-adrenergic blockade (propranolol).

Although the potent coronary vasodilating effect of nitroglycerin has been well demonstrated by coronary arteriography,\textsuperscript{22} no resultant sustained increase in coronary blood flow has been apparent in patients with coronary heart disease.\textsuperscript{23} Nonetheless, Farn and McGregor\textsuperscript{24} suggested that the primary therapeutic role of nitroglycerin is the selective coronary vasodilation of collateral vessels providing thereby enhanced retrograde flow to areas of myocardial ischemia. In studies of normal man where increments in coronary blood flow have been measured at more than 60\%, coronary sinus oxygen values failed to increase, and this suggested a "malignant" dilating effect of nitroglycerin.\textsuperscript{25} Increased heart rate and left ventricular dp/dt max at rest and during exercise, following nitroglycerin administration, offer indirect support for a deleterious augmentation of myocardial oxygen consumption, since heart rate and rate of tension development are well recognized as functions of cardiac oxygen consumption.\textsuperscript{26-28} Although tension-time index declines after nitroglycerin, recent studies by Sonnenblick and associates\textsuperscript{29} and Monroe\textsuperscript{30} indicate that left ventricular dp/dt max more closely approximates myocardial oxygen consumption.

By contrast with nitroglycerin, propranolol failed to alter favorably the functional effects of exercise on the ischemic ventricle, as evidenced by left ventricular end-diastolic and pulmonary pressure responses that were unchanged from control. When analyzed by cardiac function curves (fig. 2), the reduction in stroke index from a comparable level of end-diastolic pressure implies a further reduction in contractile properties.\textsuperscript{31} The benefits accrued from propranolol appear to result from effects generally different from those of nitroglycerin and do not seem related to a direct action on the coronary arteries. Indeed such undesirable responses as decreased coronary blood flow, widened A-V oxygen
difference and increased coronary vascular resistance have been demonstrated following propranolol. Earlier studies by Moir and DeBra, as well as those conducted in this laboratory, support the view that the beneficial action of propranolol derives predominantly from suppression of contractility and heart rate, thereby decreasing cardiac oxygen demands.

The combination of propranolol and nitroglycerin favorably altered left ventricular function during exercise by increasing mean systolic ejection rate and stroke work while reducing left ventricular end-diastolic pressure. Thus the desirable properties of nitroglycerin, reflecting improved left ventricular performance, are retained. With the addition of propranolol, left ventricular work, dp/dt tension-time index, and heart rate are significantly reduced from control values; these observations imply decreased cardiac oxygen requirements. Accordingly, this drug combination affords a unique balance whereby the salutary responses of each drug alone are altered minimally while less desirable properties are effectively attenuated. These data impart hemodynamic confirmation to the views of Russek and McAlpin and associates that a synergistic action exists between beta-adrenergic blockers and nitrates.

References


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