Immediate Hemodynamic Effects of Beta-Adrenergic Blockade with Propranolol in Normotensive and Hypertensive Man

By Milos Ulrych, M.D., Edward D. Frohlich, M.D., Harriet P. Dustan, M.D., and Irvine H. Page, M.D.

SUMMARY
Immediate hemodynamic effects of beta-adrenergic blockade were determined in six normal subjects and 21 hypertensive patients following intravenous administration of propranolol. Arterial pressure was not reduced, but cardiac output fell by approximately 20% in both groups. Nevertheless, beta-adrenergic inhibition seemed to have different effects in the two groups: Propranolol produced a greater inhibition of chronotropic activity in the hypertensive patients, and of stroke volume in the normotensive individuals whose pretreatment heart rate was slower than that of the hypertensives. This difference suggests that chronotropic beta-adrenergic activity may be increased in hypertension but does not explain reduction in arterial pressure following oral treatment with propranolol.

Additional Indexing Words:
Renovascular hypertension     Labile hypertension     Essential hypertension
Cardiac output

ELEVATED ARTERIAL PRESSURE in hypertension has been ascribed to increased peripheral resistance since cardiac output is normal.1 Beta-adrenergic receptor stimulation produces peripheral vasodilation, increased heart rate, and myocardial contractility. Inhibition of beta receptors should therefore increase vascular resistance and decrease cardiac output. Since cardiac output may be elevated in juvenile,2 labile,3 mild essential,4,5 and renovascular hypertension,6 the reported efficacy of beta-adrenergic blocking drugs in treating hypertension7,8 may be explained by reduction of output in these individuals.

In order to provide further information concerning the mechanism of blood pressure reduction in hypertension following beta-adrenergic blockade, the present study was performed to determine the immediate effects of propranolol in normotensive individuals and patients having either essential, labile, or renovascular hypertension.

Methods
Twenty-seven subjects, six healthy normotensive volunteers, and 21 patients with essential (eight), labile (seven), or nonatherosclerotic renovascular (six) hypertension were the subjects of this study. These individuals were selected from a larger group of normotensive subjects and hypertensive patients because they had no evidence of cardiac failure, primary renal disease, valvular heart lesions, or atherosclerotic heart disease. Since propranolol might produce cardiac failure in persons with low cardiac output, patients were selected for this study who had resting, supine cardiac indices and heart rates greater than 2.2 L/min/m² and 50 beats/min, respectively. For this reason, the
Table 1
Supine Hemodynamics Before and After Propranolol (10 mg Intravenously)

<table>
<thead>
<tr>
<th></th>
<th>Normotensive subjects</th>
<th>Hypertensive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>5:1</td>
<td>13:8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.85</td>
<td>1.80</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>121 ± 2.2</td>
<td>119 ± 3.0</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>72 ± 1.8</td>
<td>75 ± 2.3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88 ± 1.8</td>
<td>90 ± 2.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 2.7</td>
<td>68 ± 3.2</td>
</tr>
<tr>
<td>Ejection time, corrected (msec)</td>
<td>332 ± 11</td>
<td>327 ± 15</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3515 ± 182</td>
<td>2814 ± 166</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>48 ± 1.7</td>
<td>42 ± 1.8</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min)</td>
<td>0.014 ± 0.001</td>
<td>0.018 ± 0.001</td>
</tr>
<tr>
<td>Left ventricular ejection rate (ml/sec/m²)</td>
<td>161 ± 2.8</td>
<td>135 ± 4.5</td>
</tr>
</tbody>
</table>

ns = not significant.

Each set of figures represents the group average for each hemodynamic function ± 1 standard error of the group mean. The separate columns for paired data represent ± 1 standard error of the mean for this type of analysis and the respective probability values.
significant differences in hemodynamic functions
between essential and renovascular hypertension
previously reported were not observed.
After insertion of the arterial and venous catheters and waiting for a suitable equilibration
period, the arterial pressure, heart rate, cardiac
output, and left ventricular ejection time were
measured at least in duplicate in the supine
position.
Isoproterenol was infused at sequentially in-
creasing rates (1, 2, 3, and sometimes 4 μg/min)
during continuous recording of arterial pressure
and heart rate. When heart rate had stabilized
at one level, the rate of infusion was increased
to the next higher rate. When a sustained in-
crease in rate had been produced at the highest
infusion rate, administration of isoproterenol was
discontinued. Beta-adrenergic blockade was pro-
duced by intravenous injection of 10 mg pro-
pranolol over 10 to 15 min, and the effectiveness
of inhibition was shown by failure of heart rate
to increase with repeat isoproterenol infusion.
Hemodynamic studies were then repeated.
Cardiac output was measured as previously
described with indocyanine green dye using a
Gilford densitometer and withdrawal pump.
After inscription of each dye-dilution curve,
blood was reinfused to ensure minimal loss of
blood. Arterial pressure was measured with a
Statham P23Db transducer attached to a San-
born direct-writing oscillograph. Heart rate was
determined from a continuously recorded elec-
trocardiogram. Left ventricular ejection time was
determined by measuring at least five consecu-
tive arterial pulse waves recorded at a paper
speed of 100 mm/sec.
Derived variables were calculated in the
usual manner: total peripheral resistance by
dividing mean arterial pressure by cardiac output,
cardiac index by correcting for body surface
area, stroke volume by dividing cardiac output
by heart rate, and mean rate of left ventricular
ejection by dividing stroke index by left ventricu-
lar ejection time.
Statistical evaluation of results was performed
by use of group comparison and paired data
analysis with the Student’s t-test.

Results
Hypertensives Versus Normotensives
A summary of the hemodynamic data is
presented in table 1 and shows that pro-
pranolol failed to reduce arterial pressure in
both normotensive and hypertensive man.
Cardiac output was significantly reduced by
20% in both groups; in normotensive subjects
this was produced primarily by fall in stroke
volume, whereas a reduction in heart rate
seemed to have the greater role in the hyper-
tensive patients. Group data analysis strikingly
brings out these differences, whereas paired
data analysis (in which each individual serves
as his own control) shows the expected high-
ly significant reductions in heart rate and
stroke index for all individuals, normal or
hypertensive. Thus, heart rate and stroke in-
dex were reduced by 7 and 13%, respectively,
in the normal subjects, but by 13 and 7%,
respectively, in the hypertensive patients. The
heart rate reduction was significant only for the
hypertensive group (P < 0.005), and stroke
index reduction was significant only for the
normotensive group (P < 0.05). Total periph-
eral resistance therefore increased in both
groups with intravenous beta-adrenergic
blockade, and left ventricular ejection rate fell.

For all subjects, whether normal or hyper-
tensive, those with the highest resting cardiac
indices and heart rates had the greatest per-
cent fall with propranolol (r = 0.468, P < 0.025
and r = 0.534, P < 0.01, respectively).

Hypertension Groups
The hemodynamic data for the essential,
labile, and renovascular hypertensive patients
are summarized in table 2. As indicated
above, the significant differences in cardiac
output observed previously between patients
with essential and renovascular hypertension
were not demonstrated in this study because
propranolol was not given to individuals
with cardiac indices of less than 2.2 L/min/m²;
such decreased cardiac indices are frequently
observed in patients with essential hyper-
tension. Arterial pressure remained unchanged
in all groups following propranolol; most
important, pressure remained the same in the
groups with higher outputs (labile and
renovascular hypertension) in whom cardiac
output reduction might be expected to lower
pressure. Cardiac output was significantly re-
duced by 19, 21, and 24% in essential, ren-
ovascular, and labile hypertensive groups,
respectively. Heart rate was reduced more
in the patients with essential and renovascular
hypertension, whose pretreatment rates

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were faster than those of the labile hypertensives. Only in patients with renal arterial disease was left ventricular ejection rate not significantly reduced.

**Discussion**

Despite evidence that oral propranolol therapy is effective in hypertension,7–12 no hemodynamic studies have been reported to explain the means whereby blood pressure is reduced. The present investigation fails to provide such information since blood pressure is not immediately reduced following intravenous therapy.

Nevertheless the study does point up differences between the normotensive subjects and hypertensive patients in response to beta-adrenergic inhibition. While pressure was not reduced in either group following intravenous administration of propranolol, and cardiac output fell by 20% in both, the drug seemed to produce a greater inhibition of chronotropic activity in hypertension and of stroke volume in the normal individual. Perhaps the greater reduction in heart rate in hypertension may be explained by the faster rate in hypertensive patients than in normal persons \( P < 0.02 \); we have consistently noted this difference.6 Patients with labile hypertension, whose resting arterial pressure and heart rate are nearer to normal levels, responded more normally to propranolol; output was reduced by a greater fall in stroke index than heart rate. Thus, the labile hypertensive state may be intermediate between the normal and the established hypertensive patient. This is not to suggest or offer evidence that labile hypertension is a developmental stage of hypertension.

In a hemodynamic evaluation of nethalide (pronethalol), another beta-adrenergic blocking drug, Schröder and Werkö13, 14 also showed differences between the normotensive and hypertensive subjects who were given the drug orally for 1 week. In the normal subjects, nethalide failed to produce any hemodynamic changes at rest, but in the hypertensive patients heart rate, arterial pressure, and cardiac output were reduced. The did not comment on the significantly faster heart rates of their hypertensive patients than of their normotensive subjects.13, 14 These similarities

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**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Essential hypertension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>6:2</td>
<td>7:0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Body surface area (m^2)</td>
<td>1.83</td>
<td>1.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean arterial pressure (mm Hg)</th>
<th>Before</th>
<th>After</th>
<th>SE</th>
<th>(P&lt;)</th>
<th>Before</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>137 ± 7.9</td>
<td>135 ± 7.8</td>
<td>3.6</td>
<td>ns</td>
<td>111 ± 3.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84 ± 6.8</td>
<td>72 ± 3.6</td>
<td>1.8</td>
<td>0.001</td>
<td>72 ± 4.4</td>
</tr>
<tr>
<td>Ejection time corrected (msec)</td>
<td>321 ± 7</td>
<td>310 ± 3</td>
<td>5</td>
<td>ns</td>
<td>304 ± 12</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m^2)</td>
<td>3120 ± 212</td>
<td>2531 ± 76</td>
<td>148</td>
<td>0.02</td>
<td>3357 ± 393</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m^2)</td>
<td>38 ± 1.9</td>
<td>36 ± 1.4</td>
<td>1.3</td>
<td>ns</td>
<td>47 ± 3.8</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min)</td>
<td>0.025 ± 0.003</td>
<td>0.030 ± 0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.018 ± 0.002</td>
</tr>
<tr>
<td>Left ventricular ejection rate (ml/sec/m^2)</td>
<td>137 ± 7.9</td>
<td>125 ± 4.1</td>
<td>3.8</td>
<td>0.05</td>
<td>168 ± 14.4</td>
</tr>
</tbody>
</table>

ns = not significant.

Note: Each set of figures represents the group average for each hemodynamic function ± 1 standard error of the group mean. The separate columns for "paired data" represent ± 1 standard error of the mean for this type of analysis and the respective probability values.
BETA-ADRENERGIC BLOCKADE IN HYPERTENSION

<table>
<thead>
<tr>
<th>Labile hypertension</th>
<th>Renovascular hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>After</td>
<td>SE</td>
</tr>
<tr>
<td>111 ± 3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>64 ± 3.7</td>
<td>1.8</td>
</tr>
<tr>
<td>294 ± 10</td>
<td>4</td>
</tr>
<tr>
<td>2570 ± 243</td>
<td>210</td>
</tr>
<tr>
<td>40 ± 2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>0.023 ± 0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>140 ± 8.8</td>
<td>7.9</td>
</tr>
</tbody>
</table>

the findings suggest that diastolic hypertension may be associated with increased chronotropic, beta-adrenergic activity.

Cardiac output has been reported to be higher in the milder forms of hypertension and with increasing severity of the disease cardiac output is reduced.2-5 More recently, Bello and his co-workers15 produced beta-adrenergic blockade in nine untreated hypertensive patients, and suggested that cardiac output fell more after propranolol in patients with less severe grades of hypertension. This observation seems to coincide with our finding that the higher the pretreatment heart rate or cardiac index, the greater the percentage reduction in the respective measurement.16

Acknowledgment

The authors wish to express their appreciation to Dr. Alex Sahagian-Edwards of Ayerst Laboratories for his generous supply of propranolol, to Enid Davy, R.N., and Helen T. Kleinhenz, R.N., for their excellent technical assistance, and to Mrs. Aldona Raulinaitis for her fine secretarial work.

References


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Clinical Implications of Blood Rheology Studies: Correction

In a recent paper by Replogle, Meiselman, and Merrill on “Clinical Implications of Blood Rheology Studies” (Circulation 37: 148, 1967), certain conclusions relating to viscometric techniques and relevance are found to be incorrectly stated as follows:

1. The legend of figure 1, page 150, suggests that blood without fibrinogen is Newtonian. If this were so, curve B of figure 1 would be a straight line of slope 1. For blood at an hematocrit of 40, without fibrinogen, assumption of Newtonian flow is for most purposes correct. This figure, as well as the original figures of Merrill (Merrill, E. W.: In: Biophysical Mechanisms in Vascular Homeostasis and Intravascular Thrombosis, edited by P. N. Sawyer. New York, Appleton-Century-Crofts, 1965, pp. 121-126) incorrectly shows the viscosity to be 6 cp. It is more nearly 3 to 4 cp. At hematocrit levels significantly exceeding 50, suspensions of red cells in defibrinated isotonic media are significantly non-Newtonian.

2. On page 156, first paragraph of left column, Ostwald capillary viscometers, contrary to the statement made, are operated at widely variable wall shear rates, depending on the particulars of their design such as length to diameter ratios, hydrostatic head, etc. Values of the wall shear rate can range from 10 to several thousands of inverse seconds. In any case, a modified capillary viscometer can be used with accuracy as discussed by Merrill and associates (Merrill, E. W., Benis, A. M., Gilliland, E. R., Sherwood, T. K., and Salzman, E. W.: Pressure flow relations of human blood in hollow fibers at low flow rates. J Appl Physiol 20: 954, 1965).

The shear rate in the aorta, referred to in the same paragraph, is difficult to assess exactly. At systole, it ought to exceed the mean value (100 sec⁻¹) stated by a factor of perhaps 4 to 20 depending on maximum flow rate, diameter, etc.

In any case, the fact is that measurements in a conventional Ostwald can and usually do reveal the limiting Newtonian viscosity of blood (Merrill, E. W., and Pelletier, G. A.: Viscosity of human blood: Transition from Newtonian to non-Newtonian. J Appl Physiol 20: 178, 1967). The limiting Newtonian viscosity is a function almost exclusively of hematocrit and plasma viscosity. It remains true that the conventional Ostwald viscometer cannot easily be modified to operate in the region of low shear stress where the effect of red cell aggregation via fibrinogen dominates the flow, and that only by special instrumentation can a capillary viscometer be made to indicate reliably the yield stress.

E. W. Merrill
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