Abnormalities of Left Ventricular Contraction Induced by Beta Adrenergic Blockade

By Richard H. Helfant, M.D., Michael V. Herman, M.D., and Richard Gorlin, M.D.

SUMMARY
To understand better the hemodynamic effects caused by propranolol, its effect on the geometry of left ventricular contraction was studied in ten subjects, four with angiographic evidence of coronary artery disease and six without demonstrable heart disease. Heart rate was controlled in four subjects with right atrial pacing. After 5 mg of intravenous propranolol, there were decreases in heart rate and cardiac index in most subjects with a variable effect on left ventricular end-diastolic pressure.

Left ventricular end-diastolic volume increased in the majority of instances with a reduction in both volume ejected and per cent circumferential fiber shortening of the left ventricle. Furthermore, after propranolol the left ventricle assumed a more elongated shape. Propranolol either induced or exaggerated asynergy in five subjects, three of whom had coronary heart disease. These changes provide a morphologic basis for some of the cardiac hemodynamic effects of propranolol.

Additional Indexing Words:
Hemodynamics
Coronary artery disease
Left ventricular volume
Asynergy

THE hemodynamic effects of beta adrenergic receptor blockade with propranolol have been extensively studied in man. At rest these effects are decreased heart rate,4 slightly increased or unchanged left ventricular end-diastolic pressure, slightly increased or unchanged heart size, and a decrease in cardiac index. It has been stressed, however, that in an occasional patient whose heart is operating at borderline compensation, propranolol may precipitate clinical cardiac failure. In order to understand better these hemodynamic alterations, the effect of beta adrenergic receptor blockade on the morphology of left ventricular contraction was studied.

Methods
Ten subjects, four with coronary artery disease shown by selective cine coronary arteriography and six with no evidence of organic heart disease, were studied at the time of diagnostic cardiac catheterization in a resting, postabsorptive, supine state. None had cardiomegaly by X-ray. Informed consent had previously been obtained from all patients. Selective cine coronary arteriography was performed by the Sones technique. A subject was considered to have significant coronary atherosclerosis if single or multiple stenosis of 75% or greater of the arterial lumen of a major vessel was present. Central aortic and left ventricular pressures were obtained with Statham P23dI strain gauges and recorded on a Sanborn 560 polybeam photographic recorder. Cardiac output was determined by the dye-dilution technique, using indocyanine green and a Gilford densitometer.

In seven subjects cine ventriculography was performed in the 30-degree right anterior oblique projection at a fixed tube to camera distance, with a 9-6" dual field image intensifier,* and

recorded at 60 frames/sec on 16-mm Ilford Pan F film. In three subjects without demonstrable heart disease, biplane cineventriculography was performed in the right and left anterior oblique projections, using a 9-6" biplane dual field image intensifier,† and recorded at 100 frames/sec on 16-mm Kodak Plus X film. Pressures, outputs, and ventriculograms were obtained for each subject in a control resting state and 20 min after 5 mg propranolol had been given intravenously. The time interval between observations was sufficient to allow recovery from effects of the contrast agent.⁷ ⁸ Each subject served as his own control. In four subjects right atrial pacing was used in the control and propranolol states to keep heart rate constant and thereby eliminate the negative chronotropic effect of the drug.

Each ventriculogram was interpreted qualitatively for vigor and uniformity of contraction as well as for chamber size and shape. After calibration to life-size dimensions, using methods described in detail elsewhere,⁹ a sequential, frame-by-frame motion analysis was carried out in each subject by drawing multiple hemiaxes on the sequential frames during systole and plotting these axes against time to ascertain the sequence (synergy) and amount of regional motion in systole.⁹ End-diastolic volume was determined angiographically, using modifications of the area-length method of Dodge et al.¹⁰ for both the single and biplane studies. In the biplane cases both minor axes were used to derive the circumference of a plane that bisected the longest length at a right angle, and its per cent shortening was calculated as a function of time. Shape analysis of the left ventricle was determined by calculating the ratio of cavity length (aortic valve to apex) to the mathematically derived width (w).¹⁰ The systolic time course of both volume and shape was also determined.

The data were analyzed by the paired t-test.

Results

The effects of propranolol on heart rate, cardiac index, and stroke index are given in table 1 and are illustrated in figure 1. Heart rate decreased moderately in five out of six unpaced subjects while cardiac index decreased significantly, including all four subjects whose heart rate was controlled by right

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†Siemens Corp., Iselin, N. J.

Figure 1

Effect of propranolol on heart rate (HR), cardiac index (CI), and stroke index (SI) in liters/min/m². In the unpaced subjects the control state and propranolol state are connected by solid lines, whereas the paced subjects are connected by broken lines. CAD = subjects with coronary artery disease.
Table 1

Effects of Propranolol on Left Ventricular Hemodynamics, Volume, and Pattern of Contraction

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>CI (liters/min/m²)</th>
<th>SI (ml/bust/m²)</th>
<th>LVdp (mm Hg)</th>
<th>LVed area (cm²)</th>
<th>LVed (L/W)</th>
<th>Propranolol asynergy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
<td>P</td>
<td>R</td>
<td>P</td>
<td>R</td>
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<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>I.P.</td>
<td>−</td>
<td>40</td>
<td>86</td>
<td>1.8</td>
<td>1.5</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>E.H.</td>
<td>−</td>
<td>66</td>
<td>78</td>
<td>2.6</td>
<td>2.9</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>R.M.</td>
<td>−</td>
<td>80</td>
<td>70</td>
<td>2.5</td>
<td>2.7</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>B.S.</td>
<td>+</td>
<td>72</td>
<td>72</td>
<td>2.4</td>
<td>1.6</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.T.</td>
<td>−</td>
<td>84</td>
<td>72</td>
<td>3.4</td>
<td>2.3</td>
<td>41</td>
<td>32</td>
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<tr>
<td>J.S.</td>
<td>−</td>
<td>73</td>
<td>63</td>
<td>2.6</td>
<td>1.9</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>R.H.</td>
<td>−</td>
<td>72</td>
<td>64</td>
<td>3.6</td>
<td>3.4</td>
<td>46</td>
<td>53</td>
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<tr>
<td>A.K.</td>
<td>+</td>
<td>88</td>
<td>85</td>
<td>2.1</td>
<td>1.9</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>D.M.</td>
<td>+</td>
<td>90</td>
<td>90</td>
<td>3.6</td>
<td>2.8</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>M.B.</td>
<td>+</td>
<td>120</td>
<td>120</td>
<td>3.3</td>
<td>2.6</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>±0.20</td>
<td>±0.20</td>
<td>±2.4</td>
<td>±3.4</td>
<td>±2.4</td>
<td>±2.4</td>
<td>±6.2</td>
</tr>
</tbody>
</table>

P value | P < 0.05 | NS | P < 0.01 | NS |

Abbreviations: R = rest; P = propranolol; HR = heart rate; CI = cardiac index; SI = stroke index; LVdp = left ventricular end-diastolic pressure; LVed = left ventricular end-diastolic; L/W = length/width ratio.
atrial pacing. Stroke index decreased in eight of ten subjects.

Figure 2 demonstrates the effects of propranolol on left ventricular end-diastolic pressure and volume, as reflected by the area of the silhouette at end-diastole. Left ventricular end-diastolic pressure showed a slight and variable response after propranolol in eight subjects. However, there were marked elevations in two subjects with coronary disease and one subject with normal coronary arteries. Left ventricular end-diastolic pressure in nine of the ten subjects (P < 0.01) (fig. 2). Increased end-diastolic area in one of the three subjects studied by biplane cine ventriculography is illustrated in figure 3. These results were not influenced by the presence of coronary disease or the induction of tachycardia.

In eight of the ten subjects, the ratio of the left ventricular length to derived width increased, indicating a more elongated left ventricle after propranolol, but this did not achieve statistical significance. One of the two subjects in whom the left ventricular length/width ratio did not increase developed an area of anterior dyskinesis. This resulted in an inordinate increase in width (fig. 4, lower right silhouette). This subject will be described in greater detail later.

On the basis of a visual interpretation of displacement as a function of time, propranolol caused a decrease in the vigor of ventricular contraction. This was confirmed by the findings demonstrated in figure 5 which illustrates the effects of propranolol on the systolic time course of left ventricular volume, per cent volume change, and per cent circumferential fiber shortening (minor axis) during contraction. Note the increased volume in the propranolol state which nevertheless is
BETA ADRENERGIC BLOCKADE AND LV CONTRACTION

Control

Propranolol

RAO (30°)

LAO (60°)

HR
beats/min 84 72
SV
ml/beat 73 57

Figure 3

Graphic illustration of the ventricular silhouettes in the 30-degree right anterior oblique (RAO 30°) and 60-degree left anterior oblique (LAO 60°) in the control and propranolol state. Arrows indicate the change in ventricular dimensions from end-diastole to end-systole. Note that the size of the left ventricle increases after propranolol with a concomitant decrease in heart rate (HR) and stroke volume (SV).

Asynergy (Table 1)

Five patients exhibited a change in the morphology of left ventricular contraction after propranolol administration. Three developed asynergy for the first time; one patient (E.H.) had coronary artery disease, and two did not (D.M., J.S.). In two additional subjects with coronary heart disease (I.P., B.S.), propranolol accentuated pre-existing zones of ventricular asynergy. The types of asynergy are seen in figure 4.

Although the greatest changes in end-diastolic pressure were seen in subjects with increased asynergy, there was not necessarily a correlation between these changes. Although ventricular volume showed a consistent upward change, this again did not relate to the induction or aggravation of asynergy.

Discussion

Observations on the morphology of left ventricular systole represent another, little appreciated dimension in further understanding the hemodynamic alterations caused by
propranolol. In general, propranolol caused a decrease in the vigor of left ventricular contraction. The per cent change in both ventricular volume and fiber shortening during systole was decreased during beta blockade (fig. 5). In addition, propranolol caused an elongation in the shape of the left ventricle during both systole and diastole (fig. 2). Although the reason for this shape is unclear, it is the converse of the more spherical ventricular shape that occurs following induced hypervolemia¹¹ and with supine muscular exercise.¹² There are also factors tending to decrease return of blood to the heart after propranolol administration. Whether this concomitant effect may account in part for the observed shape change can only be speculated. It is possible that these effects represent the net result of primary myocardial depression at a time when venous return is either unchanged or actually diminished. These observations, plus the small increase in end-diastolic ventricular size, appear to be the morphologic counterpart of the hemodynamic changes caused by propranolol.¹³

Ventricular volume normally increases as heart rate decreases. That this was not the sole explanation for the changes observed herein with propranolol is shown by the fact that left ventricular volume rose when heart rate was held constant. An increased volume should increase the force of contraction and cardiac index if the Starling mechanism can be further activated. That this did not occur is further suggestive evidence of the myocardial depressant action of propranolol.

Although the hemodynamic effects of propranolol at rest are usually of small magnitude, there are occasional instances in which the depressant effect of this agent is more marked. In subjects with coronary heart disease, the marked decrease in cardiac performance caused by propranolol may be due in large part to its effect on the synergy of ventricular contraction. Studies in this laboratory have shown that local disturbances in ventricular wall motion and ventricular asynchrony provide a functional basis for the hemodynamic dysfunction seen in coronary heart disease.⁶ It has been shown that catecholamine stores are depleted in cardiac failure.¹⁴ It is also postulated that local catecholamine depletion may occur secondary to local myocardial ischemia, predisposing to asynergy.¹⁵ Regardless of the mechanism the present study clearly demonstrates that propranolol may induce or accentuate zones of ventricular asynergy irrespective of the etiology of the heart disease. This finding appears to explain morphologically why an occasional patient develops a decrease in cardiac performance and cardiac failure with propranolol treatment. Clinically, this is a relatively rare occurrence in our experience. However, it should be carefully watched for in patients with organic heart disease taking propranolol. Initiation of therapy with low doses and utilizing small increments as needed will prevent the occurrence of serious cardiac failure in the susceptible subject.

Acknowledgment

The propranolol used in the study was generously supplied as Inderal by Dr. Alex Sahagian Edwards, Ayerst Laboratories, New York, New York.

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_Circulation_. 1971;43:641-647
doi: 10.1161/01.CIR.43.5.641

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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