The Use of Isoproterenol (Isuprel) in the Evaluation of Congenital Cardiac Defects

By Arthur J. Moss, M.D., and Edward R. Duffie, Jr., M.D.

Cardiac catheterization continues to be the principal means for definitive study of a wide variety of cardiac lesions. Information essential for the selection of surgical candidates and for their postoperative evaluation is provided by this type of investigation. However, the continued search for additional laboratory studies is evidence that current methods frequently do not provide the necessary or desired data. One of the pitfalls of the past has been a failure to consider that physiologic material gathered under resting conditions does not necessarily reflect circulatory response to the activities of everyday life. In recent years this shortcoming has been partially overcome by studying the circulatory dynamics during physical exercise as well as during rest.1-8

Active physical exercise can usually be accomplished in the adult but in the infant or child, a number of obstacles are frequently encountered. Chief among these are inability to comprehend or to carry out instructions and an unwillingness to cooperate. Even when successfully accomplished, the fear, apprehension, and anxiety that prevail in the conscious child may profoundly affect cardiac output, and this may in turn give rise to significant errors in the interpretation of the data obtained.9 Since most of the catheterization studies now performed are in this younger age group, the problem is one of major proportions.

The purpose of this investigation was to attempt to produce the physiologic alterations of exercise by the intravenous infusion of a synthetic catecholamine, isoproterenol.* Isoproterenol is known to produce effects similar to those of exercise in that the respiratory rate is increased, peripheral vasodilatation occurs, and a powerful chronotropic and inotropic action is exerted on the myocardium.10-25 Infusion of this material in dogs quite accurately reproduces the performance of the left ventricle obtained with exercise.22

Material and Methods

Observations were made on 38 subjects, 19 male and 19 female, ranging in age from 1 to 17 years. Half the group had previously undergone cardiac surgery and were studied to appraise the results of operation. The remainder were studied for diagnosis. With the exception of two of the older children, a 10-per cent solution of Thiamylol* was administered rectally to all subjects under 12 years and a 2.5-per cent solution of sodium pentobarbital intravenously to all over this age. All were premedicated with meperidine hydrochloride.†

Right heart catheterization was accomplished via the right saphenous vein in children under 5 years and via the right antecubital vein in those over 5 years. Retrograde left heart catheterization was accomplished from the right brachial artery. Lehman or Goodale-Lubin cardiac catheters were used. In 35 of the 38 cases systemic arterial pressures were measured by means of an 18-gage Courand needle placed in an exposed peripheral artery. All pressures were recorded by Statham strain-gage transducers and an Offner multichannel recorder. Mean pressures were measured by electronic integration.

The heart rate was computed from a continuously recorded electrocardiogram and the respiratory rate from the respiratory fluctuations of the pulmonary artery pressure pulse. Oxygen consumption was determined by the open method. Blood oxygen saturations and contents were determined by cuvette oximetry and by the manometric method of Van Slyke and Neill. Cardiac outputs were estimated by the Fick method.

Following the catheterization studies, isoproterenol was infused into a peripheral vein in a concentration of 0.8 microgm. per ml. of 5 per

*Surital (Parke, Davis & Co., Detroit, Michigan).
†Demerol (Winthrop Laboratories, New York, New York).
Table 1

Effect of Isoproterenol on Pressure Relationship between Pulmonary Artery and Right Ventricle

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Systolic gradient (mm. Hg) Before infusion</th>
<th>During infusion</th>
<th>Site of predominant gradient</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>M</td>
<td>Tetralogy of Fallot (op)*</td>
<td>12</td>
<td>32</td>
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<tr>
<td>2</td>
<td>4</td>
<td>M</td>
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<td>6</td>
<td>26</td>
<td>Pulmonic valve</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>F</td>
<td>Ventricular septal defect (op)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>M</td>
<td>1st-degree atrioventricular block. Cause undetermined</td>
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<td>0</td>
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<tr>
<td>5</td>
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<td>0</td>
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</tr>
<tr>
<td>6</td>
<td>7</td>
<td>F</td>
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</tr>
<tr>
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<td>2</td>
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<td>Patent ductus arteriosus (op)</td>
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<td>0</td>
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</tr>
<tr>
<td>8</td>
<td>13</td>
<td>M</td>
<td>Atrial septal defect (op)*</td>
<td>2</td>
<td>24</td>
<td>Pulmonic valve</td>
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<tr>
<td>9</td>
<td>5</td>
<td>M</td>
<td>Innocent murmur</td>
<td>6</td>
<td>12</td>
<td>Pulmonic valve</td>
</tr>
<tr>
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<td>12</td>
<td>F</td>
<td>Ventricular septal defect</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>M</td>
<td>Ventricular septal defect (op)</td>
<td>4</td>
<td>14</td>
<td>Pulmonic valve</td>
</tr>
<tr>
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<td>17</td>
<td>M</td>
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<td>44</td>
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<td>13</td>
<td>M</td>
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<td>37</td>
<td>Pulmonic valve</td>
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<td>14</td>
<td>3</td>
<td>M</td>
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<td>10</td>
<td>Infundibulum</td>
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<td>15</td>
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<td>M</td>
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<td>8</td>
<td></td>
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<tr>
<td>16</td>
<td>4</td>
<td>F</td>
<td>Innocent murmur</td>
<td>4</td>
<td>15</td>
<td>Main pulmonary artery</td>
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<tr>
<td>17</td>
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<td>M</td>
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<td>8</td>
<td>25</td>
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<td>4</td>
<td>F</td>
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<td>19</td>
<td>4</td>
<td>F</td>
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<td>6</td>
<td>13</td>
<td>Infundibulum</td>
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<tr>
<td>20</td>
<td>14</td>
<td>M</td>
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<td>0</td>
<td>12</td>
<td>Pulmonic valve</td>
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<tr>
<td>21</td>
<td>5</td>
<td>F</td>
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<td>12</td>
<td>46</td>
<td>Infundibulum</td>
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<tr>
<td>22</td>
<td>8</td>
<td>F</td>
<td>Aortic stenosis and ventricular septal defect</td>
<td>2</td>
<td>5</td>
<td>Pulmonic valve</td>
</tr>
<tr>
<td>23</td>
<td>3</td>
<td>M</td>
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<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>24</td>
<td>6</td>
<td>F</td>
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<td>12</td>
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<tr>
<td>25</td>
<td>16</td>
<td>M</td>
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<td>15</td>
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<td>Ventricular septal defect (op)</td>
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<td>16</td>
<td>Pulmonic valve</td>
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<tr>
<td>27</td>
<td>6</td>
<td>F</td>
<td>Atrial septal defect*</td>
<td>12</td>
<td>34</td>
<td>Pulmonic valve</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td>F</td>
<td>Atrial septal defect*</td>
<td>12</td>
<td>28</td>
<td>Pulmonic valve</td>
</tr>
</tbody>
</table>

*Had significant pulmonic stenosis demonstrated only during infusion of isoproterenol. (op) Operated upon.

Dextrose solution. The rate of infusion ranged from .03 to .67 microgm. per Kg. per minute, depending upon the patient's size and individual response. Observations were made only after a maximum and uniform response was obtained, i.e., 2 to 4 minutes.

Observations were also made during supine active exercise in the two subjects who were not anesthetized. For this purpose, a bicycle-type ergometer was attached to the foot of the x-ray table and measurements were made after 2 minutes of pedaling at a rate of 56 r.p.m., the work load being 54 ft. lb. per revolution.

Results

The response to isoproterenol became steady after the initial 2 to 4 minutes of infusion (heart rate, respiratory rate, and arterial pressures being used as parameters). Toxic symptoms attributable to the drug itself were not encountered. Occasionally, upon withdrawal of the catheter into the right ventricle, ventricular premature beats occurred as the tip traversed the outflow tract. They were also observed when the catheter tip was initially positioned within the left ventricle but in no case did any prolonged or serious arrhythmia arise.

*Circulation, Volume XXVII, January 1963
Table 2

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>State</th>
<th>Pressure, left ventricle (mm. Hg)</th>
<th>Pressure aorta (mm. Hg)</th>
<th>Systolic gradient (mm. Hg)</th>
<th>Per cent change of resting gradient</th>
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<td>14</td>
<td>M</td>
<td>Before</td>
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<td>110/78</td>
<td>70</td>
<td>+ 93</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>During</td>
<td>225/0</td>
<td>90/60</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>8</td>
<td>F</td>
<td>Before</td>
<td>114/8</td>
<td>104/72</td>
<td>10</td>
<td>- 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>During</td>
<td>112/1</td>
<td>104/70</td>
<td>8</td>
<td></td>
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<tr>
<td>25</td>
<td>16</td>
<td>M</td>
<td>Before</td>
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<td>106/60</td>
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<tr>
<td></td>
<td></td>
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<td>During</td>
<td>144/10</td>
<td>108/60</td>
<td>36</td>
<td>+ 80</td>
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<tr>
<td>29</td>
<td>16</td>
<td>F</td>
<td>Before</td>
<td>144/4</td>
<td>108/42</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>During</td>
<td>208/-12</td>
<td>120/30</td>
<td>88</td>
<td>+145</td>
</tr>
</tbody>
</table>

Effect of Isoproterenol on Heart Rate and Respiration

The heart rate increased in all 38 subjects, rising from a mean of 90 to a mean of 141 per minute. The range of increase was from 20 to 127 per cent. The respiratory rate likewise showed a consistent increase, ranging from 12 to 59 per cent of the pre-infusion rate. The mean respiratory rate before isoproterenol infusion was 18 per minute and at the height of response, 23 per minute.

Effect of Isoproterenol on Intracardiac and Arterial Pressures

The effect of isoproterenol on the right atrial pressure was recorded in 11 subjects. In nine the mean pressure decreased, in one it remained unchanged, and in one it increased.

Observations on the pulmonary arterial pressures were made in 35 subjects. The systolic pressure decreased during infusion in 24, increased in nine, and remained unchanged in two; the diastolic pressure decreased in 23, increased in four, and was unaffected in eight; the mean pressure decreased in 27, increased in three, and was unaltered in five. Withdrawal pressure tracings from the pulmonary artery were recorded before and during isoproterenol infusion in 28 subjects (table 1). Nine had a significant systolic gradient (greater than 20 mm. Hg) across the pulmonic valve during infusion of isoproterenol, which was not detected by the usual catheterization study. Another patient had a coarctation of the pulmonary artery in which the gradient was accentuated to a significant level by the simulated exercise.

Observations on the systemic arterial pressure were made in 35 subjects before and during isoproterenol infusion. The general response here also was a reduction in pressure. Although the systolic pressure decreased in only 15, both the diastolic and the mean pressures decreased in 33 of 35 patients. The effect of isoproterenol on aortic stenosis was also studied (table 2). Three of the four subjects in this group showed a definite increase in the systolic gradient and the fourth showed no significant change.

Effect of Isoproterenol on Cardiac Output

The cardiac index was estimated before and during isoproterenol infusion in four patients, and in each case the cardiac output increased (table 3). The oxygen consumption remained essentially the same and the arteriovenous oxygen difference narrowed in all four subjects. The stroke volume increased in three.

Discussion

This investigation confirms previous reports on the physiologic effects of isoproterenol and is the first reported application of its usefulness to simulate exercise clinically. It increases the heart rate, the respiratory rate, and the cardiac output and causes the pulmonary and systemic vascular beds to dilate.\textsuperscript{10-25} The most pronounced effect is upon the heart rate although the stroke volume does rise to some extent. The rate rapidly increases to a level that parallels or even exceeds that ob-
served with exercise. As opposed to exercise, however, the arteriovenous oxygen difference with isoproterenol narrows and the oxygen consumption rises only slightly, if at all.26-28 Also, whereas the stroke volume tends to increase somewhat with isoproterenol,23, 25, 29 it shows little or no change in normal untrained individuals with exercise.27, 28, 30, 31 The peripheral vascular resistance is reduced with both isoproterenol and exercise, but, paradoxically, the systemic arterial pressure tends to fall in the former and to rise in the latter.26-28, 32 The basis for this is undoubtedly a relatively greater flow with exercise. The mean pulmonary arterial pressure tends to fall with isoproterenol when the vasculature of the lungs is normal. This suggests that isoproterenol may be of value in appraising the pulmonary vascular bed, and studies in this direction are currently in progress. With exercise, the effect on pulmonary arterial pressure is variable; it may remain the same, may diminish, or may become mildly elevated.33-36

The discrepancies that exist between the cardiopulmonary effects of isoproterenol and exercise are not important so far as the usefulness of this drug in cardiac evaluation is concerned. The principal desired effect is an increase in cardiac output, and this is achieved by both.1, 2, 13, 29, 25-29, 31, 32, 33, 37, 38 A more pronounced response may be obtained, however, with an extreme degree of exercise but this degree is rarely attained under the usual conditions of the catheterization laboratory. The striking similarity of response demonstrated by comparative studies of isoproterenol and moderate exercise in two individuals is illustrated in figure 1.

The observed fall in right atrial pressure is in agreement with findings reported by others.25, 39 This fall probably is not due to a change in the intrapleural pressure, since Eckstein and Hamilton40 have shown that the esophageal pressure does not fall with the administration of isoproterenol. It may be a reflection of increased emptying of the right ventricle due to the inotropic effect of the drug.
The results of the present investigation suggest that isoproterenol has its greatest application in the appraisal of obstructive valvular lesions. Nine subjects were found to have a mild but significant degree of pulmonic stenosis, which became apparent only after the infusion of isoproterenol. Four of these nine were postoperative patients, three of whom would have been considered completely corrected. A retrospective review of the phonocardiograms of these patients revealed evidence compatible with this diagnosis in six of them. Of the remaining three patients, one had a ventricular septal defect and one aortic stenosis, and evidence of associated pulmonic stenosis may thus have been obscured.

In one patient an obstruction was found in the main pulmonary artery during the infusion of isoproterenol. This was demonstrated by angiocardiography to be due to coarctation of the main pulmonary artery.

Four patients with clinically apparent aortic stenosis were studied, and isoproterenol accentuated the systolic gradient in three. The
gradient was sufficient in two (cases 20 and 29) to warrant operative intervention. In the fourth (case 22), only a mild degree of obstruction was demonstrated, and failure of isoproterenol to accentuate the gradient in this patient was interpreted as evidence of a good prognosis. This child was accordingly permitted full unrestricted activity.

Summary

Isoproterenol was infused intravenously at a rate of 0.03 to 0.07 μg. per Kg. per minute in 38 patients undergoing cardiac catheterization to evaluate the routine postoperative condition of 19 patients and to support or confirm the clinical diagnosis in 19 others.

A steady response was obtained in 2 to 4 minutes, and no toxic effects were observed. During the infusion the heart rate increased an average of 55 per cent; the respiratory rate, 23 per cent. The right atrial pressure fell. In general the pulmonary and systemic arterial pressures also decreased. Limited observations on the cardiac output confirmed the previously reported increase. Ten patients developed a significant systolic gradient between the right ventricle and pulmonary artery (greater than 20 mm. Hg) during the infusion. Four of these were postoperative patients, three of whom were considered completely corrected prior to infusion of the isoproterenol. Four patients with aortic stenosis were studied, and the systolic gradient increased in three (80, 93, and 145 per cent).

The results indicate that infusion of isoproterenol is a safe, practical, and effective means of simulating exercise in infants and children. Used in addition to the customary cardiac catheterization studies, it is of distinct value in appraising congenital cardiac defects.

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