Comparison of the Cardiocirculatory Effects of Exercise and Isoproterenol in Children with Pulmonary or Aortic Valve Stenosis

NESTOR J. TRUCCONE, M.D., CARL N. STEEG, M.D., RALPH DELL, M.D., AND WELTON M. GERSONY, M.D.

SUMMARY Isoproterenol infusion during cardiac catheterization as a simulator of exercise was evaluated with hemodynamic studies in children with pulmonary (15) or aortic (8) valve stenosis. Cardiac function was monitored during rest, mild exercise and isoproterenol infusion. Similar heart rates were maintained in both procedures. Peak pulmonary and aortic valve gradients as well as right and left ventricular dp/dt/p were significantly higher and cardiac index significantly lower with isoproterenol as compared to exercise. Isoproterenol induced a significantly greater decrease in systemic vascular resistance, and systemic blood pressure than did exercise. Left ventricular systolic pressure rose to similar levels and this resulted in substantially higher peak aortic gradients with isoproterenol. A consistent correlation was observed for peak valvular gradients measured during exercise and isoproterenol in both groups of patients. Accordingly, regression equations were obtained allowing reasonably accurate prediction of exercise valvular gradients on the basis of the isoproterenol data.

HEMODYNAMIC EVALUATION OF PEDIATRIC PATIENTS with pulmonary or aortic valve stenosis is usually carried out by cardiac catheterization studies in the resting state with variable degrees of sedation.2 More complete and meaningful data from exercise studies1,2,6 may not be possible in young children who may not cooperate sufficiently for systematic investigation to be carried out. The use of isoproterenol infusion to simulate exercise conditions has been proposed to study patients with pulmonary or aortic valve stenosis.4 However, it has also been argued that isoproterenol does not accurately reflect the hemodynamic status which would be expected during exercise in such patients.2

In order to evaluate the usefulness and limitations of isoproterenol infusion as a predictor of exercise response, hemodynamic studies were carried out in children with mild to moderate pulmonary or aortic valve stenosis during rest, exercise and isoproterenol administration.

Material and Methods

Twenty-three patients between the ages of 5 and 16 years were included in this study. Fifteen had isolated pulmonary valve stenosis, and there were eight children with aortic valve stenosis. All of the patients were studied after premedication with demerol, phenergan, and thorazine, in a resting state. A #18 long dwell teflon cannula was inserted percutaneously into the brachial artery for recordings of systemic arterial pressures. Cardiac output measurements were obtained using the dye dilution technique with injection of green dye into the right atrium, and sampling from the brachial artery cannula, through an X-P302 Waters cardiac output densitometer. Withdrawal pressure tracings from the pulmonary artery or aorta to the appropriate ventricles as well as measurements of right or left ventricular dp/dt/p, were obtained with a #7 high fidelity Millar catheter tip micromanometer. The ventricular pressure tracing from the tip manometer was matched to a simultaneous pressure tracing obtained from the lumen fluid-filled system present in the same catheter and connected to a P23db Statham pressure transducer.

After information was recorded during rest, exercise data were obtained using a bicycle ergometer with a workload adjusted for each patient in order to increase the heart rate to approximately 150 beats/min, considered a mild level of exercise. The patients were exercised for a period of 11 to 14 min and all parameters recorded after a steady state was reached over a period of 4 to 5 min. Each child was then allowed to rest for a period of 20 min with return of the heart rate to normal as measured prior to exercise. A continuous intravenous isoproterenol infusion was then started at 1 to 2 mcg/min, titrated in each patient in order to achieve a level of heart rate as close as possible to that obtained during the exercise study. All parameters were recorded in a similar manner as during rest and exercise, after which the isoproterenol infusion was discontinued. Confirmatory evidence of isolated pulmonary or aortic valve stenosis was then obtained by angiocardiograms, and the catheterization studies were then terminated. Data obtained in the three states for each group of patients were averaged and compared statistically using the paired t test.

Results

In the patients with pulmonary stenosis, isoproterenol induced a greater increase in peak systolic gradient across the pulmonic valve as compared to exercise at equivalent heart rates (fig. 1, left panel). Right ventricular systolic pressure averaged 42 mm Hg at rest increasing to 64 mm Hg with exercise and 73 mm Hg during isoproterenol infusion. Peak systolic gradient increased from 24 mm Hg at rest, to 38 mm Hg with exercise and 52 mm Hg with isoproterenol. Right ventricular dp/dt/p increased from an average of 28 sec−1 at rest to 42 sec−1 with exercise and 55 sec−1 with isoproterenol (table 1). Right ventricular end-diastolic and mean pulmonary arterial pressures, cardiac index, and systemic resistance index were lower with isoproterenol as compared to exercise.

In the group of patients with aortic valve stenosis,
isoproterenol induced a greater increase in peak aortic gradient as compared to exercise (fig. 1, right panel). Peak aortic gradient increased from 31 mm Hg at rest to 48 mm Hg with exercise, and to 84 mm Hg with isoproterenol. Left ventricular peak systolic pressures were equivalent with exercise and isoproterenol (table 2).

Left ventricular end-diastolic pressures, aortic pressures, cardiac index and systemic vascular resistance were lower during isoproterenol administration than with exercise, whereas left ventricular dp/dt/p rose to higher levels (table 2).

Calculations of pulmonary and aortic valve area were obtained using the Gorlin formula. In eight of the 15 patients with pulmonary stenosis in whom the quality of the pressure tracings allowed calculations of the pulmonary valve area in the three hemodynamic states, averaged values of cardiac index were lower and mean systolic gradient higher with isoproterenol as compared to exercise (table 3). This resulted in a smaller calculated area index with isoproterenol (1.33 cm²/m²) as compared to exercise (1.60 cm²/m²) \( (P < 0.01) \) (table 3). A smaller pulmonary valve area was also calculated with isoproterenol as compared to resting conditions (table 3).

In the eight patients with aortic stenosis, the averaged calculated aortic valve area was significantly smaller with isoproterenol (0.79 cm²/m²) as compared to exercise (1.04 cm²/m²) (table 4). Higher values of mean systolic gradient (table 4) and lower values of cardiac index (table 2) with isoproterenol as compared to exercise caused this difference. The greater increase in mean systolic gradient as compared to the increment in cardiac index obtained with

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**Table 1. Hemodynamic Data in Patients with Pulmonary Stenosis \( (N = 15) \)**

<table>
<thead>
<tr>
<th>HR ( (96±5) )</th>
<th>RVSP ( (42±4) )</th>
<th>PASP ( (24±4) )</th>
<th>P SG ( (6±6) )</th>
<th>RVEDP ( (10±0.6) )</th>
<th>PA ( (94±3) )</th>
<th>BA ( (4.8±0.2) )</th>
<th>CI ( (1.8±0.9) )</th>
<th>PRI ( (25±3) )</th>
<th>SRI ( (7.1±3) )</th>
<th>RV dp/dt/p ( (5.5±5) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>95±4</td>
<td>109±6</td>
<td>31±6</td>
<td>83±5</td>
<td>16±2</td>
<td>8±0.8</td>
<td>4.5±0.2</td>
<td>18.5±1.1</td>
<td>3.7±0.6</td>
<td>54±2</td>
</tr>
<tr>
<td>E</td>
<td>151±6</td>
<td>116±6</td>
<td>48±6</td>
<td>88±4</td>
<td>19±4</td>
<td>10±1.7</td>
<td>7.9±0.4</td>
<td>11.2±0.6</td>
<td>2.5±0.5</td>
<td>84±9</td>
</tr>
<tr>
<td>I</td>
<td>148±5</td>
<td>162±17</td>
<td>75±3</td>
<td>84±15</td>
<td>51±2</td>
<td>6±1.1</td>
<td>6.6±0.4</td>
<td>7.9±0.4</td>
<td>1.8±0.2</td>
<td>111±10</td>
</tr>
</tbody>
</table>

\*<0.01; exercise vs isoproterenol.

Abbreviations: \( R \) = resting; \( E \) = exercise; \( I \) = isoproterenol; HR = heart rate; RVSP = right ventricular systolic pressure; PASP = pulmonary artery systolic pressure; PS = peak systolic gradient; RVSP = right ventricular end-diastolic pressure; PA = mean pulmonary arterial pressure; PA = mean brachial artery pressure; CI = cardiac index; PRI = pulmonary resistance index; SRI = systemic resistance index; RV dp/dt/p = right ventricular dp/dt/p.

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**Table 2. Hemodynamic Data in Patients with Aortic Stenosis \( (N = 8) \)**

<table>
<thead>
<tr>
<th>HR ( (96±5) )</th>
<th>LVSP ( (140±11) )</th>
<th>AoSP ( (109±6) )</th>
<th>P SG ( (31±6) )</th>
<th>SAP ( (83±5) )</th>
<th>P A ( (16±2) )</th>
<th>LVEDP ( (8±0.8) )</th>
<th>CI ( (4.5±0.2) )</th>
<th>SRI ( (18.5±1.1) )</th>
<th>PRI ( (3.7±0.6) )</th>
<th>LV dp/dt/p ( (54±2) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>95±4</td>
<td>116±6</td>
<td>48±6</td>
<td>88±4</td>
<td>19±4</td>
<td>10±1.7</td>
<td>7.9±0.4</td>
<td>11.2±0.6</td>
<td>2.5±0.5</td>
<td>84±9</td>
</tr>
<tr>
<td>E</td>
<td>151±6</td>
<td>116±6</td>
<td>48±6</td>
<td>88±4</td>
<td>19±4</td>
<td>10±1.7</td>
<td>7.9±0.4</td>
<td>11.2±0.6</td>
<td>2.5±0.5</td>
<td>84±9</td>
</tr>
<tr>
<td>I</td>
<td>148±5</td>
<td>162±17</td>
<td>75±3</td>
<td>84±15</td>
<td>51±2</td>
<td>6±1.1</td>
<td>6.6±0.4</td>
<td>7.9±0.4</td>
<td>1.8±0.2</td>
<td>111±10</td>
</tr>
</tbody>
</table>

\*<0.01; \( E \) vs \( I \).

Abbreviations: \( R \) = resting; \( E \) = exercise; \( I \) = isoproterenol; HR = heart rate; LVSP = left ventricular systolic pressure; AoSP = aortic systolic pressure; PS = peak systolic gradient; SAP = mean systemic arterial pressure; PA = mean pulmonary arterial pressure; PA = mean brachial artery pressure; CI = cardiac index; SRI = systemic resistance index; PRI = pulmonary resistance index; LV dp/dt/p = left ventricular dp/dt/p.
isoproterenol as compared to resting conditions resulted in a smaller calculated aortic valve area with this pharmacological agent (table 4).

Linear regression equations were derived in both groups of patients in order to predict the peak systolic gradient (PSG) with exercise (E) on the basis of measurements obtained during isoproterenol (I) administration (figs. 2 and 3). Although the peak systolic gradients were greater with isoproterenol, the correlation was consistent, as shown by the proximity of individual values to the regression line, allowing close estimation of exercise gradient based on the measurements obtained during isoproterenol administration.

Pulmonary stenosis (fig. 2):
PSG (E) mm Hg = 0.9 × PSG (I) mm Hg + 9 mm Hg

Aortic Stenosis (fig. 3):
PSG (E) mm Hg = 0.5 × PSG (I) mm Hg + 7 mm Hg

Using these regression equations, pulmonary and aortic valve gradients could be predicted with 95% accuracy, to within ±10 mm Hg for pulmonary stenosis and ±12 mm Hg for aortic stenosis.

**Discussion**

Previous studies have stated that isoproterenol infusion during cardiac catheterization provides a satisfactory method of simulating exercise conditions in pediatric patients with pulmonary or aortic valve stenosis. The reports have included measurements at rest and during isoproterenol infusion but no exercise data was obtained in the same patients. A recent study by Neal et al., including hemodynamic observations at rest, exercise and isoproterenol in children with pulmonary valve stenosis, showed that isoproterenol increases the pulmonary valve gradient out of proportion to the increase in cardiac output as compared to exercise. These authors concluded that the severity of pulmonary valve stenosis will be overestimated if only the resting and isoproterenol measurements are used.

**Table 3. Calculation of Valve Area in Pulmonary Stenosis (N = 8)**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>SET (sec)</th>
<th>CI (L/min/m²)</th>
<th>MSG mm Hg</th>
<th>PVAVI (cm²/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>94</td>
<td>0.280</td>
<td>4.92</td>
<td>6.8</td>
<td>1.61</td>
</tr>
<tr>
<td>E</td>
<td>154</td>
<td>0.220</td>
<td>8.90</td>
<td>13.5</td>
<td>1.60</td>
</tr>
<tr>
<td>I</td>
<td>150</td>
<td>0.210</td>
<td>8.23</td>
<td>19.3</td>
<td>1.33</td>
</tr>
<tr>
<td>E vs I</td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

Abbreviations: R = rest; E = exercise; I = isoproterenol; HR = heart rate; SET = systolic ejection time; CI = cardiac index; MSG = mean systolic gradient; PVAVI = pulmonary valve area index.

In the present study of children with pulmonary stenosis or aortic stenosis, left or right ventricular systolic pressure was slightly higher with isoproterenol as compared to exercise and pulmonary and systemic arterial systolic pressures were lower during isoproterenol infusion. This resulted in significantly higher peak systolic gradients with isoproterenol. The effects of heart rate were eliminated by matching heart rate during isoproterenol administration and exercise in both groups of patients. Even though a period of 20 minutes was allowed upon completion of exercise in both groups of patients, with return of heart rate to resting values before the initiation of isoproterenol infusion, a potential source of error can not be completely ruled out by using this nonrandomized sequence of interventions.

The previous observation by Neal and co-workers showed that the calculated pulmonary valve area was significantly smaller with isoproterenol when compared to exercise and resting conditions. As these authors pointed out, it is unlikely that the orifice of the pulmonary valve changes in size during exercise or isoproterenol administration, and that the higher values of systolic gradients obtained with isoproterenol are most likely related to some degree of infundibular obstruction induced by this agent. This phenomena of subvalvular obstruction was probably also present in the group of patients with aortic valve stenosis, resulting in significantly higher aortic systolic gradients with

**Table 4. Calculation of Valve Area in Aortic Stenosis (N = 8)**

<table>
<thead>
<tr>
<th></th>
<th>SET (sec)</th>
<th>MSG (mm Hg)</th>
<th>Ao VAI (cm²/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>0.280</td>
<td>16.2</td>
<td>0.94</td>
</tr>
<tr>
<td>E</td>
<td>0.240</td>
<td>22.1</td>
<td>1.04</td>
</tr>
<tr>
<td>I</td>
<td>0.210</td>
<td>35.8</td>
<td>0.79</td>
</tr>
<tr>
<td>E vs I</td>
<td>0.280</td>
<td>16.2</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Abbreviations: R = rest; E = exercise; I = isoproterenol; SET = systolic ejection time; MSG = mean systolic gradient; Ao VAI = aortic valve area index.

**Figure 2.** Correlation of peak systolic gradient (PSG) measured during exercise (E) and isoproterenol (I) infusion in children with pulmonary valve stenosis (r = 0.983).

**Figure 3.** Correlation of peak systolic gradient (PSG) measured during exercise (E), and isoproterenol (I) infusion in children with aortic valve stenosis (r = 0.982).
isoproterenol as compared to exercise despite greater increment in cardiac output obtained during exertion.

Although isoproterenol and exercise both induced an increase in cardiac output and a decrease in systemic vascular resistance, the magnitude of changes in those parameters was different in the two states. The greater increase in cardiac output with exercise can be explained on the bases of metabolic vasodilation in the active muscles decreasing systemic resistance while constriction of the systemic veins and the pumping action of the skeletal muscles increases the venous return to the heart.5,6 In addition, the potent vasodilator effect of isoproterenol may have contributed to the lower values of systemic arterial pressure obtained with this agent.

The increase in ventricular systolic pressures obtained with mild exercise in our patients was most likely related to an increase in preload as well as an increase in myocardial contractility.

Our data in patients with pulmonary stenosis are in general agreement with the observations of Neal et al., regarding the increase in peak valvular gradient with isoproterenol out of proportion with the increase in cardiac output as compared to exercise. However, despite the differences in mechanisms causing increased semilunar gradients, the effects of exercise and isoproterenol were fairly consistent in patients with pulmonary or aortic valve stenosis at similar increments of heart rate. Individual values fit well to the regression line in both groups of patients (figs. 2 and 3). Thus, the linear regression equations generated from these data can be used to estimate gradients of the stenotic lesion under exercise conditions at an equivalent heart rate.

We believe that exercise studies remain the method of choice for the complete evaluation of patients with aortic or pulmonary stenosis. However, isoproterenol infusion and application of these regression equations constitute a practical and useful alternative when exercise studies cannot be carried out.

References


Congenital Heart Block in Newborns of Mothers with Connective Tissue Disease

CAROLYN M. McCUE, M.D., MICHAEL E. MANTAKAS, M.D., JON B. TINGELSTAD, M.D., AND SHAUN RUDDY, M.D.

SUMMARY Of 22 children with congenital complete heart block (CCHB) available for study, 14 (63.6%) were born to 11 mothers with clinical or laboratory evidence of connective tissue disease, primarily lupus erythematosus (LE). Seven mothers had both clinical and laboratory evidence of disease while four had only positive laboratory studies including fluorescent antinuclear antibody, rheumatoid factor, and depressed complement levels.

In adults with systemic LE, pathologic changes in the collagen surrounding the conduction system have led to fibrosis and death from heart block. Antinuclear antibodies of the IgG class cross the placental barrier and newborn infants have been reported with transient skin lesions of lupus. Placental transmission of such antibodies may affect the fetal cardiac conduction system, surrounding collagen, and myocardium, leading in some cases to CCHB. This is probably one important etiologic factor in CCHB even though the mother is asymptomatic during her pregnancy.

CONGENITAL COMPLETE HEART BLOCK was reported by Marquio1 75 years ago as a syndrome with a slow pulse, attacks of syncope, and sudden death, often occurring in families. Since then small series and individual cases have been reported,2,3 but the comprehensive cooperative study of the European and American Pediatric Cardiologists in 1972,7 presenting the results of studies on 599 infants and children, provided a clearer picture of the clinical aspects of congenital complete heart block. There were 14 families with two siblings with heart block and two families with three siblings, but no maternal history is given and the etiology of this rare condition remained obscure.

A coincidence of observing several cases of congenital heart block within a few months at the Medical College of Virginia prompted a review of the clinical findings in all children with congenital heart block seen at the Medical College of Virginia during the preceding 12 years. Since a
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