Hemodynamic Effects of Isoproterenol Infusion in Patients with Normal and Diseased Mitral Valves

By Robert E. Whalen, M.D., Allan I. Cohen, M.D., Robert G. Sumner, M.D., and Henry D. McIntosh, M.D.

Hemodynamic Effects of isoproterenol infusion have been studied in man by several groups.1-3 These observations, however, have been limited to events occurring in the right heart and lesser circulation. The purpose of this paper is to report the hemodynamic alterations associated with isoproterenol infusion that occur in the left heart of patients with normal and diseased mitral valves.

Materials and Methods

Twenty-six adult patients were studied by combined right and left heart catheterization to define or further to quantitate valvular defects suspected on clinical grounds. Right heart catheterization was accomplished in the usual fashion from an antecubital vein and the left heart was studied by combined transseptal left atrial and retrograde left ventricular catheterization.4

By use of these methods the presence or absence of a diastolic gradient across the mitral valve could be determined from the simultaneous left atrial and left ventricular pressure pulses. To determine the presence of mitral insufficiency, 1.5 ml. of a 500 mg. per cent solution of indocyanine dye was injected into the left ventricle while blood was being continuously drawn from the left atrium through a densitometer* coupled to a photographic recorder.† A deflection that occurred within 6 seconds of injection was considered evidence of mitral insufficiency (fig. 1). This interval represented transit time of the dye from catheter to the left ventricle, reflux of dye into the left atrium, and transit time of blood containing dye from left atrium to the densitometer. In this and other laboratories this method of detecting mitral insufficiency has proved more reliable than analysis of the left atrial pulse contour.5 In the majority of cases the presence or absence of insufficiency was confirmed by cineangioeardiograms in which contrast medium was injected into the left ventricle.

On the basis of these observations the 26 patients were divided into four groups:

Group I (patients with normal mitral valves) consisted of five patients in whom there was no mitral diastolic gradient and no early appearance of indocyanine dye in the left atrium after left ventricular injection. This group included two patients with functional murmurs, one with mild pulmonary hypertension of unknown etiology and two patients with mild aortic insufficiency.

Group II (patients with pure mitral stenosis) consisted of 11 patients in whom there was a mitral diastolic gradient throughout diastole but no early appearance of indocyanine dye in the left atrium after left ventricular injection.

Group III (patients with pure mitral insufficiency) consisted of five patients in whom there was no mitral diastolic gradient but who demonstrated early appearance of indocyanine dye in the left atrium following left ventricular injection.

Group IV (patients with combined mitral stenosis and insufficiency) consisted of five patients in whom there was a mitral diastolic gradient throughout diastole and early appearance of indocyanine dye in the left atrium after left ventricular injection.

All pressures were measured with Statham strain gages (P 23D) coupled to a photographic recorder. The mean mitral diastolic gradient was determined by simultaneously recording the left ventricular and left atrial pressures with equisensitive gages at a paper speed of 100 mm. per second and time lines of .04 second (fig. 2). Both pressure pulses were obtained at high sensitivities (1 mm. Hg = 3 to 12 mm. recorder deflection). The magnitude of the gradient was determined by measuring the distance between the pressure trac-
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Figure 1

Demonstrates indicator-dilution curves inscribed when indicator is injected into the left ventricle while blood is being continuously sampled from the left atrium. There is no early appearance of indicator in the top curve, which was obtained from a patient with a normal mitral valve. Early appearance of indicator is seen in the bottom curve, which was obtained from a patient with mitral insufficiency.

ings from the left atrium and left ventricle along successive time lines during 5 to 10 diastolic cycles. The measured distances were then averaged to obtain the mean diastolic gradient. All other mean pressures were obtained by electrical integration.

The average diastolic filling period per beat was obtained by determining the time between the

Total peripheral resistance =

\[
\text{points where the left atrial pressure tracing intersected the downslope and the upslope of the left}
\]

ventricular tracing during 5 to 10 diastolic cycles. The average diastolic filling period per beat was multiplied by the heart rate in order to obtain the

Mitral valve area =

\[
\frac{\text{Diastolic filling period/minute}}{31 \sqrt[3]{\text{Mean mitral diastolic gradient}}}
\]

The cardiac output was estimated by a previously described modification of the Hamilton-Stewart method. Indocyanine dye was injected in the pulmonary artery, and blood was sampled from a peripheral artery through a densitometer coupled to a multichannel photographic recorder that inscribed an indicator-dilution curve. The stroke volume was calculated by dividing the cardiac output by the heart rate recorded during inscription of the dilution curve.

The total peripheral resistance was expressed in units and calculated from the formula:

\[
\frac{\text{Mean arterial pressure (mm. Hg)}}{\text{Cardiac output (L./min.)}}
\]

The pulmonary vascular resistance was also expressed in units and calculated from the formula:

\[
\frac{\text{Mean pulmonary artery pressure} - \text{mean left atrial pressure (mm. Hg)}}{\text{Cardiac output (L./min.)}}
\]

In cases of pure mitral stenosis the mitral valve area was calculated by a modification of the Gorlin formula:

\[
\frac{\text{Diastolic filling period/minute}}{31 \sqrt[3]{\text{Mean mitral diastolic gradient}}}
\]

In cases of combined mitral stenosis and in-
Table 1

Hemodynamic Effects of Isoproterenol in Patients with Normal Mitral Values

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heart rate</th>
<th>Cardiac output (L/min.)</th>
<th>Stroke volume (mL)</th>
<th>Mean PA pressure (mm Hg)</th>
<th>Mean LA pressure (mm Hg)</th>
<th>LVED pressure (mm Hg)</th>
<th>Pulmonary vascular resistance (units)</th>
<th>Mean arterial BP (mm Hg)</th>
<th>Total peripheral resistance (units)</th>
<th>Diastolic filling period/minute (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.S.</td>
<td>73</td>
<td>105</td>
<td>3.72</td>
<td>5.47</td>
<td>51</td>
<td>16</td>
<td>16</td>
<td>6.7</td>
<td>5.1</td>
<td>2.5</td>
</tr>
<tr>
<td>J.H.</td>
<td>96</td>
<td>108</td>
<td>5.30</td>
<td>8.50</td>
<td>55</td>
<td>33</td>
<td>30</td>
<td>8.0</td>
<td>6.3</td>
<td>4.6</td>
</tr>
<tr>
<td>J.A.</td>
<td>84</td>
<td>84</td>
<td>4.14</td>
<td>5.43</td>
<td>49</td>
<td>23</td>
<td>18</td>
<td>11.5</td>
<td>9.6</td>
<td>2.8</td>
</tr>
<tr>
<td>S.G.</td>
<td>96</td>
<td>141</td>
<td>3.00</td>
<td>4.42</td>
<td>34</td>
<td>8</td>
<td>8</td>
<td>5.9</td>
<td>5.2</td>
<td>0.4</td>
</tr>
<tr>
<td>W.T.</td>
<td>52</td>
<td>64</td>
<td>2.94</td>
<td>3.85</td>
<td>46</td>
<td>18</td>
<td>17</td>
<td>10.0</td>
<td>7.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean</td>
<td>80</td>
<td>100</td>
<td>3.82</td>
<td>5.13</td>
<td>47</td>
<td>20</td>
<td>18</td>
<td>8.4</td>
<td>6.6</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Average % change from control: +25 +34 +15 -9 -21 -18 -23 +3 -32 -5

The following abbreviations apply to tables 1 to 4: PA, pulmonary artery; LA, left atrial; LVED, left ventricular end-diastolic; C, control; I, infusion.

Results

The results are listed in tables 1 to 4 and figures 3 and 4. When the average per cent change from control values are reviewed in Table 1, it is noted that cardiac output, stroke volume, mean pulmonary arterial pressure, mean left atrial pressure, and mean pulmonary vascular resistance tended to rise, while the mean pulmonary arterial pressure, mean left atrial pressure, and mean pulmonary vascular resistance fell. The mean arterial pressure and total peripheral resistance fell.

Note that patients with pure mitral stenosis had no change in stroke volume.

Figure 3

AVERAGE % CHANGE FROM CONTROL

Diastolic PVRI of control (C) and mitral valve stenosis (MV).
### Table 2

**Hemodynamic Effects of Isoproterenol in Patients with Mitral Stenosis**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heart rate (beat/min.)</th>
<th>Cardiac output (L/min.)</th>
<th>Stroke volume (ml.)</th>
<th>Mean PA pressure (mm Hg)</th>
<th>Mean LA pressure (mm Hg)</th>
<th>LVED pressure (mm Hg)</th>
<th>Mean mitral diastolic gradient (mm Hg)</th>
<th>Mitral valve area (cm²)</th>
<th>Pulmonary vascular resistance (units)</th>
<th>Mean arterial BP (mm Hg)</th>
<th>Total peripheral resistance (units)</th>
<th>Diastolic filling period/minute (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.H.</td>
<td>78</td>
<td>96</td>
<td>3.44</td>
<td>3.89</td>
<td>44</td>
<td>41</td>
<td>32</td>
<td>36</td>
<td>20.0</td>
<td>16.0</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Z.H.</td>
<td>120</td>
<td>146</td>
<td>2.94</td>
<td>3.81</td>
<td>25</td>
<td>26</td>
<td>28</td>
<td>32</td>
<td>22.0</td>
<td>26.0</td>
<td>5.4</td>
<td>1.0</td>
</tr>
<tr>
<td>R.T.</td>
<td>66</td>
<td>112</td>
<td>3.25</td>
<td>5.52</td>
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<td>52</td>
<td>28</td>
<td>37</td>
<td>22.0</td>
<td>32.0</td>
<td>14.0</td>
<td>6.5</td>
</tr>
<tr>
<td>R.J.</td>
<td>88</td>
<td>111</td>
<td>2.94</td>
<td>3.47</td>
<td>34</td>
<td>32</td>
<td>77</td>
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<td>32.0</td>
<td>34.6</td>
<td>7.6</td>
<td>4.0</td>
</tr>
<tr>
<td>L.E.</td>
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<td>108</td>
<td>3.83</td>
<td>5.25</td>
<td>55</td>
<td>49</td>
<td>15</td>
<td>18</td>
<td>12.2</td>
<td>15.5</td>
<td>7.0</td>
<td>4.0</td>
</tr>
<tr>
<td>M.R.</td>
<td>81</td>
<td>81</td>
<td>4.29</td>
<td>4.11</td>
<td>53</td>
<td>51</td>
<td>18</td>
<td>18</td>
<td>12.2</td>
<td>13.7</td>
<td>6.1</td>
<td>5.8</td>
</tr>
<tr>
<td>E.H.</td>
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<td>93</td>
<td>3.81</td>
<td>3.80</td>
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<td>41</td>
<td>16</td>
<td>15</td>
<td>9.0</td>
<td>11.0</td>
<td>8.1</td>
<td>4.0</td>
</tr>
<tr>
<td>C.S.</td>
<td>66</td>
<td>66</td>
<td>2.88</td>
<td>3.43</td>
<td>44</td>
<td>52</td>
<td>23</td>
<td>23</td>
<td>10.5</td>
<td>13.3</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>E.M.</td>
<td>97</td>
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<td>2.54</td>
<td>3.48</td>
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<td>34</td>
<td>76</td>
<td>83</td>
<td>27.6</td>
<td>32.4</td>
<td>6.0</td>
<td>5.0</td>
</tr>
<tr>
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<td>100</td>
<td>3.56</td>
<td>3.81</td>
<td>48</td>
<td>40</td>
<td>18</td>
<td>20</td>
<td>10.5</td>
<td>12.9</td>
<td>5.3</td>
<td>2.1</td>
</tr>
<tr>
<td>M.P.</td>
<td>102</td>
<td>115</td>
<td>3.60</td>
<td>3.96</td>
<td>35</td>
<td>34</td>
<td>22</td>
<td>24</td>
<td>13.8</td>
<td>16.1</td>
<td>4.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Mean</td>
<td>84</td>
<td>103</td>
<td>3.37</td>
<td>4.05</td>
<td>41</td>
<td>41</td>
<td>32</td>
<td>35</td>
<td>17.1</td>
<td>20.7</td>
<td>6.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Average % change from control: +18, +17, +8, +21, -40, +29, +1, -18, +2, -14, +3
Table 3

Hemodynamic Effects of Isoproterenol in Patients with Mitral Insufficiency

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heart rate</th>
<th>Cardiac output (L/min.)</th>
<th>Stroke volume (ml.)</th>
<th>Mean PA pressure (mm Hg)</th>
<th>Mean LA pressure (mm Hg)</th>
<th>LVED pressure (mm Hg)</th>
<th>Pulmonary vascular resistance (units)</th>
<th>Mean arterial BP (mm Hg)</th>
<th>Total peripheral resistance (units)</th>
<th>Diastolic filling period/minute (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.S.</td>
<td>66</td>
<td>4.81</td>
<td>73</td>
<td>16</td>
<td>9.5</td>
<td>7.4</td>
<td>1.1</td>
<td>104</td>
<td>21.6</td>
<td>34.8</td>
</tr>
<tr>
<td>J.H.</td>
<td>84</td>
<td>2.99</td>
<td>36</td>
<td>17</td>
<td>10.4</td>
<td>7.8</td>
<td>2.2</td>
<td>78</td>
<td>26.1</td>
<td>31.5</td>
</tr>
<tr>
<td>J.P.</td>
<td>81</td>
<td>3.66</td>
<td>45</td>
<td>17</td>
<td>9.5</td>
<td>9.2</td>
<td>2.1</td>
<td>84</td>
<td>23.0</td>
<td>33.5</td>
</tr>
<tr>
<td>L.W.</td>
<td>84</td>
<td>3.31</td>
<td>39</td>
<td>7</td>
<td>3.4</td>
<td>5.5</td>
<td>1.1 &lt;1</td>
<td>94</td>
<td>28.4</td>
<td>25.2</td>
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<tr>
<td>A.W.</td>
<td>86</td>
<td>3.14</td>
<td>39</td>
<td>19</td>
<td>12.6</td>
<td>5.1</td>
<td>2.3</td>
<td>86</td>
<td>24.2</td>
<td>30.4</td>
</tr>
<tr>
<td>Mean</td>
<td>80</td>
<td>3.58</td>
<td>46</td>
<td>19</td>
<td>11.2</td>
<td>8.5</td>
<td>2.3</td>
<td>86</td>
<td>24.2</td>
<td>31.6</td>
</tr>
</tbody>
</table>

Average % change from control: +22, +25, +8, -8, -24, -34, -17, -1, -23, -4

Note that patients with combined mitral stenosis and insufficiency showed no change in mean pulmonary artery pressure.


**Table 4**

Hemodynamic Effects of Isoproterenol in Patients with Mitral Stenosis and Insufficiency

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heart rate (C)</th>
<th>Cardiac output (L/min.)</th>
<th>Stroke volume (ml.)</th>
<th>Mean PA pressure (mm. Hg)</th>
<th>Mean LA pressure (mm. Hg)</th>
<th>LVED pressure (mm. Hg)</th>
<th>Mean mitral diastolic gradient (mm. Hg)</th>
<th>Pulmonary vascular resistance (units)</th>
<th>Mean arterial BP (mm. Hg)</th>
<th>Total peripheral resistance (units)</th>
<th>Diastolic filling period/minute (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.J.</td>
<td>87</td>
<td>3.21 3.99</td>
<td>37 28</td>
<td>19 26</td>
<td>15 24</td>
<td>5.4 5.4</td>
<td>8.9 17.4</td>
<td>1.3 0.5</td>
<td>...</td>
<td>...</td>
<td>28.8 24.1</td>
</tr>
<tr>
<td>C.W.</td>
<td>69</td>
<td>2.82 2.85</td>
<td>41 41</td>
<td>28</td>
<td>9.8 11.4</td>
<td>7.0 6.9</td>
<td>4.7 5.4</td>
<td>8.3 ...</td>
<td>...</td>
<td>...</td>
<td>33.0 35.0</td>
</tr>
<tr>
<td>L.E.</td>
<td>87</td>
<td>2.79 2.96</td>
<td>32 34</td>
<td>62 63</td>
<td>32.0 33.8</td>
<td>7.9 7.9</td>
<td>24.9 25.2</td>
<td>10.8 9.9</td>
<td>90 94</td>
<td>32.3 31.8</td>
<td>37.8 36.6</td>
</tr>
<tr>
<td>H.O.</td>
<td>84</td>
<td>4.24 5.75</td>
<td>60 64</td>
<td>50 45</td>
<td>23.2 24.7</td>
<td>16.7 9.5</td>
<td>14.0 20.0</td>
<td>4.0 3.5</td>
<td>76 65</td>
<td>11.8 7.8</td>
<td>30.0 34.3</td>
</tr>
<tr>
<td>G.L.</td>
<td>90</td>
<td>2.95 3.72</td>
<td>33 43</td>
<td>28 24</td>
<td>13.8 12.8</td>
<td>11.4 7.3</td>
<td>5.1 7.1</td>
<td>4.8 3.0</td>
<td>82 85</td>
<td>27.8 22.9</td>
<td>24.3 27.3</td>
</tr>
<tr>
<td>Mean</td>
<td>83</td>
<td>3.20 3.85</td>
<td>41 42</td>
<td>37 40</td>
<td>18.8 21.3</td>
<td>9.7 7.4</td>
<td>11.5 15.0</td>
<td>5.8 4.2</td>
<td>83 81</td>
<td>24.0 20.8</td>
<td>30.8 31.5</td>
</tr>
</tbody>
</table>

Average % change from control: +15 +20 +3 +0 +14 -23 +30 -19 -2 -13 +2
stemming from stenosis. Thus, while the stroke volume rose in this group, it did not rise as high as that of the normal or the pure mitral insufficiency group. Although the mean left atrial pressure rose in this group, it did not reach the heights noted in patients with pure mitral stenosis. The lack of any increase in mean pulmonary artery pressure lies midway between the increase noted in patients with mitral stenosis and the decrease noted in patients with normal or insufficient valves.

Isoproterenol has a variety of hemodynamic effects. The increase in heart rate seen in this study is a manifestation of its chronotropic activity.8,9 The increased cardiac output and stroke volume are consistent with its known inotropic activity.8-10 The decrease in the pulmonary vascular resistance and total peripheral resistance are manifestations of the drug’s ability to produce arterial dilatation in the pulmonary and systemic arterial circuits.8-11 The decrease in mean left atrial pressure seen in patients with normal mitral valves is consistent with earlier observations on the response of right atrial pressure to this drug.

Mitral stenosis produces marked alterations in the hemodynamic response to this drug. Whenever the resting left atrioventricular gradient is elevated, persistent increase in cardiac output above the resting level can be achieved only by a further increase in gradient. As the flow across the valve varies with the square root of the gradient, small changes in flow are associated with easily measured increases in the left atrioventricular gradient. The inotropic action of the drug leads to an increase in flow into the lungs and left atrium, but the stenotic valve prevents an equal increase in output of the left ventricle until the left atrioventricular gradient reaches its new level. Despite the fall in pulmonary vascular resistance, the pulmonary artery pressure rises, because of an increase in volume in the lesser circulation. The new gradient is achieved by a decrease in left ventricular end-diastolic pressure and an increase in left atrial pressure.

In patients with unobstructed mitral valves the fall in mean left atrial pressure is a reflection of the fall in left ventricular end-diastolic pressure, as the left atrium and ventricle become a common chamber in diastole. There are a number of mechanisms that would account for the drug-induced fall in mean left atrial and left ventricular end-diastolic pressure in patients with unobstructed mitral valves. Among these could be included a redistribution of blood away from the central reservoir, a decrease in central venous tone, and an increase in atrial and ventricular distensibility. The observation that cardiac output and mean left atrial pressure rise while left ventricular end-diastolic pressure falls in patients with mitral stenosis indicates that redistribution of blood away from the central venous reservoir and a decrease in central venous tone are not adequate explanations for the fall in left atrial and left ventricular end-diastolic pressure seen in patients with unobstructed mitral valves. This observation suggests that isoproterenol may have a direct effect on the distensibility of the left ventricle. Although the effect of isoproterenol on ventricular distensibility has not been investigated, epinephrine, a closely related compound, is reported to increase ventricular distensibility12 in dogs.

There are several alternate explanations for the findings in patients with mitral stenosis. Since the diastolic filling period changed little during drug infusion, the increase in left atrial pressure and the mean diastolic gradient cannot be attributed to the chronotropic actions of the drug. Since the left atrial pressure rose in all patients with mitral stenosis, regardless of the presence of normal sinus rhythm or atrial fibrillation, it seems unlikely that the drug’s inotropic action on the left atrium played a critical role. Furthermore, enhanced left atrial contraction would be expected to lead to an increased stroke volume, which did not occur in the mitral stenosis group.

Summary

Hemodynamic effects of isoproterenol infusion were studied in 26 patients with and
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without mitral valve disease undergoing combined right and left heart catheterization. The heart rate and cardiac output rose while the left ventricular end-diastolic pressure, pulmonary vascular resistance, and total peripheral resistance fell, regardless of the status of the mitral valve. Infusion produced little change in the mean arterial blood pressure and the diastolic filling period per minute.

While the mean left atrial and pulmonary artery pressures fell in patients with normal or insufficient valves, these pressures rose in patients with mitral stenosis. Stroke volume tended to rise in all patients but those with mitral stenosis. In patients with combined mitral stenosis and insufficiency the insufficiency appeared to modify the hemodynamic response associated with mitral stenosis.

The presence of a lowered end-diastolic pressure in the left ventricle and an increased pressure in the left atrium in patients with stenosis suggests that isoproterenol has a direct or reflex effect on the left ventricle during diastole.

References

Too Much Reading

Excessive reading may be a form of laziness . . . If you spend most of your time in reading, you are likely to be left not only with no time for the more important occupations of observing and thinking, but with no mind wherewith to do these essential things.—LORD HORDER (The Vocation of Medicine. Lancet 1948). The Quiet Art: A Doctor’s Anthology. Compiled by Dr. ROBERT COOPE. Edinburgh & London, E. & S. Livingstone Ltd., 1952, p. 42.

Circulation, Volume XXVII, April 1968
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Circulation. 1963;27:512-519
doi: 10.1161/01.CIR.27.4.512

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

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