Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease

I. Effect of Exercise

By Lars Werkö, M.D., Edvardas Varnauskas, M.D., Harald Eliasch, M.D., Jan Ek, M.D., Härje Bucht, M.D., Bengt Thomasson, M.D., and Jonas Bergström, M. K.

In 31 patients with mitral stenosis of varying severity the effect of light, steady exercise during 15 to 17 minutes on renal function and renal circulation has been studied during heart catheterization. The results have been compared with the values obtained at rest in 72 patients with mitral stenosis. Exercise produced a decrease in clearance of para-aminobipurate and sodium excretion and an increase in renal resistance, changes not produced in normal individuals. Cardiac output and pulmonary pressures increased. In patients with right heart failure exercise produced increased pressures but no increase in cardiac output, and only slight changes in clearance but increase in renal resistance and renal venous pressure.

During the last decade, renal function in heart disease has been subject to intense research. The occurrence of renal changes in congestive heart failure has been repeatedly demonstrated and its importance debated. Decreased cardiac output or elevated venous pressure have been suggested as possible causative factors but no conclusions have been reached. It had been shown earlier that there is a marked decrease of renal blood flow in cases with mitral valvular disease (without elevation of right auricular pressure), a change similar to that found in cases with right heart failure.

The present investigation constitutes an attempt to correlate changes in renal blood flow, glomerular filtration rate and sodium excretion with changes in cardiac output and blood pressures in a large series of patients with mitral valvular disease studied at rest and during exercise.

Material

The subjects studied were 72 patients considered, on clinical and radiologic evidence, to have rheumatic mitral valvular disease. They were divided in four functional groups. Selection was random.

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Patients with complicating aortic stenosis were excluded, but not patients with elevated arterial blood pressure. Some of the patients in groups III and IV had signs of right heart failure, with elevated right auricular pressure.

No patient had any record of renal disease, and, in all cases without right heart failure, the urine was free from protein and had a normal sediment.

Methods

All patients were studied in the morning, recumbent, and in the postabsorptive state. An indwelling catheter was placed in the urinary bladder. Para-aminobipurate (PAH) was given intramuscularly according to the method of Bucht and inulin intravenously, at the start of the procedure.

The pulmonary artery was catheterized according to the technic of Cournand and Ranges and an indwelling arterial needle placed in the brachial artery. Subsequently the bladder was emptied and the first urine collection period started. Every 15 to 17 minutes the bladder was again emptied and rinsed twice with distilled water and air. Simultaneously a blood sample for clearance determination was taken from the arterial needle. About 30 minutes after the heart catheter had been placed in the pulmonary artery, the first resting cardiac output was determined by the Fick method, with simultaneous sampling of blood from the brachial and pulmonary arteries and collection of expired air. Immediately afterward the blood pressures in the pulmonary artery and brachial artery, and the pulmonary capillary venous pressure were registered with the Tybjaerg-Hansen electrical manometer. In some cases the right auric-
renal circulation and function in mitral valvular disease

Table 1.—Results in 26 Cases of Mitral Stenosis Belonging to Group I–II. Rest

<table>
<thead>
<tr>
<th>BSA M²</th>
<th>Age</th>
<th>Heart vol. ml./M²</th>
<th>Art. O₂ satu. %</th>
<th>Pulse rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resistance dyne sec. cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulm. art. mean</td>
<td>PCV mean</td>
</tr>
<tr>
<td>n ......</td>
<td>26</td>
<td>26</td>
<td>21</td>
<td>26</td>
<td>19.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Mean</td>
<td>26</td>
<td>35.7</td>
<td>93.2</td>
<td>79.6</td>
<td>19.9</td>
<td>12.9</td>
</tr>
<tr>
<td>S.E.</td>
<td>26</td>
<td>512</td>
<td>0.50</td>
<td>3.35</td>
<td>1.08</td>
<td>1.13</td>
</tr>
<tr>
<td>S.D.</td>
<td>26</td>
<td>148</td>
<td>2.25</td>
<td>17.1</td>
<td>5.52</td>
<td>5.78</td>
</tr>
</tbody>
</table>

ular pressure was registered simultaneously through a second catheter; in the remaining cases the right auricular pressure was registered when the catheter was introduced.

When the pressures had been registered the bladder was rapidly emptied. During the following 15 to 17 minutes the patient performed exercise equaling about 70 kilogrammeters per minute by pedaling a cycle ergometer after the method of Eliasch and co-workers. The blood pressures were repeatedly registered and the cardiac output again determined after 10 to 12 minutes of work.

Immediately after cessation of exercise the bladder was again emptied and samples taken. In some cases another set of values was obtained after the subject had rested for 15 to 20 minutes. The technics are reported in detail earlier.

In two cases one catheter was placed in the pulmonary artery and another in the right renal vein. Renal venous blood was sampled simultaneously with arterial blood and analyzed for para-aminohippurate. The renal extraction of para-aminohippurate was calculated in per cent from the concentrations in the arterial and renal venous blood.

Results

Table 1, a and b, contains the resting values obtained in the 26 cases in group I and II. The

Table 2.—Results in 32 Cases of Mitral Stenosis Belonging to Group III. Rest

<table>
<thead>
<tr>
<th>BSA M²</th>
<th>Age</th>
<th>Heart volume ml./M²</th>
<th>Art. O₂ saturation %</th>
<th>Pulse Rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resist. dyne sec. cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulm. art. mean</td>
<td>PCV mean</td>
</tr>
<tr>
<td>n ......</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Mean</td>
<td>32</td>
<td>42.4</td>
<td>609</td>
<td>92.2</td>
<td>82.4</td>
<td>37.5</td>
</tr>
<tr>
<td>S.E.</td>
<td>32</td>
<td>28.3</td>
<td>0.55</td>
<td>3.36</td>
<td>2.88</td>
<td>0.89</td>
</tr>
<tr>
<td>S.D.</td>
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<td>160</td>
<td>2.97</td>
<td>19.0</td>
<td>16.3</td>
<td>5.81</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A-V O₂ diff. ml./L</th>
<th>Card. ind. L/min./M²</th>
<th>Clearance ml./min./1.73 M² BSA</th>
<th>Inulin</th>
<th>PAH</th>
<th>FF %</th>
<th>RBF ml/1.73 M² BSA</th>
<th>RBF % of CO</th>
<th>Renal resist. dyne sec. cm⁻²</th>
<th>Hematocrit</th>
<th>T mean sec.</th>
<th>TPV L/1.73 M² BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n ......</td>
<td>32</td>
<td>32</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>26</td>
<td>32</td>
<td>136.4</td>
<td>38.1</td>
<td>15.1</td>
<td>2.91</td>
</tr>
<tr>
<td>Mean</td>
<td>32</td>
<td>2.67</td>
<td>99.5</td>
<td>322.5</td>
<td>31.0</td>
<td>31.0</td>
<td>586.1</td>
<td>12.8</td>
<td>136.4</td>
<td>38.1</td>
<td>0.93</td>
<td>0.094</td>
</tr>
<tr>
<td>S.E.</td>
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<td>4.97</td>
<td>15.5</td>
<td>1.03</td>
<td>1.03</td>
<td>28.1</td>
<td>0.68</td>
<td>8.61</td>
<td>0.93</td>
<td>5.11</td>
<td>0.53</td>
</tr>
<tr>
<td>S.D.</td>
<td>32</td>
<td>9.95</td>
<td>27.7</td>
<td>87.6</td>
<td>5.74</td>
<td>5.74</td>
<td>163</td>
<td>3.49</td>
<td>48.7</td>
<td>5.11</td>
<td>0.53</td>
<td>0.53</td>
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</tbody>
</table>
TABLE 3.—Results in Seven Cases of Mitral Stenosis Belonging to Group IV. No right heart failure. Rest

<table>
<thead>
<tr>
<th>BSA M.²</th>
<th>Age</th>
<th>Heart volume ml./M.²</th>
<th>Art. O₂ saturation %</th>
<th>Pulse Rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resist. dyne sec. cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulm. art. mean</td>
<td>PCV mean</td>
</tr>
<tr>
<td>n . . . .</td>
<td>7</td>
<td>1.62</td>
<td>50.1</td>
<td>7</td>
<td>7</td>
<td>52.6</td>
</tr>
<tr>
<td>Mean . . .</td>
<td>7.12</td>
<td>796</td>
<td>97.4</td>
<td>6</td>
<td>7</td>
<td>24.0</td>
</tr>
<tr>
<td>S.E. . . .</td>
<td>127</td>
<td>6.14</td>
<td>8.73</td>
<td>7</td>
<td>19.8</td>
<td>5.60</td>
</tr>
<tr>
<td>S.D. . . .</td>
<td>336</td>
<td>2.51</td>
<td>23.1</td>
<td>7</td>
<td>336</td>
<td>2.51</td>
</tr>
</tbody>
</table>

Mean heart volume for these groups was 512 ml. per square meter of body surface area. The pressure in the pulmonary artery was 19.9 mm. Hg, the pulmonary capillary venous pressure, 12.9 mm. Hg and the right auricular pressure 1.13 mm. Hg. The mean cardiac index for the group was 3.59 liters per minute per square meter of body surface. The renal clearance of inulin was 108.7 ml. per minute, of para-amino-hippurate, 404.8 ml. per minute, with a filtration fraction of 27.8 per cent. The renal fraction of the cardiac output was 12.2 per cent. The total plasma volume was 3.05 liters. The thoracic mean circulation time was 11.9 seconds.

Table 2, a and b, contains the same values obtained in the 32 cases in group III. The mean heart volume was 609 ml. per square meter of body surface. The pressure in the pulmonary artery was 38.2 mm. Hg, the pulmonary capillary venous pressure, 21.9 mm. Hg and the right auricular pressure, 2.12 mm. Hg. The mean cardiac index for the group was 2.64 liters per minute per square meter of surface area.

TABLE 4.—Results in Seven Cases of Mitral Stenosis Belonging to Group IV. Right Heart Failure. Rest

<table>
<thead>
<tr>
<th>BSA M.²</th>
<th>Age</th>
<th>Heart vol. ml./M.²</th>
<th>Art. O₂ satur. %</th>
<th>Pulse rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resist. dyne sec. cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulm. art. mean</td>
<td>PCV mean</td>
</tr>
<tr>
<td>n . . . .</td>
<td>7</td>
<td>1.73</td>
<td>42.6</td>
<td>6</td>
<td>7</td>
<td>52.6</td>
</tr>
<tr>
<td>Mean . . .</td>
<td>7.12</td>
<td>307</td>
<td>90.4</td>
<td>6</td>
<td>7</td>
<td>24.0</td>
</tr>
<tr>
<td>S.E. . . .</td>
<td>133</td>
<td>1.68</td>
<td>5.93</td>
<td>7</td>
<td>16.3</td>
<td>6.29</td>
</tr>
<tr>
<td>S.D. . . .</td>
<td>296</td>
<td>4.12</td>
<td>15.7</td>
<td>7</td>
<td>314</td>
<td>2.51</td>
</tr>
</tbody>
</table>

Mean heart volume for these groups was 512 ml. per square meter of body surface area. The pressure in the pulmonary artery was 19.9 mm. Hg, the pulmonary capillary venous pressure, 12.9 mm. Hg and the right auricular pressure 1.13 mm. Hg. The mean cardiac index for the group was 3.59 liters per minute per square meter of body surface. The renal clearance of inulin was 108.7 ml. per minute, of para-amino-hippurate, 404.8 ml. per minute, with a filtration fraction of 27.8 per cent. The renal fraction of the cardiac output was 12.2 per cent. The total plasma volume was 3.05 liters. The thoracic mean circulation time was 11.9 seconds.

Table 2, a and b, contains the same values obtained in the 32 cases in group III. The mean heart volume was 609 ml. per square meter of body surface. The pressure in the pulmonary artery was 38.2 mm. Hg, the pulmonary capillary venous pressure, 21.9 mm. Hg and the right auricular pressure, 2.12 mm. Hg. The mean cardiac index for the group was 2.64 liters per minute per square meter of surface area.
### Table 5. Results in 15 Cases of Mitral Stenosis Belonging to Group I–II. Rest and Exercise

<table>
<thead>
<tr>
<th>Art. O₂ satur.</th>
<th>Pulse rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resistance dyne sec. cm⁻¹</th>
<th>A-V O₂ diff. mL/L</th>
<th>Card. ind. L/min/M²</th>
<th>Clearance ml/min./1.73 M²</th>
<th>RBF ml/L/min.</th>
<th>RBF % of CO</th>
<th>Renal resist dyne sec. cm⁻¹</th>
<th>Na⁺ μEq./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean diff.</td>
<td>−0.55</td>
<td>18.2</td>
<td>8.1</td>
<td>7.4</td>
<td>6.2</td>
<td>0.33</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>S.E. diff.</td>
<td>0.34</td>
<td>3.49</td>
<td>1.64</td>
<td>1.51</td>
<td>2.63</td>
<td></td>
<td>9.19</td>
<td>66.9</td>
<td>2.14</td>
<td>0.20</td>
</tr>
<tr>
<td>S.D. diff.</td>
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<td>13.5</td>
<td>6.36</td>
<td>5.65</td>
<td>10.2</td>
<td></td>
<td>34.4</td>
<td>250</td>
<td>8.27</td>
<td>0.77</td>
</tr>
<tr>
<td>t</td>
<td>1.62</td>
<td>5.23</td>
<td>4.94</td>
<td>4.90</td>
<td>2.36</td>
<td></td>
<td>&lt;1</td>
<td>2.61</td>
<td>11.5</td>
<td>0.01</td>
</tr>
<tr>
<td>p</td>
<td>&gt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.05–</td>
<td></td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Table 6. Results in Nine Cases of Mitral Stenosis Belonging to Group III–IV. No Right Heart Failure. Rest and Exercise

<table>
<thead>
<tr>
<th>Art. O₂ sat.</th>
<th>Pulse rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resistance dyne sec. cm⁻¹</th>
<th>A-V O₂ diff. mL/L</th>
<th>Card. ind. L/min/M²</th>
<th>Clearance ml/min./1.73 M²</th>
<th>RBF ml/L/min.</th>
<th>RBF % of CO</th>
<th>Renal resist dyne sec. cm⁻¹</th>
<th>Na⁺ μEq./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>9</td>
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<td>6</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Mean diff.</td>
<td>0.48</td>
<td>32.0</td>
<td>21.4</td>
<td>12.0</td>
<td>10.2</td>
<td>0.77</td>
<td>87.1</td>
<td>−160</td>
<td>32.9</td>
<td>−4.0</td>
</tr>
<tr>
<td>S.E. diff.</td>
<td>0.63</td>
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<td>2.30</td>
<td>2.64</td>
<td>2.33</td>
<td></td>
<td>53.0</td>
<td>74.7</td>
<td>4.10</td>
<td>0.19</td>
</tr>
<tr>
<td>S.D. diff.</td>
<td>1.77</td>
<td>10.0</td>
<td>6.91</td>
<td>7.92</td>
<td>5.71</td>
<td></td>
<td>159</td>
<td>183</td>
<td>12.3</td>
<td>0.58</td>
</tr>
<tr>
<td>t</td>
<td>&lt;1</td>
<td>9.61</td>
<td>9.30</td>
<td>4.54</td>
<td>4.38</td>
<td></td>
<td>1.64</td>
<td>2.14</td>
<td>8.02</td>
<td>3.31</td>
</tr>
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<td>&lt;0.001</td>
<td>0.01–</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Table 7. Results in Seven Cases of Mitral Stenosis Belonging to Group III–IV. Right Heart Failure. Rest and Exercise

<table>
<thead>
<tr>
<th>Art. O₂ sat.</th>
<th>Pulse rate</th>
<th>Pressure mm. Hg</th>
<th>Vascular resistance dyne sec. cm⁻¹</th>
<th>A-V O₂ diff. mL/L</th>
<th>Card. ind. L/min/M²</th>
<th>Clearance ml/min./1.73 M²</th>
<th>RBF ml/L/min.</th>
<th>RBF % of CO</th>
<th>Renal resist dyne sec. cm⁻¹</th>
<th>Na⁺ μEq./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>7</td>
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<td>7</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mean diff.</td>
<td>0.02</td>
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<td>5.4</td>
<td>4.7</td>
<td>286</td>
<td>−23.0</td>
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</tr>
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<td>S.E. diff.</td>
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<td>6.04</td>
<td>1.99</td>
<td>1.33</td>
<td>0.75</td>
<td>328</td>
<td>26.2</td>
<td>8.35</td>
<td>0.28</td>
</tr>
<tr>
<td>S.D. diff.</td>
<td>0.48</td>
<td>18.1</td>
<td>13.5</td>
<td>5.27</td>
<td>3.51</td>
<td>1.98</td>
<td>803</td>
<td>69.4</td>
<td>22.1</td>
<td>0.75</td>
</tr>
<tr>
<td>t</td>
<td>&lt;1</td>
<td>4.82</td>
<td>4.02</td>
<td>3.97</td>
<td>4.06</td>
<td>6.27</td>
<td>&lt;1</td>
<td>4.38</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<td>p</td>
<td>0.01–</td>
<td>0.05–</td>
<td>0.01–</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td>0.01–</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

[Table 5, Table 6, Table 7]
The renal clearance of inulin was 100.3 ml per minute, of para-aminohippurate, 322.2 ml per minute, with a filtration fraction of 31.4 per cent. The renal fraction of the cardiac output was 13.1 per cent. The total plasma volume was 2.97 liters. The thoracic mean circulation time was 15.3 seconds.

The cases in group IV are divided in two subgroups: seven cases without right heart failure (table 3, a and b) and seven cases in right heart failure (table 4, a and b). In the group without right heart failure the mean heart volume was 796 ml per square meter of body surface area, the pressure in the pulmonary artery was 52.6 mm Hg, the pulmonary capillary venous pressure was 24.0 mm Hg and the right auricular pressure, 1.6 mm Hg. The cardiac index was 2.11 liters per minute per square meter of body surface area. The renal clearance of inulin was 76.3 ml per minute, of para-aminohippurate, 216.4 ml per minute, with a filtration fraction of 34.9 per cent. The renal fraction of the cardiac output was 10.8 per cent. The total plasma volume was 3.89 liters. The mean thoracic circulation time was 17.8 seconds.

In the seven patients in group IV with right heart failure, the mean heart volume was 873 ml per square meter of surface area. The pressure in the pulmonary artery was 73.5 mm Hg, the pulmonary capillary venous pressure was 24.8 mm Hg and the right auricular pressure 10.4 mm Hg. The mean cardiac index of the group was 1.82 ml per minute per square meter of body surface area. The renal clearance of inulin was 72.0 ml per minute, of para-aminohippurate, 158.4 ml per minute, with a filtration fraction of 46.2 per cent. The renal fraction of the cardiac output was 9.12 per cent. The total plasma volume was 3.81 liters. The thoracic mean circulation time was 27.5 seconds.

Tables 5, 6 and 7 contain the observations made during exercise. In the cases in group I and II (table 5) exertion produced a significant increase in the pressures in the pulmonary circulation, in the arteriovenous oxygen difference and in cardiac output. The inulin clearances were not altered, but the para-aminohippurate clearance, the renal fraction of the cardiac output and the sodium excretion were decreased. The filtration fraction and the renal resistance increased during exercise. Findings recorded during exercise in the patients of groups III and IV, who were not in right heart failure (table 6), were in the same direction, differing only in numerical values from those in the former group. In the seven patients with right heart failure (table 7), on the contrary, the increase in arteriovenous oxygen difference during exertion was of such magnitude as to render the change in cardiac output insignificant. The pressures in the pulmonary artery and right auricle and the pulmonary capillary venous pressure rose. Exercise produced no change in inulin or para-aminohippurate clearance, nor in filtration fraction, renal

![Figure 1](https://example.com/fig1.png)

**FIG. 1.** Case 457. Female patient with mitral stenosis (group III). Hemodynamic and clearance values obtained on right heart and renal vein catheterisation during rest and exercise. Effort did not cause any change in para-aminohippurate extraction.
fraction of cardiac output or in renal resistance. The sodium excretion decreased significantly in this group also. Figure 1 demonstrates typical findings in one of the patients (case 459) in group III in whom a second catheter was left in the renal vein during the study. Exercise did not cause any change in para-aminohippurate extraction although the renal plasma flow decreased.

In table 8 the material has been grouped according to clinical criteria as well as para-aminohippurate clearance. These groups have subsequently been correlated according to arteriovenous oxygen difference and the numerical value of pulmonary capillary venous pressure divided by the cardiac index. The grouping according to changes in para-aminohippurate clearance gives the same distribution of arteriovenous oxygen difference and quotient for pulmonary capillary venous pressure divided by cardiac index as the clinical grouping. In the separate clinical groups, however, the cases with high para-aminohippurate clearance have a lower arteriovenous oxygen difference and quotient than the cases with low para-aminohippurate clearance, both being expressions of the severity of the disease.

### Discussion

**Methods**

When clearance determinations and heart catheterization are performed simultaneously, it is of primary importance to ascertain whether either investigation influences the results of the other. Several facts indicate that such influence is negligible. The most important reason for this assumption is the fact that in an earlier investigation in which heart catheterization and clearance studies were performed on separate days on the same subject the results obtained were almost identical with those obtained in the present study. The fact that identical clearance values were obtained in a group of normal subjects consisting of nurses and medical students when the heart was catheterized and when it was not is still another reason. Finally, disturbing factors have been methodically avoided during the investigation and no significant signs of anxiety or discomfort have been noticed during important measurements.

Cardiac output and blood pressure values obtained during the present investigation are well in agreement with results obtained earlier. It is concluded that the two investigations, heart catheterization and clearance studies, when performed simultaneously, do not significantly influence each other.

Another problem is, whether the administration of a single dose of insulin produces misleading clearance values for this substance. Fewer theoretic objections can be raised against the technic of administration by infusion than against administration of the material in a single dose. An unpublished study in which both methods were applied in normal subjects and in patients with different diseases showed that the average difference between results obtained with single dose and with drip administration is insignificant. The exception to this statement, the results in pregnant women and patients with hydronephrosis, are without bearing in this connection. It has been shown earlier that a diet as nearly salt-free as possible and perhaps combined with mercurial diuretics results in a decrease in para-aminohippurate clearance. In the
present study a few patients received a salt-free diet, but this was never extreme (2 Gm. sodium chloride each day). Mercurial diuretics were also administered but in no case during the week preceding the investigation. The results obtained, therefore, cannot be attributed to any effect of desalting the patients.

In the present study the plasma volume was estimated by the injection of T-1824 through a heart catheter. The estimation of the dye remaining in the catheter increased the error of the method. The plasma volume was somewhat larger in the patients belonging to group IV and in the patients with right heart failure (irrespective of group) than in the remaining patients in groups I, II and III, who had normal plasma volume. This difference was, however, not significant (fig 2).

Results

Observations at Rest. It is probable that the surprisingly high and nearly always constant renal blood flow found in the majority of normal individuals is physiologic and necessary and is not an unnecessary strain on circulation and heart. In certain conditions which produce "supernormal" renal blood flow, such as pregnancy and fever, the need for this augmented flow can easily be understood. In normal subjects during conditions of stress, such as heavy work, renal blood flow can be lowered and in this way allow more blood to flow to other parts of the body. Thus the increase in cardiac output is kept within narrower limits. It is unknown whether this acute decrease of renal blood flow is of any importance for the kidneys. In patients with heart disease and lowered cardiac output a similar mechanism seems to operate even when the patient is resting.  

In our study renal blood flow was significantly lowered and there was good agreement between the pulmonary artery pressure and the degree of lowered blood flow, which confirms previous observations. Inulin clearance was moderately diminished. In groups I and II values obtained at rest were lower than normal, but not significantly so. In groups III and IV inulin clearance was significantly lowered but proportionately less so than the renal blood flow; that is, the filtration fraction was elevated.

![FIG. 2. Hemodynamic findings, values for total plasma volume, para-aminohippurate clearance, filtration fraction and oxygen difference in 50 normal individuals compared with the same values in 72 patients with mitral stenosis grouped according to functional capacity.](image)

On the whole the sodium excretion during rest was lowered in proportion to the severity of the mitral stenosis, but, since the patients did not receive identical diets, this information is not very valuable.

As the severity of the mitral stenosis increased, the values for renal clearances obtained during rest more and more approached and even exceeded those obtained in normal individuals performing heavy work.

The opinion that the lowered renal blood flow in patients with heart disease is a change brought about by necessity would be less speculative if the lowering were functional and not the result of organic renal vascular change. That the lowered renal blood flow is functional seems probable since the low renal blood flow in patients with mitral stenosis can be raised to normal or nearly to normal values by the administration of Apresoline or the infusion of large quantities of isotonic glucose solution (unpublished observations). This does not exclude the possible existence of organic damage, brought about, for instance, by emboli, but indicates only that such damage, if present, does not greatly diminish renal function. Fur-
ther evidence is provided by the fact that the para-aminohippurate extraction is normal in those patients with mitral stenosis in whom this has been investigated. The high filtration fraction is another factor which makes it highly improbable that the changes in clearance values should be due exclusively to embolic changes. Postmortem examinations have shown the existence of extremely low clearance values without the coexistence of any old emboli.

Other hemodynamic data in patients with mitral stenosis are already well-known and the present results corroborated earlier findings. During rest there was an increase in pulse rate, arteriovenous oxygen difference and pulmonary pressure, decrease in the cardiac index and arterial oxygen saturation, all these changes paralleling the severity of the disease.

**Observations during Effort**

Earlier investigations on the effect of exercise (in the recumbent position) in normal individuals have led to the following conclusions: (1) Light exercise raises the oxygen consumption up to the maximum of 500 ml. of oxygen per minute and does not significantly influence para-aminohippurate clearance, inulin clearance or sodium excretion. (2) Heavier exercise produces a marked lowering of para-aminohippurate clearance and sodium excretion. Inulin clearance seems to decrease but the material supporting this statement is too small to allow any definite conclusion. Inulin clearance, however, always decreases less than para-aminohippurate clearance; that is, the filtration fraction increases. The para-aminohippurate extraction is unaffected even by heavy exercise.10

When the effect of effort on renal function in patients with mitral stenosis is discussed, it is natural to divide the material into two groups: one containing patients with normal renal venous pressure and the other patients with pathologically elevated renal venous (or right auricular) pressure (that is, above 5 mm. Hg).

**Response of Patients with Mitral Stenosis and with Normal Renal Venous Pressure.** This group was not homogeneous but the values for renal clearances obtained in the resting individuals were proportional to the severity of the stenosis whether the valvular disease was classified by clinical criteria or by pulmonary arterial pressure (which is even better in patients with mitral stenosis).

The effect of light work on patients with mitral stenosis showed the same trend: as the severity of the heart disease increased, so did the filtration fraction while sodium excretion usually decreased. There appeared to be a minimum value for renal blood flow (roughly 150 to 200 ml. of plasma per minute). When the basal value was near this, effort did not, as a rule, produce any further marked decrease. The hemodynamic changes found already at rest were even more accentuated during exercise, paralleling the severity of the disease, with the exception of cardiac index which was low during rest but increased on effort though not nearly enough, the increase being smaller as the severity of the disease increased. Venous pressure varied within the normal range.

**Response of Patients with Mitral Stenosis and Pathologically Increased Venous Pressure.** In the patients of this group the average inulin clearance was relatively low at rest and decreased somewhat on effort. Clearance of para-aminohippurate, however, did not show any further decrease on exercise probably because renal blood flow had at rest already reached its lowest possible level mainly because of the low cardiac output, which did not allow any “superfluous” renal blood flow. As to hemodynamics, a low initial cardiac index, which increased slightly or not at all on exercise, was registered. Thus, the increased arteriovenous oxygen difference on exercise could almost be considered to be a direct measure of the increased oxygen consumption. The pulmonary artery pressure was somewhat higher in the patients of group IV with right heart failure than in those without failure, and increased further on effort. Neither index nor pulmonary artery pressure differences were significant, however, and arterial oxygen saturation remained virtually unchanged. Systemic venous pressure (or rather mean right auricular pressure) increased an average 4.7 mm. Hg on effort. Only one of the patients did not have an elevated right auricular pressure at rest. Thus, in the present study, the patients with normal
right auricular pressures at rest only experienced a slight rise on effort (recumbent) while the patients with elevated pressures showed a further, marked increase.

Apparently there was no difference in the para-aminohippurate clearance or the filtration fraction in patients with right heart failure and in patients without right heart failure, if consideration is given to the fact that patients with failure had a more deficient pulmonary circulation than patients without failure. (See figure 3).

Effort apparently did not markedly influence para-aminohippurate clearance in the group with venous pressure increase on exercise. This was due apparently to low perfusion during rest and not to the elevated venous pressure as such. (See figure 3c.) One conclusion can be drawn: the decrease in renal blood flow is not due to the elevation of venous pressure but to other effects of the insufficient circulation.3,4,5

**Sodium Excretion**

The changes in sodium excretion produced by heart disease are naturally of great interest when the pathogenesis of edema6,7,26 is being discussed. Heart failure usually appears during or after effort. Consequently the effect of effort has been studied in the present material. As has been shown earlier, the correlation between changes in inulin clearance and changes in sodium excretion was poor. Of course it can be pointed out that inulin clearance is not necessarily a true measure of glomerular filtration, but this in no way solves the problem. Consequently other factors must be discussed.

As the reabsorption of sodium must by necessity be a process which demands energy, the oxygen consumption of the kidney naturally influences the excretion of sodium. Fishman and co-workers17 have shown that a further lowering of an initially low arterial oxygen saturation in patients with "cor pulmonale" increases the excretion of sodium and that breathing oxygen (that is increasing the oxygen saturation) reduces the excretion. If the present material it can be said that when oxygen saturation was low so was sodium excretion, even though the correlation was not very good.

On effort, sodium excretion was reduced

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**Fig. 3.** Para-aminohippurate clearance in 72 patients with mitral stenosis correlated with (a) pulmonary arterial pressure and (b) oxygen difference. The arrows indicate the changes produced by exercise performed by 31 of these patients. In (c) the para-aminohippurate clearance has been correlated with changes in the same produced by exercise in said cases.
while oxygen saturation either remained unaltered or perhaps was somewhat reduced. Thus, in this study we did not find that sodium excretion was related to renal oxygen supply. The “cor pulmonale” study and the present study differ, however, in one very important respect: arterial oxygen saturation was low in the former, and (probably) venous oxygen saturation was low in our experiments. (See figure 5.) Consequently, it is probable that different parts of the renal capillary system were affected (by anoxia) in the two studies. This in turn would, at least theoretically, produce entirely different effects. The patients in this study in whom the oxygen saturation of renal venous blood has been measured are too few, however, to allow reliable comparison between this value and fluctuations in sodium excretion.

Breathing carbon dioxide has been said to reduce renal blood flow. In our studies exercise resulted in a reduced renal blood flow and an elevated carbon dioxide tension. The relation of these findings to excretion of sodium must be discussed. It has been shown that breathing carbon dioxide (5 to 7 per cent), in recumbent position, does not influence sodium excretion at all but increases diuresis. This investigation also indicated that breathing carbon dioxide does not in any definite way influence renal blood flow if psychic irritation is avoided.

Little is known of the influence of other metabolites on sodium excretion. However, in our patients not in right heart failure there was fair agreement between changes in sodium excretion and renal blood flow during exercise (fig. 6). It has been shown that in patients in whom exercise produces a rise in venous pressure the blood flow is practically unchanged while sodium excretion is reduced. If the reduction in sodium excretion is to be explained hemodynamically, it seems necessary to postulate two different mechanisms. Changes in renal blood flow, however, cannot produce unmediated changes in sodium excretion. There

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**Fig. 4.** Pulmonary resistance, that is, the difference between pulmonary arterial and pulmonary capillary venous pressure compared with (a) inulin clearance, (b) clearance of para-aminoglutamate in 72 cases of mitral stenosis, 7 of which were in right heart failure (●) and with (c) changes in sodium excretion produced by effort in 31 cases of mitral stenosis. As can be seen no correlation exists between pulmonary resistance and these renal values.
must exist a factor which influences sodium excretion when renal venous pressure is elevated. With the technic used in the present investigation this possible hemodynamic factor cannot be exactly defined. Gomez' ingenious formula for estimation of resistance in different renal segments cannot be applied since there must be great, though unmeasurable, variations in interstitial pressure, especially in our patients with right heart failure. It is open to doubt, however, whether a hemodynamic factor must be found in order to explain the changes in sodium excretion produced by exercise. It is equally possible that exercise releases hormones (noradrenaline? adrenaline?) which influence renal tubular function directly. A few of the patients of our series showed pathologically high noradrenaline excretion values, but these could not be correlated either with renal blood flow or sodium excretion. It will be necessary, therefore, to investigate more closely in what way hormones which decrease sodium excretion influence the kidney, especially hormones which are released quickly enough to produce an effect as rapidly as does exercise. The effect on the kidney of metabolites produced by exercise should also be investigated more closely.

In the present study, patients with right heart failure differ from all the others only as to pulmonary vascular resistance (that is, the difference between pulmonary arterial and pulmonary capillary venous pressure). This resistance is much greater in patients with right heart failure, but it is not correlated with either inulin clearance during rest (fig. 4a) or changes in sodium excretion during effort (fig. 4b). Local conditions in the pulmonary circulation can therefore be considered as a more probable cause of the increased resistance than the incapability of the kidneys to excrete sodium and water.

**SUMMARY**

1. In 72 patients with mitral valvular disease, cardiac output, pulmonary arterial, pulmonary capillary venous and right auricular pressures were determined simultaneously with the renal clearance of inulin and para-aminohippurate, all patients being at rest and in the recumbent position.

In rough proportion to the severity of symptoms the cardiac output was reduced and the pressure in the pulmonary circulation increased. In only a few patients was the right auricular pressure elevated. The clearance of para-aminohippurate was decreased in all cases, likewise in rough proportion to the degree of alteration of the cardiodynamics. The inulin clearance showed much less alteration. There was no striking difference in those with and those without right heart failure.

2. In 31 patients the response to 15 to 17 minutes of steady, mild exercise in the recumbent position was studied.
In all patients not in right heart failure exercise produced a decrease in clearance of parainohippurate and sodium excretion and an increase in renal resistance. Similar exercise does not cause any change in renal clearances or sodium excretion in normal individuals. The cardiac output increased, as did the pressures in the pulmonary circulation. The right auricular pressure and the inulin clearance were unaltered.

In the patients in right heart failure exercise produced no increase in cardiac output, but it did produce an increase in the pressures in the pulmonary circulation. While exercise resulted in only slight change in clearance of para-aminohippurate and inulin, in the filtration fraction and in renal resistance it did result in increase in the renal venous pressure and the sodium excretion decreased.

3. These findings are briefly discussed.

**SUMARIO ESPAÑOL**

1. En 72 pacientes con enfermedad valvular mitral las presiones, arterial pulmonar, capilar pulmonar, auricular derecha y producción cardíaca fueron determinadas simultáneamente con la depuración renal de inulina y paraminohippurato, todos los pacientes estando en descanso y en la posición reclinada.

   En proporción tosa a la severidad de los síntomas la producción cardíaca fue reducida y la presión en la circulación pulmonar aumentada. En solo muy pocos pacientes la presión auricular derecha estuvo elevada. La depuración de paraminohippurato estuvo disminuida en todos los casos, de igual manera en tosa proporción al grado de alteración de la cardio-dinámica. La depuración de inulina mostró mucho menor alteración. No hubo diferencias significativas en aquellos con o sin decompensación cardíaca del lado derecho.

2. En 31 pacientes la repuesta a 15 o 17 minutos de ejercicio moderado continuó en la posición reclinada fué estudiada.

   En todos los pacientes que no tenían decompensación del lado derecho del corazón el ejercicio produjo un decremento en la depuración de paraminohippurato y excreción de sodio y un incremento en resistencia renal. Ejercicio similar no causa ningún cambio en depuración renal o excreción de sodio en el individuo normal. La producción cardíaca total aumentó, como así las presiones en la circulación pulmonar. La presión auricular derecha y la depuración de inulina permanecieron inalteradas.

   En los pacientes con decompensación cardíaca del lado derecho el ejercicio no produjo un aumento en producción total cardíaca pero produjo un aumento en las presiones de la circulación pulmonar. Aunque el ejercicio resultó en un ligero cambio en la depuración de paraminohippurato e inulina, en la fracción de filtración y en la resistencia renal, esto, resultó en un aumento en presión venosa renal y la excreción de sodio disminuyó.

3. Estos hallazgos son brevemente discutidos.

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Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease: I. Effect of Exercise
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