Cardiovascular Hemodynamic Functions in Complete Heart Block and the Effect of Isopropylnorepinephrine

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In 8 patients with complete heart block, cardiac and hemodynamic functions were determined by methods based on cardiac catheterization. The data characterize the impairment in these functions in asymptomatic subjects and indicate, in addition, the further changes over the course of several years in the same subject, the deleterious effects associated with congestive heart failure, and the changes toward normal induced by isopropylnorepinephrine, a sympathomimetic amine known to stimulate the heart and increase ventricular rate in heart block.

The purpose of this report is to present data regarding cardiovascular hemodynamic functions in patients with established complete heart block.

Levinson et al. determined cardiovascular dynamics by cardiac catheterization in 5 patients with complete heart block, without congestive heart failure at any time, and reported the following hemodynamic alterations from the normal: elevated systolic pressure in the right atrium, elevated systolic pressure in the right ventricle and pulmonary artery, increased pulse pressure in pulmonary and systemic arteries, increased stroke volume, and decreased cardiac output. The present study confirms these observations and reports additional information on the following cardiovascular aspects of complete heart block: changes in cardiovascular dynamics in the same patient over the course of several years, comparison of hemodynamic functions when there is congestive heart failure with the hemodynamic status when heart failure is absent, the hemodynamic effects of isopropylnorepinephrine, a sympathomimetic amine known to increase the ventricular rate in complete heart block. Renal hemodynamic functions of 3 of the subjects are also reported.

Methods and Material

Hemodynamic functions were measured in 8 patients with complete heart block. Except for patient P. D., who was 39 years old and had inactive rheumatic heart disease with aortic stenosis, the subjects were elderly and the heart block was due to arteriosclerotic heart disease. Five patients had never manifested signs of heart failure, 2 patients had recently recovered from congestive heart failure and 1 patient was in frank congestive heart failure (table 1). In each instance the heart block was of spontaneous occurrence and not associated with medication or myocardial infarction. The permanence and completeness of the heart block was confirmed in each patient by repeated electrocardiograms and by the persistence of complete atrioventricular dissociation following the administration of 1 to 2 mg. of atropine sulfate intravenously.

Of the 5 patients never manifesting congestive heart failure, 3 (J. Gi., E. S., T. R.) first came under observation because of Adams-Stokes attacks. The seizures were eliminated with ephedrine sulfate, which was then continued in maintenance doses and the patients were observed for 3, 9, and 5 years, respectively. They remained without further attacks and did not develop heart failure. Hemodynamic determinations were obtained shortly after their seizures disappeared and again after intervals of 1, 2½, and 3 years, respectively (tables 2 and 3). The fourth patient (P. D.) was known to have heart block for 2 years before the present observations. He had attacks of dizziness but no overt Adams-Stokes seizures. The fifth patient (A. S.) was noted to have a “slow heart” 1 year previously but had never experienced Adams-Stokes attacks or dizziness.

Of the 3 patients with congestive heart failure, hemodynamic determinations were obtained in 2 (M. K., J. G.) after they had recovered to a clinically judged maximal degree as a result of
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<table>
<thead>
<tr>
<th>Patient, sex, age, diagnosis</th>
<th>Surface area (M²)</th>
<th>Dates of study</th>
<th>Weight (lbs.)</th>
<th>Degree of failure</th>
<th>Signs of congestive heart failure</th>
<th>Medication</th>
<th>Final result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. Gl.; M, 66 (ASHD)</td>
<td>1.52</td>
<td>7/1951</td>
<td>122</td>
<td>0</td>
<td>0 0 0 0 0 0</td>
<td>Ephedrine</td>
<td>dead 38 months</td>
</tr>
<tr>
<td>E.S.; M, 77 (ASHD)</td>
<td>1.62</td>
<td>1/1950</td>
<td>133</td>
<td>0</td>
<td>0 0 0 0 0 0</td>
<td>None</td>
<td>dead 85 months</td>
</tr>
<tr>
<td>T.R.; M, 68 (ASHD)</td>
<td>1.81</td>
<td>7/1952</td>
<td>155</td>
<td>0</td>
<td>0 0 0 0 0 0</td>
<td>Ephedrine</td>
<td>dead 57 months</td>
</tr>
<tr>
<td>P.D.; M, 39 (RHD)</td>
<td>1.93</td>
<td>12/1955</td>
<td>163</td>
<td>0</td>
<td>0 0 0 0 0 0 1+</td>
<td>Ephedrine and Isuprel linguets</td>
<td>dead 3 months</td>
</tr>
<tr>
<td>A.S.; F, 53 (ASHD)</td>
<td>1.77</td>
<td>4/1957</td>
<td>152</td>
<td>0</td>
<td>0 0 0 0 0 0</td>
<td>Ephedrine</td>
<td>alive 3 months</td>
</tr>
<tr>
<td>Treated congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.K.; F, 62 (HCVD + ASHD)</td>
<td>1.71</td>
<td>5/1955</td>
<td>175</td>
<td>4+</td>
<td>4+ 4+ 4+ 4+ 4+</td>
<td>Thiomerin*</td>
<td>dead 10 days</td>
</tr>
<tr>
<td>J. Ga.; M, 72 (ASHD)</td>
<td>1.48</td>
<td>4/1955</td>
<td>127</td>
<td>2+</td>
<td>2+ 2+ 2+ 2+ 2+</td>
<td>Thiomerin†, Ephedrine Digital§</td>
<td>alive 22 months</td>
</tr>
<tr>
<td>Untreated congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F.L.; F, 67 (ASHD)</td>
<td>1.65</td>
<td>2/1953</td>
<td>165</td>
<td>4+</td>
<td>4+ 4+ 4+ 4+ 4+</td>
<td>None</td>
<td>dead 4 days</td>
</tr>
</tbody>
</table>

RHD, rheumatic heart disease; HCVD, hypertensive cardiovascular disease; ASHD, arteriosclerotic heart disease.

* Thiomerin 2 ml. intravenously on 14 occasions and 2 ml. intramuscularly on 6 occasions from admission until day of the study.
† Aminophylline 0.5 Gm. intravenously on 8 occasions from admission until day of the study.
‡ Thiomerin 2 ml. intravenously on 6 occasions from admission until time of study.
§ Digitalis leaf 1.5 Gm. from 4/19 to 4/25.
¶ Initial status: no hemodynamic determinations.
# Final result: months after initial determinations.

The following functions were measured by standard technics: cardiac output by right heart catheterization and the direct Fick method with mixed venous blood obtained from the right ventricle or pulmonary artery, cardiac and systemic blood pressures at first by Hamilton manometers and subsequently by strain gages coupled to a multichannel electronic recorder, oxygen consumption by the open method with analysis of collected exhaled air by the Beckman gas analyzer, oxygen content of arterial and mixed venous blood by the manometric method of Van Slyke and Neill, plasma and blood volumes by dye-dilution method with Evans blue dye (T-1824), glomerular filtration by inulin clearance and renal plasma flow by para-aminohippurate clearance. All determinations were made in the morning after an overnight fast. When renal hemodynamic functions were also determined, these measurements were obtained simultaneously with the measurements of cardio-
vascular dynamics. At these times the hemodynamic determinations were obtained at the mid-point of the 15-minute renal clearance periods. Usually 3, occasionally 2, successive determinations of cardiovascular and renal functions were obtained. The data presented are the mean values of the several determinations.

**RESULTS**

**Heart Block without Congestive Heart Failure**

The 39-year-old subject (P. D.) is considered separately. His cardiac dynamics (cardiac index, arterial-mixed venous oxygen difference) and total oxygen consumption were normal (table 2). His vascular pressures were altered as in the other subjects (table 3). In the 4 elderly subjects cardiac function was definitely abnormal (table 2). Cardiac indices were markedly decreased. A-V oxygen difference, a more rigorous index of cardiac function since it relates cardiac output to the body’s demand for blood, was abnormal on 5 of 7 occasions. Since aging is associated with decreased cardiac dynamic activity,9, 10 the values for the subjects with heart block are compared with the values obtained in this laboratory for 9 nonecardiac patients of the same age range (60 to 80 years). For the heart block subjects as a group, the cardiac index is still low and the A-V oxygen difference is still high (table 2). The differences for the 2 functions in the 2 groups of subjects are highly significant; \( p = 0.01 \) for both functions. In the 3 subjects with the lowest car-

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**Table 2.** Oxygen Consumption, Cardiac Output, and Renal Hemodynamics in Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of study</th>
<th>Oxygen consumption (ml./M.(^3)/min.)</th>
<th>Arterial oxygen saturation (vol. %)</th>
<th>Mixed venous oxygen (vol. %)</th>
<th>A-V ( O_2 ) difference (vol. %)</th>
<th>Cardiac index (L./M.(^3)/min.)</th>
<th>Ventricular rate (per min.)</th>
<th>Stroke volume (ml.)</th>
<th>Renal plasma flow (ml./min.)</th>
<th>Glomerular filtration (ml./min.)</th>
<th>Filtration fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No congestive heart failure</td>
<td>7/1951</td>
<td>131</td>
<td>18.85</td>
<td>93.0</td>
<td>12.44</td>
<td>6.41</td>
<td>2.05</td>
<td>32</td>
<td>98</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>7/1952</td>
<td>130</td>
<td>20.57</td>
<td>98.9</td>
<td>14.57</td>
<td>6.00</td>
<td>2.17</td>
<td>27</td>
<td>121</td>
<td>256</td>
<td>89</td>
</tr>
<tr>
<td>E.S.</td>
<td>1/1950</td>
<td>105</td>
<td>17.01</td>
<td>89.6</td>
<td>10.96</td>
<td>6.05</td>
<td>1.74</td>
<td>32</td>
<td>87</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>9/1952</td>
<td>99</td>
<td>17.56</td>
<td>93.0</td>
<td>10.48</td>
<td>7.08</td>
<td>1.39</td>
<td>33</td>
<td>70</td>
<td>203</td>
<td>41</td>
</tr>
<tr>
<td>T.R.</td>
<td>7/1952</td>
<td>103</td>
<td>16.23</td>
<td>95.6</td>
<td>9.97</td>
<td>6.26</td>
<td>1.65</td>
<td>28</td>
<td>108</td>
<td>182</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>10/1955</td>
<td>105</td>
<td>14.30</td>
<td>87.3</td>
<td>7.70</td>
<td>6.60</td>
<td>1.59</td>
<td>31</td>
<td>93</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>P.D.</td>
<td>12/1955</td>
<td>145</td>
<td>17.70</td>
<td>92.4</td>
<td>12.33</td>
<td>5.37</td>
<td>2.70</td>
<td>38</td>
<td>137</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>A.S.</td>
<td>4/1957</td>
<td>87</td>
<td>16.22</td>
<td>93.6</td>
<td>11.26</td>
<td>4.96</td>
<td>1.75</td>
<td>26</td>
<td>119</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Eight aged control patients</td>
<td>1950 to 1956</td>
<td>120</td>
<td>16.11</td>
<td>93.0</td>
<td>11.60</td>
<td>4.54</td>
<td>2.69</td>
<td>(48-84)</td>
<td>67</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Treated congestive heart failure</td>
<td>6/1955</td>
<td>110</td>
<td>20.33</td>
<td>90.8</td>
<td>13.02</td>
<td>7.31</td>
<td>1.52</td>
<td>39</td>
<td>67</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>M.K.</td>
<td>6/1955</td>
<td>116</td>
<td>15.41</td>
<td>94.5</td>
<td>8.54</td>
<td>6.87</td>
<td>1.69</td>
<td>24</td>
<td>104</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Untreated congestive heart failure</td>
<td>3/1953</td>
<td>106</td>
<td>17.01</td>
<td>92.5</td>
<td>9.43</td>
<td>7.58</td>
<td>1.40</td>
<td>26</td>
<td>89</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

For the 8 control subjects the single number is the average value, the numbers in parentheses give the range.
### Table 3.—Blood Volume, Vascular Pressures, and Vascular Resistances in Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of study</th>
<th>Plasma volume (L.)</th>
<th>Hematocrit (%)</th>
<th>Blood volume (L.)</th>
<th>B.V. ratio (actual: predicted)</th>
<th>Right atrium</th>
<th>Right ventricle</th>
<th>Pulmonary artery</th>
<th>Femoral artery</th>
<th>Systemic vascular resistance (mm. Hg/L./min.)</th>
<th>Pulmonary vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No congestive heart failure J. Gi.</td>
<td>7/1951</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.00</td>
<td>5</td>
<td>40</td>
<td>3</td>
<td>130</td>
<td>210</td>
<td>25.7</td>
</tr>
<tr>
<td></td>
<td>7/1952</td>
<td>2.19</td>
<td>46</td>
<td>4.05</td>
<td></td>
<td>3</td>
<td>35</td>
<td>3</td>
<td>6</td>
<td>104</td>
<td>3.4</td>
</tr>
<tr>
<td>E.S.</td>
<td>1/1950</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.14</td>
<td>7</td>
<td>40</td>
<td>8</td>
<td>182</td>
<td>225</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td>9/1952</td>
<td>2.19</td>
<td>43</td>
<td>3.84</td>
<td>0.82</td>
<td>8</td>
<td>60</td>
<td>10</td>
<td>56</td>
<td>112</td>
<td>43.9</td>
</tr>
<tr>
<td>T.R.</td>
<td>7/1952</td>
<td>3.90</td>
<td>37</td>
<td>6.20</td>
<td>1.14</td>
<td>3</td>
<td>35</td>
<td>5</td>
<td>211</td>
<td>205</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>10/1955</td>
<td>4.06</td>
<td>41</td>
<td>6.90</td>
<td>1.30</td>
<td>4</td>
<td>65</td>
<td>6</td>
<td>205</td>
<td>112</td>
<td>37.8</td>
</tr>
<tr>
<td>P.D.</td>
<td>12/1955</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>5</td>
<td>44</td>
<td>9</td>
<td>156</td>
<td>108</td>
<td>14.8</td>
</tr>
<tr>
<td>A.S.</td>
<td>4/1957</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>0</td>
<td>32</td>
<td>4</td>
<td>188</td>
<td>82</td>
<td>29.0</td>
</tr>
<tr>
<td>Eight aged control patients</td>
<td>1950 to 1956</td>
<td>3.20*</td>
<td>41*</td>
<td>5.12*</td>
<td>1.06*</td>
<td>2†</td>
<td>21†</td>
<td>4†</td>
<td>12†</td>
<td>103</td>
<td>22.6</td>
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<tr>
<td></td>
<td></td>
<td>(2.05-4.57)</td>
<td>(35-63)</td>
<td>(3.31-7.20)</td>
<td>(0.9-1.19)</td>
<td>(1-3)</td>
<td>(18.24)</td>
<td>(1-7)</td>
<td>(5-8)</td>
<td>(10-13)</td>
<td>(16-33)</td>
</tr>
<tr>
<td>Treated congestive heart failure M.K.</td>
<td>6/1955</td>
<td>3.68</td>
<td>51</td>
<td>7.52</td>
<td>1.79</td>
<td>2</td>
<td>31</td>
<td>2</td>
<td>174</td>
<td>56</td>
<td>34.6</td>
</tr>
<tr>
<td>J. Ga.</td>
<td>6/1955</td>
<td>2.61</td>
<td>42</td>
<td>4.50</td>
<td>1.15</td>
<td>9</td>
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<td>11</td>
<td>7</td>
<td>15</td>
<td>26.3</td>
</tr>
<tr>
<td>Untreated congestive heart failure F.L.</td>
<td>3/1953</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>13</td>
<td>44</td>
<td>15</td>
<td>165</td>
<td>80</td>
<td>29.0</td>
</tr>
</tbody>
</table>

For the 8 control subjects the single number is the average value, the numbers in parentheses give the range.

* Seven subjects only.
† Six subjects only.
‡ Four subjects only.
Diamond outputs (E. S., T. R., A. S.) total oxygen consumption was reduced and perhaps thereby may have led to a lower requirement for blood and hence a lower cardiac output. In the other subject (J. Gi.) oxygen consumption was normal but cardiac function was impaired in comparison with the control values (table 2). As indicated by the generally normal arterial oxygen saturations, pulmonary ventilation was usually adequate in all subjects. The occasional low oxygen saturations are not unusual in elderly subjects who may hypoventilate when lying flat for long periods.

In all 5 patients residual pressures in the right heart (right atrial mean pressure and right ventricular end diastolic pressure) and right ventricular systolic pressure tended to be elevated (table 3). In both the pulmonary artery and the systemic artery, systolic blood pressure was elevated while diastolic pressure was normal or low, changes due presumably to the large volume of systemic ejection and the increased time for diastolic run-off (table 3). In the older subjects, arteriosclerotic stiffening of the systemic arteries probably further intensified these changes in pressure. Systemic arterial mean pressure was essentially normal. The calculated systemic vascular resistance varied considerably but on 6 of 8 occasions was increased above normal and thereby served to maintain arterial pressure in the presence of a low cardiac output and prolonged diastolic run-off. Subject P. D., whose cardiac output was normal, had a normal systemic vascular resistance. In the 2 subjects in whom pulmonary artery pressure was measured, pulmonary vascular resistance was also increased (table 3). Neither of these patients had pulmonary disease or left heart failure.

Although the dye-dilution technic for determining blood volume has admitted deficiencies, the method does serve as a reasonable index of intravascular volume. Two subjects appeared to have normal blood volumes. The blood volume of the third subject was increased by 14 and 30 per cent (table 3).

In all 3 subjects in whom renal hemodynamic functions were determined, glomerular filtration rate and renal plasma flow were decidedly reduced (table 2). In 2 subjects the disproportionately greater reduction in plasma flow than in glomerular filtration rate indicated an increase in filtration fraction. With aging, renal hemodynamic functions decrease, but in these 3 subjects the reductions were greater than expected for their advanced years. None of the 3 patients had evidence of intrinsic renal disease.

Course of Hemodynamic Function over Several Years

Hemodynamic determinations were repeated after 1 to 3 years on 3 subjects without congestive heart failure. During the intervening years the patients suffered no reduction of their usual (reduced) activity nor did they develop congestive heart failure. In general, their hemodynamic functions appeared to be slightly more impaired (table 2, 3). After 12 months the functions in J. Gi. were about the same. After 32 and 38 months, subjects E. S. and T. R. manifested further slight reduction in cardiac index and rise in A-V oxygen difference, associated with some increase in pressure in the right heart, largely in ventricular systolic pressure.

Heart Block with Congestive Heart Failure

Although similar degrees of abnormality in individual hemodynamic functions were present in subjects with and without congestive heart failure, the presence of heart failure appeared to be associated with the more marked impairment. Thus, the subject with frank congestive heart failure (F. L.) had one of the lowest cardiac indices, the highest A-V oxygen difference and the highest residual pressures in the right heart (table 2, 3). In the 2 subjects treated for congestive heart failure the hemodynamic functions, though decidedly impaired, frequently overlapped the values for the subjects never in congestive failure. However, the overlap was with the greatest impairments of function in the group without failure and not with the less impaired values.

Hemodynamic Effects of Isopropylnorepinephrine

Isopropylnorepinephrine was administered
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in 3 ways: by single intravenous injection over 3 to 5 minutes (J. Ga., M. K.), by pump-controlled intravenous infusion for 36 minutes (T. R.), and by sublingual tablet (P. D., A. S.) (table 4). Except for subject P. D., hemodynamic measurements were obtained as follows: first control measurements, then measurements at the point of maximum increase in ventricular rate and finally determinations when the effects of the drug had worn off. Subject P. D. sustained a 6- to 8-second period of ventricular arrest shortly after the intracardiac catheter was placed in the pulmonary artery. The catheter was immediately withdrawn into the right atrium and the patient given a 10 mg. linguet of isopropylnorepinephrine. The drug-induced hemodynamic effects were determined first, when ventricular rate was maximally increased. The "control" determinations were obtained 124 minutes after the linguet was given and when ventricular rate had returned to its customary slow rate. These "control" determinations are also used as this patient's usual hemodynamic functions (table 2, 3).

Except for the results in patient A. S., which will be discussed separately, isopropylnorepinephrine produced essentially similar effects for all 3 routes of administration (table 4, fig. 1). Atrial rate increased in the 3 subjects with normal sinus rhythm. Ventricular rate increased in all 4 subjects, due to speeding up of established idioventricular foci. New ventricular foci appeared and persisted for varying, but temporary, periods at the peak of the effect in the 2 subjects (M. K., T. R.) who received the largest amount of the drug. Complete atrioventricular dissociation persisted at all times during the drug effects.

Isopropylnorepinephrine induced a decided change toward normal in cardiovascular dynamics in all 4 patients and this effect appeared to be associated with the increase in ventricular rate. Cardiac output rose strikingly; cardiac index increased by an average of 52 per cent with a range from 28 to 88 per cent (table 4). Several factors indicate that the increase in cardiac output

FIG. 1. Hemodynamic effects of isopropylnorepinephrine administered by intravenous infusion, subject T. R. For the pressure in the brachial artery (BA), the upper dots are systolic pressures, the lower dots diastolic pressures, the connecting vertical lines pulse pressures, the solid cross bars mean pressure. Right atrial (RA) pressure is mean pressure. For blood oxygen content, the upper dots represent arterial (BA) oxygen contents, the lower dots mixed venous (RA) oxygen contents and the connecting vertical lines A-V oxygen differences. For heart rate, atrial rate is represented by broken line, ventricular rate by solid line.

was an actual one. Thus, oxygen consumption remained unchanged, A-V oxygen difference decreased (average 33 per cent) to the normal range, and the decrease in A-V oxygen difference was due to a rise of mixed venous oxygen content, for arterial oxygen content did not change materially. These changes, indicating improved cardiac function, occurred whether the control values were decidedly impaired as in the 3 elderly subjects or normal as in subject P. D. Output per beat did not change consistently; stroke volume increased in 2 subjects, remained unchanged in 1, and fell in the fourth patient.

Relatively small changes in intracardiac pressures and in systemic arterial pressure
accompanied the striking increases in cardiac output (table 4). In the systemic artery, systolic pressure tended to rise slightly, while diastolic pressure and mean pressure varied slightly and inconsistently. Similarly, systolic pressure rose slightly in the pulmonary artery and right ventricle while right atrial mean pressure may have fallen. The large increase in cardiac output associated with the slight change in systemic mean arterial pressure indicates that systemic vascular resistance decreased (table 4).

The cardiovascular effects produced by intravenously administered isopropylnorepinephrine were of short duration. The control levels for all functions were reached 20 to 30 minutes after the single intravenous injections and after stopping the intravenous infusion. The effects produced in 1 subject by sublingual administration of a larger amount were of longer duration, 1 1/2 hours.

In patient A. S., a 10 mg. linguet of isopropylnorepinephrine produced but little hemodynamic change (table 4). Atrial rate remained unaltered, ventricular rate increased by only 4 beats per minute, cardiac index did not change, A-V oxygen difference increased 0.8 volume per cent, and stroke volume fell by 17 ml. Systolic pressure fell in both the right ventricle and systemic artery, by 8 and 26 mm. Hg, respectively.

**DISCUSSION**

The data presented substantiate that the cardiovascular hemodynamic state in complete heart block without congestive heart failure is characterized by increased pressures in the right heart, pulmonary artery and systemic arteries, increased systemic and pulmonic vascular resistances, reduced cardiac output, and increased stroke volume. In the elderly subjects the increase in stroke volume was not sufficient to compensate for the reduced heart rate and cardiac output was decreased. However, in the 39-year-old subject (P. D.), the increase in stroke volume did compensate for the slow heart rate, and cardiac output was normal. This finding suggests that in the elderly subjects the reduced cardiac output may have been more the result of myocardial involvement, on the basis of arteriosclerotic heart disease, than failure to achieve a normal cardiac output because of the slow heart rate alone. Such a conclusion may not be entirely permissible, for the heart rate of subject P. D. was higher than that of the 4 elderly subjects, thereby making it more possible for some increase in stroke volume to compensate for the bradycardia and to maintain a normal cardiac output.

The low cardiac output in complete heart block appeared to be associated, at least in part, with low metabolic rate, especially in the elderly subjects. Their oxygen consumptions were either reduced below normal or at the lower limits of normal. Lowered metabolic activity was further suggested by low levels of thyroid activity in 2 of 3 subjects. The 24-hour uptake of radioactive iodine by the thyroid gland was 20 per cent in J. G., 25 per cent in E. S., and 40 per cent in T. R. Decreasing the bodily demands permits a lower cardiac output without the development of heart failure and this hemodynamic relationship is characteristic of elderly people.9, 10

Nevertheless, except in subject P. D., the
HEMODYNAMIC FUNCTIONS IN COMPLETE HEART BLOCK

Hemodynamic Dynamic Effects of Isopropylnorepinephrine in Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Oxygen consumption (ml./min.)</th>
<th>Blood oxygen content (vol. %)</th>
<th>Cardiac index (L./M.²/min.)</th>
<th>Stroke volume (ml.)</th>
<th>Pressures mm. Hg</th>
<th>Systemic vascular resistance (mm. Hg/L./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial</td>
<td>Mixed varous</td>
<td>A-V diff.</td>
<td>Right atrium (Mean)</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>105</td>
<td>14.30</td>
<td>7.70</td>
<td>6.60</td>
<td>1.59</td>
<td>93</td>
</tr>
<tr>
<td>111</td>
<td>14.31</td>
<td>10.59</td>
<td>3.72</td>
<td>2.98</td>
<td>134</td>
</tr>
<tr>
<td>145</td>
<td>17.70</td>
<td>12.33</td>
<td>5.37</td>
<td>2.70</td>
<td>138</td>
</tr>
<tr>
<td>145</td>
<td>17.85</td>
<td>14.35</td>
<td>3.50</td>
<td>4.13</td>
<td>160</td>
</tr>
<tr>
<td>87</td>
<td>16.22</td>
<td>11.26</td>
<td>4.96</td>
<td>1.75</td>
<td>119</td>
</tr>
<tr>
<td>100</td>
<td>16.18</td>
<td>10.38</td>
<td>5.80</td>
<td>1.74</td>
<td>102</td>
</tr>
<tr>
<td>110</td>
<td>20.33</td>
<td>13.02</td>
<td>7.31</td>
<td>1.52</td>
<td>67</td>
</tr>
<tr>
<td>112</td>
<td>20.88</td>
<td>15.10</td>
<td>5.78</td>
<td>1.94</td>
<td>66</td>
</tr>
<tr>
<td>116</td>
<td>15.41</td>
<td>8.54</td>
<td>6.87</td>
<td>1.69</td>
<td>104</td>
</tr>
<tr>
<td>110</td>
<td>16.13</td>
<td>11.43</td>
<td>4.70</td>
<td>2.34</td>
<td>87</td>
</tr>
</tbody>
</table>

A decrease in cardiac output in the patients with heart block fell below their reduced bodily requirements. Increased extraction from the blood apparently compensated for the lowered cardiac output and A-V oxygen difference was above the normal range, even for elderly subjects (table 2). In this connection it is pertinent that in 4 patients with uncomplicated myxedema studied in this laboratory the lowered bodily requirements, as determined by oxygen consumption, were satisfied by the low cardiac output and A-V oxygen difference remained normal. Parenthetically, in the subject with the more normal oxygen consumption (J. Gi.) cardiac output was not so markedly reduced.

The question may be raised whether the hemodynamic status in the elderly subjects with complete heart block constituted heart failure. In the sense that cardiac output did not meet bodily demands and A-V oxygen difference rose, cardiac function failed. A further indication of such failure would be afforded by the occurrence of impaired hemodynamic functions of various organs. Renal hemodynamic functions were impaired in the 3 patients studied and the impairment was more marked than expected for aging alone. Furthermore, the renal hemodynamic changes, especially the elevation in filtration fraction, were of a type considered to be typical of congestive heart failure. Filtration fraction does not rise strikingly with aging.11

On the other hand, in spite of the impaired cardiac function and reduced cardiac output, clinically the heart appeared not to have failed. The syndrome of congestive heart failure did not develop, even though cardiac output and renal hemodynamic functions were reduced to values usually associated with congestive heart failure. The patients remained in satisfactory health and activity for long periods. Subjects J. Gi. and T. R. were without symptoms or heart failure during 38 and 57 months of observation. Subject E. S. remained free of symptoms for 80 months, then developed congestive heart failure, and died suddenly 5 months later. Subject J. Ga. recovered clinically from congestive heart failure and with digitalis medication remains free of symptoms 22 months later. Subjects P. D., M. K., and F. L. died suddenly and
apparently not in relation to the status of their myocardial competence.

In the final analysis, cardiac function was considered inadequate whether or not clinical symptoms or syndromes developed, for in these patients with heart block cardiac function did not provide a cardiac output commensurate with bodily needs. In these elderly subjects lowered metabolic activity and increased extraction from the blood compensated for the decreased cardiac output. With lowered bodily requirement making less demands for blood, the necessarily increased arterial-venous extraction was accordingly not too great. The resultant hemodynamic abnormality was not, therefore, so great that severe dysfunction of organs occurred and accordingly disease states and symptoms did not develop. The lowered activity of old age was therefore to these patients' benefit. The hemodynamic response to exercise was not determined. However, because the slow heart rate of complete heart block is unresponsive to physiologic stimuli, it is a reasonable conjecture that physical effort would have resulted in more marked hemodynamic abnormality, particularly extraction from the blood. It is then an interesting speculation whether overt congestive heart failure might reasonably be expected if considerable activity were undertaken by these subjects. Pertinent to this point are the observations of Starzl and Gaertner,12 that congestive heart failure was more apt to occur in the more active of their dogs with chronic complete heart block produced by surgical transection of the bundle of His.

It is entirely conceivable that the hemodynamic abnormality described in the patients studied is that of arteriosclerotic heart disease before the appearance of overt heart failure rather than the hemodynamic status associated with slow heart rates alone. Moreover, the course of illness in the different subjects suggests that the status of the primary heart disease and the degree of myocardial involvement, rather than the slow heart rate or lowered cardiac output, determine the course and duration of life in patients with complete heart block.

It is not the intent of this presentation and discussion to make too much of too little. Admittedly the number of patients studied is few and the differences between their hemodynamic functions and the functions in control subjects are often only modest. The fact remains that in heart block in man the hemodynamic abnormalities described exceed the values observed in control subjects, both by this laboratory and by others.9-11 Moreover, similar hemodynamic abnormalities, also suggestive of congestive heart failure, were observed by Starzl, Gaertner, and Baker13 in dogs with surgically induced complete atrioventricular block.

The hemodynamic effects of increasing the ventricular rate in complete heart block have not been completely determined and, indeed, the present observations represent measurements which are also incomplete. The sympathomimetic amine isopropylnorepinephrine improved cardiac function, as indicated by the increase in cardiac output and fall in A-V oxygen difference, both at normal and at lowered levels of cardiac activity. However, since isopropylnorepinephrine not only increases the activity of idioventricular foci in complete heart block, but also stimulates ventricular muscle,2, 14, 15 two possible explanations for the increase in cardiac output immediately present themselves. The increased output may be due simply to an increased frequency of ventricular ejection, or to a stimulant effect on the myocardium increasing the force and hence volume of ejection, or both factors may be operating. In animals with surgically produced complete heart block, Starzl, Gaertner, and Webb16 demonstrated that increasing heart rate alone, by electric stimulation of the ventricle, resulted in increased cardiac output and in higher vascular pressures. The data presented do not, however, resolve the point for man, unless they indicate that both possibilities may be operating together or independently to varying degrees under different circumstances. Thus, in subjects M. K. and J. Ga. the increased cardiac output was due to increased rate alone, for stroke volume
remained unchanged in M. K. and even fell in J. Ga. In contrast, stroke volume increased in T. R. and P. D., suggesting a direct myocardial effect. In view of the small number of trials, the differences between subjects, the variations in dosage and mode of administration, the present observations cannot resolve the question. Furthermore, the failure of patient A. S. to develop changes similar to the effects in the other patients remains unexplained and may be a matter of insufficient dosage or difference in response of this individual subject.

Finally, the present observations deal with the acute effects of single doses of isopropynorepinephrine and leave for future study the nature of the changes produced by long-term or maintenance medication.

Summary

The cardiovascular hemodynamic status of 4 elderly subjects with complete heart block and without clinical evidence of congestive heart failure was characterized by elevated pressures in the right heart, increased systolic and pulse pressure in systemic arteries, increased systemic and pulmonic vascular resistances, reduced cardiac output in spite of increased stroke volume, increased A-V oxygen difference, and impaired renal hemodynamic functions.

It is not evident how much of the hemodynamic alteration was due, alone or in varying combination, to the slow heart rate, the aging process or arteriosclerotic heart disease. The hemodynamic changes were suggestively similar to those encountered in mild to moderately severe congestive heart failure and yet these patients with persistent heart block remained in satisfactory health and activity for 3 to 7 years and without clinical evidence of heart failure.

Over the course of 2 to 3 years the hemodynamic abnormality became somewhat more severe in 3 subjects but their activity remained unaltered and heart failure did not occur.

The presence of clinically evident congestive heart failure in 3 additional, also elderly, subjects was associated with even greater abnormalities in the cardiovascular dynamics and very low cardiac outputs.

In 1 younger (39 years) subject with heart block the changes in systemic and cardiac pressures were the same as in the elderly subjects but stroke volume was increased sufficiently to compensate for the slow heart rate and cardiac output was normal.

The administration of isopropynorepinephrine by intravenous injection, intravenous infusion, and sublingual tablet was associated with little change in systemic or cardiac vascular pressures but with an increase in cardiac rate and cardiac output and a reduction in A-V oxygen difference in 4 of 5 subjects. The more normal hemodynamic status appeared to be due to both an increase in heart rate and to a direct effect on heart muscle, each to varying degrees in the different subjects.

Acknowledgment

The authors wish to express great appreciation to their assistants without whose careful work these observations could not have been made: Mrs. Edna Weinick, Miss Eileen Maticka, and Mr. Flavio Amerio.

Summario in Interlingua

Le stato hemodynamic cardiovascular de 4 subjectos de etates avantiante con complete bloco cardiae e sin signos clinie de congestive disfallimento cardiae eseva caracterisate per elevate pressione in le corde dextere, augmentate pression systolica e pression del puls in arterias systemic, augmentate resistentias vascular tanto systemic como etiam pulmonic, reducece rendimento cardiae in despecto de augmento del volumine per pulse, augmentate differentia arterio-venose de oxygeno, e imperfecte functiones hemodynamic renal.

Il non es clar a qual grado de alterationes hemodynamic eseva causate—individualmente o in varie combinationes—per le reletantion del frequentia del corde, per le processo de senescentia, o per un morbo arteriosclerotic del corde. Le alterationes hemodynamic eseva simile a illos trovate in casos de leve o moderamente sever congestive disfallimento cardiae, e nonobstante, iste pa-
tientes con persistente bloque cardíaco se manten
vía en un estado satisfacente de sanita
te y de actividad durante periodos de 3 a 7 años
sin la ocurrencia de signos clínicos de disfa
llimento cardíaco. In le curso de 2 a 3 años,
el anormalidad hemodinámica se aggrava
va en un cerce grado en 3 de los sujetos, sed la
actividad remaneja inalterate e disfallimento
cardíaco no ocurrieva.

Le presentia de evidencia clínica de conges
tive disfallimento cardíaco en 3 sujetos ad
ditional—etiam de etate avaintate—esessava
associate con mesmo plus grande anormali
tates del dynamica cardiovasculare e con bas
sissime valores del rendimento cardíaco.

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con le mesma alterationes del pressione sys	
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cente, sed le volume per pulso esessava su
fi
ciemente augmentate pro equilibrar le lente
frequentia cardíaco, e le rendimento del
corde esessava normal.

Le administration de isopropynorepineph
rina per injection intravenose, per infusion
intravenose, e in le forma de tabletas sublingual esessava associate con pauc alteration
el pressiones vascular systemic e cardíaco
ced con un acceleracion del corde e un a
umento del rendimento cardíaco e con un re
duction del differentia arterio-venose de oxy
genio in 4 ex 5 subjectos. Le plus normal
stato hemodinámico esessava apparentemente
causate tanto per un aumento del frequentia
del corde como etiam per un efecto directe
super le musculo cardíaco. Le grado del efficcia
de iste duo factores variava in le varie
subjectos.

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_Circulation_. 1958;17:526-536
doi: 10.1161/01.CIR.17.4.526

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

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