Some Effects of Digoxin upon the Heart and Circulation in Man

Digoxin in Combined (Left and Right) Ventricular Failure

By M. Irené Ferrer, M.D., Richard J. Conroy, M.D., and Réjane M. Harvey, M.D.

Hemodynamic studies of the effects of cardiac glycosides on the failing human heart have been numerous and have shown one consistent alteration following administration of the drug, namely, a rise in cardiac output.\textsuperscript{1-13} Alterations in lesser circulation pressures have not always been homogeneous. However, they are more or less predictable in failure of only one ventricle. When only the left ventricle fails and a sinus mechanism is present, a decrease in the elevated pulmonary artery pressures occurs after the administration of Digoxin and the normal right ventricular diastolic pressure shows no change.\textsuperscript{5, 14} In isolated right ventricular failure with this rhythm the elevated right ventricular diastolic pressure falls and pulmonary artery systolic pressure tends to rise rather than to decline.\textsuperscript{7, 15, 16} In the presence of combined ventricular failure, the behavior of these pressures has been variable.\textsuperscript{4, 6, 8, 9, 11, 12, 17} The reasons for this lack of uniformity may well be due to the presence of a number of physiologic variables, which are complications of the state of failure but which nonetheless may influence the response of the circulation to drugs.

It is the purpose of this investigation to examine the various factors influencing the response of combined left and right ventricular failure to Digoxin. Because mechanical factors such as valvular or pericardial lesions may of themselves alter pressure patterns, patients with such lesions were excluded from this presentation. It also seemed wise to group patients according to basic cardiac rhythm, since it is known that the atrial arrhythmias influence the hemodynamic picture to some extent.\textsuperscript{12}

Materials and Methods

Thirteen patients with hypertensive and/or arteriosclerotic heart disease were studied with use of the technic of cardiac catheterization. The methods utilized in this laboratory to measure blood pressures, cardiac output (by the Fick principle), and blood volume have been published previously.\textsuperscript{5-8} The stroke volume was calculated by dividing the cardiac output by the ventricular rate. The pulse pressure was determined by the difference between the average systolic and average diastolic pressures, which were measured over 2 respiratory cycles in patients with sinus rhythm and 2 or more complete cycles in those with atrial fibrillation in order to sample at least 10 consecutive beats. It is recognized that in atrial fibrillation the values for stroke volume and pulse pressure are approximate. The detailed protocol and the criteria used for evaluating significant change following the drug are the same as in previous reports.\textsuperscript{5, 7} Although several determinations of pressures were made in the control period, only one representative value is given in tables 1, 2, and 3. Following administration of the drug, pressure measurements were made every 5 to 15 minutes; however, for the sake of brevity, only the values nearest in time to the determination of cardiac output appear in the tables.

All patients had clinical evidence of marked pulmonary and pericardial congestion and were classified as IV-D at the time of study according to the...
criteria of the New York Heart Association. The patients are grouped in tables 1 and 2 according to the presence of sinus rhythm or atrial fibrillation. Details of diagnoses can be found in these tables as can the dosage of Digoxin administered. Of those with sinus rhythm, 1 (no. 625) had had symptoms of failure for 3 years and was the most disabled of this group. The duration of complaints was much shorter in the 4 others in table 1, ranging from 1 to 6 months. Two (nos. 417 and 625) had had infrequent mercurial diuretics but none of the 5 had ever received digitalis bodies. One man (no. 519) had needed 3 thoracenteses on the left but had reaccumulated pleural fluid before his catheterization. In the group with atrial fibrillation, 3 (nos. 588, 682, and 794) had had previous episodes of failure for which they had been digitalized. They had discontinued the medication, however, 6 weeks, 4 months, and 5 months, respectively, before the study. Symptoms of failure recurred almost immediately in 1 man (no. 682). In the other 2 (nos. 588 and 794) as well as in the remaining 5 who were never digitalized, the symptoms had been present for less than 1 month prior to admission to the hospital. Two subjects (nos. 453 and 794) had received 1 or 2 doses of mercurial diuretics and in 5 (nos. 453, 806, 544, 794 and 940) thoracenteses were required to alleviate severe orthopnea but chest fluid was present at the time of study, as indicated in table 2.

It is of interest that in the group of patients with sinus rhythm the symptoms of left ventricular failure preceded those of peripheral congestion by a considerable period of time, while those individuals with atrial fibrillation complained of symptoms of right ventricular failure very shortly after those of left-sided failure had appeared.

Results

Patients with Combined Left and Right Ventricular Failure and Sinus Rhythm

Prior to administration of Digoxin the cardiac output in 4 of the 5 patients (table 1) was lower than normal and there was moderate to severe pulmonary hypertension with a wide pulse pressure and an elevated right ventricular diastolic pressure. Total blood volume was increased in all 5 subjects. The plasma volume was normal only in the 1 patient (no. 417) who had had repeated diuretics. The ventilation was also elevated in all 5 but the oxygen uptake was within normal limits. Mild to moderate arterial blood oxygen unsaturation (93 to 85 per cent) occurred in 3 subjects.

After Digoxin was given (via the catheter) the cardiac output rose in all patients (9 to 94 per cent) as did the stroke output. The heart rate fell in all, although hardly in a striking fashion (from 3 to 15 beats per minute). The changes in systemic arterial pressures were not great although there was a tendency to an increase in the systolic level with little or no fluctuation in diastolic or mean pressure. The right ventricular diastolic pressure declined in all 5 patients.

In 3 of the 4 patients in whom measurements of pulmonary arterial pressures were available, the systolic, diastolic, mean and pulse pressures decreased (as exemplified by no. 519 in figure 1) while in the fourth (no. 625) the significant changes were a fall in diastolic and a rise in pulmonary artery pulse pressure (fig. 1). In this fourth case a second

**Figure 1**

Hemodynamic responses to the acute administration of Digoxin in patients with left and right ventricular failure. The symbols are identified as follows: the square indicates the cardiac index; the triangle, the stroke volume; the target dot, the ventricular rate; the solid circles, the systolic and diastolic pulmonary artery pressures; the open circles, the right ventricular end-diastolic pressures; and the cross, the pulmonary artery mean pressures. B represents values before and A values after Digoxin. Patients 519 and 625 were in sinus rhythm and the remaining 4 were in atrial fibrillation.
### Table 1

**Hemodynamic Data in Five Patients in Combined Left and Right Ventricular Failure with Sinus Rhythm before and after Administration of Digoxin**

<table>
<thead>
<tr>
<th>Case, age sex, BSA</th>
<th>Diagnosis</th>
<th>Time</th>
<th>Ventricular rate (beats/min.)</th>
<th>Cardiac index (L/min./M²BSA)</th>
<th>Stroke volume (ml.)</th>
<th>Oxygen uptake (mL/min./M²BSA)</th>
<th>Ventilation (L/min./M²BSA)</th>
<th>Arterial oxygen (vol.% blood)</th>
<th>Systemic artery s/d (mean)</th>
<th>Pulmonary artery s/d (mean)</th>
<th>Right ventricle d</th>
<th>TBV (ml./M²BSA)</th>
<th>TV (ml./M²BSA)</th>
<th>Hemocrit (%)</th>
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</thead>
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<tr>
<td>#519, 38M, 1.55</td>
<td>HCVD, EH, chr. pyelonephr. gallop, pulsed alt, lt. hydrothorax</td>
<td>Control 34*</td>
<td>115 3.95</td>
<td>21.5 29 144 5.61 6.7 15.6 92 212/132 (162) 34/36 (47) 11 3340 1940 42</td>
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<tr>
<td></td>
<td></td>
<td>62</td>
<td>109 4.18</td>
<td>59 154 6.23 3.7 14.8 90 226/121 (158) 42/18 (28) 2</td>
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<tr>
<td>#616, 32M, 1.83</td>
<td>HCVD, EH, gallop, pulsed alt. bilat. hydrothorax</td>
<td>Control 16†</td>
<td>93 3.39</td>
<td>2.56 48 161 5.81 6.3 12.4 96 173/123 (140) 56/25 (39) 10 3327 2145 33</td>
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<td>38</td>
<td>78 3.21</td>
<td>75 147 5.82 4.6 12.4 96 198/119 (152) 24/6 (14) 1</td>
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<tr>
<td>#919, 67F, 1.58</td>
<td>HCVD, EH, calc. aorta calc., K-W neph., bilat. hydrothorax</td>
<td>Control 30*</td>
<td>71 2.80</td>
<td>2.82 60 138 4.79 4.9 13.8 85 261/95 (159) 67/18 (37) 8 3668 2217 39</td>
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<td>68</td>
<td>7.29 65 137 4.67 4.9 13.2 81 276/90 (159) 67/15 (36) 5</td>
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<tr>
<td>#417, 77M, 1.47</td>
<td>ASHD, EH, CS, MF, old myo. infarct, APC, angina</td>
<td>Control 23*</td>
<td>85 3.18</td>
<td>2.18 38 139 4.66 6.4 19.9 93 145/78 (103) 40/18 (22) 9 3510 1650 53</td>
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<tr>
<td></td>
<td></td>
<td>84</td>
<td>2.22 39 137 4.09 6.2 19.3 96 165/73 (112) 36/10 (12) 1</td>
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<tr>
<td>#625, 57M, 1.61</td>
<td>HCVD, ASHD, EH, CS, MF, LBBB, gallop</td>
<td>Control 53*</td>
<td>79 2.47</td>
<td>2.47 46 131 4.11 5.3 18.6 93 174/82 (115) 29/10 (12) 2</td>
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</tr>
</tbody>
</table>

*Minutes after 1.0 mg. Digoxin via catheter.
†Minutes after 1.25 mg. Digoxin via catheter.
‡Second study 19 days after acute Digoxin study.
study was made 19 days after the first, at which time he was no longer considered clinically to be in failure. The second catheterization (table 1) revealed a cardiac output which was higher than the final post-Digoxin value in the first study, a striking decrease in all pulmonary artery pressures, a further drop in right ventricular diastolic pressure, and no change in the large blood volume. None of the subjects in this group with sinus rhythm had any change in ventilation after Digoxin.

Patients with Combined Left and Right Ventricular Failure and Atrial Fibrillation

The level of blood flow in these 8 individuals was markedly reduced (table 2) with a cardiac index of less than 2.0 liters in every instance. In each there was elevation of all lesser circulation pressures but the level of pulmonary hypertension was quite different from that of the group with sinus rhythm; the systolic and pulse pressures were much lower. Tricuspid insufficiency was present in all 8 patients as judged from the right atrial pressure curves. Total blood volume was universally increased and the only subject with a normal plasma volume (no. 453) had had several doses of mercurial diuretics. In this group too, ventilation was increased but the oxygen uptake was within normal limits. Mild arterial oxygen unsaturation (92 to 93 per cent) occurred in 3 subjects.

After administration of Digoxin the cardiac output increased, 13 to 73 per cent, and the ventricular rate declined to a greater extent than in the group with sinus rhythm. There were also large increases in stroke volume. The changes in systemic arterial pressures were the same as in the group with sinus rhythm. The right ventricular diastolic pressure fell in the 7 instances in which it was measured.

The alterations in the pulmonary arterial pressures produced by the drug in these 8 subjects can be divided into 2 types. In the first, as seen in 3 patients (nos. 453, 806, and 544), the diastolic pressure fell after Digoxin but the systolic response was variable, falling (no. 453), remaining the same (no. 806), and rising (no. 544) (fig. 1). In all, the pulse pressure rose. In the second type, as occurred in 5 patients (and as is exemplified by no. 682 in fig. 1) there were minor pressure changes in the pulmonary artery systolic and diastolic pressures but the pulse pressures increased in 4 of the 5 during the period observed. In the fifth (no. 794) the pulse pressure remained unchanged. Ventilation did not alter after Digoxin in any of these patients.

Fortunately, it was possible to restudy 4 of these 8 patients (nos. 544, 588, 682, and 794) when clinical evidences of congestive failure had disappeared. All lesser circuit pressures were lower at this later date even though blood flows were approximately in the same range as on the first study (table 2). The blood volumes were also considerably lower although not one was normal. The ventilation remained unchanged at the time of the second evaluation, despite the improvements in the circulation.

Discussion

Hemodynamic Considerations

As was expected, the inotropic effect of the drug was expressed by a rise in cardiac output in all 13 subjects. Heart rate decreased in all and contributed to the accompanying increase in stroke volume. The average increase in stroke output in the patients with atrial fibrillation was 77 per cent as compared to 46 per cent in those with sinus rhythm. The effect on ventricular rate was much greater (an average decline of 28 beats per minute) in those with atrial fibrillation than in those with sinus rhythm (8 beats per minute). Heart rate, however, and output did not always vary in a consistent manner, as there were large increases in blood flow with only small changes in rate (no. 519, table 1) and large falls in rate with less impressive rises in output (no. 453, table 2). There was no fixed relationship in time between changes in ventricular rate and cardiac output. In some patients (nos. 544 and 940, table 2) there was a progressive fall in the heart rate and a continuing rise in output, while in others the ven-
Table 2

Hemodynamic Data in Eight Patients in Combined Left and Right Ventricular Failure with Atrial Fibrillation before and after Administration of Digoxin

<table>
<thead>
<tr>
<th>Case, age sex, BSA</th>
<th>Diagnosis</th>
<th>Time</th>
<th>Ventricular rate (beats/min.)</th>
<th>Cardiac index (L/min. x M² BSA)</th>
<th>Stroke volume (ml.)</th>
<th>Oxygen uptake (ml./min. x M² BSA)</th>
<th>Venilation (L/M² BSA)</th>
<th>A-V oxygen diff. (vol.%)</th>
<th>Oxygen cont. (vol.%)</th>
<th>Oxygen sat. (%)</th>
<th>Systemic artery s/d (mean)</th>
<th>Pulmonary artery s/d (mean)</th>
<th>Right ventricle d</th>
<th>TBV (ml./M² BSA)</th>
<th>TVV (ml./M² BSA)</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#453, 69M, ASHD, EH, CS, 1.81</td>
<td>MF, AF, rt. hydrothorax</td>
<td>Control 126</td>
<td>1.71</td>
<td>6.4</td>
<td>5.0</td>
<td>94</td>
<td>136/87 (106)</td>
<td>20.6</td>
<td>16</td>
<td>13</td>
<td>21 (7)</td>
<td>13</td>
<td>3120</td>
<td>1430</td>
<td>54</td>
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<tr>
<td>#806, 62M, ASHD, EH, CS, 1.53</td>
<td>MF, AF, VPC, bilat. hydrothorax</td>
<td>Control 163</td>
<td>1.33</td>
<td>13</td>
<td>137</td>
<td>1.71</td>
<td>10.3</td>
<td>17.9</td>
<td>94</td>
<td>102/74 (85)</td>
<td>39/31 (35)</td>
<td>10</td>
<td>3297</td>
<td>1763</td>
<td>47</td>
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<tr>
<td>#544, 58M, ASHD, EH, CS, 1.88</td>
<td>MF, AF, bilat. hydrothorax</td>
<td>Control 120</td>
<td>1.70</td>
<td>27</td>
<td>128</td>
<td>5.75</td>
<td>7.5</td>
<td>18.6</td>
<td>94</td>
<td>118/87 (97)</td>
<td>41/30 (34)</td>
<td>13</td>
<td>6620</td>
<td>3320</td>
<td>50</td>
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<tr>
<td>#588, 67M, ASHD, EH, CS, 1.62</td>
<td>MF, AF, bilat. hydrothorax</td>
<td>Control 124</td>
<td>1.90</td>
<td>25</td>
<td>131</td>
<td>5.30</td>
<td>6.9</td>
<td>18.3</td>
<td>93</td>
<td>136/83 (104)</td>
<td>30/18 (23)</td>
<td>8</td>
<td>4540</td>
<td>2220</td>
<td>42</td>
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</tr>
</tbody>
</table>

(+) indicates an increase from base line.
Table 2 (Continued)

| Case, age sex, BSA | Diagnosis          | Time | Ventricular rate (beats/min.) | Cardiac index (L/min/1.73m²) | Stroke volume (ml.) | Oxygen uptake (vol./min/1.73m²) | Ventilation (L/min/1.73m²) | Oxygen content % | Oxygen sat. (%) | Arterial blood | Pressures in mm. Hg |
|--------------------|--------------------|------|------------------------------|-------------------------------|---------------------|--------------------------------|----------------------------|-----------------|----------------|----------------|------------------|-------------------|
| 437, 65M, HCVD, ASHD, 1.82 EH, CS, MF, AF | Control 18*        | 129  | 1.56                         | 22                            | 134                 | 6.1                             | 8.7                        | 18.6            | 93             | 149/106 (123) | 26/13 (19)       | 8                 | 4040              | 2090             | 48              |
|                   |                    | 57   | 1.99                         | 33                            | 144                 | 5.6                             | 7.3                        | 17.1            | 91             | 165/97 (122) | 28/16 (18)       | —                 | —                 | —                | —               |
|                   |                    | 71   | 2.48                         | 41                            | 141                 | 4.0                             | 5.7                        | 17.4            | 94             | 161/86 (112) | 29/14 (19)       | 5                 | —                 | —                | —               |
|                   |                    | (+28%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |
| 482, 68M, ASHD, EH, CS, 1.65 MF, AF, VPC | Control 31†        | 119  | 1.69                         | 23                            | 132                 | 5.9                             | 7.8                        | 16.1            | 95             | 127/78 (93)  | 41/24 (30)       | 10                | 4195              | 2440             | 42              |
|                   |                    | 64   | 2.26                         | 40                            | 133                 | 6.34                            | 5.9                        | 15.3            | 96             | 142/80 (100) | 45/23 (33)       | 11                | —                 | —                | —               |
|                   |                    | (+34%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |
| 794, 76M, ASHD, EH, CS, 1.62 old myo. infarct, AF, rt. hydrothorax | Control 22**       | 84   | 1.71                         | 33                            | 102                 | 4.15                            | 6.0                        | 16.0            | 93             | 139/87 (118) | 33/16 (22)       | 5                 | 3256              | 2003             | 38              |
|                   |                    | 44   | 1.91                         | 40                            | 118                 | 4.52                            | 6.2                        | 15.4            | 92             | 160/100 (124) | 28/13 (20)       | 3                 | —                 | —                | —               |
|                   |                    | (+12%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |
| 794, 76M, ASHD, EH, CS, 1.62 old myo. infarct, AF, rt. hydrothorax | Control 49§        | 61   | 2.00                         | 52                            | 100                 | 4.11                            | 5.0                        | 14.7            | 97             | 147/80 (101) | 30/9 (16)        | 1                 | 3015              | 1910             | 37              |
|                   |                    | 159  | 2.10                         | 17                            | 119                 | 5.23                            | 9.6                        | 18.1            | 92             | 102/87 (91)  | 28/22 (24)       | —                 | 4040              | 2160             | 47              |
|                   |                    | (+23%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |
| 940, 51M, ASHD, EH, CS, 2.09 MF, AF, bilat. hydrothorax | Control 146        | 146  | 1.21                         | 17                            | 119                 | 5.23                            | 9.6                        | 18.1            | 92             | 102/87 (91)  | 28/22 (24)       | —                 | 4040              | 2160             | 47              |
|                   |                    | 32   | 1.89                         | 32                            | 121                 | 4.92                            | 6.4                        | 17.3            | 92             | 134/96 (111) | 34/18 (25)       | —                 | —                 | —                | —               |
|                   |                    | (+55%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |
|                   |                    | 122  | 1.89                         | 32                            | 121                 | 4.92                            | 6.4                        | 17.3            | 92             | 134/96 (111) | 34/18 (25)       | —                 | —                 | —                | —               |
|                   |                    | (+52%)|                             |                               |                     |                                 |                            |                 |                |                |                  |                   |                   |                   |                 |

*Minutes after 1.5 mg. Digoxin via catheter.
†Minutes after 1.0 mg. Digoxin via catheter.
‡Minutes after 1.0 mg. Digoxin via catheter.
§Minutes after 0.75 mg. Digoxin via catheter.
Days after acute Digoxin study.
**Minutes after 0.75 mg. Digoxin via catheter.
For key to abbreviations see Table 1.
Table 3

**Hemodynamic Data in Two Patients with Pneumonia and Combined Left and Right Ventricular Failure before and after Administration of Digoxin**

<table>
<thead>
<tr>
<th>Case, age sex, BSA</th>
<th>Diagnosis</th>
<th>Time</th>
<th>Ventricular rate (beats/min.)</th>
<th>Cardiac output (L/min./M² BSA)</th>
<th>Stroke volume (ml)</th>
<th>Oxygen uptake (ml/min./M² BSA)</th>
<th>R. Q.</th>
<th>Arterial blood</th>
<th>Systemic artery</th>
<th>Pulmonary artery</th>
<th>Right ventricle d</th>
<th>THV (ml./M² BSA)</th>
<th>PY (ml./M² BSA)</th>
<th>Hematocrit (%)</th>
<th>Pressures in mm. Hg</th>
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<tr>
<td>#492, 63M, ASHD, EH, NST, 1.74</td>
<td>Control</td>
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<td>4.50</td>
<td>74</td>
<td>184</td>
<td>0.73</td>
<td>4.1</td>
<td>15.2</td>
<td>90</td>
<td>125/69 (96)</td>
<td>44/16 (31)</td>
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<td>gallop, rt. hydrothorax, bronchopneumonia</td>
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<td>140/78 (100)</td>
<td>48/16 (33)</td>
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<td>76/44 (60)</td>
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<td>APC, VPS, pulsus alternans, bilat. hydrothorax, bronchopneumonia</td>
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<td>223/128 (169)</td>
<td>79/37 (53)</td>
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<td>86</td>
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<td>68/34 (48)</td>
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*Minutes after 1.5 mg. Digoxin via catheter.
†Onset of atrial flutter occurred at 34 minutes.
For key to abbreviations see Table 1.
DIGOXIN IN VENTRICULAR FAILURE

The ventricular rate decreased before there was any rise in cardiac output (nos. 453, 588, and 682, table 2), and in still others the ventricular rate fell at first and then became relatively stable although the cardiac output continued to rise (no. 519, table 1; nos. 806, 588, 437, and 794, table 2). Furthermore, the change in ventricular rate, both in terms of magnitude and timing, gave no indication of alterations in lesser circulation pressure.

The same dichotomy between heart rate and the other hemodynamic effects of the drug can be shown in 2 other subjects (table 3) who had a rise in ventricular rate but nevertheless had increases in cardiac output and decreases in lesser circuit pressures, the latter 2 alterations speaking for a continued myocardial effect of Digoxin. Both subjects had pneumonia (no. 492 ran a temperature of 100.2° p.r. during study) which was probably responsible for the elevated oxygen uptake. Nevertheless the respiratory quotients remained normal and stable during the observation period. In one (no. 492) sinus tachycardia increased at the seventeenth minute, and in the other atrial flutter with 2:1 and 3:1 AV response began at the thirty-fourth minute after Digoxin. Despite the more rapid ventricular rate the cardiac output rose and lesser circuit pressures continued to decline.

Further evidence of improved ventricular function following Digoxin can be found in the uniform decrease in right ventricular end-diastolic pressure; presumably the increase in systolic ejection resulting in a decrease in diastolic right ventricular volume. Better emptying of the left ventricle can be inferred from the drop in the pulmonary artery diastolic pressure in the 7 patients in whom it occurred, since in the absence of vascular disease or demonstrated vasomotoricity the level of this pressure is primarily regulated by events in the left heart. In these patients the left ventricle must have ejected more blood than was offered to it by the right and therefore as a consequence of a temporary heterodynamic of the 2 ventricles, there was a reduction in pulmonary blood volume. In 5 of the 8 patients with atrial fibrillation the pulmonary arterial diastolic pressure did not fall significantly (−1 to −4 mm. Hg); nonetheless one must assume that left ventricular function was improved, since this ventricle was able to accept from the right ventricle its additional output and deliver this additional volume to the aorta. It did so, even though it could not significantly reduce its own diastolic pressure as evidenced by the lack of change in pulmonary artery diastolic pressure. Hence there was probably no change in pulmonary blood volume. The fact that the pulmonary artery diastolic pressure remained elevated and unchanged could be explained by one of these 2 mechanisms—either the left ventricular diastolic volume had not been reduced and hence the diastolic pressure remained elevated, or, there was a change in left ventricular myocardial tone, so that, despite a fall in diastolic volume, diastolic pressure remained unchanged. The lack of change in pulmonary artery diastolic pressure cannot be ascribed to pulmonary vascular disease, since a second catheterization in 3 of these 5 revealed a later drop to virtually normal levels (table 2).

A further word should be said concerning the difference in response of the pulmonary artery diastolic pressure. It could not be related to the level of total blood or plasma volumes, as these were equally large in those who did or did not have a fall in this pressure (tables 1 and 2). The dosage of Digoxin given was also similar in the 2 groups. The etiologic factor of the heart disease and age of the patient also appear not to be different. It is interesting however that 3 of the 5 patients without this pressure change had had a previous bout of cardiac failure. In all 8 patients with atrial fibrillation the clinical story suggested the onset of symptoms of right heart failure almost as soon as left, in contradistinction to patients with sinus rhythm where left-sided symptoms antedated those of right by some time. This time difference could be interpreted as indicating a more or less simul-
taneous failure of both ventricles in atrial fibrillation, with both equally involved, while in the subject with sinus rhythm there was more involvement of the left ventricle. In the latter after Digoxin, one could say that the inotropic effect of the drug would be greater in the more involved ventricle and hence it would empty more completely. This reasoning could also apply to the first 3 patients with atrial fibrillation in table 2. In the 5 patients who did not have a fall in pulmonary artery diastolic pressure, emptying was the same for both ventricles during the acute study of Digoxin. Hence there was no immediate change in pulmonary blood volume. Later, there was a reduction in pulmonary blood volume and a fall in pulmonary artery pressures. This may have occurred either because heterodynamism appeared, with the left ventricle becoming capable of emptying more than the right, or, with a fall in total blood volume (due to diuresis) the right ventricle no longer ejected as much into the lungs, the left could still discharge this amount but could then add more of its own diastolic volume to its stroke volume and thus reduce the pulmonary blood volume.

The behavior of the pulmonary artery pulse pressure was variable. This is not surprising, since pulmonary artery pulse pressure reflects not only stroke volume but also the state of distensibility of the pulmonary vascular tree. This latter is governed by the level of pulmonary blood volume and the intrinsic characteristics of the vessels themselves. The normal pulmonary vascular bed is so distensible that relatively large changes in flow have very little effect on pressure. However, once the system becomes distended, either by an increase in pulmonary blood volume or a change in the characteristics of the vasculature, then changes in volume or flow will produce changes in pressure. Thus one might expect that the greater the stroke volume or the greater the degree of pulmonary congestion, the higher will be the pulse pressure.

Since more than one physiologic variable is operating to affect pulse pressure under these conditions, their relative influence must be examined. Direct measurement of pulmonary blood volume and estimates of the characteristics of the vasculature are not yet available but one can get an indirect estimate of the degree of pulmonary congestion from the pulmonary artery diastolic pressure, provided there are no major alterations in the characteristics of the pulmonary vasculature. Since in the patients in this study one would not expect such alterations, one can assume that the diastolic pressure is largely determined by the pulmonary blood volume. Stroke volume is probably estimated fairly accurately.

Thus in order to clarify this particular problem a study of the interrelationships of pulmonary artery pulse pressure, diastolic pressure, and stroke volume was made. Since the 13 patients presented in this report would comprise a rather small group, the study was enlarged to include 67 observations in 39 patients with degenerative heart disease and pulmonary congestion. These data were secured both at rest and during exercise and include the patients found in tables 1 and 2 before digitalization. It was found that, in general, as the pulmonary artery diastolic pressure rises or falls, so does the pulmonary artery pulse pressure, as long as the stroke volume is over 30 ml. (fig. 2). The correlation coefficient is highly significant (r = 0.505, p < 0.01). Below this critical level of stroke volume, the correlation is not significant (r = 0.306, p > 0.05). The linear regression equation for the relationship between pulse pressure and stroke volume is: pulse pressure = 0.505 × stroke volume - 10.0. (fig. 2). The slope of this line is statistically significant at the 0.01 level. The correlation coefficient between the diastolic pressure and the stroke volume is 0.505, which is also statistically significant at the 0.01 level. It is evident from these data that the diastolic pressure is a more reliable index of the stroke volume than the pulse pressure. This is true even in patients with degenerative heart disease and pulmonary congestion, where the diastolic pressure is a better index of the stroke volume than the pulse pressure.
volume, there is no such correlation and pulse pressure may remain quite small, regardless of the level of diastolic pressure, unless the latter is over 30 mm. Hg (fig. 3). The influence of stroke volume on pulse pressure is not so simply defined because the level of pulmonary blood volume may also affect the relationship. As already stated, if the stroke volume is less than 30 ml., then pulse pressure remains low unless a very high level of diastolic pressure is present. Once stroke volume exceeds 30 ml., as it rises so does the pulse pressure (fig. 4). If the pulmonary artery diastolic is only slightly elevated (for example, between 10 and 15 mm. Hg as shown on fig. 4), the stroke volume produces a smaller rise in pulse pressure than the same stroke volume would cause at a higher level of pulmonary artery diastolic pressure. One can see then (fig. 5) that when stroke volume and diastolic pressure are both large, pulse pressure will be large, and when both are small, so will be the pulse pressure. Looked at from the point of view of the effect of one single variable, the higher the diastolic pressure, the higher the pulse pressure and the lower the stroke volume, the lower the pulse pressure.

The final or resultant pulse pressure in any one situation therefore will depend upon the delicate balance of the effects of these 2 variables and in all probability on which one is the more abnormal.

The variations in pulmonary artery pulse pressure seen after Digoxin can now be elucidated by considering which of the above variables is predominating as the circulation readjusts to the inotropic effect of the drug. All of the patients with sinus rhythm had a large pulse pressure (table 4) before Digoxin. In 2 (nos. 519 and 625), despite their being at the critical level of stroke volume, 29 and 30 ml. respectively, there was a very high pulmonary artery diastolic pressure and hence the latter was the dominant variable and pulse pressure was large. In the other 2 subjects stroke volume was well above the critical level, being 48 and 60 ml., hence with elevated diastolic pressures, increased pulse pressure is expected and was found. As can be seen in table 4, there was a large fall in pulmonary diastolic pressure in the first 3 subjects with sinus rhythm after the medication. Hence despite a large rise in stroke volume pulmonary artery pulse pressure fell and one can as-
sume pulmonary blood volume decreased. The fourth patient (no. 625) who had a much smaller fall in diastolic pressure with the result that this pressure did not decrease below 30 mm. Hg, responded to a rise in stroke volume (which then moved him above the critical level of 30 ml.) with a rise in pulse pressure. Since pulmonary pressures later fell markedly, (see table 1, no. 625, second study) the increased pulse pressure after Digoxin cannot be ascribed to pulmonary vascular disease but was related to a large pulmonary blood volume that later became translocated.

The 8 patients with atrial fibrillation had much smaller pulmonary artery pulse pressures before the drug than did those with sinus rhythm. The small pulse pressures were probably primarily related to the small stroke volume which was considerably less than 30 ml. in all but 1 individual (no. 794, table 4) and in this one exception it was 33 ml. Before the glycoside, the low stroke volume, by virtue of its inability greatly to distend the pulmonary tree, obscured the evidence of pulmonary congestion that might have appeared as a large pulse pressure. When Digoxin produced a very large increase in stroke volume (over 74 per cent, in table 4), distention of the tree became more evident as a rise in pulse pressure and this occurred whether or not there was a fall in pulmonary artery diastolic pressure. Therefore one can say that it occurred when pulmonary blood volume had not changed or had decreased only slightly. When stroke volume did not increase strikingly, less than 50 per cent (nos. 453, and 794 in table 4) there was little or no effect on pulse pressure. In one individual (no. 453) the 48 per cent rise in stroke volume was counterbalanced by a fall of 10 mm. Hg in pulmonary artery diastolic pressure. The other patient (no. 794) did not have much distention of the pulmonary vascular bed (as indicated by the relatively low level of diastolic pressure, 16 mm. Hg). Under such circumstances, since stroke volume was already above the critical level to begin with and rose only modestly (35 per cent) and diastolic pressure did not fall significantly, one would not expect a change in the pulse pressure.

**Clinical Considerations**

Several clinical implications that bear upon evaluation of the effects of such a drug at the bedside can be derived from this study. First, the amount of Digoxin given intravenously to a patient in congestive failure need not be the

<table>
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<th>Case no.</th>
<th>PA(_a) before Digoxin (mm. Hg)</th>
<th>(\Delta) PA(_a) before Digoxin</th>
<th>SV before Digoxin (ml)</th>
<th>(\Delta) SV</th>
<th>% (\Delta) SV</th>
<th>PA(_dp) before Digoxin (mm. Hg)</th>
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<td>6 +16</td>
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*PA\(_a\)*, pulmonary artery diastolic pressure; SV, stroke volume; PA\(_dp\), pulmonary artery pulse pressure.

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**Figure 5**

Three-dimensional graph relating stroke volume (SV), pulmonary artery diastolic pressure (PA\(_a\)) and pulmonary artery pulse pressure (indicated by the vertical bars). The upper shaded rectangle marks an area where both stroke volume and diastolic pressure are large and in which pulse pressure is also large, while the lower rectangle encloses an area in which all 3 variables are small.
so-called 'digitalizing' or 'full' dose (1.5 mg.) in order to elicit marked hemodynamic changes toward normal. Ten of the 13 subjects received less than this dose (0.75 to 1.25 mg.), and 2 of these had reached normal lesser circulation pressures at the end of the period of observation (nos. 616 and 417). The earliest moment at which any effect of the drug was noted (change in heart rate, pressures or output), was 5 minutes after the completion of the injection of drug (the administration of the drug itself took 5 minutes). All patients had had some effect from the medication by 30 minutes. It is interesting that the 2 cardiotonic effects of the drug that were measured in this study (a rise in cardiac output and a fall in lesser circulation diastolic pressures) did not necessarily occur simultaneously, i.e., one could appear before the other (nos. 919, 417, and 453). In one subject (no. 919) the right ventricular diastolic pressure fell somewhat before the pulmonary artery pressures declined and this effect was patent 10 minutes after Digoxin, before any obvious rise occurred in cardiac output. Furthermore, stroke volume had increased only slightly (5 ml.) and heart rate fallen only 6 beats. Thus it appears that improvement in ventricular function evoked by Digoxin is a complex and interdigitating series of mechanisms and the fundamental and earliest event is still unknown and is not uniformly expressed in any one hemodynamic alteration.

These observations render somewhat tenuous the present clinical method of judging digitalization in which the cardiotonic effect of the drug is timed and assumed to occur almost solely in relation to the response of the ventricular rate, the implication being that if rate is not affected the myocardial effect has not occurred. This reasoning would be particularly erroneous in patients with sinus rhythm. This concept of the secondary position held by change in rate has recently been reemphasized by McMichael on the basis of studies made in his laboratory. Although changes in rate may eventually appear following this drug, it is now clear that the contractile myocardial effects may precede them by some time. Thus one should beware of increasing the amount of glycoside early in its administration if the rate response is negligible.

Another clinical sign that has been much used to determine the so-called digitalis effect is alteration of S-T and T waves and Q-T interval of the electrocardiogram. These variables were examined in relation to the myocardial effect of the drug in 12 of the 13 patients: the one (no. 625) with left bundle-branch block was excluded. In 11 the standard leads were followed and in the twelfth only lead V1 was monitored after the drug. There were no S-T shifts in any patient; in 11 of 12 there were no significant alterations in the T waves but in one subject (no. 417) T2 became upright from an isoelectric contour. The Q-T interval was not always measurable due to low voltage T waves but in 7 of 9 subjects where this was feasible, there was no change and in 2 the interval shortened. It is obvious therefore that electrocardiographic signs are not constantly indicative of the hemodynamic results of this drug and that the well known S-T, T, and Q-T changes may not appear early in the period after Digoxin.

The bedside diagnosis of congestive (right and left) heart failure usually depends upon certain objective signs in addition to the symptoms of dyspnea, orthopnea, and fatigue. A mid or protodiastolic gallop, pulsum alternans, cardiomegaly, hyperventilation, pulmonary rales, hepatomegaly, peripheral venous congestion, edema, and cyanosis are also searched for. Following the hemodynamic evidences of marked improvement in cardiac function, the patients were reexamined at the end of the study period and before returning to their ward, in order to correlate the speed with which these objective signs would mirror the improved circulatory status. The gallop rhythm, when present, almost always subsided by the end of the study; pulsum alternans would often disappear, occasionally from one circulation, say the lesser, before the other, as previously reported. The other signs for the most part remained unaltered at the completion of the observation period. Hence it
is apparent that rales, hepatomegaly, and edema are slower to disappear than the pressure abnormalities that may be related to their production. The lungs, liver, and subcutaneous tissues are therefore depots that may remain as passive pools of congestion and give up this state rather slowly. This fact may explain some of the clinical paradoxes one sees, e.g., where the peripheral venous pressure may be normal or the patient free of dyspnea and yet hepatomegaly, edema and rales are found. The sequence of old and recent events must be considered in such eventualities and the assumption made of previous ventricular failure and slow resolution of the congestive phenomena. On the other hand, following Digoxin there was always an early subjective improvement in dyspnea and orthopnea although hyperventilation persisted, an observation also made by Eichna et al.9 Therefore the persistence of hyperventilation at an unchanged level does not represent a barrier to the relief of some of the dyspnea. Furthermore, the hyperventilation did not diminish in those patients with a decrease in pulmonary artery pressures even if these reached normal levels, tending to show that this ventilatory response is not closely linked with pressure elevations in the lung vessels. It is also worth noting here that there is no elevation in basal metabolic rate in these patients with congestive failure and pulmonary congestion.

The slow disappearance of some of the objective evidences of congestive failure despite indications of the inotropic effects of the glycoside and resolution of much if not all of the pressure abnormalities, has considerable bearing upon the clinical problem of intravenous administration of this medication in an emergency situation. It has been the practice of some to ‘‘digitalize’’ a patient orally the morning or day after an intravenous dose has been given, particularly if some of the above-mentioned signs are unaltered. From the observations just cited it can be seen that this oral exhibition would then in many instances be directed at a circulation and a myocardium radically different from what they had been before the intravenous dose. There is no information to suggest that in 12 to 24 hours the circulation has returned to the state in which it was found prior to the first administration and that a second large or ‘‘digitalizing’’ dose is needed.

Summary and Conclusions

The acute effects of intravenous Digoxin were studied, with use of the cardiac catheterization technic, in 13 patients with hypertensive or arteriosclerotic heart disease in combined (left and right) ventricular failure. Two patients who in addition had broncho-pneumonia were also included to demonstrate the dichotomy between the inotropic effects of the drug and changes in heart rate.

Digoxin produced a rise in cardiac output and a fall in right ventricular end-diastolic pressure in every case.

The readjustments of the pulmonary arterial pressures after the drug were analyzed and it became apparent that the interrelationships between stroke volume and the degree of pulmonary congestion was the basic variable regulating the several different responses found after Digoxin.

Several clinical and hemodynamic considerations bearing upon the whole concept of a ‘‘digitalizing’’ dosage, the relationship between hemodynamic and electrocardiographic alterations of the drug, the inadvisability of using the effect upon ventricular rate as a reliable guide to its inotropic behavior, and the disappearance time of the clinical signs of congestive heart failure in relation to the early hemodynamic improvements were all discussed.

Summary in Interlingua

Le effectos acute del administration intravenose de Digoxina esseva studiati per medio del technica de catheterismo cardiaque in 13 patientes con morbo cardiaque hypertensivo o arteriosclerotic in disfallimento ventricular combinato (sinistre e dextere). Duo patientes, qui habeva broncho-pneumonia additional, esseva etiam studiati pro demonstrar le dichotomia inter le effectos inotropic del droga e alteraciones in le frequenta del corde.

Digoxina produciva un augmento del rendimento

Circulation, Volume XXI, March 1969
DIGOXIN IN VENTRICULAR FAILURE

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Some Effects of Digoxin upon the Heart and Circulation in Man: Digoxin in Combined (Left and Right) Ventricular Failure

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