The Effect of Exercise on the Plasma Volume of Patients with Heart Failure

BY ROBERT P. GILBERT, M.D., AND J. K. LEWIS, M.D.

Exercise performed in the supine position by patients with congestive failure was found to cause not only a greater elevation of the peripheral venous pressure than it causes in normal persons, but also a proportionately greater fall of the plasma volume.

It is now generally accepted that in heart failure of all types the cardiac output is reduced relative to the needs of the body at that time.1–3 Beyond this however, disagreement and uncertainty still confound our ideas of the causal interrelationships between this mechanical incompetence of the heart and the phenomena of clinical heart failure. Thus, the elevation of the venous pressure is regarded by some as related directly to the decrease in cardiac output and as the primary or initiating cause of edema.4–6 By others7–9 it is viewed as a purely static manifestation produced by the increase of the extracellular fluid volume or at times by changes in venous tone. In this regard though, it is worth recalling that many observers10,11 have noted that exercise produces an abnormally great rise of the peripheral venous pressure in persons with cardiac failure even though the peripheral venous pressure at rest may have been normal. This has recently been confirmed by Felso-vanyi and Lewis12 and by others.13,14 By increasing the body’s demands beyond the capabilities of a heart barely “compensated” at rest, exercise renders latent heart failure obvious. Landis, Brown, Fauteux and Wise15 have gone into this problem, using dogs. They ligated a coronary artery or induced auricular fibrillation to simulate clinical myocardial incompetence. They then found that exercise caused the central venous pressure to rise, though it had not risen during similar exercise beforehand. They were led to propose an hypothesis to account for the sequence of events in developing heart failure which may be paraphrased as follows:

Impaired myocardial competence. → Inability of the heart to cope with the venous return when this exceeds the heart’s competence. This is intermittent at first. → Repeated and intermittent pooling of the blood on the venous side with a rise in the venous pressure. → Loss of fluid into the extravascular spaces. → The loss of fluid and the venous pooling constitute a fall in the circulating blood volume, intermittent at first. → Compensatory changes to increase the extracellular fluid volume and the blood volume. (a) Vasoconstriction, which, as it affects the kidneys, is responsible in part for the retention of water and electrolytes. (b) Vasoconstriction of vessels leading to the bone marrow with stimulation of erythropoiesis. → Further increase of venous pressure due to plethora.

The matter to be presented concerns only one step in this chain of events: the increased venous pressure consequent upon exercise in patients with cardiac failure does indeed lead to a greater fall of the plasma volume than occurs in normal subjects who show little or no rise in venous pressure.

Previous workers have studied the changes in the blood volume during exercise, and in general it has been found to fall.16–18 In the present study the amount of exercise was insufficient to produce an appreciable drop of the plasma volume in normal individuals.

METHODS

The subjects studied were patients from either the medical ward or the outpatient clinic. Control studies were done on patients with no evidence of right-sided heart failure. With few exceptions the tests were performed in the morning in the post-absorptive state, and always after at least forty-five minutes rest in the horizontal position.

The exercise was performed while supine, and consisted of repeatedly pushing a foot board to raise a weight along a given arc as described by Felso-vanyi and Lewis.12 Each stroke required the ex-
penditure of about 28 foot-pounds of work, and the usual rate was 30 to 50 strokes per minute. For patients who were made uncomfortable, the slower rate was used. When more than one test was performed by the same person, approximately the same rate was used each time. Exercise was continued for fifteen minutes except for a few instances of fairly pronounced failure.

Oiled 20 ml. syringes with 18-gage needles were used to take samples from an arm vein before and just at the conclusion of the exercise period. Every effort was made to avoid stasis. It was found to be unwise to draw blood from the three-way stopcock of the venous pressure manometer, as slight dilution by the sodium citrate solution was hard to avoid. Five ml. of blood were placed in a commercially prepared tube containing ammonium and potassium oxalate as anticoagulants. The remainder was allowed to clot in a paraffined centrifuge tube. The separated serum was centrifuged a second time.

Hematocrits were determined in duplicate or triplicate with Wintrobe tubes.

Serum protein levels were measured with the gradient tube of Lowry and Hunter. Results were found to check at least to within 0.10 Gm. per 100 cc., though the absolute accuracy was probably less.

For measuring the venous pressure in the antecubital vein an ordinary water manometer containing 2.5 per cent sodium citrate was used. By flushing out the needle and tubing from a reservoir it was possible to observe the pressure for an indefinite period. Pressures were measured from the phlebostatic level of Winsor and Burch.

The plasma volume was determined with the dye T-1524, following in general the technic described by Hopper, Tabor and Winkle except that the Coleman spectrophotometer was used.

 Alterations in plasma volume were measured in three ways. In some cases the long indirect method of Gibson and Evans was used. In view of the demonstration by Ebert and Stead that exercise caused the optical density of the serum itself to increase, control determinations were made the day before to find out in each case to what extent the exercise employed would alter the optical density of the serum. In general this correction was found to be insignificant (change in optical density of less than .005). Kaltreider found that exhausting exercise was necessary to produce the effect.

Changes in the plasma volume were also calculated from the changes in the serum protein concentration and from changes in the venous hematocrit by substituting in the relationships:

Total circulating protein = protein concentration × plasma volume

RBC volume = hematocrit × blood volume

Following exercise the total circulating protein and the red blood cell volume were assumed to have remained constant. The new plasma volume and the new blood volume were the only unknowns. The change in blood volume was assumed to equal the change in plasma volume.

It is realized that these technics are not proof from error. Arterial blood sampling would have eliminated the possibility of error due to local stasis. Increased loss of protein through the capillary membrane at higher venous pressures may have caused falsely low values for the plasma volume decrement calculated by both the long indirect dye method and the change in serum protein method. The red cell volume is overestimated by using the venous or arterial hematocrit, which have been shown to be higher than the true body hematocrit. This would cause the values for the plasma volume changes as calculated from the alterations in hematocrit to be higher than the true change. It was assumed that erythrocytes were neither added to nor lost from the circulation. Nylin was unable to show any addition to the total red cell volume on exercise. Any trapping of cells but not of plasma would lead to a decrease in hematocrit and yield falsely low values for the plasma change. The initial value obtained for the plasma volume was doubtless too high because of the poorly understood extravascular loss of dye. Some of the errors were obviated by expressing the change as a percent of the initial volume. This also made it possible to compare changes in different individuals and in the same individual after alterations of the resting plasma volume.

Results

The results are summarized in table 1. Peripheral venous pressure readings before exercise were averaged to obtain a figure for the resting venous pressure. For the exercise period the venous pressures at the end of each minute were averaged to obtain the mean level. In a few instances it was necessary to interpolate on a graph to obtain readings at the proper time intervals. The difference between the resting venous pressure and the mean level during exercise was taken as the venous pressure increment. The determinations are arranged according to the order of the resting venous pressures. With normal resting venous pressures, and viewing both tables together, it is seen that exercise may or may not produce a rise in the venous pressures. When the resting venous pressure is above the usual normal limit of 150 mm., a further rise on exercise seems quite likely to occur. An average value was also derived for the per cent change of
**EFFECT OF EXERCISE IN HEART FAILURE**

**Table 1.—Effect of Exercise on Venous Pressure and Plasma Volume**

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnoses</th>
<th>Plasma Volume</th>
<th>Resting V.P.</th>
<th>V.P. on Exercise</th>
<th>Percent Fall of Plasma Vol.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ml./Kg.</td>
<td>mm. sodium citrate</td>
<td>mm. sodium citrate</td>
<td>Max. Mean Increment</td>
</tr>
<tr>
<td>Group I: Subjects Without Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No disease</td>
<td>45</td>
<td>89</td>
<td>120</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Dermatitis</td>
<td>43</td>
<td>94</td>
<td>155</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>No disease</td>
<td>45</td>
<td>99</td>
<td>98</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>? Control. S.B.E. under treatment. Apparently compensated</td>
<td>51</td>
<td>105</td>
<td>148</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>Polycythemia vera</td>
<td>42</td>
<td>112</td>
<td>125</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>No disease</td>
<td>58</td>
<td>114</td>
<td>137</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>? Control. S.B.E. under treatment. Apparently compensated</td>
<td>51</td>
<td>117</td>
<td>163</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>? Control. Hypertension. Apparently compensated</td>
<td>45</td>
<td>127</td>
<td>160</td>
<td>13</td>
</tr>
<tr>
<td>10*</td>
<td>Same</td>
<td>45</td>
<td>150</td>
<td>170</td>
<td>16</td>
</tr>
<tr>
<td>Averages</td>
<td>..........................</td>
<td>47</td>
<td>112</td>
<td>142</td>
<td>15</td>
</tr>
<tr>
<td>Group II: Subjects with Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A†</td>
<td>R.H.D. with M.S., M.I. and A.S.</td>
<td>—</td>
<td>42</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>A.S.H.D.</td>
<td>—</td>
<td>81</td>
<td>148</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>A.S.H.D.</td>
<td>63</td>
<td>80</td>
<td>173</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>A.S.H.D.</td>
<td>—</td>
<td>93</td>
<td>134</td>
<td>30</td>
</tr>
<tr>
<td>1B‡</td>
<td>R.H.D. with M.S., M.I. and A.S.</td>
<td>64</td>
<td>93</td>
<td>173</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>A.S.H.D.</td>
<td>46</td>
<td>98</td>
<td>193</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>A.S.H.D.</td>
<td>46</td>
<td>106</td>
<td>240</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>A.S.H.D.</td>
<td>—</td>
<td>119</td>
<td>168</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>A.S.H.D.</td>
<td>47</td>
<td>134</td>
<td>154</td>
<td>17</td>
</tr>
<tr>
<td>1C§</td>
<td>R.H.D. with M.S., M.I. and A.S.</td>
<td>70</td>
<td>145</td>
<td>213</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>A.S.H.D.</td>
<td>52</td>
<td>168</td>
<td>183</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Thyrotoxicosis, congestive failure</td>
<td>53</td>
<td>203</td>
<td>278</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>A.S.H.D. Hypertension</td>
<td>—</td>
<td>204</td>
<td>372</td>
<td>109</td>
</tr>
<tr>
<td>1D</td>
<td>R.H.D. with M.S., M.I. and A.S.</td>
<td>45</td>
<td>213</td>
<td>292</td>
<td>68</td>
</tr>
<tr>
<td>1E‖</td>
<td>Same</td>
<td>70</td>
<td>220</td>
<td>337</td>
<td>104</td>
</tr>
<tr>
<td>1D</td>
<td>Same</td>
<td>15</td>
<td>335</td>
<td>73</td>
<td>5.9</td>
</tr>
<tr>
<td>Averages</td>
<td>..........................</td>
<td>56</td>
<td>141</td>
<td>217</td>
<td>59</td>
</tr>
</tbody>
</table>

* Case 10 undergoing forced water diuresis. † Case 1 after diuresis and ouabain. ‡ Case 1 after diuresis, but five days after ouabain. § Case 1 before diuresis, but after ouabain and one test after test 1E. ‖ Case 1 before any treatment.

Experiments are arranged in the order of the resting venous pressure prior to the commencement of exercise. As this varied depending upon the current status of the patient the tests for one subject are scattered throughout the table.

Key to Abbreviations: A.S.H.D., arteriosclerotic heart disease; R.H.D., rheumatic heart disease; S.B.E., subacute bacterial endocarditis; M.S., mitral stenosis; M.I., mitral insufficiency; A.S., aortic stenosis.
the plasma volume as determined by one or more of the three methods.

It is evident on inspection that the venous pressure was found to rise more in subjects with heart failure. Similarly the values for the plasma volume fall were all higher in the heart failure group. Few successive determinations were performed on subjects in a steady state, so that the spread on successive determinations cannot be determined as an index of the relationship indicated by the line on the graph. The correlation coefficient was .79. That the precision of the results obtained is not to be regarded as absolute may be inferred from the intercept on the ordinate which would indicate a plasma volume fall of 0.3 per cent with no change in the venous pressure. The values for case 4, which are circled on figure 1, are thought to be in error due to dilution from the manometer in the first instance and to stasis in the second.

**Table 2.**—Effect of Exercise on the Venous Pressure and Plasma Volume before and after the Administration of Digitoxin or Ouabain.

<table>
<thead>
<tr>
<th>Case</th>
<th>Drug and Dosage</th>
<th>Interval from Test Before</th>
<th>Venous Pressure Increment</th>
<th>Percent Fall of Plasma Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Digitoxin 1.2 mg., digitoxin 0.6 mg., then 0.1 mg. daily</td>
<td>7</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Digitoxin increased to 0.2 mg. daily</td>
<td>14</td>
<td>77</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>Digitoxin 1.2 mg. (control)</td>
<td>1</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>Ouabain 0.5 mg. just prior to second test</td>
<td>1</td>
<td>104</td>
<td>51</td>
</tr>
<tr>
<td>1†</td>
<td>Ouabain 0.5 mg. just prior to second test</td>
<td>8</td>
<td>73</td>
<td>68</td>
</tr>
</tbody>
</table>

* Plasma volume fall figures thought to be in error for technical reasons.
† Undergoing forced water diuresis.

The slope of the line in figure 1, 0.069, defines the average percent fall of the plasma volume per millimeter rise of the peripheral venous pressure over a period of fifteen minutes. For any given case the milliliters of fluid lost from the vascular tree over fifteen minutes should then be the product of the slope times the venous pressure rise in millimeters, times the plasma volume in milliliters, divided by 100. If one should assume a venous pressure rise of 50 mm. of water for fifteen minutes in a subject with a plasma volume of 3000 ml., this would be: \( \frac{0.069 \times 50 \times 3000}{100} \) or
103 ml. For a 70 Kg. subject (plasma volume of 43 ml./Kg.) this would be $\frac{103}{15 \times 5 \text{ cm.} \times 700}$ or 0.00196 ml. of fluid lost per centimeter rise of the venous pressure per minute per 100 grams of tissue. This figure can be compared with the values obtained by Landis and co-workers, one of the highest of which was 0.0033 ml. per minute per centimeter rise of venous pressure per 100 milliliters of tissue. The discrepancy is not of alarming size.

In six of the experiments included in table 1 the response to exercise was studied before and after the administration of digitoxin or ouabain. The results are shown in table 2. As indicated above the results in case 4 are thought to be in error due to technical reasons. In most instances there appears to have been a definite lessening of the venous pressure increment, and concomitantly the loss of plasma volume. Previous studies have shown that digitoxin produces a fairly constant reduction or abolition of the venous pressure rise during exercise in patients with cardiac failure.

**Discussion**

The data just cited demonstrate once more the occurrence of an abnormal elevation of the venous pressure on exercise in subjects with congestive failure. This elevation may be manifested though the resting venous pressure is normal. As suggested nearly forty years ago the obvious explanation for this observation would be an inability of the heart to increase its output. It has recently been shown that in persons with cardiac insufficiency the output fails to rise during exercise as it does in normal subjects. Furthermore, this venous pressure rise on exercise can be reduced or abolished by the digitalis glycosides which are known to raise the output of the failing heart. If it is conceded that exercise must cause the venous return to increase at once, and if the heart is unable to transfer this added blood to the arterial side, the accumulating fluid must necessarily elevate the pressure within the veins, unless there is a decrease in venous tone. The accumulated blood necessary to sustain a rise in the venous pressure could be drawn not only from portions of the systemic circuit but from the pulmonary circulation as well. Fenn and others have shown that pressure breathing can displace upwards of 500 ml. of blood from the lungs. A similar rise of the venous pressure in subjects with cardiac failure can be produced by passive leg raising or by pressure on the abdomen. In these instances there is an obvious increase of the venous return to an extent that the failing heart is unable to handle it. This rise can occur with a normal or low total blood volume and cannot be due to an increased blood volume filling out the vascular system as a whole. It does not occur in normal subjects as might be expected if sudden venous constriction were the cause.

The data presented in the table seem to justify the conclusion that the abnormal rise of the venous pressure is accompanied by a loss of fluid from the vascular tree. Indeed some degree of proportionality is evident in figure 1. From past experiences with the effects of an increased venous pressure one could safely predict this finding. In the present instance, an acute rise of the venous pressure has apparently initiated the formation of edema.

The increased venous pressure and decreased plasma volume brought about by exercise in patients with congestive failure can be viewed as a change for the worse in the balance between the ability of the heart as a pump and the demands placed upon it. Probably a similar change occurs in acute heart failure as seen clinically, except that in this instance it results from a sudden decrease in the heart's ability as a pump rather than from a sudden increase in the demands placed upon it.

To what extent these acute factors are operative in chronic heart failure is uncertain. Certainly in its early stages the repeated, if transitory, rises in the venous pressure and associated falls in the plasma volume consequent upon increased activity would be expected to initiate a compensatory retention of fluid as pointed out by Landis and others. Furthermore, Blake and Bradley have shown that elevation of the renal venous pressure alone...
may lead to decreased renal excretion of salt and water. Further discussion of the relationships between plasma volume, venous pressure and renal function is beyond the scope of this paper, and has been well covered in several recent reviews.8,9

**Summary**

1. The effects of exercise on the peripheral venous pressure and plasma volume were studied in normal subjects and in patients with congestive failure.

2. In accordance with previous work by others, exercise was found to produce a conspicuous rise of the peripheral venous pressure of patients with heart failure.

3. This transitory rise of the peripheral venous pressure was accompanied by a roughly proportionate decrease of the plasma volume.

4. It is felt that this rise in peripheral venous pressure is due to inability of the heart to sufficiently increase its output, and that the resultant fall in plasma volume may be at least partly responsible for the renal retention of water and salt.

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