Experimental Hypervolemic Heart Failure: Its Bearing on Certain General Principles of Heart Failure

By William Huckabee, M.D., Gus Casten, M.D., and T. R. Harrison, M.D.

Infusion of large volumes of fluid into normal dogs produces a progressive rise in venous pressure with an initial parallel rise in cardiac output succeeded by a fall. On the basis of these experiments and other considerations which are discussed, it is concluded that the cardinal hemodynamic defect common to all types of heart failure is a disproportion between inflow load and cardiac output. The various general circulatory disorders are classified as primary disorders of filling and primary disorders of emptying with various subgroups.

The purposes of the present communication are threefold: (1) to present experimental data concerning a type of heart failure to which relatively little attention has been paid in the past; (2) to consider the similarities between heart failure produced experimentally and that occurring in patients; (3) to offer a classification of heart failure which appears to be applicable to both conditions.

In the heart-lung preparation, failure may be induced by (1) gradual exhaustion of the myocardium, (2) excessive increase in the peripheral resistance, (3) excessive elevation of the venous reservoir. The first factor is the most important because it occurs spontaneously with the passage of time, and because the myocardial competence determines at all times the degree of load (arterial or venous) which is required to produce failure.

When we turn from the heart-lung preparation to the patient, it becomes clear that the first (myocardial exhaustion) and second (excessive arterial resistance) mechanisms of heart failure have well-recognized clinical analogues.* It is in regard to the third type of heart failure (that analogous to elevation of the venous reservoir) that uncertainty exists.

It has long been recognized that, whereas heart failure in man is usually associated with decline in the cardiac output per unit of time, in some cases this function may be normal or increased. This conclusion, originally based on older studies, with less accurate methods,¹ ² has now been amply confirmed by newer studies with more accurate methods.³ ⁴ In recent years the term “high-output failure”⁵ has been applied to patients with this functional disturbance. The present communication represents an attempt to analyze the mechanisms of “high-output failure,” and to relate them to the mechanisms of heart failure in general.

Before proceeding further with the general consideration of the principles of heart failure, it will be well to consider certain experiments which may possibly be of aid in the clarification of these principles. In these experiments as in those of previous investigators⁶-⁸ heart failure was induced by massive intravenous infusions.

* The classic analogue of heart failure developing spontaneously over a period of hours in the heart-lung preparation is that developing over a period of decades in man, i.e., senile heart failure occurring in the absence of demonstrable increase in load. The common causes, in patients, of heart failure analogous to that brought about by excessive increase of the artificial resistance in the heart-lung preparation, are hypertension and aortic stenosis. However, the analogy is relative rather than absolute, because heart failure due to these causes is rare in young subjects, and in older subjects one can never be certain concerning the relative importance of the resistance factor as compared to the myocardial aging factor. A rarer but better analogy is heart failure occurring acutely in young subjects with previously normal hearts as the results of multiple pulmonary embolism.
### Table 1. Effect of Rapid Intravenous Infusions on Cardiac Output and Related Functions

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Sample No.</th>
<th>Cardiac Output (L/min.)</th>
<th>Increase of Rt. Atrial Pressure (cm. saline)</th>
<th>Veno-Atrial Pressure Difference (cm. saline)</th>
<th>Arteriovenous O₂ Difference (vol. %)</th>
<th>Mean Arterial Blood Pressure (mm Hg)</th>
<th>Volumes Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 5% albumin in water, 4.4 cc./Kg./min.</td>
<td>1</td>
<td>1.46</td>
<td>0</td>
<td>2.8</td>
<td>2.64</td>
<td>60</td>
<td>1700 cc. in 27 min.</td>
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<tr>
<td></td>
<td>2</td>
<td>2.29</td>
<td>18.5</td>
<td>5.0</td>
<td>1.95</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.57</td>
<td>39.0</td>
<td>1.5</td>
<td>3.27</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.55</td>
<td>12.0</td>
<td>1.5</td>
<td>2.01</td>
<td>94</td>
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</tr>
<tr>
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<td>5</td>
<td>2.98</td>
<td>4.5</td>
<td></td>
<td>1.87</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>2. 5% albumin in water 3.3 cc./Kg./min.</td>
<td>1</td>
<td>2.23</td>
<td>0</td>
<td>2.0</td>
<td>3.90</td>
<td>92</td>
<td>2173 cc. in 53 min.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.08</td>
<td>2.2</td>
<td>3.3</td>
<td>1.75</td>
<td>124</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>2.98</td>
<td>26.7</td>
<td>1.8</td>
<td>2.91</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.55</td>
<td>29.2</td>
<td>2.0</td>
<td>3.12</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>3. 5% albumin in water 3.3 cc./Kg./min.</td>
<td>1</td>
<td>1.30</td>
<td>0</td>
<td>4.0</td>
<td>7.08</td>
<td>140</td>
<td>2810 cc. in 52 min.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.75</td>
<td>5.0</td>
<td>5.5</td>
<td>5.48</td>
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<td>8.0</td>
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<td>11.0</td>
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<td>4. 5% albumin in water, 3.3 cc./Kg./min.</td>
<td>1</td>
<td>3.50</td>
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<td>5.0</td>
<td>2.23</td>
<td>114</td>
<td>1355 cc. in 25 min.</td>
</tr>
<tr>
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<td></td>
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<td>2.84</td>
<td>32.3</td>
<td>1.3</td>
<td>4.58</td>
<td>100</td>
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<tr>
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<td>1.99</td>
<td>11.5</td>
<td>0.3</td>
<td>3.57</td>
<td>136</td>
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<tr>
<td>5. 5% albumin in modified Ringer’s solution, 33 cc./Kg./min.</td>
<td>1</td>
<td>3.67</td>
<td>0</td>
<td>6.3</td>
<td>2.50</td>
<td>98</td>
<td>2590 cc. in 68 min.</td>
</tr>
<tr>
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<td>5.3</td>
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<td>3.87</td>
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<td>4.43</td>
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<td>4.28</td>
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<td>-3.5</td>
<td>2.19</td>
<td>96</td>
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<td>23.3</td>
<td>-6.5</td>
<td>1.56</td>
<td>80</td>
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<tr>
<td>6. 10% albumin in modified Ringer’s solution, 3.3 cc./Kg./min.</td>
<td>1</td>
<td>5.71</td>
<td>0</td>
<td>4.3</td>
<td>1.98</td>
<td>110</td>
<td>1435 cc. in 26 min.</td>
</tr>
<tr>
<td></td>
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<td>9.50</td>
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<td>4.5</td>
<td>1.47</td>
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<td>116</td>
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<td>7. 10% albumin in water, 3.3 cc./Kg./min.</td>
<td>1</td>
<td>1.81</td>
<td>0</td>
<td>.8</td>
<td>6.03</td>
<td>134</td>
<td>1095 cc. in 21 min.</td>
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<tr>
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<td>11.30</td>
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<td>1.70</td>
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<td>23.5</td>
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<td>4.75</td>
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<td>6</td>
<td>2.85</td>
<td>1.5</td>
<td></td>
<td>4.97</td>
<td>120</td>
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TABLE 1.—Concluded

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Sample No.*</th>
<th>Cardiac Output</th>
<th>Increase of Rv. Atrial Pressure Over Control Value</th>
<th>Venous-Oxygen Pressure Difference</th>
<th>Arteriovenous O2 Difference</th>
<th>Mean Arterial Blood Pressure</th>
<th>Volumes Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Heparinized horse blood, 3.08 cc./Kg./min.</td>
<td>1</td>
<td>1.10</td>
<td>0</td>
<td>14.3</td>
<td>8.3</td>
<td>100</td>
<td>2865 cc. in 73 min.</td>
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<td>3.03</td>
<td>110</td>
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<td>7.18</td>
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<tr>
<td>9. Heparinized dog blood, 3.3 cc./Kg./min.</td>
<td>1</td>
<td>.34</td>
<td>0</td>
<td>6.5</td>
<td>10.24</td>
<td>92</td>
<td>3500 cc.</td>
</tr>
<tr>
<td></td>
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<td>3.5</td>
<td>5.83</td>
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<td>—0.8</td>
<td>4.07</td>
<td>154</td>
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<td>—1.0</td>
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<td>.85</td>
<td>22.0</td>
<td>1.3</td>
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<td>0.8</td>
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</tr>
<tr>
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<td>.57</td>
<td>1.5</td>
<td>3.3</td>
<td>8.63</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>10. 15% albumin in modified Ringer's solution variable rate</td>
<td>1</td>
<td>1.19</td>
<td>0</td>
<td>7.5</td>
<td>7.10</td>
<td></td>
<td>2730 cc. in 183 min.</td>
</tr>
<tr>
<td></td>
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<td>3.05</td>
<td>10.3</td>
<td>1.8</td>
<td>3.48</td>
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</tr>
<tr>
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<td>3</td>
<td>4.84</td>
<td>10.8</td>
<td>1.0</td>
<td>2.15</td>
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<tr>
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<td>12.8</td>
<td>0.5</td>
<td>1.94</td>
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<td></td>
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<td>16.3</td>
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<td>1.73</td>
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<td></td>
</tr>
</tbody>
</table>

* In each experiment the first sample represents the control values. Values below the cross line represent measurements made after cessation of the infusion, while the intermediate observations were made during the infusion.

**Experimental Findings**

Hypervolemia was produced in morphinized dogs by intravenous infusion of various fluids, including blood, serum albumin solution, and modified Ringer's solution. Cardiac outputs were determined according to the Fick principle, using the blood oxygen technic of Van Slyke and Neill and the Benedict apparatus for recording oxygen consumption. Venous samples were obtained from the right atrium by a cannula passed down from the external jugular vein. Arterial, venous, and atrial pressures were measured directly by means of mercury and saline manometers.

Autopsies revealed pulmonary and hepatic congestion, pulmonary edema, and cardiac dilatation.

The more pertinent experimental findings are presented in table 1. Pulse rates changed relatively little so that, in general, stroke volume paralleled minute output. (The relative constancy of the pulse rate in these experiments was probably due to the narcotic for morphine is a strong vagal stimulant in the doses used.) Slight to moderate rise in arterial pressure occurred. The arterial oxygen saturation exhibited variable changes, being sometimes low during the control observations (apparently consequent to morphine narcosis) and at another times declining during the experiment (pulmonary edema). In several instances the arterial oxygen saturation remained above 95 per cent throughout the experiment. The arterial oxygen content declined rapidly when albumin solutions were employed but remained essentially unchanged when blood was used for infusion. The arteriovenous oxygen difference characteristically decreased after the start of infusion and increased again at the time of the fall in cardiac output; it usually did not become greater than the control value. Thus even after the onset of heart failure the cardiac output tended to be elevated in proportion to the oxygen consumption.
**Venoatrial Pressure Difference.** During the control periods the femoral venous pressure usually exceeded the right atrial pressure by 2 to 7 cm. of water. When the infusion was begun, both pressures increased steadily and the pressure difference at first exhibited variable changes. Prior to the beginning of the decline in cardiac output the atrial pressure rose more rapidly and the two pressures approached each other. It should be emphasized that marked elevation of cardiac output was frequently encountered at a time when the venoatrial pressure difference was sharply reduced.

**Cardiac Output and Atrial Pressure.** During the control period the atrial pressures, cardiac outputs, and arteriovenous oxygen differences exhibited wide variations in different dogs. However, the effects of the infusion were qualitatively similar in all of the animals. Several typical experiments are shown in figure 1. The atrial pressures and cardiac output values for all of the experiments are plotted in figure 2. With the progress of infusion, the atrial and peripheral venous pressures increased steadily. Accompanying the increased filling pressure was an initial rise of cardiac output. As the...
infusion continued the venous pressure continued to increase, but the cardiac output began to rise less rapidly, and finally declined. found for the heart-lung preparation by Starling. The plateau of this curve at the end in the intact animal was not found by Starling.

If, at this point, the infusion was stopped, the atrial pressure usually underwent a slight further increment for a minute or two and then slowly declined during the next hour. Stopping the infusion resulted in variable directional alterations in cardiac output.

In one instance (table 1, Exp. 10) the atrial pressure was maintained at a constant and somewhat elevated level by varying the rate of infusion. Later a spontaneous rise in pressure occurred and this persisted after the infusion was stopped.

The mean curve of cardiac output in relation to atrial pressure (fig. 2) is similar to the curve and may represent the effect of the pericardium in preventing further dilatation of the heart.

DISCUSSION

Interpretation of Experimental Observations

The experiments which have been presented were highly artificial. Huge amounts of infusate were required to produce heart failure. The different animals exhibited marked variation in quantitative relationships between venous pressure and cardiac output. Nevertheless, the qualitative responses were similar in all of the animals and were not different in the experiments characterized by anemic anoxia and elec-
trolyte dilution (owing to the administration of serum albumin solution) from the more physiological experiments (in which blood was administered). Two findings were constant. (1) As the infusion progressed and the venous pressure rose steadily the cardiac output first increased and then decreased. (2) The difference between the peripheral venous and right atrial pressures at first increased or remained constant and then diminished even though the cardiac output was still rising. Since this observation appears somewhat paradoxic, its significance may now be considered.

The quantitative aspects of the conditions determining the flow of a liquid through a set of rigid capillary tubes (Poiseuille’s law) are expressed by the formula $Q = \frac{(P_1 - P_2)r^4}{8\mu l}$, in which $Q$ is the volume flow, $P_1$ and $P_2$ are the pressures at the two ends of the tube, $r$ is the radius, $l$ the length, and $\mu$ the coefficient of viscosity. In the body the two latter functions tend to be constant and since the blood vessels are not rigid, the formula does not apply quantitatively even to flow in the large vessels. For purposes of simplification a rough expression of the conditions existing in the veins may be achieved by combining the constants ($8\mu l$, $r^4$, and $l$) and substituting for $r^4$ a value ($R$) related to the radius but not necessarily a fixed exponent thereof. The formula then becomes $Q = K(P_1 - P_2)R = KRP_1 - KRP_2$. It is apparent that the flow of blood into the atrium from the veins will depend on the difference in pressure and on the radius of the veins. If the latter factor remains constant, the atrial inflow will be increased by a rise in peripheral venous pressure and will be diminished by a rise in atrial pressure. If the pressures remain constant, the flow will be markedly affected by alterations in the cross-sectional diameter of the veins. The increase in size of the vascular system accounts for the difference in the cardiac output of an infant and an adult with the same venous and atrial pressures. When the filling of the atria and ventricles from the venous system is considered, it is apparent that Poiseuille’s law is not applicable because one is no longer dealing with flow through rigid tubes but with flow into expandable chambers. However, the principle that certain factors (corresponding to $KRP_1$) tend to increase filling and others (corresponding to $KRP_2$) tend to decrease it is still valid.

The failure to find a strict parallelism between venous pressure and cardiac output has been noted by others in studies on man and has led some to question the validity of the Starling concept of the relation between the filling and the output of the heart. However, certain differences between the heart-lung preparation and the intact animal should be considered.

In the heart-lung preparation the pulse rate and the peripheral resistance are artificially fixed, while in the intact animal these functions are variable. Thus the adjustment of cardiac output to muscular exercise appears to be accomplished not only by increase in heart rate but also by decline in peripheral resistance. The latter adjustment makes it possible for the heart to empty more completely during systole and hence to expel a greater volume per beat without increase in diastolic size or energy expended. The decline in the volume of blood in the ventricle at the onset of diastole will result in reduction of the ventricular diastolic pressure ($P_2$ in Poiseuille’s formula) and hence will cause increased filling if other factors remain constant.

In the heart-lung preparation the venous reservoir is connected to the heart by relatively inflexible rubber tubing and hence the inflow into the heart will tend to vary directly with the height of the venous reservoir. In the intact animal the veins are readily distensible and any change in their radius ($r$ in Poiseuille’s formula) will be reflected by a marked difference in filling if other factors remain constant.

These considerations make it clear that the conditions affecting diastolic inflow (and hence systolic output) are more complex in the intact animal than in the heart-lung preparation. The tendency to fill, i.e., the amount of blood “offered” the heart from the venous system, depends, in the intact animal, not only on the venous pressure but also on the cross-sectional diameter of the veins. However, the actual filling will depend, not only on these factors, but also on the pressure existing within the cardiac chambers during filling, i.e., on the atrial and ventricular diastolic pressures. Because of the large size of the atrioventricular orifices these pressures may be considered as being essentially identical.

The dynamics of ventricular filling may be simplified by grouping together the factors which tend to increase and decrease this func-
tion, respectively. One may therefore use the term "inflow load" (KRP; above) to designate the tendency of the ventricle to fill or the amount of blood offered the ventricle.* The inflow load may be defined as the amount of blood which would enter the ventricle during dia-
stole if the ventricular diastolic pressure remained at zero throughout diastole. However, the ven-
tricular diastolic pressure does not so behave. At the onset of diastole its level depends on 
the amount of residual blood, i.e., on the com-
pleteness of emptying of the previous systole. 
As blood enters the ventricle during diastole 
the pressure rises. Any increment of ventricular 
diastolic pressure causes impairment of filling 
(corresponding roughly to KRP; above) and 
hence is immediately reflected in a rise in 
atrial pressure. The actual filling of the ven-
tricle therefore varies directly with the inflow 
load and inversely with the ventricular dia-
static pressure. As a rough and qualitative 
approximation of conditions in the body, Poi-
seille's formula may be modified and written 
as follows: Ventricular Filling = Inflow Load— 
Ventricular Diastolic Pressure.

When the original Starling curve and the 
rather similar curve as obtained in these ex-
periments (fig. 2) are examined in relation to 
these concepts, certain points emerge. (1) In 
the heart-lung preparation it is justifiable to 
consider venous pressure as a direct index to 
inflow load because the rubber tubing con-
necting the venous reservoir is relatively rigid. 
(2) In the intact animal the veins are readily 
distensible and an initial slight rise in venous 
pressure will tend to cause increase in their di-
ameter, while at high levels of venous pressure 
the veins are already fully distended and fur-
ther slight increment of pressure will cause little 
or no increase in venous diameter. Hence a lin-
ear relationship between inflow load and ven-
ous pressure does not exist in the intact animal. 
If other factors remain constant, minimal rise 
from the normally low level of venous pressure

* The term "venous load" is simpler and might 
seem preferable but has one important defect. Aortic 
and pulmonic insufficiency are states which tend to 
increase the inflow load without necessarily in-
creasing the venous load. The term "inflow load" will therefore be employed in the discussion to follow.

will tend to be reflected in large increments in 
cardiac output (table 1, fig. 2) but at high levels 
of venous pressure further increment will have 
little effect (fig. 2). (3) The plateau at the ter-

pical portion of the curve in figure 2 is not found 
in the heart-lung preparation and is presumably 
due to the intactness of the pericardium.

In the experiments reported in this study 
the heart at first responded to the increase in 
inflow load produced by the infusion by a 
well-marked increment in output. As the 
load was further increased the response became 
less marked and eventually the heart failed 
to respond further but actually pumped less 
blood than before. Since, over any significant 
period of time, the inflow and the output are 
necessarily the same, it is clear that the decline 
of output of the ventricles was necessarily as-
associated with decline of inflow. It is clear from 
the preceding discussion that such a decline 
of inflow in the presence of a steadily rising 
inflow load must have been induced by an 
increasing hindrance to filling, i.e., by a rise 
in the ventricular diastolic pressure. This in 
turn could have been only due to diminished 
completeness of systolic emptying and it is 
noteworthy that this occurred at a time when 
the actual cardiac output was markedly eli-

The sequence of events as portrayed in figure 
2 was evidently as follows. During the initial 
phase of the infusion the infusate was evi-
dently relatively evenly distributed through-
out the venous system, the diastolic volume 
of the ventricle increased sharply with rela-
tively little increase in systolic volume. (In 
fact it would appear that the systolic volume 
and the initial ventricular diastolic pressure 
may have diminished in those experiments in 
which the peripheral venous pressure rose more 
rapidly than the auricular pressure.) At a later 
stage of the infusion the systolic volume 
evidently increased at about the same rate 
as the diastolic volume and the cardiac output 
tended to remain relatively constant despite 
the rising venous pressure. At this time the 
rise in ventricular diastolic pressure was re-
lected in a sharp rise in atrial pressure so that 
the femoral-atrial pressure difference decreased
The hemodynamic defect responsible for heart failure in these experiments is therefore clear. Heart failure occurred when cardiac output failed to keep pace with inflow load and this discrepancy was brought about by decline in filling consequent to increase in ventricular diastolic pressure. The increase in ventricular diastolic pressure was evidently due to passive cardiac dilatation as the result of incomplete systolic emptying, even though the actual systolic output was much greater than normal. The experiments illustrate that the degree of systolic emptying and the systolic output may vary in opposite directions.

Although the venous pressure rose steadily while the infusion was maintained, differences occurred in the rate of rise in different parts of the venous system. Initially the increment in the femoral vein was the same as or slightly greater than that in the right atrium. Soon, however, the pressure began to rise more rapidly in the atrium than in the periphery. Since it is generally agreed that heart muscle lac's tone (in the sense of active resistance to filling), such a sequence seems to indicate that blood was accumulating in the atrium at a faster rate than in the veins. This points to some factor causing hindrance to atrial emptying and this was evidently the rise in ventricular diastolic pressure.

Thus there were two factors responsible for rise in atrial and venous pressure in the experiments. One of these was the increase in blood volume which was the chief quantitative determinant, i.e., the chief factor responsible for the absolute values of venous pressure. The other was alteration in blood distribution with a relative shift toward the heart and away from the periphery. This was apparently the result of rise in ventricular diastolic pressure and was the chief qualitative determinant, i.e., the factor responsible for the difference in the degree of rise in pressure in the central and peripheral portions of the venous system. Since it has been amply demonstrated that increase in blood volume,1 12 13 decrease in veno-atrial pressure difference,9 and increase in ventricular diastolic pressure14 15 occur in patients with congestive heart failure, it would appear likely that the same quantitative and qualitative determinants of venous pressure are operative in such individuals. Whether or not a third factor, increase in venous tone, which has been thought to be operative in causing increase in venous pressure in patients with heart failure16 was operative in these experiments is uncertain from the data.

Some Possible Relationships between the Experimental Findings and Heart Failure in Patients

It is now generally agreed that while most patients with congestive heart failure exhibit decline in the cardiac output per minute, this function may be normal or even increased.2 3 17 Hence the old conception that the manifestations of heart failure are to be ascribed to absolute decline in output is no longer considered valid. However, the idea that heart failure is necessarily associated with inadequacy of output relative to the needs of the body17 18 is widely accepted and is supported by much recent evidence.

Inadequacy of cardiac output relative to metabolic needs cannot be considered the fundamental hemodynamic disturbance responsible for heart failure produced by massive infusion. Here heart failure is accompanied not only by absolute increase in cardiac output but also by increase in output relative to oxygen consumption. Two alternative conclusions are possible. The first is that heart failure is of more than one basic type and that the different types have fundamentally different mechanisms. The second is that there may be a mechanism common to all heart failure but that this mechanism is not inadequacy of cardiac output relative to metabolic needs. The latter hypothesis may now be considered.
It has been pointed out that experimental hypervolemic heart failure (table 1, fig. 2) was regularly associated with inadequacy of cardiac output relative to inflow load and evidence has been cited for the opinion that the discrepancy was dependent on rise in ventricular diastolic pressure. The question arises as to whether similar mechanisms may be concerned in all types of heart failure.

Studies with the catheter method in general agreement in indicating that right ventricular diastolic pressure is elevated in patients with systemic congestion. Measurements of left ventricular pressure are as yet few but such as have been made have indicated elevation in patients with pulmonary congestion and this is supported by the more numerous studies which have shown elevation of pulmonary arterial and right ventricular systolic pressures in such patients with left-sided heart failure. One might therefore be tempted to draw the conclusion that failure of the left and right sides of the heart is always associated with elevation of diastolic pressure in the corresponding ventricle. Such a conclusion would be true in most patients but would in all probability be incorrect when applied to heart failure in general.

The literature does not seem to contain any references to measurements of ventricular diastolic pressures in patients with advanced stenosis of the corresponding atrioventricular orifices. Nevertheless, there is good, although indirect, evidence that such pressures are not elevated and may actually be reduced. In contrast to the marked dilatation and hypertrophy of the remaining cardiac chambers the left ventricle is sometimes found to be small and atrophic in patients with advanced mitral stenosis. Since it is very unlikely that the left ventricular diastolic pressure could be elevated in such patients, the concept of elevation of ventricular diastolic pressure as the least common denominator and the sine qua non of all heart failure is untenable.

Atrial pressure is of course elevated in patients with mitral and tricuspid stenosis and one might be tempted to conclude that elevation of atrial pressure is present in all patients with heart failure. However, such is not necessarily the case in patients with combined failure of the heart and periphery. It is probably true that in the absence of coexisting peripheral failure (such as may result from excessive sodium depletion) heart failure is always associated with elevation of atrial pressure, but it would not be correct to say that the presence of such elevation is an absolute necessity for heart failure.

It has been pointed out that heart failure produced by experimental hypervolemia is characterized by inadequacy of output in relation to inflow load. Although complete data are not available, such data as exist concerning cardiac output, venous pressure, atrial pressure, intrathoracic blood volume, and size of the great veins as observed at the bedside and at the autopsy table suggest that a similar inadequacy exists in all instances of clinical heart failure.* The same discrepancy is found in that appearing in the heart-lung preparation whether occurring spontaneously or dependent on excessive peripheral resistance or due to excessive elevation of the venous reservoir. The same discrepancy exists when heart failure appears suddenly as the result of temporary or lasting disturbances of rhythm; although quantitative studies are lacking, the clinical evidence of reduction in output despite prominence of the neck veins appears conclusive in these circumstances.

Increase in inflow load alone cannot be regarded as evidence of heart failure, for this occurs in normal persons during physical exercise and apparently in many diseases such as febrile illnesses, thyrotoxicosis, and anemia.†

* Since heart failure due to severe anemia may be accompanied by decline rather than increase in blood volume, it might be considered that the inflow load is not increased under such circumstances. However, the inflow load is related not to the total blood volume but to the volume of blood in the great veins and these are distended in such patients, as has been pointed out by McMichael. The active constriction of the peripheral venocapillary bed which appears to be present in patients with severe anemia apparently tends to increase inflow load by causing a shift of blood to the central portions of the venous system.

† The evidence that inflow load is increased in these conditions is not based on quantitative measurements but on clinical findings of prominence of the large veins. The increase in cardiac output could
Decline in cardiac output alone does not signify heart failure for this is the classical hemodynamic disturbance of peripheral circulatory failure. The available evidence indicates, therefore, that the invariable and fundamental hemodynamic disturbance of heart failure is decline in output relative to inflow load or, conversely, elevation of inflow load in relation to cardiac output.

The question naturally arises as to whether, aside from the fundamental discrepancy between inflow load and output, the type of heart failure induced in animals by massive infusions bears any similarity to clinical states. Patients with acute nephritis and desoxycorticosterone intoxication may display the classical signs of increased cardiac output (accentuation of the heart sounds, moderate tachycardia, bounding pulse, elevation of pulse pressure) even when cardiac failure is present. However, such signs are not always encountered; other factors such as hypertension or myocardial lesions are usually present, and in any case actual measurements of cardiac output are lacking in such states. Heart failure is frequently precipitated in elderly subjects by the too zealous administration of fluids. In such instances the hypervolemia is rarely if ever the sole factor; pre-existing hypertension or senile heart disease is nearly always present even though asymptomatic.

The most common example of hypervolemia as a precipitating cause of heart failure is acute pulmonary edema. Such attacks are now believed to be in many instances due to the nocturnal reabsorption in the recumbent position of excess fluid accumulated during the day in the upright position.\textsuperscript{21, 22} However, the hypervolemia is not the sole (or even the main) causative factor; valvular lesions, hypertension, or myocardial disease is always also present.

It will be evident from the foregoing discussion that primary hypervolemia, while a frequent cause of heart failure when occurring in conjunction with other cardiac disorders, rarely if ever causes heart failure in the absence of coexisting disturbances which either increase the burden on the myocardium or injure it directly.

Hypervolemia as a cause should not be confused with hypervolemia as a result of heart failure. Chronic congestive failure is usually associated with an increase in blood volume,\textsuperscript{1, 12, 13} the mechanism of which remains obscure. This secondary hypervolemia may be compensatory in the sense of serving to elevate inflow load and hence to maintain cardiac output (provided the heart is in a functional state corresponding to the left or ascending limb of the Starling curve); it is also frequently harmful in tending to aggravate the congestive phenomena. The clinical improvement induced by reduction of blood volume consequent to venesection or diuretic drugs illustrates the harmful effects of this compensatory mechanism.

Primary hypervolemic heart failure is one example of the condition which McMichael and Sharpey-Schafer\textsuperscript{5} have designated high-output failure. Other examples of high-output failure are disorders associated with primary disturbances in tissue oxidative processes (cor pulmonale with arterial anoxia, anemia, thyrotoxicosis, beriberi) and arteriovenous shunts. It would appear that the mechanism common to these several disorders is primary increase in inflow load.

\textbf{The Classification of Heart Failure}

The clinical classification into forward and backward types according to whether the dominant manifestations are mainly those of a shocklike state or of congestion has the advantages of simplicity and of often furnishing a guide to treatment. Among the disadvantages of such a classification are: (1) the confusion which may arise concerning forward failure because of the lack of comprehension of the distinction between the degree of systolic emptying and the actual stroke volume (see above), (2) the fact that all heart failure which is not complicated by coexistent peripheral failure is fundamentally backward in the sense of

also be induced by decline in peripheral resistance with consequent increased degree of systolic emptying, diminished residual blood, and reduction of ventricular diastolic pressure. The relative importance of the two mechanisms in causing the rise in cardiac output is uncertain at present.
### Table 2.—Classification of the General Circulatory Disorders

<table>
<thead>
<tr>
<th>Fundamental Mechanisms</th>
<th>Common Synonyms</th>
<th>Major Subgroups</th>
<th>Examples</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Primary Disorders of Cardiac Filling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Primary deficiency of inflow load</td>
<td>Peripheral circulatory failure. Shock</td>
<td>1. Defective blood volume (hematogenic shock)</td>
<td>Hemorrhage, trauma, dehydration</td>
<td>Blood volume too small for peripheral vascular bed, consequent deficiency of venous return</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Increased size of peripheral bed (neurogenic and vasogenic shock)</td>
<td>Emotional syncope, postural syncope</td>
<td></td>
</tr>
<tr>
<td>II. Primary excess of inflow load with adequate systolic emptying</td>
<td>Overactive heart. Hyperkinetic syndrome.</td>
<td>1. Disturbances in tissue oxidative processes</td>
<td>Thyrotoxicosis, anemia, beriberi,</td>
<td>Elevation of inflow load with parallel elevation of cardiac output</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Arteriovenous A-V fistula, patent ductus arteriosus</td>
<td>A-V fistula, patent ductus arteriosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Primary hypervolemia</td>
<td>Acute nephritis, rapid infusions</td>
<td></td>
</tr>
<tr>
<td>III. Primary excess of inflow load with inadequate systolic emptying</td>
<td>High output failure</td>
<td>As above</td>
<td>As above. Also many instances of acute pulmonary edema</td>
<td>Elevation of inflow load without corresponding elevation of cardiac output. (Myocardial disease or resistance to emptying usually also present)</td>
</tr>
<tr>
<td>IV. Mechanical hindrance to ventricular filling</td>
<td>Mechanical (i.e., nonmyocardial) heart failure</td>
<td>1. Cardiac Tamponade</td>
<td>Pericardial effusion</td>
<td>Digitalis resistant heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Stenosis of atrioventricular valves</td>
<td>Constrictive peri-carditis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3. Rarer conditions</td>
<td>Mitral stenosis</td>
<td></td>
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<td></td>
<td></td>
<td>Ball valve thrombus</td>
<td>Auricular tumors</td>
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<tr>
<td><strong>B. Primary Disorders of Cardiac Emptying</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Primary increase in resistance</td>
<td>Acute cor pulmonale</td>
<td>Pulmonary embolism</td>
<td>Collapse marked; congestion slight</td>
<td></td>
</tr>
<tr>
<td>a. Rapid onset without secondary hypervolemia</td>
<td>1. Resistance at semilunar orifices</td>
<td>Aortic stenosis</td>
<td>Congestion marked; collapse absent or minimal</td>
<td></td>
</tr>
<tr>
<td>b. Slow onset with secondary hypervolemia</td>
<td>2. Resistance in aorta</td>
<td>Coarctation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Resistance in arterioles</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Primary decline in myocardial function</td>
<td>Sudden death</td>
<td>1. Asystole</td>
<td>Ventricular fibrillation or standstill</td>
<td>Forward failure of the heart; collapse marked, congestion slight</td>
</tr>
<tr>
<td>a. Rapid onset without secondary hypervolemia</td>
<td>Cardiac syncope</td>
<td>2. Sudden brady-cardia</td>
<td>Adams-Stokes seizures</td>
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<td></td>
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<td></td>
<td>Carotid sinus syncope</td>
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<tr>
<td></td>
<td></td>
<td>Cardiac collapse</td>
<td>Auricular fibrillation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Ectopic tachycardia</td>
<td>Myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>
Table 2—Concluded

<table>
<thead>
<tr>
<th>Fundamental Mechanisms</th>
<th>Common Synonyms</th>
<th>Major Subgroups</th>
<th>Examples</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Slow onset with secondary hypervolemia</td>
<td>Myocardial insufficiency; classical heart failure</td>
<td>1. Inflammatory 2. Degenerative</td>
<td>Myocarditis  Senile heart disease; coronary arteriosclerosis</td>
<td>Backward failure; congestion marked; collapse minimal or absent</td>
</tr>
</tbody>
</table>

C. Mixed Types

Defective filling of one ventricle with defective emptying of the other
Excess inflow load on one ventricle with defective emptying of the other
Deficient systolic emptying plus deficient inflow load

Deficiency of inflow load (A.I., table 2) could be subdivided into: (1) with adequacy of systolic emptying (i.e., the usual types of peripheral failure when not complicated by myocardial failure) and (2) without adequacy of systolic emptying (i.e., advanced peripheral failure complicated by heart failure as the result of prolonged deficiency of coronary flow). Similarly there should theoretically be a disorder characterized by primary excess of cardiac emptying. Definitive evidence that such a disorder exists is lacking.

The starting point of this discussion was the observation that heart failure may exist independently of absolute decline in cardiac output or of decline relative to the metabolic needs. It was pointed out that in the absence of coexisting disorders of the peripheral circulation myocardial failure is always associated with elevation of ventricular diastolic pressure and consequent elevation of atrial pressure. This elevation of ventricular diastolic pressure is due to incomplete systolic emptying which is commonly caused by a decline in stroke volume. However, under certain conditions (e.g., primary increase in inflow load as exemplified by heart failure due to excessive infusion) the decline in systolic emptying may occur despite a normal or elevated level of stroke volume. The sine qua non of myocardial failure is therefore to be found not in the cardiac output but in the completeness of the cardiac elevation of atrial pressure, (3) the mistaken assumption that the term backward failure implies that the congestive phenomena are entirely the direct result of "back pressure" when actually hypervolemia is the more important cause, and (4) the coexistence of the two states.

The topographic classification of heart failure recognizes pericardial (tamponade), myocardial, and endocardial types. The difficulty with this classification is that while the pericardial and myocardial types each have distinctive mechanisms (primary failure of diastolic filling and primary failure of systolic emptying, respectively) no such unity exists for the various disorders of the endocardium. Thus resistance to emptying, excessive filling, and resistance to filling represent the essential mechanisms of aortic stenosis, aortic insufficiency and mitral stenosis, respectively.

A physiologic classification of heart failure should have the advantage of emphasizing the fundamental mechanisms and hence of furnishing a guide to management. Such a classification based on the general principles which have been discussed in this communication is presented in table 2. For the sake of clarity the other major general disturbances of the circulation are included, but disturbances involving local areas only (hemorrhage, thrombosis, embolism, and the like) are omitted. It should be noted that the classification as presented in table 2 is not all-inclusive. Thus primary
emptying, i.e., in the degree of dilatation and the degree of rise in the intracardiac pressures.*

All heart failure is not myocardial, however. When the pericardium is at fault, the defect is not in emptying but in filling and the rise in pressure in the ventricle presumably first appears not at the beginning but at the end of diastole. When certain types of endocardial disease (stenosis of the atroventricular valves) are present, the atrial pressure may be elevated despite normal or low values for the ventricular diastolic pressure. The conclusion that increased atrial pressure is invariably present in heart failure is, however, invalid; such need not be the case when cardiac and peripheral failure coexist.

All of the available information, whether obtained by quantitative measurement or by simple clinical observation, indicates that these various types of heart failure are uniformly attended by defective output in relation to inflow load. This concept appears to be equally applicable to the heart-lung preparation, to the patient dying suddenly of ventricular fibrillation, to individuals with acute or chronic congestive heart failure. Pending additional and more complete knowledge it appears justifiable to define heart failure as a condition in which the cardiac output is inadequate in relation to the filling load.

**Summary**

1. A group of experiments is described in which dogs were infused rapidly with large volumes of fluid. The atrial and femoral venous pressures rose steadily during infusion; the cardiac output rose to a peak and then dropped. The gradient of pressure along the veins decreased progressively during the infusion.

2. It is concluded that the hemodynamic defect in primary hypervolemic heart failure is the heart's inability to respond to an increasing filling load beyond a certain point.

3. Filling in the heart-lung preparation is contrasted to that of the whole animal. From considerations concerned with the flow of fluids through tubes it is concluded that the diameter of the veins has more influence than the venous pressure on volume flow, and that the intact animal differs from Starling's heart-lung preparation not only in respect to varying peripheral resistance but also in that the veins may vary in diameter. This is illustrated by the experiments in which only a rough correlation exists between venous pressure and cardiac output. It is suggested that the concept of inflow load, incorporating venous pressure and venous diameter, supplant that of venous pressure as the stimulus to changes in stroke output of the heart.

4. The actual flow into the ventricle depends on the relationship between the inflow load and the ventricular diastolic pressure. Thus a decline in the latter function may occur when diminished peripheral resistance leads to increased systolic emptying and under such circumstances increased inflow and output may occur with constant inflow load.

5. It is pointed out that if ventricular diastolic pressure rises, the inflow load must increase to keep the inflow and output the same. In addition, it is emphasized that rise of ventricular diastolic pressure is a consequence of incomplete emptying of the ventricle and excessive residual blood, and that this may occur not only when the cardiac output is low but also when the cardiac output is high. It is suggested that the only hemodynamic disturbance constant to all types of heart failure is that the cardiac output is reduced relative to the inflow load.

6. It is pointed out that hypervolemia may be either primary and a cause of cardiac failure or, much more commonly, secondary and a result of heart failure.

7. The point is made that in states of myocardial failure the rise in ventricular diastolic pressure necessarily results in a distributional shift of blood from the peripheral toward the central portions of the venous system.

8. The relationship between blood volume
and venous pressure is considered. If venous tone remains constant, the venous pressure is determined by total blood volume and by blood distribution.

9. On the basis of these considerations a physiologic classification of heart failure and other circulatory disturbances is presented. This classification attempts to consider the circulatory disturbances from the standpoint of primary alterations in filling and emptying of the heart respectively.

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