Studies on Cardiac Output to Blood Volume, and Renal Circulation in Chronic Congestive Heart Failure

MASAHIKO KINOSHITA

Blood volume and cardiac output were determined in patients with chronic congestive heart failure by indicator dilution method with radiocardiography (RCG). Blood volume was increased in patients of Class III and IV (New York Heart Association), and many finding supported the conclusion that the blood volume played the role of a regulatory mechanism whereby the organism compensates for a lowered cardiac output. The ratio of cardiac output to blood volume, easily calculable from RCG, appeared to indicate the "severity index" of the chronic congestive (right-sided) heart failure. ADH and aldosterone were highly sensitive to the change in blood volume, a fact that indicates that there operates a physiological response to volume change in chronic congestive heart failure. Renal plasma flow had a positive correlation with cardiac output, and showed a lower value in cases with high venous pressure for the same cardiac output.

The pathogenesis of the chronic congestive heart failure has been discussed by many authors. In 1908 Starling proposed the "backward failure theory", that failing heart was held to cause the blood to back up, increasing the venous pressure and thereby the capillary blood pressure; this provoked the transudation of fluid from the capillaries with consequent reduction of the volume of circulating plasma. This, in turn, promoted the kidney to reabsorb more than usual quantities of sodium salts and water. Maekawa, in favor of the backward failure theory, reported that the basic impairments in chronic congestive heart failure were due to the elevation of the ventricular end-diastolic pressure.

In 1944 Warren and Stead proposed a reversed hypothesis of the above theory. They called their theory "forward failure theory". The basis for this hypothesis is the presence in heart failure of inadequate cardiac output. According to the theory, the impaired renal excretion is related to the reduced cardiac output with consequent reduction in renal blood flow. This leads to a similar retention of sodium and water, resulting in the expansion of the circulating plasma volume. However, the final theory remains to be established.

In the initial phase of heart failure, there should be reduced cardiac output if the forward failure theory is true, and there should be reduced blood volume if backward failure theory is true. However, whether such an initial transient phase exists over measurable spans of
time is a matter of conjecture. In the present study transient alterations in blood volume were observed when the cardiac output was changed by the administration of digitalis and/or diuretics. Reduced or increased "activities" in aldosterone and ADH could be explained on the basis of the change in blood volume. It seems that homeostatic mechanisms are operative in heart failure in that blood volume is expanded by increased "activities" of aldosterone and ADH, and that this increase in blood volume plays a compensatory role in the face of reduced cardiac output.

METHODS AND MATERIALS

Blood volume was determined with a total of 138 measurements in 87 subjects ranging from 18 to 78 years in age, 20 of whom were normal controls. Out of sixty-seven patients with chronic congestive heart failure, 26 suffered from mitral valvular disease, 3 congenital heart disease, 8 aortic stenoinssufficiency, 17 hypertensive and arteriosclerotic heart disease, and 19 the other various heart diseases. The functional capacity of the heart was classified into 4 by appraising the patient's ability to perform physical activity according to the classification by the Criteria Committee of the New York Heart Association (N.Y. H.A.)³. The patients consisted of 7 cases of Class I, 36 of Class II, 40 of Class III, and 35 cases of Class IV.

Eighty-one radiocardiograms (RGG) were taken to determine cardiac output stroke volume and the ratio of cardiac output to blood volume (CO/BV) in 58 subjects ranging from 19 to 78 years in age. Fourteen patients suffered from mitral stenosis, 4 mitral stenoinssufficiency, 8 aortic valvular disease, 2 hypertensive and arteriosclerotic heart disease and 16 the other various heart diseases. They consisted of 4 cases of Class I, 43 of Class II, 17 of Class III and 3 of Class IV. Fourteen subjects were determined as normal controls, ranging from 18 to 25 years of age.

Blood volume was determined with dilution method, using serum albumin¹¹¹I (RISA). The stock solution was diluted to a concentration of about 0.5 microcuries per milliliter in normal saline under sterile conditions. Of the diluted solution, 1 ml was further diluted to 50 ml of which one ml was used as the standard. Plasma volume was determined in subjects at bed rest in the fasting state. Ten ml of the diluted RISA solution was injected with calibrated syringe in the antecubital vein. Ten minutes after the injection of the isotope, approximately 6 ml of the blood was drawn from the contralateral arm. The blood was delivered into a heparinized test tube and centrifuged immediately and then 1 or 2 ml of plasma was counted for two minutes in a Metrowell type counter. The hematocrit of venous blood was read from duplicated samples after centrifugation at 10,000 r.p.m. for five minutes. A correction factor for trapped plasma, 0.967 was used. The calculation was made as follows;

\[
\text{plasma volume} = \frac{\text{counts per ml per min (standard)} \times 100 \times \text{vol. inj.}}{\text{counts per one ml per min}} \times 50 \times \text{dil. fact.}
\]

\[
\text{blood volume} = \frac{\text{plasma volume}}{1 - 0.89 \times \text{venous hematocrit}}
\]

Red cell volume was measured by the modified method of STERLING and GRAY. To 20 ml of blood collected in 5 ml of modified A-C-D-solution, 30–40 microcuries of sodium chromate were added. The preparation was incubated at 37°C for forty-five minutes with occasional mixing. At the end of incubation, 50 mg of ascorbic acid was added in order to reduce the free hexavalent ⁵¹Cr, thus preventing in vivo tagging. Free ⁵¹Cr was removed by washing the tagged cells with normal saline. This procedure of washing was repeated three times. Washed ⁵¹Cr tagged red cells were suspended in saline; this represents the standard. A measured volume of suspended tagged cells in saline was administered to the patients and the remaining portion was analyzed for radioactivity content to determine the concentration and value of the standard. Twenty or thirty minutes after the injection, approximately 6 ml of blood was drawn from the antecubital vein of the contralateral arm. The blood was delivered into a heparinized tube and one or two ml of the heparinized blood was pipetted into the test tube.

\[
\text{Red cell volume} = \frac{\text{total counts of injected ⁵¹Cr-erythrocytes}}{\text{counts per one ml erythrocyte of the sample}}
\]

Radiocardiogram (RGG) was taken in the resting supine position. Time activity curves were recorded by means of a scintillation counter with an aperture of 5 cm. The counter was set in place over the center of the heart shadow, usually at the 4th intercostal space at the left sternal border, at a distance of 1.5 cm from the skin. Pulses from the photomultiplier tube were amplified and fed into a counting rate meter and tape recorders. The output of the rate meter was fed into a two channel galvonometer recorders. The response both of the ratemeter and the recorder was linear. A paper speed of 2 mm per se-

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cond was used for recording the curves. The rat-
ometer time constant was set at 0.4 second. Under
sterile conditions RISA was diluted so that 10 to 20
microcuries of $^{131}$I were contained in 1.0 ml of solu-
tion. The tuberculin syringe was adjusted to deliver
1.0 ml, and was connected via a three-way stopcock.
1.0 ml of the RISA was injected into the antecubital
vein and immediately after, flushed with 10 ml saline
solution. When distribution of the tracer in the cir-
culation became uniform (approximately 7–10 minutes),
5–6 ml of venous blood was drawn into a syringe
simultaneously, a precordial counting rate was re-
corded. One milliliter of plasma was obtained from
the blood sample. A volume of RISA solution equal
to that injected for a single curve was quantitatively
diluted with distilled water (1/1000) and duplicate
1 ml samples were assayed. The injected activity
was thus obtained as counts per minutes. Cardiac
output could be derived from Veall's and Huf's
formula:
\[
\text{cardiac output} = \frac{E}{A} \times \text{blood volume}
\]
where E is the equilibrium recording, A is the inte-
grated area under the time-activity curve, and the
ratio of cardiac output to blood volume equals that
of E to $^{10,11,12}$. Renal plasma flow (RPF) and glo-
merular filtration rate (GFR) were measured by
para-aminohippurate and thiosulfate clearance tech-
nics$^{10}$, respectively, and in part, RPF was calculated
by renogram simulation$^{13}$.

## Results

Normal Blood Volume and Cardiac Output.

The observed normal values for blood volume
and plasma volume are summarized in Table I.
The mean and standard deviation of blood volume
and plasma volume are $2.43 \pm 0.25 \text{L/M}^2$ of body
surface area and $1.52 \pm 0.15 \text{L/M}^2$, respecti-
vely, for normal adults, ranging from 20 years of age to 53.
The mean and standard
deviation of the cardiac index, stroke index and
the ratio of cardiac output to blood volume are
$4.13 \pm 0.45 \text{L/min/M}^2$, $64.2 \pm 6.9 \text{ml/beat/M}^2$,
and $1.52 \pm 0.27$, respectively, for normal sub-
jects, ranging from 18 years of age to 25.
(Table II)

Blood Volume and Cardiac Output in Congestive Heart Failure.

The average mean values and standard de-
viation of blood volume, cardiac index, stroke
index, and the ratio of cardiac output to blood
volume are summarized in Table II. As shown
in Fig. 1, blood volume in Class III and IV are
significantly higher than in Class I and II. There
is no significant difference of blood volume
between Class I and II, and also between

### Table I

<table>
<thead>
<tr>
<th>Blood Volume</th>
<th>B. V. (mean) ml</th>
<th>B. V. ml/KG</th>
<th>S. D.</th>
<th>C. V. %</th>
<th>B. V. L/M²</th>
<th>S. D.</th>
<th>C. V. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (20 cases)</td>
<td>3695</td>
<td>71.0</td>
<td>8.9</td>
<td>12.5</td>
<td>2.43</td>
<td>0.25</td>
<td>10.3</td>
</tr>
<tr>
<td>Male (11 cases)</td>
<td>4012</td>
<td>71.5</td>
<td>9.5</td>
<td>13.5</td>
<td>2.53</td>
<td>0.28</td>
<td>11.0</td>
</tr>
<tr>
<td>Female (9 cases)</td>
<td>3309</td>
<td>70.5</td>
<td>9.8</td>
<td>12.5</td>
<td>2.31</td>
<td>0.28</td>
<td>12.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma Volume</th>
<th>P. V. (mean) ml</th>
<th>P. V. ml/KG</th>
<th>S. D.</th>
<th>C. V. %</th>
<th>P. V. L/M²</th>
<th>S. D.</th>
<th>C. V. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (20 cases)</td>
<td>2277</td>
<td>44.2</td>
<td>6.3</td>
<td>14.3</td>
<td>1.52</td>
<td>0.15</td>
<td>9.8</td>
</tr>
<tr>
<td>Male (11 cases)</td>
<td>2594</td>
<td>43.8</td>
<td>6.7</td>
<td>15.3</td>
<td>1.52</td>
<td>0.09</td>
<td>5.9</td>
</tr>
<tr>
<td>Female (9 cases)</td>
<td>2143</td>
<td>45.8</td>
<td>6.2</td>
<td>13.4</td>
<td>1.52</td>
<td>0.20</td>
<td>13.1</td>
</tr>
</tbody>
</table>

$B. V.$: Blood volume  
$P. V.$: Plasma volume  
$C. V.$: Coefficient of variation

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Class II and IV. (Fig. 1) Fig. 4 shows the relation between plasma volume and red cell volume (determined by $^{51}$Cr-labeled erythrocyte as indicator). Both plasma and red cell volume are within normal limits in Classes I and II, but increase in Classes III and IV.

Resting cardiac index is normal in cases of Class I, normal or decreased in Class II, and decreased in almost all cases of Classes III and IV. (Fig. 2) The cases of Class II with sinus rhythm, on the average, show a higher cardiac index than those with atrial fibrillation. However, stroke indices are, on the average, already slightly decreased in Class I and still more so as the Class advances from II to IV. (Fig. 3) More statistically significant difference occurs among different Classes of N.Y.H.A. classification with regard to CO/BV than with regard to cardiac output and blood volume. CO/BV values are: 1.52 (range: 1.96 to 1.02) in control group, 1.48 (1.82 to 1.12) in Class I, 1.06 (2.23 to 0.40) in Class II, 0.73 (1.06 to 0.32) in Class III, and 0.44 (0.53 to 0.26) in Class IV. (Fig. 5) The difference between normal group and Class I is not significant. Although the value of CO/BV is, on the average, significantly lower in Class

<table>
<thead>
<tr>
<th>Blood Volume (L/M$^2$)</th>
<th>Cardiac Index (L/minute/M$^2$)</th>
<th>Stroke Index (ml/beat/M$^2$)</th>
<th>Cardiac Output Blood Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>S.D.</td>
<td>mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>Control</td>
<td>2.43</td>
<td>0.25</td>
<td>4.14</td>
</tr>
<tr>
<td>Class I</td>
<td>2.72</td>
<td>0.25</td>
<td>4.08</td>
</tr>
<tr>
<td>Class II</td>
<td>2.74</td>
<td>0.45</td>
<td>3.01</td>
</tr>
<tr>
<td>Class III</td>
<td>3.20</td>
<td>0.45</td>
<td>2.33</td>
</tr>
<tr>
<td>Class IV</td>
<td>3.41</td>
<td>0.56</td>
<td>1.54</td>
</tr>
</tbody>
</table>

S.D.: Standard Deviation

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Fig. 1. Relation between blood volume and functional capacity of the heart represented by the classification of New York Heart Association. Horizontal bars indicate the mean value.

Fig. 2. Relation between cardiac index and functional capacity of the heart represented by New York Heart Association. Horizontal bars indicate the mean value. Dark and light spots indicate the cases with sinus rhythm and atrial fibrillation, respectively.

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II than in Class I, it is scattered from normal range to low values in Class II. All patients of Classes III and IV show decreased values of CO/BV, to a greater extent in Class IV than in Class III. (Fig. 5)

The correlations of blood volume with cardiothoracic ratio (C.T.R.), venous pressure (VP), the change in venous pressure (ΔVP) and cardiac index are shown in Fig. 6, 7, 8, and 9, respectively. A fairly close correlation occurs between blood volume and C.T.R. (r: 0.54 p < 0.01). There is a gross correlation between blood volume and venous pressure (r: 0.36 p < 0.01), and a decrease in venous pressure is observed in most patients with heart failure when blood volume is decreased by therapy. (Fig. 8) Two patients showed elevated venous

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**Fig. 3.** Relation between stroke index and functional capacity of the heart represented by the classification of New York Heart Association. Dark and light spots indicate the cases with sinus and atrial fibrillation, respectively.

**Fig. 4.** Relation between plasma volume and red cell volume. Each class is due to functional capacity by New York Heart Association.

**Fig. 5.** Relation between the ratio of cardiac output to blood volume and functional capacity of the heart represented by New York Heart Association. Horizontal bars indicate the mean value.
pressure after the occurrence of increase in blood volume, and the other two showed elevated venous pressure in spite of a decreased blood volume. As noted in Fig. 9, there are various relations between blood volume and cardiac index among different classes of N.Y.H.A. classification. The cardiac indices are highest in Class I and lowest in Classes III and IV. The cardiac indices in Class II are overlapped with those in Classes I and III. Patients of Class IV show higher blood volume than those of Class III for the same cardiac index. (Fig. 9) As shown in Fig. 10 and 11, there is no correlation between cardiac index and venous pressure, and between CO/BV and venous pressure. Cardiac and stroke indices are compared among various heart diseases in Fig. 12 and 13. In aortic insufficiency cardiac index is higher and stroke index slightly lower than in other heart diseases. In mitral insufficiency and combined valvular

Fig. 6. Relation between blood volume and cardiothoracic ratio. Correlation coefficient (r) is 0.54 (p<0.01).

Fig. 7. Relation between blood volume and venous pressure. Correlation coefficient is 0.36 (p<0.01).

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heart diseases, cardiac index is lower than in other heart diseases in the same Class. As indicated in Fig. 14 and 15, there is a close correlation between the CO/BV and build-up time (BT) and also between the cardiac index and BT, provided that it is less than 20 seconds. The regression line for CO/BV (Y) and BT (X) is \( Y = -0.1414X + 2.908 \) and for CI (Y) and BT (X), \( Y = -0.3465X + 7.380 \).

Fig. 10. Relation between cardiac index and venous pressure. There is no significant correlation between them.

Fig. 11. Relation between the ratio of cardiac output to blood volume and venous pressure. There is no significant correlation between them.
In Fig. 16 and 17 the cardiac and stroke in-

![Graph showing cardiac index in patients with various heart diseases.](image1)

**Fig. 12.** Cardiac index in patients with various heart diseases. Each class is due to functional capacity by New York Heart Association. Abbreviations, MS: Mitral stenosis, MSI: Mitral stenoinsufficiency, CVD: Combined valvular disease, AI: Aortic insufficiency, Non-Valv: Nonvalvular heart disease.

![Graph showing stroke index in patients with various heart diseases.](image2)

**Fig. 13.** Stroke index in patients with various heart diseases. Each class is due to functional capacity of the heart by New York Heart Association. Abbreviations, MS: Mitral stenosis, MSI: Mitral stenoinsufficiency, CVD: Combined valvular disease, AI: Aortic insufficiency, Non-Valv: Nonvalvular heart disease.

![Graph showing relation between the ratio of cardiac output to blood volume and build-up time.](image3)

**Fig. 14.** Relation between the ratio of cardiac output to blood volume and build-up time. A correlation coefficient is $-0.88$ ($p < 0.01$).

![Graph showing relation between cardiac index and build-up time.](image4)

**Fig. 15.** Relation between cardiac index and build-up time. A correlation coefficient is $-0.08$ ($p < 0.01$).

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Cardiac indices are compared among patients under various treatments. The cardiac indices are: 3.79 (range 5.01 to 2.70) among patients in com-

![Cardiac index graph](image)

Fig. 16. Cardiac index in cases with Dig (−), Dig (+), and Dig (+)+Diu (+). Horizontal bars indicate the mean value. Abbreviations, Dig (−): without digitalis treatment, Dig (+): with digitalis treatment, Dig (+)+Diu (+): with digitalis and diuretic treatment.

![Stroke index graph](image)

Fig. 17. Stroke index in cases with Dig (−), Dig (+), and Dig (+)+Diu (+).

![Blood volume graph](image)

Fig. 18. Relation between blood volume and pulmonary wedge pressure. Dark and light spots indicate the cases with mitral valvular and non-mitral valvular diseases, respectively. A correlation coefficient is 0.29 (0.01 < p < 0.05).

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compensation without digitalis and diuretics, 2.72 (4.27 to 1.39) among those in compensation with digitalis, and 1.73 (2.46 to 1.03) among those in compensation only with both digitalis and diuretics.

Fig. 18 and 19 show correlations between blood volume and mean pulmonary artery wedge pressure (mmHg) and between blood volume (L/M²) and mean right atrial pressure in patients with and without mitral valvular lesion. The former correlation coefficient (r) is 0.29 (0.05 < p < 0.1) and the latter, 0.63 (p < 0.01). Blood volume are varied, from high to low values, at low pulmonary wedge and low right atrial pressure in patients without mitral valvular lesion. Normal blood volume is often observed notwithstanding high pulmonary artery wedge pressure and is found in almost all of 15 cases showing right atrial pressure less than 5 mmHg notwithstanding pulmonary artery wedge pressure higher than 14 mmHg. This fact suggests that the volume receptor exists in the right rather than in the left atrium.

Effect of Treatment with Digitalis upon Blood Volume and Cardiac Output

Eight patients with heart failure were studied with rapid digitalisation (Table III). Cases Y.O., Z.Y. and K.S. had a marked peripheraledema and liver swelling with the average venous pressure of 241 mm H₂O and the other-
cases had liver swelling with the slight peripheral edema with almost normal venous pressure. Plasma volume was increased from 2105 ml to 2456 after 6 to 24 hours in case Y. O., and it was increased from 2870 ml to 3480 in case Z.Y., and the plasma volume of both cases then gradually returned to normal, concomitant

![Fig. 19. Relation between blood volume and right atrial pressure. A correlation coefficient is 0.63 (p < 0.01).](image)

**Table III** Effect of the Treatment with Digitalis upon Plasma Volume

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Venous Pressure (mmH₂O)</th>
<th>Edema</th>
<th>Liver Swelling</th>
<th>ADH (µ/ml)</th>
<th>Plasma Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y.O.</td>
<td>49</td>
<td>MSI, AI</td>
<td>225</td>
<td>III</td>
<td>3</td>
<td>9.1</td>
<td>increased (2105→2456)</td>
</tr>
<tr>
<td>Z.Y.</td>
<td>57</td>
<td>AS</td>
<td>238</td>
<td>II</td>
<td>5</td>
<td>4.0</td>
<td>increased (2870→3480)</td>
</tr>
<tr>
<td>K.S.</td>
<td>18</td>
<td>CVD</td>
<td>260</td>
<td>III</td>
<td>2.5</td>
<td>not measured</td>
<td>increased (2210→2570)</td>
</tr>
<tr>
<td>A.K.</td>
<td>59</td>
<td>HHD</td>
<td>88</td>
<td>+</td>
<td>1</td>
<td>2.4</td>
<td>slightly increased (2000→3190)</td>
</tr>
<tr>
<td>S.K.</td>
<td>20</td>
<td>CVD</td>
<td>110</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>unchanged (3570→3590)</td>
</tr>
<tr>
<td>S.N.</td>
<td>78</td>
<td>HHD</td>
<td>132</td>
<td>III</td>
<td>2</td>
<td>0.7</td>
<td>unchanged (2510→2430)</td>
</tr>
<tr>
<td>N.M.</td>
<td>51</td>
<td>MI</td>
<td>77</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
<td>unchanged (2910→2820)</td>
</tr>
<tr>
<td>Z.S.</td>
<td>74</td>
<td>myocardial infarction</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>1.3</td>
<td>unchanged (2661→2681)</td>
</tr>
</tbody>
</table>

**Notes:**

MSI: Mitral Stenosis
AS: Aortic Stenosis
CVD: Combined Valvular Disease
AI: Aortic Insufficiency
HHD: Hypertensive Heart Disease

Fig. 20. This figure showed the case with chronic congestive heart failure with edema, dyspnea and liver swelling. An activity in plasma ADH was elevated. When lanatoside C was administered intravenously, plasma volume was increased from 2105 ml to 2545 ml with a marked reduction of venous pressure and increased diuresis. The urinary ratio of sodium to potassium was increased by therapy. Abbr: ADH: Antidiuretic hormone, UV: Urine volume, BW: Body weight, VP: Venous pressure, HR: Heart rate, BV, PV: Blood and plasma volume.

Fig. 21. This case had edema, dyspnea, and markedly increased venous pressure. Plasma ADH level was also increased. (normal: less than 2.1 μU/ml) When lanatoside C was administered parenterally, plasma volume was increased from 2870 to 3460 ml, and also increased venous pressure returned to normal. The urinary ratio of sodium to potassium was increased by treatment.

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with diuresis and disappearance of edema (Fig. 20, 21). But cases S. K., S. N., Z. S. and N. M. did not show any alteration in plasma volume notwithstanding improvement of subjective symptoms. As shown in Fig. 22 a case (A. K.) had blood volume of 3.24 L, cardiac index of 2.24 L/min/M² and stroke index of 22.2 ml/beat/M² on February 14, but blood volume was 3.08 L on February 16. About six hours after he began to be treated with digitalis, his blood volume was 3.50 L, cardiac index was 4.26 L/min/M² and stroke index was 42.5 ml/beat/M². After 3 days the blood volume and cardiac index were reduced to 3.11 L and 2.98 L/min/M², respec-

Fig. 22. This case had slight peripheral edema and dyspnea. When lanatoside C was administered intravenously, cardiac output was markedly increased with little change in plasma volume. Four days after, cardiac index and blood volume was decreased, but stroke volume increased with improvement of subjective symptoms. Abbreviation, CI: Cardiac index, BV: Blood volume, SI: Stroke index, BW: Body weight, UV: Urine volume, Vp: Venous pressure, CO/BV: Cardiac output/Blood volume.

**Table IV Lasix Test**

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Diagnosis</th>
<th>VP</th>
<th>Edema</th>
<th>CI</th>
<th>PV</th>
<th>ΔPV/ΔV</th>
<th>ADH</th>
<th>UV</th>
<th>ΔVP/ΔV</th>
<th>Na/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. U.</td>
<td>39</td>
<td>control</td>
<td>82</td>
<td></td>
<td>4.89</td>
<td>2940</td>
<td>2305</td>
<td>21.6</td>
<td>0.7→ 5.1</td>
<td>1412</td>
<td>25</td>
</tr>
<tr>
<td>Y. H.</td>
<td>18</td>
<td>control</td>
<td>24</td>
<td></td>
<td>4.69</td>
<td>2145</td>
<td>1445</td>
<td>32.6</td>
<td>1.4→ 5.7</td>
<td>944</td>
<td>13</td>
</tr>
<tr>
<td>R. T.</td>
<td>29</td>
<td>control</td>
<td>60</td>
<td></td>
<td>4.07</td>
<td>3132</td>
<td>2516</td>
<td>19.7</td>
<td>1.7→ 6.8</td>
<td>1532</td>
<td>41</td>
</tr>
<tr>
<td>K. O.</td>
<td>55</td>
<td>control</td>
<td>54</td>
<td></td>
<td>3.30</td>
<td>2219</td>
<td>1550</td>
<td>30.2</td>
<td>4.5→ 40.0</td>
<td>1536</td>
<td>24</td>
</tr>
<tr>
<td>Y. F.</td>
<td>21</td>
<td>control</td>
<td>114</td>
<td></td>
<td></td>
<td>3040</td>
<td>2475</td>
<td>18.6</td>
<td>2.1→ 4.7</td>
<td>2150</td>
<td>67</td>
</tr>
<tr>
<td>T. Y.</td>
<td>30</td>
<td>CVD.</td>
<td>209</td>
<td></td>
<td>3.57</td>
<td>2365</td>
<td>2255</td>
<td>4.7</td>
<td>1.3→ 1.7</td>
<td>1272</td>
<td>1430</td>
</tr>
<tr>
<td>S. N.</td>
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<td>CVD.</td>
<td>145</td>
<td></td>
<td>1.40</td>
<td>2445</td>
<td></td>
<td></td>
<td>2.2→ 5.5</td>
<td>1241</td>
<td></td>
</tr>
<tr>
<td>M. T.</td>
<td>55</td>
<td>M. I.</td>
<td>158</td>
<td></td>
<td>0.78</td>
<td>2845</td>
<td>2639</td>
<td>7.2</td>
<td>3.1→ 1.4</td>
<td>2016</td>
<td>656</td>
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</tbody>
</table>

VP: Venous Pressure (mm H2O), CI: Cardiac Index (L/min/M²), PV: Plasma Volume (ml)
ADH: Antidiuretic Hormone (μ/μl), ΔPV/ΔV: Percent Change of PV,
UV: Urine Volume (ml) excreted during 4 hours, ΔVP/ΔV: Venous Pressure Change per 1000 ml PV Change
CVD: Combined Valvular Disease, M. I.: Mitral Insufficiency
Na/K: Na to K ratio in urine before the administration of furosemide

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tively, with gradual diuresis, but further increase in stroke index occurred (53 ml/beat/M^2).

Effect of the Treatment with Diuretics upon Blood Volume and Cardiac Output.
i) Acute Effect of Furosemide

Three patients with congestive heart failure and five normal controls were studied. All three patients had peripheral edema, elevated venous pressure (145 to 209 mm Hg), low cardiac index (0.78 to 3.57 L/min/M^2), and liver swelling. Furosemide in dose of 40 mg was administered orally in the fasting condition at the end of 14 hours after supper. Various data are summarized in the Table IV. The rate of the decrease in plasma volume over 4 hours varied from 4.7 per cent to 7.2 per cent with an average of 6.0 per cent in patients with heart failure. An activity of plasma ADH was changed from 2.1 µu/ml (range: 0.7 to 4.5) before, to 12.5 µu/ml (range: 4.7 to 40) after furosemide administration in control group, and from 1.4 µu/ml (range: 0.45 to 2.5) before, to 2.9 µu/ml (range: 1.4 to 5.5) after the administration of furosemide in patients with heart failure. There is no difference in urine volume excreted during 4 hours after the medication between the controls and the cardiac patients. ΔP/ΔV (change in venous pressure (mm Hg) per 1000 ml change in plasma volume) was 34 (range 13 to 67) in the controls and 1043 (range: 656 to 1430) in the heart patients.

ii) Chronic Effect of Diuretic Therapy

Two patients with congestive heart failure had been treated on maintenance dose of digitalis, but could not be in amply compensated state with digitalis alone. The observations in one case, T.S., 56 years old, are shown in Fig. 23. His blood volume was decreased from 5190 ml (3.39 L/M^2) to 3460 ml (2.58 L/M^2) with little change in cardiac index (1.76 L/min/M^2 to 1.62 L/min/M^2) after trichlormethiazide had been intermittently administered for 24 days. Another case, C.T., 32 years old, had dyspnea and edema (+ + +). After the treatment with ethacrinic acid for 45 days, his body weight was decreased from 51.8 kg to 39.5 kg. A significant reduction of blood volume occurred (5180 ml to 4100 ml), but the cardiac index showed little change (1.75 L/min/M^2 to 1.95 L/min/M^2). In these cases (T.S. and C.T.),

<table>
<thead>
<tr>
<th>T.S. 56 y. M. Combined valvular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin: 0.75 mg</td>
</tr>
<tr>
<td>Trichlormethiazide: 6.0 mg</td>
</tr>
<tr>
<td>Oxygen sat.</td>
</tr>
<tr>
<td>HR:</td>
</tr>
<tr>
<td>BV: 1</td>
</tr>
<tr>
<td>PV:</td>
</tr>
<tr>
<td>TV:</td>
</tr>
<tr>
<td>CO:</td>
</tr>
<tr>
<td>L/min: 1.0</td>
</tr>
<tr>
<td>BW:</td>
</tr>
<tr>
<td>kg:</td>
</tr>
<tr>
<td>U:</td>
</tr>
<tr>
<td>V:</td>
</tr>
<tr>
<td>VP: mm Hg</td>
</tr>
</tbody>
</table>

Fig. 23. The figure showed the case with chronic congestive heart failure, which could not be compensated without digitalis and diuretics. After intermittent use of diuretics, plasma volume was decreased, but cardiac output showed little change.

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### Table V  Group I

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Cardiac Index</th>
<th>CO BV</th>
<th>RPF</th>
<th>GFR</th>
<th>FF</th>
<th>RBF CO</th>
<th>Venous Pressure</th>
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<tbody>
<tr>
<td>F. T.</td>
<td>f</td>
<td>19</td>
<td>1.35</td>
<td>0.50</td>
<td>306</td>
<td>84</td>
<td>23.3</td>
<td>32.2</td>
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<tr>
<td>K. S.</td>
<td>f</td>
<td>18</td>
<td>1.70</td>
<td>0.56</td>
<td>330</td>
<td>92</td>
<td>27.8</td>
<td>24.0</td>
<td>105</td>
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<tr>
<td>S. K.</td>
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<td>92</td>
<td>42.5</td>
<td>22.8</td>
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<td>416</td>
<td>129</td>
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<td>28.4</td>
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<td>K. Y.</td>
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<td>1.83</td>
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<td>222</td>
<td>52</td>
<td>23.2</td>
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<tr>
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<td>1.03</td>
<td>0.32</td>
<td>331</td>
<td>103</td>
<td>31.3</td>
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<td>114</td>
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<td>11.1</td>
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<td>1.52</td>
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<td>28.9</td>
<td>122</td>
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<td>S. N.</td>
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<td>1.40</td>
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<td>120</td>
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<tr>
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<td></td>
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<td>1.61</td>
<td>300</td>
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### Table VI  Group II

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<th>Cardiac Index</th>
<th>CO BV</th>
<th>RPF</th>
<th>GFR</th>
<th>FF</th>
<th>RBF CO</th>
<th>Venous Pressure</th>
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</thead>
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<tr>
<td>F. S.</td>
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<td>125</td>
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<td>76</td>
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<td>74</td>
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<td>20.1</td>
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<td>N. H.</td>
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<td>80</td>
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<tr>
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### Table VII  Group III

<table>
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<th>Sex</th>
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<th>Cardiac Index</th>
<th>CO BV</th>
<th>RPF</th>
<th>GFR</th>
<th>FF</th>
<th>RBF CO</th>
<th>Venous Pressure</th>
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<td>1.56</td>
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<td>139</td>
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<td>19.21</td>
<td>N</td>
</tr>
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<td>M. T.</td>
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<td>19.4</td>
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<td>800</td>
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<td>7.8</td>
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<td>1.30</td>
<td>600</td>
<td>130</td>
<td>21.7</td>
<td>19.1</td>
<td>N</td>
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<td>85</td>
<td>25.0</td>
<td>15.6</td>
<td>N</td>
</tr>
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<td>27.4</td>
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<td>N</td>
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<td>1.35</td>
<td>498</td>
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<td>89</td>
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<td>3.51</td>
<td>1.35</td>
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<td>94</td>
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<tr>
<td>T. Y.</td>
<td>f</td>
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<td>0.90</td>
<td>471</td>
<td>104</td>
<td>21.0</td>
<td>14.6</td>
<td>155</td>
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</tbody>
</table>

mean 27 3.85 1.54 523 103 20.0 16.9

N: Normal

blood volume was decreased without change in cardiac index when diuretics were administered for a certain period of time in addition to maintenance dose of digitalis.

Renal Circulation in Congestive Heart Failure.

Patients with heart failure are separated here into three groups according to their cardiac index;

I group; cardiac index is 1.61 L/min/M² (range: 1.03 to 1.95).
II group; cardiac index is 2.50 L/min/M² (range: 2.13 to 2.90).
III group; cardiac index is 3.85 L/min/M² (range: 3.20 to 4.77).

Various data in group I, II and III, are summarized in Table V, VI, VII.

i) Renal plasma flow (RPF) in group I is 300 ml/min/1.48 Sq. M. (range: 165 to 416), which is 50 per cent of the normal mean; RPF in group II is 396 ml/min/1.48 Sq. M. (range: 247 to 626), which is 69 per cent of the normal mean value; RPF in group III is 532 ml/min/1.48 Sq. M. (range: 315 to 982), which shows 92.3 per cent of the normal mean value (Fig. 24). There is a statistically significant difference between group I and II, between group II and III (p<0.01).

ii) Glomerular filtration rate (GFR) in group I is 86 ml/min/1.48 Sq. M. (range: 53 to 129), which is 72.2 per cent of the normal mean value; GFR in group II is 89 ml/min/1.48 Sq. M. (range: 55 to 171), which is 74.9 per cent of the normal mean value; GFR in group III is 103 ml/ml/min/1.48 Sq. M. (range: 73 to 130), which is 86.6 per cent of the normal mean value (Fig. 25).

iii) Filtration fraction (FF) in group I is 31.5 per cent (range: 16.6 to 75.8), which is 158 per cent of the normal mean value; FF in group II is 22.5 per cent (range: 15.5 to 28.2), which is 107.8 per cent of the normal mean value; FF in group III is 20.0 per cent (range: 11.1 to 29.9), which is 95.7 per cent of the normal mean value (Fig. 26).

iv) A higher renal fraction of cardiac output (RBF/CO) than normal is found in five out of fifteen cases in group I, but there is no significant difference of RBF/CO among each group. RBF/CO in group I is 23.1 per cent (range: 19.4 to 26.8).
11.1 to 32.2): RBF/CO in group II is 18.1 per cent (range: 11.1 to 29.5): RBF/CO in group III is 16.9 per cent (range: 7.8 to 27.4). (Fig. 27)

**DISCUSSION**

Criticism of the method

In the present series of the study, the blood and plasma volumes were measured after allowing 10 minutes for mixing. Compared with the blood volume calculated after 10 minutes of mixing, the blood volume calculated after 20 minutes of mixing was slightly larger, suggesting that the latter value included some of the extravascular space (Fig. 28). With RISA injected intravenously, the flattening of the disappearance slope of the precordial counting occurred at the end of 27 to 53 seconds with an average of 33 seconds in normal subjects, and it occurred at 31 to 59 seconds with an average of 50 seconds in patients with heart failure. According to Pritchard et al.¹⁴, there occurred the equilibrium of RISA at the end of 4 to 15 minutes with an average of 9 minutes in normal subjects. Wollheim¹⁵,¹⁶ proposed the concept of the "active blood volume" that was estimated using 7 to 10 minutes as mixing time. The method used in the present study with short analysis time i.e., 10 minutes after the injection of RISA, probably allows the measurement of the active blood volume. With the methods available at present it seems doubtful whether the total blood volume can be ever determined correctly. In this study blood volume was calculated, using the peripheral venous hematocrit (H), which was slightly different from

Fig. 26. Filtration fraction (FF) in patients with chronic congestive heart failure.

Fig. 27. Renal fraction of cardiac output (RBF/CO) in patients with chronic congestive heart failure.

Fig. 28. Comparison between the blood volume calculated after 10 minutes of mixing and that calculated after 20 minutes of mixing. The value for 20 minutes' mixing is slightly larger (the mean ± SD. of the percentage difference: 3.0 ± 2.5).

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the body hematocrit. The body hematocrit may be designated as \( H_o \) and is given by the ratio, cell volume/blood volume, that is \( H_o = CV/(CV+PV) \), where \( CV \) and \( PV \) are the simultaneously measured cell and plasma volume. Since \( H_o/H \) gives the factor by which the venous cell percentage must be corrected to compute body hematocrit, it is termed F cells by Reeve, Gregerson and their collaborators\(^{17}\). The average ratio \( H_o/H \) in normal adult humans was reported to fall between 0.89 and 0.94 by a large number of investigators. Schreiber et al. reported that the mean ratio of F cell was 0.937 in control patients, 0.868 in patients with congestive heart failure, and 0.908 in patients free of failure\(^{18}\). Accordingly the error induced in the blood volume measurement with \( H_o/H \) of 0.92 in the present study may be insignificant.

The validity of the external counting of cardiac output has been extensively discussed by Veali\(^{19}\), Macintyre\(^{20}\), Donato\(^{11,12}\), van der Feer\(^{21}\) et al. Ishii found a good agreement between the cardiac output calculated from radiocardiograms and that determined simultaneously by the direct arterial sampling dilution method\(^{22}\). Fig. 29 shows the reproducibility of the radiocardiographically determined cardiac output. The standard deviation of the percentage difference between the first and second determination is 5.5 per cent and this difference may be clinically insignificant. The values for cardiac output as calculated from RISA radiocardiogram are plotted against the values determined by the direct Fick method in Fig. 30. The majority of the spots fall within \( \pm 20\% \) per cent of the unity line.

Blood Volume and Cardiac Output in Congestive Heart Failure

The observations reported here indicate that the blood volume is increased in congestive heart failure. The severer the degree of congestive heart failure, the larger the blood volume. This excess of blood is composed about equally of red cells and of plasma (Fig. 4). The increase in the red cell volume may be caused by hypererythropoiesis due to, among other things, anemia\(^{23}\). Accordingly, anemia is not frequently observed in severe congestive heart failure. If it be so, why does plasma volume increase in congestive heart failure? Warren and Stead observed that plasma volume and extra-cellular fluid volume increased and decreased concordantly\(^{2}\). But there are some patients who have much increased plasma volume with little edema. Plasma volume (or blood volume) has a rather good correlation with cardiothoracic ratio \((r=0.54 \ p<0.01)\) in Fig. 6. Sjöstrand also found an excellent correlation between heart volume and blood volume in group of

---

**Fig. 29.** The reproducibility of the radiocardiographically determined cardiac output. The standard deviation of the percentage differences between the first and second determination is 5.5 per cent.

**Fig. 30.** Comparison between the values for cardiac output as calculated from RCG and the values determined by the direct Fick method. The majority of the spots fall within \( \pm 20\% \) per cent of the unity line.

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men, women, and children without evidence of heart disease. The ratio of cardiac output to blood volume is more clearly separated among different classes of the functional capacity of N.Y.H.A. classification than cardiac output and/or blood volume alone. Accordingly, blood volume should have a close relation with cardiac output. When cardiac outputs are plotted against blood volume (Fig. 9), spots for group of Class I are located in the upper parts of the figure; that is, the highest cardiac output are observed in Class I and the lowest output in Class III, for the same value of blood volume.

This fact constitutes a suggestive evidence that the cardiac output curve becomes depressed as the heart failure advances; cardiac output is more severely reduced as the Class advances, for the same systemic filling pressure. As mentioned above, blood volume is playing a regulatory role to compensate for lowered cardiac output in chronic congestive heart failure. STAUD says that when the output is increased by digitalis, the venous pressure at first falls rapidly, but it may remain above the normal level until diuresis produces a decrease in blood volume. If blood volume is decreased by treatment, venous pressure in most cases certainly falls (Fig. 8), but if venous pressure fell rapidly to normal value or below normal by digitalis treatment, plasma volume showed a tendency to increase at first, and then it gradually decreased, accompanied by diuresis and disappearance of edema and dyspnea. (Table III) The cause of this increase in plasma volume may be the reabsorption of the interstitial fluid into the intravascular space according to Starling principle since the capillary pressure perhaps rapidly decreased owing to normalized venous pressure. Changes in venous pressure have marked effects on plasma volume because of their influence on capillary pressure. LANDIS and HORTENSTINE conclude that fluid movement in the capillaries was 5 to 10 times more sensitive to changes in venous pressure than to changes in arterial pressure. The steady state between plasma and extracellular fluid is promptly affected by any disturbance in the pressure and solute concentration of fluid inside and outside the capillaries. The rate of transcapillary exchange of fluid is so great that relatively enormous shifts in plasma volume can readily occur in brief span of time. In one case (Z.Y.) the venous pressure decreased from 200 mm H₂O to 54 within a few hours, allowing, probably, an enormous reabsorption of tissue fluid into the intravascular space. This process may be compared to an intravenous infusion of saline solution. This increase in plasma volume may result in a decrease in aldosterone activity with renal release of sodium to prevent "critical expansion" of the circulating blood volume. Though there are authors who insist upon dysfunction of the volume receptors in patients with congestive heart failure, the above-mentioned evidence (the decrease in aldosterone output in response to plasma volume expansion) may indicate that the volume receptors are physiologically functioning.

In a case, e.g. S.K. in which blood volume showed little change when the output is increased by digitalis, plasma activity in ADH and urinary aldosterone excretion remains almost constant (Table III). CARPENTER et al. reported that increased excretion of aldosterone decreased markedly within 90 minutes after digitalisation in dog experiments, and also WOLFF et al. reported on female patients who had excessive pulmonary and peripheral edema, ascites and pleural effusion, whose increased excretion of aldosterone returned, after short initial rise, to normal, accompanied by loss of large amounts of sodium and water on intravenous administration of digitalis. The ratio of Na to K in urine in case Y.O. is increased when lanatoside C is administered intravenously, which suggests that urinary aldosterone has been decreased by the treatment (Fig. 20). NOHARA and SAIMIYOSHI, and KUBO also reported that digitalis-diuresis was considered as physiological as diuresis induced by taking bed rest and that urinary aldosterone output was decreased in the majority of cases when diuresis was induced by the administration of digitalis and by bed rest.

The degree of contraction of plasma volume in congestive heart failure is small after oral administration of furosemide, as compared with that in controls. As soon as diuresis begins, a marked transfer of body fluid from interstitial space to intravascular compartment. 

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may occur in patients with congestive heart failure with edema. Accordingly, activities in ADH show almost no response, owing to little change in blood volume in congestive heart failure. In contrast, activities in ADH are increased after diuresis in normal controls as the result of hemoconcentration of more than 20 per cent. There is a suggestive evidence that the cubital venous pressure, in recumbent human subjects, is close to the "mean systemic filling pressure" of Guyton, when the venous pressure is above normal. As shown in Table IV, a value of $\Delta P/\Delta V$ is very high in patients with cardiac failure. It may be that this increase in $\Delta P/\Delta V$ ratio is due to an increased vasomotor activity in congestive heart failure. The hemodynamic alterations after substantial diuresis had been studied with the intravenous injection of furosemide and mercurial diuretic. Cases T.Y., S.N., and M.T., in Table IV, showed a marked relief of subjective symptom after diuresis produced by furosemide. It may be that in these cases the reduction of the elevated intracardiac pressure and the increase in cardiac output occur. The increase in cardiac output found in severely decompensated heart failure after acute diuresis with furosemide may be considered consistent with Starling's law of the heart in man in congestive heart failure, and/or compatible with an upward shift (with rotation to the left) of the ventricular output curve, such as proposed by Guyton. However, this relief of subjective symptoms may not be due to the improvement of cardiac output with diuretic therapy, but rather due to the elimination of the circulatory congestion, because patients, who could not be amply compensated for by digitalis alone, showed little change in cardiac output after additional sustained administration of diuretics until all edema fluid had been eliminated, but they found relief from subjective symptoms. In these cases (T.S., and C.T.), the cardiac output curve remains probably depressed, though systemic filling pressure shifts to the left upon the treatment with diuretics.

It has been reported that RPF may be reduced to 1/3 to 1/6 of normal whereas the cardiac output is seldom less than 1/2 of normal in congestive heart failure, and that renal fraction of cardiac output is also decreased. As shown in Fig. 31, there is a consistent relationship between RPF and cardiac index. ($r=0.59$ $p<0.01$) But in patients with cardiac index lower than 2.00 L/min/M$^2$, values of RPF higher than 300 ml/min/1.48 Sq.M. are often observed. In these cases renal fraction of cardiac output is generally higher when the patients are in compensation with digitalis and/or diuretics although it has been reported that renal fraction of cardiac output becomes lower in chronic congestive heart failure. These facts show a suggestive evidence that the kidney, such as brain and liver, may be considerably protected from the impaired circulation.

Berne also reported on the increased renal fraction of cardiac output in dog's experiment. It will be thought that RPF not only depends upon cardiac output, but also upon venous pressure. For the same cardiac output, those with elevated venous pressure had smaller RPF. (Fig. 24, 31) In this present study, renal plasma flow (RPF) was determined not simultaneously with the measurement of cardiac output, but with the short interval.

The regulation of blood volume has been extensively discussed by a number of investigators. Volume receptors may be broadly

![Fig. 31. Relation between cardiac index and RPF. Correlation coefficient is 0.59 ($p<0.01$). Dark spots show patients with venous pressure higher than 100 mm H$_2$O.](image-url)
divided into those of the low pressure system and those of the high pressure system. The receptors of the low pressure system are chiefly located in the right atrium, left atrium, inferior vena cave, limb veins and cephalic veins; those of the high pressure system are located in the common carotid artery. The former are related to circulating blood volume and the latter, the pulse pressure of the artery.

Blood volume in congestive heart failure is more closely related to right atrial pressure than to the pulmonary artery wedge pressure (left atrial pressure). (Fig. 18, 19) This is inferred from the evidence that elevated left atrial pressure does not cause the pulmonary blood volume to be increased even if the pulmonary blood vessel is congested, but rather to be decreased in patients with high pulmonary artery resistance. On the other hand, elevated pressure in the right atrium results in congestion of the whole body, causing the blood volume to be increased. This difference in the pattern of response to elevated pressure partly depends upon the difference between vascular compliance in the two pressure systems. It has been reported that plasma ADH is increased in right sided heart failure, but not in left sided heart failure. Increased activities of aldosterone are observed also in right sided heart failure with progressive edema. The importance of the right atrium in the volume regulation may be conjectured from the above-mentioned facts.

**SUMMARY**

1) Blood volume was measured in 67 patients with heart failure and 20 normal controls, and 81 measurements of RCG were performed on 58 subjects with congestive heart failure, and 14 normal control subjects.

2) Blood volume showed a significant increase in Class III and IV of New York Heart Association classification and the greatest increase occurred in bi-ventricular heart failure.

3) A higher correlation coefficient was found between blood volume and right atrial pressure than between blood volume and pulmonary "capillary" pressure.

4) Cardiac index was within normal range in Class I, and gradually decreased as Class advanced from II to IV. All patients of Class IV showed a marked decrease in cardiac index. Conspicuously scattered values of cardiac index were noted in Class II patients.

5) Stroke index showed a slight decrease even in Class I patients, in contrast to cardiac index, and was markedly decreased as Class advanced from II to IV.

6) There was no statistically significant difference between the cardiac index in normal subjects and that in patients in compensation without digitalis, but their stroke indices were slightly decreased. Cardiac index was decreased in patients in compensation with digitalis alone and even more so in patients in compensation with both digitalis and diuretics. Stroke index was not so much decreased in patients in compensation with digitalis alone, but markedly decreased in patients in compensation with both digitalis and diuretics.

7) The ratio of cardiac output to blood volume (CO/BV), easily derived from RCG, seemed to reflect the "severity" of congestive heart failure.

8) When patients with congestive heart failure were treated with rapid digitalisation, transient increase in plasma volume occurred with decreased output of aldosterone. This fact constitutes an evidence that the physiological feedback mechanism is working in congestive heart failure.

9) When furosemide was administered orally in the fasting condition, plasma volume was decreased in normal controls, but not so much so in congestive heart failure, and plasma ADH was increased in normal controls, but decreased or unchanged in congestive heart failure. This fact constitutes an evidence that the response of ADH to volume contraction is a physiological one even in congestive heart failure.

10) There is a significant correlation between cardiac output and RPF. But RPF was even more decreased when peripheral venous pressure became high.

11) Renal fraction of cardiac output was within normal limits or slightly increased when patients were in the state of compensation with digitalis and diuretics even if cardiac index was low.

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