Whole Blood Volume Determined by Radiochromium-Tagged Red Cells

Comparative Studies on Normal and Congestive Heart Failure Patients

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Whole blood volume can be measured quite accurately by the use of radiochromium. The amount of radiation is very low; the radiochromium stays fixed in red blood cells for many hours and does not leave the circulation as may happen when plasma tags are employed. Hypervolemia was found in the majority of patients with right ventricular failure but not in those with left ventricular failure or mitral stenosis alone.

In congestive heart failure the blood volume has generally been considered to be elevated.\(^1, 6, 14, 15, 16, 18, 21, 24\) Recent investigations by Prentice and co-workers\(^19\) and by Ross and associates,\(^20\) using \(^{51}\)tagged erythrocytes, have suggested that the blood volume in heart failure often is not increased. The importance of hypervolemia in both the physiology and therapy of cardiac failure has stimulated the study of this problem.

Nylin and Hedlund\(^16\) in 1947 summarized the opinions of various investigators concerning the efficiency of the various methods. It was concluded that both the dye and the carbon monoxide methods may produce falsely high values because of leakage of dye substance from the vascular system and because of absorption of carbon monoxide by the myoglobin. More accurate determinations of blood volumes utilizing radioactive material\(^2\), \(^4, 7-12, 15, 19, 22, 23\) are now available.

Total blood volumes are usually calculated from either the red cell or plasma volume, utilizing the hematocrit reading. Higher values are usually obtained when calculating whole blood volumes from plasma volumes, presumably, because of leakage of plasma bound substances from the vascular space during the period between injection and sampling. Ross\(^20\) has submitted some evidence to support Peter's contention that this loss may be accentuated in congestive heart failure. Plasma volumes determined by radioactive iodinated serum albumin do not differ significantly from those obtained from T-1824.\(^22\) Since there are valid objections to the use of tagged-protein methods, we decided to use one of the radioactively labeled red cell methods.

Red cell volumes determined by tagging the erythrocytes with radiophosphorus,\(^11, 15\) radioiron,\(^7, 8\) and radiochromium (Cr\(^{51}\))\(^9, 23\) are approximately the same. Although all of the reported red cell methods employing radioisotopes may give consistent results, radiochromium seems to be the most useful for several reasons, which include the physical properties of Cr\(^{51}\) and ease of application from a clinical viewpoint.

Radiochromium emits mainly a gamma radiation and a scintillation crystal detects this very efficiently. This permits a low injection dose and small blood samples. Radiochromium is rapidly taken up by the red cell in vitro. The tag stability is relatively constant for at least 24 hours in vivo as has been observed by Sterling and Grey\(^9, 10, 23\) and by us.

Radiophosphorus on the other hand is a pure beta emitter, the counting of which, using a Geiger-Muller counter, involves corrections for mass absorption and coincidence. This isotope has less tag stability, necessitating sam-

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Fig. 1. Photographic showing uptake and retention of Na₂Cr⁴⁺O₄ by human red blood cells following two saline washes.

Method

Approximately 10 cc. of whole blood were drawn from the antecubital vein with a sterile heparinized syringe and transferred to a 15 cc. sterile rubber-capped pyrex tube into which was introduced 0.1 to 0.2 cc. of sodium chromate (Na₂Cr⁴⁺O₄) solution, containing Cr⁴⁺, plus the inert carrier which had been processed into a neutral solution of Na₂Cr⁴⁺O₄. The Cr⁴⁺ activity of this solution ranged between 10 and 15 microcuries (µc) and the quantity of carrier chromium varied between 100 and 300 micrograms (µg).

This blood sample containing the Cr⁴⁺ was agitated on a Fisher blood pipette shaker for 45 minutes at room temperature. Between 60 and 98 per cent of the Cr⁴⁺ (in Na₂Cr⁴⁺O₄) was taken up by the red cells, the variation being due to the total amount of chromium present in the solutions (Fig. 1). The uptake of Cr⁴⁺ by red cells is inversely proportional to the amount of carrier Cr⁴⁺ present and our results agree with those published previously by Sterling and Gray. It was also observed that lowered cellular uptake* of Cr⁴⁺ may take place when the cells are incubated in the presence of plasma; however, this difference was small enough to neglect for all practical purposes.

Following incubation and shaking, the tagged whole blood was centrifuged for five minutes at 2700 revolutions per minute (1559 gravities) and the plasma discarded along with the sodium chromate not taken up by the red cells. The tagged cells were washed three times with 5 or 6 cc. of sterile isotonic saline by means of inversion, the saline being separated by moderate centrifugation (five minutes at 1559 gravities) and discarded. This procedure removed any sodium chromate adherent to the red cells.

The last saline wash was found to contain less than 0.2 per cent of the Cr⁴⁺ present with the tagged cells. The cells were suspended in 5 or 6 cc. of saline by shaking them for a few minutes. Five tenths cc. of the cell-saline mixture was diluted to 50 cc. and 5 cc. portions of this were taken as a standard to determine the total number of counts present per cubic centimeter of the cell-saline mixture. The volume of the cell-saline mixture was carefully measured and administered to the patient by the intravenous route.

The dose to the patient was calculated to be the number of counts per second per cubic centimeter of cell-saline mixture times the number of cubic centimeters administered. In most cases the dose ranged from 4,000 to 20,000 counts per second.

In our hands 30 minutes was required for uniform mixing of tagged cells with those in the circulatory system of patients.† Samples of 6 to 7 cc. of venous

* It is felt that the presence of hemoglobin in the plasma may be responsible.
† The results of mixing-time studies in normal individuals, employing serial samples taken 5, 10, 15, 20 and 30 minutes following the injection of tagged cells, indicated that complete mixing within the normal circulation may take place by 10 minutes, but it was not complete in all cases until 30 minutes. Therefore, in order to eliminate routine serial samples, a single 30 minute sample was selected for determination of the total blood volume. A wait of 60 minutes for complete mixing was selected for some cases of cardiac decompensation.
blood were taken with a heparinized syringe at time intervals of 30 minutes to 1 hour after the tagged cells were administered. The blood volume of the solution was estimated in cubic centimeters by computing the dilution of the tagged dose using the following formula:

\[
\text{Patient's blood vol. in cc. = } \frac{\text{Total counts/sec./cc. injected}}{\text{Counts/sec./cc. blood withdrawn}}
\]

There has been considerable controversy over the validity of whole blood volumes calculated from hematocrit readings because of differences in large vessels and total body hematocrit. This debatable point was eliminated by the comparison of radioactive activity in whole blood samples rather than red cell mass; the hematocrit was then used to determine red cell and plasma volumes. Ross and associates used a similar method with radioactive phosphorus tagged red cells.40

In the Cr41 assay a 5 cc. aliquot of the standard was compared with a 5 cc. sample of blood withdrawn from the patient. All samples were pipetted into tin plate dishes which are 4 cm. in diameter. These were counted in a scintillation counter which was filtered so that only the 0.3 million electron volt gamma rays associated with the Cr41 decay was observed as counts. The efficiency of the thallium-activated sodium iodide crystal was such that 11 to 14 per cent of the total disintegrations associated with gamma emission were observed as counts. On the average each sample of blood withdrawn from the patient after the tag was administered contained sufficient Cr41 to have 4 to 20 counts per second per 5 cc. The samples were counted for a sufficient period of time to observe 4096 counts, which count has a statistical variation of less than 2 per cent. The scintillation counter was shielded with two inches of lead; this resulted in a background of 1.5 to 1.7 counts per second.

Numerous difficulties were encountered during the development of the procedure. Foremost was the poor quality of the radioactive chromium; the earlier samples contained low specific radioactivity and the blood volume results were unreliable. It is conceivable that on rare occasions, part of the tagged cells may have not been placed in the vein properly, with consequent leakage into the subcutaneous tissues giving falsely high blood volumes. Constant cross-checking of the procedure and calculations by several individuals eliminated the human error to a great extent.

Reliability of Method. The reliability of this method was observed by comparing the results of two blood volume determinations on each of 17 subjects carried out within a two hour period according to the following double injection procedure.

Approximately 20 cc. of heparinized whole blood was withdrawn sterilely and divided equally between two pyrex tubes, one containing approximately 10,000 counts per second and the other approximately 20,000 counts per second and the samples processed for injection as previously described. One hour following the first injection of 10,000 counts per second a sample was withdrawn for assay and blood volume determined, and the counts per second per cubic centimeter recorded.

A second injection of 20,000 counts per second was then administered and another sample withdrawn after one hour and assayed. The activity due to the first injection was subtracted from the activity of the combined injection in order to determine the activity due to the second injection and the second blood volume determination.

Example:

1st injection

\[ \text{10,000 c/s injected} \]
\[ 2 \text{ c/s/cc. withdrawn} \] = 5000 cc.

2nd injection

\[ \text{20,000 c/s injected} \]
\[ 6 \text{ c/s/cc.} - 2 \text{ c/s/cc.} = 4 \text{ c/s/cc.} \]

Activity due to combined injection

\[ \text{to 1st injection} \]
\[ \text{to 2nd injection} \]

= 5000 cc.

The results of this experiment are shown in table 1.

The difference in the two blood volume determinations:

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Patient} & \text{Blood Volume cc.} & \text{Diff. cc.} & \% \text{Diff.} \\
\hline
& \text{1st inj.} & \text{2nd inj.} & \\
\hline
1 & 4170 & 4140 & -30 & 0.7 \\
2 & 4780 & 4600 & -180 & 3.9 \\
3 & 3710 & 3890 & +180 & 4.6 \\
4 & 4070 & 4030 & -40 & 1.0 \\
5 & 3830 & 4190 & +360 & 8.6 \\
6 & 4330 & 4620 & +290 & 6.3 \\
7 & 4150 & 4450 & +280 & 6.3 \\
8 & 4390 & 4510 & +120 & 2.7 \\
9 & 4460 & 4400 & -60 & 1.3 \\
10 & 3880 & 3940 & +60 & 1.5 \\
11 & 3010 & 3200 & +190 & 5.9 \\
12 & 3280 & 3500 & +310 & 8.6 \\
13 & 4300 & 4230 & -70 & 1.7 \\
14 & 4900 & 5410 & +540 & 10.0 \\
15 & 4400 & 4380 & -20 & 0.4 \\
16 & 4730 & 4830 & +100 & 2.1 \\
17 & 4280 & 4240 & -40 & 0.9 \\
\hline
\end{array}
\]

* All patients were recumbent at the time of these determinations.
tions in the same patient range from 30 to 500 cc. (0.4 to 10.0 per cent) with an average of 169 cc.

Clinical Tests

To establish normal values for our method we determined whole blood volumes on 89 male hospital patients whose illnesses presumably had little effect upon their usual blood volumes. Most of these patients were waiting for surgical repairs for hernia, hemorrhoids, or varicose veins. Patients with anemias, cardiac cachexia, dehydration, liver, kidney and heart disease were excluded from this group.

Blood volumes were determined in 56 patients with cardiac disease. These cases were divided into five groups on the basis of history, physical and clinical studies. Circulation times and venous pres-

Table 2.

<table>
<thead>
<tr>
<th>Range ......</th>
<th>cc.</th>
<th>cc./Kg.</th>
<th>L./M.²</th>
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</thead>
<tbody>
<tr>
<td>2500-6084</td>
<td>45.8-81.0</td>
<td>1.79-3.05</td>
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</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td>65.5±5.95</td>
<td>2.49±0.28</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Tests

Fig. 2. Photograph showing whole blood volume in normal patients and in various types of cardiac patients in groups I to V. Presure are not reported since they were not routinely determined at the same time as the blood volumes.

Group I (17). Patients in this group had never had symptoms or signs of congestive heart failure but had various cardiac diseases such as hypertensive cardiovascular disease (HCVD), arteriosclerotic

Table 3.—Patients in Group I Had Never Had Symptoms or Signs of Congestive Heart Failure, but Had Various Cardiac Diseases Such as Hypertensive Cardiovascular Disease (HCVD), Arteriosclerotic Cardiovascular Disease (ASCVD), Rheumatic Heart Disease (RHD), and Congenital Heart Disease (CHD)

<table>
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<tr>
<td>B.C., 58</td>
<td>ASCVD, old myocardial infarct</td>
<td>183</td>
<td>72.7</td>
<td>1.94</td>
<td>5140</td>
<td>70.6</td>
<td>2.65</td>
<td>50.0</td>
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<tr>
<td>C.J., 60</td>
<td>ASCVD, angina</td>
<td>176</td>
<td>67.2</td>
<td>1.72</td>
<td>3920</td>
<td>58.3</td>
<td>2.28</td>
<td>44.0</td>
</tr>
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<td>HCVD</td>
<td>172</td>
<td>61.0</td>
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<td>4030</td>
<td>66.1</td>
<td>2.37</td>
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<td>C.O., 49</td>
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<td>1.68</td>
<td>4040</td>
<td>69.4</td>
<td>2.41</td>
<td>35.0</td>
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<td>D.G., 53</td>
<td>ASCVD, old myocardial infarct</td>
<td>180</td>
<td>68.2</td>
<td>1.86</td>
<td>4830</td>
<td>64.3</td>
<td>2.36</td>
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<td>D.A., 53</td>
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<td>4730</td>
<td>71.5</td>
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<td>F.P., 60</td>
<td>HASCVD, old myocardial infarct</td>
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<td>74.0</td>
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<td>F.E., 60</td>
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<td>1.59</td>
<td>3210</td>
<td>58.1</td>
<td>2.02</td>
<td>42.0</td>
</tr>
<tr>
<td>H.W., 51</td>
<td>LVH left outflow tract lesion</td>
<td>180</td>
<td>68.3</td>
<td>1.82</td>
<td>3850</td>
<td>55.2</td>
<td>2.11</td>
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<td>H.H., 55</td>
<td>HCVD</td>
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<td>69.5</td>
<td>1.85</td>
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<td>53.8</td>
<td>2.02</td>
<td>46.0</td>
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<td>L.C., 36</td>
<td>RHD, MS</td>
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<td>70.0</td>
<td>1.82</td>
<td>4830</td>
<td>62.7</td>
<td>2.65</td>
<td>40.0</td>
</tr>
<tr>
<td>L.S., 45</td>
<td>Tbc. pericard.</td>
<td>172</td>
<td>65.5</td>
<td>1.77</td>
<td>4280</td>
<td>65.4</td>
<td>2.42</td>
<td>31.0</td>
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<td>M.L., 53</td>
<td>HCVD</td>
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<td>2.55</td>
<td>51.0</td>
</tr>
<tr>
<td>N.C., 52</td>
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<td>84.2</td>
<td>2.02</td>
<td>4380</td>
<td>52.1</td>
<td>2.17</td>
<td>42.5</td>
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<td>S.J., 23</td>
<td>RHD. Rheum. pericard.</td>
<td>168</td>
<td>63.0</td>
<td>1.70</td>
<td>4100</td>
<td>65.2</td>
<td>2.41</td>
<td>47.0</td>
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<tr>
<td>S.R., 65</td>
<td>HCVD</td>
<td>169</td>
<td>67.0</td>
<td>1.78</td>
<td>4600</td>
<td>59.7</td>
<td>2.58</td>
<td>38.0</td>
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<tr>
<td>W.R., 30</td>
<td>Hypertension with coarct. aorta</td>
<td>173</td>
<td>75.5</td>
<td>1.89</td>
<td>4980</td>
<td>66.0</td>
<td>2.64</td>
<td>43.0</td>
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Avg. (17 pts.) = 2.37 ± 0.26 (S.D.)

p = 0.1
cardiovascular disease (ASCVD), rheumatic heart disease (RHD), and congenital heart disease (CHD).

Group II (8). This group consisted of cardiac patients who had previously been in congestive heart failure but who were now compensated following treatment in this hospital.

Group III (12). This group consisted of cardiac patients who had a history of dyspnea, orthopnea, paroxysmal nocturnal dyspnea and, when present, physical or x-ray evidence of pulmonary congestion.

Group IV (25). This group consisted of cardiac patients who had evidences of pulmonary congestion plus either two or more of the following: venous distention, enlarged liver, ascites, hydrothorax or peripheral edema.

**Table 4.** — Group II Consisted of Cardiac Patients Who Had Previously Been in Congestive Heart Failure, but Who Were Now Compensated Following Treatment in this Hospital

<table>
<thead>
<tr>
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<tbody>
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<td>B.G., 75</td>
<td>ASCVD</td>
<td>168</td>
<td>63.5</td>
<td>1.72</td>
<td>4800</td>
<td>64.5</td>
<td>2.79</td>
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<td>B.L., 38</td>
<td>RHD, AI, MS</td>
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<td>67.5</td>
<td>1.80</td>
<td>4700</td>
<td>70.0</td>
<td>2.61</td>
<td>44.0</td>
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</tr>
<tr>
<td>B.H., 63</td>
<td>ASCVD</td>
<td>172</td>
<td>49.0</td>
<td>1.53</td>
<td>3540</td>
<td>72.2</td>
<td>2.31</td>
<td>48.5</td>
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<tr>
<td>C.J., 82</td>
<td>HASCVD</td>
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<td>85.0</td>
<td>2.10</td>
<td>5650</td>
<td>66.5</td>
<td>2.69</td>
<td>38.0</td>
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<td>Pulmon. emphysema, chr. eor pulmon.</td>
<td>186</td>
<td>89.0</td>
<td>2.13</td>
<td>5900</td>
<td>66.3</td>
<td>2.77</td>
<td>61.0</td>
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<tr>
<td>S.E., 64</td>
<td>ASCVD</td>
<td>168</td>
<td>52.3</td>
<td>1.50</td>
<td>3590</td>
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<td>S.F., 55</td>
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<td>5280</td>
<td>72.0</td>
<td>2.89</td>
<td>52.0</td>
<td></td>
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</table>

**Table 5.** — Group III Consisted of Cardiac Patients Who Had a History of Dyspnea, Orthopnea, Paroxysmal Nocturnal Dyspnea and, When Present, Physical or X-ray Evidence of Pulmonary Congestion*

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>E.R., 78</td>
<td>ASHD — acute myocard. infarct</td>
<td>176</td>
<td>63.6</td>
<td>57.0</td>
<td>1.76</td>
<td>1.70</td>
<td>4140</td>
<td>65.0</td>
<td>73.6</td>
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<tr>
<td>H.H., 69</td>
<td>ASHD — old myocard. infarct</td>
<td>173</td>
<td>66.0</td>
<td>64.5</td>
<td>1.80</td>
<td>1.77</td>
<td>4490</td>
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<td>3290</td>
<td>61.5</td>
<td>65.0</td>
</tr>
<tr>
<td>J.J., 79</td>
<td>ASHD — old myocard. infarct</td>
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<td>85.7</td>
<td>2.12</td>
<td>2.10</td>
<td>5190</td>
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<td>K.P., 66</td>
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<td>66.0</td>
<td>1.78</td>
<td>—</td>
<td>3420</td>
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<td>1.64</td>
<td>3950</td>
<td>64.4</td>
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<td>88.3</td>
<td>88.0</td>
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<td>1.99</td>
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<td>1.50</td>
<td>3242</td>
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</table>

**Average (12 pts.) =**

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<tbody>
<tr>
<td></td>
<td>wet dry</td>
<td></td>
<td></td>
<td>wet dry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. (12 pts.) =</td>
<td>61.0 ± 0.6</td>
<td>66.0 ± 0.78</td>
<td>2.3 ± 0.28</td>
<td>2.39 ± 0.25</td>
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<td></td>
</tr>
</tbody>
</table>

*At the request of the editor, the details of the symptoms and findings are being omitted from this table. These will be furnished on request.*

**Group V** (4). This group consisted of patients who had primary pulmonary disease and secondary right ventricular hypertrophy plus either two or more of the following: venous distention, enlarged liver and peripheral edema.

A more complete description of the symptoms and findings of individual patients at the time of the blood volume determination may be found in tables 3 to 7.

**Results**

The whole blood volumes in the normal patients were found to range from 2500 to 6084 cc. Volumes were also calculated as cubic
TABLE 6.—Group IV Consisted of Cardiac Patients Who Had Evidences of Pulmonary Congestion Plus Either Two or More of the Following: Venous Distention, Enlarged Liver, Ascites, Hydrothorax or Peripheral Edema*

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>wet</td>
<td>dry</td>
<td>wet</td>
<td>dry</td>
<td>wet</td>
<td>dry</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>140</td>
<td>160</td>
<td>140</td>
<td>160</td>
<td>140</td>
<td>160</td>
</tr>
<tr>
<td>B.C., 39</td>
<td>Syph, HD, AI</td>
<td>160</td>
<td>75.0</td>
<td>69.0</td>
<td>1.98</td>
<td>1.92</td>
<td>5590</td>
<td>74.0</td>
</tr>
<tr>
<td>B.L., 39</td>
<td>RHD, AI, MI, MS</td>
<td>171</td>
<td>68.5</td>
<td>64.0</td>
<td>1.81</td>
<td>1.77</td>
<td>5540</td>
<td>80.4</td>
</tr>
<tr>
<td>B.H., 63</td>
<td>ASCVD</td>
<td>171</td>
<td>55.7</td>
<td>49.0</td>
<td>1.63</td>
<td>1.58</td>
<td>4650</td>
<td>83.5</td>
</tr>
<tr>
<td>C.T., 55</td>
<td>RHD with MS, MI</td>
<td>166</td>
<td>82.2</td>
<td>73.0</td>
<td>1.90</td>
<td>1.81</td>
<td>7400</td>
<td>90.0</td>
</tr>
<tr>
<td>C.D., 66</td>
<td>ASHD</td>
<td>—</td>
<td>52.3</td>
<td>49.5</td>
<td>—</td>
<td>—</td>
<td>4500</td>
<td>87.6</td>
</tr>
<tr>
<td>C.J., 63</td>
<td>HASCVD</td>
<td>156</td>
<td>80.5</td>
<td>77.0</td>
<td>2.15</td>
<td>2.05</td>
<td>5710</td>
<td>83.9</td>
</tr>
<tr>
<td>C.T., 60</td>
<td>ASCVD</td>
<td>179</td>
<td>80.5</td>
<td>80.5</td>
<td>1.98</td>
<td>1.98</td>
<td>5920</td>
<td>85.0</td>
</tr>
<tr>
<td>G.C., 60</td>
<td>Syph, HD, AI</td>
<td>165</td>
<td>57.3</td>
<td>52.0</td>
<td>1.61</td>
<td>1.58</td>
<td>4700</td>
<td>82.0</td>
</tr>
<tr>
<td>H.C., 54</td>
<td>HVCYD, Malig. hypertens.</td>
<td>183</td>
<td>61.0</td>
<td>—</td>
<td>1.80</td>
<td>—</td>
<td>4480</td>
<td>73.6</td>
</tr>
<tr>
<td>H.L., 25</td>
<td>RHD with MS, MI</td>
<td>176</td>
<td>56.5</td>
<td>57.0</td>
<td>1.76</td>
<td>1.72</td>
<td>4410</td>
<td>75.4</td>
</tr>
<tr>
<td>H.J., 56</td>
<td>ASHD</td>
<td>170</td>
<td>75.0</td>
<td>67.0</td>
<td>1.80</td>
<td>1.81</td>
<td>7030</td>
<td>94.0</td>
</tr>
<tr>
<td>J.J., 50</td>
<td>HVCYD</td>
<td>168</td>
<td>57.0</td>
<td>50.5</td>
<td>1.62</td>
<td>1.58</td>
<td>3343</td>
<td>62.3</td>
</tr>
<tr>
<td>K.G., 65</td>
<td>HASCVD—old myocard. infarct.</td>
<td>185</td>
<td>102.0</td>
<td>77.0</td>
<td>2.09</td>
<td>2.03</td>
<td>7380</td>
<td>72.5</td>
</tr>
<tr>
<td>M.E., 68</td>
<td>HASCVD—old myocardial, infarct.</td>
<td>168</td>
<td>73.3</td>
<td>64.0</td>
<td>1.81</td>
<td>1.71</td>
<td>4750</td>
<td>64.8</td>
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<tr>
<td>P.R., 70</td>
<td>HVCYD</td>
<td>170</td>
<td>80.0</td>
<td>80.0</td>
<td>1.91</td>
<td>—</td>
<td>6210</td>
<td>77.7</td>
</tr>
<tr>
<td>P.J., 65</td>
<td>ASCVD</td>
<td>175</td>
<td>51.3</td>
<td>51.0</td>
<td>1.61</td>
<td>1.61</td>
<td>4840</td>
<td>94.2</td>
</tr>
<tr>
<td>R.C., 63</td>
<td>RHD with MS, MD, AF</td>
<td>175</td>
<td>90.5</td>
<td>81.6</td>
<td>2.14</td>
<td>2.07</td>
<td>8790</td>
<td>87.7</td>
</tr>
<tr>
<td>R.J., 75</td>
<td>ASCVD, AF</td>
<td>166</td>
<td>72.0</td>
<td>65.2</td>
<td>1.82</td>
<td>1.78</td>
<td>6789</td>
<td>94.0</td>
</tr>
<tr>
<td>S.G., 70</td>
<td>ASCVD—old myocard. infarct.</td>
<td>166</td>
<td>61.3</td>
<td>58.0</td>
<td>1.72</td>
<td>1.61</td>
<td>4480</td>
<td>71.0</td>
</tr>
<tr>
<td>S.J., 56</td>
<td>ASCVD</td>
<td>176</td>
<td>88.5</td>
<td>80.0</td>
<td>2.03</td>
<td>1.97</td>
<td>6300</td>
<td>73.5</td>
</tr>
<tr>
<td>T.E., 59</td>
<td>ASHD with old myocard. infarct</td>
<td>174</td>
<td>109.0</td>
<td>94.4</td>
<td>2.22</td>
<td>2.10</td>
<td>7050</td>
<td>73.0</td>
</tr>
<tr>
<td>W.E., 47</td>
<td>ASCVD</td>
<td>170</td>
<td>82.0</td>
<td>70.5</td>
<td>1.92</td>
<td>1.82</td>
<td>5550</td>
<td>68.0</td>
</tr>
<tr>
<td>T.F., 61</td>
<td>ASCVD</td>
<td>178</td>
<td>65.1</td>
<td>64.5</td>
<td>1.84</td>
<td>1.80</td>
<td>5300</td>
<td>83.4</td>
</tr>
<tr>
<td>U.C., 56</td>
<td>ASCVD</td>
<td>177</td>
<td>57.0</td>
<td>54.5</td>
<td>1.70</td>
<td>1.67</td>
<td>4120</td>
<td>72.0</td>
</tr>
<tr>
<td>H.F., 60</td>
<td>Old myocard. infarct</td>
<td>183</td>
<td>82.6</td>
<td>68.7</td>
<td>2.04</td>
<td>1.99</td>
<td>6442</td>
<td>78.0</td>
</tr>
</tbody>
</table>

* At the request of the editor, the details of the symptoms and findings are being omitted from this table. These will be furnished on request.

In cardiac patients who had never been in congestive heart failure (group I) and in recently compensated cardiac patients (group II) blood volumes were within the normal range. Normal values were also found in patients with pulmonary congestion alone (group III). Blood volumes were significantly elevated in the majority of patients who had venous distention, liver congestion, and peripheral edema whether secondary to left ventricular failure or mitral stenosis (group IV) or to primary pulmonary disease (group V). The individual determinations in these groups of cardiac patients are compared with the normal range and mean in figure 2. The values for blood volume in cubic centimeters, cubic centimeters per kilogram and liters per square meter for each patient in the five groups are listed in tables 3 to 7.

A statistical comparison* of each group of

* The statistical comparisons of the several groups were made as follows:

\[
\text{Variance of } V = \frac{\text{dev of group I} + \text{dev of group II}}{N_1 \pm (N_2 - 2)}
\]

To calculate standard error of difference:

\[
\frac{V}{N_1} \pm \frac{V}{N_1} \times \frac{t}{N_1}
\]

where

\[
t = \frac{\text{difference between means}}{\text{standard error of difference}}
\]

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cardiac patients with normal subjects revealed the following results:

Patients in group I had blood volumes significantly lower than the volumes of normal subjects when the volumes were calculated as cubic centimeters per kilogram \(p = 0.01\) and probably significantly lower than the volumes of normal subjects when the values were calculated as liters per square meter of body surface area \(p = 0.1\).

Patients of group II did not have blood volumes significantly different from the values of normal subjects when determined either as cubic centimeters per kilogram or as liters per square meter.

The blood volumes of patients in group III were significantly lower than those of normal subjects when calculated as cubic centimeters per kilogram \(p = 0.02\) but were almost the same as normal when calculated from “dry” weight. When these same comparisons were made on a basis of liters per square meter of body surface area the blood volume was lower than the blood volume of normal subjects “wet” \(p = 0.03\) but not significantly lower, “dry” \(p = 0.3\).

Blood volumes of patients in group IV were very significantly higher than the volumes in normal subjects whether calculated as cubic centimeters per kilogram or liters per square meter “wet” or “dry” \(p\) in each case less than 0.01).

Although there were only four patients in group V the comparison was higher than

---

**Table 7.** Group V consisted of patients who had primary pulmonary diseases, secondary right ventricular hypertrophy plus either two or more of the following: venous distention, enlarged liver and peripheral edema.

<table>
<thead>
<tr>
<th>Group V</th>
<th>Diagnosis</th>
<th>Ht., cm</th>
<th>Weight, Kg.</th>
<th>Surface area, sq.M.</th>
<th>Blood Vol., cc/Kg.</th>
<th>Blood Vol., L/sq.M.</th>
<th>PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>wet     dry</td>
<td>wet     dry</td>
<td>wet     dry</td>
<td>wet     dry</td>
<td></td>
</tr>
<tr>
<td>B.F., 57</td>
<td>Pulmon. emphy-sema. Chr. cor pulmon.</td>
<td>175</td>
<td>56.0 49.0</td>
<td>1.68 1.50</td>
<td>4720    84.2 96.4</td>
<td>2.80 2.96</td>
<td>55.0</td>
</tr>
<tr>
<td>H.C., 55</td>
<td>Pulmon. emphy-sema. Chr. cor pulmon.</td>
<td>188</td>
<td>101.0 88.0</td>
<td>2.28 2.15</td>
<td>7700    76.2 87.5</td>
<td>3.37 3.48</td>
<td>51.0</td>
</tr>
<tr>
<td>T.R., 38</td>
<td>Pulmon. emphy-sema. Chr. cor pulmon.</td>
<td>175</td>
<td>57.4 51.4</td>
<td>1.70 1.62</td>
<td>4730    83.0 92.2</td>
<td>2.78 2.92</td>
<td>54.5</td>
</tr>
<tr>
<td>W.F., 42</td>
<td>Bronchiect. Pulmon. emphy-sema. Chr. cor pulmon.</td>
<td>171</td>
<td>51.6 44.5</td>
<td>1.60 1.50</td>
<td>4430    86.0 99.5</td>
<td>2.76 2.95</td>
<td>55.0</td>
</tr>
</tbody>
</table>

Avg. (4 pts.) = 82.2 ± 7.64

*At the request of the editor the details of the symptoms and findings are being omitted from this table. These will be furnished on request.

**Table 8.** Comparative Mean Values of Blood Volumes in Normal and Cardiac Patients by Weight and Surface Area

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet, cc/Kg.</td>
<td>65.5 ± 5.95</td>
<td>61.3 ± 7.6</td>
<td>66.6 ± 9.1</td>
<td>61.0 ± 6.6</td>
<td>77.7 ± 9.5</td>
<td>82.2 ± 7.6</td>
</tr>
<tr>
<td>Dry, cc/Kg.</td>
<td>2.37 ± 0.26</td>
<td>2.38 ± 0.27</td>
<td>2.31 ± 0.28</td>
<td>2.30 ± 0.25</td>
<td>3.17 ± 0.56</td>
<td>3.07 ± 0.19</td>
</tr>
<tr>
<td>Wet, L/sq.M.</td>
<td>2.49 ± 0.28</td>
<td>2.15 ± 0.26</td>
<td>2.28 ± 0.27</td>
<td>2.30 ± 0.25</td>
<td>3.17 ± 0.56</td>
<td>3.07 ± 0.19</td>
</tr>
<tr>
<td>Dry, L/sq.M.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values obtained for wet weight were calculated from the actual weight at the time of the blood volume determination. Values for dry weight were calculated from the weights obtained at the time of maximum compensation.
normal when determined either as cubic centimeters per kilogram or liters per square meter of body surface area "wet" or "dry" \( (p = 0.01) \). The comparison of the mean values and standard deviation in each of these groups with the values in normal subjects is made in table 8.

DISCUSSION

Elevated blood volumes in these patients apparently depended upon the development of right ventricular failure, whether it occurred as a result of left ventricular failure, mitral stenosis or primary pulmonary disease. This was true on comparison by weight or by body surface area. Greater accentuation of these differences was evident when calculating the congestive heart failure patient's blood volumes by the lowest weight following cardiac compensation; i.e., dry weight (see table 4).

In patients who manifested only signs and symptoms of left ventricular failure or mitral stenosis (group III), not a single blood volume determination was elevated above that of subjects in the normal group. Although five of the patients in group IV had blood volumes within the range of the mean and standard deviation of subjects in the normal group, in only one of these did the volume remain in this range when volumes were calculated by dry weight. On the basis of these studies we believe that in the fully developed picture of congestive heart failure, that is, pulmonary and hepatic congestion, venous distention and edema, the blood volume is significantly elevated, but that in a few patients in this state it may be normal. The explanation of the findings of a normal blood volume in such a patient with right and left heart failure is not clear to us.

Serial determinations were done on 16 patients with symptoms and signs of right and left ventricular failure. In general, blood volumes reverted to normal values as cardiac reserve returned; the converse was true in patients who became clinically worse or died.

Although part of the increased blood volume in congestive failure due to cor pulmonale may be explained by secondary polycythemia, serial determinations on these patients after cardiac therapy revealed a return toward the normal ranges.

Our results were in general in accord with Nylin and Hedlund\(^6\) who stated that in congestive heart failure the increase in whole blood volume is most marked in patients with severe edema, and slight in those with pulmonary congestion alone.

These results are not in agreement with those of Prentice and associates\(^9\) who found normal blood volumes in 12 of 27 patients with heart failure. The explanation of these findings which differ from ours evidently is not that their patients had predominantly left ventricular failure, for they state that only one third of the patients with normal volumes had left sided failure. If the majority of their patients had only minimal to moderate edema this may be significant since the degree of elevation of blood volume in our cases was roughly correlated with the amount of edema and excess body weight. Nor does our data support the finding of these authors that most of their patients who did have elevated blood volumes in heart failure were those with old rheumatic heart disease and that those with hypertensive and arteriosclerotic heart disease had essentially normal volumes. We found elevated blood volumes in most of the patients with concomitant left and right sided failure regardless of the etiology of the heart disease. Like ourselves, Prentice and co-workers\(^9\) found normal blood volumes in their patients with only left ventricular failure. As they state, however, there were no cases of early acute left ventricular failure in their study. We were unable to test patients with left ventricular failure until 12 to 18 hours after hospital admission; however, these patients still had signs and symptoms of failure at the time of testing.

Differences in the blood volume of normal subjects and patients with left ventricular failure from those with combined right and left failure depend to a large extent upon the correct evaluation of the patients and their proper placement in the groups as described. Certainly there is no sharp clinical division between left and right failure. Fluid retention, hepatic congestion and elevated venous pressure
during exercise may exist and may not be clinically recognized in cardiac patients. Venous pressure and circulation time often add little to this differentiation. In most instances the clinician can separate patients who have predominantly left heart failure from those with both left and right or right failure alone. Concomitant cardiac catheterization and renal studies would add greatly to the interpretation of blood volume changes.

The chain of events in the development of expanded intravascular volumes in cardiac failure has always been a controversial subject and often has been compared to the "horse and cart" problem. Needless to say the complete picture may stem from the concept of insufficient cardiac output relative to the metabolic needs of an individual. Not only are there changes resulting from poor output but there are also changes resulting from an increasing residual of blood proximal to the failing ventricle. In left ventricular failure and mitral stenosis reduced output (resulting in relative anoxia) to the organs such as the kidney, liver, and endocrine glands may result in changes such as salt and water retention. Apparently from our studies this retention does not result in hypervolemia if there is left ventricular failure or mitral stenosis alone but apparently depends upon the failure of the right ventricle as well. As Ross\(^{39}\) and others have pointed out, there may be a shift of a portion of the total circulating blood volume to the pulmonary vascular tree without a resultant increase in the total circulating blood volume. This shift into the pulmonary vascular tree is probably dependent upon an adequately functioning right ventricle relative to the left ventricle. The dyspnea, orthopnea, and pink frothy sputum occurring with left ventricular failure and mitral stenosis are probably due to this relative shift. Clinically these symptoms may disappear or lessen with the onset of right ventricular failure and mitral stenosis and this may be due to this relative shift. Consequently we feel that hypervolemia occurring only with right ventricular failure plays a definite role in the sequence of the pathologic physiology of the failing heart.

**Summary**

1. The advantages and method of using radiochromium are described for determining whole blood volume in normal and congestive heart failure patients.

2. Patients with normal heart function were observed to have whole blood volumes of 65.5 ± 5.95 cc. per kilogram or 2.49 ± 0.28 liters per square meter of body surface area.

3. Hypervolemia occurs in the majority of cardiac patients with signs and symptoms of right ventricular failure but not in those cardiac patients with left ventricular insufficiency or mitral stenosis alone.

**SUMARIO ESPAÑOL**

1. Las ventajas y el método de usar radiocromo se describen para la determinación del volumen sanguíneo total en sujetos normales y en pacientes en descompensación cardíaca.

2. Pacientes con función cardiaca normal fueron observados tener volúmenes sanguíneos total de 65.5 ± 5.95 cc. por kilogramo o 2.49 ± 0.28 litros por metro cuadrado de superficie del cuerpo.

3. Hipervolemia ocurre en la mayoría de los pacientes cardíacos con signos y síntomas de descompensación del ventrículo derecho pero no en aquellos pacientes cardíacos con insuficiencia ventricular izquierda o estenosis mitral solamente.

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5. Freinkel, N., Schreiner, G. E., and Athens, J. W.: Simultaneous distribution of T-1824 dye...
Whole Blood Volume Determined by Radiochromium-Tagged Red Cells: Comparative Studies on Normal and Congestive Heart Failure Patients
WILLIAM A. REILLY, RICHARD M. FRENCH, FRANCIS Y. K. LAU, KENNETH G. SCOTT and WILLIAM E. WHITE

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CORRECTION: In the paper by Dr. W. A. Reilly and colleagues, "Whole Blood Volume Determined by Radiochromium-Tagged Red Cells," which appeared in the April 1964 issue of CIRCULATION, the equation on page 573 should be corrected to:

\[
\text{Patient's blood vol. in cc.} = \frac{\text{Total counts/sec./injected}}{\text{Counts/sec./cc. blood withdrawn}}
\]