Change in Relationship of Blood Volume to Weight in Congestive Heart Failure


Blood volume has been estimated in a small group of nonedematous hospitalized patients and in cardiac patients in severe congestive failure by both Cr[superscript 51] labeled red cells and iodinated (I[superscript 131]) human serum albumin. In the analysis of the data attention is directed to a fallacy inherent in the usual ratio method of relating blood volume to weight. An alternative method of analysis is proposed that not only yields greater accuracy, but makes the analysis more sensitive. The authors present their interpretation of the effects of tissue wasting and accumulation of edema fluid on the changes in the relationship between blood volume and weight in congestive heart failure. Analyzing other data from the literature by this method the authors have demonstrated a relationship between the amount of edema fluid and the increase in blood volume in congestive failure.

One of the chief problems of evaluating the increases of the blood volume in congestive heart failure has been the choice of a suitable method for comparison of patients with failure and control patients. In studies with human subjects it has not been possible to observe the "normal" blood volume of individuals before they acquire heart disease. The state of compensation reached following diuretics, salt restriction, and digitalis cannot be considered normal. Each subject's normal blood volume being lacking, it has been necessary to compare the blood volumes of the group of patients under study with the blood volumes of a group of normal or other control subjects. Since there is among normal individuals a relationship between blood volume and size of the individual, the ratio of blood volume to weight (ml./Kg.) or to calculated surface area (L./M?) has frequently been used for this comparison. Tanner has pointed out that per-weight and per-surface area standards may lead to erroneous conclusions. The earlier work in this field with dyes that label circulatory protein had shown greatly increased blood volume by means of the ratio method of analysis. The results with radioactively labeled erythrocytes, however, have shown the blood volume elevated to a lesser extent if at all. The purpose of this paper is to report the results of blood volume measurements in congestive heart failure by red cell and protein labeling and to demonstrate a more advantageous method of analysis than ratio comparisons when adjustment for body weight is desired.

Methods

Selection of Patients

Of the 20 patients observed, 9 had been hospitalized for congestive heart failure. Eleven hospitalized patients, suffering from a variety of conditions not suspected to affect the blood volume, were chosen as a control group.

Each patient of the congestive failure group had edema and increased venous pressure, but the etiologic heart disease in each was believed to involve primarily the left heart. In addition, each person showed a variety of hepatomegaly, ascites, hydrothorax, cyanosis, increased circulation time, and cachexia, all indicators of serious disease. Two of the patients had received mercurial (Mercurhydrin) and 12 hours before the study. Three of the failure patients were female whereas all of the control patients were male. Each of these 2 factors is recognized as an influence toward a lower average blood volume in the failure group.

In the control group about half suffered from chronic disease and the remainder were robust middle-aged men with coronary arteriosclerosis uncomplicated by heart failure.

Blood Volume Methods

Cr[superscript 51]-Labeled Erythrocyte Method. The Cr[superscript 51]-erythrocyte-labeling method of Gray and Sterling was employed with minor modifications. The blood to be labeled was obtained from the subject, labeled, washed, and re-injected with a minimum of delay.
The cells were washed once with sterile .9 per cent sodium chloride solution and resuspended for injection. Routinely, assays demonstrated that less than 1 per cent of the radioactivity in this suspension was in the suspending saline. An aliquot of the final suspension was used for the preparation of standards in duplicate.

Following the injection of approximately 100 μc. of Cr₄¹ in a labeled cell suspension, blood samples were withdrawn without stasis from an indwelling no. 16- or no. 18-gage needle in an antecubital vein. The needle was kept patent with an obturator. The anticoagulant was dry heparin.

Following the injection of labeled cells in the opposite arm, 6 to 10 blood samples were drawn over a period of approximately 1 hour for determination of radioactivity. Since evidence was obtained that mixing was not entirely complete until about 25 minutes after injection, samples drawn earlier were not used in calculating the blood volumes. At least 5 samples of blood were used in each calculation of blood volume.

$^{51}$I-Labeled Human Serum Albumin Method. Commerically available $^{51}$I-labeled human serum albumin was used. The appropriate dilution was made so that each milliliter contained 10 μc. of $^{51}$I. With a 5-ml. Luer-lok syringe equal injections were made from the 4-ml. mark into a 1000-ml. volumetric flask and into an antecubital vein of the patient. The injection of $^{51}$I-labeled human serum albumin was made directly following the withdrawal of the last blood sample of the labeled cell procedure. Following the $^{51}$I-albumin injection, samples were withdrawn from the same indwelling needle as before at 10, 30, 50, and 70 minutes after injection. Plasma was assayed on all samples. Hematocrit values were determined on each blood sample counted, the blood being taken directly from the assayed tube after counting. Wintonre tubes were spun at 2,000 G for 1 hour.

Assays of Radioactivity. Assays of radioactivity were carried out on samples of whole blood or plasma in the liquid state, with a conventional well-type scintillation counter, 3 ml. of fluid being contained in each sample.

**RESULTS**

The physical measurements and estimations of blood volume and its components are given for each subject in tables 1 and 2. The mean height for the control group was 169.4 cm. and for the failure group 170.8 cm. In spite of this similarity in height, the absolute mean red cell volume, plasma volume, and blood volumes by Cr₄¹ cells and $^{51}$I albumin are higher in the congestive failure group than in the control group. In table 3 the probabilities that such different mean absolute values could have been obtained by chance are given in the first column. For each component of the blood volume the average of the failure group is significantly* greater than that of the control group.

* A probability value of .05 or less is taken as the criterion of significance in all statistical tests in this report.
TABLE 2.—Blood Volume Data of Failure Group

<table>
<thead>
<tr>
<th>Initials, sex, age</th>
<th>Diagnosis</th>
<th>Wt. (Kg.)</th>
<th>Ht. (cm.)</th>
<th>S.A. (M.²)</th>
<th>Hct (%)</th>
<th>RVCr (ml.)</th>
<th>PVV (ml.)</th>
<th>BVV (ml.)</th>
<th>BVV — BVCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C. M., m, 60</td>
<td>HCVD</td>
<td>67.1</td>
<td>172</td>
<td>1.78</td>
<td>40.3</td>
<td>2240</td>
<td>3650</td>
<td>5580</td>
<td>6100</td>
</tr>
<tr>
<td>2. C. H., m, 67</td>
<td>ASHD or HCVD</td>
<td>74.3</td>
<td>176</td>
<td>1.90</td>
<td>39.1</td>
<td>2220</td>
<td>4040</td>
<td>5670</td>
<td>6630</td>
</tr>
<tr>
<td>3. L. D., f, 38</td>
<td>RHD, pulmonary infarct</td>
<td>58.4</td>
<td>164</td>
<td>1.64</td>
<td>49.4</td>
<td>2070</td>
<td>2690</td>
<td>4200</td>
<td>5310</td>
</tr>
<tr>
<td>4. M. J., f, 49</td>
<td>Aortic insufficiency</td>
<td>66.1</td>
<td>162</td>
<td>1.70</td>
<td>45.7</td>
<td>2130</td>
<td>3530</td>
<td>4670</td>
<td>6480</td>
</tr>
<tr>
<td>5. P. S., m, 48</td>
<td>ASHD</td>
<td>75.8</td>
<td>166</td>
<td>1.82</td>
<td>51.8</td>
<td>2250</td>
<td>2760</td>
<td>4350</td>
<td>5730</td>
</tr>
<tr>
<td>6. O. E., f, 58</td>
<td>HCVD</td>
<td>67.1</td>
<td>160</td>
<td>1.69</td>
<td>42.6</td>
<td>2370</td>
<td>3600</td>
<td>5560</td>
<td>6380</td>
</tr>
<tr>
<td>7. T. M., m, 47</td>
<td>ASHD or HCVD</td>
<td>140</td>
<td>179</td>
<td>2.30</td>
<td>35.6</td>
<td>3440</td>
<td>7580</td>
<td>9650</td>
<td>11760</td>
</tr>
<tr>
<td>8. G. E., m, 53</td>
<td>RHD</td>
<td>77.6</td>
<td>174</td>
<td>1.91</td>
<td>44.6</td>
<td>2350</td>
<td>3550</td>
<td>5270</td>
<td>6400</td>
</tr>
<tr>
<td>9. O. R., m, 38</td>
<td>ASHD</td>
<td>86.8</td>
<td>184</td>
<td>2.09</td>
<td>48.2</td>
<td>3360</td>
<td>4090</td>
<td>6970</td>
<td>7890</td>
</tr>
</tbody>
</table>

Mean: 79.2 171 1.89 44.1 2492 3950 5769 6964
S.D.: 24.2 8 0.27 5.3 515 1444 1678 1929

TABLE 3.—Comparison of Absolute Means and Mean Ratios of the Various Components of Blood Volume with Height, Weight, and Surface Area. The p Value Derived from a t Test is Given Below Each Pair of Means

<table>
<thead>
<tr>
<th></th>
<th>Absolute ml</th>
<th>+ Height ml/cm.</th>
<th>+ Weight ml/Kg.</th>
<th>+ SA ml/M.²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>failure</td>
<td>control</td>
<td>failure</td>
</tr>
<tr>
<td>Blood volume Cr²¹</td>
<td>4264</td>
<td>5769</td>
<td>25.16</td>
<td>33.50</td>
</tr>
<tr>
<td></td>
<td>p = .01</td>
<td>p = .01</td>
<td>p = .15</td>
<td>p = .03</td>
</tr>
<tr>
<td>Blood Volume I²¹ albumin</td>
<td>4869</td>
<td>6964</td>
<td>28.75</td>
<td>40.50</td>
</tr>
<tr>
<td></td>
<td>p = .003</td>
<td>p = .002</td>
<td>p = .03</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Red Cell volume Cr²¹</td>
<td>1899</td>
<td>2492</td>
<td>11.21</td>
<td>14.52</td>
</tr>
<tr>
<td></td>
<td>p = .005</td>
<td>p = .002</td>
<td>p = .18</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Plasma volume I²¹ albumin</td>
<td>2699</td>
<td>3950</td>
<td>15.95</td>
<td>22.98</td>
</tr>
<tr>
<td></td>
<td>p = .01</td>
<td>p = .01</td>
<td>p = .05</td>
<td>p = .003</td>
</tr>
<tr>
<td>Plasma volume Cr²¹</td>
<td>2365</td>
<td>3277</td>
<td>13.96</td>
<td>19.04</td>
</tr>
<tr>
<td></td>
<td>p = .03</td>
<td>p = .03</td>
<td>p = .20</td>
<td>p = .02</td>
</tr>
</tbody>
</table>

Since the distributions of weight and surface area of the 2 groups are different, in part because all of the patients with failure had edema, covariance analysis was applied to the data. A graph was made of the blood volume plotted against the weight for each control individual, and the points representing the subjects in failure were plotted on the same graph. If each set of points was described adequately by a straight line, it was assumed that the true relation, or regression of blood volume on weight, was linear. The least squares line was obtained for each group of individuals and the question was asked: "Are these lines 2 estimates of the

FIG. 1 Top left. Plot of blood volume by the Cr²¹ method against weight. The lines are least squares regressions among the points for control patients and patients with failure. The result of covariance analysis is given in the lower left corner. The diagram on the lower right shows ratio analysis of the same data. The horizontal dashed line in each group represents the mean. In spite of a significant difference in adjusted means, the ratio comparisons fail to show a significant difference.

FIG. 2 Top right. Plot of blood volume by the I²¹ method against weight.

FIG. 3 Bottom left. Plot of red cell volume by the Cr²¹ method. The failure regression is significantly higher than the control regression. The ratio comparisons on the lower right fail to show a significant difference.

FIG. 4 Bottom right. Plot of plasma volume by the I²¹ method against weight. In this instance both methods of analysis show a significant difference.
Blood Volume (Cr$^{51}$) Vs Weight

- Controls •
- Failure □

Blood Volume (I$^{131}$) Vs Weight

- Control •
- Failure □

Red Cell Volume (Cr$^{51}$) Vs Weight

- Control •
- Failure □

Plasma Volume (I$^{131}$) Vs Weight

- Control •
- Failure □

Figs. 1-4
same linear regression or may we conclude that they represent different regressions?” This question was answered by testing the significance of the difference between the slopes of the 2 lines. If the slopes were not significantly different, 2 parallel lines were fitted to the 2 sets of points and the vertical distance between the lines was tested. The vertical distance between these parallel lines represented the difference between the mean blood volumes of the 2 groups corrected or adjusted for differences in weight and was called the difference between the adjusted means.13

Our data have been plotted and subjected to covariance analysis. Figures 1–5 are representative graphs and are described below.

Blood Volume by Labeled Cells. The plot of the blood volume, as estimated by the dilution of Cr51-labeled erythrocytes, against weight is given in figure 1. The solid line is the regression line for the control group; the broken line is the regression for the failure group. The points of the failure group fell mostly above the points of the control group but there was some mingling of the 2 sets. Since there was mingling of the 2 sets, it was not obvious that the relationship of blood volume to weight was truly different in the 2 groups. Statistical analysis showed that the slopes of these 2 lines were not significantly different, but that the difference between the adjusted means was significant ($p = .02$). Thus the relationships between the blood volume and weight were different in the 2 groups.

Blood Volume by $I^{131}$-Labeled Albumin. The covariance of blood volume as estimated by $I^{131}$-labeled human serum albumin with weight was also analyzed (fig. 2). The points of the failure group lie more strikingly above the controls in this instance than in figure 1. The difference in slopes of the 2 lines was significant ($p < .01$).

Red Cell Volume. The red cell volume as estimated by the dilution of Cr51-labeled cells is plotted against the weight in figure 3. The slopes of the 2 lines were very similar, but the line for the failure group was significantly above that for the controls ($p < .01$, adjusted means).

Plasma Volume. The plasma volume as estimated by the dilution of $I^{131}$-labeled albumin was plotted against the weight in figure 4. The slopes were significantly different. The slopes were also significantly different when plasma volume as estimated with Cr51 erythrocytes was examined.

The relationships of blood volume, red cell volume, and plasma volume to surface area have also been examined by covariance analysis. In some instances the slopes were significantly different as, for example, in figure 5, which shows the relationship of blood volume as measured by labeled cells to surface area. In the others the difference between adjusted means was significant, with the points of the failure group lying above those of the control group.

Thus it was found that the blood volume as measured by erythrocyte dilution, by albumin dilution, and by addition of red cell volume to plasma volume was higher in the congestive failure group than in the control group. This was true whether these volumes were related to weight or to surface area.
Reilly French Lau Scott & White
Blood Volume (Cr³⁻) Vs Weight

Fig. 6. Regression lines calculated from 89 normal subjects, and 37 nonedematous cardiac, and 29 edematous failure patients regrouped from Reilly and his co-workers. Covariance analysis in this instance is in agreement with the conclusions of the authors, which were based on ratio analysis such as that illustrated on the lower right.

Analysis of the Data of Reilly, French, Lau, Scott, and White. Although this more sensitive method of analysis appeared to indicate a real increase in blood volume in congestive failure when applied to our small group, larger series of such data were sought for similar analysis. The only other set of data that was made available to us was that of Reilly et al.

This much larger series of data was analyzed and is illustrated in figure 6. The blood volume as estimated with Cr³⁻ erythrocytes is plotted against the weight. We have pooled their experimental data into 3 groups: (1) 89 normal subjects; (2) 37 patients with heart disease without peripheral edema (groups I, II, and III); and (3) 29 patients with heart disease with peripheral edema (groups IV and V). The result of covariance analysis supports their conclusion that the blood volume is elevated in patients with signs and symptoms of right ventricular failure. This is true whether the edematous cardiac patients are compared with nonedematous cardiac patients or with normal control subjects. *

Discussion

Fallacy of Certain Ratio Standards. Blood volume data have usually been expressed as the ratio of the patient’s blood volume to weight or to surface area. Tanner has emphasized the fallacy of using ratios unless it can be shown that the ratio of blood volume to weight or to surface area is constant over the full range of adult body size. Several investigators have commented that the ratio of blood volume to weight is higher in small individuals than in large ones. If ratios proved constant over a large span of weight, a plot of blood volume against weight in a group of normal individuals would show points scattering about a line passing through the origin of the graph. But replotting of data from tables of “normal” adult blood volumes given in the literature shows least squares regression lines of blood volume on weight pass considerably above the origin. In figure 7, line A represents a constant ratio of 70 ml./Kg., whereas line B is an idealized line based on available data; it demonstrates that in heavy persons the ratio of blood volume to weight is smaller than in lighter individuals.

Since the relationship between blood volume and weight in normal individuals is best expressed by a line that does not pass through the origin of the graph, a person’s ratio does not indicate whether his point would be far above, close to, or far below the line.

Analysis of Our Data by Ratio Standards. The data of the present study may serve to illustrate the possible erroneous conclusions that might be drawn from ratio analysis. In the first column of table 3 the average values are compared and shown with the probability value derived from a t test. Similarly in the remaining columns, the means of ratios of volume to height, weight, and surface area are compared.

In each comparison in the table, the mean of the failure group is higher than that of the

* The authors of this work very kindly sent us a list of the individual red cell volumes, weights, heights, and hematocrit values of these 89 normal patients to make these calculations possible.
control group. In the ratio to weight column the difference in means is not significant for each of the volumes estimated with Cr\textsuperscript{51}. But in figures 1 and 3, a plot of the corresponding data indicates an increase in the blood volume in congestive failure.

Interpretation of Results of Regression Analysis in Congestive Failure. In congestive failure the body weight may be both increased by edema and diminished by tissue wasting. Let us consider the possibility that the increase in blood volume in congestive failure as shown in figure 1 was due to tissue wasting rather than to the formation of edema. The investigation of Keyes and his associates\textsuperscript{24} of the effects of semistarvation in human beings sheds light on the effects of tissue wasting on blood volume. Their data indicate that there was an actual mean fall of 500 ml in absolute blood volume during 24 weeks of semistarvation, even though the ratio of blood volume to weight rose. In figure 8 the least squares regression of blood volume on weight is given for their data obtained during the control period. The cross in this line represents the mean blood volume plotted against the mean weight. The closed circle to the left, lying on the dotted extension of the control line, is the mean blood volume and weight for the same individuals after semistarvation. It is apparent that the loss in blood volume and weight has been such that the pre-starvation blood volume-weight relationship has not been greatly disturbed. In the lower right corner of the figure, a striking and "significant" increase in the ratio of blood volume to weight in the same data is illustrated. This increase in the ratio should not be interpreted as indicating a rise in the blood volume during starvation. The authors of the work did not draw this erroneous conclusion. They were in a position to observe actual changes in blood volume in their subjects. Although neither of these 2 types of analysis is indicated in paired data such as these, in situations where different groups of individuals are used, ratios might lead to false conclusions.

Figure 9 illustrates our conception of the changes in the relationship of blood volume to weight in congestive heart failure. The heavy diagonal line represents the "normal" weight to volume slope as calculated from blood volume data in the literature. If blood volume decreases during the tissue wasting in congest-
Fig. 9 Left. Diagrammatic representation of the mechanism of departure of the blood volume-weight relationship from the normal during congestive failure. Note the ratio of 70 ml./Kg. lying above, on, and below the normal relationship.

Fig. 10 Right. Note striking relationship between blood volume increase and the amount of edema.

tive heart failure as it does during semistarvation, the concurrent blood volume and weight change of the wasting individual may be represented by the movement of his point to the left along the diagonal. If an individual gains weight by accumulating edema without an increase in blood volume, his new point will move horizontally to the right as indicated by the lines and point "weight gain without blood volume gain." Such points will fall below this normal line.

On the other hand, if an individual gains weight from edema and his blood volume increases in a manner proportional to the slope of the normal volume-weight relationship, his new point will move up along the line to the right. Whenever weight gain is accompanied by an increase in blood volume of greater magnitude than this normal slope relationship, the point will fall above the diagonal line of normal relationship. It is important to note that weight gain may be accompanied by a blood volume increase of such proportions that if only ratios (ml./Kg.) were used, no change might be demonstrated. Again in figure 9 this is illustrated by "blood volume increase proportional to weight gain." Thus it can be seen from this figure that a person might have a "normal" ratio of 70 ml./Kg. yet have an actually decreased, normal, or increased blood volume with respect to the normal relationship that has been found to exist.

In order to assess a possible relationship between the amount of edema and the increase in blood volume in patients with congestive failure, further analysis was done. From the data of Reilly et al., the height of each edematous individual's point above the normal regression line was taken to represent an objective estimate of his gain in blood volume during failure. This estimated gain in blood volume was plotted against the amount of edema as
obtained from the difference between his “wet” and “dry” weights. The scatter of the points in figure 10 shows a relationship between blood volume increase and the amount of edema. Such a relationship has been postulated by many investigators interested in the mechanism of cardiac edema.

Since the loss of tissue substance in heart failure is probably associated in general with a decrease in the blood volume, and the gain of edema with an increase, the blood volume at any moment is likely to depend on the relative importance of these 2 factors in the particular instance under observation. In instances where the tissue loss has been great and the edema was slight, the blood volume might be lower than it was when the subject was in good health. When there has been greater modification of the weight by edema than by loss of tissue substance, the blood volume will usually be increased.

**Summary**

Blood volume data on a small series of patients in congestive heart failure have been presented in illustration of the importance of proper analysis of certain types of data. By using regression analysis, it was shown that the ability to detect significant differences in small groups is increased. Not only is the acuity of analysis increased, but possible erroneous conclusions may be avoided. In the analysis of data relating to congestive failure, it was shown that: blood volume is greater than normal and that the blood or plasma volume increase is related to the amount of edema.

**Acknowledgment**

The outstanding technical assistance of Miss Barbara Jambour is gratefully acknowledged.

**Summario in Interlingua**

Es presentate datos in re le volumine de sanguine in un parve serie de patientes con congestive disfallimento cardiaque pro illustrar le importancia del appropriate analyse de certe typos de datos. Per le uso del analyse a regression il eseva monstrare que le detectibilitate de differentias significative in parve gruppos pode esser meliorate. Le acuitate del analyse es augmentate, e in plus le possibilitate de conclusiones erronee es evitate. In le analyse de datos relative a disfallimento congestive il eseva possibile monstrare che le volumine de sanguine es plus grande que normal e que le augmento del volumine de sanguine o de plasma es relacionate al quantitate de edema.

**References**


21 Reeve, E. B., and Veall, N.: A simplified method for the determination of circulating red cell volume with radioactive phosphorus. J. Physiol. 108: 12, 1949


The human understanding when it has once adopted an opinion, either as being the received opinion or as being agreeable to itself, draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects and despises, or else by some distinction sets aside, and rejects; in order that by this great and pernicious predetermination the authority of its former conclusions may remain inviolate. And therefore it was a good answer that was made by the man who was shown hanging in a temple a picture of those who had paid their vows as having escaped shipwreck. They would have him say whether he did not now acknowledge the power of the gods—'Aye,' asked he again, 'but where are they painted that were drowned after their vows?'—Francis Bacon (1561–1626).
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