The Relationship of Total Red Cell Volume to Total Body Water in Octogenarian Males

By Sergio Piomelli, David G. Nathan, James F. Cummins, and Frank H. Gardner

With the technical assistance of Alvera L. Limauro

THE MAINTENANCE of red cell volume in man depends upon constant production of erythrocytes to replace effete cells destroyed following their 120 day sojourn in the circulation. The bone marrow performs this function in a singularly constant manner in man, renewing the red cell population at a rate of approximately 0.8 per cent per day. The physiologic stimuli which control erythropoiesis have been studied in detail, and the results of such studies have led to the conclusion that the oxygen demands of the tissues strongly influence red cell production. Recent evidence indicates that the kidneys may act as "oxyreceptors" and elaborate erythropoietin to stimulate stem cell differentiation to erythroblasts, in response to a demand for increased circulating oxygen carrying capacity. Erythroid marrow recognition of tissue oxygen requirements is manifested by the close relationship of the total red cell volume to the "lean body mass" (as estimated by measurement of total body water) in normal young adults. Such studies have established predictable and reproducible normal values for total red cell volume as it relates to body water in young individuals. Previous examinations of the relationship of total red cell volume to body weight in elderly people have led to conflicting opinions. Some of the data indicate a reduction of total red cell volume whereas other studies imply that no significant reduction occurs. Interest in the physiologic control of erythropoiesis has prompted our investigation of the relationship of total red cell volume to body water and to body weight in healthy octogenarian males. This study has been performed in an attempt to establish predictable normal values for red cell volume in the elderly and to define the range of variation of red cell volume in apparently healthy octogenarians.

MATERIALS AND METHODS

I. Subjects

Ninety-one veterans of the Spanish-American War (mean age 82 years), whose medical care was supervised by the Outpatient Department of the Boston Veterans Administration, volunteered for these studies and all were included. These men were ambulatory, active individuals most of whom still held responsible positions either within their families or in places of employment. They received extensive medical, social, dietary, and psychological...
evaluation before the study. They could not be regarded as completely "normal" since many minor and a few major medical and surgical diagnoses were made in the group. Routine studies of peripheral blood (hematocrit, hemoglobin, white blood cell count, and differential count of white blood cells) were normal in all but six men whose hematocrits were between 35 and 40 per cent and in six men whose hematocrits ranged between 49 and 52 per cent. Plasma urea nitrogen (PUN) concentration\textsuperscript{11} and serum iron concentration\textsuperscript{12} were evaluated in 45 men randomly selected from the group. The mean PUN was 18 mg. per 100 ml. with a range of 9–35 mg. (normal range 8–25 mg. per 100 ml.). The mean serum iron was 91 $\mu$g. per 100 ml. of serum with a range of 46–168 $\mu$g. (normal range 50–150 $\mu$g. per 100 ml.). These values bore no predictable relationship to subsequent red cell volume studies. The mean arterial oxygen saturation* of 35 randomly selected members of the group was 93.9 per cent with a range of 77.7–98.7 per cent. These values did not correlate with red cell volume studies in a predictable manner. In fact, the lowest oxygen saturations were found in those men whose red cell volumes were among the lowest. Their nutrition was considered adequate. Repeated stool examinations were negative for occult blood. Mild cardiac failure was present in 12 of the men, but they were maintained free of edema with digitalis and diuretics, if necessary. These individuals did not selectively influence the character of the regression calculations.

The counterparts of the octogenarians were a group of 19 healthy young novitiates of the Maryknoll Brothers, Jamaica Plain, Mass. Their mean age was 22. They were in good health, had no recent weight changes and maintained a well-balanced diet.

II. Methods

The total red cell volume was measured with Cr\textsuperscript{51} by modification of the method of Read.\textsuperscript{13} Blood volume was calculated without correction for possible differences between venous and "body" hematocrit. Total body water was measured by modification of the method of Langham and his coworkers.\textsuperscript{14} The method was altered to avoid the problem of variable quenching among different sera by preparing a tritium standard in each subject's serum. An aliquot of each subject's serum was evacuated to constant weight to determine its water content. No correction was made for hydrogen exchange. A one ml. aliquot of the trichloracetic acid filtrate of serum was counted in 15 ml. of a 1:1:1 mixture of toluene, methanol and diethylene glycol dimethyl ether with three g. 2,5-diphenyloxazole and five mg. of p-bis [2-(15-phenyloxazolyl)]-benzene per 100 ml. of solvent. This procedure afforded a tritium counting efficiency of three per cent. Extracellular water was estimated by the dilution of NaBr\textsuperscript{82} by the method of McMurrey and his associates.\textsuperscript{5} Intracellular water was computed from the difference between total body water and extracellular water.

All of the above studies were completed in the young men. Red cell volume was determined in 91 of the octogenarians, total body water in 63, and bromide space in 51.

III. Calculations

To compare with accuracy the data collected in two groups of different number and age, regression lines and covariance analyses were employed. These computations were utilized to evaluate: (1) the relationship of total red cell volume to body weight, body water and intracellular water; (2) the relationship of total body water to body weight; (3) the relationship of intracellular water to total body water. The statistical methods were those discussed by Snedecor.\textsuperscript{15}

RESULTS

The results are defined in the accompanying figures 1 through 4 and table 1. The legend to figure 1 describes each of the figures. Table 1 demonstrates the mean values and ranges of the observed data.

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*Data kindly made available by Dr. John Knowles, Department of Medicine, Massachusetts General Hospital, Boston, Mass.

Fig. 1.—Total red cell volume as a function of body weight. (The data for both the young men and octogenarians are presented in two graphs, both of which have identical coordinates. Each graph contains a solid line calculated by least squares drawn through the points and bracketed by two interrupted lines which connote the two standard errors of the estimate of the regression line. Within each graph the equation for the regression line and its correlation coefficient (R) are shown. To the right of the graphs a rectangular insert contains the data derived from covariance analysis of the two sets of data. The symbol Y connotes the regression line of the young men and O the regression line of the octogenarians. A single asterisk indicates \( P = 0.05 \). A double asterisk indicates \( P = 0.01 \). Covariance analyses of slopes and intercepts were not attempted when variances were significantly different.1

Total Red Cell Volume as a Function of Body Weight (Fig. 1)

The total red cell volumes bore a surprisingly close relationship to the body weights of the young men. Since these men had come to the seminary only a few months before the study, it was concluded that their similar body compositions were not necessarily induced by their present environment. They appeared fairly muscular on physical examination, and most of them had participated in high school contact sports. All were accustomed to physical
Table 1.—Mean Values and Ranges of Red Cell Volume and Certain Body Fluid Compartments in Octogenarians and Young Men

<table>
<thead>
<tr>
<th>Age</th>
<th>B.W.</th>
<th>Ht.</th>
<th>B.V. cc./Kg.</th>
<th>R.B.C. cc./Kg.</th>
<th>T.B.W. cc./L.</th>
<th>E.C.W. cc./L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>82</td>
<td>66</td>
<td>44</td>
<td>3936</td>
<td>57.3</td>
<td>88.1</td>
</tr>
<tr>
<td>Range</td>
<td>75-92</td>
<td>58.1-52</td>
<td>2459-35-52</td>
<td>5925-36.0</td>
<td>2724-49.6</td>
<td></td>
</tr>
</tbody>
</table>

labor. The total red cell volumes of the octogenarians bore a loose relationship to body weight as has been observed by others who have studied the total red cell volume of individuals with variable body compositions. The variance of the estimate of the octogenarian data differed from that of the young men so that further comparison of the two regression lines was not attempted (see Discussion). The mean total red cell volume per Kg. of body weight (table 1) was below that of the young men with a wide range of values, some of which were markedly low and a few of which were higher than is usually observed. The hematocrit values corresponded very poorly to the actual total red cell volume measurements in the octogenarians. For example, two individuals with hematocrits of 35 and 49 respectively both had red cell volumes of 20 ml. per Kg. of body weight. An individual with an hematocrit of 52 had a total red cell volume of 29 ml. per Kg., whereas another individual with an hematocrit of 38 had a total red cell volume of 30 ml. per Kg.

Total Body Water As a Function of Body Weight (Fig. 2)

The young men exhibited a close correlation of body water to body weight, which was expected from analysis of the relationship of their red cell volumes to body weight. The relationship of body water to body weight in the elderly men was not as close but closer than is usually observed in more heterogeneous groups. Covariance analysis revealed common variance with different slopes and intercepts. The total body water comprised a significantly lower fraction of body weight in the octogenarians, and this difference increased as body weight increased.

Intracellular Water As a Function of Body Water (Fig. 3)

Intracellular water was calculated from the difference between total body water and bromide space. The two least square lines were similar in variance and slope, but their intercepts were distinctly different \((P = 0.01)\). The octogenarian intracellular water was a significantly smaller fraction of total body water than that observed in the young men. The excellent correlation of intracellular water with total body water in both groups would indicate that the two technics were adequately performed.

Total Red Cell Volume as a Function of Total Body Water (Fig. 4)

The striking feature of these studies was the relatively poor correlation of total red cell volume with total body water in the octogenarian group. The
young men maintained an excellent correlation so that the total red cell volume could be predicted fairly closely from total body water in this group. The covariance analysis showed a lack of common variance between the two least squares lines (see Discussion).

**Discussion**

The purpose of this study was to evaluate red cell volume in elderly individuals as compared to young individuals. Of prime importance in such a study is the selection of the subjects. In this study the groups were highly selected. The young men were candidates for a religious life and had similar backgrounds and interests. From a large group of such men they had volunteered for these studies so that at least two selections had taken place. The older group had been members of the last volunteer army of the United States.
They had led productive and useful lives and had lived to a mean age of 82. They had volunteered for these and subsequently for other medical studies. They appeared noticeably younger in appearance and personality than the bulk of geriatric patients observed in the medical clinics of the Peter Bent Brigham Hospital. Therefore, any conclusions regarding the changes observed in relation to the aging process alone must be somewhat guarded.

The octogenarian red cell volumes correlated poorly with body weight, whereas the red cell volume of the young men correlated quite well with body weight. The difference in variance does not allow further comparison of the data by the covariance technic. Lack of common variance indicates lack of comparability of two regression lines. The reason for the lack of common variance is probably to be found in the selection of this rather homogenous young group; for if one compares the red cell volume vs. weight of the octogenarians to such data in young men to be found in the literature, one finds common variance and a distinctly significant depression of the red cell volume and blood volume related to body weight in the octogenarian.
The selection of both groups was more helpful when the relationship of body water to body weight was studied. Both groups were fairly homogenous in this regard and complete covariance analysis of the regression lines could be employed. This revealed a significant decrease in the water fraction of body weight in the octogenarian, as has been observed by others. This may imply relative fatness of the octogenarian compared to the young men. The slopes of the two least square lines were also different, and the data indicate that increments of weight in the octogenarians were associated with more fat increase than similar increments of weight in young men. These conclusions are based, of course, on the assumption that the lean tissues of the two groups were similarly hydrated. This cannot be proven or disproven without an independent measurement of fat.

The common variance of intracellular water and total body water in both groups allowed complete comparison of the data. In this case, the extracellular...
fluid proved to be a larger portion of the total body water in the aged group, a fact which has been observed by others.\textsuperscript{19,20}

The failure to demonstrate a high correlation between total red cell volume and total body water\textsuperscript{*} in the octogenarians is an intriguing finding. Whether abnormalities of erythropoiesis or variations in hydration were responsible for this difference cannot be definitely determined without independent estimations of “lean body mass” in the two groups. However, the common variance of the regression of total body water and body weight in the two groups suggests that the latter possibility is unlikely and that variability of erythropoiesis rather independent of the oxygen demands of the lean tissues occurs in the elderly. The differences in variance of total red cell volume and total body water were significant enough to prevent complete comparison of the young and old groups by the covariance technic. The fact that in both groups the mean red cell volume per liter of total body water was nearly equal (table 1) may have no biological significance since the range of values in the older group was so much greater.

Thus standard parameters of red cell volume and blood volume which have been documented in young individuals do not apply in the selected octogenarians whom we have studied. In these octogenarian males the range of values is much greater and prediction of total red cell volume from body weight or body water is unreliable. Surprising blood volume reductions may be detected in lean-appearing elderly males with normal hematocrits and normal water content. The major clinical import of this finding is the possibility that occult hypovolemia, which is not predictable from hematocrit measurements, may have serious consequences when certain elderly individuals undergo the trauma of accident or surgery.

**Summary**

1. Studies of red cell volume, total body water and extracellular water have been carried out in a group of octogenarians and in a group of young men.
2. Differences in total red cell volume, blood volume and the distribution of body water were detected.
3. The implications and interpretations of these findings are discussed.

**Summario in Interlingua**

1. Studios del volumine erythrocytic, del aqua corporee total, e del aqua extracellular esseva effectuate in un gruppo de masculos octogenari e in un gruppo de masculos juveme adulte.
2. Esseva detegite differentias inter le valores pro le volumine erythrocytic total, le volumine de sanguine, e le distribution del aqua corporee.
3. Le signification e le explication de iste constatationes es discutite.

\textsuperscript{*}The use of intracellular water rather than total body water as a reference did not improve the correlations because of the high correlation between intracellular water and total body water.
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REFERENCES


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