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RED CELL, PLASMA, AND BLOOD VOLUME IN HEALTHY WOMEN MEASURED BY RADIOCHROMIUM CELL LABELING AND HEMATOCRIT *

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In a previous study of 201 healthy men (1), red cell volume (Vrbc) was measured by a modification of Sterling and Gray's radiochromium method (2), and whole blood and plasma volumes (Vwb and Vpl) were derived from venous hematocrits. The influence of factors other than body size on the variance of the data was studied, and standards for predicting normal volumes were derived. The present report describes a similar examination of 101 women.

SUBJECTS AND METHODS

The women, all of whom volunteered for study, were actively employed as housewives, laboratory personnel, nurses, or office workers, and most were white (Table 1). None were taking medications regularly or were subject to dietary control other than mild voluntary caloric restriction, and none were pregnant. Although some engaged in sports regularly, none were trained athletes. All had been living at sea level for at least a year. Cases of gross clinical obesity were not included. No subject was a regular blood donor, and none had given blood within 10 weeks. Health screening techniques included a medical history, physical examination, chest X-ray, and urinalysis. A hematocrit below 37 per cent, the limit of normal as defined by Wintrobe (3), caused exclusion of only one volunteer. In no subject was the arterial blood pressure over 140 mm Hg systolic or 90 mm Hg diastolic.

The method of labeling the autologous cells with $NaCr^{51}O_4$ and of determining their volume of distribution (VCr^{51}) was as described in the study on men (1, 4). Tests were performed before breakfast or, rarely, in the afternoon when lunch had been omitted. Subjects lay down for at least 30 minutes before the labeled cells were delivered and until sampling was completed no less than 35 minutes later. Precautions were taken to prevent venous congestion during sampling. Hematocrit readings were not corrected for plasma trapping, and it was assumed that $Vwb = VCr^{51}$ (no allowance was made for a difference between the hematocrit of venous blood and that of the body as a whole) (1). Cell and plasma volumes were calculated by the formulas: $Vrbc = VCr^{51} \times$ hematocrit; $Vpl = VCr^{51} - Vrbc$.

The data were treated as outlined in the study of men (1). Regression equations were calculated by the method of least squares to describe the relations between volumes (Vrbc, Vpl, and Vwb) and body measurements (weight, height, weight and height combined, and surface area). The differences between the observed volumes (Vrbc and Vpl) of each woman and the mean volumes found in women of the same height and weight were calculated by means of Equations 3 and 7, Table II. These differences, or "residuals," were used to analyze the influence of factors other than body size on the blood volumes.

RESULTS

1. Volumes in relation to height and weight

Table I summarizes the data. In Figure 1, each of the 101 subjects is represented according to her weight and height. In general, the relationship between weight and height was fairly uniform. Notable exceptions were four women weighing over 81 kg, who proved to be 23 to 58 per cent overweight for height and age according to actuarial tables (5). The weight: height ratios of these subjects were more than 2 standard deviations above the mean of the ratios of the other 97 women. For this reason and because the series included so few large women, regression equations describing the relationships of the volumes to body measurements were prepared only for the 97 women weighing less than 74 kg (Table II). The bivariate regression equations described straight lines and the trivariate equations, planes without curvature (see Figures 1 to 4). The location of the regression plane for Vrbc in rela-

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TABLE I

Data in chronologic order from experiments on 101 healthy women

Subject *	Age	Height	Weight	Hematocrit †	Red cell volume ‡	Plasma volume	Residual: Red cell volume	Residual: Plasma volume
	years	cm	kg	%	l	l	ml	ml
[redacted]	[redacted]	169	58.0	39.1	1.48	2.31	−10	+150
		172	50.6	40.5	1.41	2.06	−90	−90
		168	60.1	38.8	1.65	2.59	+130	+380
		144	51.8	38.0	1.15	1.86	−70	+80
		162	53.0	41.9	1.44	2.00	+70	+20
		175	58.7	37.2	1.40	2.34	−150	+110
		174	69.5	39.4	1.66	2.51	−30	+70
		172	63.2	43.5	1.44	1.88	−130	−430
		176	56.8	39.8	1.52	2.31	−10	+120
		165	53.3	39.7	1.41	2.12	+10	+110
		178	72.3	43.3	1.93	2.52	+160	−70
		156	51.0	38.6	1.10	1.74	−200	−130
		156	52.6	41.7	1.33	1.85	+10	−60
		166	61.5	39.0	1.55	2.41	0	+140
		162	55.2	37.6	1.32	2.19	−80	+160
		171	63.8	41.8	1.74	2.41	+150	+90
		171	50.0	42.7	1.55	2.07	+160	+90
		164	58.3	41.2	1.43	2.04	−30	−80
		163	54.2	40.4	1.44	2.11	+40	+100
		171	62.0	39.7	1.35	2.05	−220	−220
		161	53.4	39.8	1.38	2.08	+10	+100
		166	55.8	40.1	1.70	2.54	+260	+150
		166	53.5	39.9	1.41	2.13	0	+110
		171	57.0	40.7	1.70	2.48	+210	+130
		173	60.6	42.2	1.48	2.02	−80	−240
		160	51.7	37.7	1.14	1.88	−200	−50
		171	54.9	41.6	1.48	2.07	+20	−30
		160	54.8	40.5	1.30	1.92	−80	−80
		171	70.1	41.8	1.47	2.01	−210	−130
		177	58.9	38.3	1.42	2.29	−150	+40
		163	59.3	42.6	1.61	2.15	+130	0
		157	61.3	38.1	1.52	2.14	+70	+310
		172	70.0	38.7	1.84	2.90	+150	+420
		168	63.0	38.6	1.70	2.72	+130	+450
		164	54.3	40.7	1.45	2.11	+50	+80
		161	55.6	38.9	1.49	2.33	+90	+300
		157	68.1	41.1	1.40	2.01	−150	−290
		159	49.5	40.4	1.60	2.36	+300	+500
		158	61.1	41.2	1.46	2.08	0	−60
		174	57.7	42.1	1.61	2.21	+120	+20
		160	50.8	45.1	1.47	1.79	+150	−110
		159	51.0	41.9	1.37	1.69	+50	−210
		159	49.0	42.1	1.23	1.69	−60	−160
		168	57.6	41.8	1.63	2.27	+140	+130
		163	51.7	45.7	1.37	1.63	+10	−120
		162	51.7	39.1	1.59	2.47	+240	+530
		159	53.9	43.2	1.62	2.04	+200	+60
		162	55.8	41.1	1.49	2.13	+80	+90
		162	49.6	39.9	1.17	1.75	−150	−140
		171	53.3	40.8	1.30	1.89	−130	−180
		161	50.4	41.0	1.31	1.88	−10	−20
		163	53.3	41.6	1.56	2.18	+160	+150
		168	60.3	38.0	1.39	2.33	−30	+220
		167	53.1	41.8	1.39	1.85	+70	−200
		166	58.0	42.3	1.42	1.93	−50	−190
		169	56.0	42.6	1.45	1.95	−10	−100
		161	53.2	42.8	1.47	1.96	+110	−10
		174	73.3	38.2	1.50	2.42	−250	−150
		161	61.7	42.2	1.38	1.89	−110	−290
		157	66.0	45.6	1.65	1.97	+130	−270
		163	59.6	41.5	1.68	2.36	+210	+220
		166	57.3	41.5	1.57	2.23	+110	+110
		171	74.1	37.2	1.74	2.94	+20	+400

* (J) Japanese, (N) Negro, (sm) spontaneous menopause, (nm) no menses, hysterectomy.
† Uncorrected for trapped plasma and including buffy coat.
‡ Weight:height ratio exceptionally high. See Figures 1 to 4.

TABLE II

*Regression equations of red cell, plasma, and whole blood volumes to weight alone, height alone, weight and height combined, and to body surface area in women 144 to 179 cm tall, weighing 45 to 73 kg**

	Mean of all values	Predicted values	Standard deviation	Coefficient of variation
	ml	ml	ml	%
Red cell volume	1,470		177	12.0
		1. (14.64 × height) − 957	153	10.4
		2. (18.26 × weight) + 409	139	9.5
		3. (7.49 × height) + (14.32 × weight) − 603	134	9.1
		4. (1,138 × surface area) − 399	134	9.1
Plasma volume	2,130		274	12.9
		5. (21.09 × height) − 1,362	243	11.4
		6. (28.89 × weight) + 455	213	10.0
		7. (9.03 × height) + (24.13 × weight) − 766	209	9.8
		8. (1,747 × surface area) − 733	209	9.8
Whole blood volume	3,600		426	11.8
		9. (35.73 × height) − 2,320	366	10.2
		10. (47.16 × weight) + 864	319	8.9
		11. (16.52 × height) + (38.46 × weight) − 1,369	308	8.6
		12. (2,885 × surface area) − 1,131	308	8.6

* Height in centimeters, weight in kilograms, and surface area in square meters as calculated from Du Bois' formula. Values are uncorrected for trapped plasma and for differences between body hematocrit and venous hematocrit.

solid circles. Therefore, in finding the expected cell or plasma volume of a given subject, it is desirable as well as convenient to locate her on the chart by weight and height and to make the prediction graphically. A subject of unusual weight or height, like the four who were excluded from our calculations, can be recognized easily when this procedure is followed.

The extensive data of Gibson and Evans (6) appeared to show that the amount of blood per unit of body size decreases with increasing size (weight, height, or surface area), especially in females. The present results, like our data for men, fail to confirm this for subjects whose weight: height ratios are in the common range. For women 144 to 179 cm tall, weighing 45 to 74 kg, and with body surface areas of 1.4 to 1.9 square meters, sizes comparable to those of Gibson and Evans' subjects, the fitted bivariate regression equations are linear (Figures 2 to 4). The graphs and regression equations of Samet, Fritts, Fishman, and Cournand (7), relating Vrbc and Vpl to weight and surface area for "hospital control" women and men in the same ranges of size as our subjects, show results in agreement with ours. For exceptionally heavy women, predictions based on weight alone tend to be too high (Figure 3). The data for our four heavy women are in best agreement with the remainder when the regression to surface area is used (Figure 4).

The average hematocrit of the women was 40.7 per cent (SD 2.1) and of the men studied under similar conditions (1), 45.2 per cent (SD 2.6). These values are lower than Wintrobe's (3) by 1.3 and 1.8 volumes per cent for women and men, respectively. Our blood samples were taken with

TABLE III

Influence of age on red cell and plasma volume

Age	Number of women	Residual Vrbc Mean	Residual Vrbc SE of mean	Residual Vpl Mean	Residual Vpl SE of mean
years		ml	ml	ml	ml
20–24	33	−50	23	−91	36
25–29	29	2	25	21	39
30–39	17	36	33	81	51
40–49	10	42	42	88	66
50–59	4	133	67	110	105
60–77	2	100	95	20	148

TABLE IV

Influence of weight:height ratio on red cell and plasma volumes. Analysis of residuals in the 26 women with weight:height ratios beyond ± 1 SD from the mean

Group	Description	Residual Vrbc Mean	Residual Vrbc SE of mean	Residual Vpl Mean	Residual Vpl SE of mean
		ml	ml	ml	ml
A	15 women average age = 46 years weight = < 74 kg weight:height ratio = > 0.382	[illegible]	35	−20	34
B*	11 women average age = 32 years weight = < 74 kg weight:height ratio = > 0.382	[illegible]	[illegible]	[illegible]	[illegible]
C	11 women average age = 31 years weight = < 74 kg weight:height ratio = < 0.318	[illegible]	[illegible]	[illegible]	[illegible]
D	4 women average age = 41 years weight = > 81 kg weight:height ratio = 0.46–0.56	[illegible]	[illegible]	[illegible]	104

* Group A minus 4 menopausal women aged 50 or more.

great care to avoid the effects of tourniquet stasis and only after the subject had rested in a horizontal position for an hour. The hematocrits would therefore be expected to be lower than those of samples taken from ambulatory subjects under ordinary conditions of collection (4, 8). The positive correlation between residuals of Vrbc and Vpl for women and men (1) shows that the be-

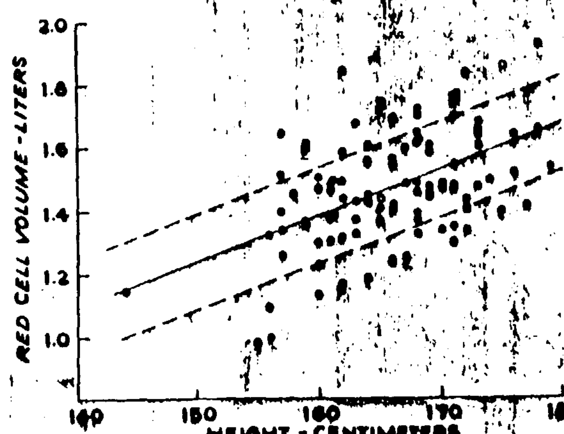

FIG. 2. RED CELL VOLUME IN RELATION TO HEIGHT. The solid line is described by Equation 1, Table II, fitted to the data for the 97 women weighing less than 74 kg (solid circles). The dotted lines represent ± 1 SD of the mean Vrbc for any given height. The open circles represent the four women with exceptionally large weight: height ratios.

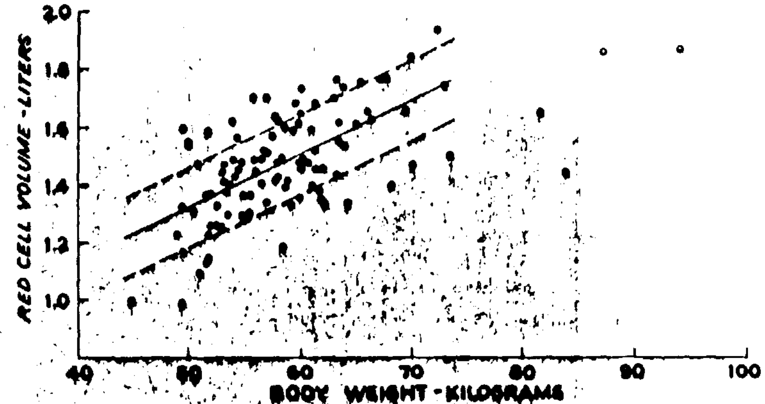

FIG. 3. RED CELL VOLUME IN RELATION TO BODY WEIGHT. The solid line is described by Equation 2, Table II, fitted to the data for the 97 women weighing less than 74 kg (solid circles). The dotted lines represent ± 1 SD of the mean Vrbc for any given weight. The open circles represent the four women with exceptionally large weight : height ratios.

matocrit is regulated within closer limits than the blood content per unit of body size.[3] Thus, healthy persons with large cell volumes tend also to have large plasma volumes. This is in contrast to the situation in anemia and polycythemia, where deficiency or excess of cell mass is often balanced by reciprocal expansion or contraction of plasma (9). In this study, the coefficient of variation (SD as per cent of the mean) was 5.1 per cent for hematocrit and 8.6 per cent for Vwb after regression to weight and height (Table II). Among the men, those with the highest hematocrits were apt to be short and heavy and those with the lowest hematocrits, tall and thin (1). The data for women showed no such relationship.

[3] The results of replicated measurements, separated by various intervals of time, in 15 members of the male series led to the conclusion that most of the observed variation of Vrbc between individuals of the same size was biological rather than methodological (1, 4).

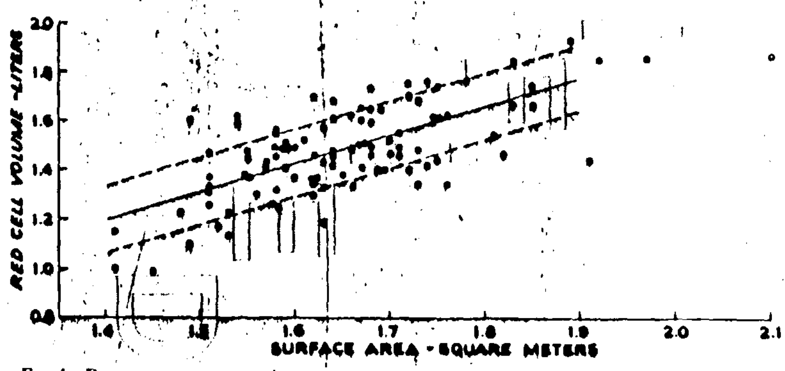

FIG. 4. RED CELL VOLUME IN RELATION TO SURFACE AREA AS CALCULATED FROM DU BOIS' FORMULA. The solid line is described by Equation 4, Table II, fitted to the data for the 97 women weighing less than 74 kg (solid circles). The dotted lines represent ± 1 SD of the mean Vrbc for any given surface area. Open circles as in Figures 2 and 3.

A comparison of the blood volumes of women and men ought only to be made within comparable ranges of heights and weights. Omission of the women under 160 cm in height and 54 kg in weight, as well as the four unusually heavy subjects, left 67 women who were within the ranges of heights and weights of the men previously studied (1). A residual value for Vrbc and Vpl was calculated for each of these women by means of the prediction equations derived from the data on men.[4] The mean residuals were Vrbc − 214 ml (SE 23) and Vpl + 85 ml (SE 29). The difference in blood content between women and men of the same height and weight in our two studies thus averages only about 130 ml. In contrast, the compilation by Allen and associates (10) of data acquired by various techniques in Boston, Stockholm, and Taipei shows an average difference of 600 ml between the blood volumes measured in nonpregnant women aged 20 to 50 and the predicted volumes for men of the same heights, weights, and ages.

The lower content of hemoglobin (11, 12), red cells (13, 14), and blood (10, 15–17) per unit of body size in women than in men is usually attributed to the higher fat content of the female. It has been reported that the difference between the sexes becomes insignificant when Vrbc is related to lean body mass calculated from body water (14) or when blood volume is related to total body water (15). Blood volumes of women were in the range of those predicted for men when fat thickness and girth were included with height and weight as the bases of prediction (16). Data for both sexes fell on the same linear regression line relating blood volume, in milliliters per kilogram, to total body density in the study of Allen and coworkers (10). Huff and Feller's findings (13) for whole blood were similar, although at any given body density women tended to have lower cell volumes and higher plasma volumes in milliliters per kilogram than men. The latter suggests that sex-associated factors other than body density or fat content may influence the Vrbc and relative cell volume.

To test whether differences in fat content could have accounted entirely for the sex differences found in our studies, we determined residual val ues for Vrbc and Vpl for the 67 women over 16 cm in height and 54 kg in weight, using the pre diction equations for men as above, but multiply ing the weight factor by 0.85. This factor wa chosen on the ground that it would overestimat slightly the difference in storage fat betwee women and men, which probably is about 12 to 1 per cent of body weights (18, 19). The mea residuals calculated on this basis were Vrbc − 5 ml (SE 35) and Vpl + 90 (SE 29). Althoug the correction achieved through this artifice very good, the possibility still remains that facto other than body composition may play a role i determining the difference between the Vrbc c men and women. Drabkin has suggested that th loss of hemoglobin due to catamenia and gestatio may contribute (12). The finding of consistentl positive residuals and higher than average vo umes in the older and nonmenstruating women c our series could be attributed to the cessation c catamenia. It is conceivable, however, that post menopausal changes in the endocrine factors ir fluencing erythropoiesis were responsible. A though the number of older people in both ou studies was small, the tendency was for residua to be negative in men and positive in women pa the age of 50.

[4] Vrbc (ml) = (8.6 × height) + (18.6 × weight) − 830 (SD 190). Vpl (ml) = (19.9 × height) + (13.1 × weight) − 2,000 (SD 240).

SUMMARY

1. Red cell volume was measured with Cr[5] labeled cells in 101 normally active women wh had been screened for general health. Volume of whole blood and of plasma were derived ind rectly from venous hematocrits.

2. The data were collected and treated as de scribed previously in a similar study on 20 healthy men. In the women, the degree of residu variation, after relation of the volumes to heigh weight, height and weight combined, or to su face area, was about the same as that found in me Trivariate regression equations relating volum to height and weight combined were derive A chart representing the equations graphically a lows convenient prediction of red cell and plasm volumes for a woman of given height and weigh

3. Sixty-seven women were of heights an weights such that they could be compared wit the men previously studied. The red cell volum of the individual women was on the average 21

ml smaller and the plasma volume 85 ml larger than would be predicted for men of comparable height and weight.

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ROLE OF FREE FATTY ACIDS IN FOREARM METABOLISM IN MAN, QUANTITATED BY USE OF INSULIN *

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Previous studies (1, 2) have demonstrated that glucose uptake by muscle of the forearm of man is inadequate to account for more than about 10 per cent of its observed oxygen consumption. Because forearm respiratory quotient (RQ) is approximately 0.7, which suggests combustion of long-chain fatty acids, it was predicted that the fraction of plasma lipid known as free fatty acids (FFA) would prove to be the missing substrate of forearm muscle. Extensive examination of this problem has, however, failed to demonstrate consistently positive arterio-deep venous (A – DV) FFA differences across the human forearm (2). There is evidence, based on isotopic studies by Friedberg, Klein, Trout, Bogdonoff, and Estes (3), that the human forearm does remove FFA from arterial blood, and the possible factors responsible for our failure to demonstrate this by simple measurement of A – DV concentration differences have been treated in detail elsewhere (2). In brief, while FFA is being extracted from plasma by forearm muscle, adipose tissue, intimately surrounding muscle, adds fatty acid to venous plasma. The net A – DV FFA difference is determined by the relative rates of these two processes.

The validity of this hypothesis could be tested if there were an agent that inhibited release of FFA from adipose tissue without also affecting FFA uptake by peripheral tissues. Insulin may be such an agent.

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There is no doubt that insulin inhibits FFA release from adipose tissue, a fact demonstrated both in vivo by Gordon (4), Estes and associates (5), and Bierman, Schwartz, and Dole (6), and in vitro (7, 8). There is, however, conflicting evidence on whether or not insulin influences FFA uptake by peripheral tissues. In excised adipose tissue, in the presence of both glucose and insulin, FFA incorporation is increased (7). But there is no such evidence from experiments in vivo. Indeed, it is unproven that there is substantial FFA uptake by adipose tissue in vivo under any circumstances. Bragdon and Gordon (9) found only 1 to 2 per cent of injected palmitic acid-1-C^{14} in adipose tissue, a figure not increased by prior administration of glucose, which stimulates insulin secretion. It has been demonstrated by Spitzer and Hohenleitner in the dog (10) and by Scow, Robert, and Chernick (11) in isolated rat parametrial adipose tissue that, while net production of FFA by adipose tissue was inhibited by insulin, significant net uptake by adipose tissue was not produced. With respect to a possible effect of insulin on FFA uptake by muscle, experiments capable of testing this crucially in vivo have not been done. Absence of any such action, however, is suggested by the fact that turnover rates of FFA, measured by use of isotopes in the dog, are not changed by insulin (6, 12). Fritz (13) showed that oxidation of palmitic acid-1-C^{14} by excised rat diaphragm was not altered by insulin.

Thus, while it is not established that insulin may not influence FFA uptake by peripheral tissues, most of the available data suggest that it does not do so in the intact animal. In the light of previous studies showing that the human forearm is remarkably sensitive to local intra-arterial infusion of small concentrations of insulin (14), a technique was available to establish the effects of insulin, injected intra-arterially at a final concentration of several hundred microunits per milli-