Effect of Obesity on Red Cell Mass Results

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Measurement of red cell mass with isotope dilution remains an important diagnostic test in the evaluation of patients with suspected polycythemia vera (PCV). Results and reference ranges are typically expressed in units normalized for body weight (mL/kg). Obesity is common in polycythemic patients, and it is important to know how the various published normative ranges compare across a wide range of body weights. **Methods:** We retrospectively reviewed 51 consecutive patients referred for red cell mass determination with ^{51}Cr red blood cell dilution. Results were expressed in milliliters per kilogram (mL/kg) by using the actual patient weight and after adiposity adjustments using ideal body weight, body mass index (BMI) and combinations of height-weight, including body surface area. Results were classified as normal, elevated or PCV. **Results:** There was a high prevalence of obesity in our population (28/51 [55%] with BMI > 27 kg/m^2, BMI range 16.0–54.8 kg/m^2). The method used to compensate for obesity had a dramatic effect on the derived red cell mass, the fraction of patients with elevated measurements and the fraction of patients meeting criteria for PCV. Concordance for categorization as normal, elevated or PCV by all methods was only 47.1%. **Conclusion:** Obesity is a common confounding factor in the interpretation of red cell mass measurements. Currently published reference ranges generate inconsistent results when extrapolated to obese patients. Further normative data on obese subjects are needed to determine which method (if any) is optimal.

Key Words: polycythemia; erythrocytes; obesity

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Polycythemia vera (PCV) refers to a chronic myeloproliferative disorder characterized by an increased total red cell mass. This is often associated with splenomegaly, leukocytosis, increased platelet counts and a predisposition to thrombosis and/or hemorrhage. In many cases, the diagnostic criteria defined by the Polycythemia Vera Study Group are easily satisfied (*1*). In other cases, however, clinical presentation is less typical and more sophisticated laboratory testing is required. Notwithstanding, the usefulness of in vitro cultures of erythroid progenitors and reduced levels of serum erythropoietin, measurement of red cell mass with radionuclide indicator-dilution techniques has been and remains an important confirmatorytest. According to these criteria, an elevated red blood cell mass (greater than 36 mL/kg for males, greater than 32 mL/kg for females) is a major criterion for PCV. The potential for PCV to present without an increased hemoglobin or hematocrit has only recently been recognized and reflects a balanced increase in red cell mass and plasma volume (*2*).

After the methodology for red cell mass measurement was first described, many groups attempted to define an appropriate normal reference method. Early techniques estimated absolute red cell mass from a combination of morphometric parameters such as height, weight and body surface area (BSA) (*3*). The International Committee for Standardization in Hematology (ICSH) subsequently recommended that red cell mass measurements be reported in terms of body weight (mL/kg) (*4*). It is observed that the relationship between blood volume and body weight varies according to body composition. Specifically, adipose tissue is oligemic compared with lean tissue and, therefore, in obese subjects, blood volumes will tend to be low in relation to actual body weight (*5–7*). Several corrections have been proposed to compensate for this effect of excess fat. The ICSH has advocated the expression of a patient's red cell mass normalized to estimated ideal or lean body mass (*4*). This may not be satisfactory in severely obese subjects in whom even the relatively small amount of blood contained by fatty tissue can contribute significantly to the total value. Furthermore, lean muscle mass may also be increased in obese subjects, albeit to a lesser extent than the increase in fatty tissue. Therefore, others have recommended that some fraction of the excess weight (defined as weight exceeding the ideal body weight [IBW]) be used in computing the weight-normalized red cell mass (*8*).

Obesity (or excess of body fat) is common in many developed nations and, therefore, it is likely to be a common confounding factor in red cell mass interpretation. A recent study of Canadian adults demonstrated that 35% of men and 27% of women were obese (defined as a body mass index [BMI = weight/height^2] exceeding 27 kg/m^2) (*9*). Similar figures have been reported in the U.S. from the National Health and Nutrition Examination Survey (NHANES III) using slightly higher cutoffs (BMI 27.8 kg/m^2 for males and 27.3 kg/m^2 for females) (*10*).

The objective of this study was to compare the various weight-normalization and obesity-compensation methods in a consecutive series of patients with suspected polycythemia who were referred for red cell mass measurements.

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MATERIALS AND METHODS

Subjects

We retrospectively reviewed 51 consecutive patients referred for red cell mass determination. All subjects had been found to have elevated hemoglobin. Not surprisingly, a prominent regression to the mean was observed in the hemoglobin measurement performed on the day of the red cell mass measurement. Hemoglobin was 183 ± 15 g/L in the referring physician's office but significantly lower (169 ± 16 g/L; $P < 10^{-8}$) on the day of red cell mass measurement.

Red Cell Mass Measurement

Our technique for red cell mass measurements is based on a standard indicator-dilution principle that uses a well scintillation multichannel analyzer (ND62; Nuclear Data Inc., Schaumburg, IL). Syringe counts are related to counting rates in the well counter by the "fixed-geometry method" (*4*) in which a custom-built plastic syringe holder maintains a 16-cm distance between the syringe and the probe. Calibration factors are repeated every 6 mo for ^{51}Cr and did not demonstrate any drift. Patient weight and height are recorded, and the patient is placed in the supine position for 20 min before radioisotope injection. The patient remains supine until all samples are collected. An intravenous catheter is established in one arm for radiopharmaceutical administration and a line in the contralateral arm is used for sample collections. Blood was labeled in vitro with 1.85 MBq (50 μCi) ^{51}Cr-sodium chromate, according to published methods (*4*). A blood sample is collected 60 min postinjection. Duplicate aliquots of whole blood are counted in the well counter and used to calculate the absolute red cell mass, based on the calibration factor and net injected activity. Plasma volume was simultaneously measured with ^{125}I-human serum albumin, but these data are not included, as plasma volume is of only secondary importance in the diagnostic evaluation of polycythemia.

Body Size Corrections

We calculated weight-normalized red cell mass (mL/kg) by dividing the measured absolute red cell mass by the patient's body weight. Because the actual body weight may not accurately reflect the volume of red cell distribution, several methods of estimating the "effective" body weight were considered: (a) actual weight; (b) IBW, determined by the middle of the range for an average frame size (*11*); (c) IBW (20% fat) for those persons whose weight exceeded the IBW by more than 4%, calculated by adding 20% of each kilogram above average IBW; (d) body-mass adjusted weight as the derived weight (based on the patient's actual height) associated with a BMI of 22 kg/m^2 (middle of the healthy weight range of 20–24 kg/m^2); and (e) body-mass adjusted weight (20% fat) for those persons whose weight exceeded the body-mass adjusted weight by more than 4%, calculated by adding 20% of each excess kilogram.

We also evaluated more complex regressions between absolute red cell mass (mL) and body size variables, because these may be better suited to patients whose body composition differs substantially from average. Specifically, we selected methods that used height alone, height and weight together and BSA (*3,12*). BSA was calculated from the standard relationship with weight (kg) and height (m) described by Du Bois and Du Bois (*13*). The following methods were selected for evaluation (see Appendix for detailed regression equations): (a) height alone (Hidalgo et al. [*12*]), (b) height-weight (Hidalgo et al. [*12*]), (c) BSA (Hidalgo et al. [*12*]) and (d) BSA (Hurley [*3*]).

Each calculated red cell mass (mL/kg) measurement was compared with gender-specific published normal ranges (normal male range 24–32 mL/kg and normal female range 22–28 mL/kg) and consensus thresholds for the diagnosis of PCV (36 mL/kg for males and 32 mL/kg for females) (*8*). Individual values were classified as normal, elevated or falling within the PCV range.

Statistics

All ranges are expressed as mean ± SD, and statistical significance was determined from $P < 0.05$. Variables were compared using 2-tailed paired or unpaired t tests, as appropriate. Product-moment (Pearson) correlation coefficients were calculated for pairs of continuous variables. Concordance rates between diagnostic categories (normal, increased or PCV range) were measured with κ statistics. As a rule of thumb, $\kappa > 0.75$ indicates excellent agreement, $0.4 \leq \kappa \leq 0.75$ indicates good agreement and $\kappa < 0.4$ indicates only marginal agreement (*14*). All statistical analysis was performed with CSS:Statistica (Statsoft Inc., Tulsa, OK).

RESULTS

Patient Population

There were 34 men and 17 women with a mean age of 54 y (range 23–84 y). The average BMI seen in this population was 29.1 ± 6.7 kg/m^2 (range 16.0–54.8). Of 51 subjects, 28 (55%) were obese (BMI > 27 kg/m^2). This exceeds the prevalence of obesity seen in recent large Canadian population surveys of 27% for women and 35% for men ($P = 0.001$ by chi-square). The severity of obesity was mild in 15 subjects (BMI 27–31 kg/m^2), moderate in 5 (BMI 31–35 kg/m^2) and massive in the remaining 8 (BMI > 35 kg/m^2).

IBW was divided by the square of the patient's actual height to calculate ideal BMI (mean 22.6 ± 0.6 kg/m^2, range 21.6–24.1). This is quite close to the middle of the healthy weight range (22 kg/m^2). There was very close correlation between the IBW and the body mass-adjusted weight, and the slope to the regression line forced through the origin was close to unity (1.03 ± 0.01, $r = 0.999$, $P < 10^{-25}$). Thus, for practical purposes, one can use an easily calculated weight associated with BMI 22 kg/m^2 rather than consulting IBW tables.

Comparative Weight Normalizations

The average absolute red cell mass for all subjects was 2449 ± 732 mL. The values were slightly greater in obese than non-obese subjects (2495 ± 703 mL versus 2394 ± 778 mL), but the difference was not statistically significant. When normalized for the patients' actual weight, the average red cell mass was 29.4 ± 8.6 mL/kg for all subjects and this was significantly less in the obese subjects (27.7 ± 6.5 mL/kg versus non-obese 32.7 ± 9.7 mL/kg; $P = 0.01$).

Table 1 summarizes the normalized red cell mass (mL/kg) calculated with each of the various weight-normalization methods. The lowest red cell mass came from using the patient's actual weight, whereas the highest were found with

TABLE 1
Effect of Weight Normalization Method on Red Cell Mass (mL/kg)

Weight normalization method	Red cell mass (mL/kg)		
	All cases*	Non-obese	Obese
Actual weight	29.4 ± 8.6	32.7 ± 9.7	27.7 ± 6.5
Ideal body weight	37.0 ± 10.7	35.2 ± 10.4	38.5 ± 10.9
Ideal body weight (20% fat)	35.1 ± 9.2	35.1 ± 9.9	35.1 ± 8.7
Body mass-adjusted weight	38.2 ± 10.8	36.5 ± 10.2	39.7 ± 11.2
Body mass-adjusted weight (20% fat)	35.8 ± 9.4	35.7 ± 10.0	35.9 ± 8.9
Height alone (Hidalgo et al. [12])	32.7 ± 8.6	34.0 ± 9.9	31.6 ± 7.4
Height-weight (Hidalgo et al. [12])	32.8 ± 8.6	34.1 ± 10.0	31.8 ± 7.4
Body surface area (Hidalgo et al. [12])	32.6 ± 8.6	33.9 ± 9.9	31.5 ± 7.4
Body surface area (Hurley [3])	31.5 ± 8.7	33.0 ± 9.4	30.2 ± 8.1

*All between-method differences were statistically significant ($P < 0.05$) except for height alone (Hidalgo) versus height-weight (Hidalgo).
Units given in mean ± SD.

TABLE 2
Effect of Weight Normalization Method on Number of Subjects Classified as Normal, Increased Red Cell Mass and Polycythemia Vera

Weight normalization method	Normal (%)	Increased red cell mass (%)	Polycythemia vera (%)
Actual weight	32 (62.7)	7 (13.7)	12 (23.5)
Ideal body weight	15 (29.4)	8 (15.7)	28 (54.9)
Ideal body weight (20% fat)	20 (39.2)	8 (15.7)	23 (45.1)
Body mass-adjusted weight	12 (23.5)	10 (19.6)	29 (56.9)
Body mass-adjusted weight (20% fat)	18 (35.3)	8 (15.7)	25 (49.0)
Height alone (Hidalgo et al. [12])	24 (47.1)	10 (19.6)	17 (33.3)
Height-weight (Hidalgo et al. [12])	24 (47.1)	9 (17.6)	18 (35.3)
Body surface area (Hidalgo et al. [12])	24 (47.1)	10 (19.6)	17 (33.3)
Body surface area (Hurley [3])	33 (64.7)	3 (5.9)	15 (29.4)

IBW (37.0 ± 10.7 mL/kg) and body mass-adjusted weight (38.2 ± 10.8 mL/kg). The normalization method had much less effect on non-obese subjects (range 32.7–36.5 mL/kg) than on obese subjects (range 27.7–39.7 mL/kg).

Large differences were found in the fraction of patients classified as having normal, increased or PCV range red cell mass (Table 2). The highest rates for a normal classification were found with normalizations based on the patients' actual weight (62.7%) and the BSA method of Hurley (64.7%). The lowest rates for a normal classification were found with normalizations based on IBW (29.4%) and body mass-adjusted weight (23.5%). There were corresponding effects on the number of cases classified as meeting the red cell mass criterion for PCV ranging from 23.5% with actual weight normalization to 56.9% for body mass-adjusted weight.

The classification concordance rates also varied considerably (Table 3). As expected, little difference was seen between normalizations using either IBW or body mass-adjusted weight (κ 0.87 with or without excess weight adjustment). Similarly, the three normalization systems of Hidalgo et al. (*12*) (BSA, height alone and height-weight) gave equivalent classifications (κ 0.98). Actual-weight normalization and BSA (Hurley) normalization showed excellent agreement (κ 0.81), but these methods showed relatively weaker concordance with all other methods (κ 0.29–0.64). Surprisingly, BSA (Hidalgo) and BSA (Hurley) showed only moderate agreement (κ 0.60).

Only 24 of the 51 patients (47.1%) were concordant for all of the normalization methods. Excluding the actual-weight method did not significantly improve the degree of concordance among the remaining six methods (25/51, 52.9%). Concordant patients were significantly lighter (78 ± 14 kg versus 92 ± 24 kg; $P = 0.013$), had lower BMI (26.6 ± 4.1 kg/m^2 versus 31.3 ± 7.8 kg/m^2; $P = 0.001$) and lower BSA (1.90 ± 0.22 m^2 versus 2.03 ± 0.25 m^2; $P = 0.041$). Predictably, very low or very high red cell mass measurements were much more likely to be concordant. Thus, 11 (84.6%) of the 13 lowest values (IBW method with 20% for each excess kilogram) were found to be concordant, as were 11 of the 13 highest values. Of the remaining 25 values, only 2 (8%) were concordant.

Substantial divergence in the predicted average red cell mass are seen from simulations of increasing body weight. Figure 1 depicts the relationship between weight (range 69.5–130 kg) and predicted absolute red cell mass (mL) for a hypothetical average 175-cm male (IBW 69.5 kg) with average red cell mass (28 mL/kg). Figure 2 presents the same comparison for red cell mass expressed in weight-normalized units (mL/kg). For the latter, the BSA regression of Hurley et al. (*3*) was selected for estimating absolute red cell mass because this method has been endorsed by the ICSH (*4*). There is good concordance of all methods in patients close to IBW, but major disagreement with massive obesity.

TABLE 3
Concordance of Weight Normalization Methods for Diagnosis of Increased Red Cell Mass and Polycythemia Vera

	Actual weight	Ideal body weight	Ideal body weight (20% fat)	Body mass-adjusted weight	Body mass-adjusted weight (20% fat)	Body surface area (Hidalgo et al. [12])	Body surface area (Hurley [3])
Actual weight	—	0.68	0.85	0.70	0.85	0.94	0.95
Ideal body weight	0.35	—	0.96	0.99	0.96	0.89	0.79
Ideal body weight (20% fat)	0.50	0.70	—	0.97	1.00	0.97	0.91
Body mass-adjusted weight	0.29	0.87	0.56	—	0.97	0.90	0.81
Body mass-adjusted weight (20% fat)	0.42	0.80	0.87	0.68	—	0.97	0.92
Body surface area (Hidalgo et al. [12])	0.64	0.52	0.72	0.41	0.60	—	0.95
Body surface area (Hurley [3])	0.81	0.36	0.45	0.30	0.43	0.60	—

Product-moment correlation coefficients between weight-normalized red cell mass methods (above the diagonal). κ statistics for concordance of diagnostic categorization (normal, elevated, polycythemia vera) by different weight normalization methods (below the diagonal).

All comparisons of variable pairs $P < 10^{-5}$.

Multivariable Analysis

For an individual patient, there should be a linear relationship between blood hemoglobin concentration and red cell mass. By extension, it is not surprising that across our entire study population, we also found a strong positive correlation between blood hemoglobin concentration and each of the weight-normalized measures of red cell mass (r = 0.63–0.71, $P < 10^{-6}$). It is, therefore, possible to indirectly assess the accuracy of the weight-normalization methods by testing the relationship between BMI and weight-normalized red cell mass after controlling for blood hemoglobin concentration with multivariate linear regression (Table 4). Red cell mass normalized to the patients' actual weight shows a statistically significant inverse correlation with BMI, and this effect persists after adjustment for blood hemoglobin ($r = -0.30$, $P < 0.05$ univariate; $r = -0.37$, $P < 0.001$ multivariate). Conversely, IBW shows a statistically significant positive correlation with BMI, and again, this effect persists after adjustment for blood hemoglobin ($r = 0.44$, $P < 0.01$ univariate; $r = 0.38$, $P < 0.001$ multivariate). The effect of BMI was minimized in the regressions of Hidalgo et al. (*12*), followed by methods that use an excess fat adjustment and the BSA regression of Hurley et al. (*3*).

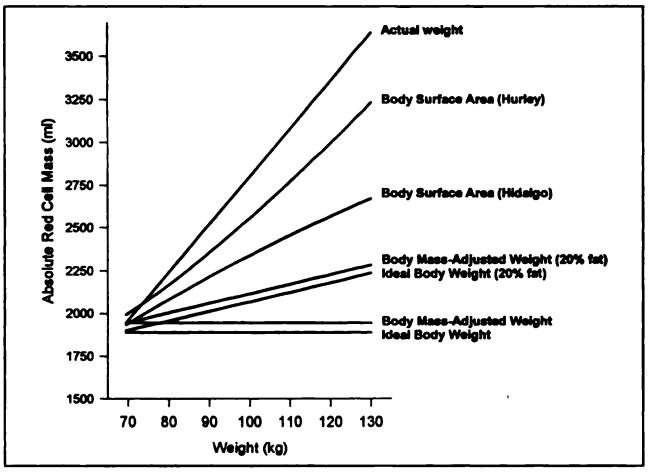

FIGURE 1. Predicted relationship between weight and absolute red cell mass for a hypothetical average 175-cm male by the following methods: actual weight (assumes fat and lean tissue have similar red cell mass), IBW (assumes fat has negligible red cell mass), IBW with 20% for excess fat (assumes fat has 20% of the red cell mass of lean tissue), body mass-adjusted weight (assumes fat has negligible red cell mass), body mass-adjusted weight with 20% for excess fat (assumes fat has 20% of red cell mass of lean tissue), BSA (Hurley) and BSA (Hidalgo).

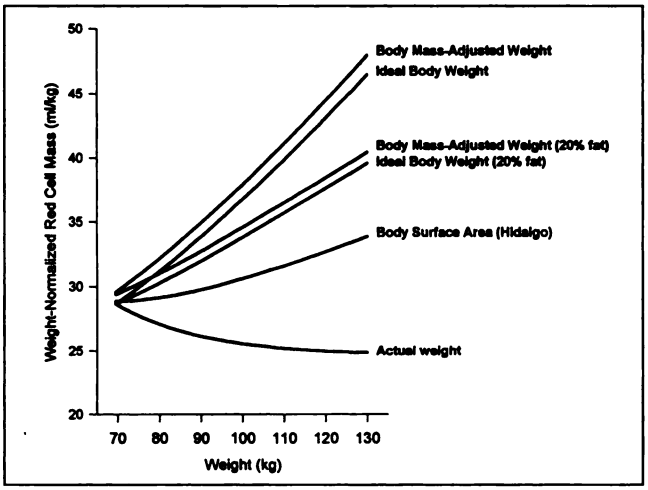

FIGURE 2. Predicted effect of weight-normalization on derived red cell mass for a hypothetical average 175-cm male using the following methods: actual weight (assumes fat and lean tissue have similar red cell mass), IBW (assumes fat has negligible red cell mass), IBW with 20% for excess fat (assumes fat has 20% of the red cell mass of lean tissue), body mass-adjusted weight (assumes fat has negligible red cell mass), body mass-adjusted weight with 20% for excess fat (assumes fat has 20% of red cell mass of lean tissue) and BSA (Hidalgo). Absolute red cell mass was predicted from the BSA method of Hurley (*3*).

TABLE 4
Blood Hemoglobin Concentration and Body Mass Index as Predictors of Weight-Normalized Red Cell Mass

Weight normalization method	Univariate		Multivariate	
	Blood hemoglobin	Body mass index	Blood hemoglobin	Body mass index
Actual weight	0.63*	−0.30†	0.66*	−0.37*
Ideal body weight	0.68*	0.44‡	0.64*	0.38*
Ideal body weight (20% fat)	0.72*	0.23	0.70*	0.16
Body mass–adjusted weight	0.67*	0.45†	0.63*	0.39*
Body mass–adjusted weight (20% fat)	0.71*	0.24	0.70*	0.17
Height alone (Hidalgo et al. [*12*])	0.71*	0.02	0.71*	−0.04
Height-weight (Hidalgo et al. [*12*])	0.71*	0.00	0.72*	−0.07
Body surface area (Hildago et al. [*12*])	0.71*	0.02	0.71*	−0.04
Body surface area (Hurley [*3*])	0.65*	−0.11	0.67*	−0.17

*$P < 0.001$.
†$P < 0.05$.
‡$P < 0.01$.
Values are correlation coefficients between the column variable(s) and the respective weight-normalized red blood cell mass (mL/kg).

DISCUSSION

We found considerable differences in the classification of patient red cell mass measurements based on the presence or absence of obesity and depending on the method used for weight adjustment. In a subsequent sensitivity analysis, we found little difference when the fat adjustment fraction was varied over the range of 10%–30% for each excess kilogram. Although the normal range for red cell mass has been well-established in persons of average weight, very little information exists on obese subjects. Therefore, on the basis of the published information, it is unclear which of these many adjustment techniques most accurately reflects "true" red cell mass. This may be a significant issue because, at least in our population, obesity was a frequent factor confounding test interpretation. It is unclear why the prevalence of obesity is so high in this population, but this probably reflects several factors. First, obesity is associated with other conditions that may increase hemoglobin measurements such as hypoventilation syndromes (with an absolute polycythemia) or diuretic therapy for hypertension and heart failure (producing relative hemoconcentration). It has also been suggested that obesity and diabetes may be directly responsible for increased hemoglobin levels, although the report referred to diabetic Libyan women and may not be applicable to other groups (*15*).

The ICSH recommendations of using IBW would have resulted in one-half of our study population being classified as having polycythemia, but less than half of these would have been so classified if the actual weight had been used. Neither of these two extremes is believed to be accurate because blood contained in adipose tissue clearly contributes to the total, albeit to a much lesser extent than lean tissue. Several lines of evidence support the notion that there is a proportionate reduction in blood flow, blood volume and metabolic activity in adipose tissue. For example, average energy expenditure in fat-free tissue is 1.35 W/kg but only 0.31 W/kg in fat (*16*). Total blood volume without adiposity has been estimated as 92.8 mL/kg, with a blood content in adipose tissue of 20.1 mL/kg (*17*). Unfortunately, no simple body measure accurately reflects the exact proportion of fat and nonfat tissue (*18*). For most practical purposes, the BMI is a satisfactory approximation but individuals may deviate substantially from the average (*19*). Age, physical activity and somatotype have not been found to improve significantly on predictive methods that use combinations of weight, height and BSA (*20*). More sophisticated methods can provide a more precise assessment of body composition (*21–23*).

Normative red cell mass data, based on healthy obese subjects, is quite limited, although this would be very helpful in answering the question about which of the many available techniques is most appropriate. For example, in the large series of Hurley (*3*), which included 784 subjects, the maximum BSA was 2.15 m^2 for males and 1.87 m^2 for females. By comparison, our series contained 12 men and 5 women with BSA exceeding these levels (maximum 2.63 m^2 and 2.04 m^2, respectively). Two studies have explicitly included and separately analyzed an obese group. Brassinne (*6*) compared 13 underweight subjects (all females) and 17 obese subjects (5 female and 12 male) with a normal-weight control group. As expected, use of the subject's actual weight led to an underestimation of absolute red cell volume in those who were underweight (−140 mL) and overestimation in the obese group (+365 mL). BSA and linear transformation of actual weight substantially reduced these systematic errors. Unfortunately, the number of obese subjects was small and the degree of obesity was relatively modest (average BMI 31.3 kg/m^2, maximum 37.5 kg/m^2). Retzlaff et al. (*7*) included 12 obese females in their series (average BMI 33.7 kg/m^2). They showed that weight adjustment (height-weight regression, BSA or ideal body mass regression) was superior to using the actual weight, but they did not have the power to identify which of the weight-adjustment techniques was the best. As our results show, morbid obesity is common in patients referred for red cell mass measurement, yet it is in this range that the various weight-adjustment methods show significant divergence.

Our analysis of the relationship between blood hemoglobin concentration and the various red cell mass measurements supports the prevailing view that neither a patient's actual weight nor IBW is optimal for weight-normalization because the independent contribution of BMI on the red cell mass measurement was not removed. Our study did not

include normal obese and non-obese subjects; therefore, the small differences between the remaining methods cannot be used to identify a "best" method.

CONCLUSION

Obesity is a frequent confounding factor in the interpretation of red cell mass measurements. Some form of weight adjustment for excess adipose tissue is necessary, especially in morbidly obese subjects, but the results are insensitive to the exact fraction used. Commonly used reference ranges generate inconsistent results when extrapolated to obese patients. Further normative data on obese subjects are needed to decide which method (if any) is optimal.

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APPENDIX

BSA (m^2) was calculated from the standard relationship between weight (kg) and height (cm) described by Du Bois and Du Bois (*13*):

$$\text{BSA} = [\text{Height}^{0.425} \times \text{Weight}^{0.725} \times 71.84] \times 10^{-4}.$$

Average predicted absolute red cell mass (mL) was calculated from the regressions of Hidalgo et al. (*12*) using the following body size regressions:

(a) height alone:

$$\text{Red Cell Mass (mL) in males} = 0.4 \times [367\ \text{m}^3 + 32.2\ \text{kg} + 604]$$

$$\text{Red Cell Mass (mL) in females} = 0.4 \times [356\ \text{m}^3 - 31.1\ \text{kg} + 183]$$

(b) height and weight:

$$\text{Red Cell Mass (mL) in males} = 0.4 \times [367\ \text{m}^3 + 32.2\ \text{kg} + 604]$$

$$\text{Red Cell Mass (mL) in females} = 0.4 \times [356\ \text{m}^3 - 33.1\ \text{kg} + 183]$$

(c) BSA:

$$\text{Red Cell Mass (mL) in males} = 1486\ \text{BSA}^2 - 4106\ \text{BSA} + 4514$$

$$\text{Red Cell Mass (mL) in females} = 1167\ \text{BSA} - 479.$$

As a comparison for the BSA-based method of Hidalgo et al. (*12*), expected red cell mass (mL) and the upper limit of normal (mL) were also calculated from the regressions of Hurley (*3*):

(a) BSA:

$$\text{Red Cell Mass (mL) in males} = 0.4 \times [3290\ \text{BSA} - 1229]$$

$$\text{Red Cell Mass (mL) in females} = 0.4 \times [3470\ \text{BSA} - 1954]$$

(b) upper limit:

$$\text{Red Cell Mass (mL) in males} = 2388\ \text{BSA}^2 - 7147\ \text{BSA} + 7488$$

$$\text{Red Cell Mass (mL) in females} = 1014\ \text{BSA}^2 - 924\ \text{BSA} + 1734.$$

We related predicted and measured absolute red cell mass measures (mL) to the commonly used weight-normalized diagnostic ranges (mL/kg) through the following:

$$\text{Red Blood Cell (RBC) Mass (mL/kg)} = \text{Average Normal (mL/kg)} \times \frac{\text{Measured Absolute RBC Mass (mL)}}{\text{Expected Absolute RBC Mass (mL)}}.$$

These weight-normalized values were then used to classify patients as normal, elevated or PCV as described in the Materials and Methods section.

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