The Importance of Correct Norms in Blood Volume Measurement

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ABSTRACT: Accurate individual norms are required for blood volume measurement to be useful in a clinical setting. The primary physiological determinant of normal blood volume is body composition. Norms have been developed based on weight and body surface area, but these have systematic errors arising from variations in body composition or body size. The only norm that specifically estimates body composition uses deviation from ideal weight. A clinically useful norm must also include a normal range that is sufficiently sensitive and specific. The ultimate test of a norm's effectiveness is how it relates to known physiological factors or outcomes in a clinical or research setting. When tested in relation to outcome results from previously published clinical studies, norms utilizing deviation from ideal weight provide the most accurate categorization of blood volume status. **KEY INDEXING TERMS:** Blood volume; Reference values; Body composition. **[Am J Med Sci 2007;334(1):41–46.]**

Radioisotopic blood volume measurement was first developed approximately 60 years ago.[1–3] For blood volume measurement to be clinically feasible, accurate norms were required.

The simplest approach to predicting normal blood volume would be to use a fixed ratio of blood volume to body weight (fixed weight ratio). Because there are clear sex differences for normal blood volume, separate ratios are used for male and female subjects. Body weight is easy to measure accurately, and a fixed ratio of blood volume to body weight is easy to apply.

In the 1950s and 1960s, several studies attempted to establish values for normal blood volume. It quickly became apparent that normal blood volume could not be easily predicted by using a fixed weight ratio. Because of the different normal vascularity of different tissues (a given mass of fat tissue contains 2/35 as much blood as an equal mass of lean tissue),[4] people with different body compositions can have widely different normal blood volumes per unit of mass.

Early attempts to establish normal blood volumes dealt with this difference by dividing subjects into different categories of body composition. In 1950, Gregersen and Nickerson[5] published a study in which they measured blood volume in normal individuals, each of whom they subjectively categorized as an ectomorph (lean and of slight build), endomorph (larger in build, muscular), or mesomorph (larger in build, more fat than muscle). They found that average blood volume to body weight ratios differed according to these body types. In the same year, Keys et al[6] published blood volume measurements of 32 normal male volunteers before and after a 6-month period of weight reduction and found the volunteers' average blood volume to body weight ratio to increase from 84.4 mL/kg to 101.3 mL/kg. In 1962, a study by Alexander et al[7] divided subjects into two categories: obese patients weighing over 300 lbs, with an average blood volume of 46 mL/kg, and nonobese patients, with an average blood volume of 86 mL/kg.

These studies found significant differences in blood volume among normal individuals with different body compositions and essentially proved that a fixed weight ratio is not a reliable measure of normal blood volume. Despite this, fixed weight ratio norms continue to be widely cited[4] and used in practice.

Body Surface Area

In the 1950s and continuing through several decades,[8–13] a number of studies proposed body surface area as a predictor of normal blood volume. Most predictions of normal blood volume are a linear function of surface area.

Based purely on the geometry, one would expect that body surface area (a two-dimensional measurement) would be a less accurate predictor of blood volume (a three-dimensional measurement) than weight, which proportionally reflects three-dimensional changes. However, studies have shown body surface area to be a closer predictor of blood volume than body mass.

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Body surface area provides a closer estimation of normal blood volume, not because it is physiologically related to normal blood volume but because the nonlinear changes in blood volume in response to differences in body composition tend to overlap nonlinear errors that arise from using a two-dimensional surface area to estimate a three-dimensional volume.

For example, a person who loses weight—who becomes more lean—will become smaller. Therefore, his or her ratio of body surface area to mass will increase; this coincides with the fact that his or her ratio of normal blood volume to mass is also increasing. Conversely, as a person becomes more obese (and hence larger), his or her ratio of body surface area to mass decreases, as does his or her ratio of normal blood volume to mass.

However, these relations are not the same. Changes in body composition and in body surface area do not occur at the same rate, and they do not account for the fact that two individuals of the same proportions but of different sizes (ie, a short lean person and a tall lean person) will have the same blood volume per unit mass but different body surface areas per unit mass (Figure 1).

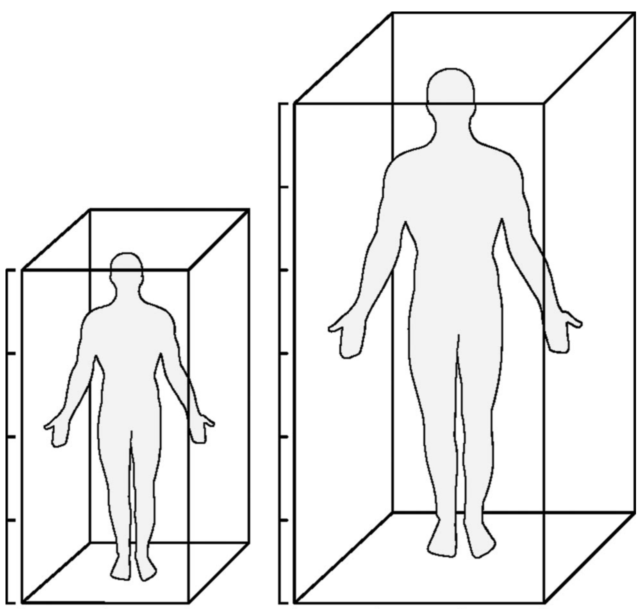

Figure 1. For two people of the exact same body composition but different sizes, the normal blood volume per unit of mass is identical. However, the ratio of body surface area to volume is different between the two individuals. As a simplification, consider the size of the box, illustrated above, filled by two people of the same proportions but different heights. The smaller person fills a box that is 2 units wide × 2 units deep × 4 units high. The surface area of this box is 40 square units, and the volume of the box is 16 cubic units. The ratio of surface area to volume is 5:2. The larger person fills a box of the same proportions that is 3 × 3 × 6. The surface area of this box is 90 square units, and the volume is 54 cubic units. The ratio of surface area to volume is 5:3—much lower than 5:2. Thus, even though these two individuals have the same body composition and hence the same blood volume per unit mass, their body surface area per unit mass is quite different. Predicting normal blood volume based on a linear relation to body surface area in these individuals would result in an error.

In 1995, the International Committee on Standardization in Hematology (ICSH) attempted to develop an improved equation for predicting blood volume.[14] The ICSH paper recognized the problems with existing methods for predicting normal blood volume and that a measurement relating to body composition would provide the best predictions of normal blood volume. The paper suggested lean body mass as an ideal but impractical solution.

The authors ultimately developed an improvement on a system for predicting norms based on body surface area, which is known to be nonphysiological, rather than dealing with the underlying error in using nonphysiological measurements. This was reflected in the fact that their final equation was presented to be used with a broad normal range of ±25% from the predicted norm, which is of very limited utility when applied to an individual case. The authors seemed to be unaware that Feldschuh and Enson[15] performed a study in 1977 that solved many of these problems.

Deviation From Ideal Weight

In 1977, Feldschuh and Enson[15] proposed a method of determining normal blood volume that was based on an estimate of body composition. They utilized the Metropolitan Life height and weight tables, a set of tables developed from over 100,000 measurements that show, for a given height, the weight range associated with the lowest mortality rates.

The underlying assumption to be tested was that individuals of ideal weight—and of the same percentage above or below ideal weight—had the same basic body composition and hence the same normal blood volume per unit mass. For practical purposes, a single ideal weight using the midrange weight for medium frame size was used. This eliminated subjective decisions.

The assumption was tested by comparing measured blood volume in 160 normal individuals of either sex, with a wide range of height, weight, and body composition, and comparing that to percent deviation from ideal weight.

This resulted in a curve that described normal blood volume per unit mass in relation to percent deviation from ideal weight (Figure 2, adapted from Feldschuh). The subjects' measured blood volumes correlated well with this curve and, most importantly, did not show any systematic deviations based on weight, height, or deviation from ideal weight. In comparison, both fixed weight ratio norms and body surface area norms showed systematic errors and/or wide scatter in relation to these factors.

The norm based on deviation from ideal weight provided improved accuracy and precision to norms based on body surface area. Its main improvement

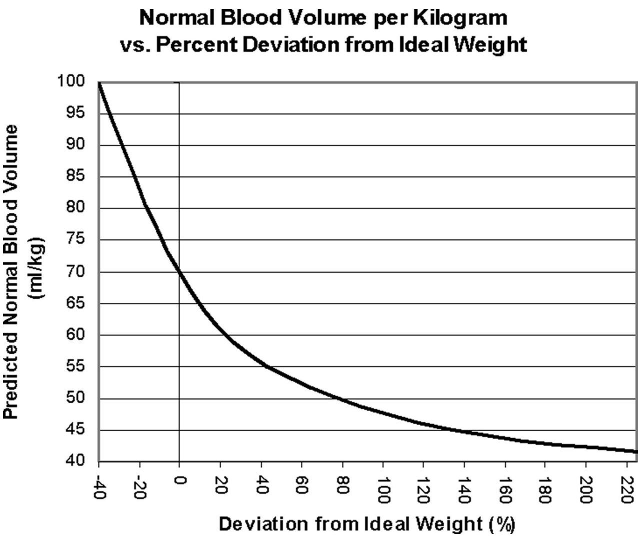

Figure 2. Curve shows normal blood volume per unit mass in relation to percent deviation from ideal weight.

over body surface area was that errors were evenly scattered over a range of height and body compositions, while body surface area showed systematic errors among individuals who were either very small or very large.

Determining a Normal Range

In addition to an accurate method for predicting normal blood volume, meaningful interpretation of blood volume results requires the establishment of a useful normal range.

Both sensitivity and specificity must be considered in determining the optimal range within which blood volume is considered normal. A range that is too wide, while highly specific about identifying only abnormal blood volumes, would result in the misclassification of many abnormal blood volumes as normal. Alternatively, a range that is too narrow, while highly sensitive in detecting abnormality, would result in the misclassification of many normal blood volumes as abnormal.

The 1995 International Committee on Standardization in Hematology paper recommends a normal range of ±25% from the predicted norm. This range includes 98% to 99% of the subjects included in the paper, thus maximizing specificity. However, they acknowledged that an individual can have a significant blood volume abnormality within this "normal" range.

Feldschuh and Enson established a category system for interpreting the presence and severity of blood volume abnormalities, using increments of ±8%. A normal blood volume was determined to be within 8% of the predicted normal value. A deviation of −8% to −16% from the predicted norm was considered mild hypovolemia, a deviation of −16% to −24% moderate hypovolemia, a deviation of −24% to −32% severe hypovolemia, and more than −32% extreme hypovolemia. Similarly, a deviation of +8% to +16% was considered mild hypervolemia, +16% to +24% moderate hypervolemia, +24% to +32% severe hypervolemia, and more than +32% extreme hypervolemia.

This increment was chosen based on the standard error found in the blood volumes of the measured subjects. This classification scheme has lower specificity than the ICSH category (an individual classified with mild hypovolemia or mild hypervolemia is more likely to actually have a normal blood volume), but much higher sensitivity. Unpublished studies by Feldschuh have found that in patients with stable conditions who receive blood volume measurements at intervals of 1 to 2 years, intrapatient volume shows normal variation of 2% to 4%, so a variation of 8% from a patient's previously measured volume indicates some significant change.

The use of incremental ranges of severity also reflects the fact that blood volume abnormalities occur in different degrees of severity and may require different treatment approaches based on severity. For example, Lucas[16] presented four categories for severity of traumatic hemorrhage based on the percentage of blood lost and included four different treatment approaches according to severity.

Presentation of a patient's percent deviation from the predicted norm in combination with a classification of the severity of abnormality can provide a balance between sensitivity and specificity. Milder deviations from normal may be identified, enabling earlier diagnosis and treatment. The lower specificity of this system may be offset somewhat by the inclusion of graded classifications. A clinician may view mild deviations in relation to that patient's specific history, clinical status, and other factors and determine whether treatment or simply additional monitoring is needed.

The Ideal Weight Norm in Clinical Practice: One Example

A recently developed, FDA-approved, semiautomated blood volume measurement system (BVA-100, Daxor Corporation) incorporates the ideal weight method into determining individual norms and presenting results. Since its approval, a number of studies in a variety of conditions have been published utilizing blood volume measurements obtained with this system.[17–22] An excellent test of the sensitivity and specificity of the ideal weight norm can be seen in several of these papers, which concern blood volume in heart failure.[19–22]

In particular, "Relation of Unrecognized Hypervolemia in Chronic Heart Failure to Clinical Status, Hemodynamics, and Patient Outcomes"[21] presented a very strong correlation between measured blood volume and outcome in heart failure. Of 43 non-

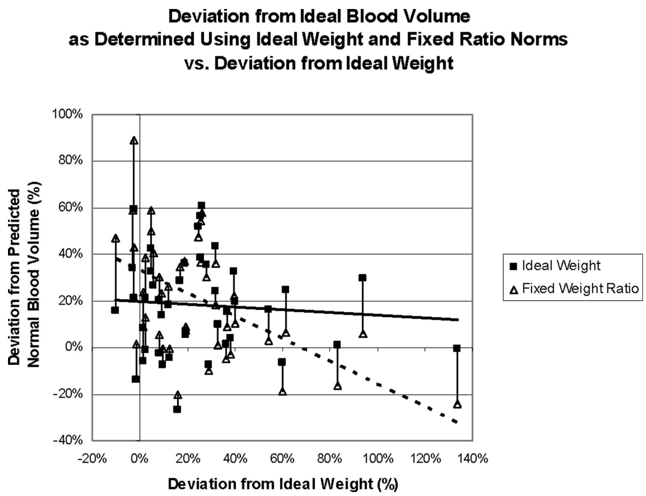

Figure 3. Each set of one solid square and one open triangle represents a single patient with two interpretations of measured blood volume: one (solid square) determined based on the ideal weight norm, and one (open triangle) determined based on a fixed weight ratio norm. Solid black line is the trend line for the ideal weight points; dotted line is the trend line for the fixed weight ratio points.

edematous patients who received blood volume measurement, 15 were found to be hypovolemic or normovolemic, and 28 were found to be hypervolemic. By the end of 1 year of follow-up, 39% of the hypervolemic patients died or underwent urgent transplantation, whereas none (0%) of the normovolemic or hypovolemic patients had these adverse events. After 2 years, mortality rates and urgent transplantation among hypervolemic patients increased to a total of 57% of patients, whereas all of the normovolemic and hypovolemic patients remained event-free (0% mortality rate).

These findings are remarkable in terms of providing a discriminatory analysis of the relation between blood volume and heart failure outcome. They provide very strong evidence for the strong value of the ideal weight system for accurately predicting norms. Had a number of patients been misclassified, the results would have been obscured or lost.

A previous study[19] found more severe heart failure and poorer outcomes to be associated with hemodilution (low hematocrit resulting from an increased plasma volume) as compared with true anemia (low hematocrit resulting from decreased red cell mass). Although not as distinct as the results from the later study, this one also emphasizes the ability for ideal weight norms to aid in discrimination between meaningful, predictive categories.

Both of these studies emphasize the importance of the accurate diagnosis of blood volume status in heart failure assessment. Although the clinical assessment of volume status is included as a key step in the evaluation of heart failure in the American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult,[23] clinical assessment has been shown to be very unreliable for accurate evaluation of volume status. In the outcome study discussed above, clinical assessment of blood volume agreed with measured blood volume for only 51% of patients.

By examining the blood volume results from the heart failure patients included in the outcome study, the errors that could arise from using less accurate norms can be seen.

A comparison of blood volume results based on fixed weight ratio norms versus ideal weight norms in these patients demonstrates a clear systematic difference (Figure 3). Using the ideal weight norm, the patients had an average blood volume expansion of about 20%, with a slight but nonsignificant trend toward decreased hypervolemia at higher levels of obesity. With fixed weight ratio norms there was a clear tendency toward the misclassification of normovolemia or hypovolemia as patients became more obese.

Using the ideal weight norms, 28 patients were found to be hypervolemic, and 15 were found to be normovolemic or hypovolemic. Using fixed weight ratio norms,[3] 21% of the patients who were classified as hypervolemic in the study would have been misclassified as normovolemic or hypovolemic by fixed weight ratio norms (Table 1).

Table 1. Classification of Hypervolemia and Hypo/Normovolemia Using Several Norms and Normal Ranges

	FWR Same	FWR Different	BSA ±25% Same	BSA ±25% Different	BSA ±8% Same	BSA ±8% Different
Hypo/normovolemic by IW norms (n = 15)	15	0	15	0	13	2 (hyper-volemic)
Hypervolemic by IW norms (n = 28)	22	6 (normo- or hypovolemic)	16	12 (normo- or hypovolemic)	27	1 (normo- or hypovolemic)

All patients on the top row were classified as hypovolemic or normovolemic using ideal weight (IW) norms and on the bottom row were classified as hypervolemic by ideal weight norms. Patients in the first two columns were classified with fixed weight ratio (FWR) norms as described by Jacobs and DeMott.[4] The second two columns contain classifications from the ICSH body surface area (BSA) norms and a normal range of ±25% and in the third set of two columns, BSA norms and a normal range of ±8%. For each norm system, the patients who were classified with the same blood volume status as by the IW method are in the left column, and patients who were classified differently are on the right column.

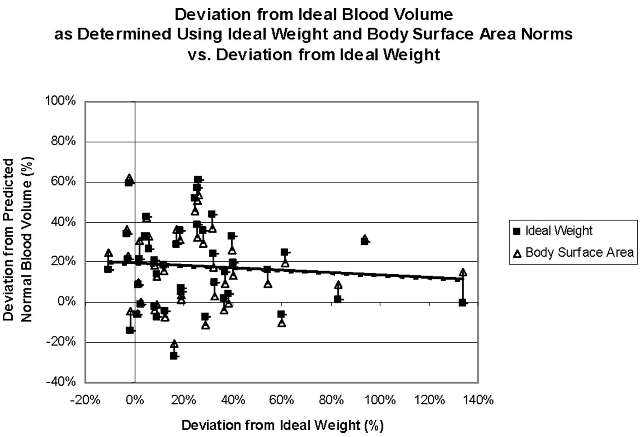

Figure 4. Each set of one solid square and one open triangle represents a single patient with two interpretations of measured blood volume: one (solid square) determined based on the ideal weight norm, and one (open triangle) determined based on the ICSH body surface area norm.

When results based on body surface area norms are compared with those based on ideal weight norms, interpreted blood volumes are closer, and the systematic difference is less clear (Figure 4). There is a tendency toward higher body surface area norms (relative to ideal weight norms) among lean and very obese patients, and lower body surface area norms among mildly and moderately obese patients.

By using the ICSH-recommended normal range of ±25%, however, 12 of 28 (43%) patients classified as hypervolemic by the ideal weight method would be misclassified as normovolemic or hypovolemic (Table 1). In this population of patients with a disorder that has a known effect on blood volume, such a broad norm will not effectively enable the identification of patients at risk for poorer outcomes or aid in the choice of appropriate treatment. The sensitivity of this normal range is simply too low for clinical use.

By using the same normal criteria as used in the ideal weight method (±8%), the results are much closer. Only 1 patient classified as hypervolemic with the ideal weight norm was classified as normovolemic with the body surface area norm, while 2 out of 15 (13%) patients classified by the ideal weight norm as hypovolemic or normovolemic were classified as hypervolemic with the body surface area norm. Although this is an improvement, results still do not equal those from the ideal weight norm.

Although the errors in this case are not as marked, it is important to have a sense of which of these two similar methods is physiologically more accurate. Body surface area has previously shown systematic errors at both low and high extremes of height and weight, whereas deviation from ideal weight has not shown any systematic errors.

Conclusion

The best evaluation of a norm occurs when it is used in an experimental or clinical setting. Does the norm provide meaningful information that can be used to predict outcomes or ultimately to improve treatment? Do measurements from the norm correlate with disease severity and with outcome when known relations exist?

Although it remains commonly used, a single volume to weight ratio does not accurately predict normal blood volume in many patients. Errors increase with the degree of a patient's leanness or obesity; thus, these systematic errors are of particular concern within populations in which patients tend to be markedly lean or obese, such as heart failure patients.

Body surface area provides improved accuracy but is physiologically unrelated to the factors that actually determine blood volume. The body surface area norms recommended by the ICSH include a normal range of ±25%, which does not provide sufficient information for clinical use.

Deviation from ideal weight has been shown to be a reasonable estimate of body composition and provides a method of predicting normal blood volume that is related to the underlying physiology. Although these norms produce results similar to those from using body surface area norms, the underlying physiological basis implies improved accuracy over body surface area norms.

When used in a clinical situation, ideal weight norms with a ±8% normal range provided a high level of predictive discrimination for classifying blood volume status.

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