CME Peripheral Blood Hematocrit in Critically Ill Surgical Patients: An Imprecise Surrogate of True Red Blood Cell Volume

Danny M. Takanishi, MD, FACS
Mihae Yu, MD, FACS
Fedor Lurie, MD, PhD
Elisabeth Biuk-Aghai, MD
Hideko Yamauchi, MD
Hao Chih Ho, MD, FACS
Alyssa D. Chapital, MD, FACS

BACKGROUND: Peripheral blood hematocrit (red blood cell volume/total blood volume) is conventionally used to determine the need for blood transfusions. In critically ill surgical patients, this variable may not accurately approximate true red blood cell volume. We compared peripheral blood hematocrit to (1) plasma volume, (2) estimated circulating blood volume, and (3) a normalized hematocrit to clarify their relationships.
METHODS: Consecutive patients admitted to the surgical intensive care unit were evaluated using the BVA-100 Blood Volume Analyzer (Daxor Corporation, New York City, NY). Plasma volume was directly measured by serial tagged albumin concentration. Red blood cell volume was calculated using plasma volume and the peripheral blood hematocrit result. All volumes were presented as percentage deviation from ideal volumes. These ideal volumes were obtained using a patented formula incorporating ideal body weight as determined by Metropolitan Life tables. The peripheral blood hematocrit was compared with a "normalized" hematocrit, defined as the hematocrit value if plasma volume was adjusted to a normal whole blood volume.
RESULTS: Eighty-six data points were recorded for 40 patients with average age 61 ± 20 yr, APACHE II score 20 ± 6, and a 13% mortality rate. The primary reasons for admission were severe sepsis/septic shock (n = 11), hemorrhagic shock (n = 7), respiratory failure (n = 20), and cardiac failure (n = 2). Bland–Altman analysis showed a mean difference of 3.4 ± 7.8 hematocrit percentage points between normalized and peripheral blood hematocrit methods, with a 95% confidence interval of 1.7–5.1 and limits of agreement of ±15.2 hematocrit percentage points. Peripheral blood hematocrit was lower than the normalized hematocrit in 48% of measurements, higher in 17%, and equivalent in 35%.
CONCLUSIONS: Peripheral blood hematocrit may not accurately estimate red blood cell volume in a cohort of critically ill surgical patients. This remains to be validated in a larger group of patients, comparing these results with the double isotope technique.
(Anesth Analg 2008;106:1808–12)

The management of critically ill patients requires resuscitation to an adequate intravascular blood volume (BV) status to achieve improved tissue oxygenation.[1,2] BV, comprising plasma volume (PV) plus red blood cell volume (RBCV), is estimated to be 60–70 mL/kg.[3] RBCV is indirectly estimated using peripheral blood hematocrit (Hct) measured in the clinical laboratory.[4] This Hct value, also called the packed cell volume, is the ratio of the RBCV relative to the total volume of whole blood in a sample of blood. Manual and automated methods for determining peripheral blood Hct show excellent correlation.[5] However, peripheral blood Hct, as a surrogate measure for RBCV, may falsely reflect a low RBCV in states of excess PV (dilutional anemia), or the Hct may falsely reflect a high RBCV when PV is low.[4,6–8]

Because the traditional method of directly measuring BV using radioisotope-labeled red blood cells (RBC) and albumin is arduous and impractical,[4,9–11] a simplified, prepackaged, semiautomated kit is used clinically for BV measurement. Although peripheral blood hemoglobin measured in the clinical laboratory, and at times by extension the Hct, is currently used to make RBC transfusion decisions, it may not represent true RBCV.[4,6–8] Euvolemic or compensatory anemia (decreased RBCV, increased PV, and normal BV) and hypervolemic or dilutional anemia (normal RBCV, increased PV, and increased BV) are well tolerated, but hypovolemic anemia (decreased RBCV, decreased

From the Divisions of Surgical Critical Care and Trauma, Department of Surgery, John A. Burns School of Medicine, University of Hawaii and The Queen's Medical Center, Honolulu, Hawaii.

Accepted for publication February 22, 2008.

Supported by the Queen Emma Research Foundation.

Address correspondence and reprint requests to Danny M. Takanishi Jr, MD, FACS, Department of Surgery, University of Hawaii, 1356 Lusitana St., 6th Floor, Honolulu, HI 96813. Address e-mail to dtakanis@hawaii.edu.

DOI: 10.1213/ane.0b013e3181731d7c

PV, and decreased BV) may be fatal in conditions associated with increased physiologic stress.

This study compared peripheral blood Hct measured in the clinical laboratory to (1) PV, (2) estimated total BV, and (3) a normalized Hct to test the hypothesis that peripheral blood Hct is an accurate indicator of RBCV.

METHODS

This study was reviewed and approved by the IRB of The Queen's Medical Center. Written informed consent was obtained from all subjects or from a legal surrogate. The study was conducted in a university-affiliated, 500-bed, urban, tertiary care teaching hospital. BV was measured in consecutive patients admitted to the surgical intensive care unit (SICU) whose intravascular volume status was clinically deemed uncertain by the treating team. The rounding team determined whether there was a clinical variable requiring treatment: low arterial blood pressure [systolic blood pressure <90 mm Hg despite adequate fluid resuscitation to a pulmonary artery occlusion pressure of 15–18 mm Hg, if a pulmonary artery catheter (PAC) was present], persistent tachycardia (defined as heart rate >100 bpm), low urine output ($<0.5\ mL \cdot kg^{-1} \cdot h^{-1}$ despite volume infusion), worsening renal function (serum creatinine increase of >20% of baseline), low cardiac index ($<2.5\ L \cdot min^{-1} \cdot m^{-2}$ with pulmonary artery occlusion pressures of 15–18 mm Hg, if a PAC was in place), oxygenation deficit (defined as PAo_2/FIo_2 ratio <200, or intrapulmonary shunt ratio, Q_s/Q_t, of >20%, if PAC in place), persistent requirement for vasopressors, or non-normalization of lactate levels.

All patients were assessed using available clinical variables: heart rate, arterial blood pressure, urinary output, PAC data, chest radiograph, arterial blood glass, B-natriuretic peptide, lactic acid, blood urea nitrogen, creatinine, and hemoglobin/Hct. Patients were excluded if they were pregnant, younger than 18 yr, or if there was a history of an iodine allergy. All BV measurements were performed after the first 24 h of acute resuscitation to minimize any impact of rapidly shifting intravascular volumes (or vasopressor and inotrope use) on peripheral blood Hct and BV analysis.

BV assessment was performed with the BVA-100 Blood Volume Analyzer (Daxor Corporation, New York City, NY), which uses injection of 1 mL of I-131-labeled serum albumin containing 25 μCi of radioactivity. After obtaining a baseline sample of 5 mL peripheral blood, 1 mL of I-131-labeled albumin was injected IV over 1 min. All blood samples were obtained with the patient in a supine position. At the time the baseline sample of 5 mL blood was obtained, a peripheral blood Hct was simultaneously acquired. Five milliliter blood samples were collected at 12, 18, 24, 30, and 36 min postinjection, and PV was measured by extrapolating to time zero. Radioactivity was measured in duplicate, with a minimum of three sample points with a SD of <3.9%. Results were available in 45–90 min.

The RBCV was calculated based on the relationship of Hct to RBCV/(RBCV + PV), and BV was calculated based on PV + RBCV. The values of PV, RBCV, and total BV are presented as percent deviation from ideal values. These ideal BV values were derived using a patented formula based on gender, height, weight, and optimum (ideal) weight as determined by the Metropolitan Life tables, and as previously validated by BV studies.[3,12] An approach for categorizing the significance of BV abnormalities was formulated by these investigators based on the standard error identified in the measurements of BV in the subjects tested, where a normal BV was ascertained to be within 8% of the predicted normal BV, hypovolemia as <8%, and hypervolemia as >8%.[3,12]

The peripheral blood Hct was further adjusted to a "normalized" Hct, the Hct value if PV was adjusted to a normal whole BV. This is a more accurate reflection of RBCV and absolute RBC mass (the degree of true anemia or polycythemia) and can be interpreted independent of PV.[4,9]

The Statistical Package for the Social Sciences (SPSS, Chicago, IL) software was used for analysis. Descriptive statistics were used to describe patient characteristics (mean and SD for continuous data). Bland–Altman analysis was applied to estimate bias and limits of agreement between peripheral blood Hct measurements and normalized Hct.[13,14] A P value of <0.05 and a 95% confidence interval were considered statistically significant.

RESULTS

Data points were collected for 40 patients (32 male/8 female) aged 61 ± 20 yr (mean ± SD) with APACHE II scores of 20 ± 6 (mean ± SD) and a 13% mortality rate (5 of 40). There were 14 trauma patients, 22 general surgical patients, and 4 patients from other surgical subspecialties. Twenty data points were obtained in subjects with a PAC. The primary reasons for intensive care unit (ICU) stay were: severe sepsis/septic shock (n = 11), hemorrhagic shock (n = 7), respiratory failure (n = 20), and cardiac failure (n = 2). The ICU day of BV measurement ranged from day 1 to day 84, with the following distribution: day 1–2 (n = 14), day 3–4 (n = 20), day 5–10 (n = 25), day 11–20 (n = 10), day ≥21 (n = 17).

Peripheral blood Hct was compared to PV and estimated total BV to determine if there was a linear relationship between these variables. This was evaluated by construction of regression (scatter) plots and calculation of coefficients of determination, R^2, to test the validity of the regression models. The R^2 was 0.0353 for peripheral blood Hct measured in the laboratory compared to PV (Fig. 1) and 0.0072 for peripheral blood Hct compared to estimated total BV (Fig. 2).

Bland–Altman analysis between measured peripheral blood Hct and normalized Hct demonstrated a

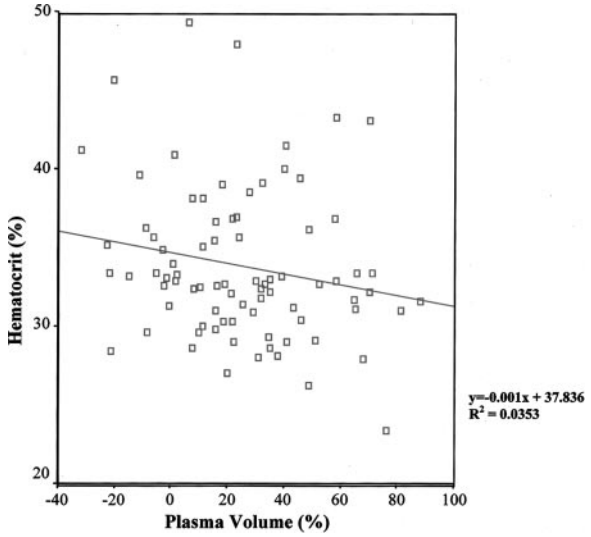

Figure 1. Relationship between peripheral blood hematocrit and plasma volume.

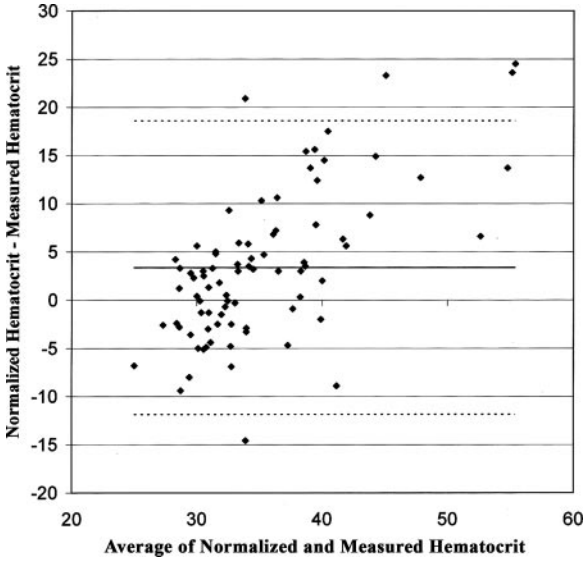

Figure 3. Difference between normalized hematocrit and peripheral blood (measured) hematocrit compared to average of methods. Bland–Altman plot. Solid line = mean; dashed lines = 2 standard deviations.

mean difference between methods (bias) of 3.4 ± 7.8 Hct percentage points, with a 95% confidence interval of 1.7–5.1 Hct percentage points (Fig. 3). The limits of agreement, determined by estimation of the mean difference and the standard deviation of the differences, were ±15.2 Hct percentage points. The peripheral blood Hct measured in the clinical laboratory was lower than the normalized Hct in 41 of 86 (48%) measurements, higher in 15 of 86 (17%), and equivalent in 30 of 86 (35%). BV data demonstrated more than 16% deficit from ideal normal in RBCV in 46% (39 of 86) of the measurements, and >24% deficit in RBCV in 26% (22 of 86) (Table 1).

DISCUSSION

The present study in SICU subjects showed that peripheral blood Hct may not reflect true RBCV and values may deviate by as much as 15 Hct percentage points. Given that Hct reflects RBCV in relation to PV and total BV, estimating RBCV based on the peripheral blood Hct alone may be misleading. There was no strong linear relationship (based on scatter plots and R^2 values) between peripheral blood Hct, PV, and estimated total BV, indicating that PV and estimated

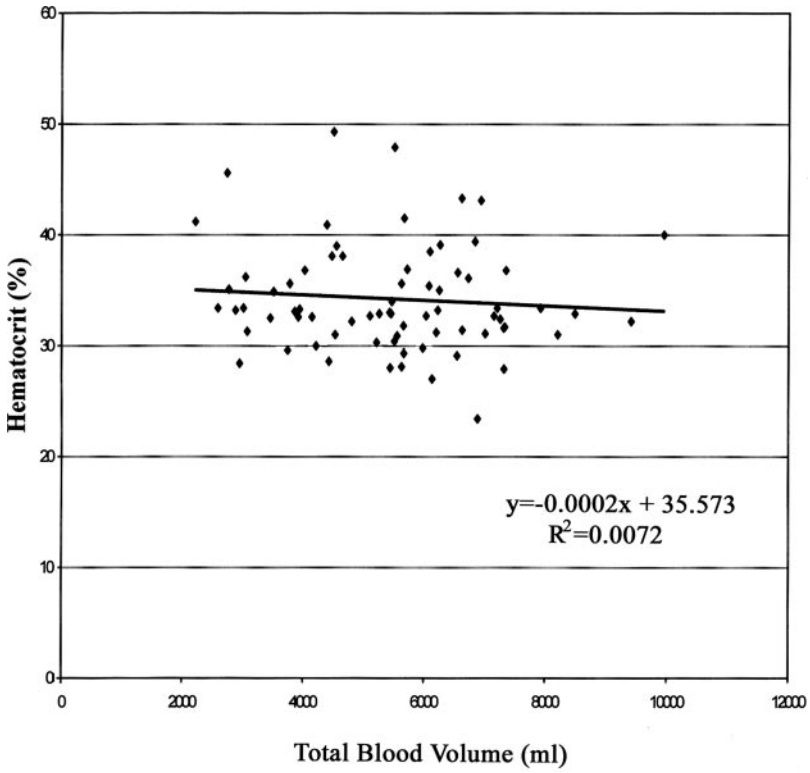

Figure 2. Relationship between peripheral blood hematocrit and estimated total blood volume.

Table 1. Patient Distribution of Red Blood Cell Volume (RBCV) Deficit and Excess Categorized by Deviation from Ideal Normal ($n = 86$)

Deviation from normal (%)	Deficit RBCV (%, $n = 67$)	Excess RBCV (%, $n = 19$)
0%–8%	6/86 (7)	7/86 (8)
>8%–16%	12/86 (14)	3/86 (3)
>16%–24%	17/86 (20)	3/86 (3)
>24%–32%	18/86 (21)	2/86 (2)
>32%	4/86 (5)	4/86 (5)

BV vary independently of RBCV. The Bland–Altman plot further suggests that a systematic proportional error may be present, with the peripheral blood (measured) Hct over-estimating the RBCV when it is in the lower range of our study (hence a negative value for normalized Hct − measured Hct) and under-estimating the RBCV when it is in the higher range (resulting in a positive value for normalized Hct − measured Hct). This may incorrectly lead clinicians to either over- or under-transfuse RBCs, both of which may have negative consequences.

Our study methodology incorporated use of multiple timed blood samples after injection of the I-131-labeled albumin. This allowed adequate mixing time to occur *in vivo*, which reliably corrected for the albumin transudation rate. This yielded true zero-time PV results. This single isotope method therefore detects and adjusts for the loss of albumin into the interstitial space that occurs with capillary leak syndrome (commonly seen in sepsis, shock states, trauma, and conditions associated with the systemic inflammatory response syndrome), and has been validated in this setting.[15] Dworkin et al. measured RBCV and total BV using simultaneous chromium-51-tagged RBCs and iodine-125-tagged albumin and compared this to iodine-131-tagged albumin and extrapolated RBCV using the BVA-100 analyzer.[16] Measurement of PV alone in this group of 27 healthy subjects was found to provide results comparable to those obtained from simultaneous measurement of both PV and RBCV, the method recommended by the International Council for Standardization in Hematology (ICSH; previously the International Committee for Standardization in Hematology).[17,18] Moreover, some institutions have completely ceased using the double isotope technique and instead use the albumin-labeled single isotope methodology to measure PV and RBCV[10] The major advantage is the relatively short time needed to obtain results with a single dye, or single radioisotope, technique. In contrast, the combined, simultaneous measurement with chromium-51-tagged RBCs and iodine-125-tagged albumin requires an average of 5 h for results.

In adults, the ICSH has provided formulas for calculating expected PV and RBCV, from which total BV can be calculated.[10,18,19] These formulas are based on gender, age, and body surface area, and were derived from double isotope techniques obtained in normal healthy subjects. In our study population, all but one PV measurement and all but seven estimated RBCV measurements were higher than published reference ranges for normal subjects.[10,18,19] The physiologic implications of and mechanisms accounting for these findings remain to be determined.

There is accumulating evidence that peripheral blood Hct is an imprecise estimate of RBCV. The peripheral blood Hct, generally measured by the venous Hct, is approximately 10% higher than the total body Hct, because the Hct in the microcirculation is less than that in the macrocirculation. Therefore, the peripheral blood Hct is not a true portrait of the functional level in the microcirculation of individual organs, which may partially account for contrasting data regarding the benefits of transfusion in critically ill patients.[19] Some investigators have reported a positive correlation between peripheral blood Hct and RBCV, but this apparent loose relationship has not allowed accurate prediction of the RBCV from the Hct value.[9] Despite these considerations, it should be emphasized that the peripheral blood Hct is currently viewed by many clinicians as the best surrogate available for estimation of total body Hct, and is the value most commonly used in contemporary clinical practice.

Potential limitations of this study include the heterogeneous SICU patient population and the fact that PV, calculated RBCV, and estimated BV determinations were performed at different points in the ICU stay. We do not believe that this variation significantly affects our results, given that laboratory Hct and BV measurements were done simultaneously in each patient enrolled. Also of relevance is that these measurements were not obtained during active fluid resuscitation of patients, so that during the BV assessment period the volume of distribution was not changing rapidly. Furthermore, in the ICU setting, the relationship between peripheral blood Hct and PV is affected by a number of factors, such as recumbency, blood transfusion, and blood sampling. All subjects in this study were supine throughout the testing and were not receiving transfusions. Additionally, no subject received diuretics for at least 24 h before and for the duration of testing, and blood sampling was limited during the testing period to that required for BV analysis only.

Lastly, one potential limitation that may have bearing on the findings derived from this study results from the sole use of radiolabeled albumin to measure BV variables. As in any single dye or single radioisotope technique, any error in measured PV is compounded when estimated RBCV and total BV are calculated.[20] Likewise, any error in measurement of the peripheral blood Hct will result in a proportional error in the calculated RBCV.[10] Blood sample radioactivity was not measured either before or after centrifuging of the RBCs, which would have provided both total BV and PV, and the technique used was the single isotope method, where only albumin (and not

RBCs) was labeled. Thus, for the present study, RBCV and BV were not directly measured, and these results can only be regarded as estimates of RBCV and BV.

Most of our subjects had Hct measurements in the clinical range of 25%–45%, and it would have been relevant to evaluate the relationship of laboratory Hct and RBCV in the presence of laboratory Hct measurements <25%. This is particularly important given that the current approach to transfusion therapy is guided to a large degree by the laboratory Hct. The rationale for this practice is substantiated by the fact that oxygen delivery is based significantly on cardiac output and hemoglobin level (and by extrapolation the Hct).

Studies such as this, if validated by others, have important clinical ramifications. In the subset of patients who have hypovolemic anemia,[4] the normal reference range Hct measured by the clinical laboratory is "adjusted" or "normalized" to a decreased total BV resulting from a decreased PV that has not compensated for the decrease in RBCV or RBC mass; thus, these patients are significantly more anemic than recognized based on their laboratory Hct. There is also a significant percentage of patients who are hypervolemic, and whose laboratory Hct may therefore decrease below established reference ranges. In these instances, patients are found to have a normal RBCV, and therefore RBC mass, when normalized to true BV status resulting from an expanded PV.[6,7,21] This cohort should not receive blood transfusions, as they are not truly anemic. For both sets of patients, their true RBCV status is not recognized by conventional laboratory measurement of Hct and other clinical surrogates of intravascular volume status. Such errors may be avoided by BV measurement that includes RBCV and PV measurement. Consideration of the laboratory Hct, RBCV, and PV will likely refine our approach to transfusion therapy in complex, critically ill surgical patients.

REFERENCES

1. Jahr JS, Lurie F, Xi S, Golkaryeh M, Kuznetsova O, Kullar R, Driessen B. A novel approach to measuring circulating blood volume: the use of a hemoglobin-based oxygen carrier in a rabbit model. Anesth Analg 2001;92:609–14
2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345: 1368–77
3. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. Circulation 1977; 56:605–12
4. Valeri CR, Dennis RC, Ragno G, MacGregor H, Menzolan JO, Khuri SF. Limitations of the hematocrit level to assess the need for red blood cell transfusion in hypovolemic anemic patients. Transfusion 2006;46:365–71
5. McNulty SE, Torjman M, Grodecki W, Marr A, Schieren H. A comparison of four bedside methods of hemoglobin assessment during cardiac surgery. Anesth Analg 1995;81:1197–202
6. Bentley SA, Lewis SM. The relationship between total red cell volume, plasma volume and venous haematocrit. Br J Haematol 1976;33:301–7
7. Hurley PJ. Red cell and plasma volumes in normal adults. J Nucl Med 1975;16:46–52
8. Lorberboym M, Rahini-Levene N, Lipszyc H, Kim CK. Analysis of red cell mass and plasma volume in patients with polycythemia. Arch Pathol Lab Med 2005;129:89–91
9. Orth VH, Rehm M, Thiel M, Kreimeier U, Haller M, Brechtelsbauer H, Finsterer U. First clinical implications of a perioperative red cell volume measurement with a nonradioactive marker (sodium fluorescein). Anesth Analg 1998;87:1234–8
10. Fairbanks VF, Klee GG, Wiseman GA, Hoyer JD, Tefferi A, Petitt RM, Silverstein MN. Measurement of blood volume and red cell mass: re-examination of ^{51}CR and ^{125}I methods. Blood Cells Mol Dis 1996;22:169–86
11. Balga I, Solenthaler M, Furlan M. Should whole-body red cell mass be measured or calculated? Blood Cells Mol Dis 2000;26:25–31
12. Feldschuh J, Katz S. The importance of correct norms in blood volume measurement. Am J Med Sci 2007;334:41–6
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10
14. Mantha S, Roizen MF, Fleisher LA, Thisted R, Foss J. Comparing methods of clinical measurement: reporting standards for Bland and Altman analysis. Anesth Analg 2000;90:593–602
15. Margarson MP, Soni NC. Plasma volume measurement in septic patients using an albumin dilution technique: comparison with the standard radio-labeled albumin method. Intensive Care Med 2005;31:289–95
16. Dworkin HJ, Premo M, Dees S. Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using I-131-tagged albumin and extrapolated red cell volume. Am J Med Sci 2007;334:37–40
17. Pearson TC, Guthrie DL, Simpson J, Chinn S, Barosi G, Ferrant A, Lewis SM, Najean Y. Interpretation of measured red cell mass and plasma volume in adults. Expert Panel on Radionuclides of the International Council for Standardization in Haematology. Br J Haematol 1995;89:748–56
18. International Committee for Standardization in Haematology. Recommended methods for measurement of red-cell and plasma volume. J Nucl Med 1980;21:93–800
19. Jones JG, Wardrop CAJ. Measurement of blood volume in surgical and intensive care practice. Br J Anaesth 2000;84:226–35
20. Davy KP, Seals DR. Total blood volume in healthy young and older men. J Appl Physiol 1994;76:2059–62
21. Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. Am J Med Sci 2007;334:47–52