Comparison of Blood Volume Characteristics in Anemic Patients With Low Versus Preserved Left Ventricular Ejection Fractions

Dmitry Abramov, MD, MS[a], Rose S. Cohen, MD[a], Stuart D. Katz, MD[b], Donna Mancini, MD[a], and Mathew S. Maurer, MD[a,*]

Anemia is a significant co-morbidity in patients with heart failure (HF) irrespective of the ejection fraction and is routinely quantified by hemoglobin concentration. Hemodilution as a cause of anemia has been described in systolic HF. The aim of this study was to further investigate the effects of plasma volume in patients with HF by (1) assessing the prevalence of dilutional anemia in patients with anemia and preserved ejection fractions and (2) exploring the relation between hemoglobin and red cell volume in these patients. Forty-six patients with anemia (as determined by standard hemoglobin measurement), 22 with HF and low ejection fractions (HFLEF) and 24 with HF and preserved ejection fractions (HFPEF), all underwent plasma volume measurement with iodine-131-labeled albumin. Hemoglobin values did not differ between subjects with HFLEF and those with HFPEF (10.8 ± 1.0 vs 11.0 ± 1.0 g/dl, p = 0.55), but a red cell deficit was found in 88% of patients with HFPEF compared with 59% of those with HFLEF (p = 0.04). This was the result of a higher prevalence of an expansion of plasma volume in patients with HFLEF (100%) compared with those with HFPEF (71%). Among all patients, no correlation was found between hemoglobin and red cell volume (r = 0.09, p = 0.54), but a correlation did exist in patients with normal blood volumes (r = 0.55, p = 0.02). In conclusion, dilutional anemia caused by an expansion in plasma volume without a red cell deficit occurs more commonly in patients with HFLEF than those with HFPEF, and hemoglobin does not correlate with red cell volume in patients with anemia and HF. **(Am J Cardiol 2008;102:1069–1072)**

The cause of anemia in patients with heart failure (HF) is multifactorial,[1–3] and several therapies have been used with varying success.[2] Although hemoglobin values are typically used to diagnose anemia, low hemoglobin, on a physiologic basis, can be the result of either (1) a true red cell deficit or (2) hemodilution with plasma volume expansion.[4] Although hemoglobin or hematocrit provides a good estimate of red cell volume in healthy patients,[5] discordance between hemoglobin and red cell volume has been described in patients with polycythemia vera[6] and liver disease[7,8] and in the presence of splenomegaly[9] due to the confounding effects of alterations in plasma volume.[5,9–11] In patients with advanced HF and low ejection fractions (EFs), almost half were reported to have anemia on the basis of hemodilution with normal red cell volumes.[4] Whether a similar percentage of patients with HF and preserved EFs (HFPEF) have such dilutional anemia is unclear. Given the mixed success in treatment of anemia,[2,12] issues surrounding the measurement of anemia deserve clarification. Accordingly, the purpose of this study was twofold: (1) to explore the correlation between hemoglobin values and red cell volume in patients with anemia and HF and (2) to determine whether patients with anemia and HFPEF have a similar prevalence of dilutional anemia as patients with HF with low EFs (HFLEF).

Methods

Subjects were outpatients referred for evaluation and treatment to the Columbia University Medical Center Heart Failure Center. Subjects aged >21 years with HF for ≥3 months' duration with stable symptoms were enrolled. All subjects had anemia (per the World Health Organization criteria: hemoglobin <13.0 g/dl in men and <12.0 g/dl in women).[2] Criteria for exclusion were acute decompensated HF, severe renal dysfunction (serum creatinine >3.5 mg/dl or history of nephrotic syndrome), and severe hepatic dysfunction (serum liver enzymes >3 times the upper limits of normal or history of cirrhosis). Cardiac medications included diuretics, digoxin, renin-angiotensin system inhibitors, and/or β-adrenergic receptor antagonists that were stable before the measurement of blood volume.

Forty-six nonedematous ambulatory patients with HF were studied: 24 with HFPEF and 22 with HFLEF. Subjects with HF were dichotomized into those with HFLEF and those with HFPEF by EFs of <45% or ≥45%; thus, patients with HFLEF had systolic HF. Blood volume measurements[4,13,14] and the degree of hemodilution in subjects with HFLEF have been reported previously[4]; however, none of the previous analyses included populations of patients with HFPEF, and none focused on the relation between blood volume components and hemoglobin, as presented herein.

[a]Columbia University Medical Center, New York, New York; and [b]Yale University School of Medicine, New Haven, Connecticut. Manuscript received March 21, 2008; revised manuscript received and accepted May 16, 2008.

Dr. Maurer is supported by grant R01AG027518-01A1 from the from the National Institute on Aging, Bethesda, Maryland.

*Corresponding author: Tel: 212-932-4537; fax: 212-932-4538.

E-mail address: msm10@columbia.edu (M.S. Maurer).

0002-9149/08/$ – see front matter
doi:10.1016/j.amjcard.2008.05.058

The Institutional Review Board at Columbia University Medical Center approved the protocol. All subjects gave written informed consent before participation.

Plasma volume was determined after the intravenous administration of iodine-131-labeled albumin, as has been described previously.[4,13,15] Blood volume and red blood cell volume were calculated from the plasma volume measurement, the measured hematocrit corrected for trapped plasma, and mean body hematocrit and then compared with normal values for age, gender, height, and weight on the basis of the ideal weight system.[16] In addition to reporting absolute values, we report percentage deviation from expected values on the basis of the ideal weight system. Normovolemia was prospectively defined as a measured blood volume within 8% of the predicted normal value, and hypervolemia and hypovolemia were defined as blood volumes >8% and <8% of the predicted value, respectively.[4]

Table 1
Demographic and clinical characteristics in patients with anemia and heart failure and low ejection fractions and those with heart failure with preserved ejection fractions

Variable	HFLEF (n = 22)	HFPEF (n = 24)	p Value
Age (yrs)	63 ± 11*	73 ± 14	0.009
Women	5 (23%)*	18 (75%)	<0.001
EF (%)	26 ± 10*	60 ± 7	<0.001
Weight (kg)	83 ± 23	85 ± 21	0.744
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	0.591
Creatinine (mg/dl)	1.5 ± 0.6	1.6 ± 0.8	0.758
Gender glomerular filtration rate (ml/min)	67 ± 41	55 ± 29	0.340
Blood urea nitrogen (mg/dl)	36 ± 22	35 ± 21	0.839
Hemoglobin (g/dl)	10.8 ± 1.0	11.0 ± 1.0	0.550
Hematocrit (%)	33 ± 3	33 ± 3	0.576
Iron (μg/dl)	67 ± 55	53 ± 20	0.274
Ferritin (ng/ml)	195 ± 200	124 ± 174	0.279
New York Heart Association class	2.7 ± 0.7	2.5 ± 0.5	0.475
Diuretic dose (mg of furosemide or equivalent)	177 ± 127*	68 ± 91	0.022

Data are expressed as mean ± 1 SD or as number (percentage).
* p <0.05.

True anemia was defined as having <95% predicted red blood cell volume on the basis of the study participant's gender and body size.[4] Hemoglobin was measured as part of a routine complete blood count from the hospital core laboratory (Sysmex XE 2100; Sysmex Corporation, Kobe, Japan).

Data are expressed as mean ± SD, unless otherwise noted. Dichotomous variables were compared using chi-square analysis with Fisher's exact test when appropriate, and continuous variables were compared using unpaired 2-tailed Students' *t* tests. Simple linear regression analysis was used to determine the correlation between hemoglobin and red blood cell volumes. A p value <0.05 was considered significant. SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

Results

The demographic characteristics of the patient populations are listed in Table 1. Subjects with HFLEF were predominately male, whereas those with HFPEF were older and predominately female. The groups did not differ with regard to body size, functional state (New York Heart Association class), renal function, and hemoglobin, but the patients with HFLEF were taking higher daily doses of loop diuretics.

Despite similar mean hemoglobin values, blood volume measurements differed between patients with HFLEF and those with HFPEF (Table 2). With respect to blood volume, of the patients with HFPEF, 38% were hypovolemic, 42% were normovolemic, and 20% were hypervolemic. Of the patients with HFLEF, none were hypovolemic, 36% were normovolemic, and 64% were hypervolemic.

Plasma volume excess was found more frequently in the group with HFLEF (100%) than in the HFPEF group (71%), and the average plasma volume excess was significantly larger in the HFLEF group (p <0.001). Red blood cell deficit was more pronounced in patients with HFPEF, and plasma volume expansion was less pronounced in comparison with the HFLEF cohort. The incidence of dilutional anemia was 41% in the HFLEF group and 12% in the HFPEF group (p = 0.04).

Among all patients with HF studied, there was no significant association found between hemoglobin and percent-

Table 2
Hematologic characteristics in patients with anemia and heart failure with low and preserved ejection fractions

Variable	HFLEF	Reference Values	HFPEF	Reference Values
Blood volume (ml)	5,809 ± 925*†	4,940 ± 568	4,487 ± 1,170	4,620 ± 791
Blood volume per kilogram (ml)	73.9 ± 17†	—	54.1 ± 15	—
Blood volume deviation (ml)	865 ± 824*	—	−132 ± 1,091	—
Blood volume deviation	18.0%*	—	−2.2%	—
Red cell volume (ml)	1,760 ± 338*†	1,958 ± 266	1,317 ± 340†	1,712 ± 326
Red cell volume per kilogram (ml)	22.1 ± 5.0*	—	15.9 ± 4.4	—
Red cell volume deviation (ml)	−199 ± 335*	—	−395 ± 323	—
Red cell volume deviation	−9.3%*	—	−22.4%	—
Plasma volume (ml)	4,049 ± 650*†	2,986 ± 327	3,170 ± 867	2,908 ± 487
Plasma volume per kilogram (ml)	51.8 ± 13*	—	38.2 ± 11	—
Plasma volume deviation (ml)	1,063 ± 599*	—	263 ± 842	—
Plasma volume deviation	36.2%*	—	10.1%	—

Data are expressed as mean ± 1 SD. Deviation refers to percentage difference from reference values on the basis of gender and body size.
* p <0.05 HFLEF versus HFPEF; † p <0.05 for HFLEF or HFPEF versus reference values.

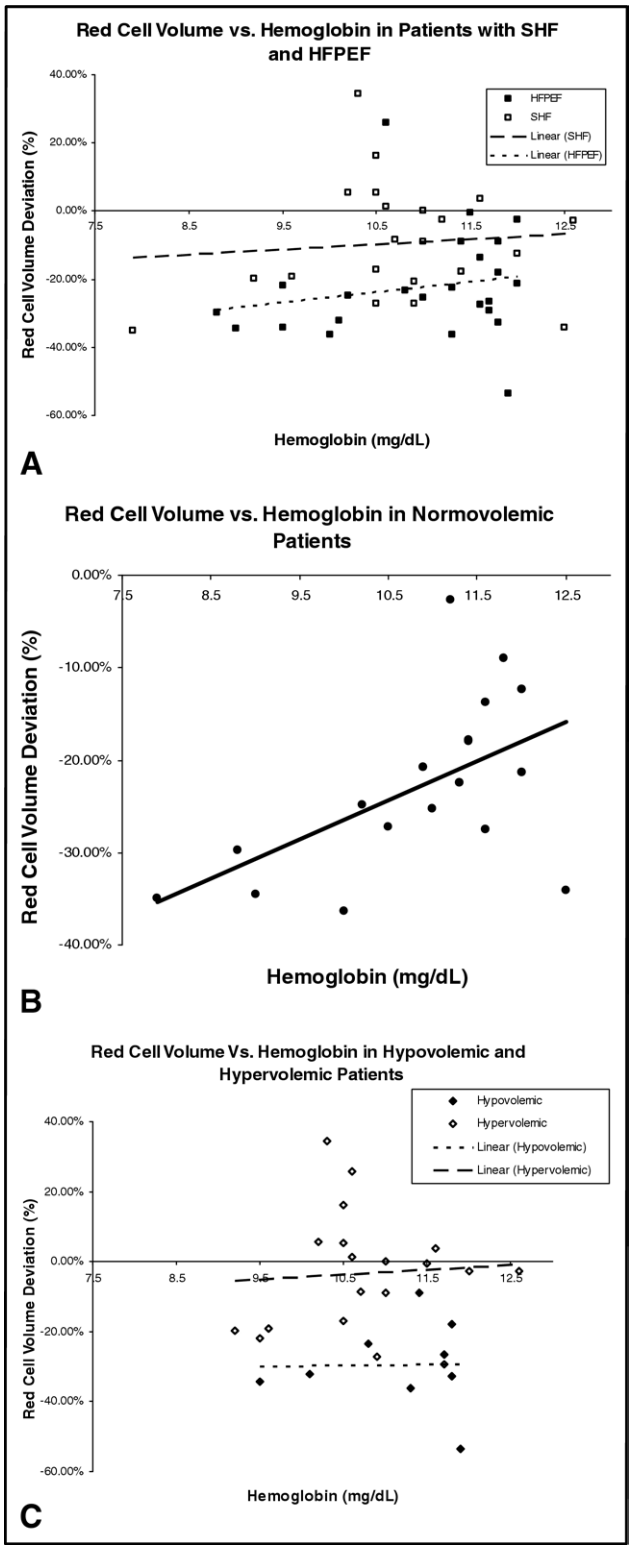

Figure 1. *(A)* Relation between red blood cell volume deviation and hemoglobin in patients with HFLEF and those with HFPEF. *(B, C)* Relationship between red blood cell volume deviation and hemoglobin graphed by volume status. Normovolemia is blood volume within 8% of the predicted normal value. Hypervolemia is blood volume >8% of the predicted normal value. Hypovolemia is blood volume <8% of the predicted normal value. Blood volume deviation refers to the percentage difference between the predicted normal value and the value determined by blood volume analysis.

age red cell volume deviation from reference values ($r = 0.09$, $p = 0.54$). This was found for patients with HFLEF and those with HFPEF ($r = 0.09$, $p = 0.69$, and $r = 0.19$, $p = 0.38$, respectively; Figure 1). However, when subjects were classified by volume status, normovolemic patients had a stronger association between hemoglobin and red cell volume ($r = 0.55$, $p = 0.02$) than either hypovolemic or hypervolemic patients, who had a nonsignificant association ($r = 0.016$, $p = 0.97$, and $r = 0.067$, $p = 0.79$, respectively; Figure 1).

Discussion

The principal findings of this study are twofold. First, in subjects with anemia and HF, the prevalence of a red cell deficit differs between patients with normal compared with reduced EFs. Specifically, most subjects with HFPEF (88% in this series) had red cell deficits, whereas slightly more than half of subjects with HFLEF had red cell deficits. Second, the correlation of hemoglobin, the standard measure by which clinicians diagnose and manage anemia in patients with HF, with red cell volume is poor irrespective of the EF. This is because of the confounding effects of alterations in plasma volume, which are common in patients with HF, caused by either the underlying disease or the concomitant use of diuretic therapy. Blood volumes in patients with HF have been evaluated in multiple studies in patients with HFLEF, with alterations of blood volume contraction and expansion described.[13,14] Blood volumes have not been described in patients with HFPEF, and our findings suggest that patients with compensated HFPEF can likewise be hypovolemic, normovolemic, or hypervolemic.

The discordance between hemoglobin and red cell volume found in this study is in accordance with research from other patient populations, in which the poor association has been attributed to alterations in plasma volume.[5,9–11] Much of the previous research in this area has been focused on polycythemia vera, in which plasma volume derangements and splenomegaly confound the utility of using hemoglobin (or hematocrit) as a surrogate for red cell volume.[9] Splenomegaly[17,18] and plasma volume expansion[13] have been described in patients with HF. Given the relevance of plasma volume to the relation between hemoglobin and red cell volume, some have noted that hematocrit (or hemoglobin) is no more a marker of red cell volume than serum sodium is of total body sodium.[9] Our data support this explanation; the association between hemoglobin and red cell volume was stronger in normovolemic patients than in those with hypovolemia or hypervolemia. Plasma volume alterations, whether leading to hemodilution or hemoconcentration, therefore appear to influence hemoglobin determination.

These observations may have implications for the treatment of anemia in patients with HF. Two main therapies have been used to treat anemia in patients with HF, intravenous iron[19,20] and erythropoietic stimulators,[21] either alone or in combination,[22,23] and data on treatment have been mixed.[2,12] The 2 therapies have been shown in small single-center studies to increase hemoglobin, quality of life, and exercise tolerance in patients with anemia and HF with systolic dysfunction.[21,23–26] However, a larger multicenter study, the Study of Anemia in Heart Failure–Heart Failure

Trial (STAMINA-HeFT), did not meet its primary end point of exercise time and quality-of-life changes.[27]

Potential explanations for the discrepant results include that treatment for anemia in these trials may have been applied to subjects with dilutional anemia as well as to those with red cell deficits. In the only study in which blood volume was measured during erythropoietin treatment,[21] the limited data suggested that that erythropoietin may have direct effects on both components of total blood volume (red cell volume and plasma volume). Erythropoietin increased hemoglobin in patients with HF with true and dilutional anemia through different mechanisms; although the 2 groups had increases in red cell volume, the patients with dilutional anemia also experienced reductions in plasma volume.[21] Although the effects on plasma volume are poorly understood, they have been observed in dialysis patients as well.[28] Although erythropoietin may therefore benefit patients with HF with both normal and reduced red cell volumes, perhaps diuresis may be the safer and cheaper approach to patients with dilutional anemia, without predisposing patients to the side effects attributed to erythropoietin.

There are several limitations to our study. Our study population consisted of patients with advanced HF receiving care at a tertiary center, which may not represent the general HF population. All patients were stable outpatients receiving high-dose, long-term diuretic therapy; hence, the alterations of plasma volume observed need to be interpreted in this context, and the relevance of these measures to the pathophysiology of the acutely decompensated state is limited. Splenomegaly was not assessed in our patients. The data measurements, including hemoglobin and blood volume measurements, were taken at a single point in time. Blood volume measurements were done with iodine-131-labeled albumin, and we did not directly measure red cell volume. However, the validity of our approach for measuring red cell volume indirectly versus the chromium-labeling technique has been demonstrated, with only small differences found between chromium labeling and the albumin dilution technique.[29]

1. Iversen PO, Woldbaek PR, Tonnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. *Am J Physiol Regul Integr Comp Physiol* 2002;282:R166–R172.
2. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation* 2006; 113:2454–2461.
3. Felker GM, Adams KF Jr, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol* 2004;44:959–966.
4. Androne AS, Katz SD, Lund L, Lamanca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. *Circulation* 2003;107:226–229.
5. Erslev AJ. Clinical erythrokinetics: a critical review. *Blood Rev* 1997; 11:160–167.
6. Johansson PL, Safai-Kutti S, Kutti J. An elevated venous haemoglobin concentration cannot be used as a surrogate marker for absolute erythrocytosis: a study of patients with polycythaemia vera and apparent polycythaemia. *Br J Haematol* 2005;129:701–705.
7. Pati HP, Dayal S, Kashyap R, Padhy AK. Masked polycythaemia vera in a patient with extrahepatic portal venous obstruction. *Eur J Gastroenterol Hepatol* 1998;10:883–885.
8. Cirera I, Elizalde JI, Pique JM, Feu F, Casadevall M, Goldin E, Teres J, Bosch J, Rodes J. Anemia worsens hyperdynamic circulation of patients with cirrhosis and portal hypertension. *Dig Dis Sci* 1997;42: 1697–1702.
9. Spivak JL. Polycythemia vera: myths, mechanisms, and management. *Blood* 2002;100:4272–4290.
10. Lorberboym M, Rahimi-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.
11. Tefferi A. Diagnosing polycythemia vera: a paradigm shift. *Mayo Clin Proc* 1999;74:159–162.
12. Murphy NF, McDonald K. Treatment of anaemia in chronic heart failure: optimal approach still unclear. *Eur Heart J* 2007;28:2185–2187.
13. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. *Am J Cardiol* 2004;93:1254–1259.
14. Feigenbaum MS, Welsch MA, Mitchell M, Vincent K, Braith RW, Pepine CJ. Contracted plasma and blood volume in chronic heart failure. *J Am Coll Cardiol* 2000;35:51–55.
15. Manzone TA, Dam HQ, Soltis D, Sagar VV. Blood volume analysis: a new technique and new clinical interest reinvigorate a classic study. *J Nucl Med Technol* 2007;35:55–63.
16. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation* 1977;56:605–612.
17. O'Reilly RA. Splenomegaly in 2,505 patients in a large university medical center from 1913 to 1995. 1913 to 1962: 2,056 patients. *West J Med* 1998;169:78–87.
18. O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1963 to 1995: 449 patients. *West J Med* 1998;169:88–97.
19. Toblli JE, Lombrana A, Duarte P, Di GF. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007;50:1657–1665.
20. Beck-da-Silva L, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. Rationale and design of the IRON-HF study: a randomized trial to assess the effects of iron supplementation in heart failure patients with anemia. *J Card Fail* 2007;13:14–17.
21. Mancini DM, Katz SD, Lang CC, Lamanca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;107:294–299.
22. Palazzuoli A, Silverberg DS, Iovine F, Calabro A, Campagna MS, Gallotta M, Nuti R. Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. *Am Heart J* 2007;154:645.e9–645.e15.
23. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737–1744.
24. Francis GS, Kanderian A. Anemia and heart failure a new pathway? *J Am Coll Cardiol* 2007;50:1666–1667.
25. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001;37:1775–1780.
26. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;369: 381–388.
27. Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008;117:526–535.
28. Macdougall IC, Davies ME, Hutton RD, Cavill I, Lewis NP, Coles GA, Williams JD. The treatment of renal anaemia in CAPD patients with recombinant human erythropoietin. *Nephrol Dial Transplant* 1990;5:950–955.
29. Dworkin HJM, Premo MBCA, Dees SC. 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.