



Blood Volume Measurements in Patients With Heart Failure and a Preserved Ejection Fraction: Implications for Diagnosing Anemia

Anemia is common in patients with heart failure (HF), associated with increased morbidity including hospitalizations, mortality, and a reduced quality of life.¹ These associations are present in HF, regardless of left ventricular ejection fraction (LVEF).^{2,3} These data have led to several randomized clinical trials using erythropoietin-stimulating agents,^{4,5} iron,⁶ and their combination,^{7,8} predominately in patients with systolic HF to determine safety and efficacy. These trials have demonstrated reduction in hospitalizations and improvement in functional capacity and ventricular function but are limited by their small sample size and short duration.⁹

The diagnosis of anemia is usually made by measurement of hemoglobin values from standard peripheral blood; however, in patients with volume overload states such as systolic HF, hemodilution has been shown to be a common cause of low hemoglobin¹⁰ and has been suggested to be the most potent factor for the low hemoglobin values observed in patients with HF and a reduced ejection fraction.¹¹

Such data raise concerns that for many patients with systolic HF, treating anemia with agents to stimulate red cell production may not be justified. Additionally, alterations in plasma volume (PV) occur as a compensation for the contracted red blood cell volume (RBCV) in order to maintain the overall blood volume (BV) at a constant level¹² and could also confound the diagnosis of anemia. Finally, the long-term use of medications such as diuretics, that act by contracting PV, could result in an underdiagnosis of anemia based on standard hemoglobin measures.

Racial differences in the prevalence of anemia in patients with heart failure have been noted. The diagnosis of anemia in heart failure patients can be confounded by many factors. Plasma volume expansion is one of the most prominent confounders. The authors investigated the difference of anemia prevalence using two different diagnostic techniques: peripheral hemoglobin recommended by the World Health Organization criteria and blood volume (BV) analysis. Racial disparities in the prevalence of anemia using both measures were compared. Sixty patients with heart failure and preserved ejection fraction (HFPEF) underwent measurement of BV by a radio-labeled albumin technique. Anemia was defined by both WHO criteria and by measured red blood cell volume (RBCV) > 10% below ideal. Anemia was found in 67% of patients by the peripheral hemoglobin technique with no racial disparity. Only 35% of the patients had anemia by the BV analysis, with a 2-fold higher prevalence among Hispanics compared with whites and blacks. In patients with HFPEF, the diagnosis of anemia based on hemoglobin is confounded by plasma volume derangements resulting in significant overdiagnosis in this cohort. Racial differences in the rate of anemia were found. Such data could have important implications for the diagnosis and management of anemia in ethnic minorities with HFPEF. Congest Heart Fail. 2011;17:14–18. ©2011 Wiley Periodicals, Inc.

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In the general population^{13,14} and among patients with HF either in the setting of a reduced or normal/preserved ejection fraction,² the prevalence of anemia is higher among blacks than whites. Despite the fact that Hispanics are the largest and fastest-growing ethnic minority in the United States,¹⁵ data on the prevalence of anemia in this cohort compared with other racial groups in patients with HF are lacking. We hypothesized that analysis of BV in patients with HFPEF could provide insights into racial differences among persons affected by this heterogeneous clinical syndrome.

Methods

Study Patients. Participants were outpatients referred for evaluation and treatment to the Columbia University Medical Center Heart Failure Center. Patients 21 years and older diagnosed with HF and a preserved ejection fraction (eg, $\geq 45\%$) were studied.

The diagnosis of HF was based on the National Health and Nutrition Examination Survey congestive HF criteria with a score ≥ 3 .¹⁶ Patients with acute decompensated HF, severe renal dysfunction (serum creatinine > 3.0 mg/dL or history of nephrotic syndrome), and severe hepatic dysfunction (serum liver

Table I. Demographic and Clinical Characteristics

| | OVERALL (N=60) | WHITES (N=20) | BLACKS (N=16) | HISPANICS (N=24) | P VALUE |
|---|----------------|---------------|---------------|----------------------|---------|
| Demographics | | | | | |
| Age, y | 70±12.9 | 75±13 | 68±15 | 67±11 | NS |
| Sex (female), % | 63 | 40 | 81 | 71 | .02 |
| Body size | | | | | |
| Weight, kg | 80±14 | 87±18 | 81±15 | 74±7 ^a | .01 |
| BMI | 30±4.3 | 31±4 | 31±5.8 | 29±3 | NS |
| BSA, m ² | 1.89±0.2 | 1.99±0.3 | 1.9±0.2 | 1.8±0.1 ^a | .01 |
| Anemic, % | 67 | 65 | 50 | 79 | NS |
| Medications, % | | | | | |
| Loop diuretics | 68 | 65 | 69 | 70 | NS |
| Thiazide diuretics | 21 | 20 | 19 | 25 | NS |
| ACE inhibitors | 66 | 65 | 81 | 58 | NS |
| β-Blockers | 66 | 45 | 56 | 92 | <.001 |
| Aldosterone antagonist | 20 | 40 | 19 | 4 | <.01 |
| Calcium channel blockers | 43 | 25 | 50 | 54 | NS |
| Blood pressure, mm Hg | | | | | |
| Systolic blood pressure | 142±16.5 | 137±18 | 145±16 | 143±15 | NS |
| Diastolic blood pressure | 73±11.4 | 73±14 | 75±11 | 73±10 | NS |
| Three-dimensional echocardiography | | | | | |
| EDVI, mL/m ² | 58±12 | 60±10 | 62±16 | 55±8 | NS |
| SVI, mL/m ² | 32±6 | 32±6 | 34±8 | 30±5 | NS |
| EF, % | 54±6 | 54±5 | 54±6 | 55±6 | NS |
| LV mass, g/m ² | 78±22 | 78±16 | 85±22 | 73±26 | NS |
| EDV/mass ratio | 0.80±0.24 | 0.80±0.2 | 0.77±0.24 | 0.83±0.26 | NS |
| Laboratory results | | | | | |
| Hemoglobin, gm/dL | 11.6±2.1 | 12±2.2 | 12±2 | 11±2 | NS |
| Hematocrit, % | 36±4.9 | 36±5.5 | 37±5 | 36±4 | NS |
| BUN, mg/dL | 32±17 | 35±16 | 31±22 | 30±15 | NS |
| Creatinine, mg/dL | 1.5±0.6 | 1.5±0.5 | 1.6±0.7 | 1.4±0.6 | NS |
| eGFR, mL/min | 52±20 | 49±15 | 53±24 | 53±22 | NS |

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BSA, body surface area; BUN, serum urea nitrogen; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LV, left ventricular; NS, not significant; SVI, stroke volume index. ^aP<.05 vs whites by analysis of variance with post hoc Bonferonni correction.

enzymes >3 times the upper limits of normal or history of cirrhosis) were excluded. Cardiac medications included diuretics, digoxin, renin-angiotensin system inhibitors, and/or β-adrenergic receptor antagonists that were stable before the measurement of BV. Sixty ambulatory patients with HFPEF were studied: 33% white, 40% Hispanic, and 27% black. The institutional review board at Columbia University Medical Center approved the protocol. All patients gave written informed consent before participation.

Hemoglobin Measures. Hemoglobin was measured as part of a routine complete blood cell count from the hospital core laboratory (Sysmex XE 2100; Sysmex Corporation, Kobe, Japan). Anemia was defined according to World Health Organization (WHO) criteria as

hemoglobin <12 g/dL in women and <13 g/dL in men.¹⁷

BV Analysis. PV was determined after the intravenous administration of iodine-131-labeled albumin, as has been described previously.^{18,19} BV and RBCV were calculated from the PV measurement, the measured hematocrit corrected for trapped plasma, and mean body hematocrit. BV components (plasma, red blood cell, and total volume) were determined and compared with normal values adjusted for age, sex, and weight on the basis of the ideal weight system to yield percentage deviations from normal. Thus, in addition to reporting absolute values, we report percentage deviation from expected values on the basis of the ideal weight system. Anemia, based on BV analysis, was defined by RBCV <10% below ideal.

To determine whether PV compensation in patients with RBCV deficits was appropriate, the absolute PV compensation in response to RBCV deficit was calculated as deviation from ideal PV – RBCV deficit, and the percentage compensation was calculated as (deviation from ideal PV – RBCV deficit)/ideal PV.

Statistical Analysis. Data are expressed as mean ± standard deviation, unless otherwise noted. Dichotomous variables were compared using chi-square analysis with Fisher exact test when appropriate, and continuous variables were compared using analysis of variance with a Bonferonni's post hoc test to control for multiple comparisons for those variables that were normally distributed. For the BV data, a nonparametric test (Kruskal Wallis) was employed given the

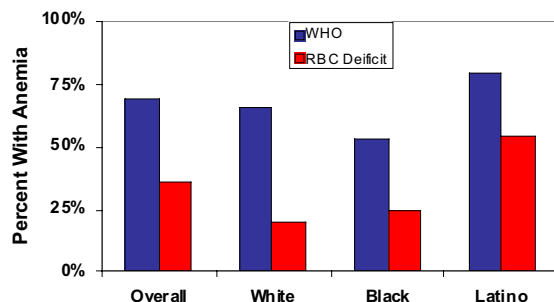
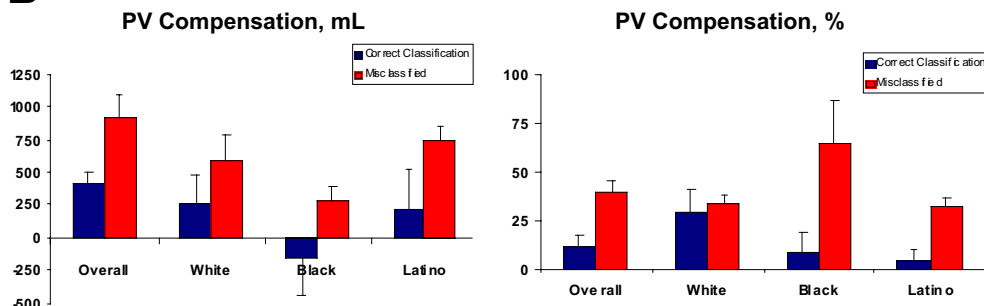
A**B**

Figure. Panel A: The prevalence of anemia in the overall cohort and in each racial subgroup by World Health Organization (WHO) criteria (blue bars) and by red blood cell (RBC) deficit (red bars). Panel B. Differences in plasma volume (PV) compensation (by volume and percentage) between patients diagnosed correctly by WHO and RBCV criteria (real anemia) and those misclassified as anemic by WHO criteria stratified by race.

non-normality of the data. A P value $\leq .05$ was considered significant. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

The patients studied were older adults, predominately women, with an average New York Heart Association (NYHA) class of 2.5 ± 0.6 and a normal ejection fraction ($54\% \pm 6\%$). They had underlying chronic renal insufficiency similar to other large series of hospitalized HFPEF patients,^{20,21} with average hemoglobin of 11.6 ± 2.1 g/dL. Racial subgroups differed with regard to sex, body weight and size, and the use of β -blocker and aldosterone antagonists but not with regard to blood pressure, echocardiographic, or laboratory assessments (Table I).

Anemia, as defined by WHO criteria, was present in 40 (67%) patients, similar to other series,²² and did not differ significantly by sex or race. However, by RBCV deficit, anemia was present in only 21 of those patients (35% overall) (Figure). In all groups studied (white,

black, and Hispanic), there was a significant difference in the rate of anemia diagnosed by WHO criteria as compared with measured RBCV deficit. None of the patients first classified as non-anemic by WHO criteria were then reclassified as anemic by BV analysis. Overall, in 45% of whites, 25% of Hispanics, and 25% of blacks, the diagnosis of anemia was reclassified when using RBCV deficit compared with hemoglobin.

BV indices overall and by racial group are shown in Table II. On average, patients with HFPEF demonstrated an expanded BV, which was primarily attributable to an increase in PV. While overall BVs, red cell volumes, and PVs differed by race, these differences were no longer significant when controlling for differences in sex and body size between cohorts (eg, % deviation did not differ). The difference in the prevalence of anemia as determined by hemoglobin and RBCV was in part attributable to greater absolute PV compensation in response to RBCV deficit. Specifically, among patients who were correctly classified by WHO criteria, PV

compensation for the red cell deficit was an appropriate physiologic response, while for patients who were misclassified by WHO criteria in comparison to red cell volume measures, the PV compensation was excessive (Figure, Panel B). The PV overcompensation was higher in misclassified patients compared with correctly classified patients in all racial subgroups, but this was particularly true for blacks and Hispanics compared with whites.

Discussion

The principal findings in this study are that among patients with HFPEF, the prevalence of anemia differs between WHO criteria that employ hemoglobin measurement as compared with BV analysis, with an overestimate of the prevalence of anemia by the WHO criteria, in part due to an excess expansion of PV in response to the red blood cell deficit. This error was present in all racial subgroups. Finally, the rate of a true anemia (eg, red blood cell deficit) was highest among Hispanics as compared with whites and blacks.

Table II. Blood Volume in HFPEF Stratified by Racial Groups

| | OVERALL (N=60) | WHITES (N=20) | BLACKS (N=16) | HISpanICS (N=24) | P VALUE ^a |
|------------------------------------|------------------------|------------------------|------------------------|------------------------|----------------------|
| Blood volume, mL | 4696±1137 (3328–6946) | 5301±1282 (3492–7808) | 4214±783 (3355–6620) | 4514±1021 (3402–6751) | .0126 |
| Excess/deficit blood volume, mL | 423±603 (–525 to 1527) | 594±682 (–5 to 2099) | 373±621 (–813 to 1459) | 313±508 (–443 to 1332) | NS |
| BV deviation, % | 9±13 (–11 to 29) | 12±14 (0–45) | 8±13 (–17 to 28) | 7±11 (–9 to 25) | NS |
| Red cell volume, mL | 1474±479 (948–2428) | 1754±612 (967–3042) | 1298±218 (1068–1797) | 1357±380 (876–2048) | .0174 |
| Excess/deficit red cell volume, mL | 65±465 (–631 to 708) | 178±424 (–387 to 1044) | 198±558 (–762 to 1469) | –117±383 (–576 to 413) | NS |
| RBC deviation, % | 4±27 (–36 to 39) | 9±27 (–25 to 63) | 11±30 (–39 to 70) | –6±23 (–34 to 27) | NS |
| Plasma volume, mL | 3223±755 (2274–4825) | 3547±761 (2495–5094) | 2915±686 (2126–4983) | 3157±718 (2269–4623) | .0145 |
| Excess/deficit plasma volume, mL | 504±456 (–10 to 1582) | 622±489 (84–1670) | 370±474 (–118 to 1914) | 495±406 (44–1311) | NS |
| Plasma deviation, % | 17±15 (0–47) | 21±15 (3–49) | 13±16 (–4 to 62) | 17±13 (2–40) | NS |

Abbreviation: BV, blood volume; HFPEF, heart failure and preserved ejection fraction; NS, not significant; RBC, red blood cell count. Values are expressed as mean ± standard deviation (95% confidence interval). ^aBy Kruskal–Wallis test.

Anemia in Multi-Ethnic Groups. Although the American Hispanic population is the fastest-growing ethnic minority in the United States, there is a paucity of data on the prevalence of anemia in this group compared with other ethnicities and no data that we are aware of regarding ethnic differences specifically in the population with HFPEF. Available data do suggest important racial/ethnic differences in the prevalence of anemia in the general population and the underlying cause. In the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of anemia in persons older than 65 years varied significantly by race, with an overall prevalence of 10.6% that was lowest for non-Hispanic whites (9.0%), slightly higher in Mexican Americans (10.4%), but substantially higher in non-Hispanic blacks (27.8%).¹³ Similarly, a study of the prevalence and incidence of anemia in patients with diabetes mellitus showed a higher prevalence of anemia among blacks and mixed ethnicities than Hispanics, whites, or Asians.²³ In that study, a multivariate model of prevalent anemia that adjusted for sex, age, clinic site, utilization, proximate estimated glomerular filtration rate, albuminuria, diabetes treatment, and EPO use found that the odds of anemia were higher among blacks (odds ratio [OR], 2.26; 95% confidence interval [CI], 2.12–2.41), those of mixed ethnicity (OR, 1.37; 95% CI, 1.31–1.44), or Hispanic (OR, 1.15; 95% CI, 1.07–1.24), compared with whites. Finally, in a population-based sample that evaluated anemia prevalence and iron status among older Hispanics of Caribbean origin compared with a cohort of whites, the prevalence of anemia was higher in older Hispanics than in non-Hispanic older whites after controlling for relevant confounders. This was in part attributable to significant ethnic differences in nutrient intake and intake of specific food items that resulted in different iron stores.²⁴ We found a higher percentage of Hispanics with HFPEF were anemic by both hemoglobin and by BV analysis than whites or blacks.

PV in Anemia and HF. Anemia in HF patients may be a result of iron

deficiency, hemodilution,¹⁹ anemia of chronic disease,²⁵ malnutrition,²⁶ renal insufficiency,²⁶ or medication-induced anemia.²⁵ Among the population with advanced systolic HF, hemodilution is common.²⁷ Similarly, our data suggest that a significant percentage of patients with HFPEF have expansions of PV that are beyond physiologic compensation for the red blood cell deficit and are in part hemodilutional in nature. Indeed, chronic anemia in the absence of HF is associated with PV expansion and edema because of decreased blood viscosity and the resulting effects of nitric oxide-mediated vasodilatation.²⁵ As a result, there is a decline in systemic vascular resistance and, because of arterial under-filling, an activation of the renin-angiotensin system and concomitant PV expansion.²⁵ Accordingly, the PV expansion in anemic patients replaces decreased red blood cell mass¹² in order to maintain a normal BV. In HF patients, alterations in PV that occur in response to the underlying cardiac and/or renal dysfunction and subsequent neurohormonal activation further add to the physiologically expanded PV in anemic patients and confound the diagnosis as shown by these data. Additionally, HFPEF patients often have concomitant comorbid conditions including obesity and renal insufficiency, which affect PV regulation and could be an explanation for the observed findings.

Clinical Implications. Appropriate treatment of anemia associated with HF may improve the outcomes of patients by enhancing physical function and quality of life,²⁶ but treatment requires an accurate diagnosis and identification of the underlying etiology in order to select effective interventions. Commonly used treatments for nondilutional anemia can put the patient under unnecessary risk secondary to adverse effects of medication and may contribute to adverse outcomes.^{28,29} The current data raise the possibility that further definition of the low hemoglobin phenotype in patients with HF using

BV analysis could provide important physiologic insights regarding therapeutic interventions. Of course, such recommendations must await the formal performance of clinical trials that are testing such hypotheses³⁰ and the recognition that PV is dynamically regulated and fluctuates widely in response to multiple physiologic signals.

Limitations

The study is limited by the small sample size with limited power to detect differences between groups and the potential for a type II (beta) error. The use of

self-reports to classify race/ethnicity, which is in part a clustering of common genetic characteristics, is also influenced by social, environmental, and lifestyle factors that may have an effect on cardiovascular health. Given the cross-sectional nature of our study, we cannot exclude the effect of residual unmeasured confounders. However, factors known to affect BV, including body size and sex, were accounted for in the current analyses, and the use of medications that could alter BV did not differ between the groups studied.

Conclusions

In patients with HFPEF, the diagnosis of anemia by hemoglobin is confounded by alterations in BV components. These differences are present in all racial subgroups. Such data could have important implications for the diagnosis and management of anemia in ethnic populations with HFPEF.

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