True Anemia—Red Blood Cell Volume Deficit—in Heart Failure: A Systematic Review

David Montero, PhD; Carsten Lundby, PhD; Frank Ruschitzka, MD; Andreas J. Flammer, MD

Background—Anemia in heart failure (HF) is commonly diagnosed according to hemoglobin concentration \([Hb]\), hence may be the result of hemodilution or true red blood cell volume (RBCV) deficit. Whether true (nonhemodilutional) anemia in HF can or cannot be generally inferred by \([Hb]\) measurements and clinical correlates remains unclear. The purpose of this study was to systematically review the literature and investigate the status and correlates of RBCV in patients with HF.

Methods and Results—MEDLINE, Scopus, and Web of Science were searched since their inceptions until April 2016 for articles directly reporting or allowing the calculation of intravascular volumes (RBCV, plasma volume) in patients with HF according to the International Council for Standardization in Hematology. Eighteen studies were included after systematic review, comprising a total of 368 patients with HF (limits for mean age=49–80 years, sex=0%–92% females, left ventricular ejection fraction=26%–61%). Mean RBCV was reduced (limits=67%–88% of normal) in all studies including HF patients with anemia (low \([Hb]\)) (7 studies, n=127), whereas only 2 of 10 studies in nonanemic patients with HF presented lower than normal mean RBCV (90% and 96%). In metaregression analyses, RBCV was positively associated with \([Hb]\) \((B=6.10, SE=1.44)\) and negatively associated with age \((B=−1.14, SE=0.23)\), % females \((B=−0.38, SE=0.04)\), left ventricular ejection fraction \((B=−0.81, SE=0.20)\), and body mass index \((B=−3.55, SE=0.46; P<0.001)\).

Conclusions—Presence or absence of true anemia in patients with HF as determined by RBCV status mainly concurs with diagnosis based on \([Hb]\) and presents negative relationships with age, female sex, left ventricular ejection fraction, and body mass index. (Circ Heart Fail. 2017;10:e003610. DOI: 10.1161/CIRCHEARTFAILURE.116.003610.)

Key Words: anemia • heart failure • hemodilution • hemoglobin • plasma volume

One of the clinical characteristics of untreated heart failure (HF) is fluid accumulation leading to hemodynamic and eventually symptomatic clinical congestion.¹ Fluid retention in HF is primarily orchestrated by the activation of baroreceptors, sympathetic nervous system, renin–angiotensin–aldosterone system, and vasopressin axes.¹² Fluid retention is interpreted as a compensatory response aiming to retrieve normal cardiac reserve by means of increasing blood volume (BV), venous return, and thereby stroke volume via the Frank–Starling mechanism, provided that cardiac pumping capacity remains operative.² Given the continuous interaction between extracellular fluid compartments, volume expansion affects both intravascular and interstitial constituents. Indeed, interstitial fluid volume may reach >30 L or 450 mL/kg body weight in untreated patients with HF, nearly tripling average values in healthy individuals.³ The massive overload of interstitial fluid volume results in generalized edema and widespread complications, such as dyspnea, ischemia, increased risk of infection, and skin ulcers, among others.⁴ Likewise, BV may exceed 100 mL/kg in patients with HF, a 1.5-fold increase compared with healthy controls.⁵ Although BV expansion contributes to a lesser degree to overall body fluid retention, it represents a fundamental challenge for accurate diagnosis and management of anemia in patients with HF.

See Clinical Perspective

Anemia occurs when the number of red blood cells, and thus oxygen carrying capacity, barely suffices to meet metabolic demands and is conventionally defined by hemoglobin concentration \([Hb]<12.0 \text{ g/dl} \text{ and } <13.0 \text{ g/dl} \text{ in adult females and males, respectively}.⁶ More than one third of patients with HF present with anemia, which is independently associated with increased risk of mortality irrespective of HF phenotype according to a large cohort comprising >150000 individuals with HF.⁷ Importantly, although \([Hb]\) is typically used to diagnose anemia, low \([Hb]\), on a physiological basis, can be the result of either hemodilution due to plasma volume (PV) expansion or a genuine red blood cell deficit as reflected by reduced total red blood cell volume (RBCV).⁸ Both hemodilutional and “true” (nonhemodilutional) anemia

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may be present with apparently variable predominance in patients with HF diagnosed with anemia conforming to low [Hb].

Determinants and treatment of anemia may, thus, differ according to the underlying pathophysiology as illustrated by the fact that only HF patients with true anemia may respond favorably, in terms of [Hb] correction, to erythropoietin therapy. Parenthetically, a recent clinical trial in patients with moderately anemic HF could not confirm the extensive benefits associated with erythropoietin treatment suggested by previous meta-analytic evidence, and erythropoiesis-stimulating agents have currently no indication in HF. In addition, intravascular volumes and therefore [Hb] in HF may be further compounded by the prescription of drugs affecting fluid homeostasis. In this regard, long-term standard HF pharmacotherapy including β-blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists and in particular diuretics may result in lower PV, whereas [Hb] and hematocrit are unaltered, in patients with HF compared with healthy age-matched and body weight-matched individuals. Hence, in these patients RBCV could be reduced and dissociated from (and thereby undetected by) [Hb] measurements.

Considered collectively, true anemia (ie, reduced RBCV) in HF might be (1) masked in patients presenting with normal [Hb] and (2) determined by factors other than those associated with [Hb]. These hypotheses are, however, unclear based on the surfeit of literature assessing intravascular volumes in patients with HF. It is possible that the small sample size, distinct HF phenotypes, and incomplete report of intravascular volumes according to established norms in some individual studies may have contributed to some uncertainty about the scope and determinants of true anemia in HF. A systematic review may help to obtain a comprehensive perspective and clarify the above issues, but to our knowledge, this has not yet been performed.

Therefore, the primary aim of this study was to perform a systematic review of available studies determining intravascular volumes in individuals with HF. We selected studies that presented intravascular volumes normalized by ideal body weight (IBW) norms according to the International Council for Standardization in Hematology or reported anthropometrical variables required to determine intravascular volume deviation from IBW.

Methods

Data Sources and Searches

Our systematic search included MEDLINE, Scopus, and Web of Science since their inception until April 2016. We used combinations of the subject headings “heart failure,” “total,” “red cell volume,” “plasma volume,” and “blood volume”; the search strategy for MEDLINE is shown in Figure I in the Data Supplement. We also performed hand searching in identified reviews, articles included in systematic review, related citations in MEDLINE and Google.

Article Selection

To be included in the systematic review, an original research article had to assess total RBCV, PV, or BV in patients with HF (1) according to International Council for Standardization in Hematology guidelines or (2) report anthropometrical variables required to determine intravascular volume deviation from IBW norms. In the event of multiple publications pertaining to the same research, the most comprehensive report was included. The selection of articles was not limited by language or publication status.

Data Extraction

The following variables were extracted into a preformatted spreadsheet: authors, year of publication, clinical characteristics of study participants (n, age, sex, height, weight, body mass index [BMI], left ventricular ejection fraction [LVEF], [Hb], hematocrit, iron status, HF phenotype, comorbidities, and medication), intravascular volumes (RBCV, PV, and BV), and characteristics of their assessment (technique and procedure). Intravascular volume data in decompensated patients with HF at hospital admission were not used for analysis.

Data Synthesis and Analysis

RBCV, PV, and BV are presented as percentage excess or deficit of normal expected volumes. Normal reference intravascular volumes were determined in relation to deviations from IBW derived from Metropolitan Life tables (>100,000 measurements) adjusted for sex, body weight, and height. This method has been recommended for the quantitative assessment of total intravascular volumes by the International Council for Standardization in Hematology for its precision and reproducibility, and it has been validated against the gold standard double-labeled technique of chromium-tagged red cells and albumin 1 to 125 with the volumes being within 1% of one another. When IBW was not explicitly reported in a given article, IBW was calculated according to BMI=22 kg/m², which is associated with lowest morbidity irrespective of sex.

Metaregression analyses were performed to estimate associations between intravascular volumes and clinical variables (age, sex, weight, BMI, LVEF, [Hb], iron concentration, and ferritin concentration), taking into account the sample size and variability of intravascular volume assessment (Comprehensive Meta-analysis, Biostat, Englewood, CO). Intravascular volumes were considered as dependent variables. In all metaregression models, studies were weighted by the inverse variance of the dependent variable. A 2-tailed P value <0.05 was considered significant.

Results

Study Selection and Characteristics

The flow diagram of the process of article selection is shown in Figure 1, which resulted in the inclusion of 14 articles. Three of these articles presented separate study groups (hence forward referred as studies), each of which was evaluated as an individual study. Table 1 shows the main characteristics of the resulting 18 studies, encompassing a total of 368 HF patients with mean age ranging from 49 to 80 years. Seven studies were comprised patients with heart failure with reduced ejection fraction (HFrEF; n=210), 6 studies comprised patients with heart failure with preserved ejection fraction (HFpEF; n=99), 1 study involved HFrEF (n=13) and patients with HFpEF (n=4), and 4 studies did not distinguish between HF phenotypes (n=42). Five studies were comprised men (n=56) and the remaining studies included men (n=200) and women (n=112). The severity of HF, based on the New York Heart Association functional class, averaged I–III in 7 studies (n=199), and III–IVa in 3 studies (n=72), whereas 8 studies did not report New York Heart Association values (n=97). With regard to prevailing comorbidities, coronary artery disease, hypertension, and diabetes mellitus were reported along with standard oral HF medical therapy in the majority of studies. Moreover, individuals with anemia—as
defined by Hb concentration < 13.0 g/dL in men and < 12.0 g/dL in women—were included in 7 studies (n = 127). Iron status was described in 6 studies (n = 189). Intravascular assessment was primarily performed through radioactive isotopes (n = 337), whereas 3 studies used dye dilution methods (n = 31). All studies reported intravascular volumes in patients with chronic HF.

### BVs According to Anemia Status

Figure 2 illustrates the comparison of mean RBCV, PV, and BV, as expressed in % of normal values, in studies comprising HF individuals without anemia (determined by [Hb]) versus those including HF individuals with anemia. RBCV was below normal values (limits 67%–88%) in all studies including HF individuals with anemia, whereas only 2 of 10 studies in patients with nonanemic HF presented lower than normal RBCV (90% and 96%). PV was augmented in all studies including HF individuals with anemia (123%–169%) and in 9 of 10 studies in patients with nonanemic HF (115%–138%). BV was predominantly elevated in studies including HF individuals with anemia (100%–133%) and studies in patients with nonanemic HF (100%–130%).

### Association Analyses Using Mean Study Values

Table 2 presents linear correlates of RBCV, PV, and BV (% of normal) obtained with metaregression analyses. RBCV was positively associated with [Hb] ($B = 6.10; SE = 1.44; P < 0.001$) and ferritin concentration ($B = 0.15; SE = 0.08; P = 0.045$), and negatively with age ($B = 1.14; SE = 0.23; P < 0.001$), sex (% females; $B = 0.38; SE = 0.04; P < 0.001$), LVEF ($B = 0.81; SE = 0.20; P < 0.001$), weight ($B = 0.67; SE = 0.22; P = 0.002$), and BMI ($B = 3.55; SE = 0.46; P < 0.001$) (Figure II in the Data Supplement). PV was negatively associated with [Hb] ($B = -6.66; SE = 2.53; P = 0.008$), whereas BV was positively associated with ferritin concentration ($B = 0.21; SE = 0.09; P = 0.018$) and negatively with LVEF ($B = -0.30; SE = 0.11; P = 0.006$).

### Discussion

**Findings**

In this systematic review, we examined summarized data from 18 studies, comprising a total of 368 patients with chronic HF with or without anemia as determined by [Hb]. The key finding of the present review is that true anemia, that is reduced RBCV, is present in all studies including individuals with HF and anemia, whereas normal RBCV predominates in studies involving patients with nonanemic HF. Augmented PV and BV are manifest in the vast majority of studies. In addition, main clinical variables, such as age, sex (% of females), LVEF, and BMI, have an inverse linear association with RBCV throughout HF phenotypes.

Nearly 4 in 10 individuals with HF present with anemia, being one of the most common comorbidities in HF. For
Table 1. Characteristics of Studies Included in Systematic Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample, n</th>
<th>Age, y</th>
<th>Female, %</th>
<th>LVEF, %</th>
<th>NYHA</th>
<th>[Hb] (g/dL−1)</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Comorbidities</th>
<th>Medication</th>
<th>Intravascular assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller and Mullan 25</td>
<td>HFrEF, 35</td>
<td>69±14</td>
<td>17</td>
<td>27±9</td>
<td>NA</td>
<td>50.2±23.9</td>
<td>CAD (68%), HTN (57%), DM (32%)</td>
<td>ACEI or ARB (100%), BB (100%), Loop DIU (100%)</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Miller and Mullan 25</td>
<td>HFpEF, 20</td>
<td>67±12</td>
<td>55</td>
<td>61±5</td>
<td>NA</td>
<td>49.4±23.4</td>
<td>HTN (75%), DM (65%), CAD (45%)</td>
<td>ACEI or ARB (100%), BB (100%), Loop DIU (100%)</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Miller and Mullan 24</td>
<td>HFpEF, 13; HFpEF, 4</td>
<td>74±10</td>
<td>24</td>
<td>34±16</td>
<td>NA</td>
<td>12.8±2.2</td>
<td>NA</td>
<td>ACEI or ARB (100%), BB (100%), Loop DIU (100%)</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Borovka et al 24</td>
<td>HFpEF, 24</td>
<td>80±11</td>
<td>64</td>
<td>58</td>
<td>NA</td>
<td>10.3±0.9</td>
<td>Anemia (100%), CAD (54%), DM (50%), COPD (11%)</td>
<td>ACEI, ARB, BB, CCB, Loop DIU, MRA, THZ</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Borovka et al 24</td>
<td>HFpEF, 14</td>
<td>76±10</td>
<td>72</td>
<td>59</td>
<td>NA</td>
<td>10.2±1.2</td>
<td>Anemia (100%), DM (83%), CAD (67%), COPD (28%)</td>
<td>ACEI, ARB, BB, CCB, Loop DIU, MRA, THZ</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Borovka et al 24</td>
<td>HFpEF, 6</td>
<td>71±8</td>
<td>67</td>
<td>54</td>
<td>NA</td>
<td>10.8±1.0</td>
<td>Anemia (100%), DM (89%), CAD (67%)</td>
<td>ACEI, ARB, BB, CCB, Loop DIU, MRA, THZ</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Bonfils et al 18</td>
<td>HFrEF, 18</td>
<td>68±4</td>
<td>0</td>
<td>38±12</td>
<td>II–III</td>
<td>13.4±1.3</td>
<td>63.0±16.7</td>
<td>CAD (72%), HTN (44%), DM (17%)</td>
<td>ACEI or ARB (100%), BB (100%), Loop DIU (78%), MRA (50%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Cohen et al 19</td>
<td>HFpEF, 11</td>
<td>=68</td>
<td>=92</td>
<td>55±7</td>
<td>NA</td>
<td>10.8±1.0</td>
<td>Anemia (100%), CRI (75%), CAD (75%), DM (75%)</td>
<td>ACEI (78%), BB (67%), CCB (67%), Loop DIU (56%), THZ (33%)</td>
<td>Radiolabeled albumin</td>
<td></td>
</tr>
<tr>
<td>Abramov et al 18</td>
<td>HFpEF, 22</td>
<td>63±11</td>
<td>23</td>
<td>26±10</td>
<td>2.7±0.7</td>
<td>10.8±1.0</td>
<td>61.0</td>
<td>Anemia (100%)</td>
<td>ACEI, BB, DGT, DIU, THZ</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Abramov et al 18</td>
<td>HFpEF, 24</td>
<td>73±14</td>
<td>75</td>
<td>60±7</td>
<td>2.5±0.5</td>
<td>11.0±1.0</td>
<td>50.1</td>
<td>Anemia (100%)</td>
<td>ACEI, BB, DGT, DIU, THZ</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Adlbrect et al 17</td>
<td>HFpEF, 99</td>
<td>61±11</td>
<td>17</td>
<td>33±10</td>
<td>I–III</td>
<td>13.7±1.6</td>
<td>71.5</td>
<td>HTN (54%), DM (40%), Anemia (26%)</td>
<td>ACEI (78%), ARB (57%), BB (91%), DIU (60%), MRA (59%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Damgaard et al 20</td>
<td>HFrEF, 12</td>
<td>57±13</td>
<td>0</td>
<td>26±7</td>
<td>II–III</td>
<td>13.5±1.1</td>
<td>64.0</td>
<td>NA</td>
<td>ACEI (92%), ASA (83%), ARB (8%), BB (58%), DGT (8%), DIU (83%), MRA (33%), NTR (17%), STN (83%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Feigenbaum et al 15</td>
<td>HFrEF, 12</td>
<td>63±8</td>
<td>0</td>
<td>31±10</td>
<td>2.5±0.5</td>
<td>15.4±1.9</td>
<td>NA</td>
<td>CAD (100%)</td>
<td>ACEI (100%), ACG (75%), BB (67%), DGT (67%), DIU (100%), NTR (75%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>James et al 22</td>
<td>HF, 15</td>
<td>51±8</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>ACEI (100%), DGT (100%), Loop DIU (100%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Kubo et al 23</td>
<td>HF, 12</td>
<td>59±8</td>
<td>33</td>
<td>30±13</td>
<td>I–II</td>
<td>13.5±1.6</td>
<td>NA</td>
<td>CAD (25%)</td>
<td>AB, DGT (58%), Loop DIU (50%), NTR (17%), THZ (25%)</td>
<td>Radiolabeled albumin</td>
</tr>
<tr>
<td>Reilly et al 26</td>
<td>HF, 8</td>
<td>60±14</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Radiolabeled RBCs</td>
</tr>
<tr>
<td>Seymour et al 10</td>
<td>HF, 6</td>
<td>66±9</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Radiolabeled RBCs</td>
</tr>
<tr>
<td>Gibson et al 31</td>
<td>HF, 13</td>
<td>49±16</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>HTN (67%)</td>
<td>DIU (83%), DGT (100%)</td>
<td>Radiolabeled RBCs</td>
</tr>
</tbody>
</table>

Data are n, prevalence (%), and mean or mean±SD. Three articles presented separate study groups that were distinguished by A, B, and C.10,16,25

AB indicates α-blockers; ACEi, angiotensin-converting enzyme inhibitors; ACG, anticoagulants; ARB, angiotensin II-receptor blockers; ASA, acetylsalicylic acid; BB, β-blockers; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CRF, chronic renal insufficiency; DGT, digitalis; DIU, diuretics; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; [Hb], hemoglobin concentration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; Loop DIU, loop diuretics; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NA, data not available; NTR, nitrates; RBCs, red blood cells; STN, statins; and THZ, thiazides.
pragmatic reasons, [Hb] is widely used as a main diagnostic marker. However, anemia is strictly defined by a reduced number of circulating red blood cells or total RBCV, which may be dissociated from [Hb] in patients with HF due to fluid retention and associated increases in PV, that is, hemodilution.\(^8\) However, preserved [Hb] and low PV, plausibly attributable to long-term or aggressive therapy targeting fluid overload, could mask true anemia in HF in the absence of thorough follow-up of clinical signs and hematologic parameters.\(^1,14,15\) Yet, RBCV status in patients with HF remains unresolved, despite the large body of literature on intravascular volumes accumulated since the first half of the 20th century in this population.\(^1,5,9,10,15-26\) A fraction

Figure 2. Mean red blood cell volume (A), plasma volume (B), and blood volume (C) in patients with heart failure grouped according to anemia status. In each group, studies are ordered from left to right according to sample size.\(^3,8,10,15-26\)
of these studies, however, did not take into account the non-linear influence of body size on intravascular volumes, thus compounding their inherent variability in the setting of HF. To our knowledge, the present investigation is the first systematic review aiming to delineate RBCV status in patients with HF. To this end, we were attentive toward articles directly reporting or allowing the calculation of standardized intravascular volumes conforming to established International Council for Standardization in Hematology norms (19 studies, n=400).27,28

Our results indicate that the presence or absence of true anemia concurs with anemia determined by [Hb] cut-off levels, in a cohort of 12,065 patients with HF.32 In this study, older age showed a negative linear relationship with RBCV, decreasing half a percentage point per 1 U increase in % females. This association may be, at least in part, independent of the reduced intravascular volumes characteristic of females, since their calculation was adjusted for sex.24,27 Although the predominance of severe anemia in females with HF has been consistently described, underlying mechanisms have yet to be elucidated. While speculative, a contributing factor could be related to the higher prevalence of kidney disease in females with advancing age compared with males.37 Additionally or alternatively, iron deficiency in females with HF could limit normal erythropoiesis, in line with the present association between RBCV and ferritin derived from a minority subset of studies. In this regard, intravenous iron therapy has been recently related to lower cardiovascular mortality and improved functional exercise capacity in iron-deficient patients with HF.39 Furthermore, we detected a negative relationship between LVEF and RBCV, which implies a distinct pathophysiology of anemia in HFrEF versus HFP EF patients, as discussed below.

 Estimates of the prevalence of anemia (low [Hb]) reach 43% or higher in patients with HFP EF40,41 and are augmented compared with individuals with HFrEF.16,40 True anemia also seems to be more common in anemic patients with HFP EF than those with HFrEF, with respective prevalences of 90% and 60%.16 The herein observation that RBCV is a linear function of LVEF across HF phenotypes agrees with previous evidence and suggests a potential central role of true anemia in the pathogenesis of HFP EF. In this respect, HFP EF is typically associated with hypertension, which has been linked to anemia, as aforementioned. Of note, hypertension in patients with HFP EF is commonly accompanied by the stiffening of central elastic arteries.43 Arterial stiffness (AS) is a fundamental hallmark of sedentary aging, which is inextricably associated with a linear increase in AS, notably if concurring with increased adiposity.44 Likewise, HFP EF is considered a disease of old age presenting with a high prevalence of obesity—as a matter of fact, BMI was negatively associated with RBCV in regression analyses. Importantly, central AS is also negatively associated with RBCV.46 Potential mechanisms explaining this relationship include AS-induced reduction of baroreflex sensitivity leading to impaired release of BV-regulating hormones directly stimulating erythropoiesis, and reduced renal perfusion.48 Alternatively, increased AS and

### Table 2. Metaregression Between Main Clinical Variables and Blood Volume Components (% of Normal) in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>RBCV</th>
<th>PV</th>
<th>BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>β</td>
<td>SE</td>
<td>PValue</td>
</tr>
<tr>
<td>Age</td>
<td>17</td>
<td>−1.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Sex†</td>
<td>17</td>
<td>−0.38</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight</td>
<td>12</td>
<td>−0.67</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI</td>
<td>12</td>
<td>−3.55</td>
<td>0.46</td>
</tr>
<tr>
<td>LVEF</td>
<td>13</td>
<td>−0.81</td>
<td>0.20</td>
</tr>
<tr>
<td>[Hb]</td>
<td>11</td>
<td>6.10</td>
<td>1.44</td>
</tr>
<tr>
<td>Iron</td>
<td>6</td>
<td>0.14</td>
<td>0.34</td>
</tr>
<tr>
<td>Ferritin</td>
<td>5</td>
<td>0.15</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Indicates regression coefficient with blood volume components (% of normal) as outcomes; BV, blood volume; [Hb], hemoglobin concentration; LVEF, left ventricular ejection fraction; n, number of studies; PV, plasma volume; and RBCV, red blood cell volume.

†Percent of females.

<Significant P values (<0.05).
reduced RBCV could be caused by a common underlying process, for example, an age-related increase in circulating (adipose tissue derived) proinflammatory cytokines, altering intrinsic arterial wall properties and proliferation/differentiation of erythroid progenitor cells. In addition, carotid AS is directly associated with a primary chronic symptom in HFP EF, severe exercise intolerance, as determined by the assessment of maximal oxygen consumption (VO\textsubscript{max}). Low VO\textsubscript{max} could be the consequence of diminished capacity to deliver oxygen essentially due to RBCV deficit. Collectively considered, true anemia may be a dominant substrate in the pathophysiology of HFP EF primarily attributed to age-related impaired hemodynamic and hematologic regulation.

**Limitations**

There are some limitations to our analyses that require comment. First, available individual patient data were sparse and analyses were performed on mean variables of relatively small studies. Second, none of the included studies presented mean LVEF between 40% and 50%, which hinders any general conclusion on intravascular volume status about HF with midrange LVEF. Third, although the majority of studies used radioactive labeling techniques, 3 studies (n=31) used dye dilution for intravascular assessment, which could overestimate impaired hemodynamic and hematologic regulation.

**Conclusions**

The current systematic review indicates that true (nonhemodilutional) anemia is common to patients with chronic HF characterized by anemia, as routinely determined by [Hb], but mainly absent in those presenting with normal [Hb]. Moreover, regression analyses suggest that the degree of true anemia, represented by RBCV status, is a linear function of older age, female sex, LVEF, and BMI in individuals with HF. These findings may contribute to clarify the complex management of intravascular volume regulation in patients with HF and facilitate early identification of patients with HF at risk for true anemia.

**Disclosures**

None.

**References**

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Approximately 40% of individuals with heart failure present with anemia as determined by hemoglobin concentration [Hb]. Low [Hb] can be the result of either hemodilution due to fluid retention or a genuine red blood cell deficit as reflected by reduced total red blood cell volume. Determinants and treatment of anemia may, thus, differ according to the underlying pathophysiology. Yet, despite the surfeit of literature assessing intravascular volumes in heart failure, it remains unclear whether true (nonhemodilutional) anemia can be primarily inferred by [Hb] measurements. We, therefore, sought to systematically review the literature and investigate the status and correlates of red blood cell volume in patients with heart failure. From a total of 18 studies comprising 368 patients with chronic heart failure, true anemia was common to patients presenting with [Hb]-based anemia, but mainly absent in those presenting with normal [Hb]. Furthermore, metaregression analyses revealed a positive association between red blood cell volume and [Hb] and negative associations between red blood cell volume and age, female sex, and body mass index.
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Supplemental Material

- **Supplemental Figure 1.** MEDLINE search strategy.

- **Supplemental Figure 2.** Meta-regression plots between mean RBCV (% difference from normal) and [Hb] ($B = 6.10; SE = 1.44; P < 0.001$) (A), age ($B = -1.14; SE = 0.23; P < 0.001$) (B), sex (% females) ($B = -0.38; SE = 0.04; P < 0.001$) (C), LVEF ($B = -0.81; SE = 0.20; P < 0.001$) (D) and BMI ($B = -3.55; SE = 0.46; P < 0.001$) (E) in studies included in systematic review. The size of each circle is proportional to the study’s ‘weight’. BMI, body mass index; [Hb], hemoglobin concentration; LVEF, left ventricular ejection fraction; RBCV, red blood cell volume.
Supplemental Figure 1. MEDLINE search strategy (Filters activated: “Humans”)

“heart failure” [All Fields]

AND

“total”[All Fields] AND “red cell volume” [All fields] OR “plasma volume” [All fields] OR “blood volume” [All Fields]
Supplemental Figure 2. Meta-regression plots between mean RBCV (% difference from normal) and [Hb] ($b = 6.10; SE = 1.44; P < 0.001$) (A), age ($b = -1.14; SE = 0.23; P < 0.001$) (B), sex (% females) ($b = -0.38; SE = 0.04; P < 0.001$) (C), LVEF ($b = -0.81; SE = 0.20; P < 0.001$) (D) and BMI ($b = -3.55; SE = 0.46; P < 0.001$) (E) in studies included in systematic review. The size of each circle is proportional to the study’s ‘weight’. BMI, body mass index; [Hb], hemoglobin concentration; LVEF, left ventricular ejection fraction; RBCV, red blood cell volume.