Association of anemia and long-term survival in patients with pulmonary hypertension

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A B S T R A C T

Background: Anemia is a marker of worsened clinical outcome in patients with heart failure from left ventricular dysfunction. Pulmonary hypertension often results in right ventricular dysfunction. Accordingly we sought to examine the association of hemoglobin levels and long-term all-cause mortality in a cohort of patients with pulmonary hypertension.

Methods: Baseline demographic information, clinical characteristics and fasting blood work were obtained in a cohort of 145 patients with pulmonary hypertension referred for pulmonary vasodilator testing. Data was retrospectively analyzed with Cox-proportional hazards analysis.

Results: Baseline characteristics of the cohort included age (mean ± SD) 55.8 ± 14.6 years, 75% women, 50% with idiopathic pulmonary hypertension, mean pulmonary artery pressure 46.1 ± 14.2 mm Hg and arterial O₂ saturation 91 ± 6%. The most commonly utilized pulmonary hypertension specific therapeutic agents in descending order of frequency were epoprostenol (27%), sildenafil (21%), bosentan (17%), and treprostinil (6%). Over a median follow-up of 2.1 years, there were 39 deaths (26.9%). Patients who died had significantly lower hemoglobin levels than those survived (12.2 ± 2.3 vs. 13.7 ± 2.0, p < 0.001). After adjustment for known predictors of death and pulmonary hypertension etiology, anemic patients were 3.3 times more likely to die than non-anemic patients (95% CI [1.43–7.51], p = 0.005).

Conclusions: Hemoglobin levels closely parallel survival in pulmonary hypertension. Modification of anemia in this disorder could alter the clinical course and calls for further research in this area.

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1. Introduction

Anemia is a strong, independent risk factor for morbidity and mortality in a number of chronic conditions including kidney disease [1] and cancer [2]. It also negatively influences the course of acute illnesses [3] including myocardial infarction [4,5] and increases periprocedural and perioperative morbidity and mortality [6,7]. By the classic World Health Organization definition [8], anemia is present in only ~9% of the United States population, but becomes significantly more common in older adults and in patients with comorbid illness [9,10]. In certain conditions such as cancer and chronic kidney disease, anemia has a well-described pathophysiological basis and is nearly ubiquitous; while in other conditions the mechanism is less clear and attributed to the so-called “anemia of chronic disease” [11]. A number of studies have described an increased prevalence of anemia in patients with heart failure (HF) resulting from left ventricular (LV) dysfunction [12,13]. Anemia occurs in up to 20% of outpatients and 30% of hospitalized patients with HF. In HF patients anemia is associated with an increased risk of cardiovascular events and is an independent predictor of mortality [14–16].

Pulmonary hypertension (PH) is a devastating clinical disorder associated with progressive right ventricular (RV) dysfunction and high rates of mortality. Patients with PH and RV dysfunction appear to have significantly worse clinical outcomes despite several new therapies [17,18]. The range of hemoglobin levels in patients with PH has not been previously established. Furthermore, the effect of PH on erythropoiesis appears more complex than in left ventricular (LV) dysfunction. Low cardiac output, one of the postulated mechanisms of anemia in patients with LV dysfunction [19], is also prevalent in PH owing to RV dysfunction. On the other hand, hypoxia is also quite common, particularly in patients with idiopathic pulmonary hypertension, and PH from interstitial lung disease, collagen-vascular disease, and cyanotic congenital heart disease. Hypoxia stimulates...
erythropoiesis and may therefore counteract the effect of RV failure. This study was designed to retrospectively investigate the prevalence of anemia in a cohort of patients with PH referred for vasodilator testing, and to examine its association with long-term all-cause mortality.

2. Methods

2.1. Patients

Consecutive patients with pulmonary hypertension were entered into a database between November 1998 and December 2007 at two tertiary care academic affiliated medical centers. Complete blood counts were collected from a fasting blood-draw on either the morning of or the evening prior to cardiac catheterization. Abnormal values were repeated for validation purposes and only stable hemoglobin measurements were used for analysis. The World Health Organization classification of anemia (< 12 g/dl for females, < 13 g/dl for males) was used for this study [6]. Although this definition remains far from optimal, no other clinically relevant definition is uniformly accepted. The updated clinical classification of pulmonary hypertension (Dana Point) was used in this study [20]. Briefly, class 1 consists of pulmonary arterial hypertension, class 2 consists of pulmonary venous hypertension from left heart disease, class 3 is associated with lung diseases and/or hypoxia, class 4 includes chronic thrombotic and/or embolic disease and class 5 is a miscellaneous category.

Patients underwent cardiac catheterization expressly for vasodilator testing or part of their diagnostic work-up prior to further clinical intervention. Exclusion criteria included patients with comorbid diseases strongly associated with anemia such as renal failure (serum creatinine ≥ 2.5) or sickle cell anemia, patients with class 2 pulmonary hypertension (left heart disease) and cyanotic congenital heart disease. This study was approved by the Duke University Medical Center and the Cleveland Clinic Institutional Review Boards.

2.2. Hemodynamic assessment

All studies were conducted in the fasting state and with minimal sedation. If a left heart catheterization was performed, all contrast injections were performed after hemodynamic assessments were completed. Right heart catheterization was performed using a single end-hole, balloon flotation catheter (Bard Pulmonary Wedge Catheter, Medtronic or Balloon Wedge Pressure Catheter, Arrow International, Inc.). Baseline hemodynamic measurements included mean right atrial pressure (RA), right ventricular systolic and diastolic pressures, pulmonary artery (PA) systolic, diastolic, and mean pressures, mean pulmonary capillary wedge pressure (PA occlusive pressure) and femoral artery systolic, diastolic, and mean pressures. In repeat measurements during inhalation of 40 ppm of nitric oxide (INO Therapeutics, Clinton, NJ), administration included PA systolic, diastolic, and mean pressures, mean pulmonary capillary wedge pressure and femoral artery systolic, diastolic, and mean pressures.

Blood samples were obtained from the main PA and femoral artery for calculation of the cardiac output using an assumed Fick method. Systemic and pulmonary vascular resistances were calculated using standard hemodynamic equations and are presented in absolute (Wood) units. A positive response to inhaled nitric oxide (INO) was defined by a drop in PA pressure ≥ 10 mm Hg to a mean pulmonary artery pressure ≤ 40 mm Hg [21].

2.3. Clinical assessment and follow-up

All patients underwent full clinical evaluation at the time of initial referral for cardiac catheterization. Baseline studies included chest radiography, chest computed tomography if chest radiography was abnormal, ventilation-perfusion scanning, full pulmonary function testing, electrocardiography and echocardiography. Patients were followed at regularly scheduled intervals and medical therapy was administered at the discretion of the referring physicians. Vital status was determined using the Social Security Death Index.

2.4. Statistical analysis

Data are presented as mean±standard deviation for continuous variables and as percentage for discrete variables. Comparison of dichotomous variables was performed using the Pearson chi square test or Fisher’s exact test when appropriate. Comparisons of continuous variables between groups were performed using two-sided t-tests and one-way analysis of variance. Statistical significance was assumed with p<0.05. Survival analyses were performed using the Kaplan–Meier and proportional hazards regression methods. The proportional hazards model was constructed using previously defined predictors developed from robust patient cohorts and PH etiology [22–24]. Assumptions of the proportional hazard model were verified graphically. Statistically significant differences in the survival functions were assessed with the Wilcoxon test. All analyses were performed using JMP version 7.0 (© SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

One hundred sixty nine patients were entered into the database between November 1998 and December 2007 and underwent invasive hemodynamic assessment including vasodilator challenge with iNO. Two patients with moderate or worse renal insufficiency (serum creatinine ≥ 2.5), 1 patient with sickle cell anemia, 13 patients with cyanotic congenital heart disease, and 7 patients with Dana Point Class 2 pulmonary hypertension were excluded. Blood counts for one patient were not complete. Of the 145 patients in the final analysis, 39 died (26.9%) over a median follow-up period of 2.1 years (range 0.01 years to 5.3 years).

Demographics of the cohort stratified by vital status at the completion of the follow-up period are listed in Table 1. Hemoglobin levels for the entire cohort ranged from 8.4 to 18.2 mg/dL and 38 patients (26.2%) were considered anemic using the World Health Organization definition [8]. In females the median hemoglobin level was 13.0 mg/dL with an interquartile range of 11.9 to 14.7 mg/dL and in males the median hemoglobin level was 14.3 mg/dL with an interquartile range of 12.8 to 15.5 mg/dL. Both males and females who died during follow-up had lower baseline hemoglobin levels compared with those who survived (12.7±2.2 vs. 14.3±2.0, p = 0.04 and 12.1±2.3 vs. 13.5±1.9, p = 0.001).

Patients who died during the follow-up were older (61.8±14.8 vs. 53.5±14.0 years, p = 0.002), had more advanced functional impairment (11/56/33 vs. 33/50/17% NYHA class I/II/IV, p = 0.01), had worsened renal function (1.1±0.4 vs. 0.9±0.3 serum creatinine mg/dL, p = 0.02), and had lower oxygen saturations (89.0±7.4 vs. 92.0±4.8%, p = 0.01). The etiology of PH, in accordance to the 2009 Updated Clinical Classification of Pulmonary Hypertension [20], did not appear to impact survival (p = 0.93) nor did the diagnosis of idiopathic pulmonary hypertension (p = 0.32).

3.2. Hemodynamic findings

Baseline hemodynamic values, again stratified by final vital status, are listed in Table 2. Survivors had lower right-sided filling pressures (RA: 9.9±5.8 vs. 12.8±7.0 mm Hg, p = 0.01, PA: 44.1±13.4 vs. 51.5±14.8 mm Hg, p = 0.005). Lower pulmonary vascular resistance was also associated with survival (8.1±6.1 vs. 11.4±7.8 Wood units, p = 0.009). Seventeen percent of patients experienced a positive vasodilator challenge to iNO defined by a drop in PA pressure of at least 10 mm Hg to a value less than 40 mm Hg. Survivors were no more likely to have experienced a positive response than those that died (19.2 vs. 10.5%, p = 0.22).

3.3. Treatment during follow-up

During follow-up, 2 patients underwent cardiopulmonary surgery (one pulmonary thromboembolectomy and one tricuspid valve repair for severe tricuspid regurgitation) and 3 patients received lung transplants. The most commonly utilized therapeutic agents in descending order of frequency were warfarin (49%), calcium channel blockers (34%), continuous flow oxygen (32%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (29%), epoprostenol (27%), spironolactone (22%), sildenafil (21%), bosentan (17%), statins (17%), digoxin (14%) and treprostinil (6%). No significant differences in drug utilization were seen among patients stratified by hemoglobin status.

3.4. Anemia characteristics

Clinical characteristics of the cohort stratified by anemic status are shown in Table 3. Patients who were anemic were older (60.8±17.0
Available medical records were reviewed to further characterize patients’ anemia. Anticoagulation therapy prior to catheterization was present in 2/3 of patients receiving anticoagulation during the follow-up period but demonstrated no association with anemic status (p = 0.59) at the time of catheterization. Available hematologic data demonstrated no difference in mean corpuscular volume (87.9 ± 9.0 vs. 90.2 ± 5.4 fL, p = 0.23) and slightly elevated red cell distribution width (17.5 ± 2.3 vs. 14.7 ± 1.7%, p < 0.001) between anemics and non-anemics.

To investigate the effect of high hemoglobin levels we compared patients in the highest hemoglobin quartile against all others for each sex (>15.5 g/dL for males and >14.7 g/dL for females). Of the 34 patients in the highest hemoglobin quartile only 4 died (11.8%). Patients who died were less likely to be in the highest hemoglobin quartile than those that survived (10.3% vs. 28.3%, p = 0.02). There were 13 patients with elevated hemoglobin levels using the upper limits of normal for standard hemoglobin measurement at our institution (>17 g/dL for males and >16 g/dL for females) and only 2 died during follow-up (15.4%, p = 0.30). Using this definition no difference was seen in the proportion of patients that had elevated hemoglobin (5.1% vs. 10.4%, p = 0.30).

3.5. Mortality according to hemoglobin status

Kaplan–Meier survival analysis demonstrated that anemic patients had significantly worse survival (p = 0.001) (Fig. 1). The hazard ratio for anemia was 3.2 (95% CI [1.7–6.1]). To assess the independent effect of hemoglobin level on mortality, we developed a proportional hazards model. The hazard ratio for hemoglobin level was 0.9 (95% CI [0.8–1.0]) per mg/dL increase in hemoglobin level.

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anemica (n = 38)</th>
<th>Normal (n = 107)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death during follow-up, no. (%)</td>
<td>18 (47.4)</td>
<td>21 (19.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.8 ± 17.0</td>
<td>54.0 ± 13.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>73.7</td>
<td>75.7</td>
<td>0.80</td>
</tr>
<tr>
<td>Race</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>81.6</td>
<td>76.6</td>
<td>0.23</td>
</tr>
<tr>
<td>African American</td>
<td>18.4</td>
<td>18.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Otherb</td>
<td>0</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Dana Point Classificationb</td>
<td>0.02c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>84.2</td>
<td>64.5</td>
<td></td>
</tr>
<tr>
<td>Class 3</td>
<td>15.8</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td>0</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Class 5</td>
<td>0</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Idiopathic PH</td>
<td>52.6</td>
<td>49.5</td>
<td>0.74</td>
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<td>NYHA Class</td>
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<td></td>
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<tr>
<td>II</td>
<td>29.7</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>35.1</td>
<td>57.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>35.1</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level (mg/dL)</td>
<td>10.6 ± 1.1</td>
<td>14.3 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean RA pressure (mm Hg)</td>
<td>12.6 ± 7.0</td>
<td>10.0 ± 5.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean PA pressure (mm Hg)</td>
<td>43.5 ± 11.7</td>
<td>47.0 ± 14.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.9 ± 1.5</td>
<td>4.4 ± 1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>6.8 ± 4.1</td>
<td>9.7 ± 7.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Arterial O2 saturation (%)</td>
<td>90.2 ± 6.0</td>
<td>90.6 ± 5.9</td>
<td>0.29</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.3</td>
<td>0.43</td>
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<tr>
<td>Positive response to INOb</td>
<td>13.2</td>
<td>17.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Rx with ACE-inhibitor</td>
<td>18.0</td>
<td>25.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Rx with epoprostenol</td>
<td>29.0</td>
<td>21.01</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± standard deviation (SD) or frequency (%). Definition of abbreviations: PH = pulmonary hypertension; NYHA = New York Heart Association; RA = right atrial; PA = pulmonary arterial; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; O2 = oxygen; iNO = inhaled nitric oxide; Rx = prescription; ACE = angiotensin converting enzyme.

b Includes Asian/Pacific Islander, Hispanic, and Native American.

c From the 2009 Updated Clinical Classification of Pulmonary Hypertension [20].

case 1 vs. Case 3 vs. Others.

d Response to inhaled nitric oxide defined as a drop in PA pressure of at least 10 mm Hg to a mean PA pressure < 40 mm Hg.
hazards regression model to investigate the effects of known predictors of mortality in PH patients including age, NYHA functional class, grade of tricuspid regurgitation, PVR, and PH etiology (Table 4). Using the WHO definition, anemia conferred an adjusted HR of 3.3 (95% CI [1.43–7.51], p = 0.005). Investigating hemoglobin as a continuous variable, each g/dL increase in hemoglobin level decreased the hazard of death by 34% (HR 0.66, 95% CI [0.52–0.83], p < 0.001) (Table 5).

4. Discussion

This study shows for the first time that anemia is common in patients with advanced pulmonary hypertension. More importantly, the presence of anemia appears to have a powerful association with clinical outcome in PH patients and its prognostic significance is independent of previously described risks for morbidity and mortality and PH etiology. Anemia, as defined by the WHO, increases the hazard of death by more than 3 fold. Since dichotomization of continuous variables (such as hemoglobin level) can be prone to bias, we also analyzed hemoglobin as a continuous variable and this revealed similarly significant results. Each g/dL increase in hemoglobin level led to a 33% reduction in the hazard of death in adjusted analysis.

The reduction in hemoglobin levels in our patients did not appear to be related to renal insufficiency as measured by serum creatinine, nor was it driven by depressed cardiac output or counterbalanced by low oxygen saturations. Mechanistically PH has been characterized as a state of enhanced inflammation [25], and several biomarkers including IL-6 have been reported to be elevated in PH patients [26–28]. Under such conditions response to endogenous and exogenous erythropoietin appears to be reduced [29]. Of note, elevations in serum erythropoietin have recently been shown to be present in patients with HF and portend a worsened clinical outcome [30].

As demonstrated in Tables 1 and 4, the etiology of PH did not appear to influence survival or anemic status. We chose a-priori to exclude patients with comorbid disease associated with anemia to prevent confounding. We also excluded patients with left heart disease (Evian class 2 PH) because anemia has already been linked to worse outcomes in these patients. Patients with cyanotic heart disease were also excluded because of complex secondary erythrocytosis that could also confound our analysis [31].

The number of vasoreactive patients in our cohort is higher than has been previously reported [32]. In 2005, Sitbon et al. retrospectively reviewed patient data and concluded that less than 10% of PH patients were vasoreactive (PA pressure reduction <10 mm Hg to a value <40 mm Hg). However, their study population had strict hemodynamic inclusion criteria, had worse functional class and utilized two different vasoreactive testing drugs which may confound their results [33]. Our study, however, utilized 40 ppm iNO for each vasodilator challenge.

Pulmonary hypertension is a disorder with serious consequences and high rates of mortality despite aggressive new therapies [34,35]. In our population 60% of patients received a prostacyclin analogue, an endothelin antagonist or a phosphodiesterase-5 inhibitor and 20% of these patients received combination therapy. Despite these medications, over a quarter of patients died within 5 years of follow-up. Clearly a need for further therapeutic advances exists in this population. This study provides important insight into a previous undescribed aspect of pulmonary hypertension, low hemoglobin levels.

It is important to note that are limitations to the study design. Although the database was prospectively collected, it was retrospectively analyzed. Therefore, it is not possible to make firm conclusions on the causation of outcome and anemia in pulmonary hypertensive patients, nor about its clinical sequelae. Larger, confirmatory studies will be very valuable in this regard. This study was performed at 2 large medical centers and was therefore subject to referral bias. It is also unknown whether direct therapy such as transfusion or erythropoietin was utilized during the follow-up period, though we could not find any evidence of this through very thorough record review.

Anemia in PH patients may simply be a marker for worsened clinical outcome as has recently been suggested in heart failure patients [36]. In this capacity measurement of hemoglobin could still provide important additional prognostic information in PH patients, as well as potentially identify which patients may require more aggressive and often more expensive therapies. Alternatively anemia may play a central role in the pathophysiology of PH. Recent studies suggest that the hemoglobin and the erythrocyte play a central role in regulating the activity of nitric oxide in the vasculature [37,38]. In particular the deoxygenated form of hemoglobin may directly reduce nitrite to nitric oxide, and anemia could therefore limit this essential step that normally promotes vasodilation of the pulmonary vascular bed.

### Table 4

Proportional hazards regression model using WHO definition for anemia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (%)</td>
<td>3.30</td>
<td>1.43–7.51</td>
<td>0.005</td>
</tr>
<tr>
<td>Age (by year)</td>
<td>1.02</td>
<td>0.99–1.05</td>
<td>0.14</td>
</tr>
<tr>
<td>Dana Point Class 1</td>
<td>0.57</td>
<td>0.15–3.65</td>
<td>0.49</td>
</tr>
<tr>
<td>Dana Point Class 3</td>
<td>0.73</td>
<td>0.16–5.13</td>
<td>0.71</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>2.08</td>
<td>1.18–3.75</td>
<td>0.01</td>
</tr>
<tr>
<td>Tricuspid regurgitation (grade*)</td>
<td>1.63</td>
<td>1.15–2.36</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline PVR (by Wood unit)</td>
<td>1.05</td>
<td>0.99–1.10</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Definition of abbreviations: WHO = World Health Organization; HR = hazard ratio; CI = confidence interval; PVR = pulmonary vascular resistance.

* Tricuspid regurgitation was qualitatively graded as 1 = none, 2 = mild, 3 = moderate, 4 = severe.

* Tricuspid regurgitation was qualitatively graded as 0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe.
Although early trials of erythropoietin treatment in left heart failure demonstrated increased functional capacity, larger randomized trials have shown less benefit [39,40]. It is therefore plausible that modifying the anemia of patients with PH through some yet to be discovered pathway or by administering pre-existent therapies such as erythropoietin may lead to clinical improvement in this challenging disorder.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [41].

References
