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Association of Anemia With Diastolic Dysfunction Among Patients With Coronary Artery Disease in the Heart and Soul Study

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Abstract

We performed a cross-sectional study to evaluate the association of anemia with diastolic dysfunction and left ventricular hypertrophy (LVH) in outpatients who had coronary artery disease. Logistic regression was used to examine the association of blood hemoglobin (Hb) concentrations with diastolic dysfunction and LVH in 822 participants in the Heart and Soul Study who had normal sinus rhythm and preserved systolic function (left ventricular ejection fraction $\geq 50\%$). Using transthoracic echocardiography, diastolic dysfunction was defined as diastolically dominant pulmonary vein flow, and LVH was defined as left ventricular mass index $>90 \text{ g/m}^2$. Anemia (Hb $<13 \text{ g/dl}$) was present in 24% of participants (197 of 822). The prevalence of diastolic dysfunction ranged from 8% in participants who did not have anemia (Hb $\geq 13 \text{ g/dl}$) to 13% in those who had moderate anemia (Hb 11 to 13 g/dl) to 24% in those who had severe anemia (Hb $< 11 \text{ g/dl}$, $p = 0.004$ for trend). After multivariable adjustment, moderate anemia (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.1 to 3.6) and severe anemia (OR 6.6, 95% CI 1.9 to 24.9) remained strongly associated with diastolic dysfunction. In contrast, moderate anemia (OR 1.4, 95% CI 1.0 to 2.1) and severe anemia (OR 1.6, 95% CI 0.6 to 4.6) were not significantly associated with LVH. We found anemia to be strongly associated with diastolic dysfunction but not with LVH in this community-based sample of outpatients who had established coronary disease.

The presence of anemia is associated with adverse outcomes in many conditions, including end-stage renal disease¹ and myocardial ischemia, but its relation to heart failure has only recently been appreciated.^{2–4} Recent studies have demonstrated that anemia is highly prevalent in patients who have heart failure and is strongly associated with systolic dysfunction.^{2,3,5–8} However, $\leq 50\%$ of patients who have heart failure have preserved systolic function,^{9–12} and the association of anemia with diastolic dysfunction in this population has not been studied. We conducted a cross-sectional study to assess the associations of anemia with diastolic dysfunction and left ventricular hypertrophy (LVH) in 822 outpatients who had known coronary artery disease with preserved systolic function.

METHODS

Study participants

The Heart and Soul Study is investigating the influence of psychosocial factors on cardiovascular outcomes in patients who have coronary artery disease. Methods have been described previously.¹³ In brief, we used administrative databases to identify outpatients who

had documented coronary artery disease at 2 Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto, California), 1 university-based medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had ≥ 1 of the following: myocardial infarction, coronary revascularization, angiographic evidence of $\geq 50\%$ stenosis in ≥ 1 coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, or a diagnosis of coronary disease that was documented by an internist or cardiologist.

All eligible participants were invited by mail to attend a baseline study appointment. Patients were excluded if they reported revascularization or hospitalization for an acute coronary event ≤ 6 months previously, deemed themselves unable to walk 1 block, or were planning to move out of the local area within 3 years. Between September 2000 and December 2002, 1,024 participants enrolled. For this cross-sectional analysis, we excluded participants who had left ventricular ejection fraction $< 50\%$ by 2-dimensional echocardiography ($n = 122$), those who were not in sinus rhythm ($n = 63$), those who had moderate or severe mitral regurgitation ($n = 5$), and those for whom the presence or absence of diastolic dysfunction could not be determined for technical reasons ($n = 12$), leaving 822 participants in the present analysis. The institutional review board at each participating site approved our protocol, and all participants provided written informed consent.

Predictor variable, anemia

Venous blood samples were drawn into tubes that contained ethylenediaminetetraacetic acid. Hemoglobin (Hb) values were obtained with the Beckman Coulter LH 750 (Fullerton, California); interassay coefficient of variation was 0.4%. Laboratory technicians who measured these values were blinded to the results of the stress echocardiogram. We defined anemia as $\text{Hb} < 13 \text{ g/dl}$ based on cutpoints used in previous studies, with mild to moderate anemia defined as $\text{Hb} 11$ to 13 g/dl and severe anemia defined as $\text{Hb} < 11 \text{ g/dl}$.^{4,14–16}

Outcome variables, diastolic dysfunction and LVH

All participants underwent echocardiography at rest with an Acuson Sequoia ultrasound system (Mountain View, California) using a 3.5-MHz transducer. A complete 2-dimensional echocardiogram at rest, including imaging and Doppler imaging in all standard views and subcostal imaging of the inferior vena cava, was performed. We obtained standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views during held inspiration and performed planimetry with a computerized digitization system to determine end-diastolic and end-systolic left ventricular volumes and left ventricular ejection fractions. One of us (NBS) interpreted all echocardiograms and was blinded to results of the Hb assay.

We categorized participants as having diastolic dysfunction if the velocity–time integral in the pulmonary vein was greater during diastole (diastolic dominant) than during systole (systolic dominant).¹⁷ To examine the association between anemia and different categories of diastolic function, we further subdivided the diastolic dysfunction (diastolic dominant) category into pseudonormal patterns ($\text{E/A wave ratio} \geq 1$ but < 2), and restrictive patterns ($\text{E/A wave ratio} \geq 2$). We also subdivided the systolic dominant category into patterns of normal relaxation ($\text{E/A wave ratio} \geq 1$) and impaired relaxation ($\text{E/A wave ratio} < 1$).^{17,18} Left ventricular mass was measured on echocardiogram at rest according to the truncated ellipsoid method.¹⁹ We considered participants who had left ventricular mass index $> 90 \text{ g/m}^2$ to have LVH.

Other measurements

Self-reported age, gender, ethnicity, medical history, and smoking status were determined by questionnaire. Alcohol use was measured with the AUDIT-C questionnaire, with a score ≥ 4 used to define regular alcohol use.²⁰ We measured angina frequency with the Seattle Angina

Questionnaire.²¹ Level of functional status was defined as class I, II, III, or IV based on the New York Heart Association classification system, with higher classes indicating worse cardiac function.²² Systolic and diastolic blood pressures were measured with a standard sphygmomanometer. We measured height and weight and calculated body mass index (kilograms per square meters). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Serum creatinine was assayed, and creatinine clearance was calculated from 24-hour urine collections.²³

Statistical analysis

Differences in baseline characteristics according to the presence of anemia were determined with analysis of variance for continuous variables and chi-square tests for dichotomous variables. We used separate multivariable logistic regression analyses to evaluate the independent association between the primary predictor variable (anemia) and the 2 outcome variables (diastolic dysfunction and LVH). Our multivariable models used a backward elimination logistic regression procedure in which all variables listed in Table 1 were entered into the model, and those variables associated with the outcome of interest (at $p < 0.1$) were retained. For these analyses, we report odds ratios (ORs) with 95% confidence intervals (CIs). Because renal dysfunction has been correlated with anemia and LVH,^{24,25} we repeated the regression models after stratifying participants by the presence of renal dysfunction, and we tested for a statistical interaction between renal dysfunction and anemia for each outcome. All analyses were performed with SAS 8 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics according to Hb level

Of the 822 participants included in the analysis, 197 (24%) had anemia (Hb < 13 g/dl), including 180 who had mild to moderate anemia (Hb 11 to 13 g/dl) and 17 who had severe anemia (Hb < 11 g/dl). Compared with participants who did not have anemia, those who had anemia were older, less likely to be men or white, and more likely to have diabetes (Table 1). Participants who had anemia had lower diastolic blood pressure and lower creatinine clearance than those who did not have anemia.

Anemia and diastolic dysfunction

A total of 77 participants (9%) had diastolic dysfunction as defined in this study, all of whom were > 40 years of age. The prevalence of diastolic dysfunction was 8% in participants (49 of 625) who did not have anemia, 13% in participants (24 of 180) who had moderate anemia, and 24% in those (4 of 17) who had severe anemia (Table 2). Hb levels were strongly and inversely associated with diastolic dysfunction (Figure 1; $p = 0.004$ for trend). After multivariable adjustment, those who had moderate anemia had a twofold odds of diastolic dysfunction and those who had severe anemia had an almost sevenfold odds of diastolic dysfunction compared with participants who did not have anemia (Table 2). When analyzed as a continuous variable, each 1 g/dl decrease in Hb was associated with a 40% increased odds of diastolic dysfunction (adjusted OR 1.4, 95% CI 1.1 to 1.6) after adjusting for history of congestive heart failure, coronary artery bypass grafting, more frequent angina, lower heart rate at rest, and lower functional class as defined by the New York Heart Association.

When we further categorized diastolic function as normal, impaired relaxation, pseudonormal, and restrictive filling, we found that the restrictive filling pattern had the strongest association with anemia compared with normal diastolic function (Table 3). In participants who had systolic dominant pulmonary vein flow, we observed no difference in the prevalence of anemia between those who had impaired relaxation and those who had normal diastolic function.

Anemia and LVH

Among the 822 participants, 415 (50%) had LVH (left ventricular mass index >90 g/m²). We did not observe an association between anemia and LVH (Figure 2). When evaluated as a continuous variable, there was a slight association, with each 1 g/dl decrease in Hb, conferring a 10% increased odds of LVH (adjusted OR 1.1, 95% CI 1.0 to 1.3, $p = 0.04$). However, we found that the categories of moderate anemia (adjusted OR 1.4, 95% CI 1.0 to 2.1) and severe anemia (adjusted OR 1.6, 95% CI 0.6 to 4.6) were not significantly associated with LVH.

Stratified analyses

We found similar associations between anemia and diastolic dysfunction in the 159 participants who had renal insufficiency (creatinine clearance <60 ml/min, adjusted OR 3.2, 95% CI 1.1 to 9.6, $p = 0.04$) and in the 615 participants who did not have renal insufficiency (adjusted OR 1.9, 95% CI 1.0 to 3.9, $p = 0.07$). Although the point estimates suggested a greater magnitude of association between anemia and diastolic dysfunction in participants who had renal insufficiency, we observed no statistical evidence of an interaction between anemia and renal insufficiency ($p = 0.55$ for interaction). Likewise, we found similar associations between anemia and diastolic dysfunction in the 415 participants who had LVH (adjusted OR 2.3, 95% CI 1.2 to 4.6, $p = 0.02$) and in the 399 participants who did not have LVH (adjusted odds ratio 2.0, 95% CI 0.8 to 5.0, $p = 0.12$, $p = 0.80$ for interaction).

DISCUSSION

We found that anemia was strongly associated with diastolic dysfunction in outpatients who had coronary disease and preserved systolic function. This association was graded, with 2 times the odds of diastolic dysfunction in those who had moderate anemia and an almost sevenfold odds of diastolic dysfunction in those who had severe anemia. Surprisingly, we did not find a strong relation between anemia and LVH, and LVH did not appear to mediate the observed association between anemia and diastolic dysfunction.

This study generates new hypotheses regarding the mechanisms by which anemia could promote the development of heart failure. Previous studies, predominantly done in cohorts that had established kidney disease, found anemia to be linked to LVH,^{25–28} so LVH was the leading hypothesis believed to explain the association of anemia with systolic heart failure. Although LVH may also be involved, our results suggest that diastolic dysfunction may be an important mediator in the pathway from anemia to heart failure. Even in the absence of LVH or renal insufficiency, anemia remained strongly associated with diastolic dysfunction, implying that this could be a unique complication of anemia.

We were surprised to find only a small association between anemia and LVH. In patients who have end-stage renal disease, anemia is a well-recognized risk factor for LVH,¹ and previous studies have suggested that development of LVH may be an important intermediary step by which anemia promotes development of heart failure.²⁶

Amin et al¹⁶ examined the relation between anemia and LVH in the Framingham cohort. In univariate analysis, hematocrit was not related to left ventricular mass index. After adjusting for confounders, there was a small but significant association between hematocrit and left ventricular mass index in men and in post-menopausal women. There was a modest association between anemia and LVH in men, but the relation was not statistically significant in women. Because of the large sample, Amin et al had greater statistical power to detect an association between anemia and LVH. We also found a significant association between anemia and LVH when Hb was entered as a continuous variable but no association when anemia was entered as a categorical variable. Together, these results suggest that there is no statistically significant relation

between Hb and LVH is unlikely to be of clinical significance in outpatients who have stable coronary heart disease.

Several mechanisms may explain the association between anemia and diastolic dysfunction. Adaptation to an anemic state involves augmentation of heart rate, cardiac index, and stroke work and increased plasma volume.^{29,30} This overall increase in sympathetic and inotropic activity places additional stress on the myocardium, perhaps leading to remodeling of myocytes and vasculature. Ventricular remodeling is particularly important over time because it leads to LVH and cardiac enlargement.²⁸ Anemia also has numerous hormonal and metabolic effects that can result in direct myocardial toxicity and in indirect cardiac strain through salt and water retention.³¹ These specific effects have been found at more severe degrees of anemia (Hb <10 g/dl) than at those analyzed in this study.³⁰ The hemodynamic effects of mild to moderate anemia have been less studied, and our findings suggest that even moderate anemia may have adverse hemodynamic effects. Because of the myriad of cardiovascular effects induced by anemia, we hypothesize that adaptation to anemia leads to ventricular remodeling, diastolic dysfunction, and systolic dysfunction in patients who have coronary disease.

Because of the cross-sectional nature of our data, diastolic dysfunction may be a predisposing factor for anemia. The effects of abnormal diastolic function on variables such as renal perfusion are unknown. Therefore, diastolic dysfunction may cause neurohormonal alterations that result in altered renal perfusion, perhaps affecting blood volume or regulation of erythropoietin secretion, ultimately resulting in anemia.

Several limitations should be considered when interpreting our results. First, due to the cross-sectional design, our findings do not address the causal direction between anemia and diastolic dysfunction or LVH. Second, our results may have been subject to unmeasured confounding. Third, although our definition of anemia was similar to those used by the World Health Organization and other studies,^{2,14,32} some investigators have used slightly different Hb levels to define anemia,^{4,33} and our cutpoint may have misclassified some participants. Fourth, measurement of diastolic function by echocardiography is an area of active investigation and accurate classification can be elusive.¹⁷ We used a criterion that is present in moderate and severe forms of diastolic dysfunction, i.e., diastolic dominant pulmonary vein flow. Fifth, our population was composed largely of elderly men who had known coronary artery disease, and our results may not be pertinent to women or to other patient populations.

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FIGURE 1.
Proportion of participants who had diastolic dysfunction by Hb level (grams per deciliter).

FIGURE 2.
Proportion of participants who had LVH by Hb level (grams per deciliter).

TABLE 1

Characteristics of 822 Study Participants With Coronary Artery Disease by Presence of Anemia

Variable	Severe Anemia [*] (n = 17)	Mild to Moderate Anemia [†] (n = 180)	No Anemia [‡] (n = 625)	p Value
Age (yrs)	65 ± 11	69 ± 12	65 ± 10	0.0005
Men	71%	63%	86%	<0.0001
White race	41%	46%	62%	0.0003
Medical history				
Hypertension	71%	78%	70%	0.12
MI	53%	46%	52%	0.41
CHF	18%	18%	13%	0.14
Stroke	12%	14%	13%	0.92
Diabetes	53%	36%	23%	0.0002
CABG	18%	31%	36%	0.20
Angioplasty	29%	34%	41%	0.16
Angina weekly or more	24%	17%	19%	0.60
NYHA class III/IV	29%	20%	21%	0.61
Habits				
Current smoking	12%	18%	22%	0.34
Regular alcohol use	29%	25%	31%	0.25
Other measurements				
Body mass index	28 ± 8	28 ± 5	29 ± 5	0.98
Heart rate at rest	69 ± 14	67 ± 12	67 ± 12	0.78
Systolic blood pressure (mm Hg)	140 ± 23	136 ± 20	133 ± 21	0.11
Diastolic blood pressure (mm Hg)	74 ± 14	72 ± 10	76 ± 11	0.001
LV mass index (g/m ²)	98 ± 19	96 ± 24	93 ± 23	0.25
Inducible ischemia	13%	26%	19%	0.11
LV ejection fraction	65.5 ± 6.2	64.9 ± 5.6	64.5 ± 5.9	0.57
Medication use				
β Blocker	53%	59%	57%	0.82
Renin-angiotensin system modifier	65%	53%	45%	0.06
Diuretic	41%	37%	24%	0.0007
Statin	53%	63%	65%	0.55
Aspirin	82%	77%	81%	0.53
Creatinine clearance	59 ± 26	72 ± 27	87 ± 28	<0.0001

Values are mean ± SD or percentages.

^{*} Hb <11 g/dL.[†] Hb 11 to 13 g/dL.[‡] Hb ≥13 g/dL.

CABG = coronary artery bypass grafting; CHF = congestive heart failure; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association.

TABLE 2

Association Between Anemia and Diastolic Dysfunction in 822 Participants With Coronary Heart Disease and Normal Systolic Function (Left Ventricular Ejection Fraction $\geq 50\%$)

Hb Level	Proportion With Diastolic Dysfunction*	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI) [†]	p Value
Normal (Hb ≥ 13 g/dl)	8% (49/625)	1.0	—	1.0	—
Mild to moderate anemia (Hb 11–13 g/dl)	13% (24/180)	1.8 (1.1–3.0)	0.03	2.0 (1.1–3.6)	0.02
Severe anemia (Hb < 11 g/dl)	24% (4/17)	3.6 (1.1–11.5)	0.03	6.9 (1.9–24.9)	0.003

* Velocity time integral in pulmonary vein greater during diastole than during systole.

[†] All variables from Table 1 were entered into a forward stepwise logistic regression model that included the anemia categories. Variables associated with diastolic dysfunction (at $p < 0.10$) in the multivariable model were history of congestive heart failure, coronary artery bypass grafting, more frequent angina, lower heart rate at rest, and New York Heart Association functional classification.

TABLE 3

Association Between Anemia (Hemoglobin <13 g/dl) and Categories of Diastolic Dysfunction in 822 Participants With Coronary Heart Disease and Normal Systolic Function (Left Ventricular Ejection Fraction $\geq$ 50%)

Diastolic Function Category	Proportion With Anemia	Adjusted OR (95% CI)*	p Value
Normal	22% (70/323)	1.0	—
Impaired relaxation	24% (99/421)	1.1 (0.8–1.6)	0.67
Pseudonormal	33% (20/61)	2.0 (1.0–3.8)	0.05
Restrictive pattern	47% (8/17)	5.1 (1.6–16.1)	0.006

* Adjusted for history of congestive heart failure, coronary artery bypass grafting, more frequent angina, lower heart rate at rest, and New York Heart Association functional classification. Abbreviation as in Table 2.