Published in final edited form as:

Am J Cardiol. 2018 October 15; 122(8): 1359–1365. doi:10.1016/j.amjcard.2018.06.045.

Lack of Association Between Anemia and Intrinsic Left Ventricular Diastolic Function or Cardiac Mechanics in Heart Failure with Preserved Ejection Fraction

Jacob A. Burns, BA, Cynthia Sanchez, BA, Lauren Beussink, RDCS, MHS, Vistasp Daruwalla, MD, Benjamin H. Freed, MD, Senthil Selvaraj, MD, MA, and Sanjiv J. Shah, MD
Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Anemia is associated with a poor prognosis in heart failure with preserved ejection fraction (HFpEF), but the reasons underlying this association are unclear. Previous studies have reported an association between anemia and diastolic dysfunction. However, these studies used volume- and flow-dependent indices of diastolic dysfunction. We hypothesized that in HFpEF, anemia is more closely associated with volume status and not markers of intrinsic myocardial dysfunction. We prospectively studied 419 outpatients in a systematic HFpEF program, all of whom underwent hemoglobin measurement and comprehensive echocardiography. Longitudinal, radial, and circumferential strain were also measured in 311 patients. We defined anemia as hemoglobin < 12 g/dL in women and < 13 g/dL in men. Linear and Cox regression analyses were used to determine the association between anemia and echocardiographic/strain variables and adverse outcomes, respectively. Over half (224/419 [53%]) of the HFpEF patients had anemia. Anemia was associated with volume (preload)-dependent markers of diastolic dysfunction including echocardiographic E/A ($p=0.004$) and E/e' ratio ($p=0.014$) and elevated right heart pressures such as right atrial pressure ($p=0.002$) and pulmonary artery systolic pressure ($p<0.001$). Anemia was not associated with markers of intrinsic myocardial dysfunction such as lateral e' ($p=0.16$) and septal e' ($p=0.65$) velocities or echocardiographic strain parameters ($p>0.05$ for all comparisons). Anemia was associated with the combined outcome of cardiovascular hospitalization or death (hazard ratio=1.50 [95% confidence interval 1.20, 1.88]; $p<0.001$). In conclusion, anemia in HFpEF is associated with markers of volume status and not intrinsic markers of myocardial dysfunction.

Corresponding Author: Sanjiv J. Shah, MD, Professor of Medicine, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Director, Northwestern HFpEF Program, Arkes Family Pavilion Suite 600, 676 North Saint Clair St, Chicago, IL 60611, Phone: 312-695-0993, sanjiv.shah@northwestern.edu.

CONFLICT OF INTEREST: None declared.

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Keywords

heart failure with preserved ejection fraction; anemia; diastolic dysfunction; echocardiography

In chronic heart failure (HF), anemia is both common and consistently associated with adverse outcomes.^{1–4} Recently, anemia was shown to be a poor prognostic indicator in HF with preserved ejection fraction (HFpEF).⁵ Diastolic dysfunction—involving impaired left ventricular (LV) relaxation and reduced LV compliance—is a major contributor to HFpEF pathogenesis.⁶ Previous studies have reported an association between anemia and volume- and flow-dependent indices of diastolic dysfunction (e.g. E/A ratio, E/e', and/or pulmonary vein flow).^{7–9} These measures may fail to accurately represent myocardial diastolic function.¹⁰ In contrast, echocardiographic measures intrinsic to the myocardium, are less preload-dependent markers of diastolic performance.¹¹ The relationship of anemia and intrinsic diastolic function in HFpEF has not been previously studied. Based on the poorer outcomes seen in anemic HFpEF patients, it is important to investigate the pathophysiologic role of anemia in HFpEF. We hypothesized that while anemic HFpEF patients have more volume overload and worse outcomes, intrinsic measures of diastolic function (e.g., tissue Doppler e' velocity) and cardiac mechanics (e.g., longitudinal strain) would not differ between anemic and non-anemic groups. We therefore studied the association of anemia with cardiac structure and function, and outcomes, in HFpEF.

METHODS

Between March 2008 and May 2011, consecutive patients were prospectively enrolled from the outpatient clinic of the Northwestern University HFpEF Program as part of a systematic observational study of HFpEF ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01030991) identifier #NCT01030991). All patients were enrolled in the outpatient setting following a HF hospitalization. Patients were identified by automated query of the inpatient electronic medical record at Northwestern Memorial Hospital using the search criteria: (1) diagnosis of HF or the words “heart failure” in the hospital notes; or (2) B-type natriuretic peptide (BNP) >100 pg/ml; or (3) administration of 2 or more doses of intravenous diuretics. Patients were offered follow-up in a specialized HFpEF outpatient program if they met the following inclusion criteria: age ≥21 years, left ventricular (LV) ejection fraction (EF) ≥50% and presence of HF as defined by Framingham criteria.¹²

The HF diagnosis was confirmed in the outpatient HFpEF clinic. All patients met the European Society of Cardiology criteria for the diagnosis of HFpEF.¹³ Patients were excluded if they had more than moderate valvular disease, previous cardiac transplantation, previous history of a reduced LVEF <40%, severe LV dilation (LV end-diastolic volume >97 mL/m²), constrictive pericarditis, or evidence of primary (World Health Organization Group I) pulmonary arterial hypertension. All study participants gave written, informed consent, and the institutional review board at Northwestern University approved the study.

We collected the following data in all study participants: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index and laboratory data, including serum sodium, blood urea nitrogen,

creatinine, hemoglobin, and BNP. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. Chronic kidney disease (CKD) was defined as eGFR < 60 ml/min/1.73 m². Coronary artery disease was defined as presence of physician-documented history of coronary artery disease, known coronary stenosis >50%, history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or abnormal stress test results consistent with myocardial ischemia. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications. Hyperlipidemia was defined as physician-documented history of hyperlipidemia or current use of lipid-lowering medications. Obesity was defined as body mass index >30 kg/m².

Anemia was defined as hemoglobin < 12 g/dl for women or < 13 g/dl for men, based on previous investigations of anemia in HF, including those from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program.¹⁴

All study participants underwent comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500, Philips Medical Systems, Andover, MA; or Vivid 7, GE Healthcare, General Electric Corp., Waukesha, WI). Blood pressure was recorded at the time of echocardiography using a digital blood pressure monitor (Omron HEM-907XL, Omron Healthcare Inc., Vernon Hills, IL). Cardiac structure and function were quantified as recommended by the American Society of Echocardiography.¹⁵⁻¹⁷ All measurements were made by an experienced research sonographer (blinded to clinical data and outcomes) using ProSolv 4.0 echocardiographic analysis software (ProSolv CardioVascular; Indianapolis, IN), and verified by an experienced investigator with expertise in echocardiography.

Comprehensive diastolic function assessment was performed according to published guidelines,¹⁷ and graded according to mitral inflow characteristics, tissue Doppler e' velocities, and E/e' ratio. All Doppler and tissue Doppler measurements were averaged over 3 beats (5 beats for patients in atrial fibrillation). Pulmonary capillary wedge pressure (PCWP) was estimated using early mitral inflow (E) and e' tissue velocity as previously described.¹⁸

Echocardiographic markers of RV structure and function, including RV end-diastolic and end-systolic area (indexed to body size)¹⁹, RV basal diameter, RV wall thickness, RV fractional area change (RVFAC), and tricuspid annular plane systolic excursion (TAPSE) were measured using 2-dimensional echocardiography and quantified as recommended by the American Society of Echocardiography.¹⁷ RV hypertrophy was defined as RV end-diastolic free wall thickness >5.0 mm (measured in the subcostal view); abnormal RVFAC was defined as < 35%.¹⁷ Pulmonary artery pressure (PASP) and right atrial pressure (RAP) were estimated as previously described.²⁰

In 311 patients from the HFpEF cohort, we performed speckle tracking analysis to calculate LV strain values to analyze intrinsic cardiac mechanics. A portion of the original cohort was excluded from speckle tracking analysis based on image quality, as described previously.

^{21,22} Briefly, this includes >1 segment dropout, missing view, or significant foreshortening of the LV. Strain was analyzed by a single investigator using a customized software package (2D Cardiac Performance Analysis, TomTec v4.5, Munich, Germany). Three consecutive cardiac cycles were recorded and averaged. LV longitudinal strain, circumferential strain, and radial strain were measured. The LV endocardial border was manually traced in the apical 4- and 2- chamber views. The software divided the LV into six segments and regions with insufficient tracking were excluded. LV strain was calculated by averaging the remaining segments for each view. For ease of reporting and interpretation, all strain values were reported as absolute values, with a lower absolute value corresponding to worse cardiac mechanics.

After enrollment, study participants were evaluated in the Northwestern HFpEF Program at least every 6 months or as clinically indicated. At each visit, inter-current hospitalizations were reviewed and categorized as due to cardiovascular or non-cardiovascular causes. For cardiovascular hospitalizations, specific causes were identified. Every 6 months, participants or their proxy were contacted to determine vital status with verification of deaths through query of the Social Security Death Index. Enrollment date was defined as the first visit to the outpatient HFpEF clinic. Date of last follow-up was defined as date of death or last HFpEF clinic visit. Follow-up was complete in all patients. Our primary endpoint was a combined outcome of cardiovascular hospitalization and death, which included hospitalization for any cardiovascular cause (including HF) and death from any cause.

We stratified the cohort by the presence or absence of anemia and compared differences in clinical characteristics, laboratory values, and echocardiographic parameters between groups. Categorical variables are displayed as count and percentage and continuous data with a normal distribution are displayed as mean±standard deviation. Right-skewed data are presented as median and 25th-75th percentile. Categorical variables were compared between groups using Chisquared tests or Fisher exact tests, as appropriate. Continuous variables were compared between groups using t-tests, or Wilcoxon rank-sum test, when appropriate.

Next, we divided the cohort into sex-specific hemoglobin quartiles in order to display the association between hemoglobin and various echocardiographic parameters. We then examined the relationship between anemia status and echocardiographic parameters using unadjusted and multivariable-adjusted linear regression analyses. For multivariable analyses, covariates were chosen through a combination of clinical relevance and association with predictor and outcome variables. For regression analyses with strain as the outcome variable, we included a model that excluded patients with chronic kidney disease, given recent data from our group which found that CKD is independently associated with worse cardiac mechanics.²²

For survival analyses, we used Cox proportional-hazards regression to evaluate the unadjusted relationship between anemia and outcomes. Models were then adjusted for age, sex, common HFpEF comorbidities, NYHA class, and LV filling pressure (estimated via the E/e' ratio). Covariates were chosen based on clinical relevance and association with anemia status. All analyses were performed using Stata 13 (StataCorp, College Station, TX).

RESULTS

Clinical characteristics for the entire cohort stratified by anemia status, are shown in **Table 1**. The majority of the participants were female and just under half were non-white. Anemia was present in 54% of patients. Common comorbidities included CAD, hypertension, hyperlipidemia, DM, CKD, obesity, and smoking. Overall, anemic patients were more likely to have DM and CKD. Obesity was less common among anemic patients. Participants in the anemia group had a faster resting heart rates and higher pulse pressures. The anemic patients also had higher BNP levels and worse NYHA functional class.

Table 2 summarizes the conventional echocardiographic and tissue Doppler parameters stratified by anemia status. Anemic patients had evidence of higher LV and left atrial (LA) chamber size, stroke volume and cardiac index compared to non-anemic patients. Anemia was not strongly associated with indicators of LV hypertrophy (i.e. LV mass index and relative wall thickness). LV ejection fraction was not significantly different between anemic and non-anemic participants.

In terms of diastolic function, anemia status and lower hemoglobin levels were associated with an elevated E/A ratio, E/e' ratio, and estimated PCWP even after adjustment for potential covariates (**Table 3** and **Figure 1**). However, tissue Doppler e' velocity, measured at either the septal or lateral mitral annulus was not associated with anemia status (**Table 3** and **Figure 1**). These findings remained after adjustment for relevant covariates. Further, no significant association was seen between anemia status and measurements of LV cardiac mechanics (**Figure 1**). This remained true after adjustment for clinical covariates and in the subgroup of participants without CKD (**Supplemental Table S1**).

Anemia was significantly associated with several indices related to RV chamber size, including RV end-diastolic area index, end-systolic area index, basal diameter, and midventricular diameter. Estimated PA systolic pressure and right atrial pressures were significantly higher in patients in the anemic group, even after multivariable adjustment (**Table 3**). Additionally, RV fractional area change, a measure of global RV systolic function was also associated with anemia. This association remained after adjustment for covariates (**Table 3**).

During a median follow-up time of 12.5 months (25th-75th percentile: 4.1–23.3 months), 163 (40%) participants experienced the composite outcome of cardiovascular hospitalization or death. **Figure 2** shows the Kaplan Meier curve for anemic vs. non-anemic groups.

Supplemental Table S2 shows that anemia was associated with the combined outcome in the univariate model and after adjusting for age, sex, diabetes, hypertension, estimated GFR and average E/e' ratio.

DISCUSSION

In our study of a well characterized HFpEF cohort, anemia was strongly associated with preload-dependent markers of diastolic function. However, anemia was not associated with intrinsic diastolic dysfunction (tissue Doppler e' velocity) or with indices of cardiac mechanics (LV strain). We detected an association between anemia and cardiac chamber

volumes and pressures (e.g., PASP) and impaired RV systolic function, measured by RVFAC. Finally, anemia was associated with the composite outcome of cardiovascular hospitalization and death.

Several previous studies have investigated the relationship between anemia and diastolic dysfunction in HFpEF. In an evaluation of 137 patients with diastolic HF, Brucks *et al.* found that hemoglobin was inversely associated with BNP and diastolic dysfunction measured by the E/e' ratio.⁷ Nair *et al.* further examined this association in 822 patients who had a preserved LVEF (>50%); these investigators defined diastolic dysfunction as diastolic-dominant pulmonary vein flow, a marker of increased LA pressure.⁸ Other studies have demonstrated a higher E/e' ratio among anemic patients in hypertensive and diabetic populations.²³

In these studies, diastolic function was evaluated using indices more indicative of plasma volume expansion as opposed to indicators of intrinsic LV diastolic function. Such markers of diastolic dysfunction are directly related to the flow of blood through the cardiopulmonary circuit, and have repeatedly been demonstrated to be highly preload dependent, thus limiting their utility in the assessment of intrinsic myocardial diastolic dysfunction.^{10,24,25} Anemia is a pathologic state frequently characterized by hemodynamic alterations including increased stroke volume, cardiac index, and LV size due to plasma volume expansion. In our study, anemic patients had significantly higher heart rate, cardiac output, and LV volumes as compared to their non-anemic counterparts. These changes may contribute to alterations in LV filling and preload. Therefore, the results of these previous studies may reflect the volume expanded state commonly seen in anemic patients,²⁶ rather than worse intrinsic diastolic function of the myocardium.

For this reason, we compared anemic and non-anemic groups in our HFpEF cohort using e' velocities, a marker of intrinsic myocardial relaxation, and myocardial strain obtained with speckle tracking analysis. In contrast to the previously discussed measures of diastolic dysfunction, tissue Doppler imaging and myocardial strain are intrinsic measures of myocardial mechanics and are less dependent on preload.¹¹ The current study challenges the hypothesis that more severely impaired myocardial diastolic function is an important pathophysiologic component of anemia in HFpEF. Therefore, it becomes important to consider other factors which may contribute to the poorer outcomes seen in anemic HFpEF patients.

Numerous large-scale studies have shown that anemia is associated with worse outcomes in HF;^{3,4,14} but the pathophysiology of anemia in the HF syndrome remains somewhat poorly understood. It has been hypothesized that anemia in HF results mainly from insufficient erythropoietin production from chronic kidney disease⁵; iron deficiency from malnutrition and inflammation-mediated impaired iron retention²⁷; and hemodilution from renal sodium retention and activation of the renin-angiotensin-aldosterone system.²⁶ Once patients become anemic, potential mechanisms for the increased risk of mortality include changes in ventricular loading, neurohormonal activation, and worsening chronic kidney disease.²⁸ The results of our study support that anemia is associated with adverse outcomes in HFpEF. Further, our findings suggest that a pathologic combination of these systemic factors, rather

than a specific derangement in myocardial function is responsible for the worse outcomes in anemic HFpEF patients.

In our HFpEF cohort, we previously found that while lower EDV₂₀, indicative of increased LV diastolic chamber stiffness, was a powerful prognostic indicator in the overall HFpEF population, its predictive value was lost in subgroup of patients with anemia.²⁹ This suggested that factors other than impaired LV compliance drive worse outcomes in the anemic patients. We also found that RV remodeling was a very strong predictor of adverse outcomes in HFpEF. In the present study, anemic HFpEF patients had higher PASP and RAP as well as a thicker RV wall and reduced RVFAC. It may be that worse RV structure/function leads to renal venous congestion and worsening chronic kidney disease, thereby resulting in anemia and further volume expansion. However, due to the cross-sectional nature of our study, we cannot prove a cause-and-effect association.

Renal impairment itself may also contribute to worse outcomes among anemic HFpEF patients. Our results demonstrate significantly worse renal function among patients with anemia. Renal disease can be an important cause of anemia in HF through various mechanisms including hemodilution and impaired erythropoietin production from interstitial peritubular cells. However, based on previous prognostic studies in HFpEF cohorts,^{28,30} it is possible that CKD is not only a cause of anemia in HFpEF, but a potent driver of adverse outcomes.

Our study has some potential limitations. The cohort in this study was enrolled from a single academic center, somewhat limiting generalizability. However, the clinical characteristics of the study participants are relatively similar to those of HFpEF epidemiological studies and observational registries. Second, recruitment occurred exclusively among patients with a prior history of HF hospitalization. Third, hemoglobin was only measured at baseline, so we are not able to examine how echocardiographic indices tracked with hemoglobin over time. Finally, we did not perform analyses to determine the etiology of anemia in the HFpEF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

This work was supported by AHA Scientist Development Grant (#0835488N) and National Institutes of Health (R01 HL107557 and R01 HL127028), to S.J.S.

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Figure 1.

Flow-Dependent (Panels A-B) and Intrinsic (Panels C-D) Indices of Left Ventricular Diastolic Function, Stratified by Sex-Specific Quartiles of Hemoglobin and Comparison of Speckle-Tracking Strain Parameters, Stratified by Anemia Status (Panel E)

Caption: HFpEF = heart failure with preserved ejection fraction, LVCS = Left Ventricular Circumferential Strain, LVLS = left ventricular longitudinal strain, LVRS = Left Ventricular Radial Strain

Figure 2.
Kaplan-Meier Curves for Survival Free of Cardiovascular Hospitalization or Death,
Stratified by Presence or Absence of Anemia

Caption: CV = cardiovascular

Table 1.

Clinical Characteristics, Stratified by Presence or Absence of Anemia

Variable	Anemia		P-value
	No (N=195)	Yes (N=224)	
Age, years	63±13	65±12	0.293
Female	134 (69%)	126 (56%)	0.009
Race			
• White	102 (52%)	114 (51%)	0.773
• Black	71 (36%)	91 (41%)	0.377
• Other	22 (11%)	19 (8%)	0.336
<i>New York Heart Association functional class</i>			0.149
• Class I	30 (15%)	20 (9%)	
• Class II	79 (41%)	86 (39%)	
• Class III	82 (42%)	110 (49%)	
• Class IV	4 (2%)	8 (3%)	
<i>Comorbidities</i>			
• Coronary artery disease	89 (46%)	111 (50%)	0.424
• Hypertension	147 (75%)	176 (79%)	0.439
• Hyperlipidemia	103 (53%)	125 (56%)	0.541
• Diabetes mellitus	54 (28%)	83 (37%)	0.042
• Chronic kidney disease	39 (20%)	100 (45%)	<0.001
• Smoker	79 (41%)	89 (40%)	0.871
• Atrial fibrillation	52 (27%)	58 (26%)	0.857
• Obesity	117 (60%)	105 (47%)	0.007
• Chronic obstructive pulmonary disease	74 (38%)	80 (36%)	0.636
<i>Physical characteristics</i>			
• Heart rate (bpm)	68±13	72±15	0.007
• Systolic blood pressure (mmHg)	125±20	125±20	0.949
• Diastolic blood pressure (mmHg)	72±11	69±12	0.005
• Pulse pressure (mmHg)	53±16	56±18	0.046
• Body mass index (kg/m ²)	33±9	32±10	0.168
<i>Laboratory data</i>			
• Serum sodium (mEq/l)	139±3	138±3	0.001
• Blood urea nitrogen (mg/dl)	20±10	28±18	<0.001
• Serum creatinine (mg/dl)	1.3±1.0	1.8±1.8	<0.001
• Estimated glomerular filtration rate (ml/min/1.73 m ²)	63.4±23.2	53.8±29.7	<0.001
• Fasting glucose (mg/dl)	118±56	120±53	0.623
• Hemoglobin (g/dl)	13.5±1.0	10.6±1.3	<0.001
• B-type natriuretic peptide (pg/ml) *	148 (37–314)	324 (117–718)	<0.001
<i>Medications</i>			
• ACE-inhibitor/angiotensin receptor blocker	114 (58%)	115 (51%)	0.144
• Beta-blocker	122 (63%)	158 (71%)	0.084

Variable	Anemia		P-value
	No (N=195)	Yes (N=224)	
• Calcium channel blocker	66 (34%)	68 (30%)	0.445
• Vasodilators	11 (6%)	42 (19%)	<0.001
• Diuretic	139 (71%)	175 (78%)	0.130
• Statin	97 (50%)	112 (50%)	0.958
• Aspirin	79 (41%)	114 (51%)	0.033

* Median (25th-75th percentile)

Table 2.

Echocardiographic Characteristics, Stratified by Presence or Absence of Anemia

Variable	Anemia		P-value
	No (N=195)	Yes (N=224)	
<i>Left sided heart parameters</i>			
Left ventricular end-diastolic volume index (ml/m ²)	38.0±9.2	43.4±12.7	<0.001
Left ventricular end-systolic volume index (ml/m ²)	15.0±5.4	17.4±7.1	<0.001
Left ventricular mass index (g/m ²)	51.1±18.3	53.2±20.2	0.276
Relative wall thickness	0.51±0.15	0.51±0.15	0.910
Left ventricular ejection fraction (%)	61±6	61±7	0.537
Stroke volume (ml)	46.8±12.6	52.6±16.6	<0.001
Cardiac index (L/min/m ²)	2.7±1.1	3.1±1.0	<0.001
Pulse pressure/stroke volume ratio (mmHg/ml)	1.2±0.5	1.2±0.5	0.45
Left atrial volume index (ml/m ²)	31.3±11.9	36.6±15.8	<0.001
E/A ratio	1.2±0.6	1.5±0.8	0.004
EDV ₂₀ (ml)	78.1±22.6	87.8±29.1	<0.001
E deceleration time (ms)	235±70	225±62	0.136
Isovolumic relaxation time (ms)	89.3±22.6	86.8±21.6	0.26
Lateral e' tissue velocity (cm/s)	9.0±3.9	9.6±3.8	0.162
Septal e' tissue velocity (cm/s)	7.0±2.7	7.1±2.7	0.646
Average E/e' ratio	14.0±7.3	16.1±8.8	0.014
<i>Right sided heart parameters</i>			
Right ventricular end-diastolic area index (cm/m ²)	12.8±3.1	14.8±4.1	<0.001
Right ventricular end-systolic area index (cm/m ²)	7.2±2.3	8.7±3	<0.001
Right ventricular basal diameter (cm)	3.7±0.6	4.1±0.7	<0.001
Right ventricular mid-ventricular diameter (cm)	4.3±0.8	4.7±0.9	0.001
Right ventricular wall thickness (mm)	4.9±1.0	5.2±0.9	0.011
Right ventricular fractional area change (%)	44±7	42±7	<0.001
Estimated pulmonary artery systolic pressure (mmHg)	39.8±14.1	46.8±15.5	<0.001
Estimated right atrial pressure (mmHg)	7.0±3.8	8.3±4.3	0.002

EDV₂₀ = Left ventricular end-diastolic volume at an idealized end-diastolic pressure of 20 mmHg

Table 3.

Association Between Anemia and Echocardiographic Parameters on Linear Regression Analysis

Parameter	Unadjusted		Comorbidity-adjusted*	
	β -coefficient (95% CI)	p-value	β -coefficient	p-value (95% CI)
Lateral e' tissue velocity	0.38 [-0.15, 0.91]	0.162	0.48 [-0.04, 1.01]	0.068
Septal e' tissue velocity	0.09 [-0.28, 0.46]	0.646	0.19 [-0.18, 0.56]	0.308
E/A ratio	0.15 [0.05, 0.26]	0.004	0.14 [0.03, 0.25]	0.011
E/e' ratio	2.82 [0.94, 4.70]	0.003	2.06 [0.12, 4.01]	0.037
Estimated pulmonary capillary wedge pressure	2.88 [0.71, 5.46]	0.009	2.32 [0.54, 4.51]	0.037
Estimated right atrial pressure	0.90 [0.33, 1.48]	0.002	0.79 [0.21, 1.38]	0.008
Estimated pulmonary artery systolic pressure	4.83 [2.45, 7.21]	<0.001	4.32 [1.89, 6.75]	0.001
Right ventricular fractional area change	-1.80 [-2.76, -0.83]	<0.001	-1.22 [-2.20, -0.25]	0.014

* Adjusted for age, sex, systolic blood pressure, body mass index, diabetes, creatinine, coronary artery disease, and chronic obstructive pulmonary disease