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Contributions of anemia to exercise intolerance in heart failure with preserved ejection fraction–An exercise stress echocardiographic study

Ayami Naito [a,b], Masaru Obokata [a,*,1], Kazuki Kagami [a,b], Tomonari Harada [a], Hidemi Sorimachi [a], Naoki Yuasa [a], Yuki Saito [a,c], Toshimitsu Kato [a], Naoki Wada [d], Takeshi Adachi [b], Hideki Ishii [a]

[a] Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
[b] Division of Cardiovascular Medicine, National Defense Medical College, Tokorozawa, Saitama, Japan
[c] Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
[d] Department of Rehabilitation Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

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ABSTRACT

Aims: Anemia is common in patients with heart failure with preserved ejection fraction (HFpEF) and is associated with exercise intolerance. However, there are limited data on how anemia contributes to reduced exercise capacity in patients with HFpEF. We aimed to characterize exercise capacity, cardiovascular and ventilatory reserve, and the oxygen (O_2) pathway in anemic patients with HFpEF.

Methods: A total of 238 patients with HFpEF and 248 dyspneic patients without HF underwent ergometry exercise stress echocardiography with simultaneous expired gas analysis. Patients with HFpEF were classified into two groups based on the presence of anemia (hemoglobin < 13.0 g/dL in men and < 12.0 g/dL in women).

Results: Anemic HFpEF patients (n = 112) had worse nutritional status and renal function, lower iron levels, and greater left ventricular (LV) remodeling and plasma volume expansion than those without anemia (n = 126). Exercise capacity, assessed by peak oxygen consumption, exercise intensity, and exercise duration, was lower in the anemic HFpEF group than in the other groups. Despite a similar cardiac output during exercise, anemic patients with HFpEF demonstrated limitations in arterial O_2 delivery, lower arteriovenous O_2 content difference, and ventilatory inefficiency (higher minute ventilation vs. carbon dioxide production slope) during peak exercise.

Conclusion: Anemic HFpEF patients demonstrated unique pathophysiological features with greater LV remodeling and plasma volume expansion, limitations in arterial O_2 delivery and peripheral O_2 extraction, and ventilatory inefficiency, which may contribute to reduced exercise capacity. Further studies are needed to develop an optimal approach for treating anemia in patients with HFpEF.

1. Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing. This phenotype has become a dominant form of HF [1]. Exercise intolerance is a primary manifestation of HFpEF. Rather than a single impairment of left ventricular (LV) diastolic dysfunction, it was found that multiple cardiac and extra-cardiac reserve limitations contribute to reduced exercise capacity in this syndrome [2,3]. Anemia is common in patients with HFpEF, and is associated with worse clinical outcomes [4–6]. Anemia in HFpEF can be caused by iron deficiency, chronic kidney disease (or cardiorenal syndrome), use of antiplatelet or anticoagulant agents, chronic inflammation, or poor nutritional status [7,8]. Exercise capacity may be reduced in HFpEF patients with anemia than in those without anemia [5,9]. However, little information is available regarding the mechanistic link between anemia and exercise intolerance in patients with HFpEF. Exercise capacity can be defined by the rate of oxygen consumption during peak exercise (peak VO_2) [10], and quantification of oxygen (O_2) transport and utilization pathways

* Corresponding author at: Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan.
E-mail address: obokata.masaru@gunma-u.ac.jp (M. Obokata).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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may allow a better understanding of the contribution of anemia to exercise intolerance in HFpEF [11,12].

Accordingly, we performed exercise stress echocardiography with simultaneous expired gas analysis to characterize the exercise capacity, cardiovascular reserve, O_2 pathway, and ventilatory response of patients with anemia with HFpEF.

2. Methods

2.1. Study population

We retrospectively enrolled consecutive patients who were referred for exercise stress echocardiography for exertional dyspnea at Gunma University Hospital, Maebashi, Japan, between October 2019 and January 2023. The diagnosis of HFpEF was defined using the Heart Failure Association Pre-test assessment, echocardiography and natriuretic peptide, functional testing, and final etiology (HFA-PEFF) algorithm in Steps 1–3. Briefly, the HFA-PEFF score was calculated as the sum of echocardiographic functional (age-specific cut-offs for early diastolic mitral annular velocity [e'], early transmitral flow velocity [E]/e' ratio, tricuspid regurgitation [TR] velocity, and longitudinal strain: maximum 2 points), morphological (rhythm-specific left atrial [LA] volume, relative wall thickness, and sex-specific measure of LV mass: maximum 2 points), and natriuretic peptide (maximum 2 points) domains. Subsequently, two or three points were added based on the E/e' ratio and TR velocity during exercise stress echocardiography. The diagnosis of HFpEF was defined by a combined score from Steps 2 and 3 of $\geq$ 5 points. If patients had elevated LV filling pressures on exercise right heart catheterization (pulmonary capillary wedge pressure [PCWP] of $>$ 15 mmHg at rest and/or $\geq$ 25 mmHg during exercise), they were classified as having HFpEF [13]. We excluded patients with an ejection fraction (EF) $<$ 50%, significant left-sided valvular heart disease (>moderate regurgitation, >mild stenosis), infiltrative, restrictive, or hypertrophic cardiomyopathy, unobtainable hemoglobin, and those younger than 20 years. Patients who did not meet the HFA-PEFF or invasive criteria were categorized as having non-cardiac dyspnea (controls).

Anemia was defined as a hemoglobin level $<$ 13 g/dL and $<$ 12 g/dL in men and women, respectively. Iron deficiency was defined as ferritin levels $<$ 100 g/L or serum ferritin 100–299 g/L with transferrin saturation $<$ 20% [14,15]. The plasma volume was estimated as: (1 − hematocrit) × (a + [b × weight in kg]), where a = 1530 for men and 864 for women and b = 41 for men and 47.9 for women [16]. Nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI) [17,18]. The study was approved by our institutional review board with the waiver of consent (HS2021-197) and was performed in accordance with the Declaration of Helsinki. All the authors have read and agreed to the final version of the manuscript.

2.1.1. Exercise stress echocardiography

Exercise stress echocardiography was performed by experienced sonographers using a commercially available ultrasound system (Vivid 95; GE Healthcare). All participants performed supine cycle ergometry exercise, starting at 20 W for 5 min, with increments of 20 W in 3-min until participant-reported exhaustion occurred, as described by our group [19,20]. Echocardiographic images were recorded at baseline and during all stages of exercise. Simultaneous expired gas analysis was performed at rest and throughout exercise to measure breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), tidal volume (V_T), respiratory rate, and minute ventilation ($V_E = V_T \times$ respiratory rate) (AE-100i; MINATO Medical Science, Osaka, Japan) [21].

EF and systolic mitral annular tissue velocity at the septal annulus (mitral s') were measured to assess the LV systolic function at rest and during exercise. The septal E/e ratio was determined to estimate LV filling pressure. Stroke volume was estimated from the LV outflow dimension and pulse Doppler velocity–time integral, and cardiac output (CO) was determined from the product of heart rate and stroke volume. Systolic tissue velocity at the lateral tricuspid annulus (TV s') and tricuspid annular plane systolic excursion (TAPSE) were measured to determine RV systolic function. Pulmonary artery systolic pressure (PASP) was calculated as 4 × (peak TR velocity)^2 + estimated right atrial pressure (RAP). RAP was estimated from the inferior vena cava diameter and its collapsibility at rest and during exercise.

2.1.2. Noninvasive O_2 pathway analysis

Arterial O_2 delivery was estimated as CO × saturation × hemoglobin × 1.34 × 10 mL/min. The arteriovenous O_2 content difference (AVO_2 diff) was determined using the Fick method (directly measuring $VO_2 \div$ CO in mL/dL) to estimate peripheral O_2 extraction and utilization [22]. The mitochondrial oxidative phosphorylation capacity (V_{max}) was estimated as previously described [11].

2.1.3. Exercise right heart catheterization

A subset of participants underwent clinically indicated right heart catheterization at rest and during supine ergometry exercise as confirmatory testing [23–25]. Exercise right heart catheterization was considered by clinicians when the results of exercise echocardiography were equivocal. RAP, pulmonary artery pressures, and PCWP were measured at end-expiration (mean of $\geq$ 3 beats) using a 7 Fr fluid-filled catheter, as previously described. After baseline data were acquired, hemodynamic assessments were performed during supine ergometry exercise, starting at 20 Watts for 5 min, increasing in 20-Watt increments in 3 min to volitional exhaustion.

2.1.4. Statistical analysis

Data are reported as mean (standard deviation), median (interquartile range [IQR]), or number (%) unless otherwise specified. Between-group differences were compared using one-way analysis of variance, Kruskal–Wallis test, or chi-square test, as appropriate. Tukey's honestly significant difference test or Steel–Dwass test was used for multiple comparisons. Correlations were assessed using Pearson's correlation coefficient. All tests were two-sided, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using JMP version 16.2.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline clinical characteristics

The final study cohort included 486 participants (248 controls and 238 HFpEF). Of the 486 participants, 58 were diagnosed based on exercise right heart catheterization (14 controls and 44 HFpEF), and hemodynamic data were presented in Supplementary Table 1. As expected, PCWP, PA and RA pressures were markedly increased during peak exercise in patients with HFpEF compared to controls. The prevalence of anemia in patients with HFpEF was 47% (n = 112). The mean hemoglobin levels were 13.5 ± 1.5 g/dL in controls (n = 248), 13.7 ± 1.2 g/dL in HFpEF patients without anemia (n = 126), and 10.9 ± 1.2 g/dL in anemic HFpEF patients (n = 112) (Table 1). Among the patients with HFpEF with complete iron data, the prevalence of iron deficiency was 65% (n = 24/37) in patients without anemia and 77% (n = 43/56) in those with anemia. Compared with the control group, patients with HFpEF were older and had a higher prevalence of diabetes mellitus, hypertension, and atrial fibrillation, with higher natriuretic peptide levels (Table 1). Sex, body mass index, and prevalence of chronic obstructive pulmonary disease were similar across the groups while interstitial pneumonia was less common in patients with HFpEF than in controls. The use of anticoagulants and neurohormonal blockers was more common in patients with HFpEF than in controls, whereas diuretics were prescribed more frequently in patients with anemia than in others. Red blood cell count, hemoglobin (per definition), hematocrit, renal function, and GNRI were the lowest, whereas the estimated plasma

Table 1
Baseline characteristics.

	Controls (n = 248)	HFpEF without anemia (n = 126)	HFpEF with anemia (n = 112)	P value
Age (years)	65 ± 13	74 ± 7*	76 ± 8*	<0.0001
Female, n (%)	142 (57%)	76 (60%)	61 (54%)	0.66
Body mass index (kg/m^2)	23.9 ± 5.2	24.4 ± 4.1	23.4 ± 5.1	0.29
Plasma volume (mL)	2274 ± 402	2249 ± 323	2464 ± 437*#	<0.0001
GNRI	106 ± 11	106 ± 10	100 ± 12*#	<0.0001
HFA-PEFF score n (%)				
0–1	34 (97%)	0 (0%)	1 (3%)	
2–4	214 (93%)	8 (3%)	7 (6%)	–
≥5	0 (0%)	118 (53%)	104 (47%)	
Comorbidities				
Diabetes mellitus, n (%)	31 (13%)	34 (27%)*	26 (23%)*	0.001
Hypertension, n (%)	157 (63%)	100 (79%)*	91 (81%)*	<0.0001
Atrial fibrillation, n (%)	39 (16%)	48 (38%)*	36 (32%)*	<0.0001
Coronary artery disease, n (%)	10 (4%)	12 (10%)	25 (22%)*#	<0.0001
COPD, n (%)	20 (8%)	7 (6%)	11 (10%)	0.46
Interstitial pneumonia, n (%)	48 (19%)	15 (12%)*	11 (10%)*	0.02
Medications				
Antiplatelet, n (%)	21 (9%)	16 (13%)	26 (23%)*	0.001
Anticoagulant, n (%)	37 (15%)	47 (37%)*	39 (35%)*	<0.0001
ACEi/ARB, n (%)	62 (25%)	50 (40%)*	54 (48%)*	<0.0001
MRA, n (%)	6 (2%)	16(13%)*	19(17%)*	<0.0001
Beta Blocker, n (%)	28 (11%)	34 (27%)*	42 (38%)*	<0.0001
Diuretics, n (%)	21 (9%)	32 (25%)*	45 (40%)*#	<0.0001
Laboratories				
BNP (pg/mL) (n = 261)	27 (13, 55)	102 (39, 162)*	124 (52, 226)*	<0.0001
NT-proBNP (pg/mL) (n = 287)	83 (47, 131)	446 (131, 858)*	461 (205, 1102)*	<0.0001
eGFR (mL/min/1.73 m^2)	69 ± 19	62 ± 17*	52 ± 24*#	<0.0001
RBC counts (10^6/μL)	4.4 ± 0.5	4.5 ± 0.4	3.7 ± 0.5*#	<0.0001
Hemoglobin (g/dL)	13.5 ± 1.5	13.7 ± 1.2	10.9 ± 1.2*#	<0.0001
Hematocrit (%)	41.2 ± 4.1	41.6 ± 3.1	34.0 ± 3.8*#	<0.0001
MCV (fL)	93 ± 5	93 ± 5	93 ± 8	0.82
MCH (pg)	30 ± 2	31 ± 2	30 ± 3	0.08
MCHC (%)	33 ± 1	33 ± 2	32 ± 1*#	0.0002
Serum iron (μg/dL) (n = 190)	78 (59, 101)	79 (59, 105)	60 (41, 87)#	0.02
Ferritin (ng/mL) (n = 179)	77 (36, 160)	78 (41, 150)	67 (23, 145)	0.50
LV and LA structures				
End-diastolic volume (mL)	73 ± 24	68 ± 28	80 ± 28*#	0.002
LV mass index (g/m^2)	76 ± 18	89 ± 23*	96 ± 24*#	<0.0001
LA volume index (mL/m^2)	24 (19, 30)	35 (27, 46)*	42 (31, 54)*#	<0.0001

Data are mean ± SD, median (interquartile range), or n (%). *p < 0.05 vs. Controls, #p < 0.05 vs. HFpEF without anemia. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and RBC, red blood cell.

blood volume was the highest in anemic patients with HFpEF. The prevalence of moderate to severe malnutrition (GNRI < 92) was significantly higher in patients with anemic HFpEF (26%) than in those without anemia (8%) and controls (8%). While there were no differences in mean corpuscular volume and mean corpuscular hemoglobin across the groups, mean corpuscular hemoglobin concentration and serum iron levels were slightly but significantly lower in anemic patients than in others. Patients with anemia had a larger LV end-diastolic volume, LV mass index, and LA volume index than those without anemia (Fig. 1**A-B**). Plasma volume was correlated with a larger LV end-diastolic volume, LV mass, and LA volume among all participants ($r = 0.41$, $p < 0.0001$; $r = 0.56$, $p < 0.0001$; and $r = 0.32$, $p < 0.0001$, respectively).

3.2. Baseline echocardiography and O_2 pathway

Heart rate, systolic blood pressure, and oxygen saturation at rest were similar between the groups (Table 2). As expected, patients with HFpEF displayed a higher mitral E-wave, E/e' ratio, and PASP, and lower mitral tissue velocities and TAPSE than controls. Stroke volume and CO were similar across the groups. Despite similar oxygen saturation and CO, arterial O_2 content and delivery were reduced in anemic HFpEF patients compared to other groups. The AVO_2 differences did not differ across the groups.

3.3. Echocardiography, O_2 Pathway, and ventilation during peak exercise

Exercise capacity was more impaired in anemic patients with HFpEF than in other groups, with lower exercise intensity, shorter exercise duration, and lower peak VO_2 (Table 2 and Fig. 1**C**). The differences between patients with and without anemia remained significant after adjusting for age and sex (all $p < 0.01$). We also found that the association between anemia and exercise intolerance was independent of the presence or absence of beta blocker use (Supplemental Table 2). A 1 g/dL decrease in hemoglobin levels was associated with a 0.56 mL/kg/min decline in peak VO_2 (peak $VO_2 = 0.56 \times Hb + 5.1$, model $p < 0.0001$). During peak exercise, the heart rate was lower in patients with HFpEF than in controls, but oxygen saturation was similar across groups. Differences in LV systolic and diastolic function and RV systolic function between the HFpEF and control groups further increased during exercise. Compared to HFpEF patients without anemia, anemic HFpEF patients demonstrated higher work-load-corrected E/e' during exercise. Despite a similar CO in HFpEF patients with and without anemia during exercise, the presence of anemia further limited arterial O_2 content and delivery in patients with anemia compared to those without anemia (Fig. 2). The AVO_2 diff and mitochondrial oxidative phosphorylation capacity during peak exercise were the lowest in patients with anemia. Anemic patients with HFpEF demonstrated ventilatory insufficiency compared with the other groups, with the lowest V_T and the highest V_E vs. VCO_2 slope.

Sensitivity analysis excluding controls with normal hemoglobin levels showed that anemic patients with HFpEF have lower arterial O_2 content and delivery as well as reduced VO_2 during peak exercise than anemic controls and patients without anemia (Supplemental Tables 3–4).

4. Discussion

In the present study, we aimed to characterize the impact of anemia on the pathophysiology of HFpEF. The major findings are as follows: (1) anemic patients with HFpEF had worse nutritional status and renal function, with greater LV remodeling and plasma volume expansion than those without anemia; (2) exercise capacity was impaired in anemic patients in comparison to in other groups, and lower hemoglobin levels were associated with lower peak VO_2; (3) anemia was associated with limitations in arterial O_2 delivery at rest and during exercise, and anemia in HFpEF was associated with ventilatory inefficiency during

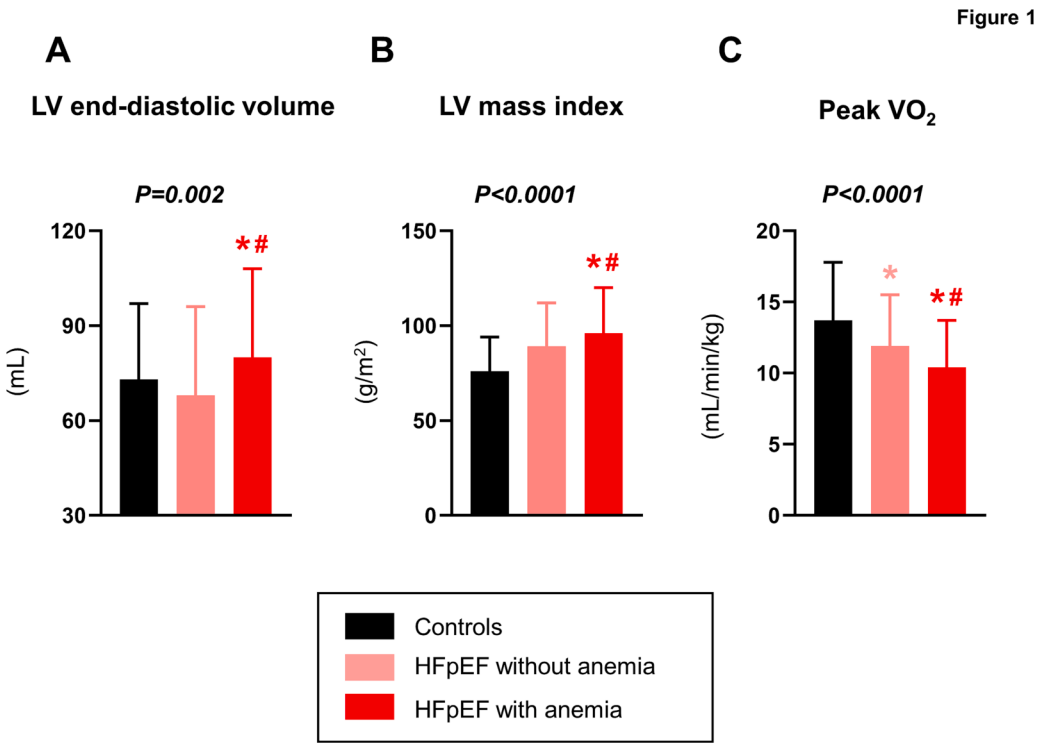

Fig. 1. Left ventricular remodeling and exercise intolerance in anemic patients with HFpEF. (A-B) Anemic patients with heart failure with preserved ejection fraction (HFpEF) demonstrated larger left ventricular (LV) end-diastolic volume and mass index than those without anemia and controls. Compared to controls and patients without anemia, anemic patients had lower peak oxygen consumption (VO_2). *$p < 0.05$ vs. controls; #$p < 0.05$ vs. HFpEF patients without anemia.

peak exercise. These data provide new insights into the pathophysiology of anemia in patients with HFpEF.

Anemia is a common comorbidity among patients with HFpEF. In the current study, the prevalence of anemia in patients with HFpEF (47%) was higher than that previously reported (28–41%) [5,6,26,27]. Anemia in HFpEF may be caused by multiple mechanisms, including iron deficiency, cardiorenal syndrome, antiplatelet or anticoagulant use, malnutrition, or chronic inflammation [27,28]. Consistently, we observed poorer nutritional status, worse renal function, and lower serum iron levels in anemic HFpEF patients than in other groups.

Anemia in patients with HFpEF is associated with reduced exercise capacity and worse clinical outcomes [5,9]. However, the mechanisms underlying the association between anemia and exercise intolerance remain unclear. To fill this gap, we examined the cardiovascular reserve and O_2 pathway in patients with HFpEF and anemia compared with those without anemia and controls without HF. In line with a previous study [5], we observed greater left heart remodeling in patients with anemic HFpEF than in those without. We further demonstrated that anemic patients with HFpEF had plasma volume expansion, and its severity was associated with worse structural remodeling. Anemia may stimulate the sympathetic nervous system or the renin-angiotensin-aldosterone system [29]. These data suggest that the activation of the RAAS or sympathetic nervous and renin-angiotensin-aldosterone systems may promote cardiac remodeling either directly or indirectly through fluid retention [30,31].

Consistent with previous studies [5,9], we confirmed that exercise capacity was the lowest in anemic patients with HFpEF. One of the potential reasons is likely related to iron deficiency, which may cause myocardial energy inefficiency, skeletal muscle weakness, and abnormal mitochondrial function [8]. The present study further extended the mechanisms underlying the association between anemia and exercise intolerance in HFpEF. In the O_2 pathway, hemoglobin plays a key role in carrying O_2 in the convective transport produced by the heart (i.e., CO). We found that LV systolic and diastolic functions and RV systolic function during peak exercise did not differ between HFpEF patients with and without anemia, leading to a similar CO during peak exercise. However, the presence of anemia limits arterial O_2 content and, thus, arterial O_2 delivery to the peripheral circulation. This led to a failure to augment peripheral O_2 extraction and utilization reflected by a low AVO_2 difference during exercise, contributing to reduced exercise capacity (Fig. 3) [22,32].

We further demonstrated ventilatory inefficiency reflected by the highest V_E vs. VCO_2 slope and the lowest V_T in anemic patients with HFpEF. This suggests a potential relationship between anemia and respiratory muscle weakness. It has been reported that exercise capacity and quality of life improve in anemic patients with HFpEF treated with erythropoietin, but cardiac remodeling does not [33]. This observation suggests that the impairment of exercise tolerance in anemia may be predominantly due to non-cardiac factors.

Anemia-related coronary ischemia could be another mechanism. Anemia reduces coronary O_2 delivery, causing myocardial oxygen supply–demand mismatch and subsequent subendocardial ischemia [34]. This myocardial ischemia may contribute to reduced exercise capacity and increased LV filling pressure in relation to exercise intensity as evidenced by workload-corrected E/e' ratio [35]. Since troponin data were not available in this study, further investigation is warranted to determine the association between anemia and myocardial ischemia.

This study has several important clinical implications. In agreement with contemporary American and European HF guidelines [14,15], our results encourage the screening assessment of anemia in patients with HFpEF. This can provide important clues to the causes of exercise intolerance, even when echocardiographic parameters reflecting diastolic function and CO during exercise are similar. The American and European guidelines recommend intravenous iron supplementation for HF patients with iron deficiency [14,15]. In contrast, oral iron therapy and erythropoietic-stimulating agent therapy are not recommended for the treatment of anemia in patients with HF due to inefficiency in repleting iron stores and the potential concern for increased embolic

Table 2
Vital signs and echocardiographic measures at rest and during peak exercise.

	Controls (n = 248)	HFpEF without anemia (n = 126)	HFpEF with anemia (n = 112)	P value
BASELINE				
Vital Signs				
Heart rate (bpm)	74 ± 13	74 ± 14	72 ± 15	0.40
Systolic BP (mmHg)	129 ± 20	128 ± 19	126 ± 20	0.40
Saturation (%)	97 ± 2	97 ± 2	97 ± 2	0.08
Left Heart				
LV ejection fraction (%)	64 ± 7	63 ± 7	63 ± 8	0.33
E-wave (cm/sec)	66 ± 16	76 ± 26*	77 ± 27*	<0.0001
Mitral e' (cm/sec)	7.1 ± 1.9	6.0 ± 1.7*	5.9 ± 1.7*	<0.0001
Mitral s' (cm/sec)	7.9 ± 1.7	6.9 ± 2.0*	6.8 ± 1.9*	<0.0001
E/e' ratio	9.6 ± 2.6	13.6 ± 6.4*	13.8 ± 5.2*	<0.0001
Stroke volume (ml)	55 ± 15	54 ± 17	58 ± 19	0.13
Cardiac output (L/min)	4.0 ± 1.2	3.9 ± 1.1	4.1 ± 1.2	0.45
Right Heart				
TAPSE (cm)	20.0 ± 4.5	18.1 ± 4.6*	18.8 ± 4.9*	0.0006
TV s' (cm/sec)	12.2 ± 2.8	11.9 ± 3.2	12.0 ± 3.1	0.53
PASP (mmHg)	21 ± 6	24 ± 8*	25 ± 9*	<0.0001
Expired gas data				
VO_2 (mL/min/kg)	3.9 ± 0.8	3.7 ± 0.8*	3.7 ± 1.0	0.039
Arterial O_2 content (mL/dL)	17.6 ± 2.0	17.7 ± 1.5	14.2 ± 1.6*#	<0.0001
O_2 delivery (mL/min)	70 ± 22	69 ± 20	57 ± 19*#	<0.0001
AVO_2 difference (mL/dL)	6.4 ± 2.3	6.1 ± 2.0	5.7 ± 2.3	0.06
V max (mL/min)	425 ± 122	398 ± 96	383 ± 116*	0.01
PEAK EXERCISE				
Exercise Tolerance				
Peak watts (W)	66 ± 26	53 ± 22*	43 ± 21*#	<0.0001
Exercise time (min)	10.6 ± 3.6	8.7 ± 3.1*	7.1 ± 3.1*#	<0.0001
Vital Signs				
Heart rate (bpm)	117 ± 21	110 ± 22*	104 ± 23*	<0.0001
Systolic BP (mmHg)	170 ± 31	163 ± 29	159 ± 34*	0.006
Saturation (%)	95 ± 4	94 ± 4	95 ± 4	0.18
Left Heart				
LV ejection fraction (%)	72 ± 7	70 ± 9*	69 ± 9*	0.0005
E-wave (cm/sec)	105 ± 23	119 ± 28*	118 ± 35*	<0.0001
Mitral e' (cm/sec)	10.0 ± 2.5	7.7 ± 2.2*	7.6 ± 1.9*	<0.0001
Mitral s' (cm/sec)	9.2 ± 2.3	7.4 ± 2.0*	7.3 ± 1.9*	<0.0001
E/e' ratio	10.9 ± 2.6	16.5 ± 6.4*	16.2 ± 5.7*	<0.0001
Workload-corrected E/e' (/watts)	0.20 ± 0.13	0.40 ± 0.33*	0.48 ± 0.32*#	<0.0001
Stroke volume (mL)	63 ± 17	59 ± 19	63 ± 20	0.12
Cardiac output (L/min)	7.3 ± 2.0	6.4 ± 2.1*	6.4 ± 2.2*	<0.0001
Del CO	3.3 ± 1.5	2.6 ± 1.6*	2.3 ± 1.5*	<0.0001
Right Heart				
TAPSE (mm)	23.7 ± 5.2	20.1 ± 5.4*	20.7 ± 5.6*	<0.0001
TV s' (cm/sec)	14.8 ± 3.0	13.0 ± 3.4*	12.8 ± 3.6*	<0.0001
PASP (mmHg)	40 ± 11	46 ± 11*	43 ± 13	<0.0001
Ventilation and gas exchange				
VO_2 (mL/min/kg)	13.7 ± 4.1	11.9 ± 3.6*	10.4 ± 3.3*#	<0.0001
Peak work/ VO_2 (W*kg*min/mL)	4.8 ± 1.5	4.6 ± 1.5	4.0 ± 1.4*#	<0.0001
Arterial O_2 content (mL/dL)	17.1 ± 2.0	17.3 ± 1.6	13.9 ± 1.5*#	<0.0001
O_2 delivery (mL/min)	126 ± 40	111 ± 36*	89 ± 33*#	<0.0001
AVO_2 difference (mL/dL)	12.1 ± 4.4	11.8 ± 4.2	10.1 ± 3.8*#	0.0005
V max (mL/min)	1508 ± 545	1310 ± 441*	1070 ± 385*#	<0.0001
Respiratory rate (/min)	32 ± 7	33 ± 8	32 ± 7	0.28
V_E (L/min)	33 ± 11	32 ± 11	29 ± 10*	0.01
V_T (mL)	1053 ± 329	1013 ± 334	899 ± 306*#	0.001
V_E vs. VCO_2 slope	35.3 ± 9.3	37.8 ± 9.6*	40.6 ± 8.6*#	<0.0001

Data are mean ± SD, or median (interquartile range). *p < 0.05 vs. Controls, #p < 0.05 vs. HFpEF without anemia. AVO_2, arterio-venous oxygen content; BP, blood pressure; E/A ratio, the ratio of early diastolic mitral inflow to mitral inflow by active atrial contraction; E/e' ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; O_2, oxygen; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TV s', tricuspid annular systolic velocity; VCO_2, carbon dioxide volume; V_E, minute ventilation; Vmax, mitochondrial oxidative phosphorylation capacity; V_T, tidal volume; TV, tricuspid valve, and other abbreviations as in Table 1.

events. Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors have attracted attention as treatments for renal anemia. Further studies are warranted to investigate the safety and efficiency in patients HFpEF [36].

The present study had several limitations. This retrospective study was conducted at a tertiary referral center, which may have led to selection and referral bias. The sample size was small. Although patients with HFpEF were carefully identified, we cannot exclude the possibility that some patients may have been missed. The control participants were not normal, given that they had shortness of breath, poor exercise capacity, and multiple comorbidities including interstitial lung disease. However, the fact that the control population was more diseased than a truly normal healthy control population only biases our data toward the null. Data on iron deficiency were available for a subset of participants. This precluded a detailed analysis of the causes of anemia. We used resting hemoglobin levels to estimate arterial O_2 content during peak exercise, which might have biased the results. Measurements of LV volumes and EF were performed using an apical 4-chamber view because of the difficulty tracking the LV anterior wall in apical 2-chamber views during exercise.

5. Conclusions

We demonstrated that anemic HFpEF patients were characterized by worse nutritional status, lower renal function, and greater left heart remodeling and plasma volume expansion than those without anemia. Anemia was associated with impaired arterial O_2 delivery, which limited the augmentation of peripheral O_2 extraction and utilization, contributing to poor exercise capacity. Patients with anemia HFpEF also demonstrated ventilatory inefficiency during exercise. These data provide new insights into the pathophysiology of anemia in patients with HFpEF.

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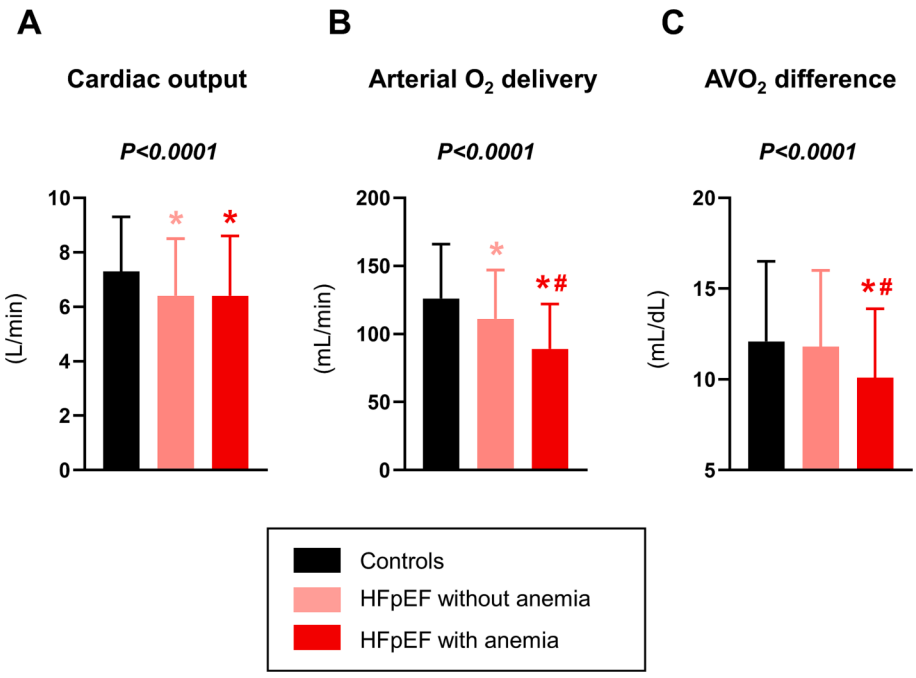

Fig. 2. Parameters reflecting oxygen pathway during peak exercise. (A, B) Despite a similar cardiac output during exercise, arterial oxygen (O_2) delivery was reduced in anemic patients with HFpEF than those without anemia. **(C)** This led to reduction in arteriovenous oxygen content difference (AVO_2 diff) during exercise in the patients with anemic HFpEF. Abbreviations as in Fig. 1.

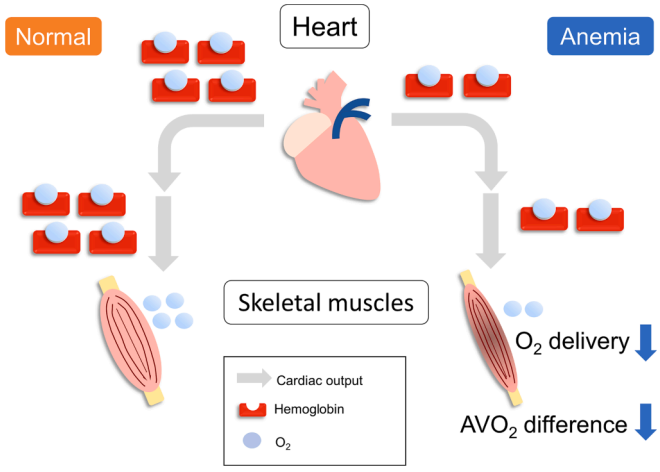

Fig. 3. Schematic illustration. In the O_2 pathway, hemoglobin carries O_2 to the periphery in the convective transport produced by the heart (i.e., cardiac output: CO). Despite a similar CO during peak exercise between HFpEF patients with and without anemia, the presence of anemia limits arterial O_2 content and thus arterial O_2 delivery to the skeletal muscle. Abbreviations as in Figs. 1 and 2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101255.

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