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Cardiovascular effects of hemoglobin response in patients receiving epoetin alfa and oral iron in heart failure with a preserved ejection fraction

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Abstract

Background Previous data from a recently conducted prospective, single blind randomized clinical trial among community dwelling older patients with heart failure with a preserved ejection fraction (HFPEF) and anemia randomized to treatment with epoetin alfa (erythropoiesis-stimulating agents, ESA) *vs.* placebo did not demonstrate significant benefits of therapy regarding left ventricular (LV) structure, functional capacity, or quality of life (QOL). However, several patients randomized to the treatment arm were non-responders with a suboptimal increase in hemoglobin. All patients in the trial also received oral ferrous gluconate, which could have contributed to increases in hemoglobin observed in those receiving placebo. Accordingly, we performed an analysis separating patients into responders *vs*. non-responders in order to determine if measured improvement in anemia would have any effect on clinical endpoints. **Methods** A total of 56 patients (age 77 ± 11 years, 68% female) were recruited who had anemia defined as a hemoglobin of ≤ 12 g/dL (average, 10.4 ± 1 g/dL) with HFPEF defined as having NHANES-CHF (National Health And Nutrition Examination Survey: Congestive Heart Failure) criteria score of ≥ 3 and an ejection fraction of > 40% (average EF = 63% ± 15%). Patients were randomly allocated to receive either ESA and ferrous gluconate or ferrous gluconate only. In this analysis, a responder was defined as a patient with an increase of 1 g/dL in the first 4 weeks of the trial. **Results** Nineteen subjects were classified as responders compared to 33 non-responders. While the average hemoglobin increased significantly at the end of 6 months for responders (1.8 ± 0.3 *vs.* 0.8 ± 0.2 g/dL, P = 0.004), 50% of the subjects assigned to ESA were non-responders. Left ventricular function including ejection fraction (P = 0.32) and end diastolic volume (P = 0.59) was unchanged in responders compared to non-responders. Responders also showed no significant improvements in New York Heart Association (NYHA) class, Six Minute Walk Test (6 MWT) and peak VO_2. Though QOL improved significantly within each group, there was no difference between the two. **Conclusions** A significant hemoglobin response to anemia treatment with ESA and oral iron does not lead to differences in LV remodeling, functional status, or QOL. Additionally, a significant percent of older adults with HFPEF and anemia do not respond to ESA therapy. Given the results of this small trial, it appears as though using objective improvements in anemia as a marker in older adult subjects with HFPEF does not have significant clinical utility.

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1 Introduction

Heart failure with a preserved ejection fraction (HFPEF) is a clinical syndrome with an increasing prevalence associated with advancing age. Among heart failure patients above the age of 70 years, 50% have a preserved ejection fraction (EF).[1] In addition to being elderly, these patients also tend to be women and have multiple other comorbidities including hypertension, chronic kidney disease (CKD), and anemia.[2] Though large randomized trials have illustrated therapeutic modalities with demonstrated clinical benefit in patients with a reduced EF, treatment options for HFPEF remain limited. It had been thought that HF symptoms were produced predominately from abnormalities in diastolic function but meta-analyses of clinical trials have shown that exercise capacity is improved without observed

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improvements in diastolic function.[3] Accordingly, some have advocated a shift of focus towards comorbidities,[4] including anemia, which has been shown to be a contributor to functional impairments in HFPEF.[5]

Epoetin alfa, a kind of erythropoetin-stimulating agents (ESA) has been shown to be highly effective in treating anemia in patients with CKD on hemodialysis[6] and in patients with cancer undergoing chemotherapy,[7] however its role in heart failure is still a subject of debate. Though there have been several small trials demonstrating favorable effects of ESA in heart failure patients with a reduced EF,[8–11] a large scale outcome trial failed to show any benefit.[12] As there remains a paucity of treatment options in patients with HFPEF, an ESA was studied in a recent trial with this specific patient population.

Our study was a single blind randomized clinical trial among community dwelling older patients with HFPEF and anemia randomized to treatment with epoetin alfa *vs*. placebo. The trial did not demonstrate significant benefits of therapy with respect to left ventricular (LV) structure, functional capacity, or quality of life (QOL).[13] However, unresponsiveness to ESA therapy may have confounded these results as several patients randomized to receive ESA had suboptimal increases in hemoglobin. All patients in the trial also received oral iron, which could have contributed to increases in hemoglobin observed in those receiving placebo. Accordingly, we performed an analysis separating patients into responders *vs*. non-responders in order to determine if measured improvement in anemia would have any effect on clinical endpoints including non-invasively measured pressure volume relations, improvements in exercise capacity, and changes in QOL.

2 Methods

2.1 Study design

The current study is a retrospective analysis of a recently completed single-center, prospective randomized single-blind trial. The results of the study have previously been reported.[8] Randomization was stratified based on sex and an estimated glomerular filtration rate of > 40 mL/min^2 or ≤ 40 mL/min^2. Eligible patients were assigned in a 1: 1 ratio to receive epoetin alfa or placebo subcutaneously every week for the course of the study, which lasted 24 weeks. The primary endpoint in the original study was reduction in end-diastolic volume (EDV).

2.2 Study patients

The patients enrolled were primarily older, community-dwelling patients with the diagnosis of both HFPEF and anemia. HFPEF was defined as meeting criteria for NHANES-CHF (National Health And Nutrition Examination Survey: Congestive Heart Failure) with a score of > 3 as well as an EF of > 40%. Anemia was defined as a hemoglobin < 12 g/dL, irrespective of gender. The patients were recruited from outpatient clinics at an urban medical center and after acute hospitalizations for decompensated heart failure. Informed consent was obtained in all patients and an institutional review board at Columbia University Medical Center approved the study, which was registered at clinicaltrials.gov (NCT 00286182).

2.3 Administration of study drug

ESA (Epoetin alpha, Ortho Biotec, Inc.) was administered subcutaneously every week with a pre-specified dosing algorithm. This algorithm was designed to make adjustments based on the rate of rise of hemoglobin during 1-week intervals as well as absolute hemoglobin values. Patients were carefully monitored to avoid rapid increases in hemoglobin or significant increases in blood pressure. Subjects randomized to the treatment arm initially received 7500 U of epoetin alfa while placebo subjects received the same injection volume of normal saline. Hemoglobin was measured weekly on a venous sample obtained in the patient's home via point of care system (Hemocue Inc., Sweden) and the dose of epoetin alfa was adjusted using an algorithm that took into account the current hemoglobin and rate of rise in the previous week.[14] All subjects in the trial were given oral iron (ferrous gluconate 325 orally twice a day).

2.4 Data collection

Three-dimensional transthoracic echocardiography was performed on each patient using a conventional real-time echocardiograph, 3-dimensional acoustic spatial locater, personal computer, and custom software to derive LV chamber EDV (LVEDV), stroke volume, and EF. Functional assessment was assessed by having subjects perform a 6-minute walk test (6MWT) (twice at baseline and at 6 months) and all patients that were capable performed a cardiopulmonary exercise test (CPET), which was performed at baseline and 6 months. Expired gas analysis was performed with a Metabolic Cart (Medical Graphics) with peak volume of oxygen (VO_2) defined as the highest value of VO_2 achieved in the final 30 s of exercise. In order to determine QOL, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was administered to all patients.[9] These questionnaires were administered at baseline and at a 6-month follow up.

2.5 Statistical analysis

Results are expressed as mean ± SE unless otherwise specified. We defined responders as those who had an increase in hemoglobin ≥ 1 g/dL in the first four weeks of the trial regardless of assigned arm and a non-responder was an individual with an increase in hemoglobin < 1 g/dL in the first four weeks which was a definition used in a published set of guidelines for poor ESA responders.[10] The primary endpoints of the original analysis were change in LVEDV as measured by freehand 3D transthoracic echocardiography and secondary endpoints included changes in stroke volume and EF, sub-maximal exercise tolerance measured via 6MWT, maximal exercise capacity measured by CPET with peak VO_2, and QOL as measured by assessing changes in scores from the KCCQ. Data from the above were collected at baseline and 6 months. Changes in these parameters at end of the trial were compared between responders and non-responders by a using an unpaired student *t* test. SAS for Windows (Version 9.1.3, SAS Institute Inc., Cary, North Carolina) was used for analyses.

3 Results

This cohort was composed predominately of older adult women (age 77 ± 11 years, 68% female) with multiple comorbid diseases including hypertension, obesity, coronary artery disease, and CKD.

Using the definition of a responder as a hemoglobin rise of ≥ 1 g/dL in the first 4 weeks of the trial there were 19 responders and 33 non-responders after accounting for dropouts. Of the 24 patients randomized to receive ESA, 50% were defined as non-responders. Subjects stratified by responder status did not differ with regards to demographic or clinical features except non-responders were more often diabetic (76% *vs*. 53%). All patients were hypertensive and baseline EF remained preserved in both cohorts (55% in responders *vs*. 59% in non-responders). The average baseline B-type natriuretic peptide was elevated in both and not significantly different (444 *vs*. 369 pg/mL), Table 1.

Though weekly hemoglobin rose in both the responder group and non-responder group, the average value increased significantly more at the end of 6 months for responders (1.8 ± 0.3 *vs*. 0.8 ± 0.2 g/dL, $P = 0.004$), Figure 1.

At the end of six months, LV function was unchanged in responders with regards to LVEDV (-5.7 ± 16.1 mL *vs*. -3.2 ± 14.8 mL, $P = 0.59$), stroke volume (0.1 ± 9.5 mL *vs*. -0.6 ± 10.2 mL, $P = 0.82$), and ejection fraction (3.4% ± 10.0 *vs*. 0.9% ± 7.4, $P = 0.32$), Table 2.

Table 1. Baseline characteristics of the study population.

	Responders	Non-responders
n	19	33
Age, yrs	78 ± 12	77 ± 9
Number receiving ESA	12	12
Gender (female)	53%	73%
Ethnicity (Hispanic)	53%	67%
Comorbid conditions		
Hypertension	100%	100%
Diabetes	53%	76%
COPD	21%	12%
CAD	63%	61%
Obesity	53%	64%
Medications		
ACE inhibitors	53%	39%
ARBs	16%	42%
Beta blockers	63%	76%
Calcium channel blockers	32%	61%
Aldosterone antagonists	26%	9%
Loop diuretics	68%	79%
Thiazide diuretics	26%	18%
Laboratory assessment		
Hemoglobin, gm/dL	10.1 ± 1.0	10.6 ± 1.0
eGFR, mL/min	49 ± 13	48 ± 20
B-type natriuretic peptide, pg/mL	444 ± 386	369 ± 297
Iron, μg/dL	60 ±57	61 ±37
Ferritin, ng/L	79 ±63	86 ±81
Transferrin saturation, %	19 ±15	20 ±14
Number meeting FAIR-HF criteria	79%	82%

Data are presented as expressed as mean ± SE. FAIR-HF criteria: inclusion criteria for patients in the study "Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency" which were defined as hemoglobin level of 9.5 to 13.5 g/dL, ferritin < 100 μg/L, or ferritin between 100 and 299 μg/L if transferrin saturation < 20%. ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agents;

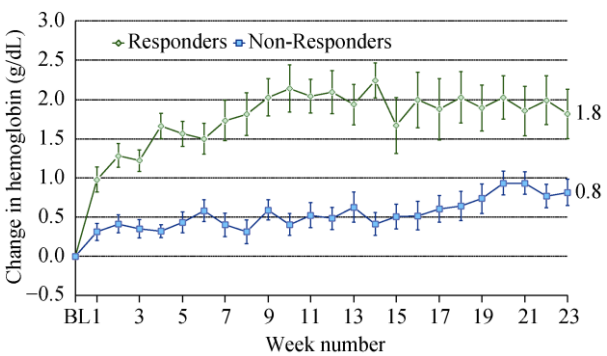

Figure 1. Change in hemoglobin (compared to baseline value) during course of trial for responders and non-responders.

Table 2. Results of measured clinical variables for responders and non-responders.

	Responders				Non-responders				
	n	**Baseline**	***n***	***in 6 months**	***n***	**Baseline**	***n***	***in 6 months**	***P***
Laboratory									
Hemoglobin, g/dL	19	10.1 ±0.23	19	1.8 ±0.3[#]	33	10.6 ±.18	29	0.8 ±0.2[#]	0.004
3D Echo									
SV, mL	18	57.5 ±5.51	18	0.1 ±2.2	33	56.2 ±8.38	29	–0.6 ±1.9	0.82
EF, %	18	54.8 ±2.1	18	3.4 ±2.4	33	59.3 ±1.8	29	0.9 ±1.4	0.32
LVEDV, mL	18	107.8 ±7.2	18	–5.7 ±3.8	33	96.8 ±5.3	29	–3.2 ±2.7	0.59
Functional									
6MWT, m	19	254.4 ±15.2	19	14.9 ±12.1	31	238.6 ±21.1	28	5.7 ±9.9	0.56
VO_2, mL/kg per minute	8	9.2 ±1.1	5	0.5 ±0.7	12	10.3 ±0.7	5	–1.1 ±0.6	0.11
Quality of life									
KCCQ	19	65.5 ±3.7	19	15.3 ±4.2[#]	33	58.2 ±4.9	29	14.3 ±4.4[#]	0.88

*Significant difference as opposed to absolute value; [#]Significant difference from baseline within group. Data are presented as expressed as mean ± SE; *P*-values were calculated using student *t* tests. EF: ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDV: left ventricular end diastolic volume; 6MWT: six-minute walk test; SV: stroke volume.

Responders showed no significant changes in the 6-min walk distance after 6 months (+15 ±9 *vs.* –9 ±2, $P = 0.56$). Measuring peak oxygen consumption required cardiopulmonary exercise testing that only a small subset of the patients could perform due to the frail nature of the study population. Of the 10 patients able to perform the test, there were no significant differences in VO_2 (+0.5 ± 1.6 *vs.* –1.1 ± 1.3, $P = 0.11$).

QOL was assessed within each group by the KCCQ. Though QOL improved significantly within each group there was no difference between the two groups (average score improvement +15 ±4.0 *vs.* +12 ±1.5, $P = 0.88$).

4 Discussion

The primary finding of this analysis is that among older adults with HFPEF, significantly improving anemia via either ESA or oral iron supplementation does not significantly change LVEDV, improve QOL, or increase functional capacity when compared to a group of non-responders to anemia treatment over a six month time period.

Many CHF patients have underlying anemia and it has been demonstrated that a lower hemoglobin is associated with greater LV mass index and increased incidence of adverse outcomes of mortality and hospitalization.[11] Additionally, previous subgroup data from randomized control trials had shown evidence of some benefit in using ESA with respect to exercise tolerance, symptom development, and reduced hospitalizations in heart failure patients with a reduced EF.[12,13]

In the original intention-to-treat analysis of data in this trial, it was found that administering epoetin alfa to older adult patients with HFPEF did not significantly change cardiac structure, improve exercise capacity, or affect QOL when compared to placebo. The placebo arm of the trial, however, also had an unanticipated rise in hemoglobin. Both cohorts received oral iron supplementation, which could have treated underlying iron deficiency anemia and contributed to the increase in hemoglobin observed in the placebo arm. This raised the question of whether or not responders to anemia treatment demonstrated improvements in cardiac function or QOL and if hemoglobin could be used as a marker for cardiovascular outcomes in this population, however the results of this analysis are in accordance with the original analysis in showing no significant clinical or structural changes.

The patients recruited in this trial were primarily older (mean age > 75 years), predominately women (67%), and had multiple comorbidities (including chronic pain and depression). This population mimics what is often seen in community-based studies of heart failure and such patients are characterized by a high percentage of non-responders to ESA therapy. Indeed, analysis of the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) suggests that non-responders as compared to responders are more often women with high body mass index (BMIs), cardiovascular disease, lower ferritins and high CRPs indicative of chronic inflammation.[14] These characteristics are all quite common in the population with HFPEF and this trial further demonstrates the high incidence of ESA non-responders in this population with 50% of the 24 patients randomized to receive ESA failing to have a hemoglobin response of 1 g/dL in the

first 4 weeks of therapy.

Further evidence suggesting a low utility for the use of ESA in heart failure was demonstrated in the Reduction of Events by Darbopoetin Alfa in Heart Failure (RED-HF) trial, which showed no improvement in all cause death or hospitalizations from heart failure but showed a significantly increased rate of thromboembolic adverse events among subjects with heart failure and reduced EF.[12] Additionally, results from TREAT trial demonstrated an elevated risk of stroke when darbopoetin alfa was used to achieve a target hemoglobin of 13 g/dL.[14]

ESA are also costly both in terms of monetary expenses of acquiring the medication as well as the cost of health care personnel time in administering the drug. A retrospective analysis of cancer patients receiving ESA for anemia estimated a weekly cost of $645 which would likely prove to be a financial burden in heart failure patients when compounded with a lack of evidence demonstrating reduced hospitalizations or improved symptom burden.[15]

Frailty is another predominant characteristic of older adult patients with HFPEF. Though there was not a formal measure of frailty included in the beginning of the trial, the baseline 6MWT for all patients demonstrated a gait speed of 0.67 m/s which is well in the range to be considered frail. Though low hemoglobin has been independently associated with frailty risk,[16] the responders in this trial did not demonstrate significant increases in gait speed when compared to non-responders (0.71 m/s *vs*. 0.66 m/s).

An important question with regards to anemia in heart failure is whether or not it merely serves as a surrogate marker for a poor prognosis or is itself a clinically important variable to modify. A large trial investigating the use of intravenous iron for iron deficiency with or without anemia in patients that also had heart failure with a reduced EF showed an improvement of symptoms, functional capacity, and QOL.[17] This potentially suggests that iron may be possible target for therapy regardless of hemoglobin, perhaps due to the fact that iron is critical for oxidative metabolism. Iron deficiency can lead to decreased exercise capacity secondary to diminished oxygen transport and decreased oxidative capacity of muscle, which can reduce VO_2.[18] And even in the absence of anemia, iron deficiency can lead to increased energy expenditure and fractional utilization of peak oxygen consumption,[19] and supplementation in iron deficient patients without anemia can correct impaired adaptation in endurance capacity.[20] Given that iron has few adverse effects compared to ESA, which have been shown to have an increased risk of thrombosis,[14] supplementing with iron appears to be a safer and still effective means of treating anemia in heart failure patients.

There were several limitations to this study. The sample size was small which would lead to a higher probability of type II error and the duration of the trial was relatively short at 6 months, which makes the results more difficult to translate into clinical practice than if a larger population were studied. A large percentage of patients were also unable to complete cardiopulmonary exercise testing thereby limiting power to detect differences. We did demonstrate a > 1 mL/kg per minute difference in peak VO_2 as would be predicted from the Fick equation with correction of anemia. However, this difference did not translate into a clinically meaningful effect though there was no significant hemoglobin difference between responders and non responders in this small subset of 10 patients (P = 0.45). Additionally, the increase in hemoglobin by responders was 1.8 g/dL but because of an increase in hemoglobin of non-responders the difference in hemoglobin throughout the trial was about 1 g/dL and potentially insufficient to effect clinically evident changes, though in the original paper the change in hemoglobin was sufficient enough to provide a statistically significant difference in peak VO_2 in those receiving ESA compared to placebo (+1.0 ± 0.5 *vs*. -1.2 ± 0.6 mL/kg per minute) based on the Fick equation. However, a trial investigating a hematocrit goal of 42% *vs*. 30% via epoetin administration in patients with congestive heart failure or ischemic heart disease undergoing dialysis showed a trend towards increased mortality and myocardial infarctions,[21] so there potentially could be some risk in using higher targets in this population.

As treatments for HFPEF remain limited at this point, a retrospective analysis was employed to assess improved outcomes purely based on a significant increase in hemoglobin. However, this analysis demonstrates that there is no improvement in ventricular function, QOL, or functional capacity when anemia is corrected in this patient population of older adults with HFPEF. Additionally, half of the patients receiving ESA were non-responders, which adding to the growing evidence for a lack of utility in using these agents in heart failure patients. Given the results of this small trial, treating anemia conservatively with oral therapy appears to be the more indicated course of action and hemoglobin itself does not seem to be directly a clinically important variable to modify.

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