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The Effect of Correction of Mild Anemia in Severe, Resistant Congestive Heart Failure Using Subcutaneous Erythropoietin and Intravenous Iron: A Randomized Controlled Study

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OBJECTIVES This is a randomized controlled study of anemic patients with severe congestive heart failure (CHF) to assess the effect of correction of the anemia on cardiac and renal function and hospitalization.

BACKGROUND Although mild anemia occurs frequently in patients with CHF, there is very little information about the effect of correcting it with erythropoietin (EPO) and intravenous iron.

METHODS Thirty-two patients with moderate to severe CHF (New York Heart Association [NYHA] class III to IV) who had a left ventricular ejection fraction (LVEF) of ≤40% despite maximally tolerated doses of CHF medications and whose hemoglobin (Hb) levels were persistently between 10.0 and 11.5 g% were randomized into two groups. Group A (16 patients) received subcutaneous EPO and IV iron to increase the level of Hb to at least 12.5 g%. In Group B (16 patients) the anemia was not treated. The doses of all the CHF medications were maintained at the maximally tolerated levels except for oral and intravenous (IV) furosemide, whose doses were increased or decreased according to the clinical need.

RESULTS Over a mean of 8.2 ± 2.6 months, four patients in Group B and none in Group A died of CHF-related illnesses. The mean NYHA class improved by 42.1% in A and worsened by 11.4% in B. The LVEF increased by 5.5% in A and decreased by 5.4% in B. The serum creatinine did not change in A and increased by 28.6% in B. The need for oral and IV furosemide decreased by 51.3% and 91.3% respectively in A and increased by 28.5% and 28.0% respectively in B. The number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% in A and increased by 57.6% in B.

CONCLUSIONS When anemia in CHF is treated with EPO and IV iron, a marked improvement in cardiac and patient function is seen, associated with less hospitalization and renal impairment and less need for diuretics. (J Am Coll Cardiol 2001;37:1775–80) © 2001 by the American College of Cardiology

Anemia of any cause is known to be capable of causing congestive heart failure (CHF) (1). In patients hospitalized with CHF the mean hemoglobin (Hb) is about 12 g% (2,3), which is considered the lower limit of normal in adults (4). Thus, anemia appears to be common in CHF. Recently, in 142 patients in our special CHF outpatient clinic, we found that as the CHF worsened, the mean Hb concentration decreased, from 13.7 g% in mild CHF (New York Heart Association [NYHA] class I) to 10.9 g% in severe CHF (NYHA 4), and the prevalence of a Hb <12 g% increased from 9.1% in patients with NYHA 1 to 79.1% in those with NYHA 4 (5). The Framingham Study has shown that anemia is an independent risk factor for the production of CHF (6). Despite this association of CHF with anemia, its role is not mentioned in the 1999 U.S. guidelines for the diagnosis and treatment of CHF (7), and many studies consider anemia to be only a rare contributing cause of hospitalization for CHF (8,9).

Recently, we performed a study in which the anemia of severe CHF that was resistant to maximally tolerated doses of standard medications was corrected with a combination of subcutaneous (sc) erythropoietin (EPO) and intravenous iron (IV Fe) (5). We have found this combination to be safe, effective and additive in the correction of the anemia of chronic renal failure (CRF) in both the predialysis period (10) and the dialysis period (11). The IV Fe appears to be more effective than oral iron (12,13). In our previous study of CHF patients (5), the treatment resulted in improved cardiac function, improved NYHA functional class, increased glomerular filtration rate, a marked reduction in the need for diuretics and a 92% reduction in the hospitalization rate compared with a similar time period before the intervention.

In the light of these positive results, a prospective randomized study was undertaken to determine the effects of the correction of anemia in severe symptomatic CHF resistant to maximally tolerated CHF medication.

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Abbreviations and Acronyms

CABG	=	coronary artery bypass graft
CHF	=	congestive heart failure
CRF	=	chronic renal failure
EPO	=	erythropoietin
%Fe Sat	=	percent iron saturation
GFR	=	glomerular filtration rate
Hb	=	hemoglobin
Hct	=	hematocrit
IU	=	international units
IV	=	intravenous
LVEF	=	left ventricular ejection fraction
NYHA	=	New York Heart Association
PA	=	pulmonary artery
sc	=	subcutaneous
SOLVD	=	Studies Of Left Ventricular Dysfunction

MATERIALS AND METHODS

Patients. Thirty-two patients with CHF were studied. Before the study, the patients were treated for least six months in the CHF clinic with maximally tolerated doses of angiotensin-converting enzyme inhibitors, the beta-blockers bisoprolol or carvedilol, aldospirone, long-acting nitrates, digoxin and oral and intravenous (IV) furosemide. In some patients these agents could not be given because of contraindications and in others they had to be stopped because of side effects. Despite this maximal treatment the patients still had severe CHF (NYHA class ≥III), with fatigue and/or shortness of breath on even mild exertion or at rest. All had levels of Hb in the range of 10 to 11.5 g% on at least three consecutive visits over a three-week period. All had a LVEF of <40%. Secondary causes of anemia including hypothyroidism, and folic acid and vitamin B_{12} deficiency were ruled out and there was no clinical evidence of gastrointestinal bleeding.

The patients were randomized consecutively into two groups: Group A, 16 patients, was treated with sc EPO and IV Fe to achieve a target Hb of at least 12.5 g%. Group B, 16 patients, did not receive the EPO and IV Fe.

Treatment protocol for correction of anemia. All patients in Group A received the combination of sc EPO and IV Fe. The EPO was given once a week at a starting dose of 4,000 international units (IU) per week sc and the dose was increased to two or three times a week or decreased to once every few weeks as necessary to achieve and maintain a target Hb of 12.5 g%. The IV Fe (Venofer-Vifor International, Switzerland), a ferric sucrose product, was given in a dose of 200 mg IV in 150 ml saline over 60 min every two weeks until the serum ferritin reached 400 μg/l or the %Fe saturation (%Fe Sat is serum iron/total iron binding capacity × 100) reached 40% or the Hb reached 12.5g%. The IV Fe was then given at longer intervals as needed to maintain these levels.

Investigations. Visits to the clinic were at two- to three-week intervals depending on the patient's status. This was the same frequency of visits to the CHF clinic as before the intervention study. A complete blood count, serum creatinine, potassium and ferritin and %Fe Sat were performed on every visit. The blood pressure was measured by an electronic device on every visit. The LVEF was measured initially and at four- to six-month intervals by MUGA radioisotope ventriculography. This technique measures the amount of blood in the ventricle at the end of systole and at the end of diastole, thus giving a very accurate assessment of the ejection fraction. It has been shown to be an accurate and reproducible method of measuring the ejection fraction (14).

Hospital records were reviewed at the end of the intervention period to compare the number of days hospitalized during the study with the number of days hospitalized during a similar period when the patients were treated in the CHF clinic before the initial randomization and entry into the study. Clinic records were reviewed to evaluate the types and doses of CHF medications used before and during the study.

The mean follow-up for patients was 8.2 ± 2.7 months (range 5 to 12 months). The study was done with the approval of the local ethics committee.

Statistical analysis. An analysis of variance with repeated measures (over time) was performed to compare the two study groups (control vs. treatment) and to assess time trend and the interactions between the two factors. A separate analysis was carried out for each of the outcome parameters. The Mann-Whitney test was used to compare the change in NYHA class between two groups. All the statistical analysis was performed by SPSS (version 10).

RESULTS

The mean age in Group A (EPO and Fe) was 75.3 ± 14.6 years and in group B was 72.2 ± 9.9 years. There were 11 and 12 men in Groups A and B, respectively. Before the study the two groups were similar in cardiac function, comorbidities, laboratory investigations and medications (Tables 1, 2 and 3), except for IV furosemide (Table 3), which was higher in the treatment group. The mean NYHA class of Group A before the study was 3.8 ± 0.4 and was 3.5 ± 0.5 in Group B. The contributing factors to CHF in Groups A and B, respectively, are seen in Table 1 and were similar. The main contributing factors to CHF were considered to be ischemic heart disease (IHD) in 11 and 10 patients respectively, hypertension in two and two patients, valvular heart disease in two and two patients, and idiopathic cardiomyopathy in one and two patients, respectively.

A significant change after treatment was observed in the two groups in the following parameters: IV furosemide, days in hospital, Hb, ejection fraction, serum creatinine and serum ferritin. In addition, the interaction between the study group and time trend was significant in all measurements except for blood pressure and %Fe Sat. This interaction indicates that the change over time was significantly different in the two groups. For example, before treatment

Table 1. Medical Conditions and Contributing Factors to Congestive Heart Failure in the 16 Patients Treated for the Anemia and in the 16 Controls

	Treatment		Control	
Medical conditions	**No.**	**%**	**No.**	**%**
Ischemic heart disease	12	75	12	75
CABG	6	37.5	7	43.8
Diabetes	6	37.5	6	37.5
Hyperlipidemia	10	62.5	8	50
Hypertension	5	31.3	7	43.8
Chronic renal failure	8	50	8	50
Mitral regurgitation	4	25	3	18.8
Atrial fibrillation	2	12.5	3	18.8
Rheumatic heart disease	1	6.3	1	6.3
Idiopathic cardiomyopathy	1	6.3	2	12.5
Smoker	6	37.5	5	31.3
Peripheral vascular disease	0	0	1	6.3

CABG = coronary artery bypass graft.

the level of oral furosemide was higher in the control group (136.2 mg/day) compared with the treatment group (132.2 mg/day). After treatment, while the dose of oral furosemide of the treated patients was reduced to 64.4 mg/day the dose of the nontreated patients was increased to 175 mg/day.

The same results of improvement in the treated group and deterioration in the control group are expressed in the following parameters: IV furosemide, days in hospital, Hb, ejection fraction and serum creatinine.

The NYHA class was 3.8 ± 0.4 before treatment and 2.2 ± 0.7 after treatment in Group A and 3.5 ± 0.7 before treatment and 3.9 ± 0.3 after treatment in Group B. The improvement in NYHA class was significantly higher ($p < 0.0001$) in the treatment group compared with the control group (Table 4).

There were no deaths in Group A and four deaths in Group B.

Case 1: A 71-year-old woman with severe mitral insufficiency and severe pulmonary hypertension (a pulmonary artery [PA] pressure of 75 mm Hg) had persistent NYHA 4 CHF and died during mitral valve surgery seven months after onset of the study. She was hospitalized for 21 days in the seven months before randomization and for 28 days during the seven months after randomization.

Case 2: A 62-year-old man with a longstanding history of hypertension complicated by IHD, coronary artery bypass graft (CABG) and atrial fibrillation had persistent NYHA 4 CHF and a PA pressure of 35 mm Hg, and died from pneumonia and septic shock eight months after onset of the study. He was hospitalized for seven days in the eight months before randomization and for 21 days during the eight months after randomization.

Case 3: A 74-year-old man with IHD, CABG, chronic obstructive pulmonary disease, a history of heavy smoking and diabetes had persistent NYHA 4 CHF and a PA pressure of 28 mm Hg, and died of pulmonary edema and cardiogenic shock nine months after onset of the study. He was hospitalized for 14 days in the nine months before randomization and for 41 days during the nine months after randomization.

Case 4: A 74-year-old man with a history of IHD, CABG, diabetes, dyslipidemia, hypertension and atrial fibrillation, had persistent NYHA 4 CHF and a PA pressure of 30 mm Hg, and died of pneumonia and septic shock six months after onset of the study. He was hospitalized for five days in the six months before randomization and for 16 days during the nine months after randomization.

DISCUSSION

Main findings. The main finding of the present study is that the correction of even mild anemia in patients with symptoms of very severe CHF despite being on maximally tolerated drug therapy resulted in a significant improvement in their cardiac function and NYHA functional class. There was also a large reduction in the number of days of hospitalization compared with a similar period before the intervention. Furthermore, all this was achieved despite a marked reduction in the dose of oral and IV furosemide.

In the group in whom the anemia was not treated, four

Table 2. Number and Percentage of Cases Taking Each Medication and the Doses used in mg/day in the Treatment and Control Groups During the Study

	Treatment			Control		
Medication	**No.**	**%**	**Dose, mg/d**	**No.**	**%**	**Dose, mg/d**
Digoxin	15	93.8	0.13 ± 0.1	14	87.5	0.12 ± 0.1
Nitrates	14	87.5	55.0 ± 22.5	12	75.0	50.0 ± 10.4
Aldospirone	15	93.8	28.3 ± 5.3	16	100	38.3 ± 35.8
Beta-blockers	13	81.3		11	68.8	
Carvedilol	10	62.5	33.9 ± 12.2	9	56.3	28.8 ± 5.1
Bisoprolol	3	18.8	10.0 ± 0	2	12.5	10.0 ± 0
ACE inhibitors	14	87.5		14	87.5	
Captopril	9	56.3	76.7 ± 46.7	10	62.5	83.75 ± 45.9
Enalapril	5	31.3	27.5 ± 8.9	4	25.0	25.5 ± 11.0
Angiotensin II receptor blockers	1	6.6		2	12.5	
Losartan	1	6.6	50.0 ± 0	2	12.5	50.0 ± 0

The dose of these medications was not changed during the study.
ACE = angiotensin-converting enzyme.

Table 3. The Effect of Correction of Anemia by Intravenous Iron and Erythropoietin Therapy on Various Parameters in 16 Patients in the Treatment (A) and 16 in the Control (B) Group

		Control		Treatment		p Value			
Parameter	Time	Mean	Std Dev.	Mean	Std Dev.	*t* tests for BL	Time Effect	Group Effect	Interaction Time × Group
IV furosemide mg/wk	Before	49.3	27.6	76.7	36.8	0.03	0.001	NS	<0.0001
	After	63.1	37.1	6.6	28.2				
Oral furosemide mg/d	Before	136.2	86.1	132.2	38.9	NS	NS	0.023	<0.0001
	After	175.0	113.0	64.4	39.1				
Days in hospital	Before	9.9	4.8	13.8	7.2	NS	0.039	0.03	<0.0001
	After	15.6	9.8	2.9	6.6				
Hb, g%	Before	10.9	0.8	10.3	1.2	NS	<0.0001	0.0004	<0.0001
	After	10.8	0.8	12.9	1.1				
Ejection fraction	Before	28.4	7.6	30.8	12.6	NS	NS	<0.013	<0.0001
	After	23.0	6.9	36.3	11.9				
Serum creatine mg%	Before	1.4	0.9	1.7	0.8	NS	0.022	NS	0.006
	After	1.8	0.5	1.7	0.7				
%Fe sat	Before	22.5	16.7	25.1	12.9	NS	NS	0.021	NS
	After	21.8	16.5	31.3	8.6				
Serum ferritin, μg/l	Before	264.0	162.5	221.4	165.1	NS	0.003	NS	0.017
	After	283.2	157.1	366.8	175.4				
Diastolic BP, mm Hg	Before	71.9	9.9	72.8	10.7	NS	NS	NS	NS
	After	72.2	10.8	73.1	12.2				
Systolic BP, mm Hg	Before	127.8	17.8	126.4	18.2	NS	NS	NS	NS
	After	127.0	21.4	127.9	20.2				

p values are given for analysis of variance with repeated measures and for independent *t* tests for comparison of baseline levels between the two groups.
BP = blood pressure; Fe Sat = iron saturation; Hb = hemoglobin; IV = intravenous; NS = not stated; Std Dev. = standard deviation.

patients died during the study. In all four cases the CHF was unremitting and contributed to the deaths. In addition, for the group as a whole, the LVEF, the NYHA class and the renal function worsened. There was also need for increased oral and IV furosemide as well as increased hospitalization.

Study limitations. The major limitations of this study are the smallness of the sample size and the fact that randomization and treatment were not done in a blinded fashion. Nevertheless, the two groups were almost identical in cardiac, renal and anemia status; in the types and doses of medication they were taking before and during the intervention and in the number of hospitalization days before the intervention. Although the results of this study, like those of our previous uncontrolled study (5), suggest that anemia may play an important role in the mortality and morbidity of CHF, a far larger double-blinded controlled study should be carried out to verify our findings.

Anemia as a risk factor for hospitalization and death in CHF. Our results are consistent with a recent analysis of 91,316 patients hospitalized with CHF (15). Anemia was found to be a stronger predictor of the need for early rehospitalization than was hypertension, IHD or the presence of a previous CABG. A recent analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) (16) showed that the level of hematocrit (Hct) was an independent risk factor for mortality. During a mean follow-up of 33 months the mortality was 22%, 27% and 34% for those with a Hct of >40, 35 to 40 and <35 respectively. The striking response of our patients to correction of mild anemia suggests that the failing heart may be very susceptible to anemia. It has, in fact, been found in both animal (17) and human studies (17–19) that the damaged heart is more vulnerable to anemia and/or ischemia than is the normal heart. These stimuli may result in a more marked reduction in cardiac function than occurs in the normal heart and may explain why, in our study, the patients were so resistant to high doses of CHF medications and responded so well when the anemia was treated.

Our findings about the importance of anemia in CHF are not surprising when one considers that, in dialysis patients, anemia has been shown to be associated with an increased prevalence and incidence of CHF (20) and that correction of anemia in these patients is associated with improved cardiac function (21,22), less mortality (23,24) and fewer hospitalizations (23,25).

Effect of improvement of CHF on CRF. Congestive heart failure can cause progressive renal failure (26,27). Renal ischemia is found very early on in patients with cardiac dysfunction (28,29), and chronic ischemia may cause progression of renal failure (30). Indeed, the development of CHF in patients with essential hypertension has been found

Table 4. Changes from Baseline to Final New York Heart Association (NYHA) Class

Initial minus final NYHA class	−1	0	1	2	3	Total
Control	7	8	1	0	0	16
Treatment	0	1	7	7	1	16

The improvement in NYHA class was statistically higher ($p < 0.0001$) in the treatment group compared with control.

to be one of the most powerful predictors of the eventual development of end-stage renal disease (31). Patients who develop CHF after a myocardial infarction experience a fall in the glomerular filtration rate (GFR) of about 1 ml/min/month if the CHF is not treated (32).

In another recent analysis of the SOLVD study, treating the CHF with both angiotensin-converting enzyme inhibitors and beta-blockers resulted in better preservation of the renal function than did angiotensin-converting enzyme inhibitors alone (26), suggesting that the more aggressive the treatment of the CHF, the better the renal function is preserved. In the present study, as in our previous one (5), we found that the deterioration of GFR was prevented with successful treatment of the CHF, including correction of the anemia, whereas the renal function worsened when the CHF remained severe. All these findings suggest that early detection and treatment of CHF and systolic and/or diastolic dysfunction from whatever cause could prevent the deterioration not only of the cardiac function but of the renal function as well. This finding has very broad implications in the prevention of CRF, because most patients with advanced CRF have either clinical evidence of CHF or at least some degree of systolic dysfunction (33). Systolic and/or diastolic dysfunction can occur early on in many conditions, such as essential hypertension (34), renal disease of any cause (35,36) or IHD, especially after a myocardial infarction (37). The early detection and adequate treatment of this cardiac dysfunction, including correction of the anemia, could prevent this cardiorenal insufficiency. To detect cardiac dysfunction early on, one would need at least an echocardiogram and MUGA radionucleotide ventriculography. These tests should probably be done not only in patients with signs and symptoms of CHF but in all patients where CHF or systolic and/or diastolic dysfunction are suspected, such as those with a history of heart disease or suggestive changes of ischemia or hypertrophy on the electrocardiogram, or in patients with hypertension or renal disease.

Other positive cardiovascular effects of EPO treatment. Another possible explanation for the improved cardiac function in this study may be the direct effect that EPO itself has on improving cardiac muscle function (38,39) and myocardial cell growth (39,40) unrelated to its effect of the anemia. In fact EPO may be crucial in the formation of the heart muscle in utero (40). It may also improve endothelial function (41). Erythropoietin may be superior to blood transfusions not only because adverse reactions to EPO are infrequent, but also because EPO causes the production and release of young cells from the bone marrow into the blood. These cells have an oxygen dissociation curve that is shifted to the right of the normal curve, causing the release of much greater amounts of oxygen into the tissues than occurs normally (42). On the other hand, transfused blood consists of older red cells with an oxygen dissociation curve that is shifted to the left, causing the release of much less oxygen into the tissues than occurs normally (42).

The combination of IV Fe and EPO. The use of IV Fe along with EPO has been found to have an additive effect, increasing the Hb even more than would occur with EPO alone while at the same time allowing the dose of EPO to be reduced (10–13). The lower dose of EPO will be cost-saving and also reduce the chances of hypertension developing (43). We used iron sucrose (Venofer) as our IV Fe medication because, in our experience, it is extremely well tolerated (10,11) and has not been associated with any serious side effects in more than 1,200 patients over six years.

Implications of treatment of anemia in CHF. The correction of anemia is not a substitute for the well-documented effective therapy of CHF but seems to be an important, if not vital, addition to the therapy. It is surprising, therefore, that judging from the literature on CHF, such an obvious treatment for improving CHF is so rarely considered. We believe that correction of the anemia will have an important role to play in the amelioration of cardiorenal insufficiency, and that this improvement will have significant economic implications as well.

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