Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 35, No. 7, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00613-6

The Use of Subcutaneous Erythropoietin and Intravenous Iron for the Treatment of the Anemia of Severe, Resistant Congestive Heart Failure Improves Cardiac and Renal Function and Functional Cardiac Class, and Markedly Reduces Hospitalizations

Donald S. Silverberg, MD, Dov Wexler, MD, Miriam Blum, MD, Gad Keren, MD, David Sheps, MD, Eyal Leibovitch, MD, David Brosh, MD, Shlomo Laniado, MD, Doron Schwartz, MD, Tatyana Yachnin, MD, Itzhak Shapira, MD, Dov Gavish, MD, Ron Baruch, MD, Bella Koifman, MD, Carl Kaplan, MD, Shoshana Steinbruch, RN, Adrian Iaina, MD

Tel Aviv, Israel

OBJECTIVES This study evaluated the prevalence and severity of anemia in patients with congestive heart failure (CHF) and the effect of its correction on cardiac and renal function and hospitalization.

BACKGROUND The prevalence and significance of mild anemia in patients with CHF is uncertain, and the role of erythropoietin with intravenous iron supplementation in treating this anemia is unknown.

METHODS In a retrospective study, the records of the 142 patients in our CHF clinic were reviewed to find the prevalence and severity of anemia (hemoglobin [Hb] <12 g). In an intervention study, 26 of these patients, despite maximally tolerated therapy of CHF for at least six months, still had had severe CHF and were also anemic. They were treated with subcutaneous erythropoietin and intravenous iron sufficient to increase the Hb to 12 g%. The doses of the CHF medications, except for diuretics, were not changed during the intervention period.

RESULTS The prevalence of anemia in the 142 patients increased with the severity of CHF, reaching 79.1% in those with New York Heart Association class IV. In the intervention study, the anemia of the 26 patients was treated for a mean of 7.2 ± 5.5 months. The mean Hb level and mean left ventricular ejection fraction increased significantly. The mean number of hospitalizations fell by 91.9% compared with a similar period before the study. The New York Heart Association class fell significantly, as did the doses of oral and intravenous furosemide. The rate of fall of the glomerular filtration rate slowed with the treatment.

CONCLUSIONS Anemia is very common in CHF and its successful treatment is associated with a significant improvement in cardiac function, functional class, renal function and in a marked fall in the need for diuretics and hospitalization. (J Am Coll Cardiol 2000;35:1737–44) © 2000 by the American College of Cardiology

The mean hemoglobin (Hb) in patients with congestive heart failure (CHF) is about 12 g Hb per 100 ml blood (g%) (1–3), which is considered to be the lower limit of normal in adult men and postmenopausal women (4). Thus, many patients with CHF are anemic, and this anemia has been shown to worsen as the severity of the CHF progresses (5,6). Severe anemia of any cause can produce CHF, and treatment of the anemia can improve it (7). In patients with chronic renal failure (CRF) who are anemic, treatment of the anemia with erythropoietin (EPO) has improved many of the abnormalities seen in CHF, reducing left ventricular hypertrophy (LVH) (8–10), preventing left ventricular dilation (11) and, in those with reduced cardiac function, increasing the left ventricular ejection fraction (LVEF) (8–10), the stroke volume (12) and the cardiac output (12).

From the Department of Nephrology and Cardiology, and Congestive Heart Failure Program, Tel Aviv Medical Center, Tel Aviv, Israel.

Manuscript received July 9, 1999; revised manuscript received December 10, 1999, accepted February 3, 2000.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CHF	= congestive heart failure
COPD	= chronic obstructive pulmonary disease
CRF	= chronic renal failure
CVA	= cerebrovascular accident
EPO	= erythropoietin
Fe	= iron
g%	= grams Hb per 100 ml blood
GFR	= glomerular filtration rate
Hb	= hemoglobin
Hct	= hematocrit
IV	= intravenous
LVEF	= left ventricular ejection fraction
LVH	= left ventricular hypertrophy
NYHA	= New York Heart Association
%Fe Sat	= percent iron saturation
SC	= subcutaneous
TNF	= tumor necrosis factor

In view of the high prevalence of anemia in CHF, it is surprising that we could find no studies in which EPO was used in the treatment of the anemia of CHF, and the use of EPO is not included in U.S. Public Health Service guidelines of treatment of the anemia of CHF (13). In fact, anemia has been considered only a rare contributing factor to the worsening of CHF, estimated as contributing to no more than 0% to 1.5% of all cases (14–16). Perhaps for this reason, recent guidelines for the prevention and treatment of CHF do not mention treatment of anemia at all (17). If successful treatment of anemia could improve cardiac function and patient function in CHF, this would have profound implications, because, despite all the advances made in the treatment of CHF, it is still a major and steadily increasing cause of hospitalizations, morbidity and mortality (18–20).

The purpose of this study is to examine the prevalence of anemia (Hb <12 g%) in patients with different levels of severity of CHF and to assess the effect of correction of this anemia in severe CHF patients resistant to maximally tolerated doses of CHF medication. A combination of subcutaneous (SC) EPO and intravenous (IV) iron (Fe) was used. We have found this combination to be additive in improving the anemia of CRF (21,22).

METHODS

Patients. The medical records of the 142 CHF patients being treated in our special outpatient clinic devoted to CHF were reviewed to determine the prevalence and severity of anemia and CRF in these patients. These patients were referred to the clinic either from general practice or from the various wards in the hospital.

Intervention study. Despite at least six months of treatment in the CHF clinic, 26 of the above patients had persistent, severe CHF (New York Heart Association [NYHA] class > III), had a Hb level of <12 g% and were resistant to maximally tolerated CHF therapy (including angiotensin-converting enzyme [ACE] inhibitors, the alpha-beta-blocker carvedilol, long-acting nitrates, digoxin, aldactone and oral and IV furosemide. These 26 patients participated in an intervention study. The mean age was 71.76 ± 8.12 years. There were 21 men and 5 women. They all had a LVEF below 35%, persistent fatigue and shortness of breath on mild to moderate exertion and often at rest, and had required hospitalizations at least once during their follow-up in the CHF clinic for pulmonary edema. In 18 of the 26 patients, the CHF was associated with ischemic heart disease either alone in four patients, or with hypertension in six, diabetes in four, the two together in three, or with valvular heart disease in one. Of the remaining eight patients, four had valvular heart disease alone and four had essential hypertension alone.

Secondary causes of anemia including gastrointestinal blood loss (as assessed by history and by three negative stool occult blood examinations), folic acid and vitamin B12 deficiency and hypothyroidism were ruled out. Routine gastrointestinal endoscopy was not carried out. The study passed an ethics committee.

Correction of the anemia. All patients received the combination of SC EPO and IV Fe. The EPO was given once a week at a starting dose of 2,000 IU per week subcutaneously, and the dose was increased or decreased as necessary to achieve and maintain a target Hb of 12 g%. The IV Fe (Venofer-Vifor International, St. Gallen, Switzerland), a ferric sucrose product, was given in a dose of 200 mg IV in 150 ml saline over 60 min every week until the serum ferritin reached 400 μg/liter or the percent Fe saturation (%Fe Sat: serum iron/total iron binding capacity × 100) reached 40% or until the Hb reached 12 g%. The IV Fe was then given at longer intervals as needed to maintain these levels.

Medication dose. Except for oral and IV furosemide therapy, the doses of all the other CHF medications, which were used in the maximum tolerated doses before the intervention, were kept unchanged during the intervention period.

Duration of the study. The study lasted for a mean of 7.2 ± 5.5 months (range four to 15 months).

Investigations. Visits were at weekly intervals initially and then 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, serum ferritin and % Fe Sat were performed on every visit. An electronic device measured the blood pressure on every visit. The LVEF was measured by a multiple gated ventricular angiography heart scan initially and at four- to six-month intervals. Hospital records were reviewed to compare the number of hospitalizations during the time the patients were treated for the anemia with the number of hospitalizations during a similar

Table 1. Initial Characteristics of the 142 Patients With CHF Seen in the CHF Clinic

Age, years	70.1 ± 11.1
Male/female, %	79/21
Associated conditions	
Diabetes	28%
Hypertension	64%
Dyslipidemia	72%
Smoking	40%
Main cardiac diagnosis	
Ischemic heart disease	74%
Dilated CMP	15%
Valvular heart disease	6%
Hypertension	5%
LVEF, %	32.5 ± 12.2
Left atrial area (n < 15 cm^2)	31.3 ± 10.3
Pulmonary artery pressure (n < 15 mm Hg)	43.1 ± 14.9
Previous hospitalizations/year	3.2 ± 1.5
Serum Na, mEq/liter	139.8 ± 4.0
Serum creatinine, mg%	1.6 ± 1.1
Hemoglobin, g%	11.9 ± 1.5

CMP = cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association class.

period of time that they were treated in the CHF clinic before the anemia was treated. Clinic records were reviewed to evaluate the types and doses of CHF medications used before and during the study.

The glomerular filtration rate (GFR) was calculated from the serum creatinine by the formula: 1/serum creatinine in mg% × 100 = GFR in ml/min. The rate of change of the GFR before and during the intervention period was calculated by comparing the change in GFR per month in the year before the intervention with that during the intervention.

Statistical analysis. Mean ± standard deviation was calculated. One-way analysis of variance (ANOVA) was performed to compare parameter levels between the four NYHA groups. Hochberg's method of multiple comparisons (23) was used for pair-wise comparison between two groups. A p value of less than 0.05 was considered statistically significant. In the intervention study, the significance of the difference between the initial values and those at the end of the study for the individual parameters in the 26 treated patients was assessed by paired student's *t* test; $p < 0.05$ was considered statistically significant. All the statistical analysis was performed by the SPSS program (Version 9, Chicago, Illinois).

RESULTS

CHF: the whole study group. The clinical, biochemical and hematological characteristics of the 142 patients seen in the clinic are shown in Tables 1 and 2. Sixty-seven patients (47%) had severe CHF as judged by a NYHA class of IV (Table 2). Seventy-nine of the 142 patients (55.6%) were anemic (Hb < 12 g%). The mean Hb level fell progressively from 13.73 ± 0.83 g% in class I NYHA to 10.90 ± 1.70 g% in class IV NYHA ($p < 0.01$). The percentage of patients with Hb < 12 g% increased from 9.1% in class I to 79.1% in class IV.

Fifty eight patients (40.8%) had CRF as defined as a serum creatinine ≥1.5 mg%. The mean serum creatinine increased from 1.18 ± 0.38 mg% in class I NYHA, to 2.0 ± 1.89 mg% in class IV NYHA, $p < 0.001$. The percentage of patients with an elevated serum creatinine (≥1.5 mg%) increased from 18.2% in class I to 58.2% in class IV. The mean ejection fraction fell from 37.67 ± 15.74% in class I to 27.72 ± 9.68% ($p < 0.005$) in class IV.

The intervention study: medications. The percentage of patients receiving each CHF medication before and after the intervention period and the reasons for not receiving them are seen in Table 3. The main reason for not receiving: 1) ACE inhibitors was the presence of reduced renal function; 2) carvedilol was the presence of chronic obstructive pulmonary disease (COPD); 3) nitrates was low blood pressure and aortic stenosis and 4) aldactone was hyperkalemia. The mean doses of the medications are shown in Table 4. The mean dose of oral furosemide was 200.9 ± 120.4 mg/day before and 78.3 ± 41.3 mg/day after the intervention ($p < 0.05$). The dose of IV furosemide was 164.7 ± 178.9 mg/month before and 19.8 ± 47.0 mg/month after the intervention ($p < 0.05$). The doses of the

Table 2. LVEF and Biochemical and Hematological Parameters by NYHA Class in 142 Patients With CHF

	NYHA Class				Significantly Different Pairs*
	I	II	III	IV	
No. of patients (total 142) (%)	11 (7.7)	26 (18.3)	38 (26.8)	67 (47.2)	
Hb, g%†	13.73 ± 0.83	13.38 ± 1.26	11.95 ± 1.48	10.90 ± 1.70	1–3, 1–4, 2–3, 2–4
Serum creatinine, mg%†	1.18 ± 0.38	1.22 ± 0.29	1.32 ± 0.38	2.00 ± 1.89	1–2, 1–3, 1–4
LVEF, %†	37.67 ± 15.74	32.88 ± 12.41	32.02 ± 10.99	27.72 ± 9.68	1–4, 2–4
Hb < 12 g%, no. (%)	1 (9.1)	5 (19.2)	20 (52.6)	53 (79.1)	
Serum creatinine ≥1.5 mg%, no. (%)	2 (18.2)	5 (19.2)	12 (31.6)	39 (58.2)	

*$p < 0.05$ at least between the two groups by pair-wise comparison between groups.
†$p < 0.05$ at least between the groups by ANOVA.

Table 3. Number (%) of the 26 Patients Taking Each Type of Medication Before and During the Intervention Period and the Reason Why the Medication Was Not Used

Medication	No. of Patients	%	Reason for Not Receiving the Medications (No. of Patients)
ACE inhibitors	20	76.9	CRF (6)
Carvedilol	20	76.9	COPD (3), low BP (2), bradycardia (1)
Digoxin	25	96.2	second degree heart block (1)
Nitrates	23	88.5	aortic stenosis (1), low BP (2)
Aldactone	19	73.1	hyperkalemia (7)
Oral furosemide	26	100	
IV furosemide	26	100	

BP = blood pressure; CRF = chronic renal failure; IV = intravenous.

other CHF medications were almost identical in the two periods.

Clinical results. DEATHS. There were three deaths during the intervention period. An 83-year-old man died after eight months of respiratory failure after many years of COPD, a 65-year-old man at eight months of a CVA with subsequent pneumonia and septic shock and a 70-year-old man at four months of septicemia related to an empyema that developed after aortic valve replacement.

HEMODIALYSIS. Three patients, a 76-year-old man, an 85-year-old woman and a 72-year-old man, required chronic hemodialysis after six, 16 and 18 months, respectively. The serum creatinines of these three patients at onset of the anemia treatment were 4.2, 3.5 and 3.6 mg%, respectively. All three had improvement in their NYHA status but their uremia worsened as the renal function deteriorated, demanding the initiation of dialysis. In no cases, however, was pulmonary congestion an indication for starting dialysis.

Functional results (Table 5). During the treatment period, the NYHA class fell from a mean of 3.66 ± 0.47 to 2.66 ± 0.70 ($p < 0.05$), and 24 had some improvement in their functional class. The mean LVEF increased from 27.7 ± 4.8 to 35.4 ± 7.6% ($p < 0.001$), an increase of 27.8%. Compared with a similar period of time before the onset of the anemia treatment, the mean number of hospitalizations fell from 2.72 ± 1.21 to 0.22 ± 0.65 per patient ($p < 0.05$), a decrease of 91.9%. No significant changes were found in the mean systolic/diastolic blood pressure.

Hematological results (Table 5). The mean hematocrit (Hct) increased from 30.14 ± 3.12% to 35.9 ± 4.22% ($p < 0.001$). The mean Hb increased from 10.16 ± 0.95 g% to 12.10 ± 1.21 g% ($p < 0.001$). The mean serum ferritin increased from 177.07 ± 113.80 μg/liter to 346.73 ± 207.40 μg/liter ($p < 0.005$). The mean serum Fe increased from 60.4 ± 19.0 μg% to 74.80 ± 20.7 μg% ($p < 0.005$). The mean %Fe Sat increased from 20.05 ± 6.04% to 26.14 ± 5.23% ($p < 0.005$). The mean dose of EPO used throughout the treatment period was 5,227 ± 455 IU per week, and the mean dose of IV Fe used was 185.1 ± 57.1 mg per month. In four of the patients, the target Hb of 12 g% was maintained despite stopping the EPO for at least four months.

Renal results (Table 5). The changes in serum creatinine were not significant. The estimated creatinine clearance fell at a rate of 0.95 ± 1.31 ml/min/month before the onset of treatment of the anemia and increased at a rate of 0.85 ± 2.77 ml/min/month during the treatment period.

Table 4. Mean Dose of Each Medication Initially and at the End of the Intervention Period in the 26 Patients

	No. of Patients	Initial Dose	Final Dose
Carvedilol (mg/day)	20	26.9 ± 15.5	28.8 ± 14.5
Captopril (mg/day)	7	69.6 ± 40.0	70.7 ± 40.4
Enalapril (mg/day)	13	25.7 ± 12.5	26.9 ± 12.6
Digoxin (mg/day)	25	0.10 ± 0.07	0.10 ± 0.07
Aldactone (mg/day)	19	61.2 ± 49.2	59.9 ± 47.1
Long-acting nitrates	23	53.2 ± 13.2	54.1 ± 14.4
Oral furosemide (mg/day)	26	200.9 ± 120.4	78.3 ± 41.3*
IV furosemide (mg/month)	26	164.7 ± 178.9	19.8 ± 47.0*

*$p < 0.05$ at least vs. before by paired Student's *t* test.

Table 5. The Hematological and Clinical Data of the 26 CHF Patients at Onset and at the End of the Intervention Period

	Initial	Final
Hematocrit, vol%	30.14 ± 3.12	35.90 ± 4.22*
Hemoglobin, g%	10.16 ± 0.95	12.10 ± 1.21*
Serum ferritin, μg/liter	177.07 ± 113.80	346.73 ± 207.40*
Serum iron, μg%	60.4 ± 19.0	74.8 ± 20.7*
% iron saturation	20.5 ± 6.04	26.14 ± 5.23*
Serum creatinine, mg%	2.59 ± 0.77	2.73 ± 1.55
LVEF, %	27.7 ± 4.8	35.4 ± 7.6*
No. hospitalizations/patient	2.72 ± 1.21	0.22 ±0.65*
Systolic BP, mm Hg	127.1 ± 19.4	128.9 ± 26.4
Diastolic BP, mm Hg	73.9 ± 9.9	74.0 ± 12.7
NYHA (0–4)	3.66 ± 0.47	2.66 ± 0.70*

*$p < 0.05$ at least vs before by paired Student's t test.
BP = blood pressure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

DISCUSSION

The main findings in the present study are that anemia is common in CHF patients and becomes progressively more prevalent and severe as CHF progresses. In addition, in patients with resistant CHF, the treatment of the associated anemia causes a marked improvement in their functional status, ejection fraction and GFR. All these changes were associated with a markedly reduced need for hospitalization and for oral and IV furosemide.

The effect of anemia on the ischemic myocardium. Rather surprisingly, the improvement in cardiac function occurred, although the baseline anemia was quite modest (mean Hb 10.16 ± 0.95 g%), and the improvement in the Hb level was only about 2 g%. Animal studies have demonstrated that the ischemic or hypertrophied heart is more sensitive to even a small drop of Hb than is the normal heart, this drop resulting in a marked worsening of the ischemia and the cardiac function (24). This detrimental effect of anemia on myocardial function has been borne out in human studies as well (24,25). This may explain why correction of the anemia in our patients had such a profound effect on cardiac function and patient functional class. Another possible explanation is that EPO may have a direct effect on improving cardiac muscle function unrelated to the effect of the anemia (26).

The effect of anemia correction on renal function. Congestive heart failure is often associated with some degree of CRF (1–3,27–29), and this is most likely due to renal vasoconstriction and ischemia (28,29). When the anemia is treated and the cardiac function improves, an increase in renal blood flow and glomerular filtration is seen (7,28). In the present study, renal function decreased as the CHF functional class worsened (Table 2). The rate of deterioration of renal function was slower during the intervention period. Treatment of anemia in CRF has been associated with a rate of progression of the CRF that is either unchanged (30) or is slowed (31–33). It is possible, therefore, that adequate treatment of the anemia in CHF may, in the long term, help slow down the progression of CRF.

Possible adverse effects of correction of the anemia. There has been concern, in view of the recent Amgen study (34), that correction of the Hct to a mean 42% in hemodialysis patients might increase cardiovascular events in those receiving EPO compared with those maintained at a Hct of 30%. Although there is much uncertainty about how to interpret this study (35), there is a substantial body of evidence that shows correction of the anemia up to a Hb of 12 g% (Hct 36%) in CRF on dialysis is safe and desirable (35–38), and results in a reduction in mortality, morbidity and in the number and length of hospitalizations. The same likely holds true for the anemia of CHF with or without associated CRF. Certainly, our patients' symptoms were strikingly improved, as was their cardiac function (LVEF) and need for hospitalization and diuretics. It remains to be established if correction of the anemia up to a normal Hb level of 14 g% might be necessary in order to further improve the patient's clinical state.

The role of Fe deficiency and its treatment in the anemia of CHF. We used the IV Fe together with EPO to avoid the Fe deficiency caused by the use of EPO alone (38,39). The Fe deficiency will cause a resistance to EPO therapy and increase the need for higher and higher doses to maintain the Hb level (39,40). These high doses will not only be expensive but may increase the blood pressure excessively (41). The IV Fe reduces the dose of EPO needed to correct the anemia, because the combination of SC EPO and IV Fe has been shown to have an additive effect on correction of the anemia of CRF (21,22,39,42). Oral Fe, however, has no such additive effect (39,42). The relatively low dose of EPO needed to control the anemia in our study may explain why the blood pressure did not increase significantly in any patient. We used Venofer, an Fe sucrose product, as our IV Fe supplement because, in our experience (21,22,43), it has very few side effects and, indeed, no side effects with its use were encountered in this study.

Severe CHF patients may be prone to Fe deficiency for other reasons than just the use of EPO. Poor food intake (cardiac cachexia) (44), malabsorption (45) or use of prophylactic aspirin (46,47) may also be contributing factors. Most of the patients in the present study had some degree of CRF, which is also associated with a reduction in Fe absorption (48–50). The importance of Fe deficiency in CHF is seen in the fact that 4 of the 26 patients we studied were able to maintain the target Hb of 12 g% with IV Fe alone even after the dose of EPO was stopped for several months.

Other factors that could contribute to the anemia of CHF. Another factor that could contribute to the anemia may be tumor necrosis factor (TNF). Tumor necrosis factor blood levels have been found to be elevated in CHF (51,52), have been found to correlate with the severity of the anemia (51,53) and may cause bone marrow depression (53), interference in the action of EPO (53) and in the cellular release and utilization of Fe (54). The use of ACE inhibitors may also cause a reduction in the Hb levels (55–57), especially when used in high doses (56), doses that are usually required in CHF (17).

Study limitations. The major limitations of this study were the small number of patients treated and the lack of a control group. Open-label, uncontrolled observations often yield positive results that, in many cases, are not corroborated by subsequent controlled studies. Certainly, special CHF clinics where experts treat these difficult patients have yielded results far better than those achieved by ordinary physicians (2,58,59). But in our study, these patients were being followed at frequent intervals in the CHF clinic for at least six months before the intervention and were already receiving the broad range of CHF medications in the maximally tolerated doses. Yet despite this intensive care and follow-up, they were still grossly symptomatic and many were being frequently hospitalized, predominantly with pulmonary edema. However, the treatment of the anemia was associated with a reduction in symptoms of CHF and less hospitalizations, despite the use of much less diuretics and no change in the doses of any of the other CHF medications. It seems most likely, therefore, that the changes that were found in the ejection fraction, functional class, hospitalization, diuretic use and renal function were due to the improvement in the anemia. Nevertheless, in order to clarify more definitively the effect of correction of anemia on CHF, we have now begun a randomized, controlled trial.

The cost effectiveness of aggressive therapy of anemia in CHF. The mean EPO dose needed to reach the target Hb of 12 g% was about 5,000 IU/week, which costs about $50/week. Thus, the yearly cost of this dose, if self-administered, would be about $2,600. The yearly cost of 22 100-mg ampoules of IV Fe (the average number needed per year in this study to supply the 2,200 mg of IV Fe needed per year) is about $330, not including the cost of the IV infusions, which would be required to give this amount in an outpatient setting. In any case, the cost of the treatment of the anemia is probably significantly lower than the cost of any of the alternatives: recurrent hospitalizations for pulmonary edema, coronary artery bypass surgery for improving the blood supply to a hibernating heart, heart transplantation or dialysis. About 40% of patients starting dialysis for end-stage renal failure have CHF (60), and the CHF may itself, in some of these patients, be the major reason for the dialysis starting earlier (61). Improving cardiac function in these cases would avoid or postpone the need for dialysis.

Importance of early treatment of the anemia of CHF. It is noteworthy, as seen in Table 2, that even in mild CHF (NYHA functional class II), 5 (19.2%) of the 26 patients in this group were already anemic. These five all had serum creatinine levels ranging from 1.9 to 2.4 mg%, indicating some degree of renal insufficiency. It is possible that treatment of the anemia in these early stages could, along with the usual treatment regimen of CHF, help in preventing both the progression of CRF and progressive congestive cardiomyopathy.

Conclusions. Many patients with mild CHF and most patients with moderate to severe CHF are anemic. The degree of anemia parallels the degree of deterioration of cardiac and renal function and may contribute to this deterioration. The correction of the anemia is associated with an impressive improvement in cardiac function that is reflected in a marked improvement in the NYHA functional class, an improvement in renal function and a striking reduction in hospitalizations and use of oral and IV furosemide. Treatment of the anemia with EPO and IV Fe may be a useful addition to the physicians' armementarium in CHF. It would seem from our findings, however, that these useful tools are grossly underutilized. Clearly, the role of anemia in the worsening of CHF and the use of EPO and IV Fe in its correction require further clarification with controlled trials.

Summary. The prevalence and significance of mild anemia in CHF and the role of erythropoietin with intravenous iron supplementation in treating this anemia are unknown. In 142 CHF patients, the prevalence of anemia (Hb $<$ 12 g%) increased progressively with the severity of CHF. Twenty-six anemic patients with severe CHF despite maximally tolerated CHF medications had their anemia corrected with the EPO-IV/Fe combination. The LVEF increased, the NYHA class improved, the days of hospitalization and dose of diuretics required fell and the rate of progression of the associated renal failure slowed. Correction of mild anemia may be an important addition to the treatment of CHF.

Acknowledgments

We thank Rina Issaky, Miriam Epstein and Hava Ehrenfeld for their secretarial assistance.

Reprint requests and correspondence: Dr. D. S. Silverberg, Department of Nephrology, Tel Aviv Medical Center, Weizman 6, Tel Aviv, 64239, Israel.

REFERENCES

1. Haber HL, Leavy JA, Kessler PD, et al. The erythrocyte sedimentation rate in congestive heart failure. N Engl J Med 1991;324:353–8.
2. Rich MW, Beckham V, Wittenberg C, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995;333:1190–5.
3. Rich MW, Shah AS, Vinson JM, et al. Iatrogenic congestive heart failure in older adults: clinical course and prognosis. J Am Geriatr Soc 1996;44:638–43.
4. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. Am J Kidney Dis 1997;30 Suppl:193–240.
5. Maeda K, Tanaka Y, Tsukano Y, et al. Multivariate analysis using a linear discriminant function for predicting the prognosis of congestive heart failure. Jpn Circ J 1982;46:137–42.
6. Volpe M, Tritto C, Testa U, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol 1994;74:468–73.
7. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris P. Pathogenesis of edema in chronic anemia: studies of body water and sodium, renal function, haemodynamics and plasma hormones. Br Heart J 1993;70:357–62.
8. Low I, Grutzmacher P, Bergmann M, Schoeppe W. Echocardiographic findings in patients on maintenance hemodialysis substituted with recombinant human erythropoietin. Clin Nephrol 1989;31:26–30.
9. Low-Friedrich I, Grutzmacher P, Marz W, Bergmann M, Schoeppe W. Therapy with recombinant human erythropoietin reduces cardiac size and improves heart function in chronic hemodialysis patients. Am J Nephrol 1991;11:54–60.
10. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. Am Heart J 1992;124:424–7.
11. Foley RN, Parfrey PS, Morgan J, et al. A randomized controlled trial of complete vs partial correction of anemia in hemodialysis patients with asymptomatic concentric LV hypertrophy or LV dilatation (abstr). J Am Soc Nephrol 1998;9:208.
12. Linde T, Wikstrom B, Andersson LG, Danielson BG. Renal anaemia treatment with recombinant human erythropoietin increases cardiac output in patients with ischaemic heart disease. Scand J Urol Nephrol 1996;30:115–20.
13. Heart failure: management of patients with left-ventricular systolic dysfunction. Quick reference guide for clinicians. No. 11. AHRCPR Publication No. 94-0613. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, 1994.
14. Ghali JK, Kadakia S, Cooper R, Ferlinz J. Precipitating factors leading to decompensation of heart failure. Traits among urban blacks. Arch Intern Med 1988;148:2013–6.
15. Opasich C, Febo O, Riccardi PG, et al. Concomitant factors of decompensation in chronic heart failure. Am J Cardiol 1996;78:354–7.
16. Michaelsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. Heart 1998;80:437–41.
17. Packer M, Cohn JN, Abraham WT, et al. Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83 Suppl 2A:1–38.
18. Massie BM, Shah NB. The heart failure epidemic: magnitude of the problem and potential mitigating approaches. Curr Opin Cardiol 1996;11:221–6.
19. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. Eur Heart J 1997;18:208–25.
20. Senni M, Redfield MM. Congestive heart failure in elderly patients. Mayo Clin Proc 1997;72:453–60.
21. Silverberg DS, Blum M, Peer G, Kaplan E, Iaina A. Intravenous ferric saccharate as an iron supplement in dialysis patients. Nephron 1996; 72:413–7.
22. Silverberg DS, Blum M, Agbaria Z, et al. Intravenous iron for the treatment of predialysis anemia. Kidney Int 1999;55 Suppl 69:79–85.
23. Hochberg Y. Some conservative generalizations of the T-methods in simultaneous inference. J Multivar Anal 1974;4:224–34.
24. Carson JL. Morbidity risk assessment in the surgically anemic patient. Am J Surg 1995;170 Suppl:32–6.
25. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348: 1055–60.
26. Wald M, Gutnisky A, Borda E, Sterin BL. Erythropoietin modified the cardiac action of ouabain in chronically anaemic-uraemic rats. Nephron 1995;71:190–6.
27. Reis SE, Holubkov R, Edmundowicz D, et al. Treatment of patients admitted to the hospital with congestive heart failure: specialty-related disparities in practice patterns and outcomes. J Am Coll Cardiol 1997;30:733–8.
28. Anand IS, Chugh SS. Mechanisms and management of renal dysfunction in heart failure. Curr Opin Cardiol 1997;12:251–8.
29. Yoshida H, Yashiro M, Liang P, et al. Mesangiolytic glomerulopathy in severe congestive heart failure. Kidney Int 1998;53:880–91.
30. Roth D, Smith RD, Schulman G, et al. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. Am J Kidney Dis 1994;24:777–84.
31. Scharer K, Klare B, Braun A, Dressel P, Gretz N. Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure. Acta Paediatr 1993;82:953–8.
32. Lopez-Gomez JM, Jofre R, Moreno F, Verde E, Valderrabano F. rHuEPO before dialysis and in dialysed patients. Nephrol Dial Transplant 1995;10 Suppl 6:31–5.
33. Kuriyama S, Tomonari H, Yoshida H, et al. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron 1997;77:176–85.
34. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339: 584–90.
35. Macdougall IC, Ritz E. The normal hematocrit trial in dialysis patients with cardiac disease: are we any less confused about target hemoglobin? Nephrol Dial Transplant 1998;13:3030–3.
36. Silverberg D, Blum M, Peer G, Iaina A. Anemia during predialysis period: a key to cardiac damage in renal failure. Nephron 1998;80:1–5.
37. Locatelli F, Conte F, Marcelli D. The impact of haematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity: the experience of the Lombardy Dialysis Registry. Nephrol Dial Transplant 1998;13:1642–4.
38. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol 1999;10:610–9.
39. Macdougall IC, Tucker B, Thompson J, et al. A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int 1996;50:1694–9.
40. Koch KM, Koene RAP, Messinger D, Quarder O, Scigalla P. The use of Epoetin beta in anemic predialysis patients with chronic renal failure. Clin Nephrol 1995;44:201–8.
41. Maschio G. Erythropoietin and systemic hypertension. Nephrol Dial Transplant 1995;10 Suppl 2:74–9.
42. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. Am J Kidney Dis 1995;26:41–6.
43. Silverberg DS, Iaina A, Peer G, et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. Am J Kidney Dis 1996;27: 234–8.
44. Schwengel RH, Gottlieb SS, Fisher ML. Protein-energy malnutrition in patients with ischemic and nonischemic dilated cardiomyopathy and congestive heart failure. Am J Cardiol 1994;73:908–10.
45. King D, Smith ML, Chapman TJ, Stockdale HR, Lye M. Fat malabsorption in elderly patients with cardiac cachexia. Age Ageing 1996;25:144–9.

46. Weil J, Colin JD, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. Br Med J 1995;310:827–30.
47. Silagy CA, McNeil JJ, Donnan GA, et al. Adverse effects of low-dose aspirin in a healthy elderly population. Clin Pharmacol Ther 1993;54: 84–9.
48. Donnelly SM, Posen GA, Ali MA. Oral iron absorption in hemodialysis patients treated with erythropoietin. Clin Invest Med 1991;14: 271–6.
49. Goch J, Birgegard G, Danielson BG, Wikstrom B. Iron absorption in patients with chronic uremia on maintenance hemodialysis and in healthy volunteers measured with a simple oral iron load test. Nephron 1996;73:403–6.
50. Kooistra MP, Niemantsverdriet EC, van Es A, et al. Iron absorption in erythropoietin-treated haemodialysis patients: effects of iron availability, inflammation and aluminum. Nephrol Dial Transplant 1998; 13:828–8.
51. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236–41.
52. Herrera-Garza EH, Stetson SJ, Cubillos-Garzon A, Vooletich MT, Farmer JA, Torre-Amione G. Tumor necrosis factor. A mediator of disease progression in the failing human heart. Chest 1999;115: 1170–4.
53. Goicoechea M, Martin J, de Sequera P, et al. Role of cytokines in the response to erythropoietin in hemodialysis patients. Kidney Intern 1998;54:1337–43.
54. Feelders RA, Vreugdenhil G, Eggermont AMM, Kuiper-Kramer PA, Van Eijk HG, Swaak AJG. Regulation of iron metabolism in the acute-phase response: interferon and tumour necrosis factor induce hypoferraemia, ferritin production and a decrease in circulating transferrin receptors in cancer patients. Eur J Clin Invest 1998;28:520–7.
55. Horl WH. Is there a role for adjuvant therapy in patients being treated with epoetin? Nephrol Dial Transplant 1999;14 Suppl 2:50–60.
56. Albitar S, Genin R, Fen-Chong M, Serveauz M-O, Bourgeon B. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. Nephrol Dial Transplant 1998;13:1206–10.
57. Erturk S, Nergizoglu G, Ates K et al. The impact of withdrawing ACE inhibitors on erythropoietin responsiveness and left ventricular hypertrophy in haemodialysis patients. Nephrol Dial Transplant 1999; 14:1912–6.
58. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol 1997;30:725–32.
59. Cline CMJ, Israelsson BYA, Willenheimer RB, Broms K, Erhardt LR. Cost effective management programme for heart failure reduces hospitalisation. Heart 1998;80:442–6.
60. US Renal Data System. Comorbid conditions and correlations with mortality risk among 3,999 incident hemodialysis patients. Am J Kidney Dis 1992;20:32–8.
61. Elhalel-Dranitzki M, Rubinger D, Moskovici A, et al. CAPD to improve quality of life in patients with refractory heart failure. Nephrol Dial Transplant 1998;13:3041–2.