

## Effect of Correction of Anemia with Erythropoietin and Intravenous Iron in Resistant Heart Failure in Octogenarians

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### Abstract

**Background:** Congestive heart failure is extremely common in octogenarians and is associated with severe fatigue, shortness of breath, recurrent hospitalizations, and death. These patients, many of whom are anemic, are often resistant to standard CHF therapy including angiotensin-converting enzyme inhibitors, beta-blockers and diuretics.

**Objectives:** To examine whether correction of the anemia (hemoglobin <12 g/dl) in CHF patients can improve their clinical condition.

**Methods:** Forty octogenarians with anemia and severe resistant CHF were administered a combination of subcutaneous erythropoietin and intravenous iron sucrose.

**Results:** This combination therapy led to a marked improvement in cardiac function, shortness of breath and fatigue, a marked reduction in the rate of hospitalization and a stabilizing of renal function.

**Conclusion:** Anemia appears to be an important but ignored contributor to the progression of CHF, and its correction may improve cardiac and renal status as well as the quality of life in elderly patients.

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Congestive heart failure is extremely common and is estimated to be present in 2–3% of the population [1]. Its prevalence has increased by 150% over the past 20 years and is one of the leading causes of mortality and morbidity in the elderly [1,2]. Individuals over the age of 65 account for about 80% of all hospitalizations and deaths attributable to CHF [1–6]. The most important factor influencing the prevalence is age [1–7]. A recent study in Portugal found that 7.63%, 12.67% and 16.14% of the population aged 60–69, 70–79 and 80+, respectively, have CHF [7]. The number of hospitalizations for CHF is also increasing dramatically, particularly among the elderly, and CHF is the commonest cause of medical admissions among people over the age of 65 [1–7]. About half of all elderly patients who survive hospitalization for CHF are readmitted again within 6 months, and up to 50% of hospitalized elderly die within 1 year [1–7]. These dismal outcomes occur despite the many advances in the field of CHF, including the use of angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, aldospirone and other diuretics, digoxin, and nitrates.

Why does treatment so often fail? Part of the reason may be that patients are not followed carefully and/or are not given these medications, or are given them in less than the desired and

tolerated doses – that is, they are being under-treated [1–7]. In a previous study [8] however, we found that even when these patients were treated in a special CHF outpatient department dedicated to CHF, with all these agents administered in the maximally tolerated doses, and with patients followed frequently and carefully, many were still resistant to therapy, still exhibited severe symptoms of CHF (particularly fatigue and shortness of breath), and often required repeated hospitalizations. We noted [8] that one characteristic often found in these resistant CHF patients was that they were anemic, i.e., hemoglobin <12 g/dl, a level indicating anemia in both men and women [9]. It is well known from studies in dialysis patients treated with erythropoietin that the higher the hematocrit (up to 39%) the lower the rate of hospitalization, the lower the mortality and the better the exercise capacity, cardiac function and quality of life [10–12]. In view of this experience we treated these anemic, resistant CHF patients with a combination of subcutaneous erythropoietin and IV iron sucrose (Venofer, Switzerland) to correct the anemia [8]. In 26 such patients we found that correction of the anemia was associated with an improvement in left ventricular ejection fraction, New York Heart Association functional cardiac class (i.e., their ability to walk further and breathe easier), and a reduced dose requirement for both oral and IV furosemide. The serum creatinine, which had been steadily increasing during the anemic period, stabilized with the correction of the anemia. Most striking of all was the fact that the rate of rehospitalization, which was very high before correction of the anemia, fell markedly after its correction. In a subsequent controlled study [13] we again found that while the NYHA functional cardiac class and LVEF improved with treatment of the anemia, they worsened in the control group in which the anemia was not corrected. The serum creatinine remained stable in the treated group and increased in the control group. Hospitalization rates fell in the treated group compared to the previous period and increased in the untreated group. The doses of oral and IV diuretics decreased in the treated group and increased in the non-treated group. We have subsequently treated 179 cases of resistant CHF with anemia [14]. The purpose of this paper is to describe our experience with the combination of subcutaneous EPO and IV iron to correct anemia in elderly people with resistant congestive heart failure.

NYHA = New York Heart Association

LVEF = left ventricular ejection fraction

EPO = erythropoietin

CHF = congestive heart failure

## Materials and Methods

### Study protocol

The study group consisted of 40 patients aged 80 years or older with severe resistant heart failure and mild to moderate renal failure. All patients received the combination of subcutaneous EPO and IV iron. The EPO was given once weekly at a starting dose of 4,000–5,000 IU per week, increasing to up to 10,000 IU per week, and then, depending on the response, decreasing the dose to once every 2–3 weeks, or discontinuing it entirely in order to achieve and maintain a target hemoglobin of 12.5 g/dl. The IV iron (Venofer-Vifor, Switzerland), a ferric sucrose product, was given in an intravenous dose of 200 mg in 150 ml saline over 60 minutes every 1–2 weeks until either the serum ferritin reached 500 µg/L, the percent Fe saturation (plasma iron/total iron-binding capacity x 100) reached 40%, or hemoglobin reached 12.5 g/dl. The IV iron was then given at longer intervals to maintain these levels. Except for oral and IV furosemide therapy, the doses of all other CHF medications, which were used in the maximally tolerated doses before the intervention for at least 3 months, remained unchanged during the study.

### Investigations

Visits were at weekly intervals initially and then at 2–4 week intervals depending on the patient's status. A complete blood count, blood urea nitrogen, serum sodium, potassium, creatinine, ferritin and percent Fe saturation were performed on every visit. In the diabetic patients HbA1c was tested every 3 months. Secondary causes of anemia such as gastrointestinal bleeding, folic acid and vitamin B12 deficiency, and hypothyroidism were ruled out.

At each visit an electronic device was used to measure blood pressure. LVEF was measured by a multiple-gated radioisotope angiography heart scan initially and at 4–6 month intervals. Hospital records were reviewed to compare the number of hospitalizations during the time the patients were treated for anemia with the number of hospitalizations during a similar period when they were treated in the CHF clinic before the anemia treatment.

The glomerular filtration rate was calculated by the Cockcroft Gault formula [15]. The rate of change of GFR before and during the intervention period was calculated by comparing the change in GFR per month in the year before the anemia correction with that during the period of correction.

A Visual Analogue Scale was employed that allowed patients to assess the severity of their own fatigue and/or shortness of breath at the beginning and at the end of the intervention period. They were shown a 10 cm line with the number zero at one end and the number 10 at the other; the number zero representing normal breathing and strength and the number 10 extreme fatigue and/or shortness of breath. They were asked to mark on the line the degree of fatigue and/or shortness of breath that they felt when they started therapy for their anemia and again at the end of the study period after they had reached and maintained the target hemoglobin of 12.5 g/dl.

**Table 1.** Changes in hematologic, biochemical and clinical parameters in octogenarians with CHF before and after correction of their anemia with EPO and IV ferric sucrose

	Before	After
Hemoglobin (g/dl)	10.3 ± 1.2	13.2 ± 1.2*
Hematocrit (%)	30.5 ± 3.8	39.2 ± 3.6*
Serum iron	60.8 ± 20	82.3 ± 52*
% Fe saturation	18.3 ± 6.4	25.1 ± 7.0*
Serum ferritin (µg/ml)	126.0 ± 99	366.3 ± 214*
Serum creatinine (mg/dl)	2.3 ± 1.0	2.3 ± 1.2
NYHA class (0–4)	3.9 ± 1.3	2.7 ± 0.4*
Ejection fraction (%)	31.6 ± 14.1	41.0 ± 12.9*
Δ Creatinine clearance (ml/min/month)	-1.0 ± 1.3	+0.5 ± 1.1*
Visual Analogue Scale	8.4 ± 1.6	2.6 ± 1.9*
No. of times hospitalized	3.6 ± 3.5	0.2 ± 0.5*
Systolic BP (mmHg)	129.6 ± 21.3	136.7 ± 31.8
Diastolic BP (mmHg)	73.9 ± 11.8	76.0 ± 13.4

\*  $P < 0.05$ .

### Statistical analysis

Mean ± standard deviation was calculated. Student's *t*-test was calculated and  $P < 0.05$  was considered statistically significant between different parameters.

## Results

The mean age of the patients was 84.4 ± 3.1, and the male/female ratio 29:11. The duration of the follow-up was 17.4 ± 10 months. The clinical, biochemical and hematologic changes are shown in Table 1.

The NYHA, LVEF and VAS index improved significantly. Hemoglobin, serum iron, ferritin and percent iron saturation all increased significantly. The mean serum creatinine and creatinine clearance, as calculated by the Cockcroft Gault formula, did not change significantly. However, the rate of fall in creatinine clearance in the period before the study was 1 ml/min/month and improved significantly during the intervention period. There was a marked and significant decrease in the number of hospitalizations compared to an equivalent period before the study. There were no significant changes in mean systolic or diastolic blood pressure. Only 2 of the 40 patients (5%) died during the intervention period, both of sudden death.

## Discussion

In this study we found that the correction of anemia in octogenarians with CHF and anemia was associated with a marked improvement in NYHA cardiac functional class, LVEF, and self-assessed fatigue and shortness of breath. Correction of the anemia was also associated with a reduction in hospital days and dose of oral and IV diuretics compared to the same time period before the intervention. The mean glomerular filtration rate, which had been decreasing quite rapidly before the anemia, was corrected and stabilized. In a recent assessment in the United States of the effect of EPO to correct anemia among Medicare patients with chronic

GFR = glomerular filtration rate

VAS = Visual Analog Scale

renal insufficiency, it was found that there were fewer hospitalizations not only for CHF but also for infections [16]. We did not analyze the major reason for hospitalizations, but infection is known to be a common cause of rehospitalization in elderly CHF patients [17]. It is reasonable to assume that correction of the CHF by preventing pulmonary congestion may contribute to the prevention of lung infections as well.

The low mortality rate (5%) over a mean of 17 months is striking. These were exceedingly high risk patients, very old, very sick and frequently hospitalized. This type of patients is known to have 1 year mortality rates of 30–50% [1–7]. Our findings of improvement in both the physician-assessed NYHA and the patients' self-assessed breathing and fatigue (the VAS scale), together with a striking reduction in hospitalization, attest to the patients' general improvement following correction of the anemia. Several studies have found that anemia is associated with a doubling of the mortality rate among CHF patients [18–20] and increases their risk of rehospitalization [21,22]. Since the only factor in our patients' treatment that was changed was correction of the anemia, it is reasonable to assume that this was a major contributor to the improvement. A similar finding was recently reported in elderly persons admitted with acute myocardial infarction [23]. Survival was highly and directly correlated with the level of initial hematocrit, and correction of the anemia in these elderly anemic patients markedly reduced their 30 day mortality. All this suggests that the ischemic or damaged heart is very susceptible to the negative effects of anemia. There are many possible causes of anemia in CHF [8]. Two of the main ones are depressed renal function with reduced EPO response to anemia and depression of both EPO production and bone marrow response to EPO caused by excessive cytokine production by the damaged heart [8].

In conclusion, our findings strongly suggest that anemia may be a major contributor to the progression of CHF and renal failure in the elderly, to their low quality of life, frequent hospitalizations, and premature death. We urge physicians to be alert to the presence of anemia in elderly patients with CHF.

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