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Intravenous Iron Reduces NT-Pro-Brain Natriuretic Peptide in Anemic Patients With Chronic Heart Failure and Renal Insufficiency

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Objectives Our objective was to evaluate in a double-blind, randomized, placebo-controlled study possible modifications in NT-pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) levels together with clinical and functional parameters, in a group of anemic patients with chronic heart failure (CHF) and chronic renal failure (CRF) receiving intravenous iron therapy, without recombinant human erythropoietin (rhEPO), versus placebo.

Background Chronic heart failure and CRF associated with absolute or relative iron deficiency anemia is a common problem. This situation is linked with a variable inflammatory status. Both NT-proBNP and CRP are recognized markers for left ventricular dysfunction and inflammatory status, respectively. In this double-blind, randomized, placebo-controlled study, modifications in NT-proBNP and CRP level and clinical and functional parameters, in anemic patients with CHF and CRF receiving intravenous iron therapy, without rhEPO, versus placebo were evaluated.

Methods Forty patients with hemoglobin (Hb) $<$12.5 g/dl, transferrin saturation $<$20%, ferritin $<$100 ng/ml, creatinine clearance (CrCl) $<$90 ml/min, and left ventricular ejection fraction (LVEF) $\leq$35% were randomized into 2 groups ($n = 20$ for each). For 5 weeks, group A received isotonic saline solution and group B received iron sucrose complex, 200 mg weekly. Minnesota Living with Heart Failure Questionnaire (MLHFQ) and 6-min walk (6MW) test were performed. NT-pro brain natriuretic peptide and CRP were evaluated throughout the study. No patients received erythroprotein any time.

Results After 6 months follow-up, group B showed better hematology values and CrCl ($p < 0.01$) and lower NT-proBNP (117.5 $\pm$ 87.4 pg/ml vs. 450.9 $\pm$ 248.8 pg/ml, $p < 0.01$) and CRP (2.3 $\pm$ 0.8 mg/l vs. 6.5 $\pm$ 3.7 mg/l, $p < 0.01$). There was a correlation initially ($p < 0.01$) between Hb and NT-proBNP (group A: $r = -0.94$ and group B: $r = -0.81$) and after 6 months only in group A: $r = -0.80$. Similar correlations were observed with Hb and CRP. Left ventricular ejection fraction percentage (35.7 $\pm$ 4.7 vs. 28.8 $\pm$ 2.4), MLHFQ score, and 6MW test were all improved in group B ($p < 0.01$). Additionally, group B had fewer hospitalizations: 0 of 20 versus group A, 5 of 20 ($p < 0.01$; relative risk = 2.33).

Conclusions Intravenous iron therapy without rhEPO substantially reduced NT-proBNP and inflammatory status in anemic patients with CHF and moderate CRF. This situation was associated with an improvement in LVEF, NYHA functional class, exercise capacity, renal function, and better quality of life. (J Am Coll Cardiol 2007;50:1657–65)

Unquestionably, the use of therapy against the renin-angiotensin-aldosterone system, angiotensin-converting enzyme inhibitors and angiotensin II type 1-receptor blockers, and beta-blockers, has favorably modified the prognosis of chronic heart failure (CHF). However, the mortality and morbidity in patients with CHF remains high (1,2). Despite the fact that poor outcomes might, in part, be due to inadequate choice or dosage of corresponding medications, it is also possible that the presence of some comorbidity such as anemia could be an important contributing factor. In support of this, anemia is widely recognized as a common comorbidity in patients with CHF (3–9). Almost one-third of patients with CHF present with anemia (3–9), and this situation is associated with an increase in left ventricular (LV) mass, a greater incidence of rehospitalization, and higher mortality (3–9). Absolute or relative iron and/or erythropoietin (EPO) deficiency are involved in the patho-

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Abbreviations and Acronyms

6MW = 6-min walk
BMI = body mass index
CHF = chronic heart failure
CRF = chronic renal failure
CRP = C-reactive protein
Hb = hemoglobin
ISC = iron sucrose complex
IV = intravenous
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NT-proBNP = NT-pro-brain natriuretic peptide
NYHA = New York Heart Association
rhEPO = recombinant human erythropoietin
TSAT = transferrin saturation

physiology of anemia in these patients, especially when some degree of chronic renal failure (CRF) is present (10). Furthermore, occurrence of anemia in these patients is also associated with increasing NT-pro-brain natriuretic peptide (NT-proBNP) level and C-reactive protein (CRP) (11,12), which are recognized markers of LV dysfunction and inflammatory status, respectively. Therefore, a therapeutic intervention, which increases hemoglobin (Hb) concentrations in these patients, may be of importance.

In the last few years, some small preliminary studies have reported that correction of low Hb concentrations by erythropoiesis-stimulating proteins such as recombinant human erythropoietin (rhEPO) or darbepoetin may significantly improve cardiac and renal function and reduce the number of hospitalizations (13–15). So far, only one study using intravenous (IV) iron without EPO in patients with CHF has been conducted (16). It was a prospective, uncontrolled, open-label study with a follow-up of 3 months using iron sucrose complex (ISC) in which the authors reported a significant increase in Hb level and substantial improvement in exercise capacity in anemic patients with CHF.

Against this background, the present double-blind, randomized, placebo-controlled study was designed in order to evaluate as primary objectives: 1) the effectiveness of IV ISC administration without rhEPO therapy for improving hematologic and renal parameters; and 2) the change in the NT-proBNP level and inflammatory status by CRP in patients with CHF and moderate CRF compared with that in patients receiving only standard CHF therapy. The secondary objectives were to determine the number of hospitalizations, exercise tolerance, and change in the quality of life in these patients.

Methods

The local research and ethics committee granted study approval. Written, informed consent was obtained from all participants. This was a small, pilot, prospective, double-blind, randomized, placebo-controlled study. The study population was composed of adult patients of both genders.

The enrolled patients were not a specific or selected group. They were the consecutive patients from the general population that spontaneously consulted the outpatient's office of the cardiology section at the Hospital Alemán Buenos Aires, Argentina, and who fulfilled the inclusion criteria for the study having a diagnosis of CHF, CRF, anemia, and iron deficiency. Afterward, they were randomized and included in the study protocol.

Inclusion criteria. Patients with: 1) LV ejection fraction (EF) ≤35%; 2) New York Heart Association (NYHA) functional class II to IV; 3) anemia with an iron deficit defined by Hb <12.5 g/dl for men and <11.5 g/dl for women, and some of the following: serum ferritin <100 ng/ml and/or with transferrin saturation (TSAT) ≤20%; and 4) creatinine clearance ≤90 ml/min were included in the study.

Exclusion criteria. Patients with: 1) hemodialysis therapy; 2) anemia not due to iron deficiency available for erythropoiesis; 3) NYHA functional class I; 4) history of allergy to the iron supplements; 5) acute bacterial infections, parasitism known in the 4 previous weeks, and neoplasm; 6) chronic digestive diseases; 7) hypothyroidism; 8) congenital cardiopathies; 9) receiving iron supplements in the 4 previous weeks; 10) receiving rhEPO in the 4 previous weeks; and 11) history of hospitalization during the 4 weeks before enrollment into the study were excluded from the study.

Once the patients had signed the informed consent, 2 groups were created by random allocation of the total population by means of a table of random numbers. One group (group A) received placebo in addition to conventional therapy for the management of the CHF while group B received additional administration of IV ISC (Venofer, Vifor Int., St. Gallen, Switzerland) 200 mg weekly for 5 weeks. No patient received rhEPO before the study and at any time during the study. A complete medical history with exhaustive physical examination was performed in each patient recording data such as age, gender, body mass index (BMI), medication, blood pressure, heart rate, and breathing rate. Symptoms were assessed according to NYHA functional classification. Complete blood count, serum ferritin, TSAT, NT-proBNP, CRP, creatinine clearance, and electrolytes were evaluated. Transthoracic echocardiogram, Minnesota Living with Heart Failure Questionnaire (MLHFQ) (17,18), and 6-min walk (6MW) test (19) were also performed in each patient.

IV iron administration. At each visit, the patient lay on a stretcher and underwent a vein cannulation in the forearm with a commercial canula no. 16 (Abbott Laboratories, Abbott Park, Illinois), which was connected to IV tubing that was connected to a bag of isotonic saline solution 0.9%. For the patients in group A (control group), the bag contained only 200 ml isotonic saline solution 0.9%, whereas in group B (intervention group) the bag contained 200 mg/200 ml of ISC. Each infusion was administered throughout 60 min. The infusion was prepared by a nurse before its application, who then put a black cover around the bag and the IV equipment so that neither the patient nor the physician was aware of which therapy was being administered. In order to maintain the double-blind procedure, the nurse who prepared the solution and put the black

cover around the bag and the IV equipment was not the same person who applied the infusion to the corresponding patients. This scheme was followed for 5 consecutive weeks.

Once the 5-week treatment phase was completed, the patients entered the follow-up phase in which monthly check-ups were carried out for the following 5 months.

Follow-up phase. Symptoms were assessed according to NYHA functional classification and MLHFQ. Exercise capacity was quantified using a 6MW test with physicians blinded to the treatment. At each check-up, hematology variables and creatinine clearance were also measured.

Echocardiography evaluation. At baseline, 3 months, and 6 months, transthoracic echocardiograms were obtained using an APLIO 80 (Toshiba, Tokyo, Japan) echocardiographic system with the corresponding transducer (2.5 MHz). Left ventricular ejection fraction was assessed in 2- and 4-chamber views following the recommendations of the American Society of Echocardiography (20). All physicians performing the echocardiographic tests were blinded to the treatment.

Biochemical procedures. Hemoglobin was determined by SYSMEX XT 1800i (Roche Diagnostics, Basel, Switzerland). Serum transferrin was determined by radial immunodiffusion (Diffu-Plate; Biocientifica, S.A., Buenos Aires, Argentina). Transferrin saturation (%) was obtained using a chemical method. Serum iron and CRP were measured using an autoanalyzer Modular P800 (Roche Diagnostics) with the correspondent reagents (Roche Diagnostic GmbH, Mannheim, Germany). The NT-proBNP was measured on the Elecsys 2010 analyzer (Elecsys proBNP Immunoassay, Roche Diagnostics) (21). Creatinine clearance and serum electrolytes were assessed by standard methods.

Statistical method. All statistical analyses were processed through GraphPad Prism, version. 4.0 (GraphPad Software, Inc., San Diego, California). When evaluating parameters with Gaussian distribution, comparisons were carried out using unpaired *t* test between the groups and paired *t* test within each group. For those parameters with non-Gaussian distribution, such as NT-proBNP and CRP, comparisons were performed by nonparametric methods using the Mann-Whitney test between the groups and the Wilcoxon matched pair test within each group. Spearman's correlation was performed to determine the linear correlation between Hb and NT-proBNP and CRP.

In order to evaluate relative risk, Fisher exact test with 95% confidence interval (using the approximation of Katz) was performed. Values were expressed as mean ± standard deviation, and a value of $p < 0.05$ was considered significant.

Results

The mean age of patients in the group A was 74 ± 8 years (range 60 to 89 years) and in the group B 76 ± 7 years (range 64 to 94 years). The etiology of CHF in the patient population is listed in Table 1.

Table 1 Etiology of Congestive Heart Failure in the 2 Groups

	Group A (n = 20)	Group B (n = 20)
Coronary artery disease	13	12
Cardiomyopathy	4	5
Hypertension	3	2
Aortic valve disease	0	1

At baseline, both groups presented nonsignificant differences between themselves concerning parameters evaluated (Table 2). Moreover, they were receiving similar medications for CHF (Table 3, top). Therapy with ISC was well tolerated in all patients, and there were no side effects reported in the 2 groups throughout the study.

At the end of the study, significant increases in Hb level as well as in the other hematology variables such as ferritin and TSAT were observed in patients in group B (Table 2, Fig. 1). These modifications appeared together with a significant improvement in the renal function, expressed bAQ:9, and a higher creatinine clearance, with the values beginning to be significant from the second month after IV iron treatment, which corresponded to the third month of the study, as shown in Figure 1. A better control in blood pressure was similarly achieved in both groups at the end of the study with respect to the baseline values (Table 2). Heart rate and BMI in group B were significantly ($p < 0.01$) lower compared with those seen in group A as indicated in Table 2.

The NT-proBNP was markedly reduced ($p < 0.01$) in patients from group B as well as CRP ($p < 0.01$) at the third month and at the end of the study in comparison with that seen in group A (Table 2, Fig. 2). There was a significant ($p < 0.01$) negative correlation between Hb and NT-proBNP at baseline in both groups, but only in group A at the end of the study (Fig. 3). At the same time, there was also a significant ($p < 0.01$) negative correlation between Hb and CRP initially and at the end of the study in both groups (Fig. 4). Concurrent with these findings, LVEF % in patients from group B was significantly increased ($p < 0.01$) compared with that in group A after the third month and at the end of the study, as illustrated in Figure 2 and Table 2.

There was a favorable and significant ($p < 0.01$) change in NYHA functional class as well as in MLHFQ score in group B versus group A from baseline to the end of the study, as indicated in Table 2. Although no major differences were observed regarding CHF medications in either group, patients in group B had lower diuretic requirements ($p < 0.05$) compared with those in group A at the end of the study (Table 3, bottom).

Concerning patient hospitalizations due to CHF, group A had 5 cases, while there were no hospitalizations because of heart failure in group B (Table 2).

The evaluation of exercise capacity by 6MW test at the end of the study indicated a mild but not significant reduction in the distance achieved during the test related to the baseline records for patients in group A. However, patients from group B showed a significant ($p < 0.01$)

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Table 2 Parameters Evaluated Throughout the Study

Mean ± SD	Baseline		Final (6-Month Follow-Up)	
	Group A (n = 20)	Group B (n = 20)	Group A (n = 20)	Group B (n = 20)
BMI (kg/m^2)	29.0 ± 3.4	28.7 ± 3.3	28.5 ± 3.2	26.7 ± 2.8*†
Heart rate (beats/min)	80.5 ± 8.1	78.7 ± 8.2	76.3 ± 10.4	67.5 ± 5.9*†
Systolic blood pressure (mm Hg)	138.8 ± 8.3	139.7 ± 8.2	134.3 ± 7.3‡	135.7 ± 6.1†
Diastolic blood pressure (mm Hg)	73.4 ± 7.5	74.4 ± 9.6	70.2 ± 6.6‡	70.1 ± 8.3†
Hb (g/dl)	10.2 ± 0.5	10.3 ± 0.6	9.8 ± 0.6	11.8 ± 0.7*†
Ferritin (ng/ml)	70.6 ± 21.4	73.0 ± 29.9	78.9 ± 30.1	240.4 ± 55.6*†
TSAT (%)	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.25 ± 0.04*†
NT-proBNP (pg/ml)	267.5 ± 114.9	255.9 ± 124.6	450.9 ± 248.8‡	117.5 ± 87.4*†
C-reactive protein (mg/l)	6.6 ± 4.3	6.1 ± 3.8	6.5 ± 3.7	2.3 ± 0.8*†
CrCl (ml/min)	37.7 ± 10.2	39.8 ± 10.1	31.7 ± 10.8‡	44.9 ± 11.0*†
EF (%)	30.8 ± 1.7	31.3 ± 3.7	28.8 ± 2.4	35.7 ± 4.7*†
NYHA functional class	2.9 ± 0.6	2.9 ± 0.7	3.3 ± 0.6‡	2.0 ± 0.2*†
MLHFQ score	58 ± 6	60 ± 5	59 ± 8	41 ± 7*†
6MW test (m)	190.7 ± 56.1	192.3 ± 60.9	184.5 ± 58.5	240.1 ± 51.2*†
Number of hospitalizations	—	—	5/20§	0/20

*$p < 0.01$ versus group A at final; †$p < 0.01$ versus group B at baseline; ‡$p < 0.05$ versus group A at baseline; §$p < 0.01$ relative risk = 2.33 (95% confidence interval 1.59 to 3.42).

BMI = body mass index; CrCl = creatinine clearance; EF = ejection fraction; Hb = hemoglobin; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = NT-pro-brain natriuretic peptide; NYHA = New York Heart Association; TSAT = transferrin saturation; 6MW = 6-min walk.

improvement, not only compared with group A at the end of the study, but also compared with baseline performance (Table 2).

Discussion

This is the first double-blind, randomized, placebo-controlled study to evaluate effectiveness of IV ISC administration, without rhEPO supply, regarding hematology, renal function, changes in NT-proBNP, inflammatory status, as well as the number of hospitalizations, exercise tolerance, and change in quality of life of anemic patients with CHF and moderate CRF over a 6-month period.

The results obtained indicate that IV ISC therapy for 5 weeks significantly increased not only Hb concentrations but also ferritin and TSAT. Furthermore, renal function evaluated by creatinine clearance was also improved with this treatment together with an increase in LVEF reduction in NYHA functional class, a better quality of life, fewer hospitalizations, and better exercise tolerance.

Despite the fact that the etiology of anemia in patients with advanced CHF is generally considered multifactorial, one of the most prevalent causes is iron deficiency. However, it is worth mentioning that, although Hb levels may be low in some patients with CHF, this can be due to a dilution factor and may not necessarily be due to iron deficiency per se. However, Nanas et al. (22) have reported a high proportion of patients with iron deficiency in their recent prospective study in nonelderly anemic patients with severe CHF. This group concludes that the iron status of patients with CHF should be thoroughly evaluated and corrected before considering other therapeutic interventions.

In accordance with this report, patients in our current study were receiving similar treatment for CHF at baseline and had similar LVEFs. Nevertheless, only those patients who received IV iron therapy displayed not only a better response in clinical and laboratory variables explored throughout the follow-up period, but also a reduction in diuretic consumption, which suggests an actual benefit in the CHF management.

It is well known that anemia causes tissue hypoxia, inducing a compensatory peripheral arteriolar vasodilatation

Table 3 Patient Medication

CHF Medication	Group A (n = 20)	Group B (n = 20)
Baseline medication		
Diuretics	19/20	19/20
ACE inhibitors	20/20	19/20
AT1 receptor blockers	4/20	5/20
Beta-blockers	20/20	20/20
Vasodilators (nitrites)	6/20	5/20
Digoxin	12/20	13/20
Aspirin	14/20	15/20
6-month follow-up medication		
Diuretics	19/20	13/20*
ACE inhibitors	20/20	18/20
AT1 receptor blockers	5/20	5/20
Beta-blockers	20/20	20/20
Vasodilators (nitrites)	7/20	4/20
Digoxin	14/20	13/20
Aspirin	15/20	15/20

*$p < 0.05$, relative risk = 4.75 (95% confidence interval 0.74 to 30.39).

ACE = angiotensin-converting enzyme; AT1 = angiotensin I; CHF = chronic heart failure.

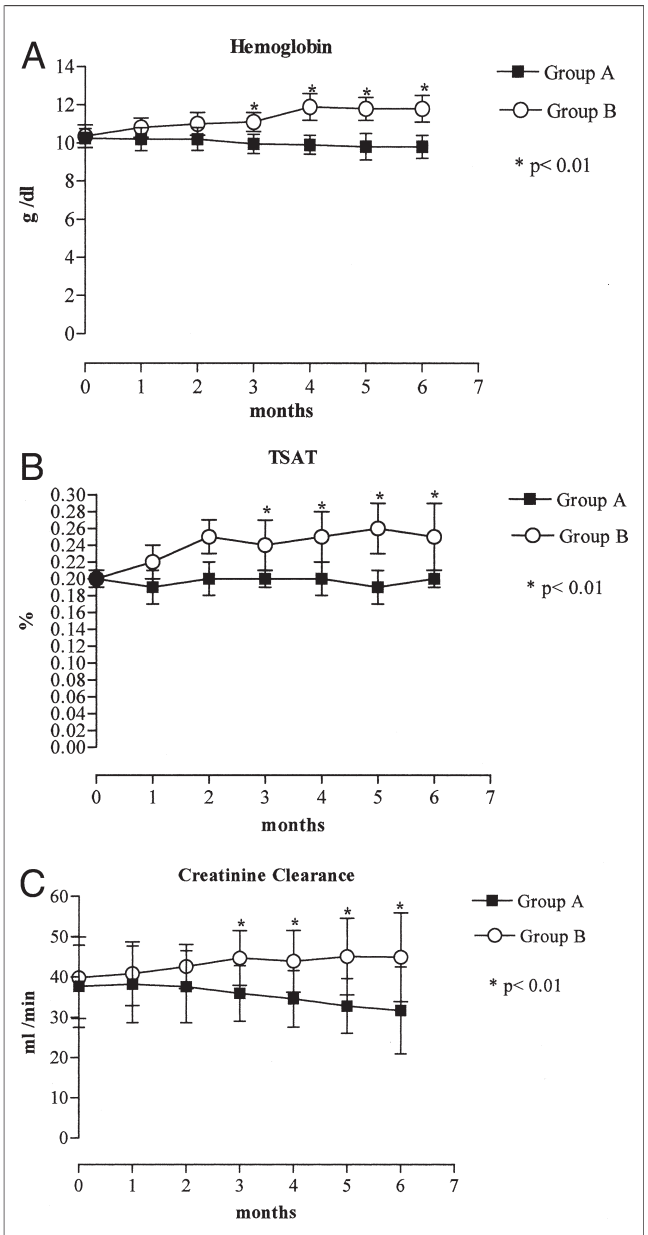

Figure 1 **Hemoglobin Concentration, TSAT, and Creatinine Clearance Throughout the Study**

(A) Note that by the third month, there was a significant difference between the groups in hemoglobin level. **(B)** There was a significant difference in transferrin saturation (TSAT) by the third month. **(C)** There was a significant difference in creatinine clearance by the third month between the groups.

response, which stimulates sympathetic activity with a decrease in renal blood flow.

Consequently, the renin-angiotensin-aldosterone system and antidiuretic hormone are activated, producing sodium and fluid retention (23). As a result, patients in this situation have higher diuretic requirements and some may show resistance to conventional CHF treatments. Reduction in diuretic therapy in patients with CHF after an increase in Hb concentration has already been described but only using a combination of rhEPO with IV iron or darbepoetin alone but never before with IV iron therapy alone as observed in our study (14,15).

It is currently accepted that one of the most useful tests for evaluating the status of patients with CHF is NT-proBNP, not only for systolic but also for diastolic LV dysfunction (11,24). A single measurement of NT-proBNP in patients with advanced CHF can help to identify patients who are at a higher risk of death, and, in one study, it was an even better prognostic marker than anemia (25). However, decreased concentrations of Hb are sufficient to produce serum concentrations of NT-proBNP above diagnostic

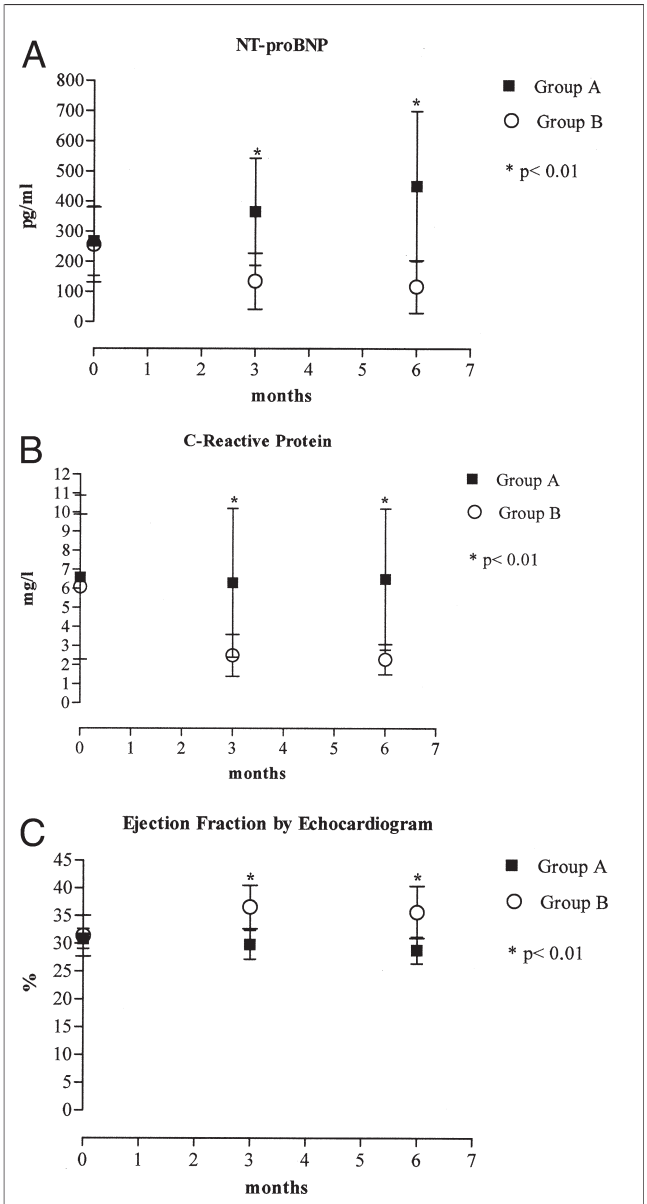

Figure 2 **NT-proBNP, CRP, and LVEF Evaluated in Both Groups Throughout the Study**

(A) NT-pro-brain natriuretic peptide (NT-proBNP); **(B)** C-reactive protein (CRP); and **(C)** left ventricular ejection fraction (LVEF) evaluated by echocardiogram in both groups.

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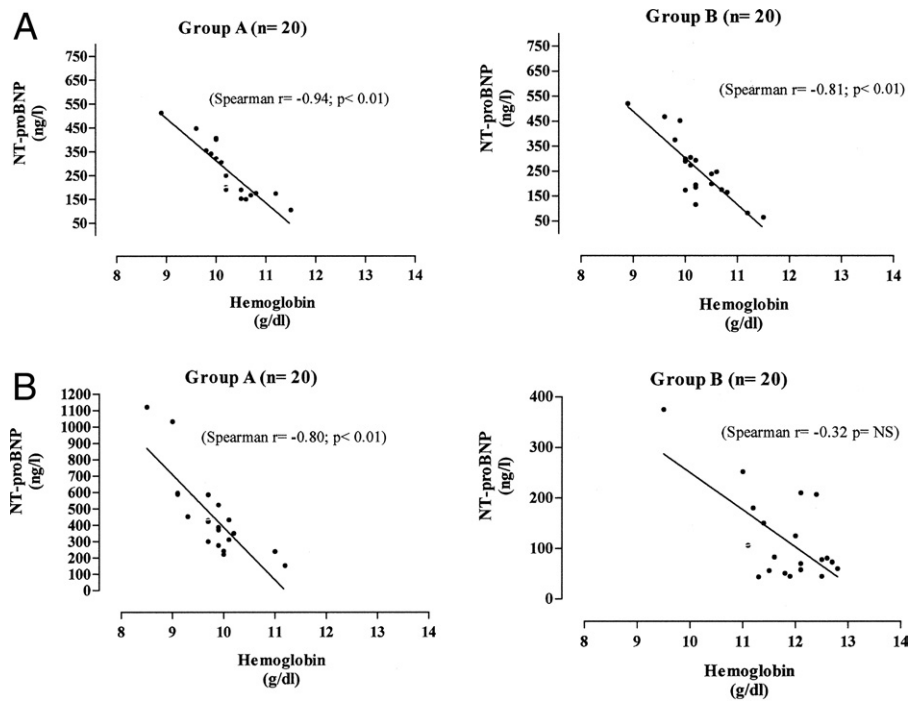

Figure 3 **Relationship Between NT-proBNP and Hemoglobin Level in Both Groups**

A significant ($p < 0.01$) negative correlation between these 2 variables was seen in both groups at baseline **(A)**, although only in group A at the end of the study **(B)**. NT-proBNP = NT-pro brain natriuretic peptide.

cutoffs in anemic patients even without CHF. This is independent of gender, BMI, renal function, LV hypertrophy, and/or valve disease (26). In the present study, IV iron therapy substantially reduced NT-proBNP level, and there was a significant negative correlation between Hb and NT-proBNP in both groups, not only at baseline but also at the end of the study. Since Hb levels are independently predictive of plasma NT-proBNP levels in patients with cardiovascular disease even without (27) or with CHF (28,29), they may represent an important confounder of the relationship between NT-proBNP, cardiac function, and prognosis. In agreement with this statement, a recent multinational trial with a considerable number of patients with dyspnea who were treated in the emergency department reported that, for men without CHF and diastolic CHF patients of both genders, a low Hb might be a confounding variable toward increasing NT-proBNP. Among systolic CHF patients, the presence of a low Hb concentration was not a factor in the interpretation of NT-proBNP results (29).

Chronic heart failure and CRF are both states of persistent inflammatory activation, and higher levels of circulating proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, are known to be associated with greater disease severity and worsened clinical outcomes (30–34).

It is likely that inflammation associated with both CHF and CRF creates a vicious circle of inflammation, with each amplifying the other. In addition, data from the Framingham Heart Study also suggest that an increase in CRP level is associated with a >2-fold increased risk for CHF (35). Chronic hypoxia due to anemia may induce overexpression of proinflammatory cytokines (tumor necrosis factor-α and interleukin-6) (36), which are partially responsible for perpetuating the inflammatory status in patients with CHF and CRF as well as potentiating the relative iron deficiency by stimulating hepcidin. This protein inhibits iron gastrointestinal absorption and also inhibits release of iron from iron stores in the macrophages (37).

Iron deficiency is associated with multiple disturbances including disturbances in the cardiovascular system. Deficiency in iron availability may cause not only an inadequate bone marrow response to anemia but also structural alterations in cardiomyocytes, as reported in experimental models of iron deficiency (38). Recently, Dong et al. (39) have reported important ultrastructural myocardial changes in a group of male rats fed with an iron-deficient diet. Ultrastructural examination revealed mitochondrial swelling and abnormal sarcomere structure in iron-deficient ventricular tissues. Cytochrome c release was significantly enhanced in these animals. Moreover, protein expression of endothelial nitric oxide synthase and inducible nitric oxide synthase, and protein nitrotyrosine formation, were significantly elevated in cardiac tissue or mitochondrial extraction. Additionally, a significant up-regulated reduced nicotinamide

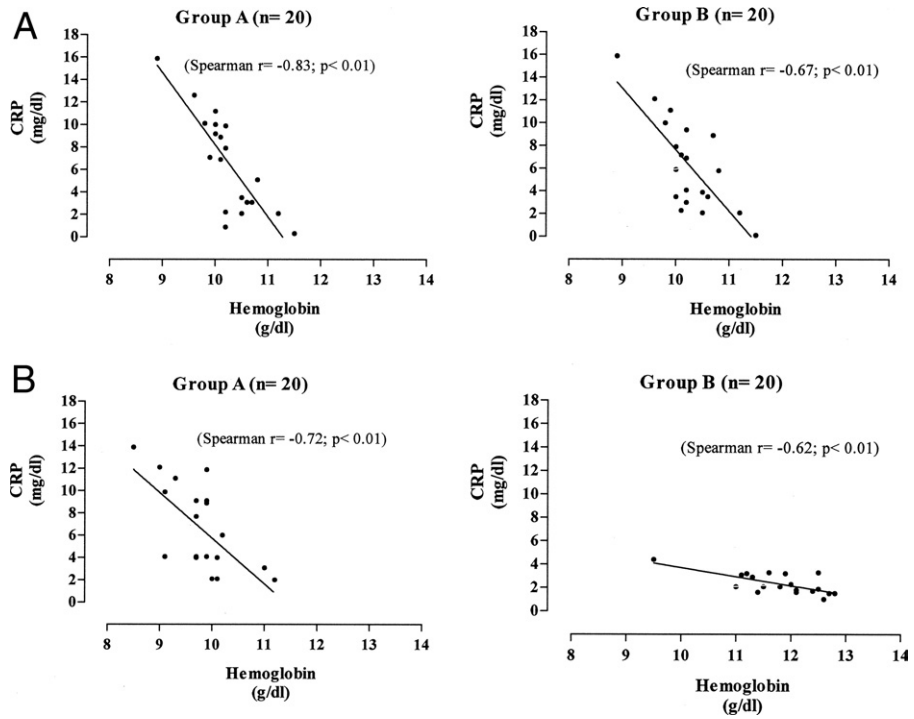

Figure 4 Relationship Between CRP and Hemoglobin Level in Both Groups

A significant ($p < 0.01$) negative correlation between these 2 variables in both groups was seen initially **(A)** and at the end of the study **(B)**. CRP = C-reactive protein.

adenine dinucleotide phosphate oxidase, caveolin-1, and RhoA expression were also detected in ventricular tissue. Therefore, in a clinical scenario, we can speculate that IV iron therapy in those patients with absolute or relative iron deficiency may provide an additional benefit beyond improving Hb level.

Since variable degrees of oxidative stress may be present in the patients with CHF and chronic kidney disease, undoubtedly some concern about oxidative stress and other possible adverse effects caused by IV iron in these patients could be taken into account. However, the amount of iron infused and its effect on ferritin level as well as TSAT were not excessive in our study, as supported by the current recommendation for the management of anemic patients with chronic kidney disease and iron deficiency (40).

In the present study, at baseline, the inflammatory status, as evaluated by CRP level, was similar in both groups. However, only the group with IV iron therapy showed a significant reduction in CRP level at the end of the study. This suggests a better control of inflammation in these patients and probably, as a consequence, an improvement in iron utilization by the bone marrow and possibly by the mitochondria of cardiomyocytes, this resulting in better cardiac performance.

Mancini et al. (41) in a randomized single-blind study with a small number of nonelderly anemic patients with CHF who were treated with rhEPO and oral iron versus placebo reported comparable positive results to those observed in our current study concerning Hb and exercise tolerance. Moreover, a recent study by Palazzuoli et al. (42) in a randomized, double-blind, placebo-controlled study of the combination of rhEPO and oral iron versus oral iron alone in patients with anemia and resistant CHF, the authors concluded that the correction of anemia with EPO and oral iron leads to improvement in NYHA functional class, renal function, and plasma BNP levels and reduces hospitalization. Furthermore, in various studies in patients with moderate-to-severe chronic kidney disease, IV iron alone has successfully increased the Hb in this group (43–46).

It is also important to consider the superiority of IV over oral iron therapy as seen in a recent study (47).

Lately, rhEPO therapy in anemic patients with stage 3 to 4 CRF has become controversial, due to a recent report from Singh et al. (48), the CHOIR (Correction of anemia with epoetin alfa in chronic kidney disease) study, in which the authors found that when using a target Hb level of 13.5 g/dl, as compared with 11.3 g/dl, the cardiovascular risk increased without incremental improvement in the quality of life. Despite a different number of patients in the CHOIR study in comparison with our small pilot study, there are other discrepancies between these 2 trials, which have to be highlighted. The main differences were that in the CHOIR study, the investigators focused on a cohort of

anemic patients with chronic kidney disease. Less than a quarter of all the enrolled patients presented CHF, most with mean TSAT value higher than 25% and a mean ferritin value over 160 ng/ml. One-third were on iron therapy but only a few were on IV iron. In addition, the inflammatory status of the patients as well as details of LV performance by echocardiogram evaluation was unclear in that study. In our study, all the patients had CHF, a marked inflammatory status, and a well-defined low LVEF.

Taking all these factors into account, treatment with rhEPO might not always be the first choice of therapy; giving IV iron alone might be a better approach, not only for increasing Hb levels but also perhaps to improve cardiac performance and life quality.

In various studies, including the present one, the improvement in the Hb level in anemic patients with CHF was unquestionably associated with a better quality of life (13,14,16,42). Even in the CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) trial (49), in which the authors reported that early complete correction of anemia (target level 13.0 to 15.0 g/dl) in patients with chronic kidney disease did not reduce the risk of cardiovascular events, they found at 2 years that the quality of life (general and mental health, and physical function) was significantly better in the group with a high Hb.

Finally, we conclude that the results presented in the current study, together with the preliminary experience by Bolger et al. (16), provide a new insight for a better understanding of the pathophysiology of NT-proBNP and the inflammatory status of anemic patients with CHF and CRF, who received IV iron therapy without rhEPO in addition to conventional treatment for CHF. Nevertheless, as a limitation of the present study, we would like to point out that since this is a small study, it needs confirmation by a large well-powered, randomized, placebo-controlled trial that is mortality driven. Therefore, we consider that our present contribution is perhaps only one of the first steps on the way to finding out the role of IV iron in the anemia of CHF.

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