

Effect of Erythropoietin on Exercise Capacity in Patients With Moderate to Severe Chronic Heart Failure

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Background—Patients with chronic heart failure (CHF) are frequently anemic. An increase in hemoglobin could enhance exercise performance by increasing oxygen delivery. We investigated the effect of erythropoietin (EPO) on exercise performance in anemic patients with CHF.

Methods and Results—Twenty-six anemic patients aged 57 ± 11 years were randomized to receive EPO (15 000 to 30 000 IU per week) or placebo for 3 months. Parameters measured at baseline and end therapy included blood parameters (hemoglobin, hematocrit, plasma volume), exercise parameters (peak oxygen consumption [$\dot{V}O_2$], exercise duration, 6-minute walk), muscle aerobic metabolism (half-time of $\dot{V}O_2$ and near infrared recovery), and forearm vasodilatory function. EPO was well tolerated by all patients. Twelve patients in the EPO group felt improvement versus 1 in the placebo group ($P < 0.05$). There were significant increases in hemoglobin (11.0 ± 0.5 to 14.3 ± 1.0 g/dL, $P < 0.05$), peak $\dot{V}O_2$ (11.0 ± 1.8 to 12.7 ± 2.8 mL \cdot min $^{-1}$ \cdot kg $^{-1}$, $P < 0.05$) and exercise duration (590 ± 107 to 657 ± 119 s, $P < 0.004$) in the EPO group but no significant changes in the control group. Resting and hyperemic forearm vascular resistance and indices of the rate of muscle oxidative capacity were unchanged in both groups.

Conclusion—EPO significantly enhances exercise capacity in patients with CHF. One mechanism of improvement in $\dot{V}O_2$ is increased oxygen delivery from increased hemoglobin concentration. (*Circulation*. 2003;107:294-299.)

Key Words: exercise ■ heart failure ■ growth substances

Erythropoietin (EPO) is a glycoprotein growth factor produced by the kidney to regulate red blood cell production.¹ In chronic diseases such as end stage renal failure, malignancy, or HIV infection, treatment with recombinant human EPO increases hemoglobin (Hb) concentration and improves quality of life. Patients with chronic heart failure (CHF) are frequently anemic,² with the prevalence of anemia increasing with disease severity. The anemia of CHF may result from chronic disease, excessive cytokine production,³ malnutrition, or plasma volume overload.⁴ Previous investigators have reported improvement in functional class, reduction in hospitalizations, and an increase in left ventricular ejection fraction in patients with CHF who are treated with erythropoietin and intravenous iron.^{2,5} Exercise capacity was not assessed in these studies.

A major limiting symptom in patients with CHF is exertional fatigue resulting from reduced cardiac output and intrinsic skeletal muscle and vascular abnormalities. Normalization of Hb concentration in patients with CHF may result in improved exercise capacity by increasing oxygen delivery. Alternatively, Hb may reduce oxidative stress in these patients by scavenging oxygen free radicals. This may improve vasodilatory capacity and/or increase rate of oxygen delivery. The purpose of our study was to investigate the effect of

erythropoietin therapy on exercise capacity in patients with CHF and to define its potential mechanism(s). Accordingly, a randomized, single-blind, controlled study of the effect of erythropoietin on exercise performance, hematologic parameters, including plasma volume, and vasodilatory function was conducted in patients with moderate to severe CHF.

Methods

Patient Population

Patients with New York Heart Association functional class III-IV CHF on a stable medical regimen for 4 weeks with a hematocrit (Hct) $< 35\%$, serum creatinine < 2.5 mg/dL, and erythropoietin level < 100 mU/mL were eligible for study. Patients were excluded if they were nonambulatory, on continuous inotropic agents, severely volume overloaded, or had exercise limited by peripheral vascular or lung disease, iron deficiency anemia, or a history of erythropoietin treatment within the past 6 months. The protocol was approved by the Columbia Presbyterian Institutional Review Board. Written informed consent was obtained from all patients.

Study Protocol

A randomized, single-blind, prospective study was performed with a 2:1 randomization of patients to erythropoietin (Amgen Inc) or placebo (0.9% saline). Patients in the control group received 1 subcutaneous injection of normal saline (0.5 mL). Patients randomized to EPO received 5000 U subcutaneously 3 times a week. If after

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4 weeks the increase in Hb was <1 g/dL, the EPO dose was increased to 10 000 IU 3 times a week. Patients randomized to EPO were prescribed ferrous gluconate 325 mg daily and folate 1 mg daily. Follow-up visits were every 2 weeks for the first month and then monthly. During each follow-up visit, a complete blood count was performed. The study duration was 3 months or until hematocrit was $\geq 45\%$.

Measurements

Assessments performed at baseline and end therapy included red blood cell and plasma volumes, peak $\dot{V}O_2$, 6-minute walk test, Minnesota Living With Heart Failure Quality of Life questionnaire, patient's global assessment, assessments of muscle aerobic capacity using half-time recovery of $\dot{V}O_2$, and near infrared absorption and vasodilatory function using forearm plethysmography.

Exercise Parameters

Maximal bicycle testing was performed in the fasting state with metabolic measurements (Medical Graphics 2001). Patients breathed through a disposable pneumotach. Exercise was begun at 0 watts and increased by 25 watts every 3 minutes until reaching the maximally tolerated workload. At the end of exercise, the patient continued breathing into the mouthpiece for 4 minutes. $\dot{V}O_2$ at the anaerobic threshold was identified as the nadir of the ventilatory equivalent for $\dot{V}O_2$. An un-encouraged 6-minute walk test was also performed. Patients completed a Minnesota Living With Heart Failure Questionnaire,⁶ and at the completion of the study were asked whether they felt improvement.

Hematinics and Plasma Volume

Serum erythropoietin level was measured by radioimmunoassay (Quest Diagnostics). The normal range was 4.1 to 19.5 mU/mL. Plasma and red blood cell volume were determined by the ¹³¹I-radiiodinated (¹³¹I) serum albumin technique as previously described⁷ to distinguish between true or dilutional anemia. Twenty-five μ Ci ¹³¹I serum albumin (Megatope, Iso-Tex Diagnostics, Inc) was injected into a peripheral vein from a prefilled syringe. Five cc of venous blood was collected before injection and every 6 minutes until 36 minutes after isotope injection. Specimens were analyzed with an automated system (BVA-100 Blood Volume Analyzer, Daxor Corp) and compared with normal values on the basis of age, sex, height, and weight.

Assessment of Muscle Oxidative Metabolism

Rate of skeletal muscle oxidative capacity was determined by near-infrared spectroscopy (NIRS) and by gas exchange analysis as previously described.^{8,9} In brief, an NIRS probe (Runman, NIM Inc) was secured to the thigh 10 cm above the patella over the vastus lateralis, and a rapidly inflating pneumatic cuff was placed above the probe. With the patient seated, the cuff was inflated to supra-systolic pressure for 3 minutes and released. The time to midpoint of recovery of the signal was measured.

Rate of skeletal muscle oxidative capacity was also measured by determining the kinetics of $\dot{V}O_2$ recovery. At the end of exercise, the workload was removed, but patients continued to breathe into the metabolic cart for 4 minutes. The half-time of recovery of oxygen consumption ($T_{1/2} \dot{V}O_2$) is the time required for a 50% fall in the peak $\dot{V}O_2$ level.

Forearm Hemodynamics

Forearm blood flow (FBF, mL/min per 100 mL of forearm volume) was determined by venous occlusion strain gauge plethysmography at rest and after 5 minutes of arterial occlusion as previously described.¹⁰ For each measurement, forearm venous blood flow was occluded just proximal to the elbow with rapid inflation of a blood pressure cuff to 40 mm Hg. A wrist cuff was inflated to supra-systolic pressures 1 minute before and during each measurement. Five plethysmographic measurements were averaged for determination of FBF at rest. Postischemic FBF was determined as the maximum forearm blood flow determined within 5 seconds after the release of

TABLE 1. Clinical Characteristics

	Control (n=8)	EPO (n=15)
Age, y	55 \pm 7	60 \pm 12
Etiology, n		
CAD	4	8
Cardiomyopathy	4	7
Sex, n		
Male	5	13
Female	3	2
LVEF, %	21 \pm 4	24 \pm 6
Hemoglobin, g/dL	10.9 \pm 1.3	11.0 \pm 0.6
Creatinine, mg/dL	1.6 \pm 0.5	1.6 \pm 0.4
EPO level, mU/L	32 \pm 16	24 \pm 14
Peak $\dot{V}O_2$, mL \cdot kg ⁻¹ \cdot min ⁻¹	10.0 \pm 1.9	11.0 \pm 1.8

CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction.

an upper arm blood pressure cuff inflated to supra-systolic pressure for 5 minutes. During each FBF measurement, mean arterial pressure was determined in the contra-lateral arm with an automated device (Dinamap, model 1846, Critikon). Forearm vascular resistance was determined as the ratio of mean arterial pressure and forearm flow.

Statistical Analysis

Intra-group differences were compared by paired *t* testing and inter-group differences by unpaired *t* testing. A *P* < 0.05 was considered statistically significant. Noncontinuous variables were compared by χ^2 analysis. All results are reported as mean \pm SD.

Results

Patient Characteristics

Twenty-six patients were enrolled and 23 patients completed the study. Two patients underwent elective transplant (1 in

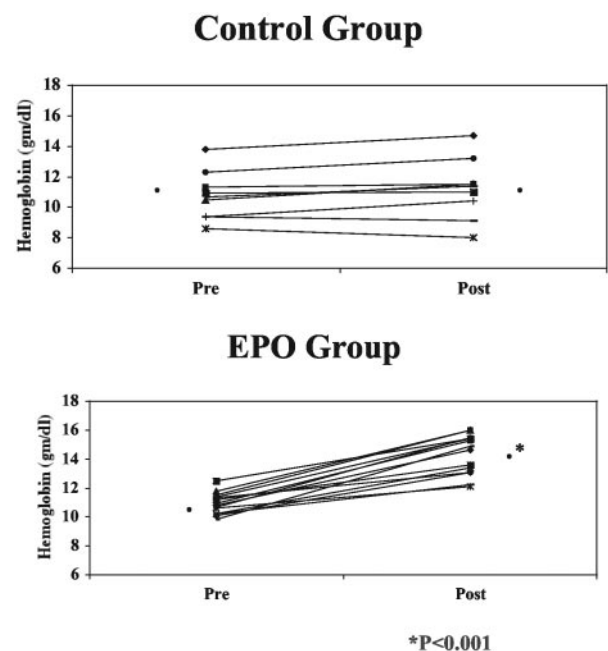


Figure 1. The effect of erythropoietin on plasma hemoglobin in the treated and control groups.

TABLE 2. Response to EPO in Low and Normal RBC Volume Subgroups

	Low RBC Volume (n=5)		Normal RBC Volume (n=4)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Hb, g/dL	11.3±0.6	14.9±1.1*	11±0.5	14.3±1.0*
$\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	12.4±2.3	14.2±3.3*	11.9±0.9	13.6±1.3*
RBC volume, mL	-410±135	312±447*	231±169†	502±47*
Plasma volume, mL	986±410	1028±543	2090±505†	1068±335*

**P*<0.05 pretreatment vs posttreatment.†*P*<0.05 anemic vs dilutional.

each group). One patient in the treatment group died from progressive heart failure. Fifteen patients received treatment with EPO and 8 patients received placebo. Clinical characteristics including age, etiology of heart failure, sex, left ventricular ejection fraction, baseline Hb, erythropoietin levels, serum creatinine, and peak $\dot{V}O_2$ did not differ between the groups (Table 1). Background heart failure therapy included treatment with diuretics, digoxin, angiotensin-converting enzyme inhibitors or AII blockers, and β -blockade and was not different between the 2 groups. One patient was not on digoxin, 2 were not on angiotensin-converting enzyme inhibitors or AII blockers, and 3 were not on β -blockers.

Tolerability

In the EPO group, duration of therapy averaged 70±11 days. Four patients were up-titrated to 10 000 U three times per week. Weight did not change in either group. Diuretic dose was increased in 5 patients in the erythropoietin group versus 3 patients in the control group (*P*=NS). EPO was well tolerated. None of the patients had thrombotic complications or hypertension. Four patients in the control group were hospitalized for decompensated CHF versus 1 patient in the EPO group, who ultimately died. The other 2 admissions in the EPO group were for syncope and pneumonia.

Hematologic Responses to EPO

Hemoglobin increased from 11±0.6 to 14.3±1.2 g/dL (*P*<0.0001, Figure 1). In the control group, hemoglobin was unchanged (10.9±1.1 versus 11.5±1.3 g/dL, *P*=NS).

Red blood cell volume estimations were performed in 15 patients with the ¹³¹I-tagged albumin technique. Six (40%) of

the 15 patients had normal red blood cell (RBC) volume as predicted from age, sex, and body surface area. The anemia in these patients was dilutional secondary to increased plasma volume.

Nine of the EPO-treated patients underwent ¹³¹I studies. At baseline, 5 patients had reduced RBC volume, whereas 4 had normal RBC volume. The response to EPO treatment for these 2 sub-groups is shown in Table 2. The increase in Hb was comparable in both groups, as was the increase in peak $\dot{V}O_2$. Mean RBC and plasma volume excess or deficit derived from the difference of the measured and ideal values are shown in Table 2. In the dilutional anemia sub-group, RBC volume seems to replace the plasma volume excess after EPO treatment.

Effect of EPO on Exercise Parameters

Heart rate and blood pressure at rest and peak exercise did not change between baseline and end assessment in either group (Table 3). The respiratory quotient at baseline and end assessment did not change in either group, indicating comparable intensity of effort between the groups and the serial studies.

Peak $\dot{V}O_2$ increased significantly from 11±0.8 to 12.7±2.8 mL · kg⁻¹ · min⁻¹ (*P*<0.05, Figure 2). In the control group, peak $\dot{V}O_2$ declined by an average of 0.5 mL · kg⁻¹ · min⁻¹ from 10.0±1.9 at baseline to 9.5±1.6 mL · kg⁻¹ · min⁻¹ (*P*=NS). Similarly, $\dot{V}O_2$ at the anaerobic threshold was significantly increased in the EPO-treated patients but was unchanged in the control group. A significant positive linear correlation was observed between the change in plasma Hb and the change in peak $\dot{V}O_2$ (Figure 3). Exercise duration

TABLE 3. Maximal and Submaximal Exercise Capacity at Baseline and End of Study

	Control				EPO			
	Baseline		End		Baseline		End	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart rate, bpm	77±9	100±19	81±11	102±22	76±9	106±14	73±7	102±13
Blood pressure, mm Hg	88±8	96±9	81±8	90±10	87±8	94±12	87±8	94±15
Respiratory quotient	0.83±0.04	1.14±0.11	0.88±0.07	1.10±0.11	0.84±0.06	1.13±0.08	0.85±0.07	1.10±0.08
$\dot{V}O_2$		10.0±1.9		9.5±1.6		11.0±1.8		12.7±2.8*
$\dot{V}O_2$ AT		8.2±1.2		7.1±0.8		7.5±1.1		8.7±1.9*
Exercise duration, s		542±115		459±172		590±107		657±119†
6-minute walk distance, ft		929±356		1052±403		1187±279		1328±254*

 $\dot{V}O_2$ AT indicates oxygen consumption at anaerobic threshold.**P*<0.05 rest vs exercise; †*P*<0.004 rest vs exercise.

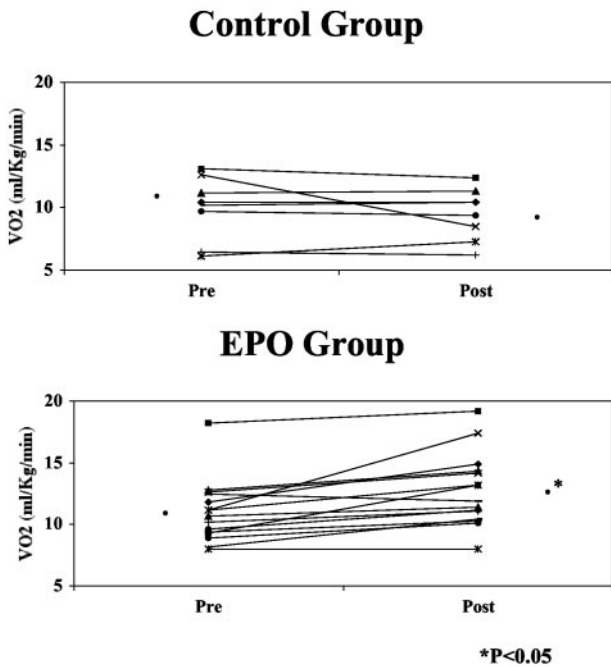


Figure 2. The effect of erythropoietin on peak $\dot{V}O_2$ in the treated and control groups.

tended to decrease in the control group but increased significantly in the EPO-treated patients. Submaximal exercise performance assessed using the 6-minute walk test increased significantly in the EPO-treated group but not in the control group (Table 3).

Quality of Life

Twelve of the 15 patients on active EPO therapy felt improved versus 1 of 8 patients in the control group ($P<0.05$). In the control group, the Minnesota Living With Heart Failure Questionnaire score rose by an average of 10 points, indicating decreased quality of life (56 to 66). In the EPO-treated group, the score declined by an average of 9 points, representing subjective improvement (46 to 37) ($P<0.04$).

Effect of EPO on Muscle Oxidative Metabolism

No change in NIR recovery time was seen in the control (pre: 28 ± 27 ; post: 34 ± 34 s; $P=NS$) or EPO-treated patients (pre: 19 ± 4 ; post: 16 ± 4 s; $P=NS$) at baseline and end studies. The

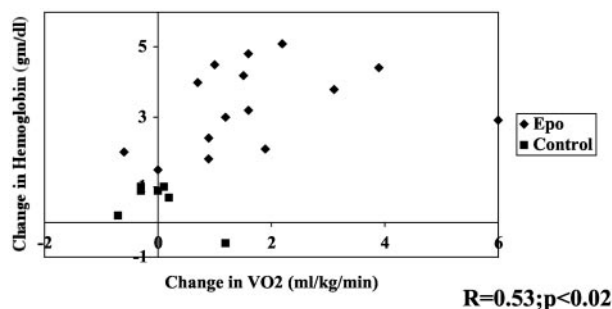


Figure 3. Correlation between the change in hemoglobin and the change in peak $\dot{V}O_2$ in all patients.

$T_{1/2} \dot{V}O_2$, another index of skeletal muscle aerobic capacity, was unchanged in the control (pre: 115 ± 35 ; post: 113 ± 30 s; $P=NS$) and EPO-treated (pre: 152 ± 35 ; post: 148 ± 29 s; $P=NS$) groups.

Effect of EPO on Forearm Vasodilation

FBF and vascular resistance at rest and after 5 minutes of arterial occlusion are shown in Table 4. Rest and postischemic FBF and forearm vascular resistance did not change before and after treatment in either group.

Discussion

This is the first study to examine the effect of EPO on exercise performance in patients with heart failure. Our findings demonstrate improved submaximal and maximal exercise capacity in this patient population. The improved exercise performance was not accompanied by changes in the rate of muscle oxidative metabolism or vasodilatory function. Thus, the mechanism for the increment in $\dot{V}O_2$ with EPO therapy seems to be derived from increased oxygen delivery from the increased Hb concentration.

Anemia in CHF

Anemia is common in elderly patients with CHF and increases with disease severity.^{2,11,12} Anemia in CHF is frequently untreated, however, despite previous reports that anemia can contribute to the worsening of CHF.¹³ Recent analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) database show that anemia is an independent risk factor for mortality in patients with left ventricular dysfunction.¹⁴ Potential mechanisms by which anemia could worsen CHF include exacerbation of myocardial and peripheral hypoxia, increased venous return and cardiac work, and consequent left ventricular hypertrophy.¹⁵ Hypoxia could also potentially lead to activation of neurohormones and cytokines. In turn, cytokines can exacerbate the anemia,³ leading to a vicious cycle, the recently coined cardio-renal-anemia syndrome.¹⁶ Normalization of Hb concentration in patients with CHF may interrupt this cycle.

The mean serum EPO level in our study was 24 mU/mL, which is slightly above the normal range of our laboratory. Previous studies reported elevated serum EPO levels in patients with severe CHF.^{17,18} The increased production of EPO in CHF patients with anemia may reflect the presence of renal hypoxia and a compensatory attempt to augment O_2 delivery to peripheral tissues through erythrocytosis.

The pathogenesis of anemia in CHF is multifactorial. A pseudo or dilutional anemia from plasma volume overload⁴ may occur. In this study, 40% of patients who underwent ^{131}I studies had normal red cell volume predicted on the basis of age, sex, and body surface area, suggesting a dilutional anemia due to plasma volume expansion. Despite the dilutional etiology of the anemia, EPO was well tolerated by the patients, with no excessive volume overload and with a significant improvement in exercise capacity. Treatment of these patients resulted in a beneficial shift in blood composition, with a reduction in plasma volume and increase in red blood cell volume that may explain the marked symptomatic improvement.

TABLE 4. Effect of EPO on Forearm Vascular Function

	Control		EPO	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Rest FBF, mL/min per 100 mL	4.76±2.16	5.17±1.66	4.49±1.37	4.08±1.26
Postischemic FBF, mL/min per 100 mL	42.9±12.0	37.7±11.2	53.2±12.9	46.8±13.0
Rest forearm vascular resistance	22.5±9.7	18.5±4.8	21.4±10.7	21.6±5.2
Postischemic forearm resistance	2.2±0.5	2.5±0.94	1.5±0.4	1.9±0.6

Use of EPO in Heart Failure

Silverberg et al^{2,5} had previously shown in nonrandomized trials that treatment of anemia with EPO and IV iron in patients with severe CHF improved the patients' functional class and cardiac function. Our study confirms the tolerability of this drug in patients with heart failure. Similar to Silverberg et al, we observed a dramatic improvement in quality of life and almost uniform improvement in the patients' global assessment with active treatment. We did not observe any improvement in renal function, similar to the second report by Silverberg et al.⁵ Although an increase in blood pressure has been reported with large doses of EPO,^{19,20} no effect on resting or exercise blood pressure was observed in our study cohort. Moreover, forearm vascular resistance was unchanged in those patients receiving active therapy.

Effect of EPO on Exercise Capacity

The effect of erythropoietin on exercise performance has previously been examined in small studies of athletes or normal subjects,^{21,22} where it was applied as a performance-enhancing drug. In these studies, an increase in exercise performance was observed. In patients with chronic renal insufficiency, EPO has also been shown to improve exercise capacity.²³ Our findings extend these observations to patients with heart failure, in whom both submaximal and maximal exercise capacity was improved.

The mechanism by which EPO improves exercise capacity is not known. In sports medicine, the mechanism has been presumed to be from increased Hb concentration leading to increased oxygen delivery. In disease states where oxidative stress is increased, however, Hb may reduce oxidative stress by scavenging for O₂ free radicals. This may improve endothelial function and/or increase rate of oxygen delivery. In end stage renal patients, EPO has been shown to improve skeletal muscle function and O₂ use,²⁴ as well as endothelial function.²⁵ In our study, however, we found no evidence of these effects. Whether the use of oral iron supplementation masked any potential vasodilatory effects is unclear.

Two indirect assessments of muscle aerobic metabolism were obtained in this study. Previous investigators have demonstrated that the half-time of $\dot{V}O_2$ recovery correlates with metabolic recovery of the muscle⁹ and is slowed in patients with heart failure. Similarly, the half-time to recover muscle oxygenation using NIRS also correlates with muscle metabolic recovery. The prolonged kinetics of oxygen recovery may be due to redistribution of blood flow after exercise to adjacent areas of nonexercising muscle because of adrenergic mediated vasoconstriction, impaired maximal metabolic vasodilatation, or decrease in blood velocity. The $\dot{V}O_2$ half-

time values in our study are comparable to those reported in patients with moderate to severe heart failure. No alteration was seen with EPO therapy. Similarly, the half-time to recover muscle oxygenation using NIRS was also unaffected by therapy. Whether this is the consequence of unaltered vasodilatory capacity or decreased blood velocity with higher Hb concentrations is unclear. Thus, in our protocol, the increment in $\dot{V}O_2$ with EPO therapy is not due to changes in muscle oxidative capacity.

The rate of rise of the Hb was more rapid in this study than that observed in prior reports.^{2,5} Rapid and near normal correction of the Hct to a mean of 42% in hemodialysis patients increased cardiovascular events compared with those maintained at a Hct of 30%.²⁶ Although there is some uncertainty about the interpretation of these findings,²⁷ there is increasing evidence that correction of anemia to a Hct of 36% is safe. In our study, this rapid replacement regimen was well tolerated, with no thrombotic or hypertensive events. Whether a slower and/or a more sustained increase in plasma Hb may have yielded greater improvement in maximal and submaximal exercise capacity as longer duration of treatment provided more time to reverse intrinsic skeletal muscle and vascular changes is unknown.

Proportional changes in Hb and $\dot{V}O_2$ would be expected on the basis of the Fick equation if we assume peak exercise cardiac output and the arterial-venous oxygen difference to be constant during the course of the study. In our study, the improvement in $\dot{V}O_2$, although significant, was less than anticipated because the average Hb in this study increased by 30%, whereas average $\dot{V}O_2$ increased by 15%. Further work is needed to determine the mechanisms underlying this discrepancy.

Study Limitations

This is a single center study that is limited by the small sample size and single blind design. The placebo group received active treatment, as at the start of the study each control subject received an injection of normal saline. The investigators were not blinded to the study, but many of the parameters that improved with treatment were objective and could not be easily biased by the investigator. Nevertheless, subtle biases can occur with the single blind design.

Clinical Implications

Our findings, together with those of Silverberg et al,^{2,5} suggest that treatment with EPO could be beneficial in anemic patients with CHF. These beneficial effects on exercise capacity and quality of life are seen whether the anemia

is true or dilutional in nature. Our findings need to be confirmed by multicenter clinical trials.

Conclusions

Correction of anemia with EPO is well tolerated in CHF patients. It increases Hb and exercise capacity in these patients. Use of EPO is not accompanied by changes in the rate of muscle oxidative capacity or vasodilatory function. One mechanism of the improvement in $\dot{V}O_2$ with EPO therapy is the increased oxygen delivery from increased Hb concentration.

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