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**CLINICAL INVESTIGATIONS****Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients**Charlotte E. van Iperen MD <sup>2</sup>Carlo A. J. M. Gaillard MD, PhD <sup>1</sup>Rob J. Kraaijenhagen PhD <sup>1</sup>Branko G. Braam MD, PhD <sup>2</sup>Joannes J. M. Marx MD, PhD <sup>2</sup>Albert van de Wiel MD, PhD <sup>1</sup>

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**Objectives:** Critically ill patients often are anemic, which may impair oxygen delivery. Transfusion of red cells and supplementation with vitamins or iron are the usual therapeutic strategies, whereas only sporadic data are available on the use of epoetin alfa in these patients. We investigated *endogenous* erythropoietin (EPO) production and the response to epoetin alfa in anemic intensive care unit (ICU) patients.

**Design:** Randomized, open trial.

**Setting:** Multidisciplinary ICU in a single secondary care center.

**Patients:** Thirty-six critically ill patients admitted to the ICU who became anemic (hemoglobin concentration, <11.2 g/dL or <12.1 g/dL in case of cardiac disease) were randomized to one of three study groups.

**Interventions:** All patients received folic acid (1 mg) daily. The control group received no additional therapy, the iron group received 20 mg of iron saccharate intravenously (iv) daily for 14 days. The EPO group received iv iron and epoetin alfa (300 IU/kg) subcutaneously on days 1, 3, 5, 7, and 9.

**Measurements and Main Results:** Blood and reticulocyte counts were measured daily for 22 days. Serum EPO, C-reactive protein, serum transferrin receptor, and iron variables were measured on days 0, 2, 6, 10, and 21. Blood loss and red cell

transfusions were recorded.

Serum EPO concentrations were inappropriately low for the degree of anemia at baseline, with no difference between patients with and without renal failure. *Exogenous* administration of EPO increased EPO concentrations from  $23 \pm 13$  to a maximum of  $166 \pm 98$  units/L on day 10 ( $p < .05$ ). Reticulocyte count increased exclusively in the EPO group from  $56 \pm 33 \times 10^9$  /L to a maximum of  $189 \pm 97$  on day 13 ( $p < .05$ ). Serum transferrin receptor rose only in the EPO group from  $3.7 \pm 1.4$  to  $8.6 \pm 3.1$  mg/L on day 10 ( $p < .05$ ) and remained elevated on day 21, indicating an increase in erythropoiesis. Hemoglobin concentration and platelet count remained identical in the three study groups.

**Conclusion:** *Endogenous* EPO concentrations are low in critically ill patients. The bone marrow of these patients is able to respond to *exogenous* epoetin alfa, as shown by elevated concentrations of reticulocytes and serum transferrin receptors. (Crit Care Med 2000; 28:2773–2778)

**KEY WORDS:** erythropoietin; epoetin alfa; anemia; critical illness; inflammation; reticulocytes; serum transferrin receptor; blood transfusions; iron metabolism; randomized clinical trial

Anemia occurs often in intensive care unit (ICU) patients as a result of inflammation [1] [2], nutritional deficiencies, renal failure or blood loss owing to frequent phlebotomies, gastric stress bleeding, coagulation disorders, or surgical procedures [3] [4] [5]. Interestingly, recently, it was reported that erythropoietin (EPO) concentrations appear to be inappropriately low in critically ill patients [6] [7] [8] [9].

No general guidelines exist for the optimal hemoglobin or hematocrit concentration in ICU patients. A low hemoglobin concentration impairs, among others, oxygen availability to the tissues, whereas a high hematocrit may be unfavorable from a rheologic point of view [10] [11]. Transfusion of red cells and supplementation with iron and/or vitamins are the usual therapies if the hemoglobin concentration falls. A number of factors such as age, cardiac performance, expected blood loss, and sometimes even religion influence the decision to transfuse a patient [12] [13] [14].

Red cell transfusions increase the risk of transmission of blood-borne agents, such as known and unknown viral infections [10] [15]; a new, so-called TT virus was recently discovered [16]. Moreover, at this stage, it is unknown whether other infective agents, such as prions, are transmitted by red cell transfusions [17]. Furthermore, red cell transfusions may cause hemolytic and nonhemolytic reactions and immunosuppression [10] [15]. Supported by the finding of relatively low endogenous EPO concentrations in critically ill patients [6] [7] [9], we undertook this open, prospective, randomized study to investigate the erythropoietic response to recombinant human erythropoietin (epoetin alfa) in anemic ICU patients.

## MATERIALS AND METHODS

### Subjects.

Thirty-six patients admitted to the ICU were included in the study, which was performed in 1996 and 1997. The ICU of the Eemland Hospital, Amersfoort, The Netherlands, is an eight-bed ward with a mixed population of medical, surgical, trauma, and neurologic patients. Patients were eligible if they

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reached a hemoglobin concentration of  $<11.2$  g/dL or, in case of cardiac disease, a hemoglobin concentration of  $<12.1$  g/dL. Other inclusion criteria were age of  $>18$  yrs, an expected ICU stay of at least 7 days, and informed consent from the patient or the patient's representative. The expected duration of the ICU stay was judged on clinical grounds and Acute Physiology and Chronic Health Evaluation (APACHE) score by the ICU team at admittance to the unit.

Patients with the following criteria were excluded: pregnancy, iron deficiency anemia (serum ferritin concentration of  $<50$   $\mu$ g/L), vitamin B<sub>12</sub> deficiency ( $<160$  pmol/L), recent use of cytostatics or recent radiotherapy, a life expectancy of  $<7$  days, chronic renal failure, and prior use of epoetin alfa.

### Study Design.

Study participants were randomly assigned to receive intravenous (iv) folic acid (1 mg daily) alone (control group), iv folic acid (1 mg daily) and iv iron saccharate (20 mg daily, Venofer, Vifor, St. Gallen, Switzerland) from days 1 to 14 (iron group), or iv folic acid (1 mg daily) and iv iron saccharate (20 mg daily) from days 1 to 14 and epoetin alfa (300 IU/kg subcutaneously, Eprex,

JanssenCilag, Tilburg, The Netherlands) on days 1, 3, 5, 7, and 9 (EPO group). A high dose of epoetin alfa was used, anticipating resistance to EPO in critically ill patients; the presence of proinflammatory mediators such as tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and interleukin-1 may impair the response of erythroid precursor cells to EPO and the production of EPO [1]. The patients were followed up from day 0 to and including day 21. Transfusion of red cells was standardized at a hemoglobin concentration of 8.9 g/dL, in cases of a cardiac history at 9.7 g/dL, or when clinically necessary. The study was approved by the Medical Ethical Committee of the Eemland Hospital, Amersfoort, The Netherlands.

## Measurements.

Clinical data were recorded at the day of admittance to the ICU and at the start of the study, including medical speciality and APACHE II score [18]. Blood loss was measured daily for 22 days (days 0-21) by counting laboratory test tubes, blood loss via drains, and blood loss during continuous hemofiltration. A conservative way of withdrawing blood was achieved by using a special device, the "Venous Arterial Blood Management Protection System" (VAMP, Baxter Healthcare, Utrecht, The Netherlands), which was connected to a canula inserted in the radial artery [19]. Bone marrow aspirates were performed on day 0 of the study, after separate informed consent was given by the patient or a representative.

## Laboratory Analysis.

Total blood count was measured (E-5000 Hematology Analyser, Sysmex Toa, Kobe, Japan) daily from day 0 up to and including day 21, as well as the reticulocyte count (flow cytometric analysis, R-1000, Sysmex) [20]. At baseline (day 0), the serum EPO concentration was measured by radioimmunoassay (Incstar, Stillwater, MN). The serum transferrin receptor was determined by enzyme-linked immunosorbent assay (Ramco, Diagnostic Products, Apeldoorn, The Netherlands). Iron metabolism was analyzed by measuring serum iron and transferrin (Hitachi 717, Boehringer, Mannheim, Germany; serum iron: normal range, 55–170  $\mu\text{g/dL}$ ; serum transferrin: normal range, 2.0–3.6 g/L), transferrin saturation (calculated from serum iron and transferrin concentration; normal range, 0.20–0.45), serum ferritin (ES 300, Boehringer; normal range, 10–200  $\mu\text{g/L}$ ), and zinc protoporphyrin (E-5000 Hematology Analyser; normal range, 0.05–0.20  $\mu\text{mol/mmol hemoglobin}$ ); vitamin B<sub>12</sub> and folic acid concentrations were analyzed (ES 300, Boehringer) as well as serum concentrations of creatinine, haptoglobin, and C-reactive protein (CRP; Hitachi 717; normal range, 0–10 mg/L). Serum EPO concentrations, the variables of iron metabolism, serum transferrin receptor, and CRP were measured additionally on days 2, 6, 10, and 21 of the study.

## Statistical Analysis.

Data are expressed as mean  $\pm$  SD or median (range), as appropriate. If data were not normally distributed, comparisons were performed on log-transformed data. Statistical analysis for parametric data included analysis of variance (ANOVA) and repeated measurements analysis of variance (RMANOVA), with the Student's Newman-Keuls' test as *post hoc* test (SigmaStat, Jandel, SPSS, Chicago, IL). Categorical data were analyzed by the Fischer's exact test or the chi-square test, whereas correlations were analyzed using multiple regression analysis (SigmaStat).

# RESULTS

## Patients Characteristics.

Except that patients in the control group had a marked longer length of stay in the ICU, there were no significant differences between groups at the moment of inclusion in the study ( Table 1 ). In the control group, four patients died within the study period at respectively days 8, 16, 16, and 21. The cause of death was multiple organ dysfunction syndrome in three cases and withdrawal of care because of a poor neurologic prognosis after resuscitation in one patient. In the iron group, two patients died within the study period on day 6 because of a fatal arrhythmia and on day 16 because of multiple organ dysfunction syndrome. One patient was withdrawn from the study because of fulminant bleeding on day 7 caused by a gastric ulcer, which needed acute surgery. In the EPO group, two patients died within the study period on day 16 (multiple organ dysfunction syndrome) and on day 21 because of fulminant pancreatitis as a complication of acute abdominal aortic surgery. Overall (ICU and non-ICU) deaths were seven, four, and five in the control group, iron group, and EPO group, respectively ( Table 1 ).

## Hematologic Findings and Serum Transferrin Receptors.

Reticulocyte counts increased significantly in the EPO group from  $56 \pm 33 \times 10^9 /\text{L}$  to a maximum of  $189 \pm 97 \times 10^9 /\text{L}$  on day 13 ( Fig. 1 ). This increase gradually disappeared when the epoetin alfa injections were stopped on day 9, and on day 21, reticulocyte counts had decreased to  $90 \pm 51 \times 10^9 /\text{L}$ . The reticulocyte count in the EPO group differed significantly from the control and iron groups from day 8 until day 15 and differed from baseline from day 6 until day 17 ( Fig. 1 ). No differences were found in reticulocyte counts among the three groups on day 21. The serum transferrin receptor, a quantitative estimation of erythropoiesis, increased only in the EPO group from day 6 onward, to reach a plateau phase at about twice baseline values ( Fig. 1 ).

Hemoglobin concentrations were similar throughout the study period in all three study groups ( [Table 2](#) ). Also, the platelet count did not differ among the study groups at any time (data not shown). The EPO response, as expressed by the maximum increase in the reticulocyte count as compared with baseline, did not correlate with age, APACHE score at admission and APACHE score at entry into the study, or with renal function as expressed by creatinine concentrations.

### **Blunted EPO Response in ICU Patients and Response to Epoetin Alfa.**

Log serum EPO concentrations of all patients in the study displayed an inverse correlation with their respective hemoglobin

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**TABLE 1** -- Baseline characteristics of critically ill patients according to study group

	Control (n = 12)	Iron (n = 12)	EPO (n = 12)
Median age, yr (range)	67 (49–89)	69 (45–80)	71 (38–89)
Male gender, no. (%)	8 (67)	8 (67)	4 (33)
Length of stay in ICU (days)	58 ± 31 <sup>a</sup>	29 ± 18	37 ± 20
Interval between admission and entry to study (days)	14 ± 7	9 ± 5	9 ± 6
APACHE II score at ICU admission	24 ± 10	26 ± 7	28 ± 8
APACHE II score at entry to study	22 ± 7	23 ± 5	24 ± 7
Survivors, no. (%)	5 (42)	8 (67)	7 (58)
Medical speciality			
Surgical	8	6	4
Medical	2	4	7
Neurologic	0	0	1
Trauma	2	2	0
Cardiac history, no. (%)	3 (25)	3 (25)	1 (8)
Sepsis, no. (%) <sup>b</sup>	7 (58)	7 (58)	9 (75)
Hemoglobin concentration at entry to study (g/dL)	9.8 ± 1.0	10.2 ± 0.6	10.3 ± 0.7
Serum creatinin at entry to study (mg/dL)	1.5 ± 0.9	1.5 ± 1.0	2.3 ± 1.4
Dialysis, no. (%)	4 (33)	3 (25)	5 (42)

EPO, erythropoietin; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

<sup>a</sup>  $p < .05$  for comparison between control and iron groups and control and EPO groups (analysis of variance, Student's Newman-Keuls');

<sup>b</sup> sepsis was defined by the presence of fever, tachycardia, and/or tachypnea and leukocytosis in the presence of a source of infection [21].

concentrations at baseline ( $r^2 = .12$ ;  $p < .05$ ) ( [Fig. 2](#) ). This relationship was, however, weaker than in the control group of patients with chronic anemia without malignant or renal diseases ( $\log\text{EPO} = -0.1831 \cdot \text{hemoglobin} + 3.45$ ;  $r^2 = .48$ ) [22]. There were no differences in baseline serum EPO concentrations between patients with and without renal function impairment defined as a serum creatinine concentration of  $>1.5$  mg/dL ( $130 \mu\text{mol/L}$ ) ( [Fig. 3](#) ). Administration of epoetin alfa increased serum EPO concentrations well beyond baseline concentrations ( [Table 3](#) ). The results did not change if EPO measurements taken  $\leq 24$  hrs after red cell transfusion were excluded. As expected, log serum EPO concentrations correlated with the absolute reticulocyte counts in the EPO group on day 10 ( $r^2 = .46$ ;  $p < .05$ ;  $n = 11$ ). Two of 12 patients showed a reduced response to epoetin alfa: they had low maximum serum EPO concentrations (61 and 38 IU/L on day 10, respectively) and a maximum reticulocyte count of only  $117$  and  $88 \times 10^9 /\text{L}$ , respectively. However, their serum transferrin receptor concentration increased on day 21 from 2.7 to 6.6 mg/L and from 4.1 to 7.2 mg/L, respectively.

### **Iron Metabolism and CRP Concentration.**

Iron metabolism showed signs of a severe inflammation with low serum iron, low transferrin and transferrin saturation, and very high serum ferritin, which was in agreement with the high CRP, in all groups of patients at all time points. An increase was found in serum iron in the control and iron groups on day 21 compared with baseline and serum transferrin in the iron group on days 10

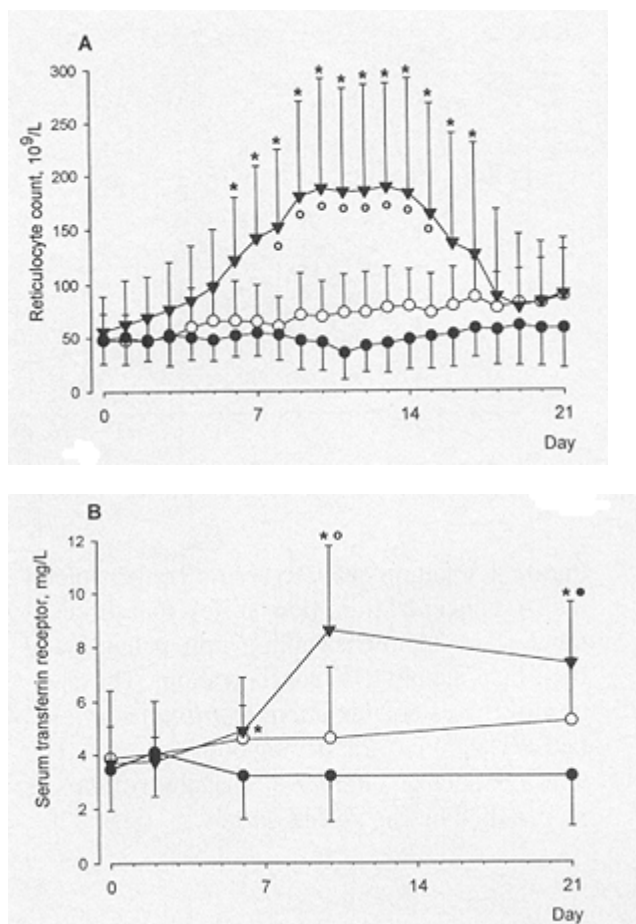
and 21. Furthermore, in the EPO group on days 10 and 21, zinc protoporphyrin concentrations were significantly increased as compared with baseline as well as with the control and iron groups, suggesting an iron-deficient erythropoiesis. CRP concentrations were positively correlated with ferritin concentrations on day 0 ( $r^2 = .20$ ;  $p = .006$ ; all patients combined) but not with other variables of iron metabolism ( [Table 4](#) ).

### Vitamin B<sub>12</sub>, Folic Acid Concentration, and Bone Marrow Aspirates.

None of the patients had a vitamin B<sub>12</sub> deficiency, and only one patient in the control group had a low concentration of folic acid (2.5 mmol/L; normal range, 4–20). Bone marrow aspirates ( $n = 10$ ; control group, 2; iron group, 4; EPO group, 4) had a normal cellularity and showed no signs of iron deficiency or megaloblastic signs.

### Blood Loss and Red Cell Transfusions.

Mean blood loss per patient in the 3-wk study period was  $1204 \pm 1030$  mL in the control group,  $826 \pm 564$  mL in the iron group, and  $1548 \pm 1309$  mL in the EPO group. An average of  $37.5 \pm 13.3$  mL,  $37.7 \pm 15.8$  mL, and  $41.0 \pm 21.5$  mL of blood was taken daily per patient for laboratory testing, respectively. There was no difference between the study groups



**Figure 1.** A, reticulocyte count. Filled circles, control group; unfilled circles, iron group; triangles, erythropoietin (EPO) group. The EPO group differed from the control and iron groups (\*  $p < .05$  compared with baseline;  $\circ$   $p < .05$  compared with the control and iron groups [two-way repeated measurements analysis of variance, group effect, time effect, and group  $\times$  time effect:  $p < .00001$ ]). B, serum transferrin receptor concentration. Filled circles, control group; unfilled circles, iron group; triangles, EPO group. \*  $p < .05$  compared with baseline;  $\circ$   $p < .05$  compared with the control and iron groups; \*  $p < .05$  compared with the control group (two-way repeated measurements analysis of variance, group effect:  $p < .01$ ; time effect and group  $\times$  time effect:  $p < .00001$ ).

**TABLE 2 -- Hemoglobin concentration (g/dL) during the study period, according to the study group**

Day	Control	Iron	EPO
0	9.8 $\pm$ 1.0	10.1 $\pm$ 0.7	10.4 $\pm$ 1.1
7 <sup>a</sup>	10.0 $\pm$ 0.9	10.3 $\pm$ 1.1	10.8 $\pm$ 0.9
14 <sup>b</sup>	10.6 $\pm$ 0.9	11.1 $\pm$ 0.9	11.2 $\pm$ 1.3

21<sup>c</sup>

10.8 ± 0.8

11.4 ± 1.3

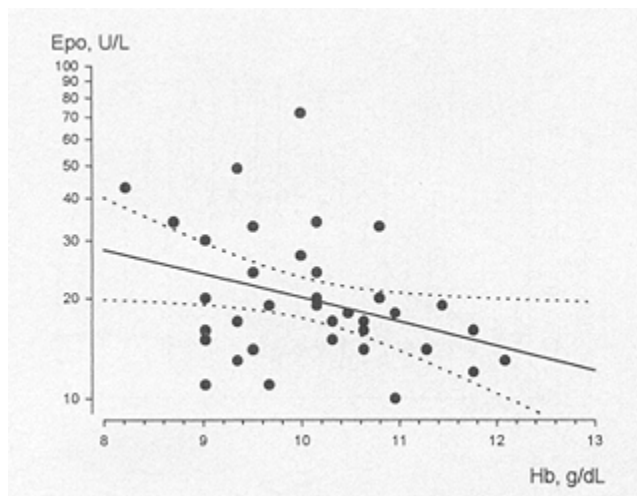
10.7 ± 1.1

EPO, erythropoietin.

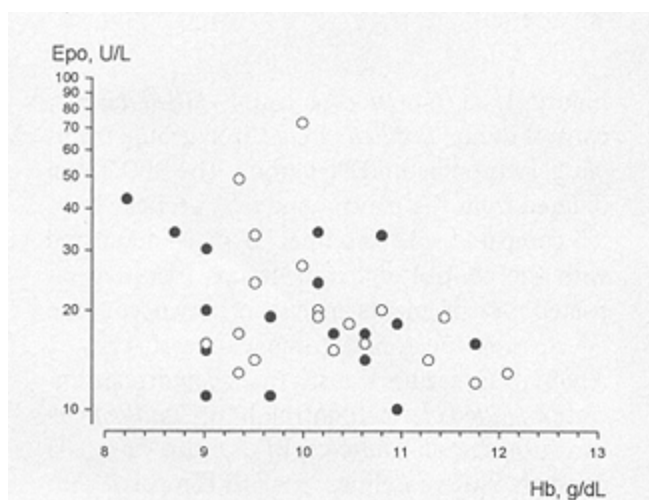
<sup>a</sup> n = 10 (iron group);<sup>b</sup> n = 11 (control group) and n = 10 (iron group);<sup>c</sup> n = 9 (control group), n = 7 (iron group), and n = 9 (EPO group). No significant difference in hemoglobin concentration was found between days or groups.

regarding any of the blood losses described. A total of 140 units of blood was transfused in the 3-wk period in the control group (average, 12 ± 14 units per patient); a total of 63 units (5 ± 7 units

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**Figure 2.** Relation between serum erythropoietin (*EPO*) concentration (log scale) measured at baseline in 36 intensive care unit patients and their hemoglobin (*Hb*) concentrations. The equation of the calculated curve (*continuous line*) is  $\log EPO = -0.0725^* \text{ hemoglobin} + 2.03$ . The 95% confidence interval of the observations is represented by the *dotted lines*.



**Figure 3.** Relation between serum erythropoietin (*EPO*) concentration (log scale) and hemoglobin (*Hb*) at baseline for patients without renal failure (*unfilled circles*) and those with renal failure (*filled circles*). Equations between both groups are not statistically different. *Unfilled circles*,  $\log EPO = -0.0832^* \text{ hemoglobin} + 2.15$ ; *filled circles*,  $\log EPO = -0.0683^* \text{ hemoglobin} + 1.97$ .

per patient) was transfused in the iron group, and a total of 82 units (7 ± 7 units per patient) was transfused in the EPO group.

## DISCUSSION

The main finding of this study is that in a mixed population of anemic critically ill patients, an exclusive and significant rise in reticulocyte count and serum transferrin receptor concentration occurred in the group that was treated with 300 IU/kg epoetin alfa subcutaneously. In addition, we found a blunted *endogenous* EPO response to anemia in these patients, which was not different in patients with or without acute renal failure. The finding that the bone marrow of critically

**TABLE 3** -- Serum erythropoietin (EPO) concentrations according to study group

Day	Control	Iron	EPO
0	21 ± 8	23 ± 16	23 ± 13
2	17 ± 5	25 ± 22	113 ± 103 <sup>a</sup>
6 <sup>b</sup>	17 ± 8	25 ± 26	94 ± 86 <sup>a</sup>
10 <sup>b</sup>	19 ± 8	16 ± 5	166 ± 98 <sup>a</sup>
21 <sup>c</sup>	28 ± 19	19 ± 9	21 ± 7

<sup>a</sup>  $p < .05$  compared with control and iron groups and compared with day 0;

<sup>b</sup>  $n = 10$  (control and EPO groups) and  $n = 9$  (iron group);

<sup>c</sup>  $n = 8$  (control group),  $n = 6$  (iron group), and  $n = 7$  (EPO group). Normal range for serum erythropoietin is 5–20 units/L in subjects without anemia; in the EPO group, 300 IU/kg epoetin alfa was given subcutaneously on days 1, 3, 5, 7, and 9.

ill patients is able to respond to *exogenous* EPO suggests that epoetin alfa has the potential to become a therapy for the anemia of patients with critical illness in the future.

The response to epoetin alfa was demonstrated by a rise in reticulocyte count (maximum on day 13) and serum transferrin receptor (plateau on days 10-21). The rapid increase in reticulocyte count is probably mainly due to rapid expulsion of reticulocytes from the bone marrow, whereas the rise in serum transferrin receptor concentration may reflect an increase in erythropoiesis [23] [24]. The two patients who showed a somewhat reduced response to epoetin alfa probably had a resorption problem with the subcutaneously given epoetin alfa. One of these patients indeed was very oedematous because of a capillary leak syndrome. The other patient was an aged man with respiratory failure owing to bilateral pneumonia, with no obvious reason for the reduced EPO response.

An increase in erythropoiesis induced by epoetin alfa leads to an increase in the iron demand of the erythroid bone marrow [25] [26]. This need is met, in otherwise healthy patients, by mobilization of iron stores and an increase in iron absorption [27]. In critically ill patients, as in patients with anemia resulting from chronic disease, these processes may be impaired [28]. The changes in iron metabolism found are indeed compatible with a functional iron deficiency. Parenteral iron supplementation was given in a low dose (20 mg daily). Nevertheless on day 21, 12 days after the last epoetin alfa injection, we found an elevated zinc protoporphyrin concentration in the EPO group, indicating iron-deficient erythropoiesis, despite the supplementation used [29]. Higher doses of iron were regarded as unfavorable because free iron may promote bacterial growth and may be disadvantageous in septic patients [30], although we did not find any disproportional elevation of serum iron throughout the study period in either the EPO or the iron group, and at no time was transferrin saturation improperly elevated. We used an iron control group to be able to ascribe the elevation in reticulocyte count to the epoetin alfa solely, and indeed, no such increase was seen in the iron group.

As described by others, we found relatively low endogenous concentrations of EPO for the degree of anemia in critically ill patients [6] [7] [9]. However, the inverse correlation between hemoglobin concentration and serum EPO concentration was preserved. Interestingly, initial serum EPO concentrations were equally low in patients with and without acute renal failure. Patients with acute renal failure are reported to have initially high concentrations of serum EPO owing to acute hypoxemia, which may decrease rapidly to the same extent as in patients with chronic renal failure [31] [32]. Only anemic patients were included in this study, and likewise, patients included were mainly in the advanced stage of acute renal failure. A possible explanation for our finding that serum EPO concentrations were equally low in ICU patients with or without renal failure is the high percentage of patients with sepsis (64%) in the study groups, suggesting that sepsis is the main factor in blunting the EPO response to anemia, irrespective of the presence of renal failure.

Advantages of the use of epoetin alfa in the ICU can be, in addition to a reduction of red cell transfusions, the possibility to achieve a higher target hemoglobin concentration, which may increase oxygen delivery [2], reduce left ventricular hypertrophy, and improve autoregulation of the coronary flow [33]. A major obstacle in demonstrating the above-mentioned

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**TABLE 4** -- Variables of iron metabolism and C-reactive protein (CRP) according to study group

	Control	Iron	EPO
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Serum iron ( $\mu\text{g/dL}$ )			
Day 0	20.5 $\pm$ 8.0	27.0 $\pm$ 13.2	34.0 $\pm$ 18.5
Day 10 <sup>a</sup>	28.4 $\pm$ 15.3	36.3 $\pm$ 19.0	43.7 $\pm$ 22.9
Day 21 <sup>b</sup>	43.3 $\pm$ 18.8 <sup>c</sup>	55.8 $\pm$ 29.4 <sup>c</sup>	44.0 $\pm$ 16.7
Transferrin (g/L)			
Day 0	1.4 $\pm$ 0.4	1.5 $\pm$ 0.4	1.5 $\pm$ 0.3
Day 10 <sup>a</sup>	1.5 $\pm$ 0.6	2.0 $\pm$ 0.7 <sup>c</sup>	1.9 $\pm$ 0.5
Day 21 <sup>b</sup>	1.7 $\pm$ 0.4	2.1 $\pm$ 0.4 <sup>c</sup>	1.9 $\pm$ 0.5
Transferrin saturation (fraction)			
Day 0	0.12 $\pm$ 0.06	0.15 $\pm$ 0.12	0.16 $\pm$ 0.09
Day 10 <sup>a</sup>	0.14 $\pm$ 0.07	0.13 $\pm$ 0.06	0.18 $\pm$ 0.10
Day 21 <sup>b</sup>	0.18 $\pm$ 0.08	0.19 $\pm$ 0.09	0.20 $\pm$ 0.13
Serum ferritin ( $\mu\text{g/L}$ )			
Day 0	891 $\pm$ 469	900 $\pm$ 909	1042 $\pm$ 487
Day 10 <sup>a</sup>	1273 $\pm$ 1051	1064 $\pm$ 608	1126 $\pm$ 682
Day 21 <sup>b</sup>	776 $\pm$ 287	1396 $\pm$ 932	1261 $\pm$ 809
ZPP (mM/MHb)			
Day 0	0.24 $\pm$ 0.07	0.19 $\pm$ 0.06	0.24 $\pm$ 0.06
Day 10 <sup>a</sup>	0.28 $\pm$ 0.06	0.22 $\pm$ 0.05	0.34 $\pm$ 0.09 <sup>d</sup>
Day 21 <sup>b</sup>	0.28 $\pm$ 0.06	0.24 $\pm$ 0.07	0.43 $\pm$ 0.17 <sup>e</sup>
CRP (mg/L)			
Day 0	158 $\pm$ 74	150 $\pm$ 71	160 $\pm$ 74
Day 10 <sup>a</sup>	105 $\pm$ 48	48 $\pm$ 53 <sup>c</sup>	90 $\pm$ 49 <sup>c</sup>
Day 21 <sup>b</sup>	83 $\pm$ 66	29 $\pm$ 22 <sup>c</sup>	103 $\pm$ 121

EPO, erythropoietin; ZPP, zinc protoporphyrin.

<sup>a</sup> n = 11 (control and EPO groups) and n = 10 (iron group);

<sup>b</sup> n = 8 (control and EPO groups) and n = 7 (iron group);

<sup>c</sup> p < .05 compared with day 0 (repeated measurements analysis of variance);

<sup>d</sup> p < .05 compared with day 0 and with iron group (repeated measurements analysis of variance);

<sup>e</sup> p < .05 compared with day 0 and with control and iron groups. Iron variables were measured 1 hr before administering 20 mg of iron saccharate iv in the iron and EPO groups.

advantages is the large amount of blood loss in these critically ill patients. This study was not designed to evaluate an effect of epoetin alfa on increases in hemoglobin concentrations or a reduction in red cell transfusions, because a rise in the hemoglobin concentration is only expected at the end of our observation period as a result of the maturation time of burst-forming unit-E and colony-forming unit-E [23]. Future studies are needed to evaluate these possible effects of epoetin alfa. An important factor may be the dosage and timing of administering epoetin alfa and iron. In this study, epoetin alfa therapy was only started when hemoglobin concentrations fell to <11.2 g/dL or, in cases of cardiac disease, 12.1 g/dL. Initiation of epoetin alfa at an earlier stage in selected patients at risk for anemia and long ICU stay may improve results. Furthermore, a higher dosage of iron supplementation or the use of vitamin C may enhance erythropoiesis when using epoetin alfa by improving the availability of iron.

We did not demonstrate a rise in platelet count in patients treated with epoetin alfa, and the platelet count did not correlate with EPO concentrations or reticulocyte count. Thrombocytosis may be expected because of the homology of EPO and thrombopoietin, the platelet growth factor. An increase in platelet count is, indeed, seen in some patients with chronic renal failure using epoetin alfa therapy [34].

In conclusion, the bone marrow of critically ill patients is able to respond to epoetin alfa in a dose of 300 IU/kg. *Endogenous* EPO concentrations are low in these patients. Whether epoetin alfa is useful in increasing hemoglobin concentrations and diminishing the need for red cell transfusions in the ICU needs to be established in further studies.

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