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Erythropoietin and renin as biological markers in critically ill patients

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Abstract

Introduction During sepsis the endocrine, immune and nervous systems elaborate a multitude of biological responses. Little is known regarding the mechanisms responsible for the final circulating erythropoietin (EPO) and renin levels in septic shock. The aim of the present study was to assess the role of EPO and renin as biological markers in patients with septic shock.

Methods A total of 44 critically ill patients with septic shock were evaluated.

Results Nonsurvivors had significantly higher serum EPO levels than did survivors on admission (median [minimum–maximum]; 61 [10–602] versus 20 [5–369]). A negative relationship between serum EPO and blood haemoglobin concentrations was observed in the survivor group ($r = -0.61$; $P < 0.001$). In contrast, in the nonsurvivors the serum EPO concentration was independent of the blood haemoglobin concentration. Furthermore, we observed significant relationships between EPO concentration and lactate ($r = 0.5$; $P < 0.001$), arterial oxygen tension/fractional inspired oxygen ratio ($r = -0.41$; $P < 0.005$), arterial pH ($r = -0.58$; $P < 0.001$) and renin concentration ($r = 0.42$; $P < 0.005$). With regard to renin concentration, significant correlations with lactate ($r = 0.52$; $P < 0.001$) and arterial pH ($r = -0.33$; $P < 0.05$) were observed.

Conclusion Our findings show that EPO and renin concentrations increased in patients admitted to the intensive care unit with septic shock. Renin may be a significant mediator of EPO upregulation in patients with septic shock. Further studies regarding the regulation of EPO expression are clearly warranted.

Keywords: biological markers, critically ill patients, erythropoietin, renin, septic shock

Introduction

Sepsis is an excessive systemic response to infection leading to numerous reactions in the host, including release of proinflammatory and anti-inflammatory cytokines [1]. During sepsis, the endocrine, immune and nervous systems produce a multitude of biological responses. Further evaluation of their role in sepsis is warranted because this may yield insights that could help us to improve therapeutic outcomes [2].

Use of steroids as an adjunct in septic shock has been proposed [3]. Some studies demonstrated adrenal insufficiency in septic patients with poor survival where supplementary

AT_1 = angiotensin II receptor subtype 1; EPO = erythropoietin; FiO_2 = fractional inspired oxygen; MAP = mean arterial pressure; PaO_2 = arterial oxygen tension; SAPS = Simplified Acute Physiology Score.

steroids were not administered [4,5]. Acute-phase protein (APP) synthesis represent a non-specific response of the liver and induce the production of similar proteins [6]. Of the acute-phase proteins studied in humans, findings with C-reactive protein have shown that this protein is a particularly useful indicator of progression of various pathological states [7,8].

Erythropoietin (EPO) is a response element that is related to hypoxic injury [9]. It is also a glycoprotein hormone that is primarily released by the kidney, and which stimulates red blood cell production in order to increase oxygen transfer and delivery [10]. *In vitro* and *in vivo* evidence suggests that hypoxia and anaemia are the most important stimuli of increased EPO production [11]. Reduced arterial oxygen content associated with anaemia or hypoxia is the predominant stimulus for EPO production [12,13]. Conditions associated with anaemia usually result in an exponential increase in EPO synthesis within minutes to hours [14]. The EPO response to known physiological stimuli is blunted in critically ill patients, and so EPO deficiency may contribute to the development of anaemia in these patients [15]. Abnormally high serum EPO levels appear to be a negative prognostic indicator in patients suffering from septic shock [16,17]. However, little is known regarding the mechanisms responsible for the final level of circulating EPO in septic shock.

Recently, some authors have emphasized a possible influence of the renin–angiotensin system on EPO gene expression [18]. Renin is released by the kidney, and its regulatory mechanisms include stimulation by postcapillary output in kidney perfusion and adrenergic stimulation by β-receptors [19,20]. Current evidence suggests that angiotensin II may be involved in the regulation of renal EPO production [18]. The signal appears to be mediated via angiotensin II receptor subtype 1 (AT_1) receptors [21]. Thus, angiotensin II may be considered an important physiological modulator of EPO production in humans.

The aim of the present study was to assess the potential utility of EPO and renin as biological markers in patients with septic shock.

Methods

Patients

The present study was approved by the Hospital Ethics Committee and written informed consent was obtained from each patient's closest relative. The study included 50 consecutive patients with septic shock, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Conference Consensus Committee, over 1 year (November 1999–November 2000). Patient inclusion criteria, after optimal volume resuscitation, were as follows (at baseline): mean arterial pressure (MAP) below 60 mmHg; signs of altered perfusion, such as as oliguria (<30 ml/hour) or increased lactate level; and a cardiac index greater than 3.5 l/min per m^2.

All patients were included in the study within 24 hours of meeting these criteria. Volume resuscitation was considered optimal when, at a given level, infusion of additional fluids was no longer accompanied by an increase in cardiac index. After optimal volume resuscitation, vasopressor agents were administered according to the therapeutic protocol. For noradrenaline (norepinephrine), the dose was started at 0.3 μg/kg per min. The infusion rate was titrated with respect to MAP at 5-min intervals to achieve a MAP in excess of 80 mmHg with a stable or increased cardiac index. If necessary, after the first hour the vasopressor agent was again titrated to achieve the same MAP. Dobutamine was administrated to patients with low cardiac index (<2.5 l/min per m^2).

In addition, a diagnosis of sepsis required confirmation of an ongoing infectious process, as indicated by one of the following criteria: one positive blood culture of a known pathogen; and suspected or evident source of systemic infection, from which a known pathogen was cultured.

The Multiple Organ Dysfunction Score was calculated as described by Marshal and coworkers [22]. The severity of illness was assessed using the Simplified Acute Physiology Score (SAPS) II within 24 hours after admission to the medical intensive care unit. Patients were followed for 28 days after the start of the study or until death.

Excluded from the study were patients with a previous medical story of malignant disease (cancer and haematologic malignancy), AIDS, chronic renal failure (measured creatinine clearance <50 ml/min), chronic hepatic insufficiency, severe chronic obstructive pulmonary disease requiring oxygen therapy, refractory anaemia (iron deficiency, aplastic anaemia) or acute anaemia (haemolytic anaemia, pulmonary haemorrhage), or prior administration of EPO or transfusion. To describe specifically the hormonal response elicited by the sepsis process itself, we excluded patients with pre-existing diseases that could be responsible for hormonal dysfunction, particularly in the hypothalamic–hypophyseal–adrenal axis and the renin–angiotensin–aldosterone system. Because EPO deficiency may be expected in acute renal failure, as in chronic renal failure, we excluded six patients with acute renal failure.

Data and blood sampling and processing

Descriptive data consisting of demographics, diagnosis, clinical data, and severity score were recorded. Blood samples were collected from patients on admission to the medical intensive care unit. Then, blood samples were obtained every 24 hours for the following 48 hours. Patients who died were sampled in this sequence until the time of death. Except for analyses that were performed immediately (gas pressure, ionogram, haemogram), blood samples were collected in EDTA-containing tubes, centrifuged for 10 min at 1300 *g* and stored in multiple aliquots at -70°C. Plasma samples were thawed at

37°C once before use in the assays to obtain results among specific samples of hormone analysis.

Routine laboratory evaluation

Routine laboratory tests were performed at baseline and included arterial blood gas evaluation, creatinine, bilirubin, platelets, leucocytes, and the arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) ratio (hypoxaemia score).

For lactate measurements, arterial blood samples were collected in tubes containing fluoride oxalate. Lactate was measured using an enzymatic colorimetric method adapted for an automatic analyzer (Beckman Instruments, Paris, France) and 2 mmol/l was considered the upper limit of the normal range.

Erythropoietin measurement

EPO concentrations were determined using an immunoenzymatic assay (R & D Systems, Paris, France). This assay is highly specific and can detect EPO concentrations as low as 0.25 UI/l. The normal range in healthy adults is 5–25 UI/l. For values from 10 to 500 UI/l the assay accuracy was better than 7% and 5% during intra-assay and interassay comparisons, respectively.

Renin measurement

Renin was measured on the basis of its action on angiotensin in plasma, generating angiotensin I. Renin concentrations were determined by radioimmunoassay (SANOFI Pasteur, Paris, France). Normal values in healthy adults range between 7 and 19 ng/l.

Statistical analysis

Qualitative values were analyzed using Fischer's exact test. Differences between admission values for survivors and nonsurvivors were tested for significance using Mann–Whitney U-test. Correlation between two variables was assessed using the Spearman rank test. Differences between variables on day 1 and on subsequent days were evaluated using the Wilcoxon signed rank test. The results of these tests are expressed as mean ± standard deviation, or as median (range; minimum–maximum). $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the patients

In the present study a total of 44 patients were followed up over 1 year. The baseline demographic data for the patients are shown in Table 1. The mean patient age was 61 ± 10 years in the survivors and 58 ± 11 in the nonsurvivors. The mean SAPS II score on admission was 52 ± 10.6 in survivors and 56 ± 9.5 in nonsurvivors. Thirteen out of 44 patients had died by day 28, two of them in the second day after admission. The cause of death was sepsis-related multiple organ failure. The sources of infection leading to study admission are also listed in Table 1. Thirteen patients had hypoxaemia, defined as partial oxygen saturation below 88%. After optimal volume resuscitation, vasopressor agents were administered. All patients received noradrenaline or noradrenaline/dobutamine. Noradrenaline was administered to 29 patients and noradrenaline/dobutamine was administered to 15 patients at doses shown in Table 1. Anaemia developed in all patients, but there were no significant differences between survivors and nonsurvivors at admission or after 24 or 48 hours (Table 2). Blood haemoglobin concentrations were 10.5 (9.8–11.2) g/dl and 10.2 (9.3–11.3) g/dl, respectively, in survivors and nonsurvivors at admission. No patient received a blood transfusion during the study, and none received steroids during this observational study.

Predictive value of admission parameters

Admission values for patients were stratified according to whether they survived or died and were compared between groups (Table 3). Comparisons were made to determine whether differences in routine parameters could serve as prognostic indicators. When admission values were stratified in this manner, three variables (arterial pH, PaO_2/FiO_2 ratio, and serum bilirubin) were significantly different between the two groups.

Time course of erythropoietin and renin levels

The time course of EPO and renin values are shown in Table 2, with patients stratified according to survival. Nonsurvivors had significantly higher serum EPO levels than did survivors throughout the study (61 [10–602] UI/l versus 20 [5–369] UI/l on admission). No significant changes in the survivor patients were observed from admission to the end of day 2 (admission 20 [5–369] UI/l, 1 day 15 [1–512] UI/l, 2 days 14 [1–191] UI/l).

On admission, nonsurvivors exhibited high renin levels. However, this difference did not reach statistical significance in comparison with survivors (82 [7–1020] mmol/l in nonsurvivors versus 47 [2–1060] mmol/l in survivors). Survivors exhibited a significant decrease from their initial values on day 1 and day 2, whereas no change was observed in nonsurvivors. The number of patients, particularly nonsurvivors ($n = 13$), was limited, and this may limit the ability to detect significant relationships.

Correlations between different variables

A negative relationship between serum EPO and blood haemoglobin concentrations was observed in the survivors ($n = 31$; $r = -0.61$; $P < 0.001$). In contrast, in nonsurvivors ($n = 13$) the serum EPO concentration was independent of the blood haemoglobin concentration (Fig. 1).

On admission there was a significant correlation between EPO and SAPS score ($r = 0.6$; $P < 0.001$). However, serum renin concentration was independent of SAPS score ($r = -0.005$; not significant) on admission (Table 4). On examining relationships between admission variables and outcome, we

Table 1

Demographic data for the study population (n = 44)

Parameter	Survivors ($n = 31$)	Nonsurvivors ($n = 13$)	P
Age (years)	61 ± 10	58 ± 11	NS
Sex (n)			
Male	14	7	NS
Female	17	6	NS
SAPS II	50 ± 10.6	56 ± 9.5	NS
MODS	12 ± 8.4	14 ± 6.9	NS
Length of ICU stay (days)	6.1 (4–21)	7.4 (5–23)	NS
Primary site of infection			
Lung	15	7	NS
Urinary tract	5	3	NS
Blood	8	2	NS
Skin	3	1	NS
Patients on inotropes			
Noradrenaline	20	9	NS
Noradrenaline/dobutamine	11	4	NS
Drug titration (μg/kg per min)			
Noradrenaline	0.7 ± 0.45	0.72 ± 0.25	NS
Dobutamine	5 ± 2.2	5.2 ± 1.8	NS

Values are expressed as mean ± standard deviation, or as median (range). ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; NS, not significant; SAPS, Simplified Acute Physiology Score.

Table 2

Erythropoietin, renin and haemoglobin values in survivors and nonsurvivors at different times: admission, 24 hours and 48 hours

Parameter	Admission	24 hours	48 hours
Erythropoietin (UI/l)			
Survivors	20 (5–369)	15 (1–512)	14 (1–191)
Nonsurvivors	61 (10–602)*	100 (7–652)*	35 (13–477)*
Renin (mmol/l)			
Survivors	47 (2–1060)	21 (2–442)	20 (3–219)
Nonsurvivors	82 (7–1020)	80 (10–706)*	77 (22–410)*
Haemoglobin (g/dl)			
Survivors	10.5 (9.8–11.2)	10.4 (10–10.8)	10.2 (9.3–10.8)
Nonsurvivors	10.2 (9.3–11.3)	10 (9–10.5)	10.3 (9.5–10.5)

Values are expressed as median (range). *$P < 0.05$ versus survivors.

found the greatest correlation for EPO concentration. Furthermore, on admission we observed significant relationships between EPO concentration and lactate ($r = 0.52$; $P < 0.001$), PaO_2/FiO_2 ratio ($r = -0.41$; $P < 0.005$), arterial pH ($r = -0.58$; $P < 0.001$) and renin concentration ($r = 0.42$; $P < 0.005$).

Figure 2 shows the receiver operating characteristic curves for EPO, renin, lactate and arterial pH on admission. A cutoff point was determined graphically for each parameter. An EPO concentration of 50 UI/l, a renin concentration of 50 ng/l and an arterial pH of 7.35 were the most sensitive and specific cutoff points (EPO: sensitivity 77%, specificity 81%; renin: sensitiv-

Table 3

Haemodynamic and metabolic variables in the study population on admission

Variable	Survivors ($n = 31$)	Nonsurvivors ($n = 13$)	P
MAP (mmHg)	58.2 ± 10	57.3 ± 12	NS
Heart rate (beats/min)	115 ± 35	120 ± 41	NS
PaO_2/FiO_2	274 ± 116	140 ± 55	0.0005
Arterial pH	7.39 ± 0.10	7.27 ± 0.10	0.0001
Leukocyte count (cells × 103/mm3)	14 ± 11	12 ± 4.1	NS
Platelet count (cells × $10^3/mm^3$)	167 ± 98	142 ± 86	NS
Serum bilirubin (μmol/l)	22 ± 24	50 ± 35	0.0008
Serum lactate (mmol/l)	4.5 ± 4.4	6.8 ± 4.8	NS

Values are expressed as mean ± standard deviation. MAP, mean arterial pressure; NS, not significant; PaO_2/FiO_2, arterial oxygen tension/fractional inspired oxygen ratio.

ity 70%, specificity 53% [$P = 0.20$]; lactate: sensitivity 62%, specificity 68% [$P = 0.07$]; arterial pH: sensitivity 85%, specificity 77% [$P < 0.001$]). This model shows that EPO and arterial pH on admission predicted outcome optimally (Table 5). On admission, renin and lactate were poor predictors of prognosis in this model.

For renin, we found significant correlations with lactate ($r = 0.52$; $P < 0.001$) and arterial pH ($r = -0.33$; $P < 0.005$). No correlation was found between renin concentration and other biological parameters.

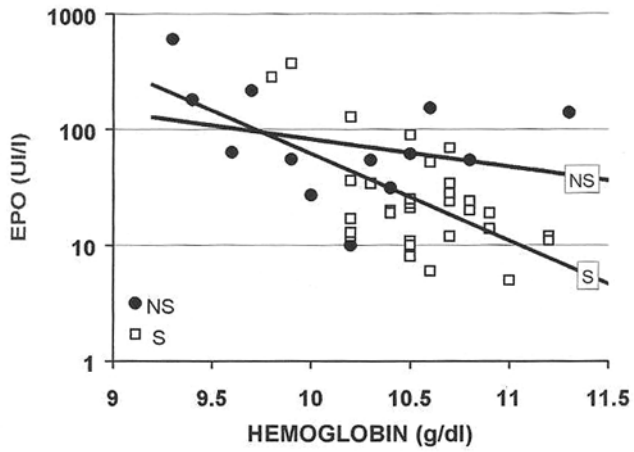
Discussion

The results presented here indicate that EPO and renin concentrations increased in patients admitted to a medical intensive care unit with septic shock. Maximal concentrations of EPO and renin were also observed in nonsurvivors. A significant difference was apparent in EPO and renin levels from admission to day 2 between patients who survived and those who died. Furthermore, EPO levels were significantly correlated with disease severity, as determined using clinical scores (SAPS II, organ score failure score). EPO in critically ill patients and its relationship with prognosis have previously been reported [16,23]. Abnormally high serum EPO level appeared to be a negative prognostic indicator in those patients. We report here, for the first time, a cutoff value of EPO that separates survivors and nonsurvivors with good sensitivity and specificity. Analysis of receiver operating characteristic curves showed that, under the conditions of the present study, a cutoff for EPO of 50 UI/l on admission was optimal for predicting death. Our data also suggest that EPO synthesis is activated to a greater degree in nonsurvivors than in survivors. The data presented here regarding the prognostic value of EPO confirm and extend findings of similar, limited studies conducted in critically ill patients, particularly in children [17].

Erythropoiesis is regulated principally through EPO, a hormone glycoprotein that is produced in the renal peritubular cells, which is responsible for the maturation and proliferation of the erythroid cell line [24]. *In vivo*, plasma EPO concentrations represent a complex interaction between EPO synthesis and degradation [25]. EPO is metabolized in the liver, undergoes renal excretion and is probably catabolized after utilization in erythropoietic tissues. Increased plasma EPO concentrations can be observed within 2 hours of exposure of individuals to acute hypoxic or anaemic conditions [26,27].

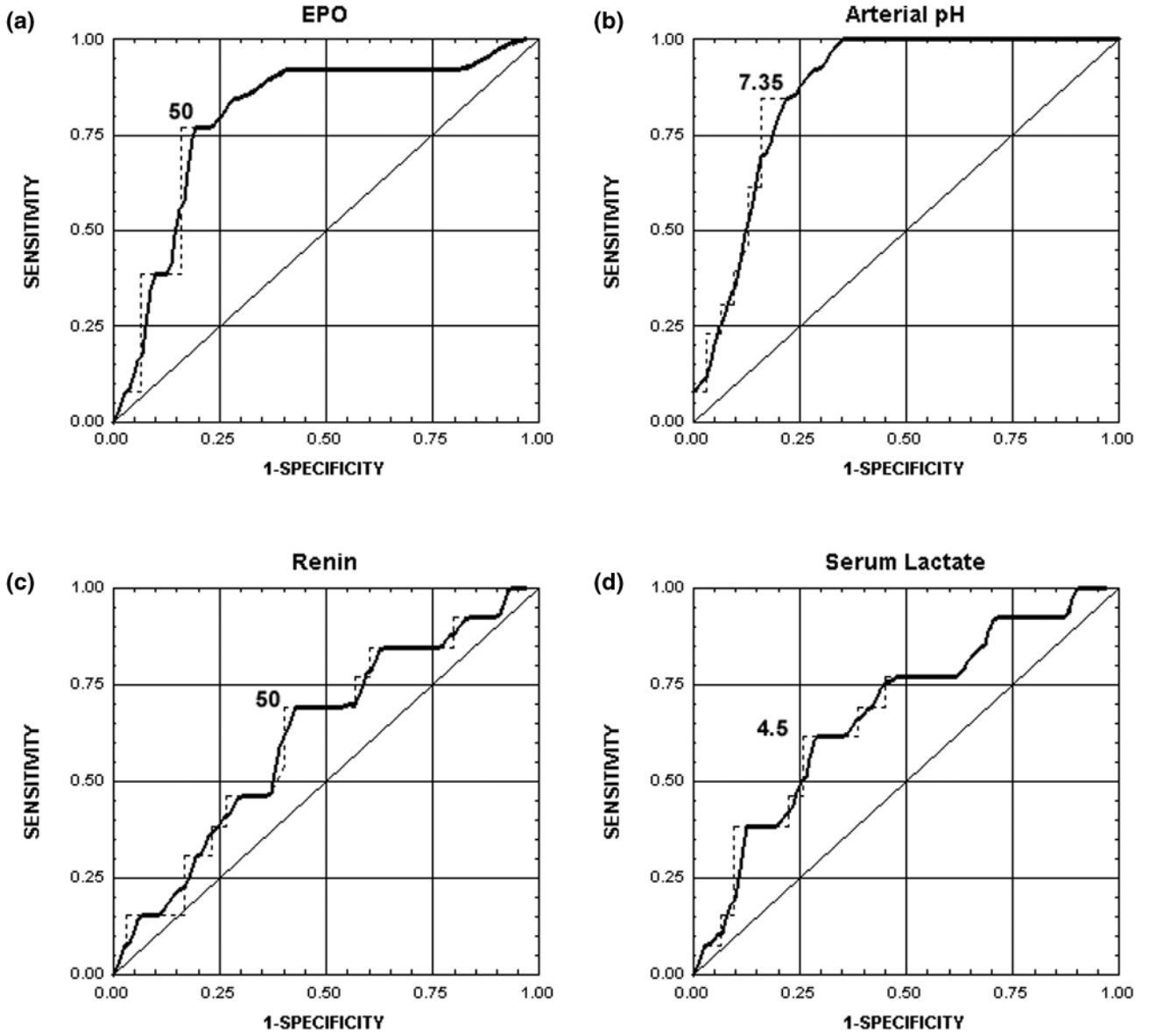
Local and circulating substances, including prostaglandin, arachidonic acid, adenosine, glucocorticoids and cytokines, are known to modulate EPO production [27]. Cytokines have been shown to suppress the *in vitro* synthesis of EPO in human cell cultures [28,29]. Interleukin-6 upregulates EPO expression in a dose-dependent manner, whereas interleukin-1 and tumour necrosis factor downregulate EPO production [10]. Therefore, control of EPO production in sepsis remains unclear. These cytokines are thought to play an important role in blunting the EPO response to anaemia during sepsis

Figure 1



Relationship between haemoglobin and erythropoietin (EPO) concentrations in survivors (S) and nonsurvivors (NS).

Figure 2



Receiver operating characteristic curves for **(a)** erythropoietin (EPO), **(b)** arterial pH, **(c)** renin and **(d)** lactate. The cutoff point for each parameter is specified in the text.

[30,31]. Our immunoassay data indicate that EPO production is not lowered in septic shock patients, despite the inflammatory response. Several studies have reported that EPO levels are unexpectedly low in critically ill patients in relation to their haemoglobin levels, and that could play a role in the development of anaemia in these patients. In the present study, serum EPO concentrations were independent of blood haemoglobin concentration in the nonsurvivors. In contrast, in survivors the serum EPO concentration was dependent on blood haemoglobin concentration. The differences between these studies may be due to the timing of blood samples taken to determine EPO concentration.

We also demonstrated a significant correlation between serum EPO concentration and hypoxia score (PaO_2/FiO_2 ratio) and lactate values. However, these data do not demonstrate a direct causal relationship between EPO concentration and hypoxic injury in septic shock. In the absence of anaemia, EPO is increased by tissue hypoxia induced by extreme physiological conditions and during septic shock [32]. EPO synthesis is subject to regulation by tissue hypoxia with negative feedback (EPO has a blood half-life of 5 hours) when the recovery of normal oxygen pressure occurs [33,34]. During these extreme conditions, hypoxia also induced stress hormone release [35]. In sudden infant death, increased EPO lev-

Table 4

Correlations of related variables with plasma levels of erythropoietin and renin on admission in patients with septic shock

Variable	EPO		Renin	
	r	*P*	*r*	*P*
Serum lactate H0 (mmol/l)	0.5	<0.001	0.52	<0.001
PaO_2/FiO_2	-0.41	<0.005	-0.24	NS
Arterial pH	-0.58	<0.001	-0.33	<0.05
Leukocyte count (cells × $10^3/mm^3$)	-0.11	NS	-0.003	NS
Platelet count (cells × $10^3/mm^3$)	-0.13	NS	0.02	NS
Serum bilirubin (μmol/l)	0.08	NS	0.08	NS
Serum EPO (mmol/l)			0.42	<0.005

EPO, erythropoietin; NS, not significant; PaO_2/FiO_2, arterial oxygen tension/fractional inspired oxygen ratio.

els suggested the presence of heavy hypoxic stress before death [36]. Evidence of the involvement of common mechanisms in controlling hypoxia, and of interleukin-6-dependent induction of the EPO gene and of several acute-phase protein genes has been reported [37-39]. Further studies are required if we are to understand fully the regulation of EPO expression by hypoxia and inflammatory mediators during septic shock.

Downregulation of adrenergic receptors (AT_1 and AT_2), which represents a link between the renin–angiotensin system and angiotensin II induced adrenal catecholamine secretion, could be responsible for the lack of endogenous catecholamines during sepsis [40,41]. It is suggested that this downregulation of angiotensin II receptors is the main reason for the attenuated responsiveness of blood pressure to angiotensin II. Our results demonstrate an increased renin level in all patients and a significant relationship between EPO and plasma renin. Plasma renin progressively decreased in survivors, but it remained significantly elevated in the nonsurvivors on day 2. In a recent report it was suggested that angiotensin II can increase renal EPO production in humans [42,43]. The influence of the renin–angiotensin system on EPO production can be blocked by specific AT_1 receptor antagonists [21]. One signal for the control of EPO production in humans may be mediated by angiotensin II (AT_1) receptors. Thus, angiotensin II may be considered an important physiological modulator of EPO production in humans. Renin could potentially be responsible for the final increase in circulating EPO in nonsurviving patients with septic shock.

In sepsis, the endocrine, immune and nervous systems produce a multitude of biological responses. High serum EPO and renin levels appeared to be negative prognostic indicators in these patients. The mechanisms responsible for the final increase in circulating EPO in critically ill patients remain unclear. According to our findings, renin may be considered an important mediator of EPO upregulation in patients with septic shock. Nevertheless, further studies of the regulation and the role played by EPO expression are warranted in patients with septic shock.

Key messages

- We found high levels of EPO and renin in serum to be negative prognostic indicators in patients with septic shock.
- The mechanisms responsible for the elevated circulating EPO levels in these critically ill patients are unclear.
- Renin may be considered an important mediator of EPO upregulation in patients with septic shock

Table 5

Multivariate predictors of outcome to septic shock

Variable	Odds ratio	95% CI	*P*
EPO	11.8	2.7–52	0.0001
Renin	2.4	0.8–9	0.2
Arterial pH	15.95	3–74	0.0001
Lactate	3.2	0.9–11	0.07

CI, confidence interval; EPO, erythropoietin.

Competing interests

None declared.

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