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Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock-induced acute renal failure

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Abstract *Objective:* Hyperreninemic hypoaldosteronism has been described in critically ill patients. The present study investigated the plasma aldosterone concentration (PAC) in septic shock patients and its relationship with clinical course. *Design and setting:* Prospective descriptive study in a medical intensive care unit (ICU) of a university hospital. *Patients:* Forty-six consecutive patients with septic shock as defined by the ACCP/SCCM criteria. *Intervention:* A corticotropin stimulation test, followed by treatment with low doses of hydrocortisone and fludrocortisone. *Measurements and results:* Plasma renin activity, PAC, and cortisol levels were measured before and after the test. PAC measurements were repeated for 1 week. Relevant clinical and laboratory variables were recorded for ICU stay. Patients were divided into two groups according to PAC/renin activity ratio: above 2 (n=24 patients) and below 2 (n=22). Patients with PAC/renin activity less than 2 had higher total volume of infused fluid, serum creatinine level, and fractional excretion of sodium values; aldosterone and serum creatinine were negatively correlated. Hypoaldosteronism was reversible within 1 week. Duration of ICU stay (p=0.0026) and the need for renal replacement therapy (p=0.0021) were greater in the group with PAC/renin less than 2. *Conclusions:* Transient hyperreninemic hypoaldosteronism is common in patients with septic shock. These abnormal aldosterone levels are associated with greater sodium and fluid depletion and are followed by enhanced incidence of acute renal failure requiring renal replacement therapy and prolonged length of stay in ICU.

Keywords Septic shock · Intensive care unit · Renal failure · Aldosterone · Renin-angiotensin system · Outcome

Introduction

Septic shock remains a major problem in the intensive care unit (ICU), and reported mortality rates increase up to 60% in patients presenting with severe forms of shock [1, 2, 3]. During the sepsis-induced stress response several hormonal systems of the sympathoadrenal and the hypothalamopituitary-adrenal axes are involved. These contribute to the complex defense mechanisms directed against microbiological agents that provide optimal intravascular volume, perfusion pressure, and substrate availability [4]. An increase in blood levels of catecholamines and glucocorticoids is usually observed. Nevertheless, an inappropriately low response of the hypothalamopituitary-adrenal axis to septic shock has been reported, with the lack of adrenal reserve, associated with increased risk of death [5, 6].

Another mechanism involved by the septic shock stress response is the regulation of fluid and volume status by the renin-angiotensin-aldosterone axis [4]. Release of re-

nin by the renal juxtaglomerular cells is triggered by volume depletion and low blood pressure. Its cascade effect is angiotensin II activation and then aldosterone production by the zona glomerulosa of the adrenal cortex. Aldosterone, the major mineralocorticoid which can also be directly stimulated by hyperkalemia and to some extent by ACTH is responsible for a large part of sodium and water reabsorption in the distal nephron [7]. A dissociation of plasma renin activity (PRA) and aldosterone production has been observed in about 20–30% of critically ill patients, namely those with hyperreninemic hypoaldosteronism [8, 9]. This syndrome is characterized by normal metabolic clearance of aldosterone, normal production of angiotensin II, appropriate hypercortisolemia, and decreased levels of 18-hydroxycorticosterone, the aldosterone precursor. Hyperkalemia is not a clinical feature of these patients. A transient diffuse impairment of the zona glomerulosa has been implicated [9]. Some authors report increased severity of the underlying disease and increased mortality associated with this syndrome [8, 9, 10]. However, little is known about the aldosterone secretion regarding septic shock patients in intensive care settings.

Therefore we designed a prospective and longitudinal study: first to test specifically in patients with septic shock the basal serum aldosterone levels and the aldosterone response to corticotropin stimulation to describe the adrenal reserve in the zona glomerulosa and, second, to evaluate the relationship between an inappropriately low aldosterone level, the renal function, and clinical outcome.

Methods

Study population

The study was approved by the Ethics Committee of the University Hospital of Caen and conducted in a 22-bed medical intensive care unit between September 2001 and June 2002. All consecutive patients admitted to ICU with septic shock were enrolled in the study if they met the following criteria, as described previously [11]: (a) clinical diagnosis of septic shock made within the past 48 h with a documented bacterial infection and (b) at least two of the following criteria: heart rate higher than 90 beats/min; fever (body temperature >38°C) or hypothermia (<36°C); respiratory rate higher than 20 breaths/min or $PaCo_2$ lower than 32 torr; white blood cell count higher than 12,000 cells/mm^3, lower than 4,000 cells/mm^3, or more than 10% immature (band) forms; persistent hypotension with systolic blood pressure of less than 90 mmHg for at least 1 h despite both adequate fluid replacement (assessed by a central venous pressure above 8 mmHg) and continuous administration of inotropic or vasopressor support (norepinephrine was the vasopressor agent of choice, and dopamine was not used); and (c) the presence of at

Table 1 Baseline characteristics of septic patients according to the PAC/PRA ratio at the onset of shock; values are *n*, mean ±SD, or median (range) where appropriate

Variable	PAC/PRA<2 (*n*=22)	PAC/PRA>2 (*n*=24)	*p*
Age (years)	61.7±15.1	60.2±14.2	0.67
Gender: M/F	13/9	16/8	0.76
Simplified Acute Physiology Score II	62.8±16.7	60.5±14.5	0.71
Underlying disease[a]			0.47
Nonfatal	15	15	
Ultimately fatal	6	9	
Rapidly fatal	1	0	
Stay in hospital prior to septic shock (days)	5 (0–22)	4 (0–21)	0.72
Sites of infection			0.64
Lung	13	11	
Abdominoperitoneal	3	6	
Urinary	5	4	
Endocarditis	1	2	
Cellulitis	0	1	
Micro-organisms			0.59
Gram-positive	12	10	
Gram-negative	5	7	
Mixed	2	5	
Negative microbial results	3	2	
Organ dysfunction[b]			0.96
One	2	2	
Two	9	11	
Three	7	7	
Four	2	3	
Five	2	1	

[a] McCabe and Jackson [14] score
[b] Multiple organ dysfunction dyndrome as defined in [11]

least two signs of organ dysfunctions (metabolic acidosis; arterial hypoxemia (PaO_2/FIO_2 ratio lower than 250); oliguria (<30 ml/kg for 3 h); intravascular disseminated coagulopathy; or abrupt alteration in the mental status). Sixty patients aged over 18 years were admitted to ICU with septic shock during the study period. Thirteen were not eligible because of cirrhosis (n=1), severe immunodepression (advanced form of cancer, n=3; AIDS, n=1; chronic steroid administration, n=3), and recent use of drugs, such as converting enzyme inhibitors (n=3) or calcium antagonists (n=2). One eligible patient was withdrawn because of the lack of adequate follow-up data for analysis. Thus 46 critically ill patients were enrolled. Baseline characteristics are shown in Table 1.

Acute renal failure (ARF) was defined as follows: (a) a serum creatinine of 180 μmol/l or more in patients without preexisting renal disease; (b) a serum creatinine value 50% higher than basal concentration, when chronic renal insufficiency preexisted; or (c) a mean urine output of less than 30 ml/hour (oliguria) over the preceding 3 h.

Protocol

The ACTH stimulation test was carried out in all patients. A control blood sample was taken to measure basal plasma aldosterone concentration (PAC; by radioimmunological method; normal range 30–70 ng/dl; Aldosterone RIA, Immunotech; Coulter, France), PRA (by radioimmunoassay as described in [12]; normal range 0.2–1.6 ng/ml per hour; Renin RIA, ARUP, Salt Lake City, Utah, USA), and plasma cortisol levels (by enzyme-linked fluorescent assay; normal range 6–28 μg/dl; VIDAS Cortisol, Bio-Mérieux, France). Thereafter we intravenously injected 250 μg synthetic ACTH (Synacthène, Ciba-Geigy, Rueil-Malmaison, France). The PAC/PRA ratio was considered as normal above a value of 2, and as subnormal below 2 [13]. Post-ACTH blood samples were taken 30 and 60 minutes later. The adrenocortical response to corticotropin stimulation was defined as the difference between the basal cortisol and aldosterone concentrations, and the highest of the 30- and 60-minutes concentrations after the test [13]. A cortisol response less than 9 μg/dl was considered as an impaired adrenal function [6]. Then hydrocortisone (300 mg daily given intravenously) and fludrocortisone (50 μg tablet once daily) were given for 7 days. Serial PAC measurements were taken every 2 days over the first week to analyze the course of aldosterone levels. Because diuretics may increase the fractional excretion of sodium and aldosterone urinary excretion, the use of diuretics was forbidden during the study.

Collection of data

To assess the severity of the critical illness the estimated prognosis of the underlying disease [14], and the Simplified Acute Physiology Score II (SAPS II) [15] were determined within 24 h following the admission to ICU. The number of failing organs according to the multiple organ dysfunction syndrome (MODS) criteria [16] was recorded once daily before ICU discharge. The following parameters were also collected: age, sex, total amount of fluid infusion, urine output within 6 h following ICU admission, creatinine and sodium concentrations in serum and urine to calculate the urinary fractional excretion of sodium (FeNa), gazometric parameters and arterial pH, serum electrolytes, and lactate levels. In addition, the need for mechanical ventilation and the length of invasive ventilation, the duration of norepinephrine infusion and the total amount of the drug infused were recorded. We also registered the need for renal replacement therapy, if any, the number of intermittent hemodialysis sessions or the duration of hemodiafiltration per patient and the duration of acute renal failure until renal function recovery. All patients were evaluated for the complete ICU stay, and length of stay in ICU and outcome were reported.

Patients were divided into two groups: those with PAC/PRA ratio below 2 (subnormal; n=22), and those with PAC/PRA above 2 (normal; n=24). There was no statistically significant difference between the two groups regarding age, gender, McCabe score, SAPS II, number of organ dysfunctions, sites of infection, type of involved micro-organisms, need for mechanical ventilation, mean arterial pressure and heart rate, plasma electrolytes, lactate level, or arterial pH (Tables 1 and 2).

Statistical analysis

We calculated that a sample size of at least 36 patients was necessary to achieve a 40% difference in renal function, at a β error of 0.1 and an α error of 0.05 (one-tailed hypothesis), assuming that the incidence of hyperreninemic hypoaldosteronism for septic patients may be of the same magnitude as the abnormal cortisol response to corticotropin stimulation (40–50%) [6]. Statistical analysis was performed by Statview 5.0 (SAS Institute, Cary, N.C., USA). Categorical variables were analyzed by the χ^2 test, with continuity correction when appropriate. Proportions were compared using Fisher's exact test. Nonnormally distributed variables were compared using the Mann-Whitney U test, and normally distributed variables using Student's t test. Correlations between initial FeNa values, serum creatinine concentrations, and plasma aldosterone concentrations were determined using linear regression analysis. Analysis of variance was used to compare repeated measurements, followed when appropriate by paired t test. Results are expressed as mean ±SD. Statistical significance was defined as p<0.05.

Results

Patients with subnormal PAC/PRA required a greater total volume of infused fluids within 24 h after admission (36.2±8 vs. 26.3±6.3 ml/kg, p<0.001). Regarding renal function these patients had also greater incidence of acute renal failure (13 vs. 5, p=0.015), higher serum creatinine concentration (180.2±59.4 vs. 123.3±48.3 μmol/l, p=0.0012), urine sodium concentration (88.7±36.1 vs. 19.1±10.7 mmol/l, p<0.001), fractional excretion of sodium (2.7±1.7 vs. 0.6±0.8%, p<0.001), and lower urine output within 6 h after enrollment (41.5±13.8 vs. 52.5± 19.5 ml/h, p=0.033, Table 2).

ACTH stimulation test

Basal cortisol concentrations were high and did not differ between the groups (27.9±6.1 vs. 27.2±5.7 μg/dl). Cortisol response to corticotropin was equivalent in the two groups (Table 2). A maximum cortisol response to ACTH less than 9 μg/dl was observed in the same proportions in both groups (10/22 with subnormal vs. 9/ 24 with normal; Table 2). PRA was elevated in all subjects and did not differ between the two groups before or after the test. Basal plasma aldosterone levels averaged 102.2± 47.5 ng/dl in patients with normal PAC/PRA but was inappropriately, 25.8±6.6 ng/dl, in patients with subnormal PAC/PRA (p<0.001). Neither group exhibited a significant increase in aldosterone after exogenous ACTH (Fig. 1). Administration of heparin and previous intravenous etomidate administration, which can alter adrenal hormone levels, was similar in the two groups (Table 2).

Table 2 Clinical and biological characteristics according to PAC/PRA ratio; values are *n* (%), mean ±SD, or median (range) where appropriate (*FeNa* fractional excretion of sodium)

Variable	PAC/PRA<2 (*n*=22)	PAC/PRA>2 (*n*=24)	*p*
Mechanical ventilation (*n*)	18	17	0.818
Mean arterial pressure (mmHg)	67.5±9	69.2±9.8	0.575
Heart rate (beats/min)	115.1±18	110.2±13.1	0.555
Norepinephrine infusion	22	24	
Acute renal failure	13 (59%)	5 (21%)	0.015
Diuretics/dopamine	None	None	
Fluid loading (ml/kg)	36.2±8	26.8±6.3	<0.001
Serum protein level (g/l)	52.6±7	54±7.7	0.535
Lactate (mmol/l)	3.8±0.9	3.7±0.7	0.904
Arterial pH	7.26±0.1	7.28±0.1	0.362
Serum potassium (mmol/l)	4.8±0.6	4.7±0.7	0.535
Serum bicarbonate (mmol/l)	18±3.5	17.9±3.2	0.849
Serum sodium (mmol/l)	135.7±4.3	135.5±3.8	0.936
Serum creatinine (µmol/l)	180.2±59.4	123.3±48.3	0.0012
Urine output (ml/h)[a]	41.5±13.8	52.5±19.5	0.033
Urine sodium (mmol/l)	88.7±36.1	19.1±10.7	<0.001
FeNa (%)	2.7±1.7	0.6±0.8	<0.001
Etomidate administration	17	20	0.718
Time interval[b]	9 (2–26)	8 (3–25)	0.772
Heparin administration	20	21	0.694
Cortisol level (µg/dl)[c]			
Before test	27.9±6.1	27.2±5.7	0.703
Maximum variation after test	12.2±9.2	13.1±7.1	0.342
Variation less than 9 µg/dl	10	9	0.765
Plasma renin activity (ng ml^{-1} h^{-1})[d]			
Before ACTH test	16.1±3.8	13.3±4.1	0.101
After ACTH test	19.4±5.3	17.7±4.8	0.173

[a] Urine output within 6 h following admission
[b] Time period between etomidate administration and blood sampling
[c] Basal value before the corticotropin stimulation test, and response (difference between the basal concentration and the highest of the 30 and 60 min values after the test); a cortisol response less than 9 µg/dl corresponds to impaired adrenal function reserve [6]
[d] PRA normal range 0.2–1.6 ng ml^{-1} h^{-1}

Correlation between PAC and renal function

As expected, we observed a positive correlation between serum creatinine concentration and FeNa values (R^2= 0.2623, p<0.001) and a negative correlation between plasma aldosterone concentrations and FeNa values (R^2= 0.2977, p<0.001; data not shown). In addition, PAC and serum creatinine concentrations (R^2=0.232, p=0.0015) were inversely correlated at the onset of shock (Fig. 2).

Course of PAC during the week following admission to ICU

Initial aldosterone levels differed significantly between the groups during the study period at the onset of shock (p<0.001), on the third day (p=0.001), and on the fifth day (p=0.0041). On the seventh day PAC was similar between the groups (p=0.112). Analysis of variance with serial measurements showed significant changes in aldosterone concentrations between groups (p<0.01) within groups during the week following the onset of shock.

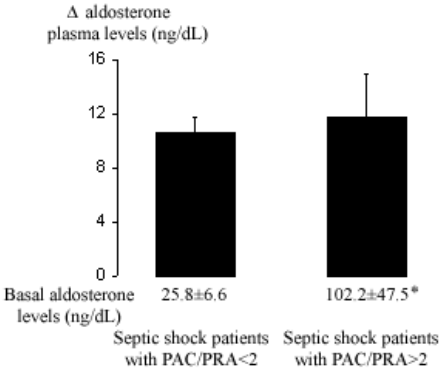

Fig. 1 Aldosterone response to corticotropin stimulation test (250 µg Synacthène given intravenously) in septic shock patients with PAC/PRA <2 (*n*=22) or PAC/PRA >2 (*n*=24). Mean ±SD. *p<0.001 vs. other group

Table 3 Clinical outcome of septic patients according to initial PAC/PRA ratio; values are *n* (%) or mean ±SD where appropriate (*IHD* intermittent hemodialysis, *ARF* acute renal failure, *ICU* intensive care unit)

	PAC/PRA<2	PAC/PRA>2	*p*
Number of failing organ[a] on day 7	1.9±0.9	1.6±0.6	0.201
Renal replacement therapy	10 (45%)	3 (12.5%)	0.021
IHD (*n*/patients with ARF)	8.3±2.8	7.7±3.1	0.811
Hemodiafiltration (days)	3.1±1.6	2.3±0.6	0.573
Duration of ARF (days)	20.1±5.3	15.7±6.7	0.286
Norepinephrine support			
Duration of infusion (h)	90.2±39.1	73.3±38.5	0.177
Total dose (mg)	162.4±70.3	134±69.4	0.230
Duration of mechanical ventilation (days)	13.8±7.1	10.8±5.4	0.103
ICU length of stay (days)	18.6±7.1	12.8±5.3	0.0026
ICU mortality	9 (41%)	5 (21%)	0.202

[a] Multiple organ sysfunction syndrome as defined in [11]

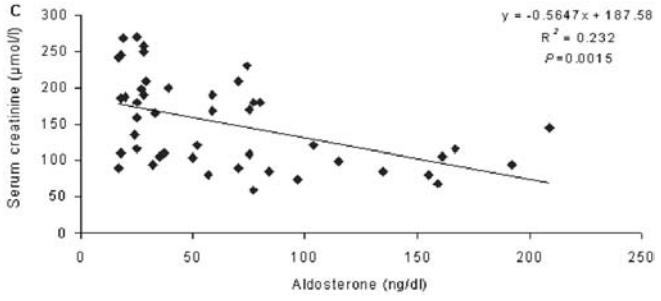

Fig. 2 Correlation between serum creatinine and aldosterone concentrations at the onset of shock

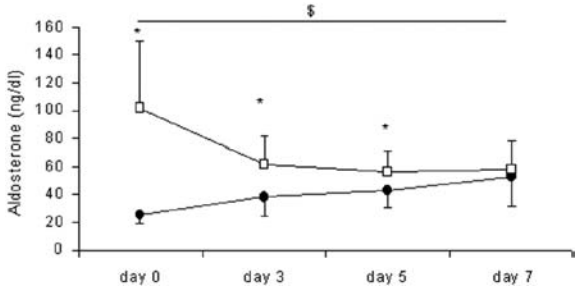

Fig. 3 Evolution of aldosterone levels over 1 week in septic shock patients according to PAC/PRA <2 (*filled circles*) vs. PAC/PRA >2 (*open squares*). Mean ±SD. **p*<0.01 between groups, $*p*<0.01 within groups over time

PAC increased in patients with initial subnormal PAC/PRA ($p<0.01$), and decreased in those with initial normal PAC/PRA ($p<0.01$; Fig. 3).

Outcome of septic shock patients in ICU according to initial PAC/PRA ratio

The main adverse events and characteristics of septic patients are reported in Table 3. The two groups were similar regarding the number of failing organs on day 7, corresponding to the end of the treatment with steroids, the need for vasopressor administration, the duration of mechanical ventilation, and ICU mortality, but there was a trend toward a higher mortality in patients with inappropriately low aldosterone levels (41% vs. 21%, $p=0.202$). By contrast, patients with basal hypoaldosteronism developed more ARF requiring renal replacement therapy and had higher length of ICU stay than other (45% vs. 12.5%, $p=0.021$; 18.6±7.1 vs. 12.8±5.3 days, $p=0.0026$).

Discussion

In the current study we found that 48% of patients with septic shock had a low inappropriate plasma aldosterone level at the onset of the shock. These abnormal aldosterone levels were associated with the lack of renal sodium and water reabsorption and with increased serum creatinine, without diuretic administration, followed by increased development of acute renal failure requiring renal replacement therapy, and prolonged length of intensive care unit stay.

Theoretically, a compensatory mechanism to maintain blood renal perfusion is involved in shock-induced ARF: stimulation of the renin-angiotensin system. Nevertheless, some seriously ill patients are affected by a syndrome termed hyperreninemic hypoaldosteronism [8]. In the present study all patients suffering from septic shock presented markedly elevated PRA. The increase in PRA is consistent with volume depletion during septic shock but may also result of catecholamines-induced stimulation of β-adrenergic receptors [17]. Nevertheless, when PRA increased, a dissociation with plasma aldosterone concentrations was recorded in 48% of patients. Because the appropriate response to high renin activity is enhanced aldosterone secretion, a "normal" aldosterone level is considered as inappropriate [10]. These inadequate low PAC were probably not related to a stress response-induced decrease in angiotensin-converting enzyme [18] since impairment of angiotensin II has been excluded in previous studies [8, 9, 19], or to

the lack of cortisol reserve, as assessed by the markedly high basal cortisol levels and by the similar maximum cortisol response to corticotropin in the two groups. Although the high-dose (0.25 mg) corticotropin stimulation test is unphysiological since it produces circulating levels of corticotropin above 1,000-fold the upper physiological level during stress, this test may be useful for prognosis since decreased response indicates adrenal dysfunction [6, 20]. Of note, in patients with normal PAC/PRA ratio (>2) the lack of aldosterone response to ACTH may be explained by the maximal basal levels that obscure detection of ACTH response [13]. Furthermore, dopamine, a tonically inhibitor of aldosterone production was not used [21, 22]. Etomidate administration, which is known to specifically suppress adrenocortical function by inhibition of 11 β-hydroxylation [23], was similar in the two groups and was not correlated with the lack of cortisol reserve in the group with subnormal PAC/PRA. In addition, despite the need for total volume of infused colloid solution elicited for patients with hypoaldosteronism, the plasma dilution following volume loading was not associated with low cortisol concentrations [24]. As a consequence our data suggest that hyperreninemic hypoaldosteronism results from septic shock-induced impairment of the zona glomerulosa rather than from insufficient stimuli for aldosterone secretion, plasma dilution, or exogenous inhibition [8, 9, 13]. Persistent hypotension may be the main factor that induces impaired aldosterone response to hyperreninemia [10], and underperfusion of the zona glomerulosa-induced hypoxia and ischemic necrosis emerged as the most probable explanations.

The incidence of acute renal failure remains high (3–25%) in patients admitted to ICU. The mortality rate of ARF, even modest degrees not resulting in dialysis treatment [25], varies from 20% to 50%, despite advances in renal replacement therapy [26, 27, 28]. To reduce this mortality rate improvements in outcome of the septic shock might be achieved by better understanding of the involved disturbances. Several factors such as sepsis, hypotension, hypoxia, mechanical ventilation, and drug toxicity are known to contribute to ARF. In the current study we observed an increase in renal disturbances that mimic tubular cell injury, related to basal low aldosterone levels. Basal PAC were inversely correlated with the increase in serum creatinine concentrations. Thus, persistent hypotension-induced ARF may also be a consequence of the hypoaldosteronism-induced lack of sodium and water reabsorption. Altogether these data suggest, first, that in these severe conditions of septic shock initial elevated FeNa values are related either to renal tubular injury or hypoaldosteronism, and, second, that hypoaldosteronism is a risk factor for the development of acute renal failure.

In this small single-center study the observed overall mortality was 30%, but we found no significant difference in mortality rates between groups. Nevertheless, there was a trend toward greater delayed shock reversal, as judged by cessation of vasopressor therapy, longer time of respiratory failure, as assessed by duration of mechanical ventilation, and higher number of death in group of patients with basal hypoaldosteronism. These data are in line with those of studies regarding all critically ill patients [8, 9].

By contrast, our study shows that patients with "abnormal" aldosterone levels suffered more frequently from ARF requiring renal replacement therapy and had prolonged length of ICU stay. The delayed discharge from ICU, which was not affected by a change in treatment between the groups, may be attributed to the renal dysfunction. Indeed, all patients received the same protocol for septic shock management, including fluid resuscitation, hemodynamic support with catecholamines, and adapted antibiotics. In addition, they received mineralosteroids and corticosteroids because adrenal insufficiency could not be ruled out in the tested hypothesis, and because the benefit on mortality and morbidity of a treatment with hydrocortisone combined [29] or not [30, 31] with fludrocortisone has been demonstrated in patients with septic shock. One explanation of the positive effects of corticosteroids is their ability to inhibit the expression of inducible nitric oxide synthase in vascular endothelial cells [32] and to potentiate the catecholamine effect by increasing the number of α_1-adrenergic receptors [33]. Corticosteroids may also increase renal sodium transport by type I and type IV corticoid receptor mediated effects [34, 35]. However, the doses and duration of corticosteroids are still controversial. Interestingly, our study also demonstrates that hyperreninemic hypoaldosteronism is transient and is reversible over 1 week when shock reversal is effective. Consequently the high incidence of hypoaldosteronism at the onset of the shock and its deleterious effect on renal function suggest that a short course of fludrocortisone, as a direct substitute for aldosterone and in addition to that of adrenal glands and to glucocorticoids may be beneficial in the management of catecholamine-dependent septic shock, as proposed in primary adrenal insufficiency [20].

We conclude that transient hyperreninemic hypoaldosteronism is frequent in septic shock patients. These abnormalities of the endocrine response to septic inflammatory reaction enhance the incidence of acute renal failure are associated with a trend to a deleterious impact on the course of organ dysfunctions and delay ICU discharge. Plasma aldosterone measurement should be required at the onset of the shock to identify patients with high risk of renal function impairment. Further studies are needed to clarify the predictive factors of hypoaldosteronism and the involved mechanisms and to define the best steroid therapy.

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