The Absence of Adrenal Gland Enlargement during Septic Shock Predicts Mortality

A Computed Tomography Study of 239 Patients

Boris Jung, M.D., Ph.D.,* Stephanie Nougaret, M.D.,† Gérald Chanques, M.D., Ph.D.,‡ Gregoire Mercier, M.D.,§ Moussa Cisse, M.D.,‡ Sophie Aufort, M.D.,‖ Benoit Gallix, M.D., Ph.D.,# Djillali Annane, M.D., Ph.D.,** Samir Jaber, M.D., Ph.D.††

ABSTRACT

Background: Assessment and management of septic shock associated adrenal function remain controversial. The aim of this study was to explore the prognostic value of adrenal gland volume in adults with septic shock.

Methods: A short cosyntropin test and determination of adrenal volume by computed tomography were performed within 48 h of shock in patients with septic shock (n = 184) and in 2 control groups: 40 ambulatory patients and 15 nonseptic critically ill patients. The primary endpoint was intensive care unit mortality.

Results: At intensive care unit discharge, 59 patients with septic shock died. Adrenal volume was 12.5 cm^3 [95% CI, 11.3–13.3] and 8 cm^3 [95% CI, 6.8–10.1] in the nonseptic group ($P < 0.05$ with both septic cohorts) and 7.2 cm^3 [95%CI, 6.3–8.5] in the ambulatory patient group ($P < 0.05$ in patients with septic shock). In patients with septic shock, adrenal volume less than 10 cm^3 was associated with higher 28-day mortality rates with an area under the receiver operating curve of 0.84 [95% CI, 0.78–0.89]. Adrenal volume above 10 cm^3 was an independent predictor of intensive care unit survival (hazard ratio = 0.014; 95% CI [0.004–0.335]).

Conclusion: A total adrenal gland volume less than 10 cm^3 during septic shock was associated in univariate and multivariate analysis with mortality at day 28 in patients with septic shock. Whether adrenal gland volume can be a surrogate of adrenal gland function and used to guide hydrocor-

What We Already Know about This Topic

- The use of low dose steroids in patients with septic shock appears to improve mortality in subgroups of patients, but identification of patients who will benefit is difficult

What This Article Tells Us That Is New

- Computed tomography identification of adrenal gland volume may be helpful in identifying septic patients who might benefit from steroid therapy

* Assistant Professor of Anesthesiology and Critical Care, Saint Eloi University Hospital, Centre Hospitalier Universitaire Montpellier, Montpellier, France. † Research Fellow of Radiology, Department of Abdominal Imaging, Saint Eloi University Hospital. ‡ Staff Intensivist, Anesthesia and Critical Care Department, Saint Eloi University Hospital. § Assistant Professor of Medical Statistics, Department of Medical Statistics, Arnaud de Villeneuve University Hospital, Centre Hospitalier Universitaire Montpellier. ‖ Staff Radiologist, Saint Eloi University Hospital, Centre Hospitalier Universitaire Montpellier. # Professor of Radiology and Chairman, Department of Abdominal Imaging, Saint Eloi University Hospital, Centre Hospitalier Universitaire Montpellier. ** Professor of Critical Care, Chairman, Department of Critical Care Medicine, Raymond Poincaré University Hospital, Paris V University, Paris-Ouest Faculty of Medicine, Garches, France. †† Professor of Anesthesiology and Critical Care and Chairman, Department of Anesthesiology and Critical Care and Equipe soutenue par la Région et l'Institut National de la Santé et de la Recherche Médicale 25, Saint Eloi University Hospital, Centre Hospitalier Universitaire Montpellier.

Address correspondence to Dr. Jaber: Intensive Care Unit, Anesthesia and Critical Care Department, Saint Eloi Teaching Hospital, University Montpellier 1; 80 avenue Augustin Fliche, 34295 Montpellier CEDEX 5, France. s-jaber@chu-montpellier.fr. This article may

tisone therapy in septic shock patients needs to be further investigated.

BUNDLE therapy of septic shock, a disease with a mortality rate ranging from 30 to 50%,[1–5] may include low-dose steroid.[6–11] Indeed, independent factors of poor outcome include hypothalamic–pituitary–adrenal axis impairment resulting in critical illness-related corticosteroid insufficiency.[8,9,11–16] Several studies have reported that daily treatment of certain patient subgroups presenting with septic shock with a prolonged (5–7 days) low dose (200–300 mg) of hydrocortisone offers potential benefits of reduced intensive care unit (ICU) length of stay or mortality.[6,8,13,14,17] However, one multiple center study failed to confirm the effect of such treatment on mortality[18] and the recent international consensus conference on critical illness-related corticosteroid insufficiency management in the ICU setting recommended considering low-dose steroid therapy only for vasopressor-dependent patients with septic shock.[15] Key patient selection criteria may include diagnosis of impaired hypothalamic–pituitary–adrenal axis or a poor response to endogenous steroids.[10,11] However, currently there is no absolute plasma cortisol concentration that distinguishes adequate and inadequate adrenal response.[11,12,15] More sophisticated tests are not routinely performed and are therefore not recommended to guide treatment.[11,15] In a pilot study using computed tomography (CT), we previously reported an increased adrenal gland volume, unrelated to adrenal hemorrhage, in patients with septic shock.[19,20]

The aim of the current study was to describe adrenal gland volume and its accuracy as a prognostic value in septic shock. We hypothesized that the absence of adrenal gland volume enlargement could be associated with mortality in patients with septic shock.

Materials and Methods

Study Design

This study was conducted from January 2005 to January 2009 in a 16-bed medical–surgical ICU. In accordance with French law, informed consent was not mandatory, given that this observational study did not modify current diagnostic or therapeutic strategies. The study design is represented in figure 1. Our study followed the Standards for Reporting Diagnostic Accuracy (STARD) recommendations concerning the report of studies of diagnostic accuracy.[21,22] This study was approved by the Montpellier University Hospital Institutional Review Board, Montpellier, France.

Study Population

Septic Shock

Consecutive patients were included if they presented with septic shock[23] and had been explored, within the first 48 h of shock, with an abdominal CT and measurements of basal and response plasma cortisol concentrations, before and after a short cosyntropin test with 250 μg cosyntropin intravenous injection (fig. 1). In our ICU, it is part of the standard of care to order a body CT scan in the early phase of septic shock to rule out any surgical or interventional radiology treatment for source control but also to assess the initial pattern of an acute lung injury. Thus, more than 70% of the

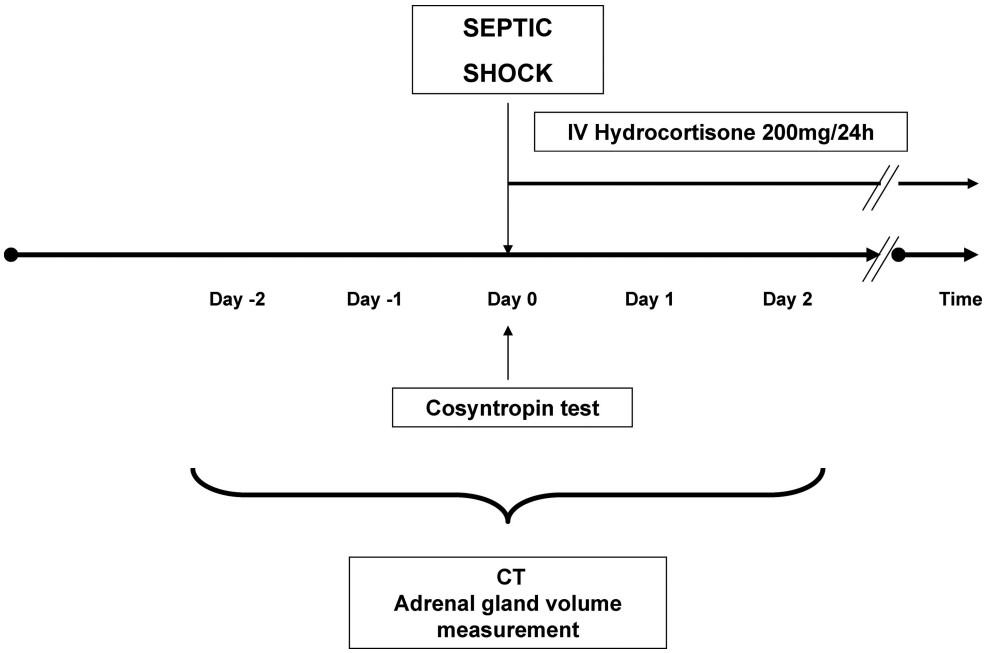


Fig. 1. Design of the study. Cosyntropin test was done at the time of the shock onset. Hydrocortisone treatment was started once the test had been done. To be included in the study, patients needed to be explored with an abdominal computed tomography (CT) scan within the first 48 h of the shock onset.

Table 1. Characteristics of the 239 Studied Patients (184 Septic Shock, 15 Nonseptic ICU, and 40 Control Patients)

	Septic Shock Group (n = 184)	Nonseptic ICU Group (n = 15)	Control Group (n = 40)
Age (yr)	64 [61–67]	60 [41–74]	57 [53–61]*
Male sex	128 (70)	10 (67)	22 (55)
SAPS II on admission	49 [46–51]	41 [15–63]	NA
Type of admission	—	—	—
Medical	85 (46)	6 (40)	NA
Surgical	99 (54)	9 (60)	—
Type of septic shock	—	—	
Lung	41 (22)	NA	NA
Abdominal	88 (48)	—	—
Both	66 (36)	—	—
Positive blood cultures	22 (12)	—	—
Gram-negative bacilli	16 (9)	0	NA
Gram-positive cocci	6 (3)	—	—
Proven samples with encapsulated organisms	7 (4)	0	NA
Neisseria meningitidis	1 (1)		
Streptococcus pneumoniae	6 (3)		
Plasma cortisol concentration (μg/dl)	—	—	—
Before corticotropin test	19.8 [20.9–25.6]	ND	NA
60 min after corticotropin test	29.7 [28.8–33.9]	—	—
Cosyntropin test responders	84 (46)	NA	NA
Total adrenal gland volume (cm^3)	12.3 [12.0–13.4]	8 [6.8–10.1]†	7.2 [6.3–8.5]*
ICU length of stay (days)	11.0 [13.9–24.7]	4 [1–15]†	NA
ICU mortality	59 (32)	3 (20)	NA

Data are median and 95% confidence interval or n (%). Cosyntropin test responders were patients with a Δ plasma cortisol concentration 60 min after a short corticotropin test of more than 9 μg/dl. (To convert values for cortisol to nM/l, multiply by 27.6.)
*$P < 0.05$ between septic shock and control groups. †$P < 0.05$ between septic shock and nonseptic ICU groups.
ICU = intensive care unit; NA = not applicable; ND = not done; SAPS II = Simplified Acute Physiology Score.

CT scans performed combine both lung and abdominal CT. CT may be delayed or not performed when the cause of sepsis is obvious and/or its risks overwhelm its benefits. In this study, patients younger than 18 yr, who are pregnant, with pituitary or adrenal disease, or with a history of steroid use were excluded.

During the study period, septic shock management followed the 2004 Surviving Sepsis Campaign guidelines.[4,5] All patients were treated with intravenous hydrocortisone, 50 mg four times a day, during 5–7 days regardless of the result of the cosyntropin stimulation test.[2]

Control Subjects

Patients without sepsis admitted to the ICU (ICU nonseptic group, n = 15) and 40 consecutive ambulatory patients who had a normal virtual colonoscopy served as control subjects (control group, n = 40).

Measurements and Clinical Evaluation

We collected data for sex, age, date, reason for ICU admission, and Simplified Acute Physiology Score II[24] for all ICU patients (tables 1 and 2).

Laboratory Variables

No laboratory variables were collected in the control group. In the ICU groups, cortisol was assayed at baseline and 60 min after cosyntropin stimulation. Plasma cortisol concentration was measured using immunoradiology assay (SP2100, Beckmancoulter SAS, Roissy, France). Response to cosyntropin stimulation was considered to be positive if T60-T0 (Δ) was above 9 μg/dl.[8,9] In the septic shock group, we also recorded serum protein and albumin concentrations and the results of the blood cultures as well as plasma creatinine, bilirubin, lactate, platelets, leukocytes, hemoglobin, and procalcitonin (tables 1, 2).

CT Scan of the Adrenal Glands

Semiautomatic measurement of the adrenal glands by CT scan was performed as previously described by our group in a pilot study.[20] The measurement technique was reproducible as we reported in the pilot study a concordance correlation coefficient between the radiologist and the intensivist of 0.87 (95% CI, [0.76–0.93]) for the total gland volume measurement. The adrenal contour was semiautomatically traced by one radiologist (SN), who was unaware of the clinical status of the subjects, every 3-mm section. The radiologist traced the contour twice for each patient in random order. The scanner software automatically calculated the adrenal volume by summing the area on each slice. Adrenal gland volume between control and septic shock groups were compared.

Table 2. Characteristics of the 184 Septic Shock Patients

	Survivors (n = 125)	Nonsurvivors (n = 59)	*P* Value
Age (years)	66 [60–71]	67 [62–71]	0.18
SAPS II	43 [41–50]	53 [46–59]	0.0069
Male sex	90 (72)	39 (66)	0.52
Comorbidities	—	—	—
COPD	20 (16)	9 (15)	0.83
Diabetes mellitus	23 (18)	12 (20)	0.91
Cirrhosis	14 (11)	8 (14)	0.93
Admitting diagnosis group, medical	62 (50)	24 (41)	0.33
Sepsis site source	—	—	—
Abdominal	36 (29)	9 (15)	0.07
Lung	52 (42)	19 (32)	0.29
Both	35 (28)	31 (53)	0.0021
Biology upon ICU admission	—	—	—
Plasma albumin (g/l)	26 [25–28]	25.5 [23–27]	0.36
Plasma lactate (mM/l)	2.7 [2.2–3.0]	4.3 [3.2–6.4]	0.0002
Creatinine plasma (μM)	118 [108–136]	160 [128–220]	0.01
Total plasma bilirubin (μM)	19 [14–24]	27 [18–47]	0.03
Leukocytes (*10 ^{3}/mm^3), lowest value	9.7 [8.3–10.4]	7.7 [5.9–12.1]	0.26
Leukocytes (*10 ^{3}/mm^3), highest value	14.8 [13.3–18.0]	14.7 [12.5–17.5]	0.7
Hemoglobin (g/l)	94 [88–98]	91 [86–97]	0.43
Platelets (*10 ^{3}/mm^3)	172 [147–195]	107 [66–161]	0.004
Plasma procalcitonine (mg/ml)	7.6 [4.4–14.5]	16.8 [3.0–25.8]	0.12
Basal plasma cortisol concentration (μg/dl)	22.2 [18.0–25.1]	20.7 [17.2–31.5]	0.72
Response plasma cortisol concentration (μg/dl)	6 [4.6–8.6]	5 [2.3–9.7]	0.33
Adrenal gland volume during septic shock (cm^3)	13.8 [13.0–15.1]	9.7 [8.8–9.9]	<0.0001
Total hydrocortisone treatment during ICU stay (mg)	1,000 [749–1226]	1,150 [650–1580]	0.42

Data are median and 95% CI or n (%).

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score.

Study Outcomes

The main endpoint was mortality in the ICU in relation to adrenal gland volume. The secondary endpoints were to analyze total adrenal gland volume in relation to septic shock, and to the cosyntropin stimulation test results.

Assumptions for the sample size calculation were based on previous studies on septic shock performed in our ICU.[25] Assuming a 40% mortality in the ICU in the group with adrenal gland volume above 10 cm^3 during septic shock, we calculated that 154 patients would need to be studied to detect a 50% absolute increase in mortality if the adrenal gland volume was less than 10 cm^3; with 80% statistical power and a one-sided α value of 0.05.

Statistical Analysis

Data are represented as mean ± SD or median and 95% CI. Continuous data were compared with Student *t* test or Mann-Whitney U test when appropriate. Categoric data were analyzed with chi-square and Fisher exact test. The Pearson correlation coefficient was used to assess the correlation between the cosyntropin test results and adrenal gland volume measurement. Sensitivity and specificity of adrenal volume and basal/response plasma cortisol concentration curves to predict mortality were assessed using receiver operating characteristics (ROC) curves and compared with the Mann-Whitney U test. The cutoff point for ROC was predetermined by the statistics software to automatically minimize the mathematic distance between the ROC curve and the ideal point as a method to minimize misclassification of patients.[21] As previously reported, we also determined two cutoff points to detect volume, which predicts mortality with the best sensitivity and the best specificity.[21] Survival at day 28 was estimated by the Kaplan–Meier method and compared between groups with the log-rank test. A theory-driven logistic regression model was also developed in three steps. First, we identified all variables previously reported as associated with mortality in septic shock. Then, we assessed the

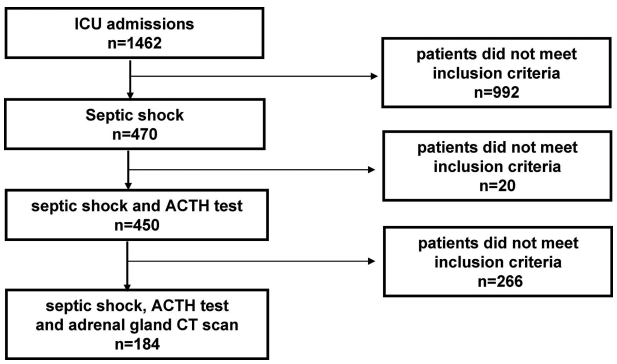


Fig. 2. Flow chart of the study. ACTH = adrenocorticotropic hormone; CT = computed tomography; ICU = intensive care unit.

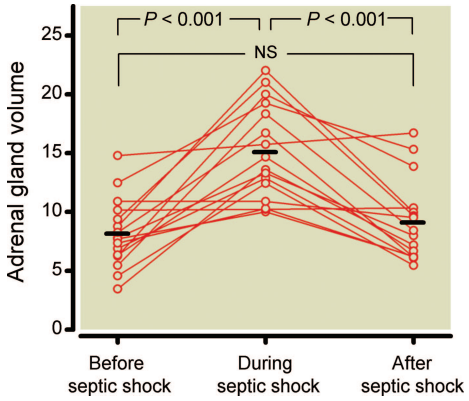


Fig. 3. Individual adrenal gland volume values of the 16 patients explored with an adrenal computed tomography scan before, during, and after resolution of sepsis. Although total adrenal gland volume increased more than 50% in each patient during sepsis ($P < 0.001$), it returned near to its baseline value after sepsis resolution.

colinearity among the candidate variables and selected the more clinically relevant variable in case of high correlation. Finally, we constructed a full multivariable model forcing all selected predictors (age, sex, Simplified Acute Physiology Score II, comorbidities, plasma creatinine and lactate, basal and random plasma cortisol concentration) and adding the total adrenal gland volume during septic shock. Two-way multiplicative interactions were systematically evaluated. The statistical significance of predictors was assessed using bootstrap resampling with replacement (200 samples). Odds ratio of dying was calculated along with 95% CI. All values were two-tailed and $P < 0.05$ was considered significant. Statistical analysis was performed with SAS v9 (Cary, NC) and checked by an independent statistician (GM).

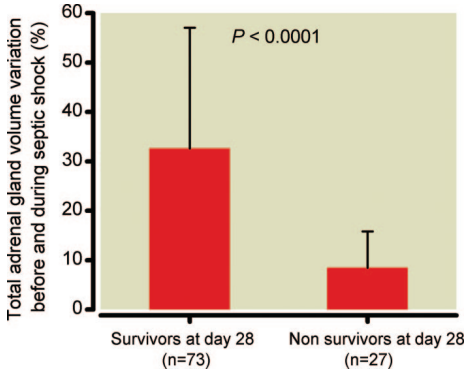


Fig. 4. Total adrenal gland volume variation expressed in percentage for the 100 patients with septic shock who were evaluated with a computed tomography scan before and during septic shock. Total adrenal gland volume during septic shock compared with volume measured before septic shock increased more in survivors than in nonsurvivors (+33% ± 24 *vs.* + 8% ± 7, respectively, $P < 0.0001$).

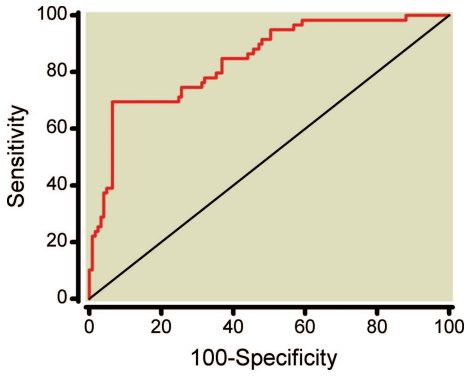


Fig. 5. Receiver operating characteristic (ROC) curves between adrenal gland volume and mortality in the 184 patients with septic shock. Best cutoff value was 10 cm^3 and was associated with a sensitivity of 70% [95% CI, 56–81%], a specificity of 92% [95% CI, 86–96%], a positive predictive value of 82%, an accuracy of 84% and an area under the ROC curve of 0.84 [95% CI, 0.78–0.89].

Results

Patients

During the study period, among 1,462 patients admitted to the ICU, 470 presented with septic shock. Among these 470, 266 either did not have a cosyntropin test or CT scan or had CT but not in the first 48 hours of septic shock. Thus, 184 consecutive patients meeting the inclusion criteria were analyzed (fig. 2). Table 1 shows the main characteristics of the patients with septic shock (n = 184), the ICU patients without sepsis (ICU nonseptic group, n = 15) and the control

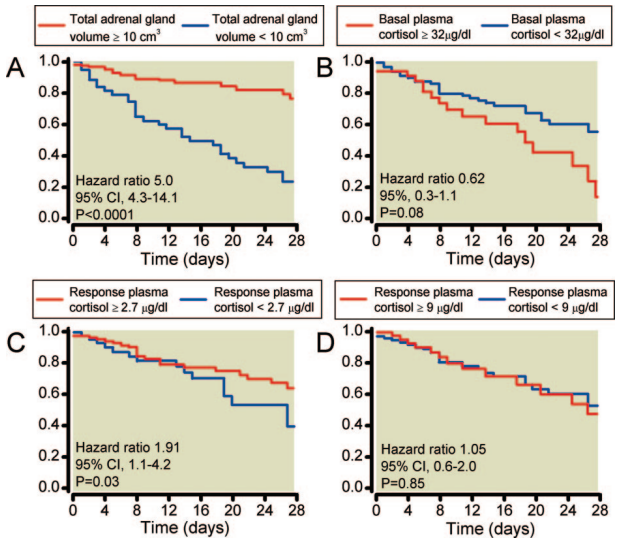


Fig. 6. Survival curves of patients according to total adrenal gland volume (≤ or more than 10 cm^3) (*A*), basal (< or ≥ 32 µg/dl) (*B*), response plasma cortisol concentration (≤ or more than 2.7 µg/dl) (*C*) and response plasma cortisol concentration (< or ≥ 9 µg/dl)[8] (*D*) in the validation 184 septic shock patients (n = 184). (*A*), Twenty-two of the 139 patients with total adrenal gland volume of 10 cm^3 or more died at day 28 compared with 37 of the 45 with total adrenal gland volume less than 10 cm^3; $P < 0.01$. (To convert values for cortisol to nM/l, multiply by 27.6).

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Mortality in the 184 Septic Shock Patients

Factor	Approximate Coefficient	Approximate Standard Error	Approximate Odds Ratio	Approximate Lower Confidence Limit	Approximate Upper Confidence Limit
Age	0.018	0.020	1.019	0.976	1.059
SAPS II on admission	0.018	0.020	1.019	0.977	1.059
Plasma creatinine on ICU admission	0.005	0.003	1.005	0.998	1.009
Plasma lactate on ICU admission	0.056	0.072	1.058	0.911	1.209
Cosyntropin test responders	1.071	0.613	2.920	0.743	8.229
Total adrenal gland volume during shock greater than 10 cm^3	−4.210	1.113	0.014	0.004	0.339

ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score.

group (n = 40). Table 2 shows the comparison between survivors and nonsurvivors in the 184 patients with septic shock.

Adrenal Gland Volume in Control, Nonseptic, and Septic Shock ICU Groups

In the septic shock group, CT was performed 1 day [95% CI, 1–2 days] after the cosyntropin test, which was performed in the first 12 hours [95% CI, 8 to 16 h] after the administration of vasopressors for septic shock.

Total adrenal gland volume of the 184 patients in the septic shock group (12.5 cm^3 [95% CI, 11.3–13.3])was significantly higher in comparison with the 15 patients in the nonseptic ICU group (8.0 cm^3 [95% CI, 6.8–10.1]; $P <$ 0.0001 for both comparison), and with the 40 patients in the control group (7.2 cm^3 [95% CI, 6.3–8.5], $P < 0.0001$ for both comparison). There was no significant difference in total adrenal gland volume between the nonseptic ICU and control groups (table 1).

Among the 184 patients with septic shock who had a CT scan and cosyntropin test, 100 were also explored before septic shock and had a medical checkup that could be considered as a baseline value (time before septic shock onset: 123 days [95% CI, 26–618 days]). During septic shock, adrenal gland volume increased in comparison with this baseline value (12.4 cm^3 [95% CI, 11.3–13.3] *vs.* 8.8 cm^3 [95% CI, 7.8–9.6]; $P < 0.0001$).

Furthermore among those 100 patients, 16 survivors were explored with a third CT scan after ICU discharge (time after ICU discharge: 100 days [95% CI, 44–214 days]) at the referent physician's discretion for a systematic follow-up or for any reason other than sepsis. Interestingly, in those 16 survivors adrenal gland volume returned to baseline value (fig. 3).

Table 4. Mortality Comparisons in the 184 Septic Shock Patients by Combining Adrenal Gland Volume and Plasma Response Cortisol

Day 28 Mortality, n (%)	Adrenal Gland Volume >10 cm^3 (n = 135)	Adrenal Gland Volume ≤10 cm^3 (n = 49)	*P* Value
Plasma response cortisol >9 μg/dl	9/66 (14)	14/18 (78)	<0.001
Plasma response cortisol ≤9 μg/dl	7/69 (10)	21/31 (68)	<0.001

P comparisons between adrenal gland volume higher and less than 10 cm^3. To convert values for cortisol to nM/l, multiply by 27.6.

Adrenal Gland Volume and Cosyntropin Test Results

There was no evidence for a correlation between adrenal gland volume measurement during septic shock and baseline cortisol concentration (r = 0.09; [CI 95%, −0.11–0.29], $P = 0.36$) and a weak correlation with the Δ cortisol (r = 0.34 [CI 95%, 0.15–0.51], $P < 0.001$).

Adrenal Gland Volume, Cosyntropin Test Response and Outcome

In septic shock, total adrenal gland volume during shock was 13.8 cm^3 [95% CI, 13.0–15.1] in the 125 survivors compared with 9.7 cm^3 [95% CI, 8.8–9.9] ($P < 0.0001$) in the 59 nonsurvivors. In the 100 patients who had a CT scan before and during septic shock, adrenal glands volume increased more during shock in the survivors (+33 ± 24%) than in the non survivors (+8 ± 7%) ($P < 0.0001$) (fig. 4).

In the 184 patients with septic shock, ROC analysis identified a total adrenal gland volume of 10 cm^3 as the best predictor of death with a sensitivity of 70% [95% CI, 56–81], a specificity of 92% [95% CI, 86–96], a positive predictive value of 82%, an accuracy of 84%, and an area under the ROC curve of 0.84 [95% CI, 0.78–0.89] (fig. 5). Using this threshold, the likelihood ratio of death in the ICU was 8.7 times greater if the total adrenal gland volume was less

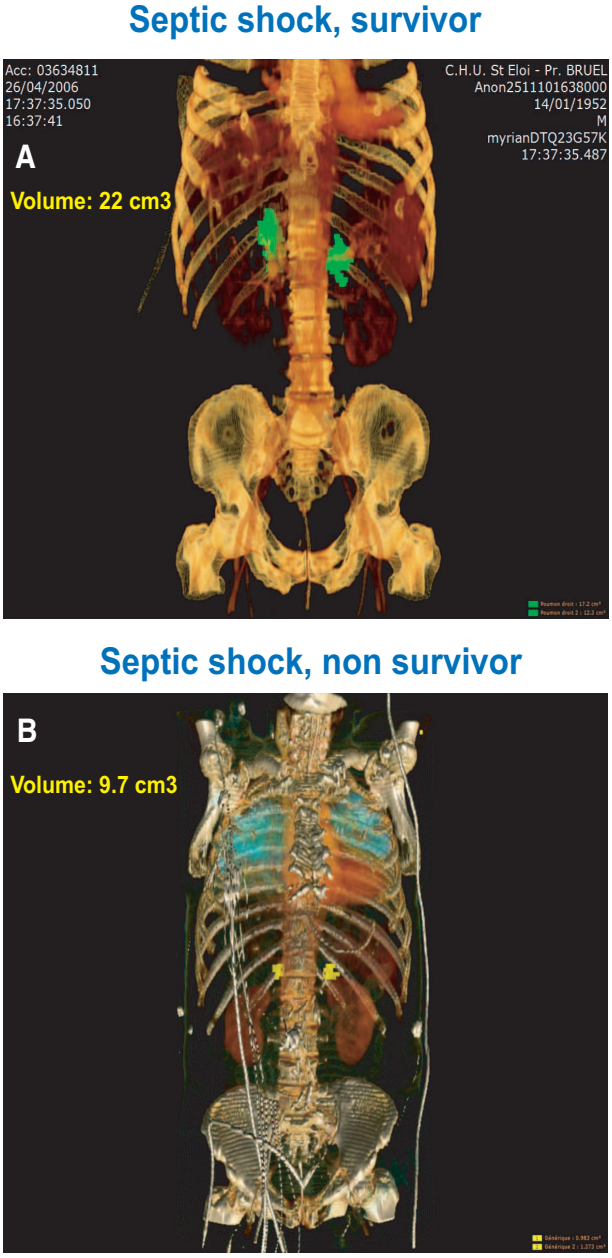


Fig. 7. Representative patients included in this study with three-dimensional computed tomography reconstruction. (*A*) A patient who survived. His total adrenal gland volume was 22 cm^3, measured with a semiautomated, dedicated software for volumetry measurement (Myrian®, Intrasense, Montpellier, France). (*B*) A patient who died. His total adrenal gland volume was 9.7 cm^3.

than 10 cm^3. To better describe the ROC analysis, we also determined the cutoff value that resulted in the best sensitivity (15 cm^3 allowing a sensitivity of 98% [95% CI, 91–99] but a specificity of 41% [95% CI, 32–50]) and in the best specificity (7.3 cm^3 allowing a specificity of 98% [95% CI, 93–99] but a sensitivity of 25% [95% CI, 15–38]).

The best cutoff value for baseline plasma cortisol concentration was 32 μg/dl with a sensitivity of 33% [95% CI, 20–47], a specificity of 79% [95% CI, 70–86] and an area under the ROC curve of 0.52 [95% CI, 0.44–0.59] and 2.7 μg/dl for response cortisol concentration with a sensitivity of 44% [95% CI, 30–60], a specificity of 73% [95% CI, 63–82] and an area under the ROC curve of 0.55 [95% CI, 0.46–0.63].

The area under the ROC curves was significantly higher for total adrenal gland volume than basal cortisol concentration ($P < 0.001$) and than peak cortisol concentration ($P < 0.001$). Figure 6 shows the survival curves in the sepsis validation for total adrenal gland volume ($\leq$ or more than 10 cm^3) (fig. 6A), basal plasma cortisol concentration ($\leq$ or more than 32 μg/dl) (fig. 6B), and response cortisol concentration ($\leq$ or more than 2.7 μg/dl) (fig. 6C) and Δ cortisol ($\leq$ or more than 9 μg/dl)[9] (fig. 6D). Total adrenal gland volume was strongly associated with 28-day survival (hazard ratio 5.0 [95% CI, 4.3–14.1]; $P < 0.0001$) (fig. 6A). Although Simplified Acute Physiology Score II, lactate, platelets, plasma creatinine, and total bilirubin concentration were associated with mortality on univariate analysis (table 2), multivariate analysis showed that adrenal gland volume was the sole independent risk factor of mortality at day 28 (table 3). Interestingly, 68% of the patients with Δ cortisol less than 9 μg/dl and a total adrenal gland volume of less than 10 cm^3 died before day 28, whereas only 14% of the patients with a total adrenal gland volume higher than 10 cm^3 and a Δ cortisol higher than 9 μg/dl died before day 28 ($P < 0.0001$) (table 4). Four representative patients are presented in figures 7 and 8.

In a multiple regression model including sex, age, Simplified Acute Physiology Score upon ICU admission, admission category, sepsis source, and total hydrocortisone dose as independent data and adrenal gland volume as the dependent data; male sex and total hydrocortisone dose were statistically associated with adrenal gland volume (table 5). There were 3 of 15 deaths (20%) at 28 days in the nonseptic ICU patient group. In this group, adrenal gland volume was not associated with 28-day mortality.

Discussion

This study shows that, in septic shock, total adrenal gland volume measured by CT scan was an independent prognostic factor for 28-day mortality. Adrenal gland volume was nearly doubled in septic shock groups in comparison with the nonseptic ambulatory group, and was increased by 35% in comparison with the nonseptic ICU group. Second, in hydrocortisone–treated septic shock, the cosyntropin test result was poorly correlated with adrenal gland volume. Finally, by multivariate analysis, we report for the first time that total adrenal gland volume less than 10 cm^3 during septic shock may represent a mortality risk factor.

Adrenal glands volume was evaluated with a semiautomated organ volumetric technique by a radiologist (SN) by CT and dedicated software (Myrian®, Intrasense, Montpellier, France). This software is widely available

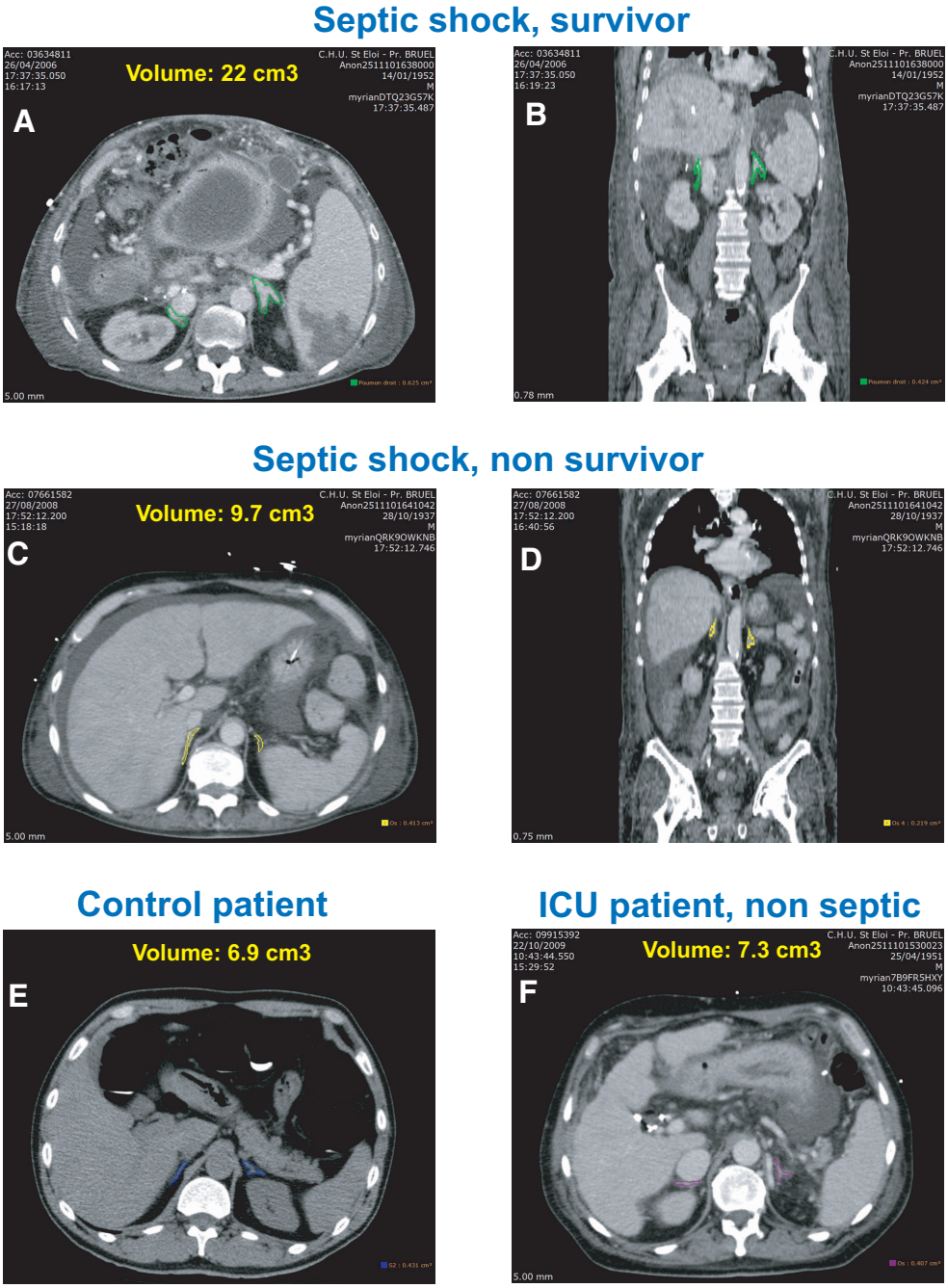


Fig. 8. Representative patients included in this study. (*A* and *B*) A patient who survived septic shock. His total adrenal gland volume was 22 cm^3. (*C* and *D*) A patient who died of septic shock. His total adrenal gland volume was 9.7 cm^3. A control patient (*E*) was explored by virtual colonoscopy as well as a nonseptic intensive care unit (ICU) patient (*F*). Total adrenal gland volume was similar in those 2 patients with a volume of 6.9 cm^3 and 7.3 cm^3, respectively.

and is certified for organ volume measurement. The use of semiautomated organ volumetry technique has become part of a routine process in radiology for various situations, such as liver or gastric surgery,[26] but volumetry has been poorly studied in intensive care medicine[27–29] and was used only once for adrenal gland volume measurement, in a pilot study.[20] Adrenal gland volume has been previously shown to increase in stress conditions such as depression[30] and Cushing disease.[31]

In this study, adrenal gland volume was not correlated with basal cortisol but showed some correlation with cortisol response to cosyntropin. These findings suggested that morphologic assessment of the adrenal glands may provide additional information on adrenal function to improve the diagnosis of critical illness-related corticosteroid insufficiency, which remains challenging.[11,12,15,32] In practice, patients with adrenal gland volume less than 10 cm^3 had higher risk of death (fig. 5 and 6). In the current study, every patient

Table 5. Multiple Regression Analysis Examining Adrenal Gland Volume as the Independent Variable

Factor	Coefficient	Standard Error	*P* Value
Total hydrocortisone dose	−0.0014	0.00067	0.04
Male	3.37	0.97	<0.01

Other variables entered in the model were age, medical *versus* surgical, site of sepsis (lung, abdominal, other), and SAPS II (Simplified Acute Physiology Score).

with septic shock was treated with hydrocortisone. Multiple regression showed that a higher total dose of hydrocortisone was associated with a smaller adrenal gland (table 5). More than a very unlikely direct effect of a very short hydrocortisone treatment on adrenal gland,[33] this association may be interpreted as the sicker the patients, the longer they were treated with hydrocortisone and the smaller the adrenal gland volume.

The mechanisms leading to the increased volume did not include adrenal gland hemorrhage or necrosis. Furthermore, there was no sign of excess fluid loading between septic shock groups on CT (such as ascitis or bowel edema) and it is then unlikely that adrenal gland enlargement could be related to a gland edema. Interestingly, in 16 patients who had been evaluated before, during, and after recovery of sepsis, we were able to demonstrate that the morphologic changes in adrenal glands were reversible (fig. 3).

This study has some limitations. Although the external validity of this study may be limited because of its single center and observational design, we included all consecutive patients in whom a CT and a cosyntropin test were prescribed within the 48 h of septic shock onset, representing 40% of patients with septic shock (fig. 2). All patients with septic shock received hydrocortisone as part of routine management. Therefore, we could not analyze the effect of this treatment on both adrenal morphology and patient outcome or speculate on the adrenal gland volume in patients with septic shock who were not treated with hydrocortisone. In this first study showing the association between adrenal gland volume and mortality, we did not include patients who did not have septic shock or those acutely treated with steroids, which could represent a limitation to our study. Finally, although we clearly demonstrated a link between adrenal gland volume and mortality, our study was not designed to explain the potential pathophysiologic pathways. However, according to the gland density profile similar to normal parenchyma, the radiologist did not observe any sign of gland edema, hemorrhage or necrosis.

In conclusion, our findings show that in septic shock, CT of the adrenal gland may contribute to assess adrenal function and a total adrenal gland volume less than 10 cm^3 may identify high-risk patients. Further studies may evaluate the adrenal gland volume in association with the cosyntropin stimulation test in other populations at high risk of critical illness-related corticosteroid insufficiency such as brain dead[34] or multiple trauma patients[35] and whether assessment of adrenal gland morphology on CT may identify patients likely to respond to corticosteroids.

The authors thank Christian Bonnel, M.D., Medical Coordinator, Intrasense Company, Montpellier, France, for the technological support of CT volumetry (Myrian® Software, Montpellier, France) and Julie Carr, M.D., Fellow, Anesthesia and Critical Care Department, Saint Eloi University Hospital, Centre Hospitalier Universitaire Montpellier, Montpellier, France, for her English editing.

References

1. Annane D, Bellissant E, Cavaillon JM: Septic shock. Lancet 2005; 365:63–78
2. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36:296–327
3. Menon K, Ward RE, Lawson ML, Gaboury I, Hutchison JS, Hébert PC, Canadian Critical Care Trials Group: A prospective multicenter study of adrenal function in critically ill children. Am J Respir Crit Care Med 2010; 182:246–51
4. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine 1992. Chest 2009; 136:e28
5. Wheeler AP: Recent developments in the diagnosis and management of severe sepsis. Chest 2007; 132:1967–76
6. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU: Corticosteroids in the treatment of severe sepsis and septic shock in adults: A systematic review. JAMA 2009; 301: 2362–75
7. COIITSS Study Investigators, Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. JAMA 2010; 303:341–8
8. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Chaumet-Riffaut P, Bellissant E: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862–71
9. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. Jama 2000; 283:1038–45
10. Jaeschke R, Angus DC: Living with uncertainty in the intensive care unit: Should patients with sepsis be treated with steroids? JAMA 2009; 301:2388–90
11. Marik PE: Critical illness-related corticosteroid insufficiency. Chest 2009; 135:181–93
12. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P: Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med 2006; 174:1319–26
13. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998; 26: 645–50

14. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. Crit Care Med 1999; 27:723–32
15. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M, American College of Critical Care Medicine: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008; 36:1937–49
16. Rivers EP, Gaspari M, Saad GA, Mlynarek M, Fath J, Horst HM, Wortsman J: Adrenal insufficiency in high-risk surgical ICU patients. Chest 2001; 119:889–96
17. Briegel J, Sprung CL, Annane D, Singer M, Keh D, Moreno R, Möhnle P, Weiss Y, Avidan A, Brunkhorst FM, Fiedler F, Vogeser M, CORTICUS Study Group: Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. Intensive Care Med 2009; 35: 2151–6
18. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J, CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358:111–24
19. Chanques G, Annane D, Jaber S, Gallix B: Enlarged adrenals during septic shock. Intensive Care Med 2007; 33:1671–2
20. Nougaret S, Jung B, Aufort S, Chanques G, Jaber S, Gallix B: Adrenal gland volume measurement in septic shock and control patients: A pilot study. Eur Radiol 2010; 20:2348–57
21. Ray P, Le Manach Y, Riou B, Houle TT: Statistical evaluation of a biomarker. ANESTHESIOLOGY 2010; 112:1204–10
22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC, Standards for Reporting of Diagnostic Accuracy: Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. Ann Intern Med 2003; 138:40–4
23. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101:1644–55
24. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. Jama 1993; 270:2957–63
25. Lefrant JY, Muller L, Raillard A, Jung B, Beaudroit L, Favier L, Masson B, Dingemans G, Thévenot F, Selcer D, Jonquet O, Capdevila X, Fabbro-Peray P, Jaber S, Sepsi d'Oc Study Group in the AzuRéa Group: Reduction of the severe sepsis or septic shock associated mortality by reinforcement of the recommendations bundle: A multicenter study. Ann Fr Anesth Reanim 2010; 29:621–8
26. Parrish FJ: Volume CT: State-of-the-art reporting. AJR Am J Roentgenol 2007; 189:528–34
27. Constantin JM, Grasso S, Chanques G, Aufort S, Futier E, Sebbane M, Jung B, Gallix B, Bazin JE, Rouby JJ, Jaber S: Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. Crit Care Med 2010; 38:1108–17
28. Malbouisson LM, Muller JC, Constantin JM, Lu Q, Puybasset L, Rouby JJ, CT Scan ARDS Study Group: Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2001; 163: 1444–50
29. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Herrmann P, Mascia L, Quintel M, Slutsky AS, Gattinoni L, Ranieri VM: Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 2007; 175:160–6
30. Amsterdam JD, Marinelli DL, Arger P, Winokur A: Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: A pilot study. Psychiatry Res 1987; 21:189–97
31. Pojunas KW, Daniels DL, Williams AL, Thorsen MK, Haughton VM: Pituitary and adrenal CT of Cushing syndrome. AJR Am J Roentgenol 1986; 146:1235–8
32. Hamrahian AH, Oseni TS, Arafah BM: Measurements of serum free cortisol in critically ill patients. N Engl J Med 2004; 350:1629–38
33. Arlt W, Allolio B: Adrenal insufficiency. Lancet 2003; 361: 1881–93
34. Nicolas-Robin A, Barouk JD, Amour J, Coriat P, Riou B, Langeron O: Hydrocortisone supplementation enhances hemodynamic stability in brain-dead patients. ANESTHESIOLOGY 2010;112: 1204–10
35. Hoen S, Asehnoune K, Brailly-Tabard S, Mazoit JX, Benhamou D, Moine P, Edouard AR: Cortisol response to corticotropin stimulation in trauma patients: Influence of hemorrhagic shock. ANESTHESIOLOGY 2002; 97:807–13