Hydrocortisone Supplementation Enhances Hemodynamic Stability in Brain-dead Patients

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ABSTRACT

Background: Hemodynamic instability is frequent in brain-dead patients and may result, in part, from absolute or relative adrenal insufficiency. Corticosteroid supplementation is widely used to restore hemodynamic stability in septic shock and to reduce the time of shock resolution. The authors verified that supplementation with hydrocortisone may enhance hemodynamic stability in brain-dead patients.

Methods: All consecutive brain-dead patients with hypotension requiring vasopressor agents were included in this single-center noninterventional clinical observation study. Assessment of baseline and adrenocorticotropic hormone (ACTH)-stimulated plasma cortisol concentrations was performed. Immediately after, patients were systematically treated with a single intravenous injection of hydrocortisone (50 mg), and norepinephrine administration was adjusted every 15 min to maintain mean arterial pressure between 65 and 90 mmHg. Adrenal insufficiency was defined as baseline plasma cortisol concentration less than 15 μg/dl and/or delta plasma cortisol concentration less than 9 μg/dl. Patients were considered as ACTH responders when delta cortisol concentration was more than 9 μg/dl 30 min after ACTH injection.

Results: Among the 31 patients included, the incidence of adrenal insufficiency was 87% [95% CI, 70–96%]. A significant (≥30%) decrease in norepinephrine dose was obtained 180 min after hydrocortisone injection in 18 (59%) patients, from 0.31 [0.16–0.44] μg · kg^{-1} · min^{-1} to 0.18 [0.10–0.24] μg · kg^{-1} · min^{-1} ($P < 0.01$). The incidence of hemodynamic response was greater in ACTH non-responders than in ACTH responders: 86% *versus* 50%, respectively, $P < 0.05$.

Conclusions: Adrenal insufficiency with hemodynamic instability is frequent in brain-dead patients. After ACTH stimulation testing and hydrocortisone infusion, hemodynamic stability is enhanced especially in patients with true adrenal nonfunction.

What We Already Know about This Topic

❖ Hemodynamic instability is common in brain-dead patients
❖ Although hydrocortisone infusion is recommended in this setting, its efficacy has not been examined

What This Article Tells Us That Is New

❖ In 31 brain-dead patients, adrenal insufficiency was present in 87%
❖ Hydrocortisone infusion significantly reduced the dose of norepinephrine required for hemodynamic stability

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DESPITE improved management and stabilization of patients on the transplant waiting list, the mortality during this period in the United States, as in other countries, has remained as high as 15% in 2005, with 42% of patients waiting for more than 2 yr.[1] Thus, increasing the number of potential donors is a real challenge. Hemodynamic instability occurs in 80% of the potential donors, and it is at the origin of 10% of lost potential donors because of refractory hypotension despite adapted fluid infusion and norepinephrine administration.[2] Although 60% of hemodynamic instabilities are corrected with fluids and norepinephrine infusion, vasopressors are known to be an independent risk factor of cardiac dysfunction in brain-dead patients and to delay renal graft function.[3,4]

Adrenal insufficiency may be primary due to impairment of adrenal glands dysfunction or secondary due to impairment of pituitary gland and/or hypothalamus, or both (hypothalamic-pituitary-adrenal insufficiency). Disruption of the hypothalamic-pituitary-adrenal axis could contribute to hemodynamic instability in brain-dead patients because of the decrease in circulating levels of cortisol-adrenocorticotropic hormone (ACTH) and arginine-vasopressin. Critical illness-related adrenal insufficiency is now well described, and the benefit of hydrocortisone supplementation has been suggested in patients with vasopressor-dependent septic shock and in patients with early severe acute respiratory distress syndrome.[5] Despite the fact that supplementation with

intravenous hydrocortisone infusion is already recommended in brain-dead patients with hemodynamic instability,[6] the effectiveness of this treatment has never been evaluated. The aim of this study was to investigate the benefit of supplementary-dose hydrocortisone in brain-dead patients in decreasing hemodynamic instability and norepinephrine requirements.

Materials and Methods

Patient Selection

All brain-dead patients 18 yr or older admitted to our intensive care unit during a 7-month period and who required norepinephrine were included prospectively. Before inclusion, brain death was diagnosed clinically with usual criteria (unresponsiveness to noxious pain stimuli, abolition of brainstem reflexes and apnea in the absence of hypothermia, metabolic or electrolyte disturbances, and depressant drugs) and then was confirmed with cerebral angiography or electroencephalography. The inclusion of the patients in the study was performed before any discussion with families about potential organ donation. Patients were excluded in case of severe cardiac failure defined by echocardiographic left ventricular ejection fraction less than 50%, sepsis, or if they had received corticosteroids during the previous 7 days or etomidate during the previous 3 days.[7]

The study was approved by our ethics committee (Comité de Protection des Personnes se prêtant à la Recherche Biomédicale de l'Hôpital Pitié-Salpêtrière, Paris, France) and was performed in accordance with the Declaration of Helsinki. Waived informed consent was authorized because diagnosis of adrenal insufficiency and hormone resuscitation are routinely performed in our unit for the assessment of brain-dead patients and because interventional procedures to evaluate the potential organ donor are authorized before the presumed consent could be verified. This study was also conducted in accordance with French laws concerning multiple organ procurement.

Study Protocol

Hemodynamic Evaluation. All patients were fully equipped with continuous heart rate monitoring and an indwelling radial artery catheter for continuous arterial blood pressure assessment. All patients were tracheally intubated and ventilated in a pressure-controlled mode with peak airway pressures adjusted to deliver a constant tidal volume of 8–10 ml/kg body weight and was maintained at less than 25 cm H_2O. If necessary, respiratory rate was increased to obtain normocapnia.[8] The inspiratory-to-expiratory time ratio was set to 1:2, and positive end-expiratory pressure was set at 5 cm H_2O. Left ventricular systolic function assessment was performed with transesophageal echocardiography. Preload assessment was performed with respiratory variation of arterial pulse pressure measurement (ΔPP). If ΔPP was superior or equal to 13%, fluid loading was performed with 500 ml of a colloidal solution (Gelofusine®; B.Braun Medical, Boulogne-Billancourt, France) infused over 30 min and adjusted to obtain ΔPP less than 13%, suggesting that no significant hemodynamic improvement would be expected with further fluid challenge.[9,10] After optimization of fluid loading, and only if required, the dose of norepinephrine was adjusted to obtain a mean arterial pressure between 65 and 90 mmHg.[11] Apart from norepinephrine, no inotropic agent was used in these patients without major decrease in left ventricular ejection fraction. Diabetes insipidus (defined as a diuresis >4 ml · kg^{-1} · h^{-1} and urine density less than 1.003 g/cm^3 in the absence of urinary glucose or less than 1.005 g/cm^3 in the presence of urinary glucose) was treated with a single intravenous 1 μg desmopressin bolus.[12]

ACTH Stimulation Testing. After hemodynamic stabilization had been obtained for at least 60 min (i.e., mean arterial pressure maintained between 65 and 90 mmHg after correction of hypovolemia and stable concentration of norepinephrine infused continuously), the capacity of adrenal gland to respond to tetracosactrin was tested with the use of the standard short tetracosactrin test, which measured the total plasma cortisol concentration before (T_0, baseline cortisol concentration), 30 min (T_{30} stimulated cortisol concentration), and 60 min (T_{60} stimulated cortisol concentration) after an intravenous injection of 250 μg of tetracosactrin (Synacthène®; Novartis Pharma SAS, Rueil Malmaison, France). Delta percentage of baseline plasma cortisol was calculated at T_{60} as 100 $\times$ (plasma cortisol concentration T_{60} − cortisol plasma concentration T_0)/plasma cortisol concentration T_0. Adrenal insufficiency was defined as baseline plasma cortisol concentration less than 15 μg/dl and/or delta plasma cortisol concentration less than 9 μg/dl in response to 250 μg tetracosactrin, measured at T_{30} or T_{60}.[13] Delta plasma cortisol concentration more than 9 μg/dl defined "ACTH responder" patients, whereas delta plasma cortisol concentration less than 9 μg/dl defined "ACTH nonresponder" patients.[5]

Norepinephrine Dose Adjustment. After ACTH stimulation testing, patients were treated with a single intravenous injection of hydrocortisone (50 mg; Roussel-Uclaf, Romainville, France). Every 15 min for 180 min, the norepinephrine dose was adjusted to maintain mean arterial pressure between 65 and 90 mmHg. After 180 min, delta percentage of baseline norepinephrine dose more than or equal to 30% defined "hemodynamic responders," and delta percentage of baseline norepinephrine dose less than 30% defined "hemodynamic nonresponders."

Endpoints

The primary endpoint was hemodynamic stability assessed by the norepinephrine dose required after hydrocortisone infusion. The secondary endpoint was to assess the incidence of adrenal insufficiency incidence in brain-dead patients.

Statistical Analysis

A sample size of 28 patients was needed to achieve a statistical power of 90% and an α-risk of 5% to detect a decrease by 30% the norepinephrine dose when the initial mean norepinephrine dose was 0.4 μg · kg^{-1} · min^{-1} before treatment in our population of brain-dead patients (preliminary data not shown).

Table 1. Baseline Characteristics of Patients

	n = 31
Age, yr	49 ± 13
Men	19 (61)
Women	12 (39)
Weight, kg	72 ± 7
Cause of brain death	
Trauma	8 (26)
Cerebrovascular	23 (74)
Interval accident/brain death, days	4 ± 5
SAPS 2	52 ± 12

Data are expressed as mean ± SD or n (%).
SAPS = Simplified Acute Physiology Score.

Data are expressed as mean ± SD for parametric variables or median (25–75 interquartiles) for nonparametric variables, or number (percentage and its 95% CI). Comparison of means was performed using the Student *t* test for parametric variables or the Mann–Whitney U test for nonparametric variables. All *P* values were two tailed, and a *P* value <0.05 was considered significant. Statistical analysis was performed using NCSS 2007 software (Statistical Solutions Ltd., Cork, Ireland).

Results

Forty-two consecutive brain-dead patients were screened in this prospective study. Six patients were treated with corticosteroids during the previous 7 days, one patient did not require norepinephrine infusion, and five patients had echocardiographic left ventricular ejection fraction less than 50%. Therefore, 31 patients were included in the study, and their baseline characteristics are presented in table 1.

Adrenal Insufficiency and Response to ACTH Stimulation
The incidence of adrenal insufficiency was 87% [95% CI, 70–96%]. In 85% [95% CI, 66–96%] of the cases, the adrenal insufficiency was total (hypothalamic-pituitary-adrenal insufficiency) or secondary (fig. 1). Twenty-four patients were ACTH responders (77% [95%CI, 55–87]), whereas seven were ACTH nonresponders (23% [95%CI, 10–41]) (fig. 1). Time between cerebral injury and brain death diagnosis was longer in ACTH responders than in ACTH nonresponders (6 ± 6 *vs.* 1 ± 0 days, respectively, *P* < 0.05) (fig. 2).

Initial Glasgow Coma Score, systemic hemodynamics, total fluid infusion, and norepinephrine dose were not significantly different between patients with or without adrenal insufficiency (table 2). At T_0, baseline plasma cortisol was significantly lower in ACTH responders than in ACTH nonresponders (5.5 [3.0–9.2] μg/dl *vs.* 14.5 [9.9–33.5] μg/dl, respectively, *P* < 0.01). In patients with adrenal insufficiency, baseline plasma cortisol was significantly lower than in patients without adrenal insufficiency (fig. 3A). In contrast, there was no significant difference between the concentration of baseline plasma cortisol in hemodynamic responders and hemodynamic nonresponders (fig. 3B). After ACTH stimulation testing, delta percentage of baseline plasma cor-
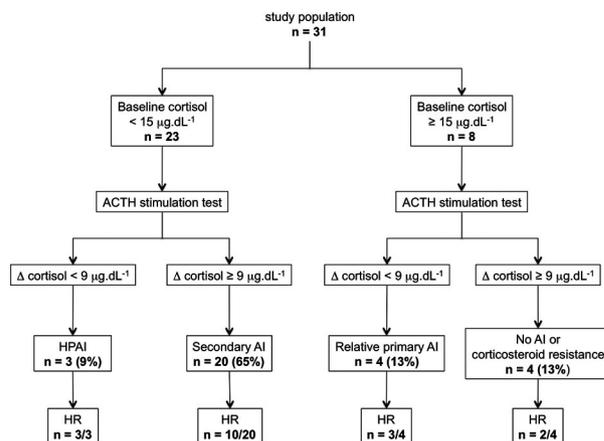

Fig. 1. Distribution of patients according to baseline plasma cortisol concentration and response to cortisol-adrenocorticotropic hormone (ACTH) stimulation. Δ cortisol = delta plasma cortisol concentration 30 or 60 min after 250 μg of tetracosactrin infusion; HPAI = hypothalamic-pituitary–adrenal insufficiency; AI = adrenal insufficiency (see definition in Study Protocol—ACTH Stimulation Testing section); HR = hemodynamic responders (see definition in Study Protocol—Norepinephrine Dose Adjustment section).

tisol concentration at T_{60} was not significantly different between patients with or without adrenal insufficiency (fig. 3C) and between hemodynamic responders and hemodynamic nonresponders (fig. 3D).

Total Norepinephrine Dose
In all patients, total norepinephrine dose significantly decreased at 180 min after ACTH stimulation testing and hydrocortisone infusion, from 0.31 [0.16–0.44] μg · kg^{-1} · min^{-1} to 0.18 [0.10–0.24] μg · kg^{-1} · min^{-1} (*P* < 0.01), without significant decrease in mean arterial blood pressure (from 81 ± 12 mmHg to 83 ± 9 mmHg, nonsignificant). The initial norepinephrine dose was similar in patients with or without adrenal insufficiency (0.31 [0.18–0.48] μg · kg^{-1} · min^{-1} and 0.31 [0.16–0.49] μg · kg^{-1} · min^{-1}, respectively, nonsignificant). The delta percentage of baseline norepinephrine dose, reflecting the hemodynamic response intensity, was similar in patients with or without adrenal insufficiency
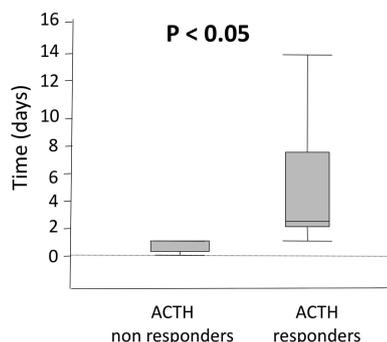

Fig. 2. Comparison of time between brain injury and brain death between cortisol-adrenocorticotropic hormone (ACTH) responders and ACTH nonresponders (see definition of ACTH in Study Protocol—ACTH Stimulation Testing section). Data are *box plot* (median, 25th and 75th percentiles, and *whiskers*).

Table 2. Characteristics of Patients with Adrenal Insufficiency and No Adrenal Insufficiency

	Adrenal Insufficiency (n = 27)	No Adrenal Insufficiency (n = 4)
Initial GCS		
3–7	18	2
8–13	6	2
14–15	3	0
Hemodynamic variables at T_0		
HR, beats/min	96 ± 24	87 ± 19
SAP, mmHg	112 ± 13	106 ± 19
MAP, mmHg	82 ± 11	77 ± 14
Norepinephrine dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.31 [0.18–0.48]	0.31 [0.16–0.49]
Volumic expansion, ml/kg	15 ± 10	12 ± 6

No significant difference between groups. Data are expressed as mean ± SD, median (25th and 75th percentiles), or number of patients.

GCS = Glasgow Coma Score; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure.

(−47% *vs.* −15%, respectively, nonsignificant) and was similar in ACTH responders and nonresponders (−28% *vs.* −50%, respectively, nonsignificant). A hemodynamic response was obtained in 18 patients (58% [95% CI, 39–75]). However, the incidence of hemodynamic response was higher in ACTH nonresponders than in ACTH responders: 86% *versus* 50%, respectively, $P < 0.05$ (fig. 1). The hemodynamic response intensity was independent of the response
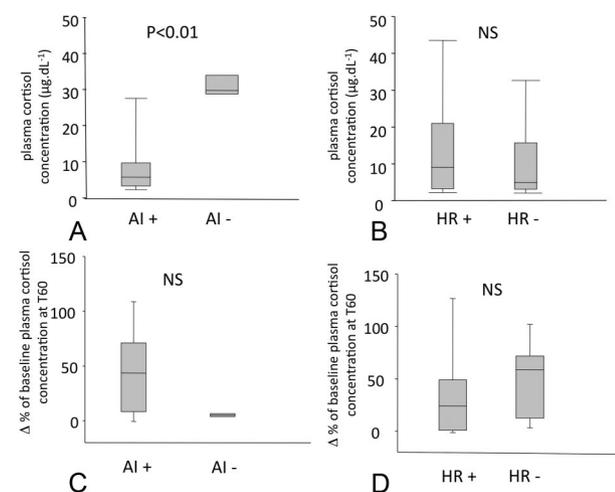

Fig. 3. Comparison of baseline plasma cortisol concentration and delta percentage of baseline plasma cortisol concentration at T_{60} between patients with (AI+) and without (AI−) adrenal insufficiency (see definition in Study Protocol–ACTH Stimulation Testing section) (*A, C*) and between hemodynamic responders (HR+) and hemodynamic nonresponders (HR−) (see definition in Study Protocol—Norepinephrine Dose Adjustment section) (*B, D*). Data are *box plot* (medians, 25th and 75th percentiles, and *whiskers*). NS = nonsignificant.

to ACTH stimulation testing and independent of the presence or type of adrenal insufficiency.

Discussion

Hydrocortisone supplementation significantly enhanced systemic hemodynamics and decreased norepinephrine dose by more than 30% in 58% of brain-dead patients with hemodynamic instability. In our study, 87% of brain-dead patients had adrenal insufficiency, which resulted from a low plasma cortisol concentration in three quarters of cases (secondary adrenal insufficiency) and a lack of response to ACTH stimulation in one quarter of cases (primary adrenal insufficiency). A hemodynamic response occurred more frequently in patients with primary adrenal insufficiency.

In our study, the incidence of adrenal insufficiency is in agreement with previous studies in which adrenal insufficiency was defined by a stimulated plasma cortisol concentration less than 18 μg/dl.[14] Previous studies investigating the adequacy of cortisol secretion in the setting of brain death have led to variable conclusions. On the basis of baseline plasma cortisol concentration, corticosteroid function in brain-dead patients was still a matter of debate,[14–17] being found as normal,[18] decreased,[19] or increased.[17] The prevalence of adrenal insufficiency varies widely, depending on the diagnostic criteria. There is no absolute plasma cortisol concentration, which distinguishes an adequate from an insufficient adrenal response. However, a baseline plasma cortisol concentration less than 15 μg/dl has been suggested to be inadequate in critical illness situations.[13]

In our study, 24 of 31 patients (77%) were ACTH responders. In brain-dead patients, Dimopoulou *et al.*[14] found that only 4 of 17 patients (24%) were ACTH responders. However, they used a different definition: ACTH responders were defined by a delta plasma cortisol concentration more than 18 μg/dl. Moreover, they used a less specific ACTH stimulation testing (1 μg)[18] compared with the recommended test used in our study (250 μg).[5]

Among brain-dead patients, we can distinguish four pathophysiologic groups according to baseline and stimulated plasma cortisol concentration. (1) Approximately two thirds of patients have a low baseline plasma cortisol concentration and are ACTH responders, reflecting a hypothalamic-pituitary failure (secondary adrenal insufficiency).[20] Intracranial hypertension may impair oxygenation of the hypothalamus and pituitary, being responsible for a low release of corticotropin-releasing hormone and ACTH. After tetracosactrin infusion, the intact adrenal glands produce cortisol. (2) Approximately 10% of patients have a normal baseline cortisol concentration and are ACTH nonresponders, suggesting a maximal stimulation of the hypothalamic-pituitary-adrenal axis and thus a relative primary adrenal insufficiency[21]: adrenal glands cannot increase their production of cortisol, which is insufficient in regard to the stress-induced needs. (3) Approximately 10% of patients have a low baseline cortisol concentration and are ACTH nonresponders, reflecting a hypotha-

lamic-pituitary-adrenal insufficiency. (4) Approximately 10% of patients have a normal baseline cortisol concentration and are ACTH responders, suggesting no hypothalamic-pituitary-adrenal axis dysfunction.

The value of supplementary dose of hydrocortisone infusion has been demonstrated variously in patients with septic shock.[22,23] Annane *et al.*[21] demonstrated that 7-day shock reversal was achieved significantly more often in treated patients *versus* in controlled patients, implying a decrease in mortality rate of 31%. The Corticosteroid Therapy of Septic Shock study did not confirm these results, maybe partly because of the lower severity of illness in enrolled patients.[23] These results were independent of the responsiveness to a short corticotropin test.[24] In our study, we demonstrated that supplementary dose of hydrocortisone infusion was more often efficient in enhancing hemodynamic stability in ACTH nonresponders (86%) than in ACTH responders (46%), suggesting that exogenous steroids have a higher likelihood of producing a hemodynamic response when there is no endogenous response to ACTH stimulation. Supplementary dose of hydrocortisone infusion was efficient in some patients without any adrenal insufficiency too (50%), suggesting a possible corticosteroid tissue resistance. In 22% of patients, the lack of response to ACTH stimulation testing suggests the absence of cortisol adrenal reserve. Moreover, as described in patients with septic shock,[25] the time between brain injury and brain death seems to be playing an important role in response to ACTH stimulation testing and hemodynamic response intensity. These results could be explained by the fact that corticosteroid effects result from the restoration of α- and β-adrenoceptors pathway[26,27] altered by down-regulation and later by desensitization[28] in patients with shock treated with catecholamines. In brain injury, an explosive increase in intracranial pressure is also known to induce a systemic peak of catecholamines release followed by a drop 60 min after the brain death onset.[29] After the initial stress at the origin of large cortisol release, the overstimulated hypothalamic-pituitary-adrenal axis adrenal gland induced by brain death may be unable to restore the stock of cortisol. In our study, the effectiveness of hydrocortisone infusion on norepinephrine dose decrease was observed in one quarter of patients with a baseline plasma concentration more than 15 μg/dl and no ACTH response. As established, septic shock, down-regulation of β-adrenergic receptors,[28] and possibly α-adrenergic receptors[30] may contribute to the vascular hyporesponsiveness to catecholamines. In addition, as recently shown in different myocardial pathology, overexpression of β_3-adrenoceptor could be involved as well.[30,31] Negative inotropic effect induced by β_3-adrenoceptor in parallel to down-regulation of β_1-adrenoceptor is known to decrease inotropic effect of β-adrenergic stimulation, whereas the increase of sympatic drive is an important mechanism for maintaining cardiac output. In this way, corticosteroids may reverse receptor desensitization[26,27] and further allow reduced catecholamine dosage. Methylprednisolone may improve hemodynamics[31] and restore the normal β_1-adreno-

ceptor/β_3-adrenoceptor ratio in patients with circulatory shock treated with catecholamines for more than or equal to 72 h, whereas earlier glucocorticoid infusion does not improve hemodynamics.

Beneficial effects of glucocorticoids in brain death could be also induced by their antiinflammatory effect. Because adrenal insufficiency results from multiple cytokine release such as tumor necrosis factor α, interleukin-1, interleukin-6, and overexpression of cell adhesion molecules such as intercellular adhesion molecule-1 and E-selectin,[32,33] hydrocortisone treatment may decrease the proinflammatory response.[34]

To summarize, baseline cortisol measurement and ACTH stimulation testing are useful to distinguish the type of adrenal insufficiency but cannot predict which brain-dead patients are hemodynamic responders, even if most of ACTH nonresponders are hemodynamic responders. Conversely, no adverse effect has been reported with ACTH stimulation testing or with low-dose glucocorticoid infusion. For this reason, and because no adverse effect has never been reported, we suggest to test the adrenal response to ACTH stimulation and infuse a supplementary dose of hydrocortisone in all brain-dead patients with hemodynamic instability requiring norepinephrine.

Several limitations of our study should be noted. First, because this study was not randomized, a causality link cannot be demonstrated concerning the administration of glucocorticoids and the changes observed in norepinephrine dose. Nevertheless, we assume that, because hemodynamic stability, and thus norepinephrine dose, was ensured during a 60-min period before glucocorticoid administration and because patients with severe cardiac dysfunction had been excluded, this causality link remains likely. Moreover, the comparison between subgroups remains valid. Second, we did not assess the consequences of glucocorticoid administration on the prognosis of organ transplantation. It should be pointed out that these consequences would be difficult to analyze because brain-dead patients receive high doses of glucocorticoids for immunogic purposes just before organ harvesting. Conversely, a recent study has demonstrated that high dose of vasoactive drugs in donor was a major determinant for primary graft failure in heart transplantation.[35] Further evaluation would be useful to evaluate the benefit of the decrease of norepinephrine requirement in donors for cardiac and other transplants. Third, because measurement of the free cortisol concentration is currently not widely available, we measured total plasma cortisol concentration, rather than the protein-bound fraction, whereas the free cortisol is responsible for the physiologic function of the hormone. In critical illness, the concentrations of albumin and corticosteroid-binding globulin are commonly decreased. Therefore, measured total plasma cortisol concentration can be misleadingly lower than anticipated, resulting in the incorrect conclusion that adrenal function is impaired.[36] However, these considerations do not change the hemodynamic response incidence and intensity, which was the aim of our study. In any event, further studies are necessary to establish the nor-

mal range of free cortisol in critically ill patient, and experts do not recommend the use of free cortisol measurements for the diagnosis of adrenal insufficiency at this time.[5]

In conclusion, our findings suggest that the incidence of adrenal insufficiency is important in brain-dead patients (87%) and that ACTH stimulation followed 1 h later by a supplementary dose of hydrocortisone enhanced the systemic hemodynamic stability whatever their pathophysiologic corticosteroid status, with or without primary and/or secondary adrenal insufficiency.

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◼ ANESTHESIOLOGY REFLECTIONS

"Prize-Bearing" Salicylates of Athlophoros
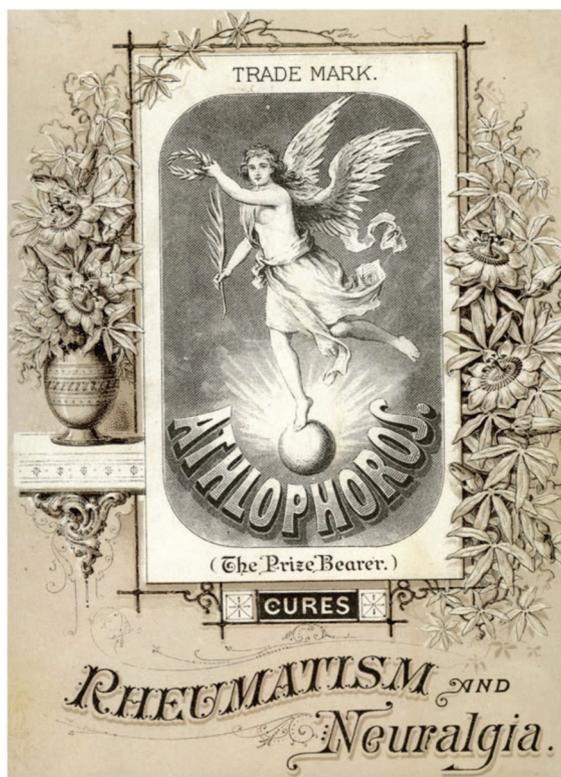
"Put your hand in a vise, turn the screw until the pain is all you can bear, and that's *rheumatism*; turn the screw once more and that's *neuralgia*…." From the 1880s to the 1910s, both ailments were advertised as "cured" by a salicylate preparation named after the ancient Greek word for prize-bearer, *Athlophoros*. Its namesake company trademarked itself by surrounding the goddess Nike's image as winged Victory with sedative-laden Purple Passionflowers (*see above,* courtesy of the Wood Library-Museum). Rather than from that botanical, the popularity of the nostrum's original compounding likely stemmed from its 6.5-mg oral dose of morphine sulfate (every 3 h "until relieved")—perhaps the real "prize" borne by this analgesic. Not surprisingly, laxative "Athlo-Tablets" were soon needed to relieve "constipated rheumatics" who had overindulged in this opiate-laden panacea. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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