Does Adrenal Size Matter?

STRESS is a state in which homeostasis is actually threatened or perceived to be so.[1] External adverse forces, such as critical illness, induce a stress response that is a complex repertoire of behavioral and physiologic adaptive responses that attempt to restore homeostasis. The hypothalamic-pituitary-adrenal axis is an important part of this stress reaction. In this issue of ANESTHESIOLOGY, Jung *et al.*[2] present data suggesting that activation of hypothalamic-pituitary-adrenal axis is an important aspect of the psychoneuroimmunologic adaptation that helps survival during septic shock. In patients with septic shock without evidence of adrenal insufficiency, Jung *et al.* observed that adrenal gland volume, measured by computed tomography, was an independent predictor of mortality. Plasma cortisol concentrations measured in response to cosyntropin stimulation correlated with adrenal gland volume, suggesting biologic relevance of the observed increase in adrenal size.

Neuroanatomy and Physiology of the Stress Response in Critically Ill Patients

Stress is superimposed upon the body's circadian tone, such that the magnitude and duration of the stress response is variable depending on the nature and intensity of the stimulus and the circadian phase.

Changes take place in the central nervous system and in various peripheral organs during stress. The central components of this system include hypothalamic hormones (vasopressin, corticotropin-releasing hormone, and proopiomelanocortin-derived peptides), the locus ceruleus, and autonomic norepinephrine centers in the brainstem.[1]

The hypothalamus is the center of the stress system that regulates homeostasis. Under homeostatic conditions (in the absence of critical illness), the paraventricular neurons secrete two or three pulses of corticotrophin-releasing hormone and arginine vasopressin per hour into the hypophyseal portal system. When these pulses peak (early in the morning), they increase the magnitude of corticotrophin, the key regulator of glucocorticoid secretion by the adrenal gland. Glucocorticoids as end-effectors of the hypothalamic-pituitary-adrenal axis are the most important natural inhibitors of inflammation. Their metabolic and immunogenic effects can help restore an impaired homeostasis during severe infection.[3]

Inflammatory signals (such as nuclear transcription factor-κ-B) and glucocorticoid receptor α-activation (by endogenous or exogenous glucocorticoids) have opposing functions in restoring homeostasis.[4] In addition to their antiinflammatory effects, glucocorticoids can restore homeostasis by modulation of metabolism and cardiovascular function. In the central nervous system, the stress response facilitates neural pathways to achieve adaptation to restore homeostasis. Note that arousal, vigilance, and focused attention help achieve adaptation, whereas inhibition of the neural pathways involved with appetite, growth, and reproduction occurs, as these pathways do not contribute to acute adaptation. In addition, the stress reaction induces an increased delivery and consumption of oxygen in the brain, heart, and skeletal muscles.[5]

Stress in Critically Ill Patients

Hypoxia, hypothermia, trauma, cancer, renal failure, liver failure, transfusion, noise, and/or pain induce local or systemic inflammatory reactions, such that cytokines escape into the systemic circulation. The cytokines then cause systemic symptoms and induce inflammatory signaling at multiple levels, including at the hypothalamus, in the central noradrenergic system, and in the pituitary and adrenal glands (fig. 1). Plasma cortisol concentrations increase to peak values that may exceed concentrations achieved with maximal stimulation doses of corticotropin-releasing hormone. Notably, despite these responses, adrenal insufficiency is also a frequent finding in critically ill patients; adrenal insufficiency in these patients is associated with a high mortality rate.[6,7]

What Did the Study of Jung *et al.* Add to the Existing Literature?

Jung *et al.* observed an association between high adrenal gland volume and survival in septic shock. What is the mech-

Accepted for publication May 11, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article. Figure 1 in this article was redrawn by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

 Anesthesiology 2011; 115:223–5

◆ This Editorial View accompanies the following article: Jung B, Nougaret S, Chanques G, Mercier G, Cisse M, Aufort S, Gallix B, Annane D, Jaber S: R2: The absence of adrenal gland enlargement during septic shock predicts mortality—a computed tomography study of 239 patients. ANESTHESIOLOGY 2011; 115:334–43.

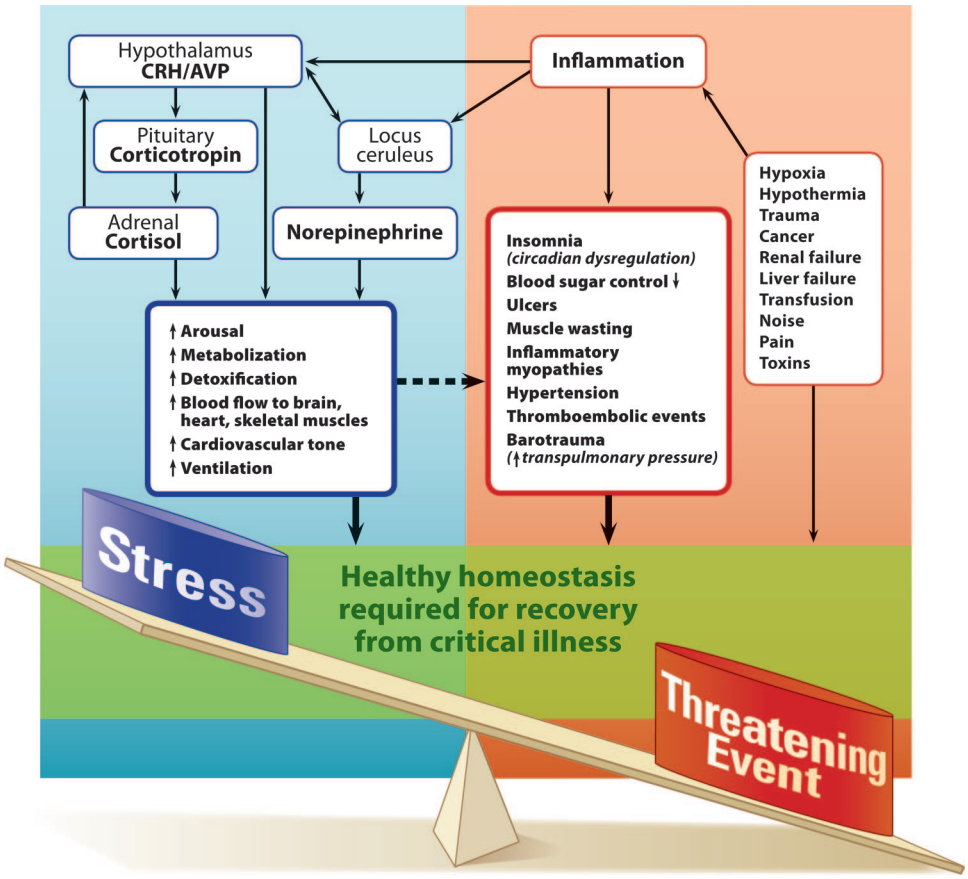

Fig. 1. Regulation of homeostasis by a stress reaction in critically ill patients. Homeostasis (*green*) is defined as the internal property of the body to maintain a stable, constant condition, which is regulated by positive and negative feedback. In critically ill patients, numerous inciting events (*red*) can put the healthy homeostasis required for recovery from critical illness at risk. The stress reaction (*blue*) regulates homeostasis by a variety of physiologic and behavioral responses that may be sufficient to restore homeostasis. However, an excessive stress reaction itself can resemble what electrical engineers call a "flip-flop switch," representing a state in which healthy homeostasis is threatened by the consequences of an excessive stress reaction (*dotted lines*). AVP = arginine vasopressin; CRH = corticotropin-releasing hormone.

anism of the adrenal hyperplasia? Both stress and adrenal insufficiency induce corticotrophin stimulation of the adrenal cortex that produces both hypertrophy and hyperplasia.[8] Therefore, a bigger adrenal size does not explain an increased incidence of recovery from septic shock. But if the adrenocortical hypertrophy is evidence of increased adrenocortical function, then the hypertrophy might explain a positive survival benefit.[9]

Reversible adrenal insufficiency in critically ill patients is demonstrated by either a low basal cortisol concentration or by a low cortisol concentration in response to corticotropin stimulation.[10] According to Annane *et al.*,[11] the best evidence for adrenal insufficiency in critically ill patients are an increase in total serum cortisol of less than 9 mg/dl after the administration of corticotrophin (250 mg) or a random total cortisol measurement of less than 10 mg/dl. The data provided by Jung *et al.* documents basal cortisol concentrations of 19.8 [20.9–25.6] and stimulated concentrations of 29.7 [28.8–33.9], suggesting that the patients studied did not have adrenal insufficiency. As the plasma cortisol concentrations measured in response to cosyntropin stimulation correlated with the adrenal gland value, the hypertrophy appeared to be due to increased function. Based on these considerations, in the absence of adrenal insufficiency, a decreased adrenal volume in patients with septic shock appears to represent decreased function.

Jung *et al.* presented observational data; their investigation was not designed to evaluate the administration of steroids so it is not possible to draw any conclusions from this study as to whether steroids should be given to patients with small adrenal glands. To evaluate whether adrenal size can be used to predict the effectiveness of steroid therapy in septic shock, a randomized controlled study that implements disease entity-based subgrouping and formal testing results for adrenal failure (random cortisol and corticotropin stimulation) will be required. Jung *et al.* are commended for having taken a first step in defining a target population for steroid therapy in septic shock.

Matthias Eikermann, M.D., Ph.D., Ulrich Schmidt, M.D., Ph.D., Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. meikermann@partners.org

References

1. Chrousos GP: Stress and disorders of the stress system. Nat Rev Endocrinol 2009; 5:374–81
2. Jung B, Nougaret S, Chanques G, Mercier G, Cisse M, Aufort S, Gallix B, Annane D, Jaber S: R2: The absence of adrenal gland enlargement during septic shock predicts mortality—a computed tomography study of 239 patients. ANESTHESIOLOGY 2011; 115: 334–43
3. Chrousos GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995; 332:1351–62
4. Meduri GU, Yates CR: Systemic inflammation-associated glucocorticoid resistance and outcome of ARDS. Ann N Y Acad Sci 2004; 1024:24–53
5. Venkataraman S, Munoz R, Candido C, Witchel SF: The hypothalamic-pituitary-adrenal axis in critical illness. Rev Endocr Metab Disord 2007; 8:365–73
6. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, Briegel J, Keh D, Singer M, Moreno R, Bellissant E, Annane D, Corticus Study Group: Adrenal function in sepsis: The retrospective Corticus cohort study. Crit Care Med 2007; 35:1012–8
7. 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
8. Akana SF, Shinsako J, Dallman MF: Relationships among adrenal weight, corticosterone, and stimulated adrenocorticotropin levels in rats. Endocrinology 1983; 113:2226–31
9. Harvey PW, Sutcliffe C: Adrenocortical hypertrophy: Establishing cause and toxicological significance. J Appl Toxicol 2010; 30:617–26
10. Neary N, Nieman L: Adrenal insufficiency: Etiology, diagnosis and treatment. Curr Opin Endocrinol Diabetes Obes 2010; 17:217–23
11. 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