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Managing Stress in Critical Illness: A Question of Balance

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Physiological and emotional stress is a concomitant of critical illness regardless of its underlying cause, but our understanding of the influence of the stress response on clinical outcomes and how the response can be managed remains rudimentary. The review by Cuesta and Singer (1) in this issue of *Critical Care Medicine* provides an informative historical overview of our understanding of the stress response as described by philosophers and researchers from the age of Hippocrates to the present. Cuesta and Singer explain that the biologic concept of stress emerged from a simpler mechanical concept introduced by Robert Hooke describing the deformation of an elastic body (strain) as linearly related to the externally applied force (stress). Similarly, biologic stresses or stressors act on individuals to disturb normal homeostasis. However, the term “strain” is not used to describe the resulting homeostatic disruption. Rather the term “stress” is applied to this situation making the use of stress as a term in biology imprecise. Furthermore, stressors elicit multiple biological responses that vary depending on the nature of the stressor, and the relationship of these responses to most stressors is generally non-linear and time-varying. This complexity underlies the intricate theories that have been advanced over the years by prominent scientists and are elegantly summarized in Cuesta and Singer’s review (1).

Of central importance to the role of stress in critical illness is the recognition that the stress response has both beneficial and detrimental components. This dichotomy has been described most fully by neuroendocrine and behavioral scientists. Acute stressors studied by these investigators are most often stimuli that do not affect homeostasis directly but rather are associated with impending danger based on previous experience or evolutionary pressure. Such stressors elicit neuroendocrine, autonomic, and immune responses that are preparative for fight or flight from danger and are potentially beneficial to defend homeostasis in the event of physical harm. Short-lived and infrequent episodes of this variety of stress are benign. However, the evidence suggests that persistent stress such as psychosocial stress related to poverty, poor nutrition, or racial discrimination predisposes individuals to chronic ailments that include metabolic syndrome, hypertension, and affective disorders. Behavioral stress of greater intensity such as experience in battle can elicit post traumatic stress disorder that persists well past the period of exposure. The central neural, endocrine, and immunologic responses that underlie the mechanisms involved in these examples are detailed in several of the works cited by Cuesta and Singer (2–4).

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In critical illness the central neural, autonomic, endocrine, and immune responses are similar to those in the more well-studied behavioral models. However, the dynamics of the responses and how they affect recovery in patients with varied genomes, phenotypes, pathologies, and histories are poorly understood. Events that lead to critical illness excite multiple sensory modalities to initiate the stress response. As an example traumatic injury with blood loss precipitates sensory neural signals from pain and baroreceptor pathways in addition to tissue damage that leads to the release of inflammatory mediators to activate the central neural pathways outlined by Cuesta and Singer (1). This initial input is then followed by clinical interventions that include additional stressors such as surgery. Other interventions such as intravenous resuscitation and pharmacologic sedation act to diminish the stress response. Thus, the overall response throughout the course of illness is complex. Furthermore, experimental studies in animals show that the response to stressors of different modalities such as pain and hypovolemia can be synergistic (5), and that the response to a stressor is affected by earlier stress history (6). These experimental findings are consistent with the time-dependent view of resilience to stress that is expressed near the end of Cuesta and Singer's review (1).

The review also posits that the stress response in critical illness acts at the cellular level through mitochondria as a common pathway. Thus, the overall effect of stress in critical illness can be viewed as a time-variant dynamic process with a profound and complex influence on cellular function. The ultimate result ranges from recovery to multiple organ failure and death. The challenge is to determine if the stress response can be modulated to optimize recovery and avoid lethality. Modern critical care strives to reverse ongoing pathology by improving tissue perfusion, oxygen delivery, and metabolic status to promote tissue repair and host defense. However, as pointed out in the review overly aggressive tactics that target normal homeostatic endpoints may suppress beneficial components of the stress response. In this regard, ongoing debate continues as to the best strategies for the cardiovascular (7) and pulmonary (8) support of critically ill patients. Manipulation of the stress response through interventions such as corticosteroid therapy has been explored (9), and potential therapeutic targets such as mitochondria are and will be investigated. Yet, definitive strategies have not been identified. The response of central neural stress pathways in a rat model of peritoneal sepsis is prolonged but shows increasing variability from animal to animal over several days (10). This variability is a common feature of critical illness with a potentially strong relationship to outcome that may warrant preclinical investigation. A recent behavioral study used brain imaging techniques to monitor stress responses in three mouse lines selectively bred for high, intermediate, or low stress reactivity (11). As a suggestion, a similar approach for experimental models of clinical illness has the potential to identify stress response patterns that are predictive of outcome or that provide new or refined therapeutic targets to guide treatment. Striking the right balance between therapies that are stressors in and of themselves, goal-directed therapies to physiologic end-points, and therapies designed to augment or modulate the stress response might then preserve the positive effects of the ongoing stress response to bolster the patient's innate mechanisms for recovery.

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