Adrenal Insufficiency, Heart Rate Variability, and Complex Biologic Systems: A Study of 1,871 Critically Ill Trauma Patients

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BACKGROUND: Reduction in integer heart rate variability (HRVi), one potential measurement of complex biologic systems, is common in ICU patients and is strongly associated with hospital mortality. Adrenal insufficiency (AI) and reduced HRVi are associated with autonomic dysfunction. Failure of the autonomic nervous system can be associated with loss of biologic complexity. We hypothesize decreased HRVi is associated with AI, and HRVi improves after treatment of AI, suggesting "recomplexification" (resumption of normal stress response to injury).

STUDY DESIGN: Of 4,116 trauma ICU admissions from December 2000 to November 2005, 1,871 patients had sufficient physiologic, laboratory, pharmacy, and demographic data for analysis. Seventy-five patients failing cosyntropin-stimulation testing were defined as AI; the remaining 1,796 were defined as no AI. HRVi was calculated as integer heart rate standard deviation over 5-minute intervals. HRVi 10th, 50th (median), and 90th percentiles were calculated over the 72 hours pre-, or poststeroid, or both administration (AI). HRVi percentiles in non-AI patients were evaluated at the same interval and compared with AI using Wilcoxon's rank-sum test. In patients with AI, daily HRVi was computed 3 days before and after steroid administration, and compared between survivors and nonsurvivors.

RESULTS: There were 2.9 million heart-rate intervals measured. HRVi stratified patients with AI (cosyntropin failure), and without AI. HRVi was similar in AI survivors and nonsurvivors before steroid treatment, but differed after treatment. HRVi increased substantially in survivors after steroid administration, yet did not change in nonsurvivors. HRVi does not increase in patients who are unresponsive to steroids and die.

CONCLUSIONS: Reduced heart-rate variability, a potential measurement of complex biologic systems, is associated with cosyntropin-confirmed AI; improved in patients responding to steroid therapy; and is a noninvasive, real-time biomarker suggesting AI. (J Am Coll Surg 2007;204:885–893. © 2007 by the American College of Surgeons)

Adrenal insufficiency (AI) is common in the ICU. It is characterized by hypotension unresponsive to fluid and vasopressor administration and can be difficult to recognize clinically in trauma patients.[1] Diagnosis is confirmed using cosyntropin stimulation.[2] Our previous work suggested that integer heart rate variability (HRVi) can serve as a biomarker to identify a subpopulation of patients at high risk for AI.

We have demonstrated previously in trauma patients that reduced HRVi measurements based on standard deviation predict mortality in the first 24 hours after injury[3]; predict mortality independent of the cause of death[4]; consistently predict mortality 3 to 4 days in advance of death throughout the ICU stay; are associated with traditional measurements of shock and diminished physiologic reserve (acidosis, coagulopathy, hypothermia)[5]; and reduced HRVi is associated with relative autonomic dysfunction.

The autonomic nervous system is divided into two components: central and peripheral. The peripheral component is involved in acute adaptations to stressful stimuli.

Competing Interests Declared: None.

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Abbreviations and Acronyms

AI = adrenal insufficiency
HR = heart rate
HRVi = integer heart rate variability
SIMON = signal interpretation and monitoring
VUMC = Vanderbilt University Medical Center

These functions are usually achieved through a complex system of neurotransmitters, which exert their effects on various body organs through various receptor systems.

These varied functions are centrally integrated by the central autonomic network, which has extensive circuitry involving all areas of the medulla, hypothalamic regions, brain stem, and areas of the forebrain. We hypothesized that disturbances in the central autonomic network system, reflected by decreased heart rate (HR) variability, mediated alterations in the hypothalamic adrenal axis.

In this article, we demonstrate, in a large population of patients, that global changes in the autonomic nervous system manifested by reduced HRVi and by failure of the hypothalamic adrenal axis (relative adrenal insufficiency) are associated with increased mortality. Survivors responding to treatment for AI manifested immediate restoration of HRVi, and HRVi remained low in patients who died despite therapy.

METHODS

Setting

Vanderbilt University Medical Center (VUMC) is the only Level I trauma center serving an 80,000 square-mile catchment area. There are 3,200 trauma admissions annually, with > 1,800 admitted to a 31-bed dedicated trauma unit. Fourteen beds in this unit are classified as ICU beds, accommodating over 800 admissions per year. Currently, all ICU beds are equipped with signal interpretation and monitoring (SIMON), a continuous physiologic data capture and management system.

Data sources

VUMC's clinical and research information infrastructure, as described previously,[6-8] provided the linked demographic, physiologic, laboratory, medication, and outcomes data required for this study. Components of this infrastructure relevant to the current analysis include the following data sources.

SIMON

SIMON[9-12] is an ongoing effort of the VUMC Division of Trauma and Surgical Critical Care. Physiologic data from bedside medical devices has been continuously captured and stored from trauma ICU beds since December 2000. Captured parameters include HR, invasive and noninvasive blood pressures, intracranial and cerebral perfusion pressures, arterial and venous oxygen saturations, core temperature, pulmonary and central venous pressures, cardiac index, and end diastolic volume index. Since November 2006, data has been collected for over 4,500 patients for their entire length of ICU stay in a SIMON-monitored bed. This represents > 390,000 total hours of continuous monitoring and over 4 billion data points.

Trauma Registry of the American College of Surgeons

The VUMC Division of Trauma has maintained a trauma registry since 1986 and has participated in the Trauma Registry of the American College of Surgeons since 1996. All patients admitted to VUMC with trauma or burns are entered into this database, which includes all patients with SIMON data. Data are maintained locally and shared quarterly with the national repository. Currently, more than 300 parameters are captured through retrospective chart review, including patient demographics, injuries, diseases, operative procedures, hospital disposition, complications, costs, resource use, and length of stay at various levels of care.

Clinical laboratory and order-entry systems

VUMC first implemented electronic clinical laboratory reporting systems in the mid-1980s, and computerized physician order entry in 1996. These systems were used for all laboratory data reporting and all physician medication orders required for this study.

Deidentified dataset

After approval by the VUMC Institutional Review Board, a dataset was created linking information from these sources, and then deidentified before analysis.

Study population

This cohort included all patients who were trauma admissions to our institution from December 2000 to October 2005 (n = 17,629) as shown in Figure 1; were admitted directly to the ICU (n = 4,061); had continuously monitored physiologic data available in SIMON (n = 3,050)—reasons for not having SIMON data include admission to a non-SIMON bed in our ICU (SIMON was not fully implemented in all ICU beds early in the study period) or admission to another ICU under the care of the trauma service because of bed capacity; had AI, defined as a failed cosyntropin-stimulation test followed by steroid therapy (n = 93), with sufficient HR data before and after steroid therapy for analysis (n = 75). Inclusion required HR data within 72 hours before and after steroid therapy; did not