Uncoupling of the autonomic and cardiovascular systems in acute brain injury

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Goldstein, Brah m, Daniel Toweill, Susanna Lai, Karen Sonnenthal, and Brent Kimberly. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1287–R1292, 1998.—We hypothesized that acute brain injury results in decreased heart-rate (HR) variability and baroreflex sensitivity indicative of uncoupling of the autonomic and cardiovascular systems and that the degree of uncoupling should be proportional to the degree of neurological injury. We used HR and blood pressure (BP) power spectral analysis to measure neuroautonomic regulation of HR and BP and the transfer function magnitude (TF) between BP and HR as a measure of baroreflex modulation of HR. In 24 brain-injured patients (anoxic/ischemic injury (n = 7), multiple trauma (n = 6), head trauma (n = 5), central nervous system infection (n = 4), and intracranial hemorrhage (n = 2)), neurological injury and survival was associated with low-frequency (0.01–0.15 Hz) HR and BP power and TF. Brain-dead patients showed decreased low-frequency HR power [0.51 ± 0.36 (SE) vs. 2.54 ± 0.14 beats/min², P = 0.03] and TF [0.61 ± 0.16 (SE) vs. 1.29 ± 0.07 beats·min⁻¹·mmHg⁻¹, P = 0.05] compared with non-brain-dead patients. We conclude that 1) severity of neurological injury and outcome are inversely associated with HR and BP variability and 2) there is direct evidence for cardiovascular and autonomic uncoupling in acute brain injury with complete uncoupling during brain death.

variability; power spectral analysis; transfer function magnitude; brain death

We hypothesized that acute brain injury results in decreased heart-beat oscillations and baroreflex sensitivity indicative of uncoupling of the autonomic and cardiovascular systems. Furthermore, the degree of uncoupling between the two systems should be proportional to the degree of neurological injury. We used power spectral analysis of low (0.01–0.15 Hz) and high (0.15–1.0 Hz)-frequency heart rate and blood pressure to measure neuroautonomic regulation of heart rate and blood pressure oscillations and the magnitude of the low-frequency transfer function between blood pressure and heart rate as a measure of the sensitivity of baroreflex modulation of heart rate. Taken together, these measures provide a novel means of assessing the coupling between the autonomic and cardiovascular systems.

Power spectral analysis of periodic oscillations in heart rate and blood pressure provides an indirect, noninvasive measure of autonomic regulation of cardiovascular function during various pathophysiological states (1, 6, 9, 24). Spectral analysis of time series data sets, such as the electrocardiogram (ECG) or arterial pressure waveform, detects and quantifies periodicities in cardiovascular oscillations and deconvolutes the original time series into a sum of component sinusoidal functions of different frequencies (29). In humans, three major components of heart rate power spectra have been identified: one at the respiratory frequency (~0.25–0.50 Hz), another at a low frequency (~0.1 Hz), and a third at a very low frequency (~0.03 Hz; see Ref. 29). The high-frequency component is solely under parasympathetic regulation via cardiac vagal activity and represents heart beat oscillations occurring as a result of the respiratory frequency, i.e., the respiratory sinus arrhythmia. Low-frequency components of the heart rate power spectrum are under joint sympathetic and parasympathetic control in the nonstressed state, with sympathetic effects predominating during periods of stress (10, 15, 24). Similarly, in arterial blood pressure spectra, the high-frequency component is also related to the effects of respiration on cardiovascular control, whereas periodic oscillations at low frequency (~0.1 Hz, i.e., Mayer waves) are under sympathetic regulation (29). Thus power spectral analysis of heart rate and blood pressure provides quantitative information about neuroautonomic cardiovascular regulation that cannot be determined by measurements of the mean or variance or by assessment of an isolated segment of the neuroregulatory feedback system (e.g., renal sympathetic nerve activity, plasma catecholamine levels, etc.).

The transfer function estimates the relative power and timing of two signals over a range of frequencies (2, 6, 18, 25, 29). The transfer magnitude represents the relative amplitude, or gain, of the output signal for a given input signal at a given frequency. The transfer phase quantifies the degree of phase lead or lag between two signals at a given frequency. The coherence function indicates the fraction of the output signal that is set by the input as a function of frequency.
Therefore, for a phase of ±180° at low frequencies and a coherence = 1, the transfer function magnitude between mean blood pressure (input) and heart rate (output) may be used as an indirect measure of sympathetically mediated arterial baroreflex control of the heart (25, 29).

To test our hypothesis, we studied 24 patients with a diagnosis of acute brain injury. Data were obtained within the first 24 h of admission to the pediatric intensive care unit between September 1994 and March 1997.

**METHODS**

General. This study was approved by the institutional review board of Oregon Health Sciences University. All patients were studied in the supine position. There were 14 females and 10 males. The age range was from 0.2 to 17.5 yr [mean = 5.9 ± 5.1 yr (SD)]. Diagnoses included anoxic/ischemic injury (n = 7), multiple trauma (n = 6), head trauma (n = 5), central nervous system infection (n = 4), and intracranial hemorrhage (n = 2). The Glasgow Coma Scale (GCS) score (27) was determined at the time of the study. Mean GCS score was 5 ± 9 (SD). The Glasgow Outcome Score (GOS; see Ref. 14) was determined at discharge from the pediatric intensive care unit. Mean GOS was 3 ± 2 (SD). There were 17 survivors and 7 nonsurvivors, three of which were diagnosed as brain dead according to published criteria (26a).

Electrocardiogram and arterial blood pressure signals. Electrocardiogram (ECG) and impedance respiratory signals were obtained from a standard lead II ECG. Continuous blood pressure was measured using either a standard 20- or 22-gauge indwelling arterial catheter or a Finapres blood pressure monitor (model 2300; Ohmeda, Englewood, CA). The Finapres digital photoplethysmograph was applied to the second digit of the hand and maintained at the level of the subject's heart during the study period. Analog ECG, respiration, and blood pressure signals were recorded using Hewlett Packard monitor models 7829A and 78212D (Hewlett Packard, Palo Alto, CA) with a low-pass filter at 100 Hz. Data were collected using a Zeos Pantera 90-MHz Pentium personal computer (PC) in conjunction with a PC-LMP-16 data acquisition card. Sampling rate for data collection was done at 1 kHz. Sampling at 1 kHz was determined to be sufficient to meet Nyquist sampling criteria. Signals were analyzed offline on the Zeos PC.

Power spectral and transfer function analysis. HRView software (Boston Medical Technologies, Boston, MA) was used for digital signal (ECG and arterial pressure waveform) acquisition and analysis of heart rate and blood pressure variability, power spectral analysis, and determination of transfer function phase and magnitude. ECG, respiratory, and arterial pressure signals were recorded for 600 s. From each 600 s data set, a 128-s time series that was artifact free was chosen for analysis by one author (Goldstein) blinded to the patient’s condition. Time series data were linearly detrended and analyzed using a modification of the methodology described by Saul et al. (25) for determining mean heart rate and blood pressure, SD and power spectral analysis of heart rate and blood pressure, and transfer function magnitude between mean blood pressure and heart rate. Total power (area underneath the curve) from 0.01 to 0.15 Hz (low-frequency power) was used to quantify sympathetically mediated heart rate oscillations (6, 24, 25). Transfer function plots were visually inspected for a phase of ±180° at low frequencies. The transfer function between low-frequency systolic blood pressure and heart rate was determined at that frequency bandwidth. The transfer function magnitude at low frequencies between mean blood pressure (input) and heart rate (output) was then calculated and used as a measure of arterial baroreflex control of the heart (29).

Statistical analysis. Data were analyzed using log transformation, linear (GCS, GOS) and logistic regression (survival, brain death), and Poisson regression (GOS). Data were analyzed using Minitab statistical software on a Macintosh IIci computer.

**RESULTS**

We found significant correlations between GCS and mean heart rate (P = 0.006, r2 = 0.212), heart rate SD (P = 0.015, r2 = 0.377), and low-frequency heart rate power (P < 0.001, r2 = 0.453). GOS correlated with mean heart rate (P = 0.02, r2 = 0.234), heart rate SD (P = 0.03, r2 = 0.194), low-frequency heart rate power (P = 0.003, r2 = 0.339), and low-frequency mean blood pressure power (P = 0.05, r2 = 0.192). Figure 1 demonstrates heart rate and blood pressure variability, power spectral, and transfer function magnitude plots for patients with different degrees of acute brain injury.

In addition, we found significant correlations between survival and mean heart rate (P = 0.004, r2 = 0.294), heart rate SD (P = 0.006, r2 = 0.144), low-frequency mean blood pressure power (P = 0.009, r2 = 0.458), and transfer function magnitude (P = 0.002, r2 = 0.411). Brain death was correlated with mean heart rate (P = 0.02), heart rate SD (P = 0.005, r2 = 0.09), and transfer function magnitude (P = 0.002, r2 = 0.571). Figure 2 shows the differences among variables studied between subjects grouped into survivors vs. nonsurvivors and brain dead vs. non-brain dead.

**DISCUSSION**

We have previously shown that power spectral analysis of heart rate variability, particularly at low frequencies, diminishes in proportion to the degree of neurological injury, correlates with neurological outcome, and approaches zero during brain death (7, 8). To further evaluate the effect of neurological injury on coupling between the autonomic and cardiovascular systems, we studied additional patients who suffered acute brain injury from multiple causes. In this current study, we were able to demonstrate that physiological uncoupling between the autonomic and cardiovascular systems occurs on multiple levels, including the brain, the sinoatrial node, the peripheral vasculature, and arterial baroreceptors. Similar to previous studies (7, 8), our results indicate that the autonomic and cardiovascular systems are completely uncoupled at all levels during brain death.

Anatomic basis for autonomic cardiovascular uncoupling during acute brain injury. Peripheral and central brain regions involved in the regulation of the cardiovascular system include myelinated and unmyelinated fibers in cranial nerves X and IX, which connect to neurons in the dorsal medial region of the nucleus tractus solitarius (NTS; see Ref. 19). Projections from the NTS lead to neurons in the caudal
ventral lateral medulla (CVLM). Axons from the CVLM synapse on the excitatory neurons in the rostral ventral lateral medulla (RVLM). The RVLM is the major source of tonic excitatory input to the sympathetic pregangli-
Pathophysiology of neuroautonomic cardiovascular interactions. A number of clinical situations analogous to our current study have been reported, including orthotopic heart transplantation (3, 23, 28), traumatic quadriplegia (11, 12), brain death (7, 8), acute surgical or pharmacological autonomic blockade (1, 20, 21), and endotoxin administration (5). Uncomplicated heart transplantation is an extreme example of physical uncoupling and results in near-zero levels of heart rate variability and power spectral values as all nervous connections to the heart have been severed (3, 23, 28). During allograft rejection episodes, there is a partial restoration of broad band frequency activity in the power spectra, suggesting an immunologically mediated interference with intracardiac conduction involving the supraventricular conducting system (3, 23, 28). Diminished or absent heart rate and blood pressure variability has been reported in traumatic quadriplegia in humans (11, 12). These patients demonstrated retention of high-frequency (parasympathetic) oscillations with near-zero levels at low frequencies (sympathetic) consistent with preservation of vagal pathways, which should not be expected to be affected with spinal cord injury. The authors concluded that cervical cord spinal injury resulted in interruption, or uncoupling, of the spinal pathways linking the supraspinal cardiovascular centers with peripheral sympathetic outflow (3, 12) to the sinoatrial node and peripheral vasculature. Brain death is another example of extreme physical uncoupling at yet another level within the nervous system as there is no central processing of afferent signals, resulting in complete interruption of both sympathetic and parasympathetic cardiovascular efferent activity (7, 8).

A recent example of the progression toward severe uncoupling was reported by Godin and Buchman (4) who suggested that evolution from the systematic inflammatory response syndrome to sepsis to septic shock to the multiple organ dysfunction syndrome results in changes in the functional relationship among organs and that restoration of the functional relationships was necessary for recovery. They found that human volunteers who received endotoxin infusion had decreased heart rate variability consistent with physiological uncoupling of vital organ systems (4). Our results suggest that, as severity of acute brain injury increases, there is a proportionately greater degree of physiological uncoupling among the autonomic and cardiovascular systems. We have previously shown that neurological recovery after acute brain injury results in restoration of heart rate variability toward healthy levels (7, 8), a finding that is consistent with the Godin and Buchman paradigm of restoration of functional relationships, or recoupling, necessary for recovery.

Clinical implications. Cardiovascular functions are regulated and adjusted automatically without our attention. Most short-term adjustments of heart rate arise from changes in neural input to the heart. Signals from the baroreceptors initiate the cardiovascular baroreflexes that help maintain blood pressure and ensure
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adequate end-organ perfusion. Although acute denervation results in diminished heart rate variability (3, 23, 28), the chronic effect of denervation of the baroreceptors is not a change in mean blood pressure but rather an increase in the beat-to-beat variability in blood pressure (26). Our results suggest that the brain death state results in near-zero heart rate and blood pressure oscillations. We know that brain death results in eventual cessation of cardiovascular function regardless of artificial, mechanical, or pharmacological supportive measures. We suggest that loss of the uncoupling of the autonomic and cardiovascular systems with subsequent loss of baroreceptor function may be a primary mechanism by which this phenomenon occurs. If substantiated, our findings may have direct impact on future therapies designed to improve preservation of transplantable organs in brain-dead donors. Indeed, some investigators have already concluded that replacement of circulating neurohumoral transmitters or hormones may be essential in prolonging organ function in the brain-dead milieu (13, 16, 17, 30, 31), and specific hormonal replacement protocols are in current use. Our findings suggest that the use of other treatment modalities that mimic cardiovascular variability and feedback control loops, such as artificial pacemakers cycled at specific underlying frequencies or infusion of circulating neurotransmitters in a periodic fashion, may help prolong donor organ viability before transplantation.

We conclude that severity of neurological injury, outcome, and survival are inversely associated with the degree of cardiovascular variability and baroreceptor sensitivity. Brain death results in near-zero levels of variability in cardiovascular signals and baroreceptor sensitivity. Finally, the cardiovascular and autonomic systems are uncoupled at multiple levels during acute brain injury in proportion to the degree of neurological injury. Monitoring the degree of uncoupling of autonomic and cardiovascular systems may lead to better understanding of neuroautonomic cardiovascular interactions during acute brain injury.

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