Low-frequency Spectral Power of Heart Rate Variability Is Not a Specific Marker of Cardiac Sympathetic Modulation

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Background: Heart rate variability in the frequency domain has been proposed to reflect cardiac autonomic control. Therefore, measurement of heart rate variability may be useful to assess the effect of epidural anesthesia on cardiac autonomic tone. Accordingly, the effects of preganglionic cardiac sympathetic blockade by segmental epidural anesthesia were evaluated in humans on spectral power of heart rate variability. Specifically, the hypothesis that cardiac sympathetic blockade attenuates low-frequency spectral power, assumed to reflect cardiac sympathetic modulation, was tested.

Methods: Ten subjects were studied while supine and during a 15-min 45° head-up tilt both before and after cardiac sympathetic blockade by segmental thoracic epidural anesthesia (sensory block: C6–T6). ECG, arterial pressure, and respiratory excursion (Whitney gauge) were recorded, and a fast-Fourier-transformation was applied to 512-s data segments of heart rate derived from the digitized ECG at the end of each intervention.

Results: With cardiac sympathetic blockade alone and the subjects supine, both low-frequency (LF, 0.06–0.15 Hz) and high-frequency (HF, 0.15–0.80 Hz) spectral power remained unchanged. During tilt, epidural anesthesia attenuated the evoked increase in heart rate (+11 min⁻¹ ± 7 SD vs. +6 ± 7, P = 0.024). However, while during tilt cardiac sympathetic blockade significantly decreased the LF/HF ratio (3.68 ± 2.52 vs. 2.83 ± 2.15, P = 0.041 vs. tilt before sympathetic blockade), a assumed marker of sympathovagal interaction, absolute and fractional LF and HF power did not change.

Conclusions: Although preganglionic cardiac sympathetic blockade reduced the LF/HF ratio during tilt, it did not alter spectral power in the LF band during rest or tilt. Accordingly, low-frequency spectral power is unlikely to specifically reflect cardiac sympathetic modulation in humans. (Key words: Anesthesia techniques: thoracic; epidural. Anesthetic, local: bupivacaine. Autonomic nervous system: cardiac innervation. Position: head-up tilt.)

SPINAL sympathetic outflow during epidural anesthesia is attenuated by preganglionic neural blockade.¹–³ Unfortunately, however, there exists no validated noninvasive method to assess in humans cardiac autonomic tone during central neuraxis block. Assessment of whether and to what extent cardiac sympathetic and/or parasympathetic modulation is altered under these circumstances may be important for identification of patients at risk for cardiovascular complications. Conversely, our understanding of cardiovascular control may be improved by evaluating the contribution of cardiac sympathetic fibers to heart rate variability in the frequency domain.

Analysis of heart rate variability in the frequency domain has been used to assess fluctuations in heart rate thought to be mediated by alterations in cardiac autonomic tone.⁴⁻⁸ In general, two major components can be identified in the heart rate spectrum: a high-frequency (HF, >0.15 Hz) component, associated with respiratory fluctuations, and a low-frequency (LF, <0.15 Hz) component. While there is agreement that the high-frequency component reflects parasympathetic outflow to the heart, the origin of the low-frequency component is less certain. It has been hypothesized that low-frequency spectral power is a marker of cardiac sympathetic modulation in humans.⁸ However, the effects of neurogenic (preganglionic) sympathetic blockade of the heart on low-frequency spectral power have not been evaluated.

If low-frequency spectral power of heart rate variability reflects cardiac sympathetic autonomic control,
sympathetic blockade by segmental thoracic epidural anesthesia should abolish or at least attenuate low-frequency spectral power. If, on the other hand, the low-frequency band does not reflect cardiac sympathetic modulation, sympathetic blockade by epidural anesthesia will have no effect. Accordingly, we determined in humans the effects of preganglionic cardiac sympathetic blockade evoked by segmental thoracic epidural anesthesia on spectral components of heart rate variability, both at rest and during a 15-min head-up tilt. Specifically, we evaluated alterations of absolute and fractional low-frequency spectral power as a presumed marker of cardiac sympathetic modulation. Our results show that low-frequency spectral power is not diminished by preganglionic sympathetic blockade during segmental thoracic epidural anesthesia and, therefore, do not support the hypothesis that this component of heart rate variability solely reflects sympathetic cardiac control.

**Methods**

**Patients**

The study was approved by the ethical committee of the Heinrich-Heine-Universität Düsseldorf. After having given their informed written consent, 14 subjects of either sex (age 45.5 yr ± 11.2 SD, body weight 69.3 kg ± 14.8) scheduled for elective thoracic or upper abdominal surgery were studied. All patients were free of cardiovascular disease (by history, physical examination, 12-lead ECG, chest x-ray) and received no drugs before the study. Also, patients were not premedicated on the evening or morning before surgery and had fasted overnight. Ten patients received an epidural injection of the long-acting local anesthetic bupivacaine to induce cardiac sympathetic blockade. In addition, instead of epidural bupivacaine, two patients received an intravenous infusion of bupivacaine, while in another two, saline was injected into the epidural space.

Experiments were always performed in the morning at 7 AM in a quiet separate room with the ambient temperature held constant around 24.5°C, i.e., in the thermoneutral range. An intravenous catheter for fluid replacement and a radial artery catheter for blood pressure measurements were inserted under local anesthesia. A mercury-in-silastic strain gauge (Whitney) was placed around the lower thorax to derive respiratory frequency. Normal saline was infused intravenously at a rate of 20 ml·h⁻¹, and no blood volume expansion or drugs were used throughout the study.

**Measurements**

Instantaneous heart rate was derived from a three-lead ECG (KONE, model 507), and arterial pressure was measured electromanometrically via the arterial cannula and transducer (COMBITRANS, model 521042/9, Braun, Melsungen, Germany). The transducer was taped to the skin of the forearm near the elbow with the position of the arm and transducer remaining at the level of the heart throughout the study. Respiratory excursions were assessed by the Whitney gauge. Signals were recorded continuously on both magnetic tape (REVOX, model A 77, 9.5 cm/s) and an ink recorder (Gould Brush, model 260).

As an indicator for the spread of sympathetic blockade, skin temperatures were measured by infrared thermography (C 600 M, Linear Laboratories) on the hand (digit V) and foot (little toe), as described previously. The instrument is calibrated for the emissivity of human skin, linear over a temperature range from 10°C to 50°C, with a sensitivity of 0.1°C, and has a time constant of less than 1 s. The coefficient of variation for repeated measurements of human skin (same spot sampled over a period shorter than 30 s) was less than 0.5%. Skin temperatures were recorded intermittently every 10 min, while ambient and rectal temperatures were recorded continuously with thermistors (YSI model 402, Yellow Springs).

Arterial blood for the measurement of epinephrine and norepinephrine was withdrawn into chilled tubes prefilled with sodium disulfide (0.1 ml per 4 ml whole blood) and immediately placed in crushed ice. After centrifugation, samples were stored at −80°C until analysis. Epinephrine and norepinephrine were measured by high-pressure liquid chromatography with electrochemical detection, as described previously. Briefly, we used a Waters-Millipore pump, M 510, and a Nova-Pak C18 column (4 μm, 3.9·150 mm, Millipore, Milford, MA). The detection electrode (glassy carbon, BAS, West Lafayette) was set to 650 mV against Ag/AgCl. The mobile phase contained 1.0 m acetic acid, 0.2 mM EDTA and 6 mM octanesulfonic acid-Na-salt; the flow was 1.2 ml·min⁻¹. Arterial blood for the measurement of vasopressin, active renin, and bupivacaine concentrations was handled the same way except for the addition of sodium disulfide to the tubes. Arg⁹-Vasopressin was measured by radioimmunoassay (¹²⁵I vasopressin, Euro-Diagnostics) using rabbit antivasopressin antiserum calibrated against the WHO-standard and with a sensitivity of 0.8 pg·ml⁻¹ following ethanol extraction. Goat anti-rabbit
gamma globulin bound on solid phase was used as separation reagent. Sample and control results were corrected for procedural losses during extraction by determining percent recovery. Cross-reactivity with Lys-Vasopressin, vasotocin, and Oxytocin was <0.1%. Active renin was measured by immunoradiometric assay with two antirenin monoclonal antibodies (Renin Irma Pasteur, Marnes-la-Coquette, France). Briefly, this assay uses a pair of antirenin monoclonal antibodies: the first monoclonal antibody is covalently linked to the magnetic solid phase and recognizes both the active and inactive (prorenin) forms of renin. The second monoclonal antibody is labelled with iodine and specifically recognizes the active form of renin. The assay involves two incubation and two washing steps as well as eight internal standards. Intra- and interassay coefficients of variation ranged from 3% to 6% and from 6% to 9%, respectively, with a detection limit of 3.5 pg·ml⁻¹, and a recovery of 96–106%. Serum osmolality was measured by a freezing point osmometer (Knauer, Bad Homburg, Germany). Bupivacaine plasma concentrations were measured by high-pressure liquid chromatography and UV-detection, as described previously.

**Assessment of Spectral Heart Rate Variability**

Instantaneous heart rate was assessed by measuring the interval between two R-waves. An electronic circuit (derivative threshold detection algorithm, automatic amplitude adaptation) generated a square wave pulse (duration 140 ms) when 75% of the R-wave amplitude was reached. The time between subsequent pulses was measured using a self-written computer program (AT-compatible computer, 16 MHz, numeric coprocessor), as described previously. The accuracy of RR-interval measurement was tested by an electronically generated signal, and the maximum error was found to be less than 2 ms. The measured RR-interval length was converted on-line to heart rate and stored on the hard disk with a parallel time axis. Before further analysis, the heart rate file was edited visually to exclude artifacts, extrasystoles, and postextrasystolic beats. In such rare instances, these beats were eliminated, and the gap was filled by linear interpolation. For later analysis, the digitized ECG (sampling rate 200 Hz/10 bit resolution) was stored on a floppy disk.

The digital filters and the Fast-Fourier transformation, applied for calculation of spectral heart rate variability, require equidistant intervals between the single data points. Accordingly, the RR-interval series was transformed into a time series with a sampling interval of 500 ms, as described previously. After digital low-pass filtering (cutoff frequency 0.02 Hz) and subtraction of mean heart rate from the equidistant sampled heart rate, a Fast-Fourier transformation of data segments of 512-s length (1,024 data points, cosine function windowing) was performed at the end of each experimental period, i.e., during steady-state conditions. Three frequency domains were assessed: very low frequency (VLF, 0.02–0.06 Hz), low frequency (LF, 0.06–0.15 Hz), and high frequency (HF, 0.15–0.8 Hz). Values of spectral power are presented as absolute units (min⁻²) and normalized (fractional) units, i.e., as a percentage of total spectral power.

**Epidural Anesthesia**

Thoracic epidural catheterization was performed after local infiltration anesthesia with the patient in the right lateral decubitus position. The epidural space was identified between the fourth and fifth thoracic intervertebral space by the loss-of-resistance technique and a catheter advanced so that the tip was between the seventh cervical and third thoracic vertebral body, as described previously. Thereafter the patient was turned supine and the trunk covered with a blanket.

For epidural anesthesia, 0.75% bupivacaine was injected into the epidural catheter with the dose adjusted to each patient’s height (mean dose 6.8 ± 0.7 ml). To minimize the risks of unintended intrathecal or intravascular injection, the total dose was given in two increments, i.e., 3 ml as a test dose followed by the remaining dose 5 min later.

Extension of sensory blockade along the body’s length axis was evaluated by the pinprick method (22-G needle), i.e., the needle was moved in 1-cm increments across the upper limb and trunk in a craniocaudal direction. Measurements were always performed twice and by the same investigator to ensure reliable data. Borders were defined as the most cranial and caudal dermatomes rendered unresponsive to the stimulus.

**Study Protocol**

After insertion of the various catheters, the patients rested in the supine position for at least 30 min to ensure a stable baseline. Each patient was studied under four experimental conditions: (1) at baseline (supine, 15 min), (2) during a 40° head-up tilt (15 min) with the sympathetic system intact, (3) during preganglionic cardiac sympathetic blockade by segmental epidural anesthesia alone (supine, 35 min), and (4) during a
second 40° head-up tilt with cardiac sympathetic blockade (15 min). To account for time-dependent effects, two patients, instead of epidural bupivacaine, received the same volume of normal saline epidurally, undergoing an otherwise identical protocol.

Finally, to exclude that any effects, if present, were caused by bupivacaine absorbed into the blood stream and not by cardiac sympathetic blockade, normal saline was injected epidurally in another two patients while bupivacaine was infused intravenously (1.5 mg·min⁻¹) for 50 min, i.e., during stages 3 and 4 of our study protocol. The infusion was titrated to achieve plasma bupivacaine concentrations in the range of or above those expected after epidural anesthesia.

Arterial blood for measurements of vasopressin, active renin, epinephrine, norepinephrine, and bupivacaine concentration in plasma was withdrawn from the arterial catheter at baseline and at the end of each intervention period and was replaced by aliquots of lactated Ringer’s solution.

**Statistical Evaluation**

Values are presented as means ± SD. Two a priori null hypotheses were tested: (1) There is no difference in values of variables between supine baseline and cardiac sympathetic blockade by epidural anesthesia. (2) There is no difference in values of variables during tilt before and after cardiac sympathetic blockade. Values of variables were compared by using the Friedman-ANOVA followed by a post hoc Wilcoxon-rank test. Statistical significance was assumed with an a-error (P) less than 0.05.

**Results**

Despite sympathetic cardiac blockade, there were no significant alterations in the spectral components of heart rate variability either at rest or during the 40° head-up tilt. However, the LF/HF ratio during tilt was diminished significantly by cardiac sympathetic blockade.

The time course of dermatomal spread of sensory blockade is shown in figure 1. Sensory blockade developed gradually in both the cephalad (C 6.1 ± 3.3) and caudal direction (T 6.3 ± 1.3), reaching a plateau 25 min after epidural bupivacaine injection and without further change for the remainder of the study. As an indicator of sympathetic blockade, skin temperatures of both hand and foot increased after epidural injection also reaching a plateau after 25 min. At this time, temperature of digit V had increased from 29.0°C ± 3.1 to 31.9°C ± 3.9 (P = 0.041), while that of the little toe had increased from 26.2°C ± 2.2 to 27.7°C ± 2.9 (P = 0.036), suggesting widespread sympathetic blockade.

The time courses of cardiovascular and neurohumoral variables are presented in figure 2 and table 1, respectively. With cardiac innervation intact, the 40° head-up tilt induced a significant increase in heart rate from 74 · min⁻¹ ± 9 to 85 ± 11 (P = 0.0059) and a minor decrease in mean arterial pressure of 5 mmHg. Epidural anesthesia alone decreased heart rate from 74 · min⁻¹ ± 9 to 67 ± 10, (P = 0.014) whereas mean arterial pressure decreased by 6 mmHg.

During preganglionic cardiac sympathetic blockade, tilt still evoked a significant increase in heart rate (from 67 · min⁻¹ ± 10 to 73 ± 14), albeit to a significantly lesser extent when compared to tilt with the sympathetic system intact. Mean arterial pressure decreased from 87 mmHg ± 15 to 82 ± 15. One patient almost fainted with the 40° tilt after epidural anesthesia and tolerated only a 30° tilt.

Most important, no significant changes in absolute spectral power densities of heart rate variability were seen with cardiac sympathetic blockade, either in the supine position or during tilt (fig. 3 and table 1). In particular, low-frequency spectral power as the pre-

![Cardiac Innervation intact](chart1.png)

**Fig. 1.** Dermatomal spread of sensory blockade (pinprick). Mean ± SD from 10 awake subjects. After injection of bupivacaine into the epidural space (indicated by the full vertical line) sensory blockade developed gradually, reaching a plateau after 25 min and extending from C6.1 ± 3.3 to T6.3 ± 1.3. This level was maintained for the remainder of the study. Because preganglionic cardiac sympathetic fibers emerge from the spinal cord between T1 and T4, this extent of sensory blockade implies cardiac sympathetic blockade.
Thoracic epidural anesthesia and heart rate variability

The assumed marker of cardiac sympathetic modulation remained unchanged with tilt during cardiac sympathetic blockade. With tilt and the sympathetic system intact, absolute low-frequency spectral power increased to a variable extent in six subjects but decreased in the other four (fig. 3). With sympathetic blockade alone, low-frequency spectral power increased in two, remained unchanged in one, and decreased slightly in seven subjects ($P = 0.22$ vs. baseline). Tilt during cardiac sympathetic blockade was associated with a decrease and increase in LF spectral power in five subjects each ($P = 0.88$ vs. epidural anesthesia alone), respectively. Thus, there were no clear-cut alterations of low-frequency spectral power in response to the interventions.

This was also apparent when low-frequency spectral power data were analyzed considering each patient individually or as a group in relation to the level of sensory blockade obtained (raw data provided in tables 2 and 3). Even in those individuals for whom sensory blockade included upper thoracic as well as cervical dermatomes, low-frequency spectral power either increased or decreased during epidural anesthesia with or without tilt when compared to baseline. Similarly, no systematic responses were found when only tilt-induced changes were considered. Thus, pooling of data did not obscure individual responses.

In contrast, the LF/HF ratio significantly ($P = 0.041$) increased during tilt with the cardiac sympathetic system intact but not with tilt during cardiac sympathetic blockade (fig. 3). The LF/HF ratio during tilt was significantly ($P = 0.041$) lower in the presence of cardiac sympathetic blockade. High-frequency fractional power decreased significantly with head-up tilt before but not after cardiac sympathetic blockade, whereas fractional power of the low and very low-frequency bands remained unchanged (table 1). In contrast, absolute HF power remained unchanged (fig. 3).

Respiratory rate remained unchanged throughout the study.

Vasopressin plasma concentrations increased significantly with tilt during sympathetic blockade but not with the sympathetic system intact (tab. 1). Epinephrine, norepinephrine, and active renin concentrations as well as serum osmolality did not change throughout the study, and plasma bupivacaine concentrations were very low, even after epidural anesthesia (table 1). As expected, no relationship was apparent between plasma renin or vasopressin concentrations and the level of sensory blockade or alterations in spectral heart rate variability when the data were analyzed considering each patient individually or as a group (see raw data tables 2 and 3).

In the patients with epidural saline injection, except for the reproducible effects of tilt, no obvious changes in variables occurred over time. In the two patients with intravenous infusion of bupivacaine, heart rate, heart rate spectral power, and arterial pressure, if anything, tended to increase. Plasma bupivacaine concentrations in these two patients were 2.3 and 3.6 $\mu g \cdot ml^{-1}$, respectively, at the end of the infusion period.

No complications occurred during the study and, subsequently, the epidural catheters were used to provide analgesia after surgery.

Fig. 2. Time course of heart rate, arterial pressure, and respiratory rate with a 40° head-up tilt before and during cardiac sympathetic blockade by epidural anesthesia. Mean ± SD from 10 awake subjects. Time of epidural injection of bupivacaine is indicated by the full vertical line. Tilt with the sympathetic system intact (open symbols) induced a significant increase in heart rate and a slight decrease in arterial pressure. During cardiac sympathetic blockade (closed symbols), the increase in heart rate evoked by tilt was significantly attenuated. Respiratory rate remained unchanged throughout the study period. *$P < 0.05$.

Anesthesiology, V 82, No 3, Mar 1995
Table 1. Neurohumoral Effects of Preganglionic Cardiac Sympathetic Blockade by Thoracic Epidural Anesthesia during Supine Rest and 40° Head-up Tilt

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Innervation Intact</th>
<th>Cardiac Sympathetic Blockade</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Tilt</td>
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<tr>
<td>PowerRF (min⁻²)</td>
<td>1.85 ± 1.48</td>
<td>3.10 ± 3.09</td>
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<tr>
<td>PowerLF (min⁻²)</td>
<td>2.56 ± 2.95</td>
<td>4.18 ± 7.06</td>
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<tr>
<td>PowerHF (min⁻²)</td>
<td>1.23 ± 1.17</td>
<td>0.94 ± 0.95</td>
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<tr>
<td>PowerTotal (min⁻²)</td>
<td>5.57 ± 4.60</td>
<td>8.13 ± 10.82</td>
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<tr>
<td>VLF (% total power)</td>
<td>37 ± 17</td>
<td>48 ± 17</td>
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<tr>
<td>LF (% total power)</td>
<td>37 ± 15</td>
<td>39 ± 14</td>
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<tr>
<td>HF (% total power)</td>
<td>26 ± 18</td>
<td>13 ± 6.0</td>
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<tr>
<td>LF/HF ratio</td>
<td>2.47 ± 2.10</td>
<td>3.68 ± 2.52*</td>
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<tr>
<td>Heart rate (min⁻¹)</td>
<td>74 ± 9</td>
<td>85 ± 11*</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>93 ± 14</td>
<td>88 ± 11*</td>
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<tr>
<td>Norepinephrine (pg·ml⁻¹)</td>
<td>110 ± 48</td>
<td>109 ± 43</td>
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<tr>
<td>Epinephrine (pg·ml⁻¹)</td>
<td>16 ± 7</td>
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<td>Vasopressin (pg·ml⁻¹)</td>
<td>3.9 ± 2.6</td>
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<tr>
<td>Active renin (pg·ml⁻¹)</td>
<td>24.8 ± 15.2</td>
<td>30.0 ± 18.7</td>
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<td>Bupivacaine (µg·ml⁻¹)</td>
<td>0.13 ± 0.10</td>
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<tr>
<td>Osmolality (mosm·kg⁻¹)</td>
<td>298 ± 8</td>
<td>305 ± 11</td>
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Data are from 10 awake subjects without cardiovascular disease, mean ± SD.

VLF = very low frequency spectral power (0.02–0.06 Hz); LF = low frequency spectral power (0.06–0.15 Hz); HF = high frequency spectral power (0.15–0.8 Hz).

* P < 0.05 versus baseline.
† P < 0.05 versus epidural anesthesia alone.
‡ P < 0.05 versus tilt with cardiac innervation intact.

Discussion

Although the LF/HF ratio, a presumed marker of sympathovagal interaction, was diminished significantly by cardiac sympathetic blockage during tilt, absolute spectral power densities of heart rate variability remained unaltered. In particular, neither absolute nor fractional low-frequency spectral power, i.e., the presumed marker of sympathetic cardiac autonomic modulation, was abolished following neural blockade at rest or during head-up tilt. Thus, the low-frequency band of spectral heart rate variability is unlikely to specifically reflect cardiac sympathetic control in humans. By the same token, its value as a monitoring tool for sympathetic function during epidural anesthesia appears questionable.

Critique of Methods

These results emerged when factors potentially critical to measurement and interpretation of heart rate variability such as environmental or subject characteristics were strictly accounted for. All experiments took place in a quiet separate laboratory and, to account for possible circadian variability of measurements, with experiments starting always at the same time in the morning. Ambient temperature was maintained in the thermoneutral temperature range to avoid temperature induced alterations in autonomic tone. All patients were free of cardiovascular disease, did not take any drugs, and were awake and unsedated. Furthermore, resting catecholamine plasma concentrations in our patients were low, indicating that the patients were well adapted to the laboratory environment and not excited by the interventions. In addition, bupivacaine plasma concentrations were very low at baseline following subcutaneous infiltration for placement of the epidural, venous, and arterial catheters. Finally, respiratory rate remained unchanged and, therefore, probably did not influence our results. That epidural injection of bupivacaine evoked preganglionic cardiac sympathetic blockage in our subjects is supported by several arguments: (1) Mean sensory blockade extended from C6 to T6. Because sympathetic blockage is present not only within spinal segments rendered insensitive but rather exceeds the dermatomal borders of sensory blockade, and preganglionic cardiac sympathetic fibers escape from the spinal cord between segments T1 and T4, cardiac sympathetic
blockade should have been present. (2) Because efferent sympathetic fibers to the hand and heart emerge from the same spinal cord segments,\textsuperscript{19} the significant increase in skin temperature on the hand observed after epidural anesthesia also indicates preganglionic blockade of cardiac sympathetic efferents. (3) The heart rate response to tilt was significantly blunted by epidural blockade, also indicating attenuation of sympathetic cardiac outflow.

Although, at present, there is no way in awake humans to directly record phasic cardiac sympathetic outflow, data from the literature support the conclusion that cardiac sympathetic blockade is complete during thoracic epidural anesthesia. In anesthetized open chest dogs, epidural blockade from C7 to T6 abolished the directly recorded cardiac sympathetic activity at baseline and completely prevented its increase in response to coronary artery constriction.\textsuperscript{20} Furthermore, in anesthetized rabbits, epidural anesthesia from T2 to L5 also abolished directly recorded efferent sympathetic splanchnic nerve activity.\textsuperscript{1} Finally, in humans, calf muscle and skin efferent sympathetic nerve activity is abolished by lumbar epidural anesthesia.\textsuperscript{2,3} Thus, in our patients, cardiac sympathetic blockade was present after epidural anesthesia, and very likely it was complete.

The observed changes resulted from cardiac sympathetic blockade and not from the local anesthetic when absorbed into the blood stream, because plasma bupivacaine concentrations were very low and unlikely to have any systemic hemodynamic effects.\textsuperscript{21,22} Even with intravenous bupivacaine infusion associated with bupivacaine plasma concentrations in the range well above those attained after epidural injection, heart rate, arterial blood pressure, and spectral heart rate variability measures, if anything, were increased rather than decreased.

A 40° head-up tilt is a stimulus strong enough to activate the sympathetic system. This is supported by results obtained during graded passive head-up tilt in healthy volunteers. Here, intraneurally recorded sympathetic activity increased 3.5-fold with a 40° head-up tilt when compared to the supine position.\textsuperscript{23} Moreover, in our study, vasopressin concentrations increased during tilt in the presence but not in the absence of preganglionic sympathetic blockade. Thus, the 40° head-up tilt was a stimulus strong enough to provoke vasopressin release in the presence of sympathetic blockade with loss of efferent sympathetic cardiac and diminution of vasoconstrictor tone. On the other hand, the 40° head-up tilt appeared to be the best compromise between activating sympathetic efferents and avoiding syncope associated with greater tilt angles in the presence of epidural blockade. One of our subjects nearly fainted with the 40° tilt during epidural blockade and therefore could be tilted only 30°.

Finally, given the wide interindividual ranges of heart rate variability measures,\textsuperscript{8,13} by using each subject as its own control, we minimized any bias with regard to interindividual variabilities in the response to tilt. Thus,
Table 2. Effects of Preganganglion Cardiac Sympathetic Blockade by Thoracic Epidural Anesthesia (EA) during Supine Rest and 45° Head-up Tilt

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<th>Patient No.</th>
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<td>70</td>
<td>64</td>
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<td>64</td>
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</tbody>
</table>

Individual raw data are from 10 awake, unmedicated patients without apparent cardiovascular disease submitted before and during thoracic epidural anesthesia.

our experimental protocol was suitable to detect during preganglionic cardiac sympathetic blockade systematic changes in spectral heart rate variability, if present.

**Spectral Heart Rate Variability Indexes as a Measure of Cardiac Autonomic Modulation**

This study is the first to assess in humans the effects of preganglionic sympathetic cardiac denervation by thoracic segmental epidural anesthesia on heart rate variability in the frequency domain. In the resting supine position, cardiac sympathetic denervation did not alter absolute or fractional spectral power in the low- or high-frequency domain. Therefore, our data indicate either that there is no tonic cardiac sympathetic modulation in the supine resting position or that, in contrast to previous speculations, sympathetic modulation does not contribute in a quantitatively important fashion to spectral power in the low-frequency domain. Indeed, preganglionic sympathetic blockade in the supine position had little effect on measures of heart rate variability or on mean heart rate, consistent with the hypothesis that heart rate at rest appears to be primarily under vagal control in both dogs and humans. Our findings are also consistent with experiments in resting humans, wherein intravenous injection of the β-adrenoceptor antagonist propranolol (0.2 mg/kg) failed to diminish low-frequency spectral power, in contrast to experiments in resting conscious dogs.

Although cardiac sympathetic blockade significantly blunted the increase in heart rate in response to tilt, it had no effect on low-frequency spectral power, the presumed marker of cardiac sympathetic drive. This indicates that spectral heart rate variability in the LF band is not or not predominantly of cardiac sympathetic origin.

This interpretation is based on the assumption that an effenter cardiac sympathetic tone is already present at rest or evoked during tilt, which can be attenuated by preganglionic cardiac sympathetic blockade. Head-up tilt has been used previously by many investigators evaluating heart rate variability to provoke an increase in effenter sympathetic outflow to the heart. Indeed, head-up tilt activates the sympathetic system, as shown by sympathetic nerve recordings. Because, in humans, during activation of the sympathetic system, sympathetic outflow to both heart and muscle increases (as assessed by cardiac norepinephrine spillover and direct nerve recordings, respectively), activation of cardiac sympathetic efferents with tilt certainly occurred in our experiments. Accordingly, epidural sym-
**THORACIC EPIDURAL ANESTHESIA AND HEART RATE VARIABILITY**

Table 3. Effects of Preganglionic Cardiac Sympathetic Blockade by Thoracic Epidural Anesthesia (EA) during Supine Rest and 45° Head-up Tilt

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Sensory Blockade</th>
<th>Baseline</th>
<th>Tilt</th>
<th>EA</th>
<th>EA + Tilt</th>
<th>Baseline</th>
<th>Tilt</th>
<th>EA</th>
<th>EA + Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>51</td>
<td>C3-T8</td>
<td>7.6</td>
<td>12.5</td>
<td>12</td>
<td>11.2</td>
<td>1.9</td>
<td>2.9</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>59</td>
<td>C6-T10</td>
<td>39.1</td>
<td>43.5</td>
<td>63.8</td>
<td>91.8</td>
<td>2.2</td>
<td>2.2</td>
<td>5</td>
<td>19.8</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>T1-T6</td>
<td>9</td>
<td>20</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>11</td>
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<td>11</td>
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<td>4</td>
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<td>36</td>
<td>C3-T6</td>
<td>44.2</td>
<td>51.2</td>
<td>52.3</td>
<td>47.4</td>
<td>3.3</td>
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<tr>
<td>5</td>
<td>M</td>
<td>25</td>
<td>C6-T6</td>
<td>28.2</td>
<td>50.7</td>
<td>26.4</td>
<td>43.1</td>
<td>2.1</td>
<td>1.8</td>
<td>2.6</td>
<td>3.4</td>
</tr>
<tr>
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<td>F</td>
<td>56</td>
<td>C4-T5</td>
<td>24</td>
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<td>31.6</td>
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<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>48</td>
<td>T1-T6</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
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<td>NM</td>
<td>NM</td>
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<tr>
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<td>F</td>
<td>32</td>
<td>T2-T6</td>
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<td>5.1</td>
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<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
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<td>9</td>
<td>M</td>
<td>51</td>
<td>C3-T4</td>
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<td>11</td>
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<tr>
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<td>M</td>
<td>43</td>
<td>C6-T6</td>
<td>45.3</td>
<td>48.7</td>
<td>30.9</td>
<td>37.8</td>
<td>6.2</td>
<td>5.6</td>
<td>7.2</td>
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</tr>
</tbody>
</table>

Individual raw data are from 10 awake unsedated patients without apparent cardiovascular disease studied before and during thoracic segmental epidural anesthesia. NM = not measured.

pathetic blockade, at least during head-up tilt, should have diminished cardiac sympathetic modulation, hitherto speculated to be reflected in the low-frequency band of heart rate spectral variability.7,8

Preganglionic cardiac sympathetic blockade in the current study had no effect on either absolute or fractional power of spectral heart rate variability in the LF spectral domain, even during head-up tilt. This was apparent not only from analysis of group mean values but also when data were considered for each patient individually and in relation to the level of sensory blockade obtained. Even in those individuals for whom sensory blockade included upper thoracic as well as cervical dermatomes, low-frequency spectral power either increased or decreased during epidural anesthesia with or without tilt when compared to baseline. Thus, pooling of data did not obscure individual responses.

These findings appear at variance with results previously reported for systemic β-adrenoceptor blockade.7 In this widely quoted study, an increase in fractional low-frequency power observed in response to a 90° head-up tilt was reported to be significantly attenuated (by -16%) during propranolol-induced acute β-blockade. Several differences between this study may explain the discrepancy: (1) Absolute values of low-frequency spectral power density were not presented by Pagani et al.,7 leaving the possibility that at least part of this attenuation originated from corresponding alterations of absolute high-frequency spectral power. In another study, head-up tilt did not increase absolute low-frequency spectral power in either young or old subjects,25 consistent with our data. (2) Epidural (preganglionic) cardiac sympathetic denervation blocks neural traffic to the β1-receptors, which are directly innervated by sympathetic fibers.32-34 In contrast, systemic β-adrenoceptor antagonists, such as propranolol, block in the periphery both β1- and β2-receptors and, therefore, also the effects of circulating norepinephrine and epinephrine. In our study, norepinephrine and epinephrine plasma concentrations remained unchanged during segmental preganglionic sympathetic blockade. Thus, changes in β-receptor stimulation via circulating catecholamines can be excluded from influencing heart rate variability measures in our study but may have occurred in that of Pagani et al.7 In addition, with systemic β-blockade, there can be a striking dissociation between effects on sympathetic outflow and those on target organs. Propranolol (0.15 mg·kg⁻¹, intravenous) did not alter the increase in muscle sympathetic activity evoked by lower body negative pressure even though it substantially attenuated the evoked increase in forearm and calf vascular resistances,35 possibly explained by propranolol’s effect on presynaptic β-receptors. Accordingly, the use of intravenous propranolol as an experimental model to evaluate cardiac autonomic modulation may be invalid. (3) Different methods for the analysis of spectral heart rate variability are unlikely to be responsible for the different results, because autoregressive and conventional spectral analyses yield qualitatively nearly identical results under the same experimental conditions.27

Therefore, our results fail to support the hypothesis that low-frequency spectral power of heart rate vari-

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ability specifically reflects cardiac sympathetic control. They rather suggest that this variable is a poor marker of cardiac sympathetic modulation. In support of our findings, during baroreflex-induced activation of the sympathetic nervous system evoked by intravenous infusion of sodium-nitroprusside, fractional and absolute low-frequency spectral powers have been found to correlate only weakly or not at all with increases in muscle sympathetic nerve activity or plasma norepinephrine concentration. 

In our study, only fractional but not absolute high-frequency spectral power significantly decreased during tilt and with the sympathetic system intact. This decrease in fractional high-frequency power is in accordance with previous studies and most likely explained by a diminished parasympathetic drive to the heart. 

Although neither sympathetic blockade alone nor tilt during cardiac sympathetic denervation evoked changes in low-frequency spectral power, the LF/HF ratio during tilt was significantly reduced by preganglionic blockade. This indicates that shifts in the sympathovagal balance occurred after cardiac sympathetic blockade. That the LF/HF ratio increased with tilt alone is consistent with previous data. However, while diminution of the LF/HF ratio by preganglionic cardiac sympathetic blockade during tilt may indicate some contribution of sympathetic modulation to this marker, we were unable to pinpoint specific alterations in the low- and high-frequency bands, thought to reflect sympathetic and parasympathetic modulation of the heart, respectively. Nevertheless, the largest changes in spectral power induced by tilt were attributable to the high-frequency rather than the low-frequency range, in terms of both absolute power and percentage of total power, suggesting that changes in vagal modulation were the dominant factor.

Heart rate variability, especially in the low-frequency spectral band, has been used as an index of sympathovagal interaction after acute myocardial infarction, with the observed increase in low-frequency spectral power 2 weeks after infarction interpreted as an indicator of increased sympathetic tone. Spectral power densities in the various frequency bands have been used to assess the risk of mortality after myocardial infarction. Accordingly, it is of great clinical importance whether alterations in specific power spectral densities can be unequivocally related to well defined neural pathways.

In conclusion, although cardiac sympathetic blockade decreased significantly, heart rate and the LF/HF ratio during head-up tilt, both absolute and fractional spectral power densities in the low-frequency band, remained unaltered by preganglionic cardiac sympathetic blockade at supine rest and during tilt. Thus, the specificity of low-frequency spectral power as a marker of cardiac sympathetic modulation appears uncertain.

References


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