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Autonomic Nervous System Response to Epidural Analgesia in Laboring Patients by Wavelet Transform of Heart Rate and Blood Pressure Variability

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Background: **Epidurals are effective in relieving labor pain but result in a sympathectomy that may compromise maternal hemodynamic stability and fetal perfusion. Decreases in blood pressure and heart rate can be corrected, but markers of autonomic activity would be useful to predict and prevent such changes. The goal of this study was to find markers describing the changes in autonomic nervous system activity with epidural anesthesia in laboring patients.**

Methods: **The authors analyzed heart rate variability and blood pressure variability in 13 laboring patients using wavelet transform, a time-frequency analysis that accommodates rapid changes in autonomic activity. Heart rate and blood pressure variability were obtained 5 min before and 10 min after injection of 20 ml bupivacaine, 0.125%, and 50 μg fentanyl in the epidural space.**

Results: **Blood pressure and heart rate were not affected by epidural analgesia. However, high-frequency power of heart rate variability increased after epidural (increase in parasympathetic drive). The ratio of low-frequency:high-frequency power of heart rate variability decreased. High- and low-frequency power of blood pressure variability decreased (decrease in sympathetic outflow).**

Conclusions: **Indices of parasympathetic and sympathetic activity after neuraxial blockade in laboring patients can be obtained by analysis of both heart rate variability and blood pressure variability. The analysis by wavelet transform can discern changes in autonomic activity when values of blood pressure and heart rate do not vary significantly. Whether this technique could be used to predict and prevent hemodynamic compromise after neuraxial blockade merits further studies.**

EPIDURAL analgesia is widely used to alleviate the pain of labor. However, neuraxial blockade also inhibits efferent sympathetic preganglionic outflow. Depending on the level of the spinal segment blocked, different hemodynamic responses may be observed. Sympathetic block of lumbar segments results in relatively little change in blood pressure and heart rate, because vasodilatation of the lower limb has limited capacitance for blood volume,[1] and cardiac acceleratory fibers are located in thoracic segments. As the block spreads to thoracic segments, there is vasodilatation of the highly compliant splanchnic bed, and systemic arterial pressure decreases because of venous pooling of blood in this region.[1] Because pain relief from the first stage of labor requires a block to segment levels T10–T11, there is considerable risk of hypotension after labor epidural analgesia. Because there is no autoregulation of placental blood flow, a decrease in maternal blood pressure is equivalent to a decrease in placental and fetal perfusion. Changes in autonomic activity have been described in pregnant patients, with increases in sympathetic and decreases in parasympathetic activity, compared with the nonpregnant state.[2–4] The increase sympathetic activity is thought to help ensure optimal placental perfusion throughout pregnancy,[5] but it may also render pregnant patients particularly susceptible to hemodynamic consequences of sympathectomy from epidural analgesia. In recent years, strategies using more dilute epidural solutions and combining spinal with epidural analgesia have been used to diminish hemodynamic complications from epidural analgesia.[6] Nevertheless, monitoring of maternal blood pressure and heart rate and fetal heart rate is mandatory after epidural analgesia so that hemodynamic stability can be maintained. The decrease in sympathetic tone precedes the changes in vascular tone, and markers of autonomic activity would be useful to predict and prevent decreases in maternal blood pressure.

Analysis of heart rate variability (HRV) has become a popular method to assess autonomic modulation of the heart and to study physiologic and pathologic mechanisms responsible for heart rate fluctuation.[7–12] However, analysis of HRV seems to reflect mostly parasympathetic drive, and attempts to use HRV as an index of sympathetic drive have yielded disappointing results.[13] Because vascular tone is largely under the control of the sympathetic nervous system and because beat-to-beat variations in blood pressure have frequency components that can be studied by time-frequency analysis,[14–17] analysis of blood pressure variability (BPV) may be used as an index of changes in sympathetic outflow. Therefore, the goal of this study was to use analyses of HRV and BPV as markers of changes in parasympathetic and sympathetic activity after epidural analgesia in laboring parturients.

Materials and Methods

Subjects

After approval from the institutional ethics committee was obtained, 13 laboring patients aged 21–39 yr, with gestational ages between 37 and 41 weeks, were recruited at the Birthing Center of the Royal Victoria Hos-

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pital (Montreal, Quebec, Canada), and written informed consent was obtained. Patients with absolute or relative contraindication to epidural anesthesia or with major cardiovascular, pulmonary, neurologic, endocrine, or metabolic disorder or recent exposure to medications affecting heart rate (*e.g.*, β-adrenergic blockers or agonists, muscarinic agonists or antagonists) were excluded from the study. Patients with a cardiac rhythm other than sinus and showing multiple premature ventricular beats were also excluded.

Protocol

Lead II electrocardiogram (ADInstruments, Mountain View, CA), respiratory rate (Respiratory Belt Transducer; ADInstruments), fetal heart rate, and uterine contraction (ultrasonography and tocometry, Hewlett Packard 8041A; Andover, MA) were recorded. A noninvasive continuous blood pressure measurement based on arterial tonometry (Colin 7000; San Antonio, TX) was used on the right radial artery to obtain arterial blood pressure waveforms. The performance of this apparatus ranges between pressures of 60 and 250 mmHg systolic and 40 and 220 mmHg diastolic and pulse rates between 30 and 180 beats/min. Electrocardiogram, blood pressure, and respiratory signals were collected *via* an analog-to-digital converter at a sampling rate of 1,000 Hz/channel (Powerlab; ADInstruments) and stored on a portable computer (Powerbook G4; Apple Computers, Cupertino, CA).

Control data was recorded for 5 min with the patient in left lateral decubitus position. When the patient was in active labor and asked for pain control, an epidural at the lumbar 3–4 interspace was placed. Twenty milliliters bupivacaine, 0.125%, was given in fragmented doses followed by 50 μg epidural fentanyl. The patient was then placed in left lateral decubitus position, and data were acquired for 10 min. The dermatome level of the block was determined by loss of cold sensation to ice, first by recognizing the feeling of ice on the shoulder, then by going from no sensation to cold sensation. Pain scores were assessed by a scale, 0 = no pain and 5 = worse possible pain, 5 and 10 min after epidural. The patients did not receive a fluid bolus before the epidural.

HRV and BPV Analysis

Discrete wavelet transform of HRV and BPV was accomplished as described in detail elsewhere.[18] Briefly, the analysis extracts characteristic frequencies of a signal that is composed of the consecutive R-R intervals for HRV analysis or consecutive beat-to-beat blood pressures for BPV analysis. Discrete wavelet transform analyzes nonstationary signals and thus, unlike fast Fourier transforms (FFTs), there is no prerequisite for the stability of the frequency content of the signal. The analysis consists of sliding a window of different weights containing a wavelet function along the signal. The mother wavelet function used in this study was Daubechies 4. Serial lists of coefficients called *wavelet coefficients* are obtained, which represent the evolution of the correlation between the signal and the wavelet for different wavelet functions. The smallest scaled wavelet compares the length of two (2^1) consecutive R-R intervals or blood pressures, which is the highest frequency analyzed. The wavelet function immediately above compares the length of four (2^2) consecutive R-R intervals or blood pressures and thus compares half as much length of the signal, and the frequency analyzed is halved compared with the previous wavelet function. In this study, the maximum number of increments of wavelet functions was 5 (2^5) or 32 consecutive R-R intervals or blood pressures. The variability power is calculated as the sum of the squares of the coefficients for each wavelet function for a given time interval. We chose 5-min intervals in the current study. The mathematical analysis was made using MATLAB and the dedicated Wavelet Toolbox software (version 6; MathWorks, Inc., Natick, MA). Wavelet functions 2, 4, and 8 approximate the high-frequency power level (0.15–0.4 Hz) in the FFT analysis, with the frequency decreasing by half at every consecutive wavelet function. Wavelet functions 16 and 32 approximate low-frequency power level (0.04–0.15 Hz) in the FFT analysis.[18] The ratio of low-frequency:high-frequency power was calculated using the sum of the variability power of wavelet functions 16 and 32, divided by the sum of the wavelet functions 2, 4, and 8.

Statistical Analysis

Power coefficients calculations were averaged over 5-min intervals. Baseline, 5-min postepidural, and 10-min postepidural values were compared for all (2, 4, 8, 16, and 32) wavelet functions for heart rate and blood pressure. Beat-to-beat mean blood pressure was used for BPV analysis. Statistical analysis was performed using the software InSat® (GraphPad Software, Inc., San Diego, CA). All data passed the Kolmogorov-Smirnov test for Gaussian distribution criteria. A one-way repeated-measures analysis of variance was used to compare the results over time. When significant, a Dunnett multiple comparisons test was performed. Significance level was set at $P < 0.05$. Data are presented as mean ± SD unless otherwise specified.

Results

There was no change in blood pressure, heart rate, or respiratory rate before or after epidural analgesia (fig. 1). After 10 min, block height reached levels between T6 and T2, and pain level was 0 or 1 out of 5.

The variability power of HRV increased significantly after epidural at the highest frequency (wavelet function 2, baseline of 95 ± 75 s^2 to postepidural value of 160 ± 113 s^2 at 10 min; $P < 0.05$). The HRV power of wavelet

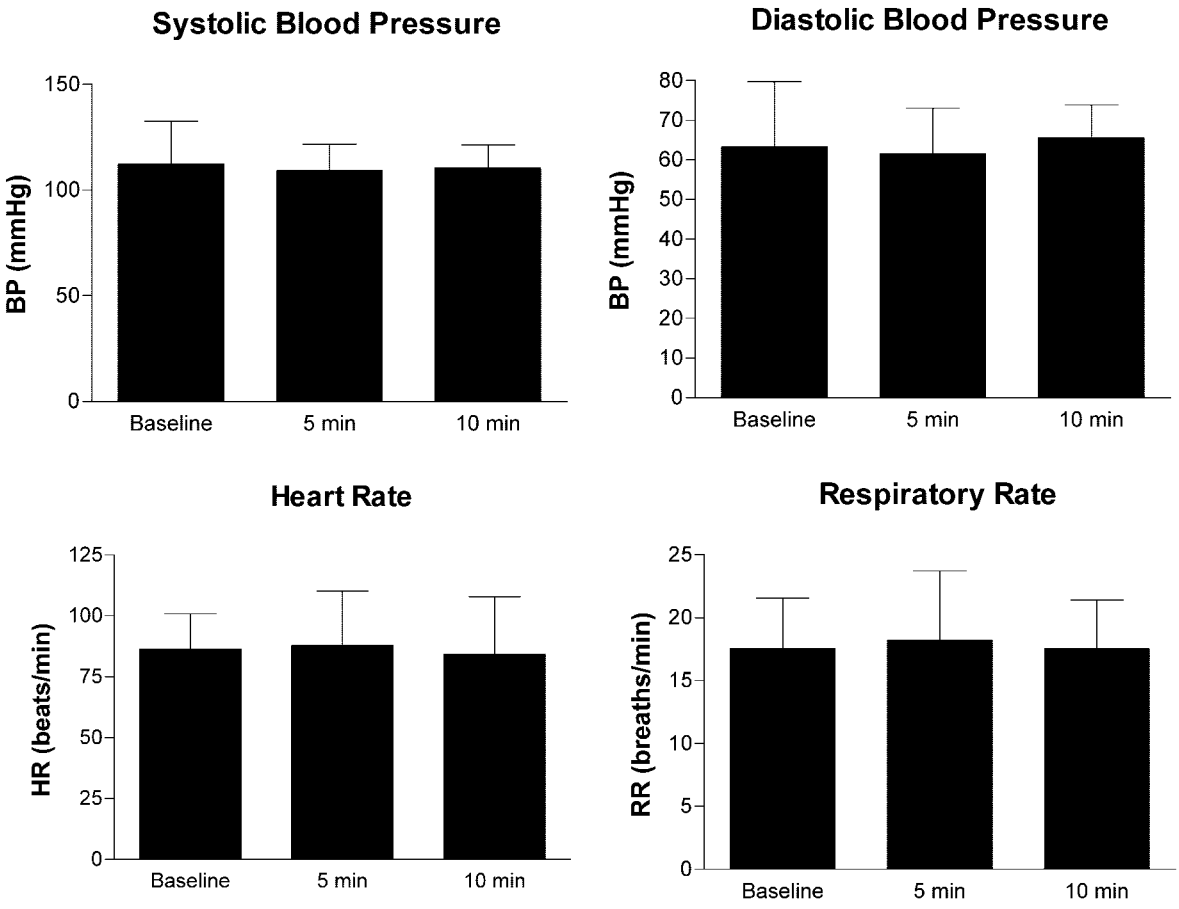

Fig. 1. Systolic and diastolic blood pressure (BP), heart rate (HR), and respiratory rate before and after neuraxial blockade (n = 13). Data are presented as mean ± SD for baseline, 5 min after epidural, and 10 min after epidural. There was no significant difference in any of these parameters over time.

function 4 increased nonsignificantly at 5 and 10 min (fig. 2). These results indicate an increase in parasympathetic activity after epidural analgesia. No significant changes in HRV power occurred at low frequency (wavelet function 16 and 32). The ratio of low-frequency: high-frequency power of HRV decreased from a baseline of 0.44 ± 0.20 to 0.29 ± 0.09, 10 min after epidural analgesia, but this decrease is entirely due to the increase in high-frequency power of wavelet function 2.

The variability power of BPV decreased from baseline at high frequency (wavelet functions 2, 4, and 8) and low frequency (wavelet function 16; fig. 3), indicating a decrease in sympathetic activity. Only the lowest frequency, wavelet function 32, showed no difference in variability power. The changes in BPV power occurred earlier than those seen with either the ratio of low-frequency:high-frequency power or HRV power (compare figs. 2 and 3). Values for BPV power of wavelet function 2 were 1,742 ± 1,609 $mmHg^2$ for baseline, 810 ± 804 $mmHg^2$ at 5 min, and 797 ± 1,250 $mmHg^2$ at 10 min after epidural ($P < 0.01$). Values of BPV power of wavelet function 4 were 1,137 ± 673 $mmHg^2$ for baseline, 618 ± 543 $mmHg^2$ at 5 min, and 450 ± 406 $mmHg^2$ at 10 min after epidural ($P < 0.01$). At 5 min after epidural, the value of wavelet function 8 BPV power decreased from a baseline of 884 ± 564 $mmHg^2$ to 458 ± 356 $mmHg^2$ ($P < 0.05$). At the same time period, the value of wavelet function 16 BPV power decreased from a baseline of 474 ± 363 $mmHg^2$ to 258 ± 183 $mmHg^2$ ($P < 0.01$).

Discussion

The current study demonstrates that indices of changes in parasympathetic and sympathetic activity can be obtained from wavelet transform of HRV and BPV, respectively, even when absolute values of blood pressure and heart rate do not vary significantly after epidural analgesia. The effect of spinal and epidural anesthesia on autonomic tone has been studied using FFT of HRV.[19] All frequency bands, total power, low-frequency power, and high-frequency power of HRV were decreased with the neuraxial block, and the ratio of low-frequency:high-frequency power did not change. These results were interpreted as a total decrease in autonomic activity. These results contrast significantly from our findings

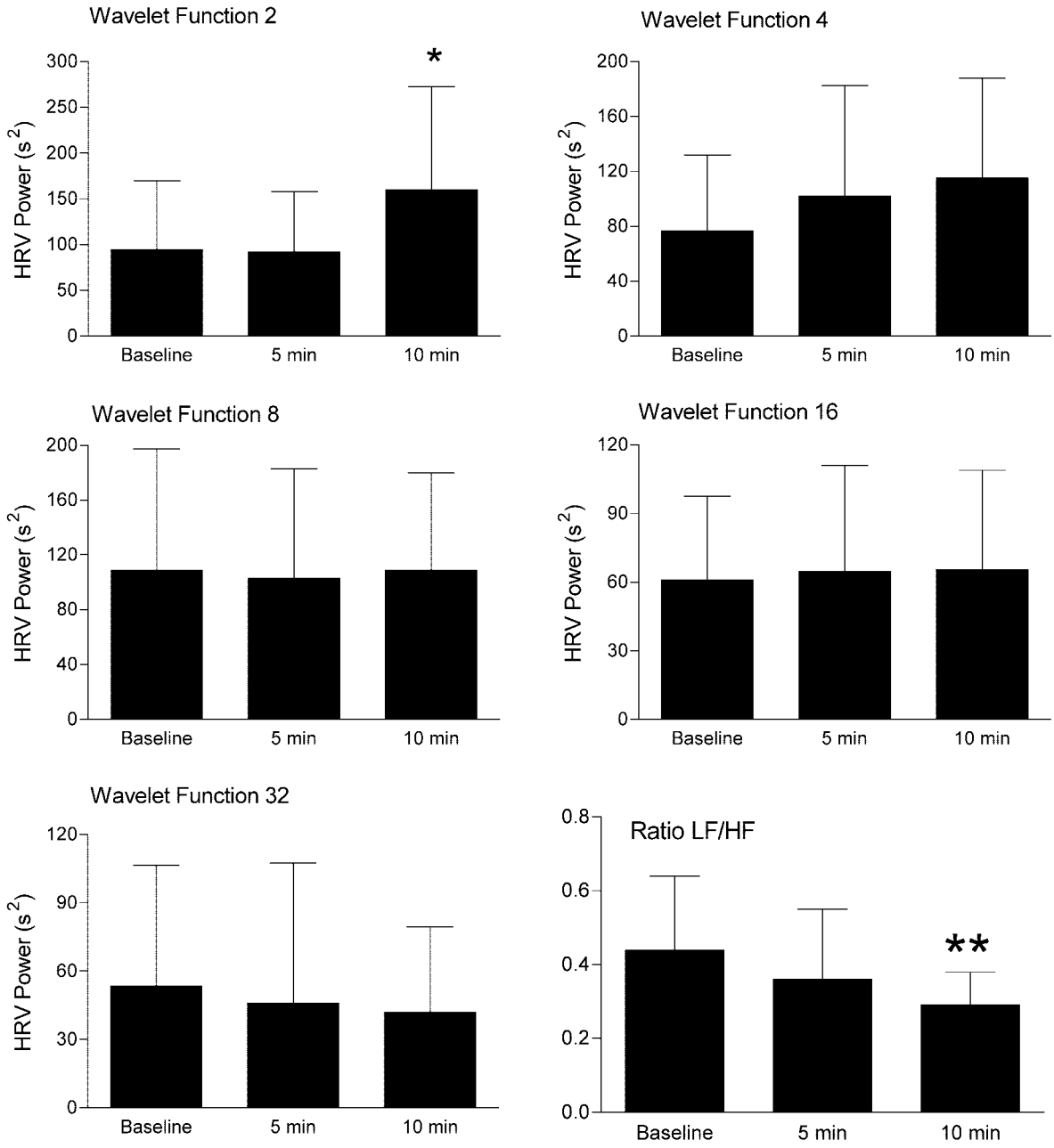

Fig. 2. Wavelet transform analysis of heart rate variability (HRV) before and after neuraxial blockade, averaged over 5-min periods (n = 13). Data are presented as sum of squares of coefficients of wavelet transform analysis plotted against time, before (baseline) and after (5 min, 10 min) lumbar epidural for labor pain. Levels 2, 4, and 8 reflect high-frequency (HF) power. Levels 16 and 32 reflect low-frequency (LF) power. The ratio LF:HF was calculated using the sums of levels 16 and 32 over the sum of levels 2, 4, and 8. * $P < 0.05$, ** $P < 0.01$ *versus* baseline.

where high-frequency power of HRV increased after epidural anesthesia. The discrepancy between these results and ours may, in part, reflect the requirement for a stationary period for data acquisition with the FFT technique or the fact that the patients were not in labor.

Factors such as the height of the somatosensory block[20] and age[21] have been shown to affect the autonomic outflow. Other factors, such as parity, stage of labor, cervical dilatation, or fluid boluses, may influence the autonomic tone as well. We did not administer fluid boluses to our patients, and we did not standardize for these other factors. Nevertheless, changes in both sympathetic and parasympathetic outputs were seen early after epidural. This suggests that central factors, such as pain, predominate during labor. The influence of factors such as age, stage of labor, and parity may be important when pain is not present. The influence of the height of the block and fluid boluses should be studied individually. Central sympathetic stimulation from pain and anxiety is most likely the reason why changes in BPV pre-

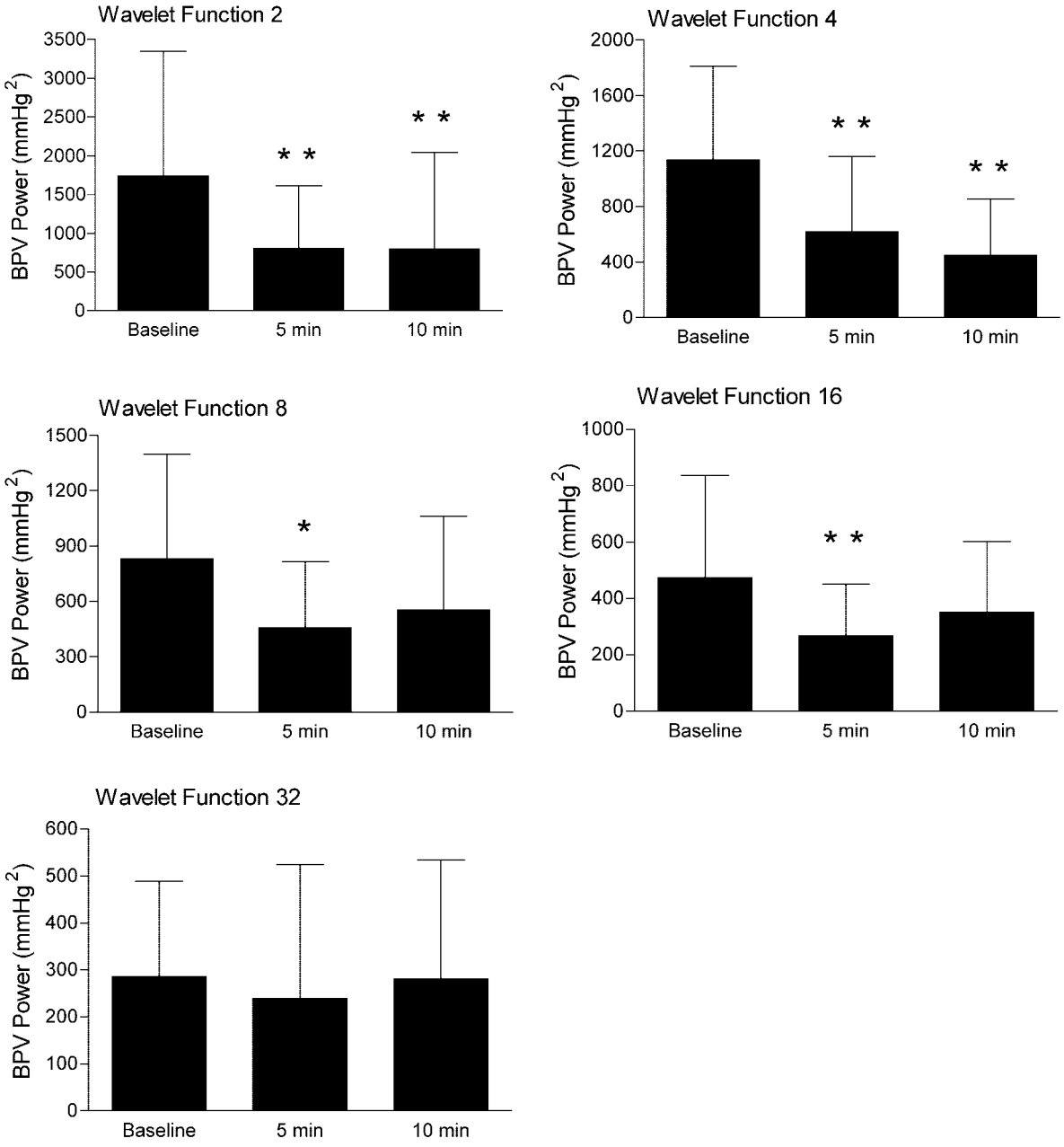

Fig. 3. Wavelet transform analysis of blood pressure variability (BPV) before and after neuraxial blockade, averaged over 5-min periods (n = 13). Data are presented as sum of squares of coefficients of wavelet transform analysis plotted against time, before (baseline) and after (5 min, 10 min) lumbar epidural for labor pain. Levels 2, 4, and 8 reflect high-frequency power. Levels 16 and 32 reflect low-frequency power. * $P < 0.05$, ** $P < 0.01$ *versus* baseline.

ceded the changes in HRV. As pain is alleviated after epidural and anxiety levels decrease, the central sympathetic drive should decrease as well. A differentiation between central *versus* regional sympathetic output influence on labor has been suggested previously.[22] Lumbar sympathetic blocks were found to decrease the duration of labor, whereas epidurals block did not. A comparison between lumbar sympathetic blocks and epidural analgesia on the analysis of HRV and BPV in laboring parturients would be of interest.

Most studies have used FFT for analysis of HRV. Although FFT requires statistically stationary signals with means and variance independent of time, this requirement is rarely met. FFT thus demands filtering of the signals, resampling, and sequential analysis to accurately describe the frequency characteristics of HRV. We have previously used, in anesthetized patients, an analysis of HRV and BPV that can manage rapidly varying signals.[23] Likewise, because autonomic outflow changes produced by neuraxial blockade are dynamic, wavelet transform of HRV and BPV was used to analyze statistically varying signals over time. Wavelet transform provides a tempo-

rally localized sliding analysis of the signal, thus giving access at any time to the status of the variability.[24–26] Wavelet transform of HRV has been used to characterize nonstationary signals associated with arousal from anesthesia,[27] aerobic fitness,[26,28] post–myocardial infarction,[29] and pharmacologic interventions.[30]

Analysis of BPV was used to obtain a reliable index of changes in sympathetic activity because of disappointing results from HRV analysis for this purpose. For example, low-frequency power and the ratio of low-frequency: high-frequency power of HRV have been used extensively as indicators of changes in sympathetic tone.[31–33] However, studies have shown no change in low-frequency power with cardiac sympathetic blockade[13] and no change in the ratio of low-frequency:high-frequency power with spinal or epidural anesthesia for cesarean deliveries.[19] We showed a decrease in the ratio of low-frequency:high-frequency power after neuraxial blockade. This change can be explained entirely by the increase in high-frequency power (parasympathetic) while low-frequency power remained stable. Therefore, a change in this ratio seems to be simply another representation of the change in parasympathetic outflow.

Blood pressure variability analysis to estimate changes in sympathetic tone has been used previously. In studies in which autonomic outflow was altered by controlled hemorrhage,[15,34] increased rennin secretion,[35] amiodarone infusion,[36] or subarachnoid hemorrhage,[37] there was a close correlation between BPV and sympathetic outflow. This was true even when absolute values for blood pressure did not vary, while there were significant changes in BPV and in sympathetic outflow (measured directly).[35,38] Combining spectral analysis of both HRV and BPV has been suggested to provides a more complete picture of the autonomic nervous system activity.[15,34]

After epidural analgesia, our analysis of BPV and HRV suggests that sympathetic outflow decreased while parasympathetic outflow increased, even though values of blood pressure and heart rate were not significantly affected. Sympathectomy of the thoracolumbar segments by the epidural explains the decrease is sympathetic outflow, whereas the increase in parasympathetic activity demands further consideration. Because the response of the target organ reflects the balance between the sympathetic drive and the parasympathetic drive, it is tempting to suggest that the decrease in sympathetic activity unmasks the endogenous parasympathetic drive. Alternatively, the effect of the epidural on anxiety and pain associated with labor may result in a shift in the balance of the autonomic nervous system favoring an increase in parasympathetic output as the sympathetic tone decreases.

In summary, wavelet transforms of HRV and BPV can be used as indices of change in parasympathetic and sympathetic activity, respectively, after epidural analgesia. Whether markers of autonomic nervous system activity can be used to predict and prevent hemodynamic instability after neuraxial blockade merits further studies.

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