Heart Rate Variability Predicts Severe Hypotension after Spinal Anesthesia

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Background: Hypotension due to vasodilatation after spinal anesthesia (SA) may be harmful. Heart rate variability, an indirect measure of autonomic control, may predict hypotension.

Methods: One hundred patients were studied. Retrospectively, heart rate variability was analyzed in 30 patients, classified depending on the lowest systolic blood pressure (SBP) after SA. Seventy patients were studied prospectively, assigned to one of two groups by their low to high frequency ratio (LF/HF) before SA. Sensitivity and specificity of LF/HF for prediction of decrease of SBP greater 20% of baseline were tested.

Results: Retrospective analysis showed differences of LF/HF depending on the degree of hypotension after SA. Prospective analysis demonstrated significant differences of SBP after SA depending on baseline LF/HF (mean ± SD): low LF/HF (1.3 ± 0.7) = > SBP: 91 ± 8% of baseline versus high LF/HF (5.5 ± 2.4) = > SBP: 66 ± 10% of baseline (P < 0.05). Baseline LF/HF as well as high frequency and proportional decrease of SBP after SA correlated significantly, in contrast to baseline hemodynamic parameters heart rate and SBP. A receiver operator curve characteristic analysis showed a sensitivity and specificity of LF/HF > 2.5 of 85% to predict SBP decrease of greater than 20% of baseline after SA.

Conclusions: Heart rate variability analysis before SA may predict hypotension after SA with high sensitivity and specificity. LF/HF may be a tool to detect patients at high risk of hypotension due to SA. This indicates that the predictive value of LF/HF is superior to established predictors.

SPINAL anesthesia (SA) is widely used in daily clinical routine. Although regional anesthesia can be advantageous in some respects (i.e., postoperative outcome, respiratory function), hypotension after SA is a common adverse event.4,5 No strategy of preventing the relative hypovolemia caused by regional anesthesia—intravenous crystalloids and colloids as well as prophylactic intramuscular or intravenous vasopressors—has proved entirely satisfactory and applicable to all patients.5,6 Systemic hemodynamic regulation is modulated by the autonomic nervous system (ANS).7 Hypotension due to central neuroaxial block is mainly a result of decreased systemic vascular resistance after blockade of preganglionic sympathetic fibers. Differences in the regulation of the ANS among patients may explain hemodynamic differences in response to SA. Preoperative determination of the ANS regulation may provide an opportunity to detect patients at risk of significant hemodynamic compromise. A noninvasive method of measuring the activity of the ANS is the analysis of heart rate variability (HRV).8 Recent studies have shown the predictive value of HRV for hypotension after SA in pregnant patients scheduled to undergo elective cesarean delivery.9,10 The sympathetic activity is known to be increased during pregnancy.11,12 Therefore, the applicability of the results on nonpregnant patients remains speculative.

We hypothesized that (1) retrospectively analyzed preoperative HRV may differ between patients depending on the severity of hypotension after SA and (2) prospectively analyzed HRV may predict hypotension after SA.

Materials and Methods

After approval of the Institutional Ethics Committee of the University Hospital Schleswig-Holstein, Campus Kiel, Germany, and written informed consent were obtained, 100 men (American Society of Anesthesiologists physical status class I or II) scheduled to undergo prostate brachytherapy during SA were studied. Exclusion criteria were lack of sinus rhythm, chronic medication with antiarrhythmics, coexisting infections, history of bleeding disorder, history of diabetes, and chronic alcohol abuse. All patients received oral premedication of 3.75 or 7.5 mg midazolam, depending on the clinical decision of the attending anesthesiologist, 30 min before anesthesia.

Heart rate variability analysis was performed according to the Task Force recommendations.13 Five-minute recordings of the fast peaks of R waves on the electrocardiogram were detected with a sample rate of 1,024 Hz (TF4; Varia Cardio, Olomouc, Czech Republic). The beat-to-beat variability of consecutive R waves of the sinus rhythm was measured. Data were investigated based on time as well as frequency domain analysis. For time domain analysis, the mean interval of consecutive beat-to-beat intervals and the SD of mean beat-to-beat intervals were investigated, both known to reflect parasympathetic activity.14,15 Frequency domain analysis was based on fast Fourier transformation. Power spectrum densities were calculated for low frequencies (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.4 Hz) in normalized units, defined as the LF or HF proportional part of the total power. Breathing was controlled at a rate of 14–16 breaths/min as recommended for HRV measurements.16 Because fast Fourier transformation analysis requires stationary data, patients were asked to...
lie calmly in the supine position during measurements. Beat-to-beat intervals were measured and stored continuously on a personal computer in all patients. HRV analysis was performed off-line by an investigator blinded to the hemodynamic changes after SA. Artifacts were eliminated by computer-based artifact detection followed by an investigator’s evaluation. Beats were rejected if they varied more than 40% from the preceding beat. These intervals were replaced by the mean of the previous and consecutive beat-to-beat intervals. At most, 5% of a specific measurement was allowed to be re-placed. Otherwise, this specific measurement was not included in the analysis.

**Measurements**

Six events were defined for HRV analysis and measurement of hemodynamic parameters (systolic blood pressure [SBP], heart rate [HR], and oxygen saturation): event 1: on the day before surgery (DBS); event 2: on the day of surgery (DOS), baseline before prehydration (DOS-BL), event 3: on the DOS after prehydration (PRE); event 4: 5 min after administration of SA (SA+5); event 5: 15 min after administration of SA (SA+15), event 6 of HRV: 45 min after administration of SA (SA+45); event 6 of hemodynamic parameters: lowest value after onset of SA.

**Administration of SA**

All patients received rapid infusion of 500 ml hydroxyethyl starch, 6%/130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany), as prehydration according to the literature.17 Thereafter, standardized SA was performed: The puncture site was interlumbar space L3–L4 or L4–L5 isobaric bupivacaine, 0.5%, was injected via a 25-gauge Sprotte needle with the side port of the needle pointing cephalad. The level of sensory blockade was aimed at reaching vasopressor infusion. If vasopressor boluses were necessary, HRV measurement was started thereafter.

**Group Assignment**

This study was performed in two parts: Retrospectively, 30 patients were assigned to the derivation cohort to develop a risk profile based on HRV analysis before SA. Patients were classified into three groups depending on the proportional decrease of baseline SBP after SA: MILD (stable hemodynamic parameters, lowest SBP > 80% of baseline), MODERATE (moderate hypotension, lowest SBP 70–80% of baseline), and SEVERE (severe hypotension, lowest SBP < 70% of baseline). HRV was analyzed retrospectively. The aim was to confirm our previous findings in a different group of patients who may present differences in their underlying baseline ANS regulation.10 Prospectively, 70 patients were assigned to the validation cohort. A predictive model was built to confirm our hypothesis in another group of patients. The cutoff point to discriminate high- and low-risk patients was defined based on a previous study. It was hypothesiz ed and tested prospectively that LF/HF > 2.5 indicates a high risk of hypotension after SA, whereas LF/HF < 2.5 indicates a low risk of hypotension after SA. Hypotension was defined as an SBP less than 80% of baseline. The number of prospective patients was defined according to a power analysis. It indicated that a sample size of 25 patients per group would have a power of 80% at the 5% significance level to detect a difference of 20% of SBP. To cover for dropouts, 35 patients per group were analyzed. Therefore, a total of 100 patients were enrolled in the study.

In all patients, hypotension was treated in a standard-ized manner, if necessary. Decrease of SBP within 20% of baseline required no treatment. Decrease of SBP to 80% to 70% of baseline required rapid infusion of another 500 ml hydroxyethyl starch. If SBP increased to “no treatment” level, no further therapy was administered. If SBP remained below 80% of baseline, an intravenous vasopressor (0.5 ml Akrinor®; AWD Pharma, Dresden, Germany; 0.5 ml = 50 mg cafedrin-1 HCl, 2.5 mg theodrinalin-HCl) was given. A maximum of 1 ml of the vasopressor was injected. If MODERATE patients received more than 1 ml vasopressor, they were assigned to the SEVERE group. Decrease of SBP to less than 70% of baseline was treated with intravenous vasopressor boluses of 0.5 ml and simultaneous rapid infusion of 500 ml hydroxyethyl starch until SBP increased to at least 80% of baseline. The total amount of vasopressor was analyzed for each group. HRV was not determined during vasopressor infusion. If vasopressor boluses were necessary, HRV measurement was started thereafter.

**Statistics**

Prospective data were analyzed using standard software (PRISM 4.0 GraphPad Software; San Diego, CA). All data were checked for normal distribution using the Kolmogorov-Smirnov test based on the Dallal and Wilkinson approximation to the Lilliefors method. Normally distributed data and normalized HRV data during different events were analyzed using two-way analysis of variance factoring for event and LF/HF ratio, followed by Bonferroni correction for multiple comparisons. The Pearson correlation was used to demonstrate correlation between LF/HF, HF, HR, and baseline SBP and degree of hypotension ($r > 0.5, P < 0.05$). All parametric data (hemodynamic data and prospective HRV data) are expressed as mean ± SD, and nonparametric data (retrospective HRV data) are expressed as median, 25th–75th percentile, and range. $P < 0.05$ was considered statistically significant. Receiver operator characteristic curve analysis was performed to evaluate sensitivity and specificity of the threshold LF/HF of 2.5 as well as HF of 30% of total power to detect patients who showed a decrease.
of SBP of more than 20% of baseline after SA.\textsuperscript{18} The performance of two other parameters, baseline preoperative HR and SBP, was investigated by use of receiver operator curve analysis.\textsuperscript{19}

Results

Demographics

One hundred patients completed the study according to the protocol. All patients showed normal HR (<100 beats/min) and normal blood pressure (100 mmHg < SBP < 160 mmHg, 50 mmHg < diastolic blood pressure < 100 mmHg) on the DBS. Thirty patients were assigned to one of three retrospective groups depending on post-SA hypotension: MILD (n = 13), MODERATE (n = 10), and SEVERE (n = 7). Seventy patients were studied prospectively: 31 patients were assigned to group LF/HF < 2.5, and 39 patients were assigned to group LF/HF > 2.5. The groups were comparable with respect to demographic data (age, weight, height, American Society of Anesthesiologists physical status), and level of sensory block (table 1). Preanesthetic laboratory values of all patients were within normal limits. No perioperative complications other than hypotension were recorded in any of the patients.

Retrospective Part

Hemodynamic data (table 2 and fig. 1) showed no differences between groups at DBS and DOS-BL. Changes of SBP after SA showed the predefined differences between patients (fig. 1A). The needs for vasopressor boluses to restore blood pressure in MODERATE and SEVERE patients were comparable: MODERATE: 0.5 ± 0.1 ml versus SEVERE: 0.8 ± 0.2 ml. HRV data are shown in table 3 and figure 2. Parameters LF/HF (fig. 2A) and HF (fig. 2C) differed significantly between groups at DOS-BL. Increased LF/HF decreased after prehydration in MODERATE and SEVERE patients. LF/HF of SEVERE patients remained significantly higher compared with that of MILD patients until onset of SA in SEVERE patients. Results of time domain analysis are demonstrated in table 3 as well. There were no significant differences between groups found at any of the defined events.

Prospective Part

Hemodynamic data are shown in table 2 and figure 1. No differences were found between groups at DBS and DOS-BL. Patients demonstrated significant differences of SBP after SA depending on LF/HF at DOS-BL (fig. 1B). SBP of LF/HF < 2.5 patients decreased to 91 ± 8% of baseline, whereas SBP of LF/HF > 2.5 patients decreased significantly to 66 ± 10% of baseline (P < 0.05 vs. baseline; P < 0.05 vs. LF/HF < 2.5). LF/HF < 2.5 patients required no vasopressor intervention, whereas in LF/HF > 2.5 patients, a mean of 1.0 ± 0.1 ml was administered to restore blood pressure (P < 0.05). HRV data of prospectively assigned patients are demonstrated in figure 2A.
suitable to detect high-risk patients.

Discussion

Heart rate variability was analyzed in 100 patients scheduled to undergo prostate gland brachytherapy during SA perioperatively. Thirty patients were assigned to the derivation cohort to develop a risk profile based on the degree of hypotension after SA. Seventy patients were assigned to the validation cohort. Groups were defined by LF/HF before SA. Retrospectively assigned patients with severe hypotension after SA demonstrated a significantly higher LF/HF and lower HF at baseline. Prospectively assigned patients with increased LF/HF at baseline had development of severe hypotension after SA. LF as well as HF showed significant differences between subgroup LF/HF < 2.5 and subgroup LF/HF > 2.5. Sympatholysis due to SA was reflected by a significant decrease of LF/HF as well as LF and a significant increase of HF in the course of SA. Receiver operator curve analysis showed a high sensitivity and specificity of the parameter baseline LF/HF for prediction of hypotension after SA.

Invasive direct measures of autonomic control are not possible in a clinical setting. Analysis of HRV is a noninvasive, thus indirect measure of autonomic regulation.14,15,20–23 Time as well as frequency domain parameters were investigated in this study. It has been suggested that LF/HF may reflect the balance of the ANS regulation; LF may reflect vasomotor activity, which is an indirect index of sympathetic nerve activity as well as partially affected by parasympathetic activity; and HF as well as time domain parameters may reflect vagal nerve activity.14,15,20,21 Nevertheless, interpretation of LF is less certain than interpretation of HF.24,25 Based on the study results and previous findings, we suggest that LF may to some extent reflect sympathetic activity of the ANS, and LF/HF may reflect the relation between sympathetic and parasympathetic function.10

**HRV Analysis for Prediction of Hypotension**

Retrospective as well as prospective study design has been introduced by our group in women scheduled to...
HEART RATE VARIABILITY PREDICTS SPINAL HYPOTENSION

Table 3. HRV Data

<table>
<thead>
<tr>
<th>Event</th>
<th>HRV</th>
<th>MILD</th>
<th>MOD</th>
<th>SEV</th>
<th>LF/HF &lt; 2.5</th>
<th>LF/HF &gt; 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBS</td>
<td>LF, %</td>
<td>30 (14/52)</td>
<td>53 (25/69)</td>
<td>36 (25/58)</td>
<td>35 ± 14</td>
<td>34 ± 12</td>
</tr>
<tr>
<td></td>
<td>HF, %</td>
<td>49 (24/62)</td>
<td>27 (12/54)</td>
<td>26 (12/48)</td>
<td>35 ± 19</td>
<td>26 ± 17</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>0.7 (0.3/0)</td>
<td>1.8 (0.7/3.1)</td>
<td>2.4 (0.7/4.4)</td>
<td>1.5 ± 1.2</td>
<td>2.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>ToPo, ms²</td>
<td>138 (80/369)</td>
<td>406 (169/496)</td>
<td>523 (255/891)</td>
<td>1,820 ± 2,400</td>
<td>460 ± 420‡</td>
</tr>
<tr>
<td></td>
<td>Mean R-R, s</td>
<td>0.8 (0.65/1.3)</td>
<td>1.0 (0.7/1.4)</td>
<td>0.9 (0.7/1.1)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>SD R-R, ms</td>
<td>25 (15/36)</td>
<td>35 (15/36)</td>
<td>35 (25/74)</td>
<td>47 ± 34</td>
<td>33 ± 12</td>
</tr>
<tr>
<td>DOS-BL</td>
<td>LF, %</td>
<td>23 (15/37)</td>
<td>35 (22/67)</td>
<td>39 (34/57)*</td>
<td>31 ± 13</td>
<td>51 ± 14‡</td>
</tr>
<tr>
<td></td>
<td>HF, %</td>
<td>39 (15/50)</td>
<td>12 (9/21)*</td>
<td>5 (3/6)*</td>
<td>36 ± 22</td>
<td>11 ± 5‡</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>0.7 (0.4/1.2)</td>
<td>3.0 (1.4/2.2)*</td>
<td>7.5 (4.1/11.0)*</td>
<td>1.2 ± 0.8</td>
<td>5.5 ± 2.5‡</td>
</tr>
<tr>
<td></td>
<td>ToPo, ms²</td>
<td>253 (155/484)</td>
<td>379 (172/691)</td>
<td>393 (132/449)</td>
<td>1,600 ± 1,090</td>
<td>480 ± 430‡</td>
</tr>
<tr>
<td></td>
<td>Mean R-R, s</td>
<td>0.8 (0.7/1.2)</td>
<td>0.8 (0.7/1.1)</td>
<td>0.8 (0.6/0.9)</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>SD R-R, ms</td>
<td>33 (22/96)</td>
<td>33 (19/68)</td>
<td>32 (17/69)</td>
<td>107 ± 58</td>
<td>34 ± 14‡</td>
</tr>
<tr>
<td>DOS-PRE</td>
<td>LF, %</td>
<td>26 (16/30)</td>
<td>41 (22/67)*</td>
<td>43 (34/57)*</td>
<td>28 ± 12</td>
<td>38 ± 11§‡</td>
</tr>
<tr>
<td></td>
<td>HF, %</td>
<td>29 (23/36)</td>
<td>24 (10/32)</td>
<td>14 (7/17)*</td>
<td>39 ± 23</td>
<td>16 ± 11§‡</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>1.0 (0.5/1.2)</td>
<td>1.4 (0.7/5.2)</td>
<td>3.5 (1.4/6.9)*</td>
<td>1.3 ± 1.0</td>
<td>3.9 ± 3.0‡</td>
</tr>
<tr>
<td></td>
<td>ToPo, ms²</td>
<td>176 (140/680)</td>
<td>134 (104/416)</td>
<td>325 (89/434)</td>
<td>1,550 ± 1,070</td>
<td>490 ± 375‡</td>
</tr>
<tr>
<td></td>
<td>Mean R-R, s</td>
<td>0.9 (0.6/1.3)</td>
<td>0.8 (0.7/1.2)</td>
<td>0.8 (0.7/1.3)</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>SD R-R, ms</td>
<td>33 (18/83)</td>
<td>26 (13/50)</td>
<td>26 (14/58)</td>
<td>60 ± 56</td>
<td>32 ± 17</td>
</tr>
<tr>
<td>DOS-SA+15</td>
<td>LF, %</td>
<td>34 (18/42)</td>
<td>29 (10/43)</td>
<td>28 (19/38)</td>
<td>23 ± 14</td>
<td>31 ± 12§‡</td>
</tr>
<tr>
<td></td>
<td>HF, %</td>
<td>38 (24/52)</td>
<td>14 (8/24)</td>
<td>21 (7/41)</td>
<td>49 ± 22§‡</td>
<td>24 ± 17‡</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>0.8 (0.5/1.7)</td>
<td>2.1 (0.6/5.0)</td>
<td>2.6 (0.7/5.7)</td>
<td>0.8 ± 0.6</td>
<td>2.2 ± 1.9§†</td>
</tr>
<tr>
<td></td>
<td>ToPo, ms²</td>
<td>296 (165/2,149)</td>
<td>285 (168/534)</td>
<td>445 (221/657)</td>
<td>2,130 ± 1,930</td>
<td>470 ± 410‡</td>
</tr>
<tr>
<td></td>
<td>Mean R-R, s</td>
<td>0.9 (0.7/1.2)</td>
<td>0.9 (0.8/1.3)</td>
<td>0.9 (0.7/1.1)</td>
<td>1.0 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>SD R-R, ms</td>
<td>25 (11/115)</td>
<td>28 (14/43)</td>
<td>40 (27/61)</td>
<td>65 ± 51</td>
<td>32 ± 16</td>
</tr>
<tr>
<td>DOS-SA+45</td>
<td>LF, %</td>
<td>23 (14/27)</td>
<td>25 (15/32)</td>
<td>18 (10/29)</td>
<td>23 ± 12§</td>
<td>29 ± 13</td>
</tr>
<tr>
<td></td>
<td>HF, %</td>
<td>45 (22/58)</td>
<td>19 (10/27)</td>
<td>35 (8/41)</td>
<td>48 ± 22</td>
<td>22 ± 15‡</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>0.6 (0.4/1.4)</td>
<td>1.3 (1.0/2.3)</td>
<td>0.7 (0.3/4.0)*</td>
<td>0.9 ± 0.7</td>
<td>2.2 ± 2.0‡</td>
</tr>
<tr>
<td></td>
<td>ToPo, ms²</td>
<td>904 (351/1516)</td>
<td>620 (271/999)</td>
<td>532 (188/840)</td>
<td>2,200 ± 2,100§</td>
<td>850 ± 690†</td>
</tr>
<tr>
<td></td>
<td>Mean R-R, s</td>
<td>1.0 (0.8/1.3)</td>
<td>1.0 (0.8/1.2)*</td>
<td>0.9 (0.8/1.1)*</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>SD R-R, ms</td>
<td>52 (9/100)</td>
<td>32 (13/56)</td>
<td>52 (21/86)</td>
<td>69 ± 52</td>
<td>45 ± 19</td>
</tr>
</tbody>
</table>

Retrospective groups: Data are presented as median and minimum/maximum. Prospective groups: Data are presented as mean ± SD.  
* P < 0.05 vs. MILD. † P < 0.05 MOD vs. SEV. ‡ P < 0.05 LF/HF < 2.5 vs. LF/HF > 2.5. § P < 0.05 within group in the course of spinal anesthesia compared with DOS-BL.

DBS = day before surgery; DOS-BL = day of surgery baseline; DOS-PRE = day of surgery after prehydration; DOS-SA+15 = measurement 15 min after spinal anesthesia; DOS-SA+45 = measurement 45 min after spinal anesthesia; HF = high frequency; HRV = heart rate variability; LF = low frequency; LF/HF = low to high frequency ratio; LF/HF < 2.5 = prospective group with low baseline low to high frequency ratio; LF/HF > 2.5 = prospective group high baseline low to high frequency ratio; Mean R-R = mean of consecutive beat-to-beat intervals; MILD = retrospective group with mild hypotension; MOD = retrospective group with moderate hypotension; SD R-R = SD of mean R-R interval; SEV = retrospective group with severe hypotension; ToPo = total power.

undergo elective cesarean delivery during SA.10 Retrospective findings indicate that patients who had development of hypotension after SA had higher LF/HF and lower HF preoperatively. Results were confirmed in a larger prospective group. These results are in good agreement with previous findings in women scheduled to undergo elective cesarean delivery during SA.9,10 Chamchad et al.9 demonstrated the predictive value of HRV for hypotension accompanying SA for cesarean delivery. Point correlation dimension (PD2), a measure of HRV, was investigated, and significant differences between hypertensive and normotensive patients were demonstrated. Recently, we showed the predictive value of HRV for hypotension after SA in obstetric patients. It was demonstrated that LF/HF > 2.5 correlated significantly with hypotension. The same LF/HF level introduced in pregnant women was defined to discriminate low and high risk of hypotension in elderly men aiming at a simple measure of risk evaluation applicable to different groups of patients.10 We conclude that LF/HF of 2.5 may be a cutoff value independent from underlying individual conditions. To evaluate its predictive value, preoperative LF/HF was correlated with the degree of SBP decrease after SA. A significant correlation was demonstrated, and a high sensitivity and specificity of LF/HF > 2.5 to predict hypotension was shown. In addition, baseline HF (reflecting vagal activity) was correlated with the percentage decrease of SBP. A significant correlation was demonstrated confirming the view that human cardiac function is mainly controlled via vagal mechanisms.26 Nevertheless, receiver operator curve analyses of LF/HF demonstrated better sensitivity and specificity compared with receiver operator curve analysis of HF. Better sensitivity and specificity of LF/HF
Fig. 2. Heart rate variability, retrospective groups. (A) Low to high frequency ratio (LF/HF). (B) Low frequency (LF). (C) High frequency (HF). DBS = day before surgery; DOS-BL = day of surgery baseline; MILD = mild hypotension; MOD = moderate hypotension; PRE = after prehydration; SA+5 = 5 min after spinal anesthesia; SA+15 = 15 min after spinal anesthesia; SEV = severe hypotension. Data are presented as median, 25th and 75th percentile, and range. * \( P < 0.05 \) versus MILD. \( # P < 0.05 \) versus SEVERE. + \( P < 0.05 \), significant difference within groups between different events.

Fig. 3. Heart rate variability, prospective groups. (A) Low to high frequency ratio (LF/HF). (B) Low frequency (LF). (C) High frequency (HF). DBS = day before surgery; DOS-BL = day of surgery baseline; LF/HF < 2.5 = baseline LF/HF less than 2.5; LF/HF > 2.5 = baseline LF/HF greater than 2.5; PRE = after prehydration; SA+5 = 5 min after spinal anesthesia; SA+15 = 15 min after spinal anesthesia; SA+45 = 45 min after spinal anesthesia. Data are presented as mean ± SD. * \( P < 0.05 \) versus LF/HF < 2.5. + \( P < 0.05 \), significant difference within groups between different events.
may indicate that sympathetic control reflected by LF affects cardiac regulation as well. Therefore, the ratio of low to high frequency, reflecting sympathetic to parasympathetic balance, is superior to HF alone. Time domain parameters mean R-R interval and SD of R-R interval did not differ significantly between groups depending on postspinal hypotension. These parameters mainly reflect parasympathetic regulation. Therefore, frequency domain analysis, especially the LF/HF ratio, may be more sensitive for prediction of postspinal hypotension com-

Fig. 4. Correlation of baseline parameters and hypotension. (A) Correlation of low to high frequency (LF/HF) and decrease of systolic blood pressure (SBP). (B) Correlation of high frequency (HF) and decrease of SBP. (C) Correlation of heart rate (HR) and decrease of SBP. (D) Correlation of baseline (BL) SBP and decrease of SBP. \( r > 0.5, P < 0.05 \).

Fig. 5. Receiver operator curve (ROC) analyses. (A) ROC of low to high frequency ratio (LF/HF). (B) ROC of high frequency (HF). Area = area under the curve. \( P < 0.05 \).
pared with parameters solely reflecting parasympathetic control.

There is evidence that baseline HR and SBP may indicate the risk of post-SA hypotension.\textsuperscript{19,27–29} Therefore, these parameters were correlated with hypotension in our study. In contrast, we found no correlation between hemodynamic parameters and hypotension and only weak sensitivity and specificity for prediction of hypotension of HR and SBP in our study. Therefore, different levels of LF/HF, which may reflect sympathovagal balance, correlate with comparable baseline hemodynamic parameters. HRV analysis may be superior compared with baseline HR or SBP for risk stratification of post-SA hypotension.

The sympathovagal balance is the result of sympathetic as well as parasympathetic influences. Basically, HRV analysis is based on measuring the beat-to-beat interval of the sinus rhythm. These changes vary based on many influences, such as volume status, respiration, intrathoracic pressure, and baroreceptor reflexes. If LF/HF may reflect sympathovagal balance, it is an interesting question whether changes of LF, HF, or both result in modifications of LF/HF. Only baseline HF, not LF, was significantly different between retrospectively defined groups. In prospectively assigned patients, both parameters, LF as well as HF, were significantly different at baseline, resulting in a significant difference of LF/HF.

HF and vagal activity seem to be more clearly associated baseline, resulting in a significant difference of LF/HF. Parameters, LF as well as HF, were significantly different at groups. In prospectively assigned patients, both parameters, LF as well as HF, were significantly different at baseline, resulting in a significant difference of LF/HF.

The authors suggested that indicators of vagal activity, including HF of HRV, were best correlated with hypotension after induction of general anesthesia. Especially impaired parasympathetic activity, reflected by HF, indicated a high risk of hemodynamic instability. Latson \textit{et al.}\textsuperscript{31} investigated ANS regulation in patients with underlying autonomic reflex dysfunction due to diabetes mellitus. Various tests, including HRV, were performed to investigate autonomic nervous system regulation. It was demonstrated that patients with impaired ANS regulation were at high risk of hypotension after induction of general anesthesia. Especially impaired parasympathetic activity, reflected by HF, indicated a high risk of hemodynamic instability.

\textit{HRV in the Course of SA}

Hypotension during SA is mainly a result of decreased systemic vascular resistance caused by inhibition of preganglionic sympathetic nerve fibers. High thoracic blockade may in addition block sympathetic innervation of the heart by blocking nervi accelerantes, resulting in bradycardia and decrease of stroke volume. The coincidence of a decrease of LF with hypotension was demonstrated in patients during SA. SA provoked a decrease of LF and a small increase of HF resulting in a decrease of LF/HF.\textsuperscript{32} These changes of HRV during the course of SA were comparable to our results. LF/HF and LF decreased after SA accompanied by hypotension. In contrast, patients who showed low baseline LF/HF and LF as well as increased HF did not have development of significant changes of HRV after SA, reflected by only minor changes of hemodynamic parameters. The importance of the balance of LF/HF was previously demonstrated.\textsuperscript{35} A depression of LF as well as HF in patients undergoing cesarean delivery during SA or epidural anesthesia was demonstrated. Consequently, LF/HF remained unchanged, accompanied by stable hemodynamic parameters. We conclude that blockade of preganglionic sympathetic fibers and blockade of sympathetic innervations of the heart are associated with a decrease of LF/HF and LF. These findings suggest that LF/HF and LF may be indirect measures of the sympathetic activity of the ANS regulation.

\textit{Limitations}

Some limitations of our study should be noted. HRV is only an indirect measure of autonomic activity. It was established in this clinical setting because noninvasive direct measures of autonomic regulation are not available. Artifacts during HRV data recording were inevitable to some degree. However, artifacts were eliminated by computer-based artifact detection followed by an evaluation by an expert blinded to the hemodynamic effects of SA. Because fast Fourier transformation analysis requires stationary data, patients were asked to lie calmly in the supine position during measurements. Because of the minimally invasive technique of the surgical procedure with almost no blood loss and minimal surgical manipulations, stillness was secured throughout the measurements. Vasopressor boluses after SA for treatment of hypotensive episodes may influence HRV measurements in the course of SA.

Heart rate variability measurements are based on standard electrocardiographic recordings at high acquisition rates, and commercial tools offer computerized interpretation. Therefore, in principle, the technique could easily be implemented in routine clinical monitoring. HRV measurements may contain important prognostic information about individual hemodynamic reaction after SA. Our data suggest a correlation between an increased sympathetic activity indicated by HRV before SA and hypotension in the course of regional anesthesia. A high sensitivity and specificity of LF/HF greater than 2.5 for prediction of hypotension was demonstrated. Therefore, HRV analysis before SA may be suitable to detect patients at high risk of hypotension. The predictive value of LF/HF may be superior to established predictors.
References


