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Heart Rate Variability Predicts Severe Hypotension after Spinal Anesthesia for Elective Cesarean Delivery

Robert Hanss, M.D., Berthold Bein, M.D.,* Thomas Ledowski, M.D.,* Marlies Lehmkuhl, M.S.,* Henning Ohnesorge, M.D.,* Wiebke Scherkl, M.S.,* Markus Steinfath, M.D.,† Jens Scholz, M.D.,‡ Peter H. Tonner, M.D.§*

Background: **Hypotension due to vasodilation during subarachnoid block (SAB) for elective cesarean delivery may be harmful. Heart rate variability (HRV), reflecting autonomic control, may identify patients at risk of hypotension.**

Methods: **Retrospectively, HRV was analyzed in 41 patients who were classified into one of three groups depending on the decrease in systolic blood pressure (SBP): mild (SBP > 100 mmHg), moderate (100 > SBP > 80 mmHg), or severe (SBP < 80 mmHg). Prospectively, HRV and hemodynamic data of 19 patients were studied. Relative low frequency (LF), relative high frequency (HF), and LF/HF ratio were analyzed.**

Results: **Retrospective analysis of HRV showed a significantly higher sympathetic and lower parasympathetic drive in the groups with moderate and severe compared with mild hypotension before SAB (median, 25th/75th percentiles): LF/HF: mild: 1.2 (0.9/1.8), moderate: 2.8 (1.8/4.6), $P < 0.05$ *versus* mild; severe: 2.7 (2.0/3.5), $P < 0.05$ *versus* mild. Results were confirmed by findings of LF and HF. Prospectively, patients were grouped according to LF/HF before SAB: low-LF/HF: 1.5 (1.1/2.0) *versus* high-LF/HF: 4.0 (2.8/4.7), $P < 0.05$; low-LF: 58 ± 9% *versus* high-LF: 75 ± 10%, $P < 0.05$; low-HF: 41 ± 10% *versus* high-HF: 25 ± 10%, $P < 0.05$. High-risk patients had a significantly lower SBP after SAB (76 ± 21 *vs.* 111 ± 12 mmHg; $P < 0.05$).**

Conclusions: **Retrospectively analyzed HRV of patients scheduled to undergo elective cesarean delivery during SAB showed significant differences depending on the severity of hypotension after SAB. Preliminary findings were prospectively confirmed. High LF/HF before SAB predicted severe hypotension. Preoperative HRV analysis may detect patients at risk of hypotension after SAB.**

MORBIDITY and mortality directly related to anesthesia for cesarean delivery has decreased in past decades to 1.7 per million.[1] The higher risk of maternal complications associated with general anesthesia compared with regional anesthesia has led to an increased use of subarachnoid block (SAB) and epidural anesthesia (EDA) for both elective and emergency cesarean delivery.[2] Although SAB is generally well tolerated, hypotension is a common adverse effect of SAB in some patients.[3] Hypotension during central neuroaxial block is mainly a result of decreased systemic vascular resistance after blockade of preganglionic sympathetic fibers. In pregnant women, it was demonstrated that sympathetic regulation is increased as compared with that of nonpregnant women.[4–6] Further differences of the regulation of the autonomic nervous system (ANS) among healthy pregnant patients may explain hemodynamic differences in response to SAB.

Vasovagal episodes in association with regional anesthesia are not rare; rates of up to 90% have been reported.[7,8] Anesthesia-induced hypotension may have severe adverse effects for mother and child. 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.[9,10] Preoperative determination of the ANS control might provide an opportunity to detect patients at risk of severe hemodynamic impairment.

Systemic hemodynamics are modulated by the ANS.[11] A noninvasive method of measuring the activity of the ANS is the analysis of heart rate variability (HRV).[12] Several studies have investigated the influence of general and regional anesthesia on HRV,[11,12] but to date, only one study included patients for elective cesarean delivery during SAB.[13] There has been no investigation studying the predictive value of HRV on hemodynamic parameters after regional anesthesia.

We hypothesized that (1) retrospectively analyzed preoperative HRV may differ between patients in relation to the severity of hypotension after SAB, (2) prospectively analyzed HRV can predict hypotension after SAB, and (3) HRV may identify patients in whom prehydration would be beneficial.

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Materials and Methods

After approval of the Institutional Ethics Committee of the University-Hospital Schleswig-Holstein, Campus Kiel, Germany, and written informed consent, 60 women (American Society of Anesthesiologists physical status class I or II) with an uneventful pregnancy, at term, scheduled to undergo elective cesarean delivery during

* Staff Anesthesiologist, † Professor of Anesthesiology, ‡ Professor of Anesthesiology and Chair, § Professor of Anesthesiology and Vice-Chair.

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Address correspondence to Dr. Hanss: Department of Anaesthesiology and Intensive Care Medicine, University-Hospital Schleswig-Holstein, Campus Kiel, Schwanenweg 21, 24105 Kiel, Germany. Address electronic mail to: hanss@anaesthesie.uni-kiel.de.

SAB, were studied. Exclusion criteria were as follows: signs of active labor; gestational or chronic hypertension; preeclampsia; hypertension, elevated liver enzymes, and low platelets syndrome; coexisting infections; bleeding disorder; emergency cases; age less than 18 yr; and known fetal abnormalities. All preanesthetic laboratory values were within normal limits. All women showed sinus rhythm, normal heart rate (HR; < 110 min^{-1}), and stable blood pressure (100 mmHg $<$ systolic blood pressure [SBP] < 140 mmHg, 50 mmHg $<$ diastolic blood pressure < 90 mmHg) on the day before surgery (DBS). Patients received no premedication and no intravenous fluids before entering the study.

HRV Measurements

Three HRV analyses were performed, all of them before SAB: (1) on the DBS; (2) on the day of surgery (DOS), baseline before prehydration (DOS-BL); and (3) on the DOS after prehydration. HRV analysis was performed according to the Task Force recommendations.[14] Five-minute recordings of the fast peaks of R waves on the electrocardiogram were detected with a sampling rate of 1,024 Hz. The beat-to-beat variability of consecutive R waves of the sinus rhythm was measured. Data were analyzed by a personal computer using fast Fourier transformation (Vario Cardio TF4; Olomuk, Czech Republic). Power spectrum densities were calculated for low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz) in normalized units, defined as either LF's or HF's relative part of the total power. LF is thought to reflect sympathetic and parasympathetic control, whereas HF reflects parasympathetic control.[15] The ratio of absolute values of LF and HF (LF/HF) was reported to correlate with sympathovagal balance[16]; this parameter was also calculated for each group. Because fast Fourier transformation analysis requires stationary collection of the data, patients were ask to lay calmly in the supine position with left uterine displacement during measurements. R-R intervals were measured and stored on a personal computer continuously in all patients. Artifacts were eliminated by computer-based artifact detection followed by an evaluation by an expert blinded to the study results. 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 R-R intervals. At most, 5% of a specific measurement was allowed to be replaced. Otherwise, this specific measurement was not included in the analysis.

Spinal Anesthesia

All patients received rapid infusion of 500 ml hydroxyethyl starch 6%/130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany) as prehydration according to textbook recommendations.[17] Thereafter, standardized SAB was performed: The puncture site was interlumbar space L2–L3 or L3–L4, with the patient in a sitting position. Hyperbaric bupivacaine, 12.5 mg (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 T4–T5. Immediately after injection, patients were positioned supine with left uterine displacement. Oxygen (5 l/min) was administered *via* facemask. The level of sensory blockade was tested by pinprick test.

Cardiovascular Monitoring

Systolic blood pressure, HR, and oxygen saturation were recorded at DBS and at DOS. Five different events were defined for hemodynamic measurements. Time 1 was defined as DBS; time 2 was DOS-BL; time 3 was DOS after prehydration; and time 4 was the first measurement after SAB, with the patient positioned supine with left uterine displacement. After SAB, hemodynamic parameters were measured minute by minute until SAB was fixed and SBP remained stable. Time 5 was defined as the lowest value between onset of SAB and delivery of the newborn (event Low). The time period between onset of SAB and delivery of the newborn was recorded as well as the interval between onset of SAB and measurement of lowest SBP.

Group Assignment

This study was performed in two steps. First, patients were classified into one of three groups by the lowest SBP as follows: Patients with an SBP greater than 100 mmHg were included in the mild group, patients with an SBP of 80–100 mmHg were included in the moderate group, and patients with an SBP less than 80 mmHg were included in the severe group. HRV was analyzed retrospectively depending on the patient's classification. Second, based on the preliminary data, a predictive model was built to confirm our hypothesis prospectively in another group of patients. Based on the retrospective data, a cutoff point of the LF/HF ratio was defined. Two prospective groups were defined: a low-LF/HF group (LF/HF < 2.5) and a high-LF/HF group (LF/HF > 2.5). SBP and HR were analyzed as described above.

In all patients, hypotension and bradycardia were treated in a standardized manner if necessary. If SBP was greater than 100 mmHg and HR was greater than 60 beats/min, no treatment was given. If SBP was between 80 and 100 mmHg or HR was less than 60 beats/min, rapid infusion of another 500 ml hydroxyethyl starch was administered for treatment of hypotension or 0.5 mg atropine was administered for treatment of bradycardia. If SBP and HR increased to "no treatment" levels, no further therapy was administered. If SBP remained below 100 mmHg, an intravenous vasopressor bolus (0.5 ml Akrinor; AWD Pharma, Dresden, Germany; 0.5 ml = 50 mg cafedrin-1HCl, 2.5 mg theodrenalin-HCl) was given. A maximum of 1 ml of the vasopressor was

Table 1. Demographics, Level of Sensory Block, and Blood Loss

	Retrospective			Prospective	
	Mild (n = 15)	Moderate (n = 9)	Severe (n = 17)	Low-LF/HF (n = 10)	High-LF/HF (n = 9)
Age, yr	30 ± 5	31 ± 4	31 ± 6	34 ± 4	37 ± 4
Weight, kg	81 ± 13	89 ± 18	81 ± 22	80 ± 7	87 ± 17
Height, cm	164 ± 5	168 ± 5	165 ± 5	168 ± 6	166 ± 6
ASA physical status, I/II	12/1	10/1	15/2	10/0	9/0
Pregnancy, weeks	39 ± 1	38 ± 2	38 ± 1	38 ± 1	38 ± 1
Sensory block, T	T5 ± 1	T4.5 ± 1	T4.5 ± 1	T5 ± 1.5	T5 ± 1.5
Blood loss, ml	450 ± 140	500 ± 70	600 ± 250	470 ± 120	530 ± 100

No differences between groups. Data are presented as mean ± SD.

ASA = American Society of Anesthesiologists; HF = high-frequency; High-LF/HF = LF/HF > 2.5; LF = low frequency; Low-LF/HF = LF/HF < 2.5; Mild = patients with mild hypotension after SAB (SBP > 100 mmHg); Moderate = patients with moderate hypotension after SAB (100 mmHg > SBP < 80 mmHg); Prospective = prospective assignment of patients by LF/HF ratio; Retrospective = retrospective classification of patients by severity of hypotension after SAB; SAB = subarachnoid block; SBP = systolic blood pressure; Severe = patients with severe hypotension after SAB (SBP < 80 mmHg); T = thoracic level of sensory block.

injected. Moderate group patients who required further vasopressor boluses were included in the severe group. Persistent bradycardia was treated with a second bolus of 0.5 mg atropine. If moderate group patients received more then 1 mg atropine, they were included in the severe group. An SBP less than 80 mmHg was treated with intravenous vasopressor boluses of 0.5 ml and simultaneous rapid infusion of 500 ml hydroxyethyl starch until SBP increased to 100 mmHg. After surgery, all patients remained in the delivery department and were monitored until SAB diminished completely.

Data were analyzed using standard software (PRISM GraphPad Software, San Diego, CA). All numeric data were checked for normal distribution using the Kolmogorov-Smirnov test. 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. Within-group differences over time were analyzed using one-way analysis of variance followed by the Bonferroni correction for multiple comparisons. Differences between groups were analyzed using an unpaired Student *t* test. All parametric data are expressed as mean ± SD, and nonparametric data are expressed as median, 25th/75th percentiles, and range. A value of $P < 0.05$ was considered statistically significant.

Results

Demographics

A total of 60 patients completed the study according to the protocol. Forty-one patients were classified into one of three retrospective groups depending on post-SAB hypotension: mild (15 patients), moderate (9 patients), or severe (17 patients). Two patients were included in the severe group because they required more than two vasopressor boluses to restore SBP. A total of 19 women were studied prospectively: 10 patients were assigned to the low-LF/HF group, and 9 patients were assigned to the high-LF/HF group. Patients of the retrospective as well as the prospective groups were comparable with respect to demographic data (age, weight, height, American Society of Anesthesiologists physical status), blood loss, and level of sensory block (table 1). Apgar levels at 1, 5, and 10 min after delivery, as well as umbilical pH and infant height and weight, were also comparable between groups (table 2).

Table 2. Children's Demographic Data: Weight, Height, Apgar Scores, and Umbilical pH

	Retrospective			Prospective	
	Mild (n = 15)	Moderate (n = 9)	Severe (n = 17)	Low-LF/HF (n = 10)	High-LF/HF (n = 9)
Apgar 1	8.5 ± 1	9 ± 0.6	9 ± 0.7	8.3 ± 1	8.3 ± 1
Apgar 5	10 ± 0.5	9 ± 0.7	10 ± 0.3	9.2 ± 0.8	9.2 ± 0.7
Apgar 10	10 ± 0.5	10 ± 0.7	10 ± 0.2	9.6 ± 0.4	9.5 ± 0.4
pH	7.31 ± 1.8	7.31 ± 1.0	7.31 ± 1.2	7.3 ± 0.1	7.3 ± 0.1
Newborn weight, g	3,450 ± 520	3,530 ± 810	3,430 ± 320	3,153 ± 626	3,532 ± 684
Newborn height, cm	51 ± 2	52 ± 3	51 ± 2	50 ± 1.5	51 ± 2.0

No differences between groups. Data are presented as mean ± SD.

Apgar 1 = Apgar score 1 min after birth; Apgar 5 = Apgar score 5 min after birth; Apgar 10 = Apgar score 10 min after birth; HF = high frequency; High-LF/HF = LF/HF > 2.5; LF = low frequency; Low-LF/HF = LF/HF < 2.5; Mild = patients with mild hypotension after SAB (SBP > 100 mmHg); Moderate = patients with moderate hypotension after SAB (100 mmHg > SBP < 80 mmHg); Prospective = prospective assignment of patients by LF/HF ratio; Retrospective = retrospective classification of patients by severity of hypotension after SAB; SAB = subarachnoid block; SBP = systolic blood pressure; Severe = patients with severe hypotension after SAB (SBP < 80 mmHg).

Table 3. Hemodynamic Parameters: Blood Pressure and Heart Rate

	DBS	DOS-BL	Prehyd	SAB + 1	Low
Retrospective					
Mild					
SBP, mmHg	137 ± 15	137 ± 15	137 ± 17	134 ± 12	112 ± 10
DBP, mmHg	80 ± 17	82 ± 8	83 ± 8	74 ± 16	64 ± 8
MAP, mmHg	96 ± 17	100 ± 9	101 ± 10	94 ± 12	80 ± 8
HR, beats/min	80 ± 11	88 ± 11	88 ± 10	86 ± 12	82 ± 9
Moderate					
SBP, mmHg	121 ± 6	133 ± 19	133 ± 19	139 ± 18	94 ± 5*
DBP, mmHg	83 ± 16	82 ± 10	81 ± 11	76 ± 11	53 ± 10*
MAP, mmHg	95 ± 13	99 ± 13	98 ± 13	97 ± 12	68 ± 9*
HR, beats/min	80 ± 15	93 ± 10	90 ± 10	99 ± 11*	89 ± 17
Severe					
SBP, mmHg	121 ± 14	129 ± 16	131 ± 18	120* ± 23	78 ± 9*†
DBP, mmHg	79 ± 8	77 ± 9	75 ± 12	74 ± 13	45 ± 9*
MAP, mmHg	93 ± 6	93 ± 10	94 ± 11	89 ± 15	56 ± 8*
HR, beats/min	81 ± 15	90 ± 9	95 ± 12	97 ± 18	101 ± 26*
Prospective					
Low-LF/HF					
SBP, mmHg	121 ± 5	129 ± 15	142 ± 13	137 ± 12	111 ± 12
DBP, mmHg	83 ± 16	80 ± 11	89 ± 15	76 ± 9	64 ± 11
MAP, mmHg	95 ± 12	96 ± 11	107 ± 12	97 ± 10	80 ± 10
HR, beats/min	76 ± 14	74 ± 8	84 ± 11	89 ± 8	75 ± 12
High-LF/HF					
SBP, mmHg	127 ± 16	130 ± 9	146 ± 13	115 ± 13	76 ± 21‡§
DBP, mmHg	77 ± 10	81 ± 12	84 ± 10	68 ± 11	45 ± 18‡§
MAP, mmHg	98 ± 15	97 ± 10	104 ± 11	84 ± 9	56 ± 15‡§
HR, beats/min	82 ± 12	80 ± 6	94 ± 10	102 ± 12	101 ± 29‡

Data are presented as mean ± SD.

* $P < 0.05$ *vs.* Mild. † $P < 0.05$ Moderate *vs.* Severe. ‡ $P < 0.05$ LF/HF < 2.5 *vs.* LF/HF > 2.5. § $P < 0.05$ DOS-BL *vs.* Low.

DBP = diastolic blood pressure; DBS = day before surgery; DOS-BL = day of surgery baseline; HF = high frequency; High-LF/HF = LF/HF > 2.5; LF = low frequency; Low = lowest values after SAB; Low-LF/HF = LF/HF < 2.5; MAP = mean arterial blood pressure; Mild = patients with mild hypotension after SAB (SBP > 100 mmHg); Moderate = patients with moderate hypotension after SAB (100 mmHg > SBP < 80 mmHg); Prehyd = DOS after prehydration; Prospective = prospective assignment of patients by LF/HF ratio; Retrospective = retrospective classification of patients by severity of hypotension after SAB; SAB = subarachnoid block; SAB + 1 = measurement right after SAB; SBP = systolic blood pressure; Severe = patients with severe hypotension after SAB (SBP < 80 mmHg).

Definition of Prospective Groups

Based on the preliminary retrospective findings, two prospective groups with high or low LF/HF were defined. The median mild LF/HF was 1.4, the median moderate LF/HF was 2.8, the median severe LF/HF was 2.6, and the overall median LF/HF was 2.2. An LF/HF ratio greater than 2.5 may indicate a high risk of hypotension after SAB (high-LF/HF group). An LF/HF ratio of less than 2.5 may indicate a low risk of hypotension after SAB (low-LF/HF group). This hypothesis was tested prospectively.

Hemodynamic Data

Blood pressure and HR are shown in table 3. Blood pressure and HR showed no differences between retrospective groups or prospective groups at DBS and DOS-BL. The SBP at event Low showed the defined differences in retrospective patients with significantly lower values in the moderate and severe groups compared with the mild group. The time period between the onset of SAB and event Low was 9 ± 5 min for the mild group, 7 ± 3 min for the moderate group, and 5 ± 2 min for the severe group. The moderate and severe groups received an additional infusion of 500 ml hydroxyethyl starch. The moderate group required significantly fewer vasopressor boluses compared with the severe group (0.4 ± 0.5 *vs.* 3.4 ± 1.5 boluses; $P < 0.05$) to restore blood pressure. HR showed significant differences between the mild and moderate groups at the first measurement after SAB and between the mild and severe groups at event Low. The time period between the onset of SAB and delivery of the newborn did not differ significantly, being 18 ± 3 min in the mild group, 17 ± 2 min in the moderate group, and 17 ± 4 min in the severe group.

The SBP of prospective groups showed significant differences depending on LF/HF at DOS-BL. The SBP of the low-LF/HF group remained significantly higher than that of the high-LF/HF group (low-LF/HF: 111 ± 12 mmHg *vs.* high-LF/HF: 76 ± 21 mmHg; $P < 0.05$). A significant decrease in SBP was found in the high-LF/HF group between DOS-BL and event Low. The time period between the onset of SAB and event Low did not differ between groups (low-LF/HF: 8 ± 2 min *vs.* high-LF/HF: 10 ± 4 min). The low-LF/HF group required significantly fewer vasopressors to restore blood pressure compared with the high-LF/HF group (0.4 ± 0.6 *vs.* 2.5 ± 2.0

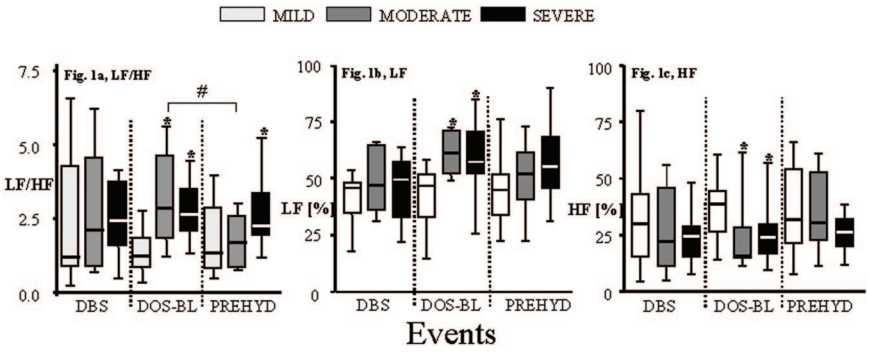

Fig. 1. Retrospective heart rate variability analysis. (*A*) Low frequency (LF)/high-frequency (HF) ratio; (*B*) LF in normalized units; (*C*) HF in normalized units. DBS = day before surgery; DOS-BL = day of surgery, baseline measurement before prehydration; Mild = patients with mild hypotension after SAB (SBP > 100 mmHg); Moderate = patients with moderate hypotension after SAB (100 mmHg > SBP < 80 mmHg); Prehyd = prehydration with 500 ml hydroxyethyl starch 6%/130/0.4; SAB = subarachnoidal block; SBP = systolic blood pressure; Severe = patients with severe hypotension after SAB (SBP < 80 mmHg). Data are presented as median, 25th/75th percentiles, and range. * *P* < 0.05 *versus* Mild; # *P* < 0.05 within groups *versus* before.

boluses; $P < 0.05$). HR at event Low was significantly higher in the high-LF/HF group compared with the low-LF/HF group. The time periods between the onset of SAB and delivery of the newborn were comparable between groups: 15 ± 4 *versus* 15 ± 5 min. No atropine was administered to any of the patients.

HRV Analysis

Data of the retrospective groups are shown in figures 1A–C. No significant differences between the groups in terms of LF/HF, LF, or HF were found at DBS. LF/HF (fig. 1A) tended to be higher in the moderate and severe groups at DBS. The ratio differed significantly at DOS-BL between both the moderate and severe groups compared with the mild group. After prehydration, LF/HF remained unchanged in the mild and severe groups, with significantly higher values in the severe group as compared with the mild group. The LF/HF of the moderate group decreased significantly after prehydration to values comparable to those of the mild group. Differences of LF/HF were reflected by changes in LF and HF (figs. 1B and C). At DOS-BL, LF was significantly higher and HF was significantly lower in the moderate and severe groups as compared with the mild group. Prehydration led to a significant decrease of sympathetic outflow in the moderate group.

Data of the prospective groups are shown in figures 2A–C. No significant differences were found at DBS. LF/HF (fig. 2A) showed the defined differences with significantly higher values in the high-LF/HF group compared with the low-LF/HF group. Prehydration did not affect the ratio in either group. Individual values of high-LF/HF patients spread in a wide range. Prospective LF (fig. 2B) and HF (fig. 2C) differed significantly with higher LF and lower HF in the high-LF/HF group. These significant differences were still present after prehydration. The variance increased especially in the high-LF/HF group after prehydration.

Interestingly, two patients who experienced a remarkable decrease in LF/HF ratio and LF as well as an increase in HF after prehydration (P3: LF/HF = 5.66 → 1.94, LF = 85% → 66%, HF = 15% → 34%; P14: LF/HF = 2.70 → 0.61, LF = 73% → 38%, HF = 27% → 62%) showed only a moderate decrease in SBP after SAB (patient 3: 140 mmHg → 97 mmHg; patient 14: 125 mmHg → 108 mmHg).

Discussion

Heart rate variability was analyzed in women scheduled to undergo elective cesarean delivery in SAB perioperatively. Because no data were present, first, differences in HRV parameters were studied retrospectively. Depending on the degree of hypotension after SAB, patients were classified into one of three groups. HRV analysis before prehydration and SAB showed significant differences depending on the hypotension after SAB. Patients in whom moderate hypotension developed

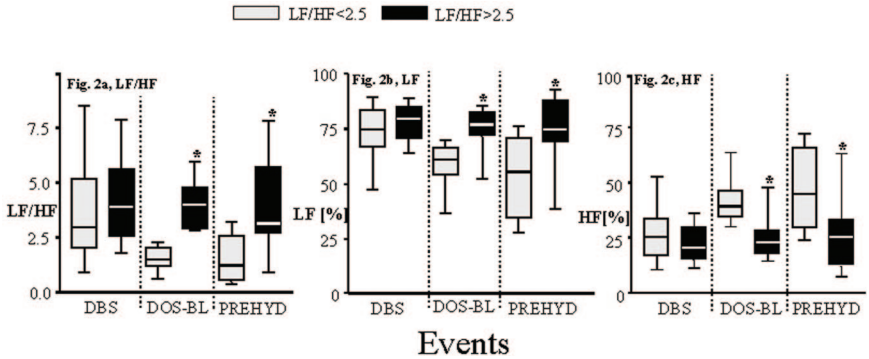

Fig. 2. Prospective heart rate variability analysis. (*A*) Low frequency (LF)/high-frequency (HF) ratio; (*B*) LF in normalized units; (*C*) HF in normalized units. DBS = day before surgery; DOS-BL = day of surgery, baseline measurement before prehydration; LF/HF < 2.5 = patients assigned by LF/HF < 2.5; LF/HF > 2.5 = patients assigned by LF/HF > 2.5; Prehyd = prehydration with 500 ml hydroxyethyl starch 6%/130/0.4. Data are presented as median, 25th/75th percentiles, and range. * *P* < 0.05.

showed a significantly higher sympathetic activity at baseline, which was significantly reduced by prehydration. Severe hypotension after SAB correlated with an increased sympathetic outflow before anesthesia, and prehydration did not decrease sympathetic drive. Second, based on these preliminary data, two groups were defined, with either high or low LF/HF. The risk of hypotension was tested prospectively. Patients with an LF/HF ratio greater than 2.5 at DOS before prehydration were at high risk of hypotension after SAB.

Interpretation of HRV is an ongoing discussion. There is strong evidence that the LF/HF ratio represents the balance of sympathetic and parasympathetic parts of the ANS, whereas LF reflects sympathetic and parasympathetic influences, and HF represents vagal nerve activity.[12,16,18–21] Nevertheless, interpretation of LF is controversial. Hopf *et al.*[22] investigated changes of HRV due to EDA. Because LF did not decrease significantly after epidural block, the authors concluded that LF is unlikely to reflect cardiac sympathetic modulation in humans. Interestingly, HR increased significantly as a result of a tilt maneuver, which is a strong indicator of incomplete sympathetic block; therefore, LF was unlikely to decrease. In addition, the authors demonstrated a significant decrease of the LF/HF ratio, reflecting a shift of the ANS toward the parasympathetic regulation due to EDA. Others investigated different influences on ANS regulation, isoflurane anesthesia, and hemorrhage.[23] Definite changes of HRV due to the interventions were not found. Interpreting these data together with our own results, we conclude that LF mainly reflects the sympathetic outflow of ANS.

In a recent observational study, it was demonstrated that hemodynamic instability during hemodialysis in terms of hypotension was associated with differences in HRV before hemodialysis.[24] The LF/HF ratio was significantly lower in patients who experienced hypotension. Hypotension and bradycardia during central neuroaxial block is mainly a result of decreased systemic vascular resistance, caused by inhibition of preganglionic sympathetic fibers and sympathetic innervation of the heart.[15] A preliminary study reported on the changes of parasympathetic and sympathetic activity after EDA for alleviating labor pain in 13 women.[25] Wavelet transformation of HRV and blood pressure variability was analyzed for estimating changes of the ANS due to EDA. A significant decrease in the sympathetic drive and a significant increase in the parasympathetic drive of the ANS were demonstrated. Our retrospective findings indicate that women who experienced hypotension after SAB had higher sympathetic activity preoperatively. In addition, a high sympathetic outflow decreased in moderate group patients after prehydration, reflected in a decreased LF/HF ratio and LF. Prehydration attenuated sympathetic outflow before SAB; sympathetic block due to SAB was accompanied by only moderate hypotension. The sympathetic outflow of the severe group was comparable to that of the moderate group at DOS-BL. However, in contrast to the moderate group, prehydration had no effects on LF/HF ratio or LF. Sympathetic outflow remained increased, and sympatholysis due to SAB was accompanied by severe hypotension. We conclude that a high sympathetic outflow before SAB can be attenuated by prehydration in some patients, preventing severe hypotension. In patients who did not respond adequately to a single infusion of 500 ml hydroxyethyl starch, severe hypotension occurred. One may speculate that further prehydration is necessary in these patients. These preliminary findings were confirmed prospectively. A high LF/HF ratio predicted hypotension in another group of patients. Two patients demonstrated a high LF/HF ratio at DOS-BL and a remarkable decrease after prehydration. These changes were reflected by changes in LF. Both women had only a moderate decrease in SBP after SAB. Data from these two patients were comparable to changes of the moderate group. The greater variance of HRV parameters after prehydration compared with DOS-BL underline our findings that prehydration provoked changes in HRV that differ between patients. These effects may explain hemodynamic reactions after SAB. Differences in the need for vasopressors were found in retrospective as well as prospective patients. The more pronounced the decrease of SBP was, the more vasopressor boluses were needed to restore it. In addition, severe hypotension occurred more quickly than moderate or mild hypotension. We conclude that changes of the ANS due to SAB are more rapid and pronounced compared with those due to EDA. Rapid and pronounced changes of ANS regulation are more likely to result in significant changes in hemodynamic parameters. The data from both studies support our findings in patients scheduled to undergo SAB.

Women with preeclampsia, eclampsia, or gestational hypertension are thought to develop a higher level of sympathetic tone.[26] It might be contradictory that these patients tolerate EDA or SAB well.[27] Nevertheless, harmful side effects have been reported.[28] Hemodynamic adverse effects due to SAB are more pronounced compared with EDA in preeclamptic patients.[29] In at least 40% of patients receiving SAB for elective cesarean delivery, hypotension is observed.[30] Changes of the ANS due to pregnancy and further shifts due to preeclampsia or gestational hypertension have been thoroughly investigated in the past years. Sympathetic outflow is increased in healthy pregnant women, pregnant women with preeclampsia, and pregnant women hospitalized for other complications.[4–6] Others have demonstrated an additional increase of sympathetic outflow in preeclamptic women compared with healthy pregnant women.[31] We conclude that in the current literature, there is consensus in terms of increased sympathetic control in pregnant women compared with nonpreg-

nant women. Further changes due to preeclampsia or gestational hypertension are still controversially discussed. With respect to our own data, we summarize that ANS regulation is generally modified during pregnancy, with specific differences directly before elective cesarean delivery. These differences may predict hypotension after SAB.

It has been suggested that hypotension can be minimized or prevented by administration of intravenous fluids, positioning of the patient using left uterine displacement, and by the prophylactic and/or therapeutic use of vasopressors.[3,32] Of these, only the use of left uterine displacement seems to be an accepted practice by obstetric anesthesiologists.[30,33–35] Despite numerous articles discussing fluid loading and the prophylactic use of vasopressors, this issue is still debated. Hypotension is observed in at least 40% of patients after fluid loading, and negative side effects, such as volume overload, anaphylaxis, and coagulopathy, although exceedingly rare, must be considered.[30] Of note, prophylactic vasopressor therapy has not proved to be effective. The effect of 30 mg ephedrine was investigated in patients undergoing elective cesarean delivery during SAB. In 35% of the patients, hypotension was not prevented, and 50% experienced a reactive hypertension.[36] A review of the literature shows that some patients benefit from these therapeutic interventions, others do not, and each intervention may have important side effects. In our study, it was conceivable that mild group patients were at risk of hypertension and volume overload. Moderate and severe group patients with comparably high baseline levels of sympathetic drive responded differently to prehydration. In the moderate group, volume led to a reduction of sympathetic drive. These women were probably treated adequately because volume decreased sympathetic tone and minimized the incidence of severe hypotension after SAB. These changes were also observed in two individual patients in the prospective group with a LF/HF greater than 2.5, supporting the findings in the moderate group. Severe group patients might have benefitted from even more prophylactic prehydration or vasopressor therapy before SAB, with a minimum risk of volume overload or hypertension. However, because sympathetic drive was not reduced after prehydration, the total volume administrated may have still been inadequate. HRV analysis may be a tool to optimize routine anesthetic care in these patients. Further studies are necessary to answer the question of whether a HRV-based prophylactic treatment can improve hemodynamic stability.

Interestingly, differences in HRV were only present at DOS. No significant differences were found at DBS between retrospective groups or prospective groups. At this time, the LF/HF of the mild group tended to be lower compared with the moderate and severe groups, but differences were not statistically significant. In addition, LF, reflecting sympathetic influences of the ANS, seemed to be higher in moderate and severe group patients at DBS, too. HF, an indicator of parasympathetic control, was comparable in all three retrospective groups. Differences at DBS between the two prospective groups were comparable to differences between retrospective groups. The reasons for differences between DBS and DOS remain speculative. The *non per os* state at least 6–10 h before surgery may result in individual changes of the ANS. Stress and anxiety are known to affect HRV.[37] Because no psychological tests were performed before the operation at DBS and at DOS we can only speculate on the influences of these factors. Besides these reasons, the ANS may change on a very short-term basis. Therefore, we conclude that HRV analysis to predict hemodynamic changes after SAB should be performed close to the time of regional anesthesia.

Some limitations of our study should be noted. Artifacts during HRV data recording, *e.g.*, due to movements of the patient, 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 SAB. No measurement had to be deleted completely.

Measurement of HRV is clinically simple, although the underlying mathematical background is somewhat complex. Measurements are based on normal electrocardiographic recordings, and commercial tools offer a computerized interpretation. Artifacts can be easily and reliably eliminated based on computerized artifact detection. The technique could be easily implemented in routine clinical monitoring, and physicians could be trained for interpretation in a reasonable amount of time. HRV measurements would obtain important prognostic information about SAB for elective cesarean delivery. Our data suggest a correlation between increased sympathetic drive indicated by HRV before SAB and hypotension in the course of regional anesthesia. Results of a preliminary retrospective study design were confirmed prospectively in another group of women. The higher the sympathetic drive before SAB was, the more pronounced hypotension due to sympatholysis was. Some patients showed a decrease of LF/HF and LF due to prehydration resulting in an attenuation of hypotension. Therefore, HRV analysis before SAB may be suitable to detect patients who are at risk of hypotension, and HRV may predict patients in whom prehydration would be beneficial. Further studies are necessary to investigate HRV as a diagnostic and therapeutic tool for patients at risk.

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