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# Chapter 8

Preoperative short-term pulse rate variability as a predictive tool for intraoperative hypotension: a pilot study

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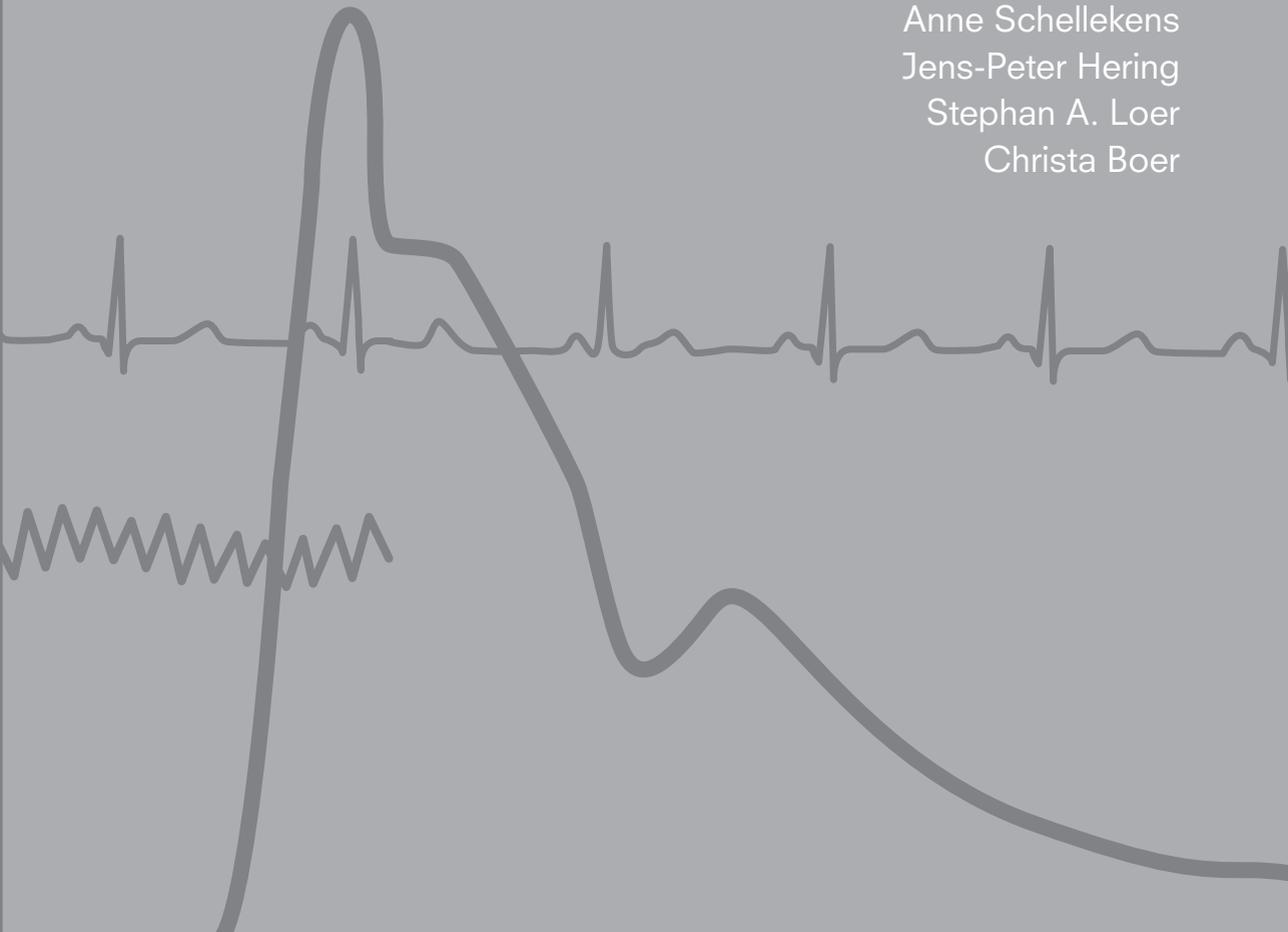
# ABSTRACT

**Introduction:** Depressed preoperative autonomic function as measured by short-term heart rate variability (HRV) has been shown to be predictive for bradycardia and hypotension in patients under general anaesthesia. However, as perioperative HRV measurements with an electrocardiogram are easily affected by movement artefacts or electrical interference during the surgical procedure, short-term pulse rate variability (PRV) derived from continuous arterial blood pressure measurements may be a valuable alternative. In this study we investigated whether PRV assessed in the preoperative period is predictive of haemodynamic changes in patients undergoing anaesthesia, and further assessed whether there are distinct associations between the PRV and haemodynamic parameters in subgroups of patients exposed to local or general anaesthesia.

**Methods:** In this prospective observational study, interbeat intervals and non-invasive blood pressure waveforms were recorded simultaneously in the preoperative period and during anaesthesia, in 64 patients undergoing local or general anaesthesia for eye, ENT, reconstructive, orthopaedic, urologic or breast cancer surgery. The low frequency (LF) and high frequency (HF) power domains were subtracted from a preoperative 5-minute PRV measurement using spectral analysis. The predictive value of the LF+HF components with a cut-off at 500 ms$^2$ for the intraoperative lowest heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), were evaluated using a receiver operating characteristics (ROC) curve and univariate regression analysis.

**Results:** While preoperative heart rate and blood pressure were similar among groups, patients exposed to general anaesthesia were younger (60 ± 15 vs 73 ± 8 years; P<0.001) and showed a higher total PRV power (2273 (987-3494) vs 1172 (627-2180) ms$^2$; P=0.03), than patients undergoing local anaesthesia, respectively. The drop in systolic and diastolic blood pressure after anaesthesia induction was more profound in patients undergoing general anaesthesia. The area under the ROC curve for the predictive value of a LF+HF ≤ 500 ms$^2$ for the lowest heart rate, SBP and DBP, was 0.65, 0.62 and 0.54, respectively. A LF+HF greater than 500 ms$^2$ was associated with a lower heart rate in patients undergoing local anaesthesia (r=-0.34;

P=0.03). In patients exposed to general anaesthesia, a LF+HF > 500 ms$^2$ was predictive of a higher SBP (r=0.49; P=0.015) or higher DBP (r=0.57; P=0.003) during anaesthesia.

**Conclusions:** A LF+HF power ≤ 500 ms$^2$ assessed in the preoperative period is predictive of a higher heart rate as measured during local anaesthesia, and a lower blood pressure during general anaesthesia. Our data show that preoperative assessment of short-term PRV may be valuable in the prediction of hypotension during general anaesthesia.

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# INTRODUCTION

Intraoperative hypotension is associated with unfavourable outcomes [1-3]. Identification of patients at increased risk of development of intraoperative hypotension may contribute to the prevention of perioperative complications and improvement of perioperative recovery.

Blood pressure regulation is partly controlled by the autonomic nervous system. Traditionally, the diagnosis of autonomic dysfunction requires a battery of tests for parasympathetic and sympathetic function [4-6]. This battery of tests is however cumbersome to enrol in the preoperative setting due to the time required. Increasing evidence shows that these autonomic function tests may be replaced by measurements of short-term heart rate or pulse rate variability [7-10]. It was shown that a decline in heart rate variability (HRV), which is largely controlled by the parasympathetic and sympathetic nervous system, is predictive for perioperative cardiovascular events and intensive care outcomes [8-10]. However, most of these investigations used long-term HRV to predict haemodynamic alterations, which requires a registration of heart rate over a period of about 30 minutes [8-9] up to 24 hours; this is unfeasible to implement in the perioperative setting. Nevertheless, recent publications show that short-term HRV analysis over a period of 5 minutes may be alternatively used to assess autonomic function in patients, and to predict haemodynamic alterations in the intraoperative period [11-14].

In the study of Hanss et al., preoperative total power of heart rate variability was predictive for low blood pressure and bradycardia after induction of anaesthesia in high-risk patients [15]. In particular, patients were selected with a high Cardiac Risk Index, and all received cardiovascular medication. From this study it was revealed that a total HRV power derived from the summation of the very low frequency (VLF), low frequency (LF) and high frequency (HF) domain of less than 500 ms$^2$ was predictive for the development of hypotension and/or bradycardia [15]. However, as the meaning of the VLF component for the assessment of autonomic function is not clear [16], the summation of the LF and HF power components might be preferred over the total power as used by Hanss et al. [15].

We previously showed that pulse rate variability (PRV) derived from non-invasive continuous arterial blood pressure measurements are a valuable alternative for HRV measurements [17-18]. The robustness of PRV measurements in the perioperative setting is higher than for HRV measurements, as the electrocardiogram is sensitive to movement ar-

tefacts and electrical interference due to diathermy [17]. In the present study we investigated whether the LF+HF power domain from the PRV is predictive for haemodynamic changes in patients undergoing anaesthesia, and further evaluated whether there are distinct associations between the PRV and haemodynamic parameters in subgroups of patients exposed to local or general anaesthesia.

## METHODS

### Patient population

In this observational clinical study, pulse rate variability and blood pressure measurements were acquired in 83 patients undergoing elective eye, ENT, reconstructive, orthopaedic, urologic or breast cancer surgery under local or general anaesthesia in the Westfries Gasthuis (Hoorn, the Netherlands). Only surgical procedures with no influence on the haemodynamic situation of the patient (expectation of no blood loss) were chosen. Patients aged 18-85 years were recruited the day of operation. The study was approved by the local Human Subjects Committee, and informed consent was waived. Patients were excluded when they revealed cardiac arrhythmias, including atrial fibrillation.

### Study design

Five-minute pulse rate variability (PRV) measurements were acquired before surgery when the patient was admitted to the preoperative holding. Participants were connected to a non-invasive continuous finger arterial blood pressure measurement device (Nexfin HD, Edwards Life Sciences, the Netherlands) to obtain interbeat intervals and continuous blood pressure waveforms.

Furthermore, interbeat intervals, systolic and diastolic blood pressure were recorded for at least 15 minutes after the induction of anaesthesia to analyse the predictive value of short-term preoperative pulse rate variability and alterations in intraoperative heart rate and blood pressure. During the perioperative period, the starting heart rate, systolic and diastolic blood pressure and the lowest heart rate, systolic and diastolic blood pressure values were recorded. Other data included patient demographics and surgical characteristics.

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**Anaesthesia techniques**

Local anaesthesia implied topical, retrobulbar or parabulbar anaesthesia (all patients in the subgroup of local anaesthesia underwent eye surgery).

General anaesthesia was induced with propofol 1.5-2.5 mg/kg in all patients (elective eye, ENT, reconstructive, orthopaedic, urologic or breast cancer surgery). Patients who underwent general anaesthesia were endotracheal intubated or received a laryngeal mask airway. Before intubation patients received a bolus of remifentanil (0.5-0.75 µg/kg) or sufentanil (0.15-0.2 µg/kg), thereafter a perfusion of 0.25-0.4 µg/kg per minute remifentanil or an extra bolus of sufentanil. For endotracheal intubation rocuronium 0.25-0.3 mg/kg or succinylcholine 1 mg/kg was given. Ventilation started at volume control (PEEP 5 mmHg, tidal volume 6 ml/kg lean body mass, 15 rates/minute).

**Pulse rate variability analysis and the definition of autonomic dysfunction**

The interbeat intervals were recorded with a sample rate of 200 Hz. Data were visually inspected for premature or irregular beats and movement artefacts. Data were analysed by spectral analysis using the Fast Fourier Transformation with commercially available software (Kubios HRV version 2.0, University of Kuopio, Finland) [19].

Pulse rate variation analysis included the assessment of mean interbeat intervals (mean NN), the standard deviation of normal-to-normal (i.e. sinus rhythm) interbeat intervals (SDNN) and the root mean square of successive differences between normal-to-normal interbeat intervals (RMSSD). Furthermore, the very low (VLF; 0.0-0.04 Hz), low (LF; 0.04-0.12 Hz) and high frequency band (HF; 0.12-0.4 Hz) and the total spectral power in the preoperative period were determined from interbeat intervals. The Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology discussed the value of the VLF component in short-term HRV, which they found ''dubious'' [16]. Therefore, we used the summation of LF and HF as representative of the two branches (sympathetic and parasympathetic control of heart rate) of the autonomous nervous system to diagnose autonomic dysfunction. The summation of the LF and HF power spectra with a cut-off value of 500 $ms^2$ was used as predictor for low heart rate, SBP and DBP during anaesthesia.

**Statistical analysis**

Data were analysed using SPSS version 22.0 (IBM, New York, USA). Data were expressed as mean ± standard deviation, median with interquartile range or frequencies. Baseline differences between patients

undergoing local or general anaesthesia were analysed using a Student's T-test for normally distributed data, a Mann-Whitney U test for ordinal data and a Chi-square test for categorised data. Within-patient comparisons were tested using a paired T-test. LF+HF was categorised as lower or higher than 500 ms$^2$ to assess specificity and sensitivity for the detection of the lowest heart rate, SBP or DBP value during anaesthesia induction using a receiver operating characteristics (ROC) curve. For univariate linear regression analysis, the LF+HF power domain was coded as a dummy variable, where 0 indicated a LF+HF $\leq$ 500 ms$^2$ and 1 a LF+HF > 500 ms$^2$. A P-value of <0.05 was considered as statistically significant.

## RESULTS

**Study population**

The total study population included 83 patients undergoing elective surgery. After exclusion of patients with atrial fibrillation during Nexfin measurements (n=8) and technical problems (n=11), 64 patients were eligible for data analysis. Patients undergoing local anaesthesia (n=40) were older, suffered more frequently from hypertension and coronary artery disease, and revealed a lower VLF, LF and HF power spectrum in the preoperative period than patients undergoing general anaesthesia (n=24; see Table 1).

Figure 1 shows the preoperative heart rate (HR; panel A), systolic blood pressure (SBP; panel B) and diastolic blood pressure (DBP; panel B) at rest in patients undergoing local and general anaesthesia. Baseline heart rate and blood pressure were not different among groups. Panels C, D and E show the association of the preoperative LF+HF power with heart rate, SBP and DBP values at rest, respectively. There was no correlation between LF+HF with heart rate (r=-0.16; P=0.21), SBP (r=-0.03; P=0.79) or DBP values (r=0.10; P=0.42) before anaesthesia induction.

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Table 1.
Description of the preoperative characteristics of the study population

| Patient demographics | Local anaesthesia | General anaesthesia | P-value |
|---|---|---|---|
| N | 40 | 24 | |
| Age (years) | 73 ± 8 | 60 ± 15 | 0.001 |
| Gender (males; n/%) | 19/47.5 | 13/54.2 | 0.61 |
| BMI (kg/m$^2$) | 26.6 ± 4.8 | 25.1 ± 2.8 | 0.19 |
| Type II diabetes mellitus (n/%) | 9/22.5 | 2/8.3 | 0.15 |
| Hypertension (n/%) | 20/50.0 | 5/20.8 | 0.02 |
| Coronary artery disease (n/%) | 10/25.0 | 0/0 | 0.01 |
| COPD (n/%) | 4/10.0 | 3/12.5 | 0.76 |
| Baseline PRV parameters | Local anaesthesia | General anaesthesia | P-value |
| Mean interbeat interval (ms) | 875 ± 130 | 833±121 | 0.20 |
| SD interbeat interval (ms) | 42 ± 19 | 53 ± 27 | 0.07 |
| Root mean squared successive SD (ms) | 29.7 ± 23.0 | 31.4 ± 15.8 | 0.76 |
| VLF power (ms$^2$) | 597 (284–994) | 899 (508-1874) | 0.09 |
| LF power (ms$^2$) | 253 (133-569) | 620 (202-1028) | 0.01 |
| HF power (ms$^2$) | 207 (114-477) | 327 (147-1009) | 0.19 |
| Total power (ms$^2$) | 1172 (627-2180) | 2273 (987-3494) | 0.03 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation; VLF, very low frequency; LF, low frequency; HF, high frequency. Data are expressed as mean ± standard deviation, median with interquartile range or frequencies.

Figure 1.
Baseline values for heart rate (HR; panel A), systolic and diastolic blood pressure (SBP and DBP; panel B), and the correlation between the summation of the pulse rate variability low and high frequency (LF+HF) power domains with heart rate (panel C), SBP (panel D) and DBP (panel E) in the preoperative period. Data represent mean ± SD.
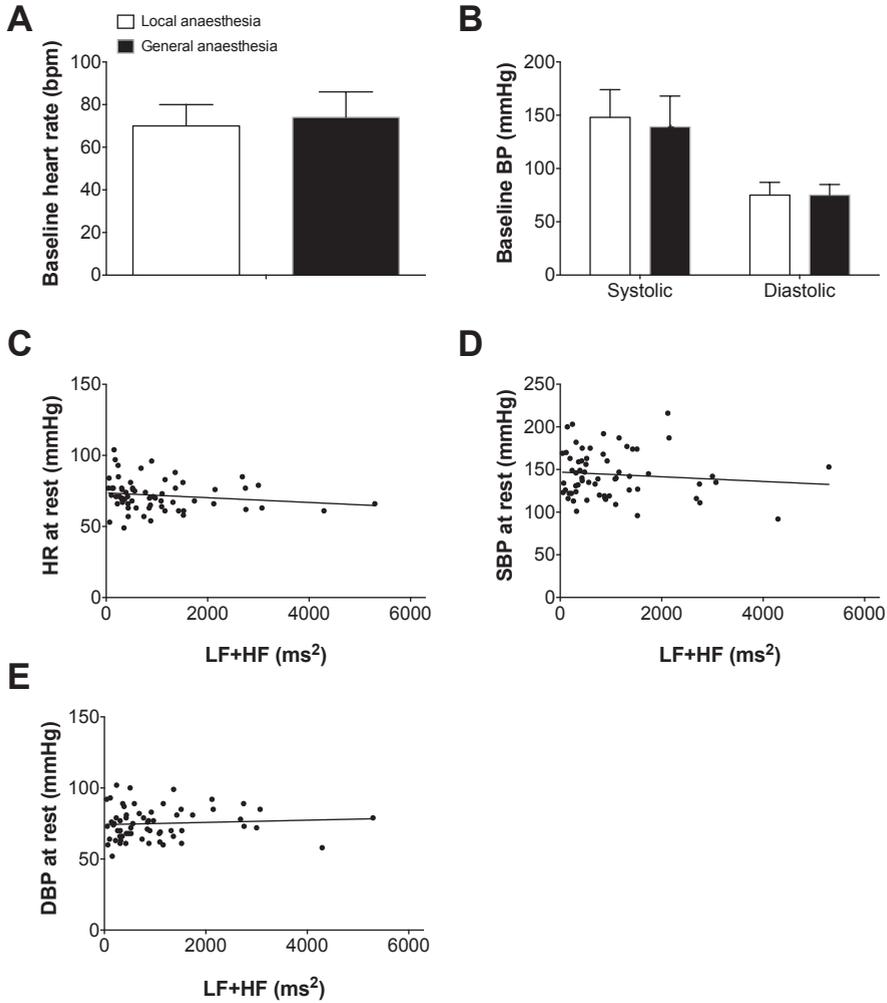
Figure 2 shows the difference in heart rate (panel A), systolic blood pressure (panel B) and diastolic blood pressure (panel C) between the start of anaesthesia induction and the lowest value during intraoperative measurement. Both local anaesthesia and general anaesthesia induction were associated with a reduction in heart rate. The drop in systolic and diastolic blood pressure was the most profound in patients undergoing general anaesthesia.

Figure 2.
Difference between (HR; panel A), systolic blood pressure (SBP; panel B) and diastolic blood pressure (DBP; panel C) at the start of anaesthesia induction and the lowest measured value for patients undergoing local or general anaesthesia. Data represent mean ± SD.
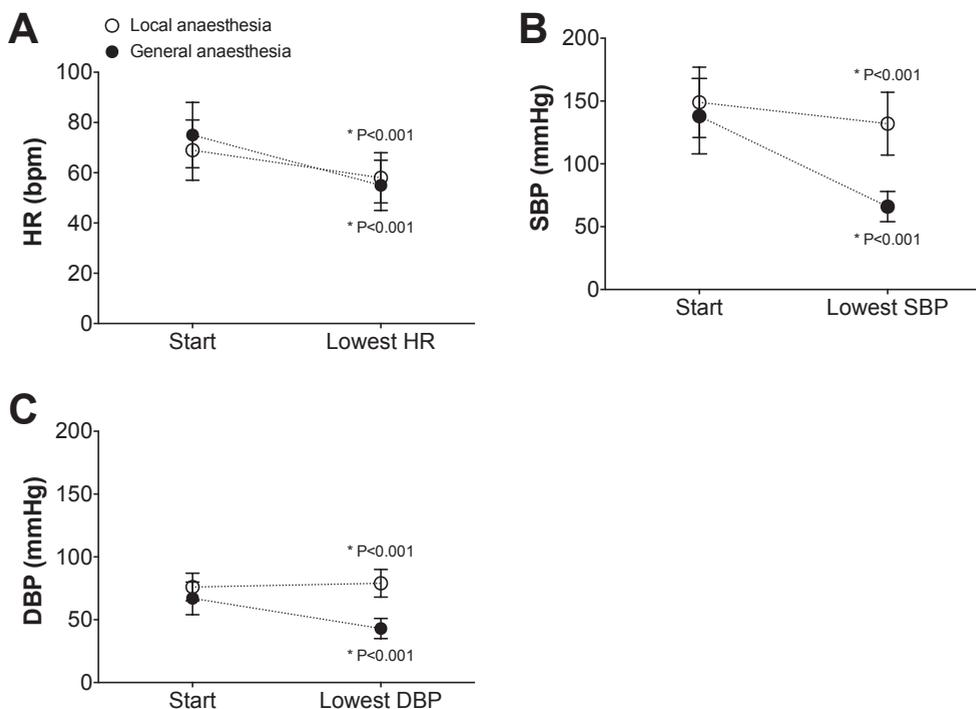
In order to assess the sensitivity and specificity of the LF+HF power domain of the pulse rate variability, a receiver operating characteristics (ROC) curve was obtained with a LF+HF value of 500 ms$^2$ as cut-off value to predict the lowest heart rate, SBP or DBP value during anaesthesia induction (Figure 3).

Table 2 shows the area under the curve and the specificity and sensitivity for the use of a threshold value of LF+HF ≤ 500 ms$^2$ to predict a low heart rate or blood pressure during anaesthesia induction.

Figure 3.
Receiver operating characteristics (ROC) curve for the use of the LF+HF power ≤ 500 ms$^2$ for the lowest value of heart rate (black line), systolic blood pressure (SBP; dashed line) or diastolic blood pressure (DBP; dotted line). The area under the curve and sensitivity and specificity for the three ROC curves is shown in Table 2.
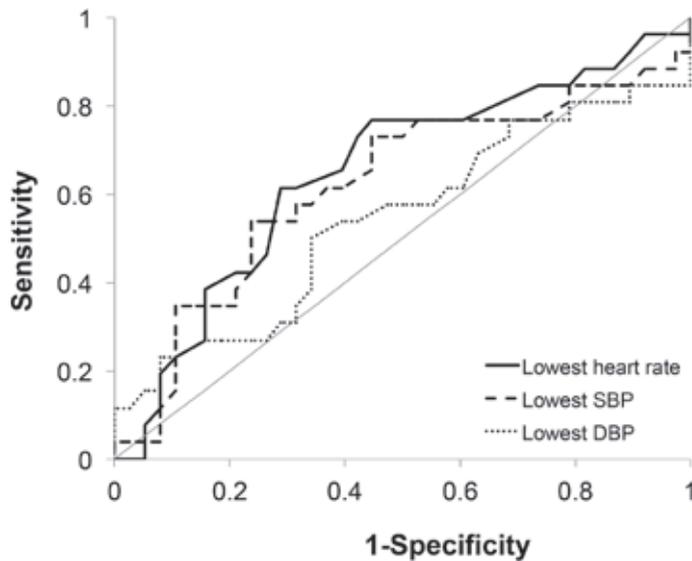


Table 2.
Parameters of the Receiver Operating Characteristics (ROC) curve for the use of a preoperative LF+HF threshold of ≤ 500 ms2 to predict a low heart rate or blood pressure during anaesthesia induction.

| Variable | AUC | Sensitivity | Specificity |
| --- | --- | --- | --- |
| **Lowest heart rate (bpm)** | 0.65 | 0.77 | 0.55 |
| **Lowest systolic blood pressure (mmHg)** | 0.62 | 0.73 | 0.55 |
| **Lowest diastolic blood pressure (mmHg)** | 0.54 | 0.58 | 0.52 |

LF, low frequency domain in the pulse rate variability; HF, high frequency domain in the pulse rate variability; AUC, area under the curve; SBP, systolic blood pressure, DBP, diastolic blood pressure.

Using univariate linear regression analysis, the association between the LF+HF power domain and the lowest heart rate, SBP and DBP values during anaesthesia induction were assessed for the total study population and subgroups of patients exposed to local or general anaesthesia (Table 3).

In the total population, we found a weak, but statistically significant association between the LF+HF power and the lowest heart rate. The relationship between the LF+HF power with haemodynamic variables during anaesthesia induction became more distinct when patients were categorised in the subgroups local or general anaesthesia. A LF+HF power > 500 ms$^2$ was associated with a lower heart rate in patients exposed to local anaesthesia, while in patients exposed to general anaesthesia a LF+HF power > 500 ms$^2$ was associated with higher systolic and diastolic blood pressure values (Table 3).

Table 3.
Univariate regression analysis of the association between the LF+HF power spectrum categorised as a dummy variable (≤ 500 ms$^2$ or >500 ms$^2$) with the lowest heart rate, SBP and DBP values during anaesthesia induction for the total study population and for subgroups of patients exposed to local or general anaesthesia.

| Variable | Beta | t | P-value |
|---|---|---|---|
| **Total population** | | | |
| Lowest heart rate (bpm) | -0.25 | -2.06 | 0.04 |
| Lowest systolic blood pressure (mmHg) | -0.21 | -1.65 | 0.10 |
| Lowest diastolic blood pressure (mmHg) | -0.07 | -0.59 | 0.56 |
| **Local anaesthesia** | | | |
| Lowest heart rate (bpm) | -0.34 | -2.24 | 0.03 |
| Lowest systolic blood pressure (mmHg) | -0.12 | -0.73 | 0.47 |
| Lowest diastolic blood pressure (mmHg) | 0.23 | 0.14 | 0.89 |
| **General anaesthesia** | | | |
| Lowest heart rate (bpm) | -0.21 | -0.10 | 0.92 |
| Lowest systolic blood pressure (mmHg) | 0.49 | 2.65 | 0.015 |
| Lowest diastolic blood pressure (mmHg) | 0.57 | 3.29 | 0.003 |

# DISCUSSION

In the present study we show that short-term pulse rate variability (PRV) derived from a 5-minute non-invasive arterial blood pressure measurement recording in the preoperative period is predictive of low blood pressure after induction of general anaesthesia. Moreover, a preoperative LF+HF power ≤ 500 ms$^2$ is predictive of a higher heart rate value as measured during local anaesthesia. Our data show that short-term PRV measurements in the preoperative period may be useful in the recognition of patients at risk for hypotension in the intraoperative period.

**Interpretation of results**

There are a limited number of publications showing that a depressed autonomic function as assessed by short-term heart rate variability (HRV) analysis is predictive for perioperative haemodynamic changes. In 2007, Fujiwara and colleagues published three different papers focusing on the association of lack of entropy in the R-R interval and haemodynamic alterations during anaesthesia [20-22]. In particular, they found that a low entropy in the R-R interval before the start of propofol anaesthesia was related to a greater fluctuation in blood pressure and the prevalence of hypotension defined as a systolic blood pressure below 80 mmHg in non-diabetic subjects with or without hypotension [20, 22]. Moreover, they showed that R-R entropy was predictive for intraoperative blood pressure fluctuations, whereas the LF/HF ratio as marker for the sympatho-vagal balance showed a better relation with heart rate fluctuations [21]. In a retrospective study, Hanss et al. subtracted the LF/HF ratio from 5-minute R-R recordings and related these ratios to three predefined lowest systolic blood pressure categories that were measured during the induction of spinal anaesthesia for caesarean delivery [12]. Women with the most severe levels of hypotension showed the highest preoperative LF/HF ratios. However, this study was limited to frequency analyses, rather than an evaluation of the predictive value of LF/HF ratio for perioperative haemodynamic alterations. Moreover, since pregnancy influences autonomic function, a subsequent investigation focused on patients undergoing prostate gland brachytherapy. They demonstrated again that an LF/HF ratio exceeding 2.5 showed a sensitivity and specificity of 85% to predict a 20% decrease in baseline SBP after the induction of spinal anaesthesia [13]. The investigators also showed that prophylactic treatment using vasopressor therapy or fluid infusion during spinal anaesthesia guided by the LF/HF ratio resulted in prevention of a severe blood pressure drop in patients with a predetermined risk of

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hypotension [23]. In a recent study, Raimondi et al. further showed that the predictive value of the LF/HF ratio for blood pressure drops during spinal anaesthesia also applied to a group of healthy subjects [24]. All afore-mentioned studies suggest that preoperative autonomic function assessment using the LF/HF ratio is of value in the recognition of patients at risk for severe haemodynamic alterations during neuraxial or general anaesthesia.

In subsequent studies, it was however stated that the LF/HF ratio has a low predictive value for bradycardia and hypotension in patients with underlying cardiovascular disease [15], and is influenced by physiological parameters like respiration and heart rate [25]. Alternatively, the total power of VLF+LF+HF may be used to predict haemodynamic alterations during anaesthesia procedures [15].

Hanss et al. showed superiority for the total power of the HRV below 500 $ms^2$/Hz as predictor for intraoperative hypertension than for the LF/HF ratio, in particular with respect to the specificity of the ROC curve [15]. The present study was in three aspects different from the study by Hanss et al. Firstly, we used the variation in pulse rate as assessed by a non-invasive continuous arterial blood pressure measurement device as alterative for HRV, as this method is less sensitive for movement artefacts and electrical interference. Secondly, the summation of LF and HF was used instead of the total power to predict a low heart rate or blood pressure during anaesthesia induction. Thirdly, while Hanss et al. included patients with cardiovascular diseases [15], we focused on a mixed patient population undergoing elective eye, ENT, reconstructive, orthopaedic, urologic or breast cancer surgery. Hanss et al. found a similar sensitivity and specificity for the predictive value of the total power for the lowest heart rate and blood pressure value. In contrast, the LF+HF had the best predictive value for a higher heart rate in patients undergoing local anaesthesia, while the predictive value of the LF+HF in patients undergoing general anaesthesia was the most abundant for systolic and diastolic blood pressure. The influence of general anaesthesia induction and subsequent mechanical ventilation may be explanatory for these distinct relationships.

**Methodological considerations**

In the present study we focused on the lowest heart rate and blood pressure during anaesthesia. Others have shown that it might have been interesting to perform perioperative PRV analyses as an indicator of haemodynamic variation during anaesthesia. In particular, it has been shown that HRV may reflect anaesthesia depth, and alterations in the HRV may

provide complementary information to the Bispectral Index (BIS) regarding the differential effects of intraoperative interventions [26]. Moreover, alterations in the HRV may be predictive for postoperative myocardial ischemia and prolonged intensive care unit stay in patients undergoing cardiac surgery [27-28]. In abdominal aortic surgery, the HRV measured on the first postoperative day was predictive for the total length of hospital stay [29].

Our study is limited by the small group size in the category of patients undergoing general anaesthesia. Moreover, PRV measurements are an indirect indicator of autonomic activity, and cannot replace the total of autonomic function tests as proposed by Ewing et al. [4-5]. There were artefacts in the non-invasive continuous arterial blood pressure measurement recordings, but we performed off-line analysis and elimination of these artefacts. Unfortunately, we have no data available on the use of vasopressor therapy or fluid infusion to treat anaesthesia-induced changes in heart rate and blood pressure. Furthermore, because of the small sample size we did not include comorbidities like diabetes mellitus or vascular disease in our prediction models. It should be noted that these treatment modalities or comorbidities might have been of influence on the lowest recorded values for heart rate or blood pressure.

**Conclusions**

The present study shows that it is feasible to perform a short-term PRV analysis, and to subsequently predict which patients are at risk for hypotension during the induction of general anaesthesia. However, as the spectral analyses using the Fast Fourier Transformation can only be performed in an off-line mode following surgery, new devices should incorporate on-line analyses of PRV or HRV to broaden the implementation of autonomic function assessment in the perioperative setting. The use of automated devices for autonomic function may contribute to improved recognition of patients at risk of intraoperative hypotension during preoperative risk assessment.

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