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Does heart rate variability predict hypotension and bradycardia after induction of general anaesthesia in high risk cardiovascular patients?*

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Summary

This study investigated whether heart rate variability predicts haemodynamic events in high risk patients, defined as Revised Cardiac Risk Index score = 3, scheduled for general anaesthesia. Fifty patients underwent baseline measurement of heart rate variability and were then assigned according to haemodynamic events (hypotension or bradycardia) after standardised induction of anaesthesia into 'stable' (n = 39) and 'unstable' patients (n = 11). Unstable patients had significantly lower baseline total power. Total power < 500 $ms^2.Hz^{-1}$ was associated with high sensitivity and specificity for the prediction of hypotension or bradycardia. Prospectively, 29 patients with total power < 500 $ms^2.Hz^{-1}$ were compared with 21 patients with total power > 500 $ms^2.Hz^{-1}$. Differences were found in the lowest mean arterial pressure and heart rate after induction of anaesthesia. We conclude that the pre-operative total power of heart rate variability in high risk patients may indicate the occurrence of haemodynamic events with high sensitivity and specificity. Heart rate variability may be a suitable tool to identify patients at high risk of a haemodynamic event and may be used to indicate need for intensive monitoring and, perhaps, prophylactic treatment.

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Patients with underlying cardiovascular disease are at high risk of peri-operative cardiovascular events and death [1, 2]. Adverse events during anaesthesia and surgery may increase the risk further in this patient population. Specifically, following induction of general anaesthesia, hypotension and bradycardia are often observed and may lead to insufficient organ perfusion and ischaemic events [3–5].

Haemodynamic parameters are controlled, to some extent, by the autonomic nervous system. The activity of the autonomic nervous system is reflected in the heart rate variability (HRV) [6–8]. Several authors have demonstrated depressed long-term HRV in patients with underlying cardiovascular disease [9–11] and HRV has proved to be highly predictive for cardiovascular morbidity and mortality in these patients [12–14]. Recently, short-term HRV analysis (5 min) has been shown to be a reliable tool to predict hypotension after spinal anaesthesia [15, 16]. The low to high frequency ratio (LF/HF) was demonstrated to be a highly sensitive parameter to predict hypotension [17] and LF/HF-guided prophylactic therapy was able to prevent hypotension [18]. Only preliminary data have been published on the incidence of hypotension or bradycardia after induction of general anaesthesia in patients with underlying autonomic dysfunction [19, 20]. A retrospective subgroup analysis of a small number of patients with diabetes demonstrated that pre-operative depression of sympathetic and parasympathetic activity was correlated with a significantly greater incidence of hypotension after induction of anaesthesia. However, these results were not confirmed prospectively.

This study was designed to investigate the predictive power of HRV in patients with underlying cardiovascular disease. We hypothesised that differences in pre-operative

HRV are present in patients with underlying cardiovascular disease, that these differences are associated with bradycardia or hypotension after induction of general anaesthesia, and that pre-operative HRV predicts the likelihood of these events.

Methods

With the approval of the Institutional Ethics Committee of the University-Hospital Schleswig-Holstein and written informed consent the study was performed in two parts. Firstly, patients were assigned to one of two groups depending on whether they had hypotension or bradycardia after induction of general anaesthesia. Secondly, a predictive model was built and confirmed prospectively in another group of patients.

One hundred patients (American Society of Anesthesiologists (ASA) physical status 3 or 4) were included in the trial. All patients were scheduled for major vascular or abdominal surgery under general anaesthesia. The patient's age, body weight, gender and underlying diseases were recorded. Inclusion criteria were evidence of high peri-operative cardiovascular risk based on the Revised Cardiac Risk Index (high risk surgery, history of coronary artery disease, history of congestive heart failure, history of cerebrovascular disease, pre-operative treatment with insulin, pre-operative serum creatinine > 180 $\mu mol.l^{-1}$) [2]. To be included in the trial a subject had to present with at least three of the six risk factors. All patients were receiving chronic cardiovascular medication that was continued throughout the study. Exclusion criteria were lack of sinus rhythm, emergency cases, and age < 18 year.

HRV analysis was performed according to Task Force recommendations [21]. Five-minute recordings of the fast peaks of 'R' waves on the electrocardiogram were detected with a sample rate of 1024 Hz (Varia Cardio TF4; Olomouc, Czech Republic). Spectral analysis was performed by fast Fourier transformation. Power spectrum densities were calculated for total power (TP), low frequencies (0.04–0.15 $ms^2.Hz^{-1}$), and high frequencies (0.15–0.4 $ms^2.Hz^{-1}$) in normalised units, defined as the proportional part of the specific frequency of total power. Breathing was controlled at a rate of 14–16 $breaths.min^{-1}$, as recommended for HRV measurements [22]. Baseline HRV was recorded on the day of surgery before induction of anaesthesia. Analysis of the data was performed after the end of the operation by an expert blinded from intra-operative haemodynamic events. Anaesthetists taking care of the patients assigned to the prospective group were not aware of the HRV results.

The occurrence of hypotension or bradycardia between induction of general anaesthesia and the point of skin incision was recorded. The lowest mean arterial blood pressure (MAP) and heart rate within this time period were recorded as absolute values. Hypotension was defined as either a decrease of MAP to < 60% of baseline, or a MAP < 60 mmHg. Bradycardia was defined as either a decrease of heart rate to < 60% of baseline, or a heart rate < 50 $beats.min^{-1}$. Hypotension and bradycardia were treated in a standardised manner with 3 mg ephedrine and 0.5 mg atropine, respectively, repeated if necessary. Drugs were administered until the MAP increased to 60 mmHg or greater, or heart rate increased to 60 $beats.min^{-1}$ or greater, respectively. The amount of rescue medication was recorded.

All patients received oral premedication with midazolam (3.75 or 7.5 mg at the discretion of the attending anaesthesiologist) 30 min prior to anaesthesia. Induction and maintenance of anaesthesia were performed in a standardised manner in all patients: anaesthesia was induced with propofol 1.5 $mg.kg^{-1}$ and maintained with a continuous infusion (3 $mg.kg^{-1}.min^{-1}$). Remifentanil was administered continuously starting at 0.3 $\mu g.kg^{-1}.min^{-1}$ until the trachea was intubated, and then 0.2 $\mu g.kg^{-1}.min^{-1}$. Tracheal intubation was facilitated with 0.6 $mg.kg^{-1}$ rocuronium. Depth of anaesthesia was controlled using a Bispectral Index (BIS) monitor (BIS XP, Aspect Medical Systems, Norwood, MA) aiming at a BIS level between 40 and 50. If the BIS value exceeded 50, the propofol infusion was increased stepwise by 0.5-$mg.kg^{-1}.min^{-1}$ increments. The study ended at the time of skin incision.

The study was performed in two steps. In the first part (the retrospective analysis) patients were assigned to one of two groups depending on haemodynamic events as defined above. The group 'unstable' was compared with the group 'stable'. HRV was analysed retrospectively depending on the patient's group assignment. A receiver operator characteristics curve (ROC) analysis was performed using the HRV data. This type of analysis identifies the threshold value of a specific parameter with the best sensitivity and specificity for prediction of hypotension or bradycardia. A ROC graph demonstrates sensitivity on the ordinate and 1–specificity on the abscissa. If the parameter is neither sensitive nor specific for prediction of haemodynamic events the (ROC) curve would be close to the bisector line, the so-called line of identity. The more the ROC curve differs from this line, the greater the sensitivity and specificity, reflected by an area under the curve close to 1.0. Based on preliminary data, a predictive model was built to confirm our hypothesis prospectively in another group of patients. Based on the retrospective data, a threshold value of TP was defined. Two prospective groups were then defined: patients with TP less than 500 $ms^2.Hz^{-1}$ (group

TP < 500 $ms^2.Hz^{-1}$) and patients with TP greater than 500 $ms^2.Hz^{-1}$ (group TP > 500 $ms^2.Hz^{-1}$).

Data were analysed using standard software (PRISM 4.03 GraphPad Software, San Diego, CA). All data were checked for normal distribution using the Kolmogorov–Smirnow test based on the Dallal and Wilkinson approximation to Lilliefors method. Non-parametric HRV within group data were analysed with the Wilcoxon matched pairs test. Comparisons of non-parametric HRV data between groups were performed using the Mann–Whitney test. Data are expressed as median and range. Parametric data were compared using Student's *t*-test. Data are expressed as mean (SD). Fisher's exact test was used to compare the incidence of hypotension and bradycardia. Receiver operator characteristic curve analysis was performed to evaluate sensitivity and specificity of the threshold value TP of 500 $ms^2.Hz^{-1}$ as well as LF/HF < 2.5, to detect patients at high risk of hypotension or bradycardia. A p value of < 0.05 was considered significant.

Results

One hundred patients were included in the study. Demographic data are provided in Table 1. The ASA status classification as well as the Revised Cardiac Risk Index score demonstrated the severe underlying comorbidity and high peri-operative risk in these patients. Nearly all patients took chronic cardiovascular medication. In the prospective part of the study, more patients were taking beta-blockers in group TP > 500 $ms^2.Hz^{-1}$ compared with group TP < 500 $ms^2.Hz^{-1}$ (Table 2).

The results of the 50 patients analysed retrospectively depending on the occurrence of hypotension or bradycardia are shown in Fig. 1. At baseline, there were no differences in MAP or heart rate. Eleven patients (four women, seven men) demonstrated haemodynamic events after induction of general anaesthesia; four patients had a bradycardia and seven had hypotension. Thirty-nine patients remained stable after induction of anaesthesia. As defined, the MAP and heart rate fell in unstable group ($p < 0.05$) and the lowest mean heart rate and lowest mean MAP differed significantly between the two groups ($p < 0.05$). Patients in group unstable required a significantly greater mean dosage of ephedrine compared with stable group to restore the blood pressure (7.5 mg vs 3.0 mg, $p < 0.05$). Atropine requirements were comparable between groups.

At baseline, significant differences of HRV were found depending on whether hypotension or bradycardia was present after induction of anaesthesia (Table 3). Total power differed significantly between groups with higher values in stable group compared with unstable group

Table 1 Demographic data of the retrospective and prospective groups. Data are number or mean (SD). (ASA = American Society of Anesthesiologists physical status, RCRI = Revised Cardiac Risk Index).

	Retrospective study		Prospective study	
	Unstable *n* = 11	Stable *n* = 39	TP < 500 $ms^2.Hz^{-1}$ *n* = 29	TP > 500 $ms^2.Hz^{-1}$ *n* = 21
ASA 3/4	11/0	37/2	26/3	20/1
RCRI 3/4	6/5	25/14	26/3	18/3
Age; years	65 (6)	67 (8)	69 (9)	67 (8)
Weight; kg	79 (12)	77 (12)	78 (15)	81 (14)
Height; cm	170 (6)	172 (9)	172 (7)	173 (8)

Table 2 Chronic cardiovascular medication of the retrospective and prospective groups. Data are in numbers.

	Retrospective study		Prospective study	
	Unstable *n* = 11	Stable *n* = 39	TP < 500 $ms^2.Hz^{-1}$ *n* = 29	TP > 500 $ms^2.Hz^{-1}$ *n* = 21
Beta-blocker	3	21	7	12*
Calcium-channel blocker	4	4	7	8
ACE-inhibitor	9	23	17	13
AT-II antagonist	0	2	1	3
Diuretic	5	14	6	7
Other	11	39	29	21

*p < 0.05 for differences between groups in that part of the study.

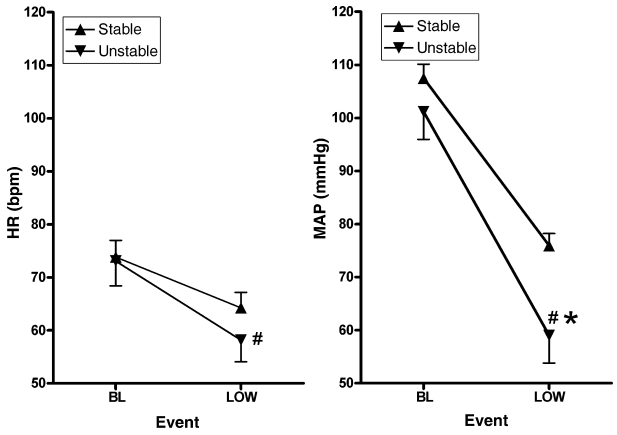

Figure 1 Heart rate (HR) and mean arterial blood pressure (MAP) changes in the two retrospective groups: Stable and Unstable. BL, baseline; LOW, lowest value after induction of anaesthesia. #Difference between groups at LOW, $p < 0.05$; *difference between baseline and LOW, $p < 0.05$.

Table 3 Baseline heart rate variability data of the retrospective and prospective groups. Frequencies are given as percentages of total power. Data are given as median (range).

	Retrospective study		Prospective study	
	Unstable	Stable	TP < 500 $ms^2.Hz^{-1}$	TP > 500 $ms^2.Hz^{-1}$
TP; $ms^2.Hz^{-1}$	402 (120–1454)	875 (92–3587)*	203 (11–472)	787 (558–4503)*
LF/HF	1.3 (0.1–20.2)	1.1 (0.1–10.6)	1.9 (0.1–18)	1.8 (0.1–9.5)
LF; %	36 (3–94)	34 (3–78)	32 (1–75)	36 (5–81)
HF; %	27 (5–56)	39 (7–91)	19 (3–88)	17 (5–86)

*$p < 0.05$ for differences between groups in that part of the study.
TP, total power; LF/HF, low frequency/high frequency ratio; LF, low frequency; HF, high frequency.

($p < 0.05$). No differences were found in terms of LF/HF, LF or HF.

A cut-off value of TP was calculated based on the retrospective study results. The median TP of group stable was 875 $ms^2.Hz^{-1}$ (range: 92–3587 $ms^2.Hz^{-1}$). The median TP of group unstable was 402 $ms^2.Hz^{-1}$ (range: 120–1454 $ms^2.Hz^{-1}$). ROC curve analysis revealed a sensitivity of 81% and a specificity of 71% for a baseline TP < 500 $ms^2.Hz^{-1}$ for prediction of postoperative hypotension or bradycardia (Fig. 2). The sensitivity and specificity of a baseline LF/HF < 2.5 were found to be 87% and 28%, respectively.

The use of a threshold baseline value of TP < 500 $ms^2.Hz^{-1}$ for prediction of hypotension or bradycardia after induction of general anaesthesia was tested prospectively in 50 patients. Baseline HRV analysis was undertaken prior to induction of anaesthesia. Twenty-nine patients had a TP below 500 $ms^2.Hz^{-1}$ (six women, 23 men) and 21 patients had a TP greater than 500 $ms^2.Hz^{-1}$ (five women, 16 men). Data from these groups are shown in Fig. 3. The heart rate did not differ between groups prior to induction. Both groups had a non-significant decrease in HR. Nevertheless, the lowest recorded values after induction of anaesthesia were significantly less in group TP < 500 $ms^2.Hz^{-1}$. MAP did not differ at baseline but fell in both groups. At the time of the lowest recorded MAP, the absolute blood pressure values of group TP < 500 $ms^2.Hz^{-1}$ differed from group TP > 500 $ms^2.Hz^{-1}$, with a lower MAP in group TP < 500 $ms^2.Hz^{-1}$. More patients in group TP < 500 $ms^2.Hz^{-1}$ needed vasopressor administration to restore mean arterial blood pressure compared with group TP > 500 $ms^2.Hz^{-1}$ (6.0 mg vs 3.0 mg, respectively, $p < 0.05$). No differences were found in atropine administration for treatment of bradycardia.

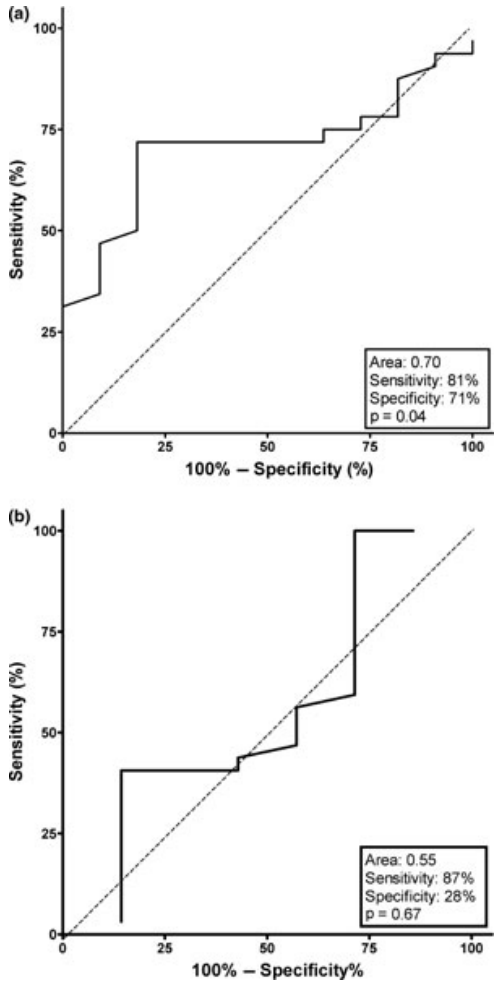

Figure 2 Receiver operator characteristics curve for use of total power < 500 $ms^2.Hz^{-1}$ (a) and for low frequency/high frequency ratio < 2.5 (b). The dashed line indicates the line of identity.

Discussion

In this prospective clinical trial we investigated the value of HRV for prediction of hypotension and bradycardia after induction of general anaesthesia. Patients with a high risk of postoperative cardiovascular events indicated by Revised Cardiac Risk Index score were included in the study. In patients assigned by haemodynamic events after induction of anaesthesia, significant differences were found in terms of the TP of HRV. Baseline

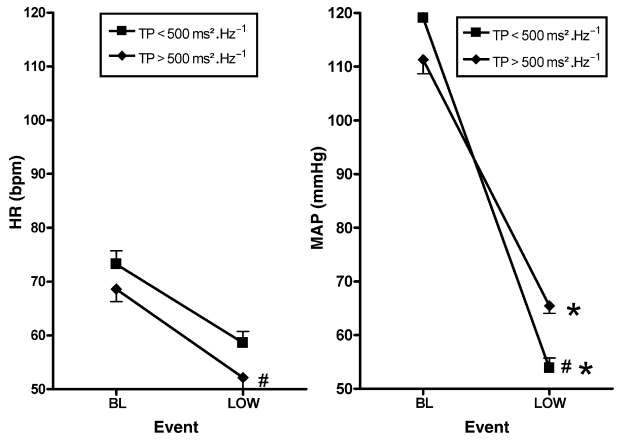

Figure 3 Heart rate (HR) and mean arterial blood pressure (MAP) changes in the two prospective groups: TP < 500 $ms^2.Hz^{-1}$: patients with baseline total power < 500 $ms^2.Hz^{-1}$ and TP > 500 $ms^2.Hz^{-1}$: patients with baseline total power > 500 $ms^2.Hz^{-1}$. BL, baseline; LOW, lowest value after induction of anaesthesia. #Difference between groups at LOW, $p < 0.05$; *difference between baseline and LOW, $p < 0.05$.

TP < 500 $ms^2.Hz^{-1}$ predicted hypotension and bradycardia after induction of anaesthesia with high sensitivity and specificity. These results were confirmed in another group of patients assigned by baseline TP.

It has been demonstrated that hypotension during anaesthesia may worsen patient outcome [23–25]. More than 50 years ago, Kleinerman et al. [23] showed that the degree of hypotension correlated with the decrease of cerebral blood flow. A MAP decrease of 26% resulted in a decrease of cerebral blood flow of 12%, whereas a MAP decrease of 50% correlated with a drop of cerebral blood flow of 20%. Monk et al. identified three independent risk factors for 1-year mortality following surgery in 1064 patients, one of which was intra-operative hypotension [24]. A third investigation found that the incidence of postoperative delirium was higher (9% vs 4%) in patients with MAP between 45 and 55 mmHg compared with patients with MAP between 55 and 70 mmHg [25]. During general anaesthesia, bradycardia has been described mostly in the context of propofol infusions [26–28]. Deutschman et al. demonstrated that a decrease of sympathetic activity, reflected in a decrease of the low frequency of HRV, is the underlying pathophysiology of this effect [26]. They found a significant decrease of TP due to propofol infusion was associated with bradycardia and hypotension. Patients with low baseline TP may be at greater risk of haemodynamic side-effects with a propofol infusion.

We have recently demonstrated the use of HRV for predicting hypotension after administration of regional anaesthesia [16, 17]. LF/HF, reflecting the balance of sympathetic to parasympathetic activity, was demonstrated to predict the incidence of hypotension with high sensitivity and specificity in different groups of healthy patients without underlying cardiovascular risk factors. An LF/HF of 2.5 was identified as the threshold value. A high risk of hypotension was found in patients with LF/HF > 2.5, interpreted as high sympathetic activity, whereas patients with an LF/HF < 2.5 reflecting low sympathetic activity, demonstrated stable blood pressure after onset of spinal anaesthesia. In contrast to our findings prior to spinal anaesthesia, in the present investigation which enrolled high-risk cardiac patients, the predictive value of baseline TP for subsequent hypotension or bradycardia was superior to using the baseline LF/HF. The different results may be due to differences in the patients' physical status and chronic medication. The patients included in the HRV analysis for prediction of hypotension after spinal anaesthesia were healthy, as underlying cardiovascular disease or chronic cardiovascular medication had been defined as exclusion criteria. The autonomic nervous systems of these patients should have been intact. In contrast, all patients in the present study were receiving medication for treatment of hypertension, arrhythmia or congestive heart failure. Chronic medication may have a considerable effect on LF/HF. This may have resulted in the observed inferior predictive value of LF/HF in patients with underlying cardiovascular disease. The results of research on LF/HF are inconsistent, even in patients with underlying cardiac disease. In two recent studies, Filipovic et al. demonstrated that LF/HF < 2.0 was an independent predictor of long-term mortality, cardiac events [12] and all-cause mortality after major non-cardiac surgery [29]. In contrast to our findings, they found a depressed baseline LF/HF (< 2) indicated a greater risk of adverse events. LF/HF < 2 as a predictor for hypotension or bradycardia was tested 'post hoc' to compare our findings with these previously published results. Sensitivity was good, whereas specificity was low (area: 0.55, sensitivity: 81%, specificity: 28%, $p = 0.67$). We believe that in our patient population the integrity of the autonomous nervous system is better reflected by TP and that a higher TP is correlated with better compensation of haemodynamic side-effects of intravenous anaesthetics. This assumption is supported by better sensitivity and specificity of TP compared with LF/HF.

Until now, the predictive value of HRV for cardiovascular events during general anaesthesia has only been investigated in retrospective investigations [19, 20, 30]. Several years ago, Latson et al. [30] demonstrated a greater incidence of hypotension and bradycardia after induction of general anaesthesia in patients with autonomic reflex dysfunction evaluated by a battery of tests

including HRV analysis. Changes of heart rate due to forced breathing and the Valsalva manoeuvre, as well as resting HRV, were investigated. These tests revealed a pre-existing autonomic reflex dysfunction which was correlated with hypotension after induction of general anaesthesia. More recently, Huang et al. [19] investigated 46 patients with diabetes mellitus and compared them with 87 non-diabetic patients in a retrospective, observational trial. In the diabetic patients, the incidence of autonomic reflex dysfunction, indicated by low baseline TP, was significantly greater than in healthy controls. This subgroup of diabetic patients demonstrated a greater incidence of hypotension after induction of general anaesthesia. These results have been confirmed by another investigation in a comparable group of patients [20]. Both of these studies were retrospective analyses.

A significantly greater number of patients assigned to group TP > 500 $ms^2.Hz^{-1}$ were receiving beta-blocker therapy (12 vs seven patients, $p < 0.05$). An improved outcome due to use of beta-blocker therapy has been described in several studies [31–33]. It has been demonstrated that beta-blockers significantly increase both time domain parameters of HRV and TP [34, 35]. The increase in TP due to beta-blocker therapy may be the result of improvements of autonomic nervous system regulation and lead to the better outcome.

Some limitations of this study should be noted, in particular the small sample size. The study was performed as a single centre trial. A large scale, multicentre study is required to confirm our results.

In conclusion, pre-operative TP < 500 $ms^2.Hz^{-1}$ predicted hypotension and bradycardia after induction of general anaesthesia in patients with cardiovascular risk factors, with high sensitivity and specificity. Therefore, TP may be a suitable tool to detect patients at high risk of these events and indicate the need for intensified monitoring and prophylactic treatment.

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