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Pre-operative measurement of heart rate variability predicts hypotension during general anesthesia

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Background: Peri-operative hymodynamic instability is one of the major concerns for anesthesiologists when performing general anesthesia for individuals with autonomic dysfunction. The purpose of this study was to examine the potential usage of pre-operative measurement of heart rate variability (HRV) in identifying which individuals, with or without diabetes, may be at risk of blood pressure (BP) instability during general anesthesia.
Methods: We studied 46 patients with diabetes and 87 patients without diabetes ASA class II or III undergoing elective surgery. Participants' cardiovascular autonomic function and HRV were assessed pre-operatively, and hymodynamic parameters were monitored continuously intra-operatively by an independent observer.
Results: Only 6% of the participants were classified as having cardiovascular autonomic neuropathy (CAN) based on traditional autonomic function tests whereas 15% experienced hypotension. Total power (TP, $P = 0.006$), low frequency (LF, $P = 0.012$) and high frequency (HF, $P = 0.028$) were significantly lower in individuals who experienced hypotension compared with those who did not. Multivariate logistic regression analysis revealed that TP [odds ratio (OR) = 0.15, 95% confidence interval (CI) = 0.05–0.47, $P = 0.001$] independently predicted the incidence of hypotension, indicating that each log ms^2 increase in total HRV lowers the incidence of hypotension during general anesthesia by 0.15 times. After stepwise multiple linear regression analysis ($R^2 = 11.5\%$), HF ($\beta = -11.1$, SE = 2.79, $P < 0.001$) was the only independent determinant of the magnitude of systolic blood pressure (SBP) reduction at the 15th min after tracheal intubation.
Conclusions: Spectral analysis of HRV is a sensitive method for detecting individuals who may be at risk of BP instability during general anesthesia but may not have apparent CAN according to traditional tests of autonomic function.

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Key words: cardiovascular autonomic neuropathy; diabetes; general anesthesia; heart rate variability; hypotension.

Cardiovascular autonomic neuropathy (CAN) is a neuropathic disorder that results from damage to the fibers of the autonomic nervous system (ANS) with associated abnormalities of heart rate (HR) control and vascular dynamics (1, 2). It is perhaps one of the most overlooked complications of diabetes, and yet it is associated with an increased risk of mortality in individuals with diabetes (1). Other medical conditions may also cause varying degrees of ANS dysfunction (3–5). Intra-operative hymodynamic instability is one of the major concerns for anesthesiologists when performing general anesthesia in individuals with CAN (6). It has been demonstrated that intra-operative vasopressor support was needed more often in diabetic patients with autonomic neuropathy than in those without (6). Therefore, pre-operative cardiovascular autonomic screening plays a crucial role in planning the anesthesia management for individuals with CAN.

Standardized tests of cardiovascular ANS function include the E:I ratio, the Valsalva ratio, and the standing 30 : 15 ratio (2, 7). Although these tests may provide useful information for anesthesiologists, they are both time-consuming and labor-intensive, making routine use of ANS tests impractical. Moreover, researchers have reported that diabetic patients with two or more abnormal ANS function test results did not experience more intra-operative hypotension than diabetic patients with one or no abnormal test result (8). In patients with diabetic neuropathy, reduced power in all spectral bands of heart rate variability (HRV) has been reported (9, 10). In addition, a reduction of the absolute power of low frequency (LF) and high frequency (HF) components of HRV has been reported to precede the clinical manifestation of autonomic neuropathy in diabetes (9). Hence, spectral analysis of HRV may be a useful alternative in identifying individuals with autonomic neuropathy (11). Previously, a study that included 26 patients scheduled for elective surgery demonstrated that mid-frequency HRV (0.07–0.15HZ), HF (0.15–0.3 Hz) and total HRV power (0.03–0.3Hz) measured pre-operatively were significantly lower in individuals who experienced hypotension than those who did not (12). However, the other study did not find an association between autonomic function that was determined by spectral analysis of HRV and hymodynamic behavior during anesthesia induction (13). Of notice is that in those two studies participants treated with medications that are known to affect HRV such as beta blocker, calcium channel blockers, or angiotensin converting enzyme inhibitor (ACEI), were not excluded.

The purpose of this study was to compare two techniques to assess ANS function in identifying which individuals, with or without diabetes, may be at risk of blood pressure (BP) instability during general anesthesia. In addition, we evaluated the potential relationship between pre-operative ANS status and the hymodynamic response to induction as well as the occurrence of hypotension during anesthesia maintenance. In the present study, we included a larger sample size and excluded individuals who were receiving beta blocker, calcium channel blocker, and ACEI pre-operatively. We selected premedication agents, muscle relaxants and drugs for anesthesia induction with minimal cardiocircularoty suppression to minimize provoking hymodynamic instability. A non-invasive beat-to-beat radial tonometry was employed to improve the accuracy and quality of BP recordings during anesthesia. We measured HRV according to the Task Force recommendations by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology in 1996 (11). We hypothesized that (i) the absolute power of frequency domain parameters of HRV is significantly lower in those who need vasopressor support during general anesthesia compared with those who do not, and (ii) frequency domain parameters of HRV can predict the magnitude of reduction in BP in the phase of deep anesthesia during anesthesia maintenance.

Participants and grouping

The study was approved by the Institutional Review Board of the Mackay Memorial Hospital, Taipei, Taiwan. All participants gave written informed consent. Included in this study were 57 men and 76 women [American Society of Anesthesiologists (ASA) physical status class II or III], aged from 31 to 70 years, scheduled to undergo elective surgery. We excluded individuals with HR below 50 beats/min or cardiac arrhythmias. In addition, individuals who were receiving beta-blockers, calcium channel blockers, or ACEIs were excluded.

Participants were divided into two groups: patients with diabetes ($n = 46$) and patients without diabetes ($n = 87$). Those participants who required intra-operative vasopressor during general anesthesia were categorized as the H group ($n = 20$) whereas those who did not were categorized as the N group ($n = 113$).

Materials and methods

Preceded by a 10-min stabilization period, 5-min recordings of HRV under paced breathing were obtained from all participants immediately before administration of any sedative medications. Briefly, precordial electrocardiogram (ECG) was measured via three skin sensors placed in the standard Lead II position. During the ECG recording, participants were resting in a supine position and breathing in a controlled rate of 12–15 breaths per minute in a quiet waiting area adjacent to the operation room. Frequency domain parameters of HRV were recorded and analyzed with the use of a data acquisition and analysis device (MP100; Biopac Systems, Inc., Goleta, CA), coupled with AcqKnowledge software (Biopac Systems Inc., Goleta, CA, USA), with a sampling rate of 512 Hz.

All participants also underwent a battery of standardized autonomic function tests. These tests were performed before administration of any sedative medications to identify patients with CAN. For these tests, the time intervals between R-waves of the QRS complexes were measured in milliseconds using the MP100 device. Beat-to-beat BP and HR were continuously monitored and recorded beginning in the pre-induction period until 15 min after intubation with a non-invasive BP monitoring system (Vasotrac; Medwave, Inc., St. Paul, MN). The pre-operative measurements of HRV and ANS function as well as the intra-operative monitoring of BP and HR were performed by an independent observer.

Power spectral analysis of heart rate variability

As indicators of sympathetic and parasympathetic activities as well as sympathovagal balance, the frequency domain parameters of HRV were calculated from 5-min recordings of ECG under resting conditions, pre-operatively. The measurements of HRV followed the standards suggested by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology in 1996 (11). Two main spectral components: the LF (0.04–0.14 Hz) and HF (0.15–0.4 Hz), and TP were obtained in absolute power (ms^2). Due to large between-subject variability, logarithmic transformation was performed on these HRV parameters. The ratio of LF to HF was calculated and expressed as LF/HF.

Tests of cardiovascular autonomic function

During the deep breathing test, the patient's respirations were standardized at six breaths per minute. The E:I ratio is a ratio of the mean of the maximal (longest) R-R intervals during deep expiration to the mean of the minimal (shortest) R-R intervals during deep inspiration.

In the Valsalva maneuver, the supine participant, connected to the Biopac device, was asked to forcibly exhale for 15 s against a fixed resistance with an open glottis while the pressure is maintained at 40 cmH_2O over the 15-s interval. The Valsalva ratio is the longest R-R divided by the shortest R-R occurring within 45 s of peak heart rate.

To test the HR response to standing, the patient was asked to stand to an upright position from the supine position, and the R-R intervals were monitored for an additional period while standing. In normal subjects, standing causes a rapid increase in HR with the maximum rate generally found at the 15th beat after standing and it slows at around the 30th beat after standing (7). The 30 : 15 ratio is the ratio of the longest R-R interval after standing to the shortest R-R interval after standing. In this study, we adopted the cut-off values for the three ANS function tests from a previous study that calculated normal range of values (<95th percentile) from 100 diabetics; the cut-off values for E:I ratio, Valsalva ratio and the 30 : 15 ratio were: 1.06, 1.08, and 1.04, respectively (14). Participants were classified as having CAN if two of these three tests were above its respective cut-off value (7,14).

Anesthesia management

After completion of the pre-operative measurement of the ANS function and HRV, a 20-gauge intravenous (i.v.) catheter was inserted and 300 ml of Ringer's lactate solution was infused over 5 min. Immediately before induction of anesthesia, all participants received i.v. midazolam (0.08 mg/kg), atropine (0.3–0.5 mg) and fentanyl (2 μg/kg). Anesthesia was then induced with etomidate (0.1–0.2 mg/kg over 60 s) and the Bispectral Index (BIS) monitor (Aspect Medical System, Newton, MA) was used to monitor the depth of hypnosis. Rocuronium (1 mg/kg) was administered to facilitate tracheal intubation and a peripheral nerve stimulator was used to ensure adequate neuromuscular block before intubation. Intubation was preformed after loss of response to train-of-four and BIS < 50. After tracheal intubation, sevoflurane in oxygen-air (1 : 1 l/min) was used for anesthesia maintenance and ventilation was controlled with a ventilator to achieve an end-tidal CO_2 of 30–35 mmHg and an end-tidal sevoflurane concentration of 1 MAC. A decrease in mean arterial blood pressure (MAP) of greater than 30% or systolic blood pressure (SBP) of less than 85 mmHg was determined as hypotension. Hypotensive episodes were treated with phenylephrine.

Beat-to-beat blood pressure monitoring

Beat-to-beat BP was measured using the Vasotrac non-invasive BP monitoring system. The Vasotrac system measures BP with a wrist sensor positioned over the participant's radial artery. Using a method of measuring radial artery waveforms, the Vasotrac system calculates accurate SBP, diastolic blood pressure (DBP) and MAP.

Statistical analysis

Comparisons between groups were made using Fisher's exact test for categorical variables, Student's *t*-test for normally distributed continuous variables and the Mann–Whitney *U*-test for continuous variables that were not normally distributed. To examine the predictors of the incidence of hypotension, logistic regression using the stepwise backward elimination procedure was performed. Pearson's correlation analysis was used to examine the correlations between components of HRV and the magnitude of SBP reduction in the phase of deep anesthesia during anesthesia maintenance. Using the stepwise procedure, multiple linear regression was performed to identify the determinants of the magnitude of SBP reduction. A P-value < 0.05 was considered significant.

Results

A comparison of baseline characteristics between patients with diabetes and patients without diabetes showed that the former group was older, had a higher percentage of individuals with hypertension and a higher percentage of individuals classified as ASA class III than the latter group (Table 1). A t-test analysis revealed that test results of the E:I ratio and the 30 : 15 ratio were significantly lower in patients with diabetes than without diabetes, whereas the Valsalva ratio showed no significant difference between groups (Table 2). A t-test analysis of the frequency domain parameters of HRV showed that the two groups were significantly different in LF, HF, and TP with the patients with diabetes having lower power whereas LF/HF was not statistically different between groups (Table 2).

Only eight (6%) participants (seven patients with diabetes and one patient without) had two or more ANS function test abnormalities and were classified as having CAN. Of those eight participants with CAN, six (75%) experienced hypotension. Results also showed that 30% of patients with diabetes experienced hypotension compared with 7% of patients without ($P < 0.001$).

Of 133 study participants, 20 (15%) experienced hypotension (H group) and required intra-operative vasopressor during anesthesia maintenance. The H group was older ($P = 0.007$), had a higher percentage of individuals with diabetes ($P < 0.0001$) and a higher percentage of individuals classified as ASA class III ($P = 0.014$) compared with the N group, whereas no significant difference was observed between groups in gender ($P = 1$) and the percentage of individuals with hypertension ($P = 1$). Results from the Mann–Whitney U-test revealed that the H group had significantly lower E:I ($P = 0.003$) and Valslva ratios ($P = 0.004$) compared with the N group. However, the 30 : 15 ratio ($P = 0.207$) was not statistically different between the H and N groups. With regard to the measurements of HRV components, TP ($P = 0.006$), LF ($P = 0.012$), and HF ($P = 0.028$) were significantly lower in the H group than in the N group whereas LF/HF ($P = 0.67$) was not significantly different between the groups.

Table 1

Baseline characteristics of the diabetic and non-diabetic groups.

	Diabetics ($n = 46$)	Non-diabetics ($n = 87$)	P
Age*	56.37 ± 8.34	48.30 ± 8.19	<0.0001
Gender† (%)			0.2
Female	47.8	60.7	
Male	52.2	39.3	
Hypertension† (%)			<0.0001
Yes	39.1	3.4	
No	60.9	96.6	
ASA class† (%)			<0.0001
II	60.9	95.5	
III	39.1	4.5	

ASA, American Society of Anesthesiologists.*Group comparison using the Student's t-test. †Group comparison using Fisher's exact test.

Table 2

Results of autonomic function tests and heart rate variability in participants with and without diabetes.

	Diabetics ($n = 46$)	Non-diabetics ($n = 87$)	P
Valsalva ratio	1.30 ± 0.21	1.46 ± 0.48	0.05
30 : 15 ratio	1.06 ± 0.07	1.10 ± 0.11	0.03
E:I ratio	1.12 ± 0.09	1.22 ± 0.12	<0.0001
LF/HF	2.51 ± 2.66	1.71 ± 1.55	0.066
LF (l ms^2)*	1.84 ± 0.71	2.41 ± 0.43	<0.0001
HF (l ms^2)*	1.65 ± 0.68	2.32 ± 0.55	<0.0001
TP (l ms^2)*	2.57 ± 0.60	3.02 ± 0.43	<0.0001

HF, high frequency; LF, low frequency; TP, total power. Values are mean ± SD. * All power values are log transformed. Diabetics vs. non-diabetics, using the Student's t-test.

Univariate logistic regression showed that age ($P = 0.009$), ASA class ($P = 0.021$), DM ($P = 0.001$), E:I ($P = 0.004$), Valsalva ratio ($P = 0.013$), TP ($P = 0.001$), LF ($P = 0.001$) and HF ($P = 0.004$) were associated with the incidence of hypotension whereas hypertension ($P = 0.996$), gender ($P = 0.834$), LF/HF ($P = 0.863$), and 30 : 15 ($P = 0.336$) were not. Multivariate logistic regression analysis, using the stepwise backward elimination procedure, revealed that only TP independently predicted the incidence of hypotension (OR = 0.15, 95% CI of OR = 0.05–0.47, p = 0.001), indicating that each log ms^2 increase in TP lowers the incidence of hypotension by 0.15 times with an odds ratio of 0.15. Variables with a P-value of greater than 0.05, including age, DM, ASA class, E:I, Valsalva ratio, LF, and HF, were eliminated from the model.

Correlational analyzes revealed that the magnitude of SBP reduction at 15 min after tracheal intubation negatively correlated with LF ($r = -0.21$, $p = 0.02$), HF ($r = -0.34$, $P < 0.0001$) and TP ($r = -0.25$, $p = 0.006$), and positively correlated with LF/HF ($r = 0.26$, $p = 0.005$). However, the three standardized ANS function tests were unrelated to the magnitude of SBP reduction at the 15th min after tracheal intubation. Male sex ($P = 0.015$) and DM ($P = 0.003$) were associated with significantly larger SBP reductions whereas age, history of hypertension, and ASA class were not associated with the magnitude of SBP reduction. After stepwise multiple linear regression analysis ($R^2 = 11.5\%$), HF ($\beta = -11.1$, SE = 2.79, $P < 0.001$), but not gender, history of DM, LF, TPLF/HF, was the only independent determinant of the magnitude of SBP reduction at the 15th min after tracheal intubation. This finding revealed that lower HF power was associated with larger SBP reductions during anesthesia maintenance.

Discussion

This study sought to determine the possibility of using frequency domain parameters of HRV to identify which individuals may be at risk of BP instability during anesthesia maintenance. We demonstrated that LF, HF and total HRV power were significantly lower in individuals who required intra-operative vasopressors compared with those who did not. The salient finding from this study is that even after controlling for age, ASA class, history of DM and other indices of autonomic function, total HRV power independently predicted the incidence of hypotension during general anesthesia. The results from this study also support our hypothesis that HRV can predict the magnitude of BP reduction during anesthesia maintenance as we demonstrated that HF was the only independent determinant of SBP reduction at the 15th min after tracheal intubation, with lower HF power associated with larger SBP reductions. It seems that individuals with impaired autonomic function (i.e. lower TP and HF) failed to compensate the vasodilatory effect of sevoflurance via normal autonomic reflexes (e.g. reflexed tachycardia), resulting in further decreases in BP.

Concurs with previous findings (6), in the present study 30% of patients with diabetics required intra-operative vasopressors compared with 7% of patients without diabetes. Our findings confirm the notion that patients with diabetes are susceptible to BP instability during general anesthesia. Consistent with previous studies (9, 13), we found that patients with diabetes had significantly reduced LF and HF power compared with patients without diabetes but LF/HF could not differentiate between patients with diabetes from patients without diabetes.

It is well established that the efferent vagal activity is a major contributor of HF fluctuations (11, 15). However, the interpretation of LF fluctuations is the subject of controversy (11). It was postulated that they represent baroreceptor-mediated BP control and therefore sympathetic activity (15). Although anesthetics-induced hypotension is mainly attributed to a decrease in alpha-adrenergic vasoconstrictive response, volatile anesthetics, such as isoflurane and sevoflurane have been reported to depress baroreflex sensitivity (16). Baroreflex function is an important short-term regulatory system for maintaining BP stability. Hence, judging from our data, we speculate that ineffective baroreflex regulation of BP may play a role in anesthetics-induced hypotension. Although the interpretation of the ratio of LF to HF remains controversial, it has been proposed as an indicator of sympthovagal balance (11). Our results seem to suggest that sympathovagal imbalance is not involved in hymodynamic instability during general anesthesia as LF/HF was not different between individuals with and without hypotension.

Previous results regarding the relationship between risk of hypotension during general anesthesia and ANS abnormalities were conflicting (6, 8, 12, 13). As aforementioned, participants in previous studies did not exclude individuals who were chronically treated with medications known to affect ANS drive/tone. A case–control study demonstrated that the percentage of patients who required intra-operative vasopressors was higher in patients chronically treated with ACEI than in controls, probably because of the ACEI-induced attenuation of adrenergic vasoconstriction response (17). Thus, the interaction effects of pre-operative medications and anesthetics on peri-operative hymodynamics cannot be ruled out in previous studies assessing the relationship between ANS dysfunction and hypotension during general anesthesia. The present study excluded individuals who were treated with beta-blockers, calcium-channel blockers, and ACEIs. Our findings confirm that individuals with ANS dysfunction are indeed susceptible to anesthetics-induced hypotension.

The use of pre-operative HRV analysis in detecting patients who may be at risk of hypotension during spinal anesthesia has been supported by a recent study (18), which demonstrated that high LF/HF before subarachnoid block predicted severe hypotension during spinal anesthesia for elective cesarean delivery. That study and the present study each contributed distinct information that may help evaluate the usefulness of pre-operative HRV measurements. Hypotension during subarachnoid block at T4–T5 is mainly a result of decreased systemic vascular resistance after blockade of preganglionic sympathetic fibers. Maintenance of vascular tone in individuals with higher pre-operative LF/HF is sympathetic dominant. Although it has been called into question the completeness of sympathetic block produced by spinal anesthesia (19), individuals with higher pre-operative LF/HF may be prone to hypotension after spinal anesthesia. On the other hand, the regulation of BP during general anesthesia is a more complex process. A recent study demonstrated that pre-operative hypotension, ASA III –IV, age $\geq$ 50 years, the use of propofol for induction of anesthesia, and a higher dosage of fentanyl were predictors of hypotension after general anesthesia (20). In the present study, we restricted the study participants to those classified as ASA II–III. We chose etomidate for anesthesia induction instead of propofol and limited the dosage of fentanyl to 2 μg/kg. Results from the present study showed that during general anesthesia impaired autonomic function (i.e. decreased HF and TP) is related to hypotension. Our results are in concert with those demonstrated by a previous study in which significantly lower LH and HF were observed in the group experienced hypotension during hemodialysis as compared with the group with stable hemodyanamics (21).

Six out of eight participants who had two or more abnormal autonomic function test results developed hypotension which required vasopressor support suggesting that traditional autonomic function test abnormalities are closely related to hypotension during general anesthesia. The sensitivity and specificity of the CAN criteria in detecting hypotension during general anesthesia were 30% (6/20) and 98% (111/113), respectively. However, only 6% of the participants in the present study met the criteria for making a diagnosis of CAN (i.e. two or more abnormal ANS function test results) compared with a much higher incidence (15%) of hypotension during general anesthesia, making these tests hardly cost-efficient in terms of pre-operative screening for the risk of hymodynamic instability during general anesthesia.

In summary, spectral analysis of HRV is a sensitive method for detecting individuals who may be susceptible to BP instability during general anesthesia but may not have apparent CAN according to standardized tests of ANS function. Results from the present study pinpoint the potential usage of resting HRV in identifying individuals who are at risk of hymodynamic instability during general anesthesia.

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