Assessment of cardiovascular autonomic function in the anaesthesia population

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Chapter 7

Cardiovascular autonomic function testing under non-standardised and standardised conditions in cardiovascular patients with type II diabetes mellitus

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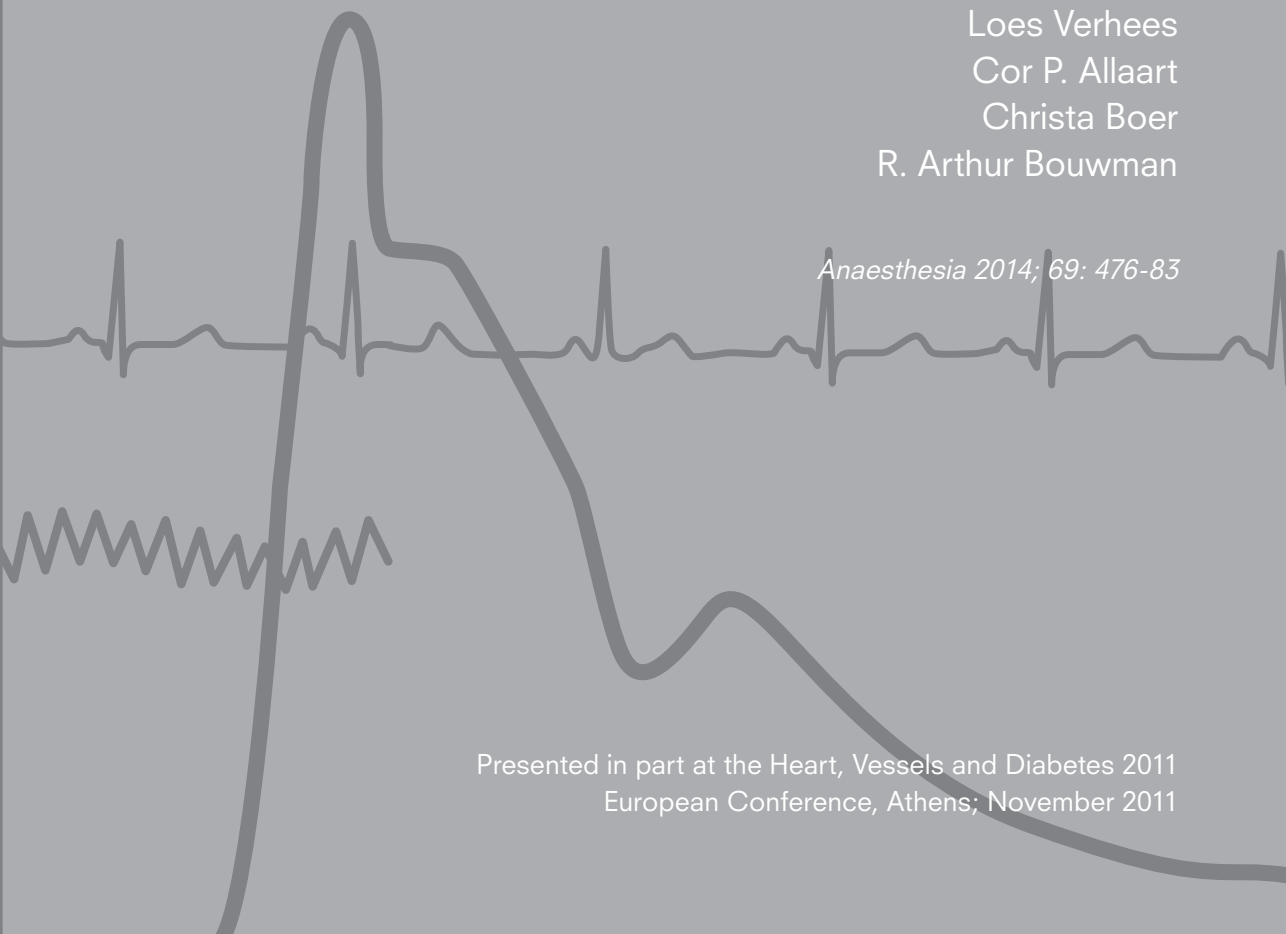

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ABSTRACT

Introduction: Autonomic function tests require standardised test conditions. We compared testing under non-standardised and standardised conditions and investigated the agreement between heart and pulse rate variability in 30 subjects with diabetes mellitus.

Methods & Results: Deep breathing, Valsalva manoeuvre and quick standing tests showed non-standardised reproducibility intraclass correlations (95% CI) of 0.96 (0.82-0.99), 0.96 (0.81-0.99) and 0.75 (-0.98 to 0.94), respectively. Intraclass correlations for sustained handgrip and quick standing were poor. Heart and pulse rate variability showed high-frequency band intraclass correlations (95% CI) of 0.65 (-0.07 to 0.89) and 0.47 (-0.88 to 0.85) for the very low-frequency band, respectively, 0.68 (0.00-0.90) and 0.70 (-0.09 to 0.91) for the low-frequency band, and 0.86 (0.57-0.95) and 0.82 (0.39-0.95) for the high-frequency band. Reproducibility under standardised conditions was comparable. The mean difference (95% limits of agreement) between heart and pulse rate variability was 0.99 (0.80-1.22) for very low frequency, 1.03 (0.88-1.21) for low frequency and 1.35 (0.84-2.16) for high frequency, with a Spearman's correlation coefficient of 1.00, 0.99 and 0.98, respectively.

Conclusions: We demonstrated a high agreement between heart and pulse rate variability and acceptable reproducibility with most autonomic function tests, heart and pulse rate variability.

INTRODUCTION

Cardiovascular autonomic neuropathy in diabetes mellitus is associated with impaired haemodynamic control and cardiovascular complications [1]. Autonomic neuropathy-related cardiovascular complications may especially become abundant under conditions of stress, such as severe illness or surgery [2-3]. Indeed, patients with cardiovascular autonomic neuropathy are at increased risk for perioperative complications like myocardial ischaemia or sudden cardiac death [4-5]. Preoperative recognition of cardiovascular autonomic neuropathy in diabetic subjects may therefore be useful in the prevention of perioperative complications.

Standardised classical Ewing cardiovascular autonomic function tests and heart rate variability analysis are accepted diagnostic and prognostic tools for cardiovascular autonomic neuropathy [6-9]. However, they require standardised conditions to eliminate the influence of cyclic variations and environmental factors such as smoking, eating and drinking, which hamper implementation of these tests in daily clinical practice [7-8].

Moreover, in the intraoperative setting, movement artefacts and electrical interference complicate R-wave detection for heart rate variability analysis by electrocardiography. Pulse rate variability can easily be derived from continuous non-invasive blood pressure measurements and may replace heart rate variability in the outpatient clinic setting [10-11]. We recently showed that Ewing autonomic function tests and heart rate variability provide reproducible results under non-standardised and standardised test conditions, and we found a high level of agreement between heart and pulse rate variability analysis [12-13]. However, our results were limited to the healthy population, while cardiovascular autonomic neuropathy is more prevalent in chronic diseases such as heart failure and diabetes mellitus.

In the present study we investigated the reproducibility of autonomic function testing (classical Ewing cardiovascular autonomic function tests, heart and pulse rate variability) under non-standardised and standardised conditions in patients with type II diabetes mellitus. We particularly focused on type II diabetes mellitus due to the increasing prevalence of this condition in the surgical population. Secondly, we studied the level of agreement between traditional heart rate variability derived from an ECG, and pulse rate variability derived from blood pressure waveforms in this particular patient population.

METHODS

Study population

The Institutional Human Subjects Committee of the VU University Medical Centre Amsterdam approved this prospective observational study, and all participants gave written informed consent (NL26318.029.08). Patients were recruited in the cardiology outpatient clinic of the VU University Medical Centre. Patients with type II diabetes mellitus and an age of 40-85 years were included. Patients with a pacemaker or renal disease requiring haemodialysis or peritoneal dialysis were excluded. To simulate the clinical situation, patients with cardiovascular co-morbidities such as hypertension, heart failure and myocardial ischaemia were not excluded, and participants continued with their prescribed medication.

Autonomic function measurements

Thirty patients were asked to perform the autonomic function test battery (classical Ewing cardiovascular autonomic function tests, heart and pulse rate variability) under non-standardised test conditions to compare the level of agreement between heart and pulse rate variability. Non-standardised cardiovascular autonomic function tests were performed under random test conditions without restrictions regarding oral intake or measurement time point (n=30). The second and third autonomic function measurements under standardised test conditions were performed in a subgroup of 14 patients. Standard test conditions included fasting from 00:00 am and refraining from smoking and caffeine-containing beverages. The measurements were performed in the morning (08:00 am - 10:30 am) in a room with a quiet ambiance and temperature of 19-22°C [8, 12-14].

Parasympathetic cardiovascular reflex tests included the heart rate response during deep breathing, the Valsalva manoeuvre and quick standing, whereas the sympathetic tests included the blood pressure response during the sustained handgrip test and quick standing [8, 15].

The deep breathing test consisted of six deep breaths in one minute to determine the maximum and minimum R-R intervals during each breathing cycle. The R-R intervals during inspiration and expiration were expressed as the longest R-R interval/shortest R-R interval. The Valsalva manoeuvre consisted of a forced expiration in a manometer against 40 mmHg for 15 seconds. The Valsalva-ratio was expressed as the division of the longest R-R interval by the shortest R-R interval. During the quick standing test, the heart rate response after standing was derived from the R-R intervals at 15 and 30 beats after standing, and reported as the ratio of the

longest versus the shortest R-R interval. The sympathetic component of the standing test was based on the systolic blood pressure response at two minutes after standing. The last test consisted of the diastolic blood pressure response during the sustained handgrip. The subject squeezed a handgrip dynamometer to establish a maximum developed force, followed by a handgrip squeeze of 30% of the maximum force for five minutes.

Heart and pulse rate variability were simultaneously measured in all patients using an ECG monitor coupled to a non-invasive continuous arterial blood pressure monitor based on the volume-clamp technique (ccNexfin, BMEYE Edwards Lifesciences, Amsterdam, the Netherlands) [14]. Heart and pulse rate variability were measured after stabilisation of heart rate and blood pressure in the supine position. The heart rate variability was derived from the R-R intervals in the ECG, while pulse rate variability was based on arterial blood pressure interbeat intervals [12-13]. Both R-R and interbeat intervals were recorded during five minutes of spontaneous breathing.

Autonomic function analysis

R-R intervals were derived from the ECG signal using a QRS detector (sample rate 1000 Hz) for the heart rate variability analysis, and the interbeat intervals derived from the blood pressure waveforms (sample rate 200 Hz) were used for the pulse rate variability analysis. The data were visually inspected for premature or irregular beats and movement artefacts. The R-R intervals and interbeat intervals were analysed by spectral analysis using Fast Fourier Transformation with Kubios (Kubios HRV version 2.0, University of Kuopio, Finland) after correction for premature or irregular beats and movement artefacts [16]. The heart and pulse rate variability power spectra were divided into the three peaks of the very low frequency band (0.0-0.04 Hz), the low frequency band (0.04-0.12 Hz) and the high frequency band (0.12-0.4 Hz). These frequency bands are influenced by the sympathetic nervous system (very low frequency), the parasympathetic nervous system (high frequency) or both (low frequency) [13, 17-18].

Statistical analysis

Data were entered into a database created in SPSS version 18.0 (IBM, New York, USA). The reproducibility of the non-standardised tests versus the first standardised test, and the first standardised test versus the second standardised test was analysed by intraclass correlation coefficients (two-way random model, absolute agreement, average measures). The

Spearman rank correlation coefficient was utilised to define the agreement between heart and pulse rate variability. Logarithmic transformation of heart and pulse rate variability parameters was performed to construct Bland-Altman plots and to calculate the bias and the limits of agreement between both tests [19]. A P-value <0.05 was considered statistically significant.

RESULTS

The study included 30 patients with type II diabetes mellitus, and four subjects were excluded due to chronic cardiac arrhythmias. The 26 remaining patients had an average age of 67 years with a standard deviation (SD) of 12 years. More patients were female (65%) and the mean body mass index was 28 kg/m^2 (4 kg/m^2). Mean systolic and diastolic blood pressures were 129 mmHg (24 mmHg) and 62 mmHg (7 mmHg), respectively, with a heart rate of 68 beats per minute (10 beats per minute). Cardiovascular risk factors or co-morbidities included smoking (19%), hypercholesterolemia (31%), hypertension (38%), intermittent cardiac arrhythmia (31%), chronic heart failure (11%), and ischaemic coronary artery disease (31%).

The test results and intraclass correlation coefficients of three consecutive measurements of deep breathing, Valsalva manoeuvre, sustained handgrip, the quick standing test, heart and pulse rate variability are presented in Table 1.

The deep breathing test (0.96 (95%CI: 0.82-0.99 (P<0.001)) and Valsalva manoeuvre (0.96 (95%CI: 0.81-0.99 (P<0.001)) were highly reproducible between non-standardised and standardised test conditions. We found a low reproducibility for the sustained handgrip and blood pressure response to quick standing when non-standardised and standardised test conditions were compared. The heart response to quick standing showed a good intraclass correlation coefficient (0.75 (95%CI: -0.98-0.94 (P=0.033)) between non-standardised and standardised test conditions, but with a large confidence interval (CI).

The intraclass correlation coefficients for the low and high frequency power spectra of the heart rate variability (0.68 (95%CI: 0.00-0.90 (P=0.027)) and 0.86 (95%CI: 0.57-0.95 (P=0.001)), respectively) and pulse rate variability (0.70 (95%CI: -0.09-0.91 (P=0.034)) and 0.82 (95%CI: 0.39-0.95 (P=0.005)), respectively) for the non-standardised versus standardised tests were moderate to good. The reproducibility

of the very low frequency for heart and pulse rate variability was moderate to low (0.65 (95%CI: -0.07-0.89 (P=0.035)) and 0.47 (95%CI: -0.88-0.85 (P=0.155)), respectively).

We further repeated the autonomic function tests under standardised test conditions to investigate the intraclass correlation coefficients under similar settings. For the deep breathing and Valsalva manoeuvre the intraclass correlations were highly reproducible between standardised and standardised test conditions (0.89 (95%CI: 0.53-0.98 (P=0.003)) and 0.91 (95%CI: 0.60-0.98 (P=0.002)), respectively). The sustained handgrip and blood pressure response to quick standing demonstrated a poor reproducibility (0.11 (95%CI: -1.00-0.79 (P=0.435)) and 0.17 (95%CI: -1.00-0.81 (P=0.395)), respectively) as did the non-standard test conditions. An intraclass correlation coefficient of 0.91 (95%CI: 0.61-0.98 (P=0.002)) was determined for the heart response to quick standing. Moderate to good intraclass correlation values were obtained for heart and pulse rate variability analysis for all frequency bands after repeating these tests under standardised test conditions. The intraclass correlation coefficients for the very low frequency, the low frequency and high frequency band were for the heart rate variability 0.77 (95%CI: 0.13-0.94 (P=0.005)), 0.77 (95%CI: 0.15-0.94 (P=0.006)) and 0.86 (95%CI: 0.48-0.96 (P=0.001)), respectively. For the three consecutive frequency bands (very low, low and high frequency band) of the pulse rate variability the intraclass correlation coefficients were 0.68 (95%CI: -0.21-0.93 (P=0.020)), 0.71 (95%CI: -0.06-0.93 (P=0.031)) and 0.84 (95%CI: 0.36-0.96 (P=0.006)), respectively (Table 1).

The Spearman's correlation coefficient between heart and pulse rate variability estimated 1.00 (P<0.001), 0.99 (P<0.001) and 0.98 (P<0.001) for the very low, low and high frequency power spectra respectively (Table 2). Bland-Altman analysis showed a good level of agreement between heart rate variability and pulse rate variability for the very low frequency (Figure 1, panel A), low frequency (Figure 1, panel B) and high frequency (Figure 1, panel C) in diabetic subjects. Antilog mean differences and 95% limits of agreement between the ECG and Nexfin-derived power spectra were estimated for the very low frequency 0.99 (0.80-1.22), for the low frequency 1.03 (0.88-1.21) and for the high frequency 1.35 (0.84-2.16). This is represented in Table 3.

Table 1.
Reproducibility of the cardiovascular reflex tests under non-standardised and standardised conditions.
Data are represented as mean (standard deviation) or median (IQR [range]).

Autonomic function test	Non-standard conditions	Standard conditions I	Standard conditions II	ICC NS/S-I (95% CI)	ICC S-I/S-II (95% CI)
Deep breathing; HR response (ratio)	1.13 (0.08)	1.09 (0.05)	1.08 (0.04)	0.96 (0.82-0.99) P<0.001	0.89 (0.53-0.98) P=0.003
Valsalva manoeuvre; HR response (ratio)	1.25 (0.14)	1.24 (0.08)	1.24 (0.09)	0.96 (0.81-0.99) P<0.001	0.91 (0.60-0.98) P=0.002
Sustained handgrip; BP response (mmHg)	21 (13)	21 (12)	14 (8)	0.24 (-1.00-0.77) P=0.319	0.11 (-1.00-0.79) P=0.435
Quick standing; BP response (mmHg)	-3 (28)	6 (16)	-3 (16)	-0.32 (-1.00-0.62) P=0.681	0.17 (-1.00-0.81) P=0.395
Quick standing; HR response (ratio)	1.19 (0.12)	1.18 (0.09)	1.17 (0.07)	0.75 (-0.98-0.94) P=0.033	0.91 (0.61-0.98) P=0.002
HRV; VLF (< 0.04 Hz) (ms^2)	217 (145-412 [34-1171])	358 (207-496 [75-1173])	371 (312-1164 [182-2269])	0.65 (-0.07-0.89) P=0.035	0.77 (0.13-0.94) P=0.005
PRV; VLF (< 0.04 Hz) (ms^2)	218 (143-436 [46-2418])	381 (183-509 [73-1059])	560 (332-1313 [180-2262])	0.47 (-0.88-0.85) P=0.155	0.68 (-0.21-0.93) P=0.020
HRV; LF (0.04-0.12 Hz) (ms^2)	75 (45-205 [14-1732)	71 (46-194 [16-634])	174 (64-634 [9-1550])	0.68 (0.00-0.90) P=0.027	0.77 (0.15-0.94) P=0.006
PRV; LF (0.04-0.12 Hz) (ms^2)	79 (47-211 [15-1794)	89 (57-304 [16-624])	175 (63-712 [7-1797)	0.70 (-0.09-0.91) P=0.034	0.71 (-0.06-0.93) P=0.031
HRV; HF (0.12-0.40 Hz) (ms^2)	126 (43-174 [18-861])	67 (30-170 [10-424])	136 (105-268 [29-699)	0.86 (0.57-0.95) P=0.001	0.86 (0.48-0.96) P=0.001
PRV; HF (0.12-0.40 Hz) (ms^2)	164 (71-228 [27-2517])	74 (57-320 [16-439)	197 (73-331 [47-722])	0.82 (0.39-0.95) P=0.005	0.84 (0.36-0.96) P=0.006

HR = heart rate; BP = blood pressure; HRV = heart rate variability; PRV = pulse rate variability; VLF = very low frequency power spectrum; LF = low frequency power spectrum; HF = high frequency power spectrum; ICC = intraclass correlation coefficient; NS = non-standardised test conditions; S = standardised test conditions

Table 2.
The Spearman's correlation coefficient between heart and pulse rate variability.

	r	P-value
VLF power (<0.04 Hz)		
HRV		
PRV	1.00	<0.001
LF power (0.04-0.12 Hz)		
HRV		
PRV	0.99	<0.001
HF power (0.12-0.40 Hz)		
HRV		
PRV	0.98	<0.001

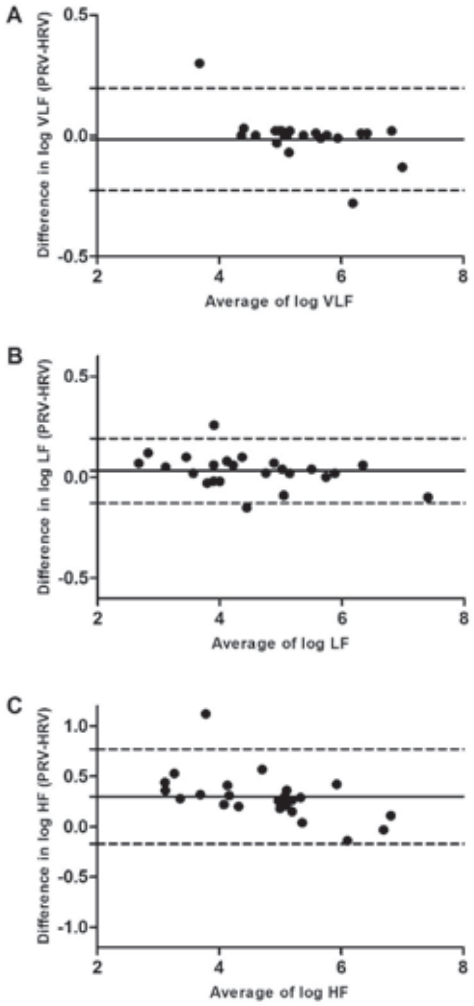
HRV = heart rate variability; PRV = pulse rate variability; VLF = very low frequency power spectrum; LF = low frequency power spectrum; HF = high frequency power spectrum.

Table 3.
The antilog mean differences and 95% limits of agreement between the spectra of heart and pulse rate variability.

	Antilog mean difference	Antilog 95% LoA
VLF power (<0.04 Hz)	0.99	0.80-1.22
LF power (0.04-0.12 HZ)	1.03	0.88-1.21
HF power (0.12-0.40 Hz)	1.35	0.84-2.16

HRV = heart rate variability; PRV = pulse rate variability; VLF = very low frequency power spectrum; LF = low frequency power spectrum; HF = high frequency power spectrum; LoA = Limits of agreement.

Figure 1.
Bland-Altman plot. Difference (pulse rate variability – heart rate variability) versus average very low frequency (panel A), low frequency (panel B) and high frequency (panel C) variability measures calculated with ECG-derived R-R intervals and Nexfin derived interbeat intervals. Bold lines mark the mean difference. Dashed lines indicate the range of 95% limits of agreement.



DISCUSSION

In this study we investigated the reproducibility of autonomic function testing under non-standardised and standardised test conditions, and the level of agreement between heart rate variability and pulse rate variability in patients with type II diabetes mellitus. We found that most classical Ewing cardiovascular autonomic function tests, heart and pulse rate variability in type II diabetic patients performed with an ECG-monitor and non-invasive blood pressure waveform device provided similar results under standardised and non-standardised test conditions. In particular, the heart rate responses during deep breathing, the Valsalva manoeuvre and heart response to quick standing showed high reproducibility under both test conditions. In contrast, the sustained handgrip and blood pressure response to quick standing showed a low reproducibility. In agreement with previous findings in healthy volunteers, this study supports the performance of cardiovascular autonomic function tests under non-standardised test conditions as an alternative to standardised test conditions in type II diabetic patients, which may facilitate implementation of autonomic function testing during preoperative assessment [12-13]. Moreover, we found a good agreement between heart and pulse rate variability, suggesting that, if ECG signals are disturbed or not available, pulse rate variability analysis derived from blood pressure waveforms may provide data comparable with that provided by heart rate variability analysis derived from an ECG.

Until now, the requirement of standardised test conditions hampered clinical implementation of cardiovascular autonomic function tests for risk stratification in the preoperative or cardiology outpatient clinic. Our results however suggest that implementation of particular autonomic function tests under non-standardised conditions, including deep breathing, the Valsalva manoeuvre, heart and pulse rate variability analysis are feasible. However, autonomic function tests based on sustained handgrip and blood pressure responses showed poor reproducibility in diabetic subjects. In particular, the sustained handgrip is subject to bias of the (proper) execution of the test [20-21]. This was also demonstrated by Kolwalewski et al. [20], who showed intraclass correlation coefficients of 0.15 to 0.52 for the reproducibility of the sustained handgrip during standardised conditions in healthy volunteers.

The relatively low and moderate intraclass correlation coefficients for the very low frequency band is a consistent finding and can be explained by our recording of short-term heart rate variability. According to recommendations of the Task Force of the European Society of Cardiology,

reliable assessment of the very low frequency band requires long-term (24 hours) heart rate variability recording [22]. Heart and pulse rate variability data are comparable with previous results in healthy subjects but showed a slightly wider confidence interval, probably because of a smaller sample size of follow up [12-13, 20].

Pulse rate variability obtained from blood pressure waveforms using a non-invasive, continuous blood pressure monitor correlated well with heart rate variability derived from ECG. This is consistent with healthy individuals [13]. Despite the excellent correspondence, the Bland-Altman analysis demonstrated an overestimation of the high frequency band of 35%, whereas the difference of the very low and low frequency were 1% and 3%, respectively. In healthy individuals however, pulse rate variability overestimated both very low and low frequency with only 1% and high frequency power spectrum only with 14% [13]. In previous studies Carrasco et al., McKinley et al. and Giardino et al. compared interbeat intervals derived by finger plethysmography (Finapres) and ECG for calculation of heart rate variability [10-11, 23]. They showed a high correspondence between the two methods, but the high frequency band was again overestimated. Although the high frequency band derived from pulse rate variability was overestimated, these data are clinically acceptable.

The mechanism behind overestimation of the high frequency band is not completely understood, but several factors may contribute. Periodic differences in the frequency range of respiratory activities as well as the influence of sampling rate on the correlation between ECG and plethysmograph-derived intervals may be involved [23]. A decrease in sampling rate may decrease the correspondence between ECG and plethysmograph-derived intervals [23]. We used a sampling rate of 1000 Hz for the R-R intervals and 200 Hz for the Nexfin-derived interbeat intervals, which might have a larger impact on the high frequency band analysis.

In addition, several factors such as arterial stiffness, pulse transit time and pulse wave velocity influence the shape of blood pressure wave forms, and may explain the differences between heart and pulse rate variability. Moreover, patients with diabetes are predisposed to increased arterial stiffness (arteriosclerosis, hypertension, etc.), which may lead to early pulse wave reflection and may have increased the overestimation of the high frequency band in the present study.

Although our study was limited by its small sample size, most findings were in agreement with our data in healthy subjects. However, more evidential value could be obtained with an expanded group of subjects [24].

Better insight into cardiovascular autonomic function helps cardiovascular risk stratification, which is likely to become increasingly important

as the prevalence of both type II diabetes mellitus and cardiovascular disease is rapidly increasing in the general patient population [25]. Furthermore, the use of non-invasive measures of cardiovascular variability for deducing autonomic function and for risk stratification remains a topic of discussion, and further research is needed to determine whether the derived information can be used to influence perioperative outcome [12, 26-27].

In conclusion, our data show that cardiovascular autonomic function tests correspond well during standardised and non-standardised test conditions in diabetic and cardiovascular subjects. Therefore, non-standardised conditions might be used in clinical or research settings where standard conditions are difficult to organise. Secondly, our data also show that in this patient population pulse rate variability derived from non-invasive blood pressure waveforms obtained with the Nexfin corresponds well with traditional heart rate variability derived from ECG under resting conditions. Therefore, pulse rate variability may be used in clinical or research settings where an ECG signal is absent or disturbed.

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