## Assessment of cardiovascular autonomic function in the anaesthesia population

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# Chapter 4

## Level of agreement between heart rate variability and pulse rate variability in healthy individuals

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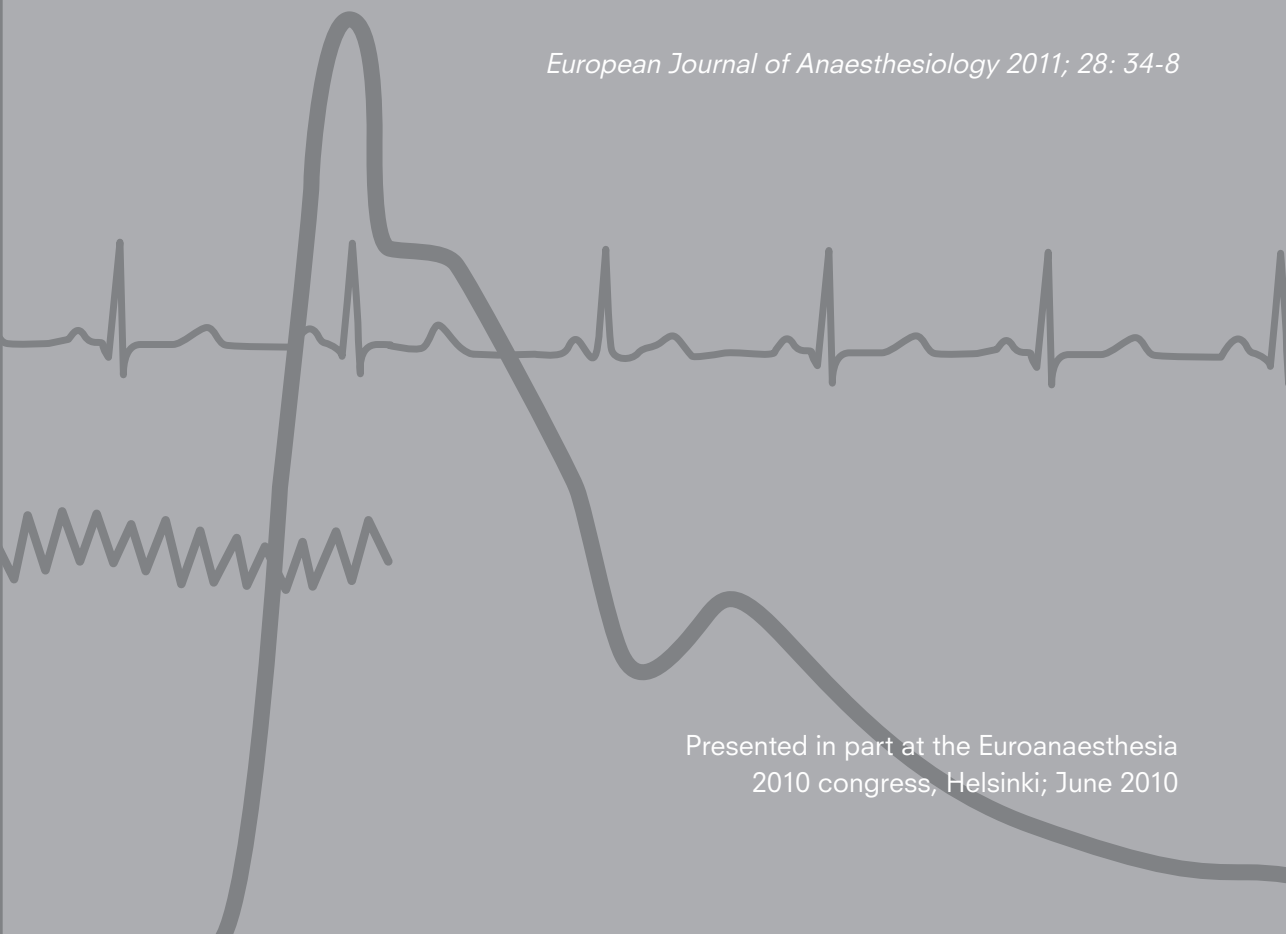

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## ABSTRACT

**Introduction:** According to international standards, autonomic function is assessed by heart rate variability (HRV) calculated from R-R intervals obtained with an electrocardiogram (ECG). However, intraoperative movement artefacts and electrical interference may complicate R-wave detection. Pulse rate variability (PRV) derived from continuous blood pressure measurements may provide a feasible alternative for HRV. We aimed to investigate the level of agreement between PRV and traditional HRV using a novel beat-to-beat non-invasive blood pressure monitoring device.

**Methods:** In this prospective observational study R-R intervals and non-invasive blood pressure waveforms were recorded simultaneously from 20 healthy male individuals at rest. HRV and PRV were analysed offline by spectral analysis, which divides the signal into its composing frequencies. Spearman's correlation coefficient, intraclass correlation coefficients and Bland-Altman analysis were used to study the level of agreement between HRV and PRV.

**Results:** The correlation coefficient between HRV and PRV was 0.99 ($p<0.001$). Level of agreement was excellent with a mean difference of 1% in the very low frequency and low frequency band and 14% in the high frequency band. Reliability of both HRV and PRV was moderate to high.

**Conclusion:** Our data show that PRV derived from non-invasive blood pressure waveforms corresponds well with traditional HRV derived from ECG. These results indicate that under standard conditions blood pressure waveforms may replace HRV in healthy individuals and that the use of PRV in the perioperative setting should be further evaluated.

# INTRODUCTION

Autonomic dysfunction in the surgical population is a frequently overlooked complication of cardiovascular diseases, such as heart failure, coronary artery disease and diabetes mellitus [1-2]. The presence of autonomic dysfunction may have important clinical and prognostic implications due to its association with perioperative haemodynamic instability, postoperative outcome, increased mortality after myocardial ischemia and sudden cardiac death [3-5].

Evaluation of autonomic function is commonly performed by quantitative assessment of beat-to-beat heart rate variability (HRV) reflecting parasympathetic and sympathetic control of the sinoatrial node [6-8]. Particularly, in case of impaired autonomic innervation, the characteristic oscillations in heart rate are reduced. International standards recommend the use of R-R intervals derived from an electrocardiogram (ECG) to calculate HRV [9]. In the intraoperative setting movement artefacts and electrical interference due to diathermy may however complicate R-wave detection. Pulse rate variability (PRV) derived from continuous blood pressure measurements may provide a feasible alternative for HRV with less sensitivity to perioperative environmental disturbances. However, several potential sources of error exist that may interfere with accurate determination of cardiac cycle length. In contrast to the ECG R-wave, a pressure pulse wave lacks a sharp peak. Furthermore, the shape and velocity of the pressure pulse wave strongly depends on stroke volume, ventricular pressure, vascular tone and pulse transit time [10]. These potential limitations for accurate pulse peak detection raised the question whether PRV is comparable to HRV and can be used to evaluate autonomic function.

Recently, the Nexfin HD monitor has become available which uses an updated implementation of the Finapres method for non-invasive, beat-to-beat blood pressure measurements [11-12]. Using Nexfin HD we investigated the level of agreement between PRV derived from blood pressure waveforms and traditional HRV derived from an ECG.

# METHODS

**Ethics**

This prospective observational study (Ethical Committee number 2009/249) was approved by the Human Individuals Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands on 17 September 2009. All participants gave written informed consent.

**Study population**

Healthy male individuals were recruited among institute staff, residents and medical students. Individuals with a history of cardiovascular disease, antihypertensive treatment, diabetes mellitus or a body mass index (BMI, $kg/m^2$) < 15 or > 35 were excluded.

**Study protocol**

Individuals were studied on two occasions. Both measurements were performed by the same investigator between 8.00 a.m. and 10.00 a.m. after overnight fasting. Individuals were asked to refrain from smoking and caffeine containing beverages 12 hours before testing. On each occasion individuals were studied during 5 minutes of spontaneous breathing in the supine position. After stabilisation of heart rate and blood pressure R-R intervals were obtained using standard bipolar ECG leads connected to a recorder. Simultaneously, interbeat intervals (IBI) derived from blood pressure waveforms were recorded using a continuous finger arterial blood pressure measurement device (Nexfin HD, BMEYE, the Netherlands). The finger cuff was applied to the middle finger of the right hand according to the manufacturer's instructions. The Nexfin uses updated technology of the Finapres device which was developed in the 1980s based on the volume clamp methodology by Penãz [13]. Briefly, volume clamping keeps the finger artery at its unloaded volume, the point at which finger cuff pressure and intra-arterial pressure are equal and transmural pressure is zero. The arteries are kept at this unloaded diameter by changing finger cuff pressure in parallel with intra-arterial pressure. Cuff pressure thus provides an indirect measure of intra-arterial pressure [14-15].

**Heart rate variability analysis**

R-R intervals were recorded using a QRS detector with a sample rate of 1000 Hz and the IBI data obtained with the Nexfin were recorded with a sample rate of 200 Hz. Heart rate and blood pressure signals were visually inspected for premature or abnormal beats and movement artefacts.

Both signals were digitised and stored on a personal computer for further analysis using free available software (Kubios HRV version 2.0, University of Kuopio, Finland) [16]. The software extracts R-R or interbeat intervals, constructs time series and subsequently performs spectral analysis using Fast Fourier Transformation. This technique divides the overall variability of a signal into its composing frequencies and provides insight in to what extent a frequency contributes to the overall variability of the signal. The power spectrum of HRV and PRV has been shown to consist of three peaks: the very low frequency (VLF) band (< 0.04 Hz), the low frequency (LF) band (0.04-0.12 Hz) and the high frequency (HF) band (0.12-0.40 Hz) [8, 17]. The VLF fluctuations are thought to be mediated primarily by the sympathetic system, the LF fluctuations by both the sympathetic and parasympathetic system and the HF fluctuations are under parasympathetic control.



**Statistical analysis**

All statistical analyses were carried out using SPSS statistical software version 15.0 (SPSS Inc., Chicago, IL, USA). Sample size was calculated on the basis of the correlation between ECG-derived HRV and Nexfin-derived PRV. We chose a correlation of at least 0.9 as a potentially meaningful correlation. For an $\alpha = 0.01$ and a $\beta = 0.10$, a sample size of 10 patients was calculated. To compensate for dropouts, 20 patients were enrolled.

The association between HRV and PRV was analysed using Spearman's rank correlation coefficient. Level of agreement was analysed by constructing Bland - Altman plots. HRV and PRV parameters were checked for heteroscedasticity and, if necessary, log-transformed prior to calculation of the limits of agreement (LoA) [18].

Finally, to assess test-retest reliability of HRV and PRV the intraclass correlation coefficients (ICC) were calculated for pairs of repeated measurements (two-way random model, absolute agreement, average measures). A p-value of $<0.05$ was considered statistically significant.

# RESULTS

### Baseline characteristics

Twenty healthy male individuals aged between 19 and 34 years were studied. Data were obtained on two occasions with 57 ± 14 days apart. In one subject, the retest data were excluded because of significant heart rhythm disturbances affecting the results of spectral analysis.

### Correlation and agreement between HRV and PRV

The correlation between the variability in heart rate and pulse rate is shown in Table 1, which was 0.99 for all frequency bands.

Bland – Altman analysis (Figure 1) revealed a mean difference between PRV and HRV of 1% in the VLF (panel A) and LF band (panel B), while PRV was 14% higher than HRV in the HF band (panel C). Antilogs of the LoA revealed that for 95% of cases in the VLF band, PRV will be between 0.97 and 1.04 times HRV. This indicates that PRV measurements may differ from HRV measurements by 3% below to 4% above. In the LF band the difference between PRV and HRV ranges from 5% below to 8% above and in the HF band from 4% below to 36% above (Table 2).

Table 1.
Spearman's rank correlation coefficient ( r ) between ECG- and Nexfin-derived power spectrum.

| Spectrum | Median ($ms^2$) | $10^{th}$ – $90^{th}$ centiles ($ms^2$) | r |
|---|---|---|---|
| **VLF power** (< 0.04 Hz) | | | |
| HRV | 1305 | (394 – 4390) | |
| PRV | 1301 | (386 – 4368) | 0.99* |
| **LF power** (0.04 – 0.12 Hz) | | | |
| HRV | 1037 | (373 – 4505) | |
| PRV | 1033 | (379 – 4547) | 0.99* |
| **HF power** (0.12 – 0.40 Hz) | | | |
| HRV | 1611 | (412 – 8920) | |
| PRV | 1793 | (610 – 10706) | 0.99* |

Values are median and $10^{th}$–$90^{th}$ percentiles. HF, high frequency; HRV, heart rate variability; LF, low frequency; PRV, pulse rate variability; VLF, very low frequency. P<0.001.

Figure 1.
Difference (PRV – HRV) versus average VLF (panel A), LF (panel B) and HF (panel C) variability measures calculated with Nexfin and ECG-derived intervals. Original measurements (in $ms^2$) were log-transformed prior to construction of Bland-Altman plots because of heteroscedasticity [18]. Bold lines indicate mean differences. Dashed lines mark boundaries of 95% limits of agreement.

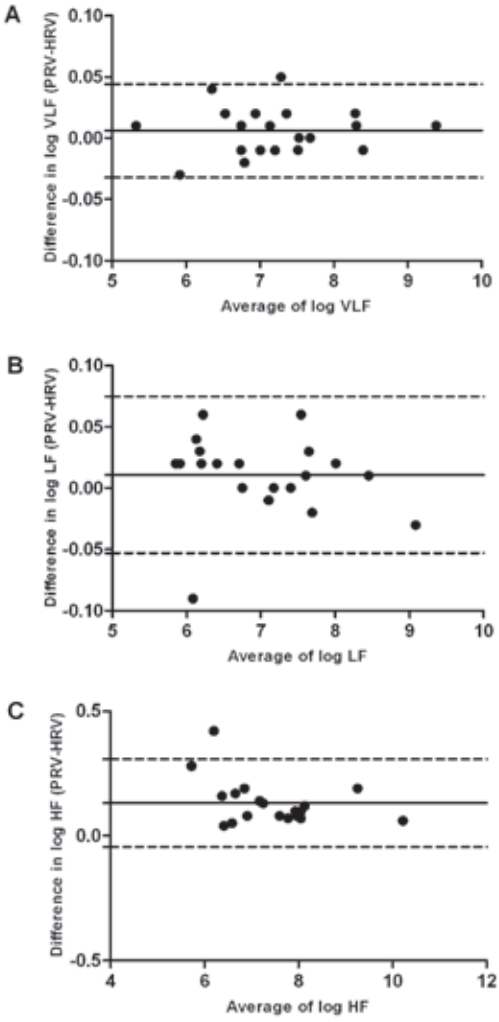


Table 2.
Antilog mean differences and 95% limits of agreement between ECG- and Nexfin-derived power spectrum.

| | Antilog mean difference | Antilog 95% LoA |
|---|---|---|
| **VLF** | 1.01 | 0.97 – 1.04 |
| **LF** | 1.01 | 0.95 – 1.08 |
| **HF** | 1.14 | 0.96 – 1.36 |

HF, high frequency; LF, low frequency; LoA, limits of agreement; VLF, very low frequency.

Table 3.
Intraclass correlation coefficients for test-retest reliability of ECG- and Nexfin-derived data.

| | HRV | PRV |
|---|---|---|
| **VLF** | 0.38 (-0.66 – 0.77) | 0.44 (-0.47 – 0.80) |
| **LF** | 0.93 (0.81 – 0.97) | 0.92 (0.80 – 0.97) |
| **HF** | 0.66 (0.08 – 0.87) | 0.69 (0.14 – 0.89) |

Intraclass correlation coefficients are given with 95% confidence intervals. HF, high frequency; HRV, heart rate variability; LF, low frequency; PRV, pulse rate variability; VLF, very low frequency.

### Test-retest reliability of HRV and PRV

Intraclass correlation coefficients (ICC) calculated for the test-retest reliability of HRV and PRV are shown in Table 3. The ICC values range from moderate (r = 0.38) to good (r = 0.93) and were comparable for both HRV and PRV.

## DISCUSSION

The present study provides merits to use pulse rate variability (PRV) as alternative for traditional heart rate variability (HRV) in the detection of disturbances in autonomic function. PRV derived from blood pressure waveforms using non-invasive, beat-to-beat blood pressure monitoring showed a high correlation and level of agreement with traditional HRV obtained with an ECG. Furthermore, both PRV and HRV showed a moderate to high test-retest reproducibility. These results imply that PRV, which is less influenced by environmental disturbances than HRV, may be used for autonomic function assessment in the perioperative period.

Our findings are consistent with previous reports investigating alternative methods for heart rate variability assessment [19-21]. McKinley et al. [19] studied the reliability of interbeat intervals by finger plethysmography (Finapres) and ECG for calculation of HRV parameters under different conditions. Although correspondence between the two methods was excellent, the Finapres overestimated the power in the HF (0.15 – 0.40 Hz) band during supine rest. This overestimation was more pronounced during exercise but the level of agreement remained acceptable. Giardino et al. [21] also compared finger plethysmography with ECG in providing accurate cardiac cycle duration for calculation of HRV. Both methods

correlated highly for low (0.07 – 0.15 Hz) and high (0.15 – 0.40 Hz) frequency HRV. However, during rest and exercise plethysmography-derived HRV overestimated the power in the HF band, and to lesser extent the power in the LF band. Finally, Carrasco et al. [20] studied ECG- and Finapres-derived HRV and reported a high correlation between the two acquisition methods but with significant overestimation of the HF band using Finapres data during standing and exercise. Our data also demonstrate excellent correspondence for the VLF and LF band. Although the HF band derived from PRV was overestimated, these data are clinically acceptable.

The explanation for the overestimation of HF variability under various conditions remains unclear, but several factors may contribute to differences between PRV and HRV. Giardino et al. [21] investigated the influence of sampling rate on the correlation between ECG- and plethysmograph-derived intervals. The correlation between the two methods decreased with a decrease in sampling rate. In our study, Nexfin-derived intervals were obtained with a sample rate of 200 per second and the R-R intervals with a rate of 1000 per second, which may have contributed partly to the difference in ECG- and Nexfin-derived HF band. Another possible explanation is suggested by the observation that the differences between the two methods occurred periodically within the frequency range of respiratory activity [21]. Whether the periodical influence of respiration is indeed capable of influencing high frequency PRV requires further research.

Cardiac cycle duration detected with finger plethysmography may also differ from ECG-derived intervals because the shape of the pressure waveform is dependent on different characteristics of the peripheral vasculature. For example, various studies showed that arterial stiffness decreases in healthy individuals during exercise thereby reducing pulse transit time and pulse wave velocity [22-23]. Other factors that may influence arterial stiffness are increasing age, arteriosclerosis and hypertension. Whether changes in arterial stiffness and pulse transit time alter the shape of the pressure waveform in a way that affects determination of cardiac cycle duration remains to be elucidated. Therefore, the possibility of extrapolating our results to conditions that affect shape and velocity of the pulse wave, such as peripheral or cardiovascular disease and critically ill patients requiring vasoactive medication, needs to be explored in future studies.

The test-retest reliability of HRV and PRV measurements are comparable. Previous studies focusing on reliability of HRV using short-term recordings have shown similar results [24-25]. The relatively low ICC for

the VLF band is consistent with the report from the Task Force of the European Society of Cardiology that recommend to assess the VLF band from long-term (24 hours) recording to ensure maximal reliability [9].

The following limitations should be taken into account in the interpretation of the present results. As previously stated, in this study we only included healthy individuals and therefore no conclusions can be drawn about the use of PRV under pathological conditions, such as increased sympathetic stress or autonomic dysfunction. Furthermore, the agreement and reliability of PRV were obtained during supine rest and not during exercise, which limits comparison to other studies. However, current guidelines recommend to perform spectral analysis under resting conditions for optimal systematic evaluation [2]. In addition, age- and sex-specific reference values for the different frequency bands are only studied for resting HRV, making this the most important clinical parameter [24, 26]. Finally, in this study we used the Nexfin, which derives arterial blood pressure waveforms with a specific finger probe by the volume clamp methodology. Although this methodology has been established in autonomic function testing, its intraoperative use under different clinical conditions largely remains to be validated [11, 24]. We therefore emphasise that further studies investigating the value of pulse rate variability to evaluate perioperative autonomic function under various clinical conditions are warranted.

In conclusion, our data show that under resting conditions PRV derived from non-invasive blood pressure waveforms obtained with the Nexfin corresponds well with traditional HRV derived from ECG. These results indicate that in healthy individuals under standard conditions blood pressure waveforms may replace HRV in the evaluation of autonomic function. Therefore, PRV can be used in research settings where an ECG signal is absent or unwanted. These results further expand the use of PRV in autonomic function testing and future investigations should explore whether its use can be extrapolated to different clinical conditions and patient subgroups.

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