Assessment of cardiovascular autonomic function in the anaesthesia population

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Chapter 6

Reproducibility of non-standardised autonomic function testing in the preoperative assessment screening clinic

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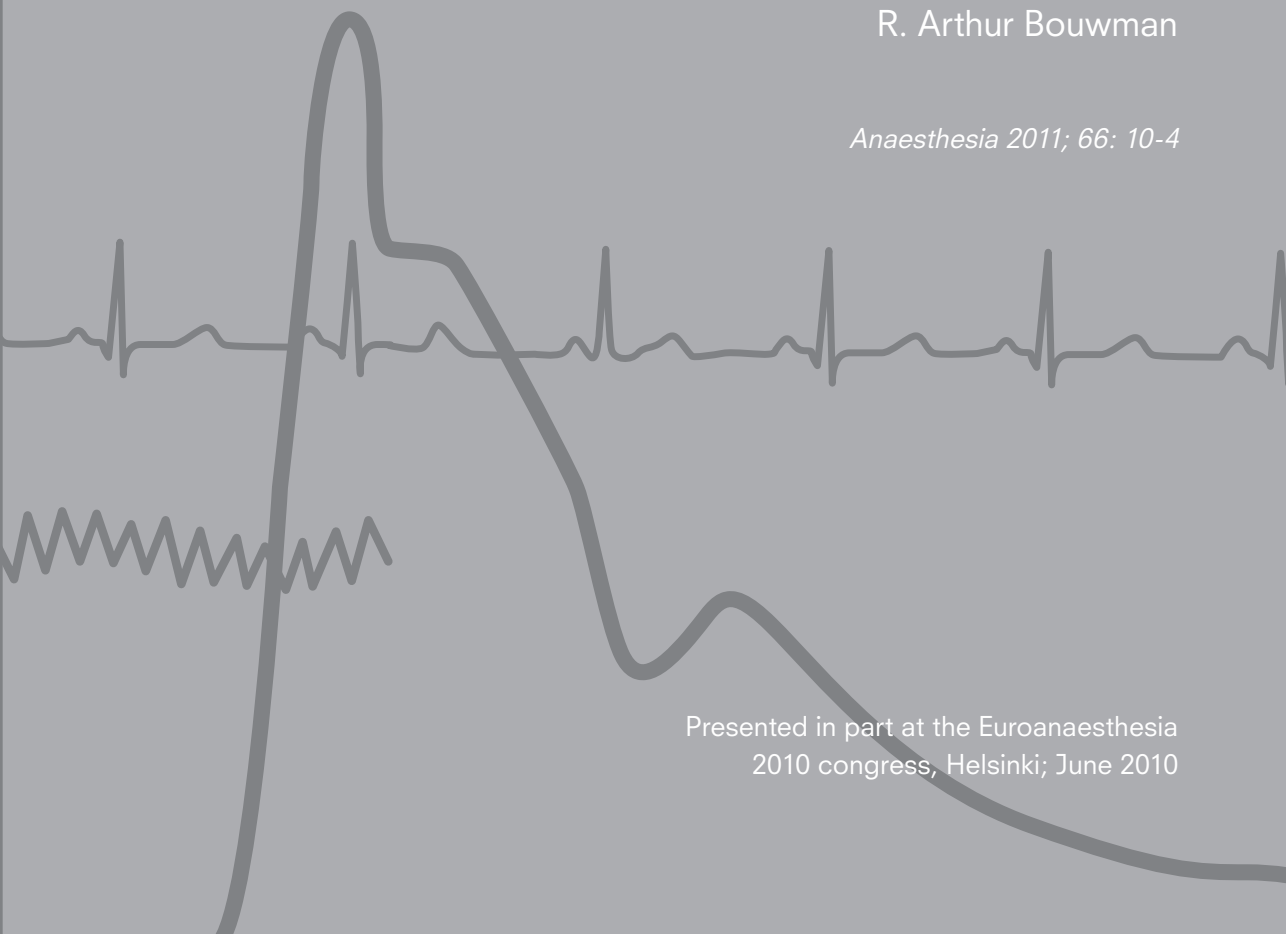

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ABSTRACT

Introduction: By convention, autonomic function tests are undertaken under standard test conditions that limit their implementation during routine preoperative assessment. We therefore evaluated the comparability of autonomic function tests under both non-standardised and standardised test conditions in 20 healthy male subjects.

Methods: Autonomic function was assessed using an ECG monitor and a continuous non-invasive blood pressure measurement device in 20 healthy male volunteers.

Results: Under non-standardised conditions, intraclass correlation for heart rate variability analysis was good for the low and high frequency bands (0.87; 95% CI 0.58-0.96 and 0.83; 95% CI 0.56-0.94, respectively), but moderate (0.65; 95% CI 0.14-0.86) for the very low frequency band; reproducibility was high for the expiration/inspiration ratio (0.89; 95% CI 0.71-0.96), Valsalva ratio (0.76; 95% CI 0.37-0.91) and handgrip test (0.76; 95% CI 0.35-0.91) (all $P < 0.05$) but was low for the response to quick standing. Reproducibility under standardised conditions was comparable to the above values.

Conclusion: We demonstrated that reproducibility for most autonomic tests under non-standardised conditions is acceptable and suggest that implementation of these tests during preoperative assessment might be feasible.

INTRODUCTION

Elderly patients and those suffering from obesity, hypertension and diabetes increasingly dominate the anaesthetic preoperative assessment clinic. Preoperative risk assessment and optimisation of these patient groups may lead to prevention of perioperative complications. In particular, diseases such as diabetes are frequently complicated by impaired cardiovascular autonomic innervation and, in the later stages, cardiovascular autonomic neuropathy. It has been shown that the presence of cardiovascular autonomic neuropathy is predictive of perioperative haemodynamic instability and postoperative complications [1-4]. Indeed, it has been shown that diabetic patients with autonomic neuropathy are prone to develop unstable blood pressure and hypothermia during anaesthesia [2-5]. This suggests that routine preoperative assessment of the integrity of cardiovascular autonomic control may be valuable for perioperative cardiovascular risk prediction and management.

Cardiovascular autonomic function is classically evaluated using the Ewing tests and quantitative assessment of beat-to-beat heart rate variability [6-8]. By convention, these tests are undertaken under standardised conditions in order to eliminate the influence of cyclic physiological variations and environmental factors. Current guidelines recommend that patients should refrain from smoking, eating and drinking, and that the tests be performed in a quiet ambiance at room temperature [7], conditions that are difficult to implement during routine preoperative evaluations. For testing to be feasible during routine preoperative assessment, these standardised conditions would need to be relaxed. We therefore investigated whether the results of autonomic function testing performed under non-standardised conditions yielded comparable test results to those obtained under standardised conditions.

METHODS

Study population

The study was approved by the Institutional Human Subjects Committee of the VU University Medical Centre, Amsterdam. We recruited 20 healthy male subjects (aged 18-35 years) from institute staff, residents and medical students. Subjects with a history of cardiovascular disease, antihypertensive treatment, diabetes mellitus or a body mass index < 15 or > 35 kg/m^2 were not studied. Written consent was obtained from all participants.

Study design

For each participant, cardiovascular autonomic function testing was performed at three consecutive time points, two using standardised conditions to test for intra-test variability and one using non-standardised conditions to test for inter-test variability. The same investigator performed all tests. For the standardised test conditions, the participants fasted from midnight and were asked to refrain from smoking and consuming caffeine-containing beverages. The autonomic function tests took place between 08:00 and 10:30 hours in quiet conditions with a room temperature of 19-22 °C [7]. For the non-standardised test conditions, autonomic function tests were repeated randomly during the preoperative screening clinic in the same subjects between 12:00 and 16:00 hours, without any restrictions with regard to oral intake.

Participants' heart rate and blood pressure responses were monitored using a standard ECG and a non-invasive continuous finger arterial blood pressure measurement device (Nexfin HD, BMEYE, the Netherlands). The finger cuff of the Nexfin was applied to the middle finger of the right hand according to the manufacturer's instructions. This method is based on the development of the dynamic (pulsatile) unloading of the finger arterial walls using an inflatable finger cuff with a built-in photo-electric plethysmograph. From the finger pressure waveform, heartbeats are detected and systolic, diastolic and mean pressures and pulse rate are displayed in a beat-to-beat manner [9].

Autonomic function measurements

Subjects were initially placed in the supine position and, after stabilisation of their blood pressure and heart rate; the ECG was recorded for 5 minutes during spontaneous breathing for subsequent heart rate variability analysis. Conventional cardiovascular reflex tests were then performed with blood pressure and heart rate responses measured

during deep breathing and Valsalva (Valsalva ratio), sustained handgrip and quick standing manoeuvres [6].

Parasympathetic function was assessed during deep breathing, a Valsalva manoeuvre, and using heart rate analysis during standing. For the deep breathing test, subjects were asked to perform six deep breaths in 1 minute, during which the maximum and minimum R-R intervals were measured from the ECG. The R-R intervals during expiration and inspiration were then determined and expressed as a ratio; in healthy subjects the ratio of these intervals is larger than 1.17. For the Valsalva manoeuvre, the subjects were required to exhale forcibly through a manometer against a pressure of 40 mmHg for 15 seconds; again, the ratio of R-R intervals was calculated, being > 1.21 in healthy subjects. For assessment of heart rate during quick standing, R-R intervals were measured at 15 and 30 beats; in healthy subjects, the ratio of the longest R-R interval to the shortest R-R interval is > 1.04.

The assessment of sympathetic function included a sustained handgrip test and blood pressure changes during quick standing. The sustained handgrip test requires the subject to squeeze a handgrip dynamometer to establish a maximum developed force. Subsequently, the grip is then squeezed at 30% maximum force for 5 minutes. In healthy subjects, diastolic blood pressure should increase by more than 16 mmHg in the opposite arm. To assess changes in blood pressure during standing, systolic blood pressure was measured in the resting, supine subject. Two minutes after rapid standing, the measurement was repeated; in healthy subjects the fall in systolic blood pressure after the test should be less than 10 mmHg.

Autonomic function analysis

For all study participants, the ECG was analysed for heart rate variability by visual inspection for premature or irregular beats and movement artefacts, followed by spectral analysis using fast Fourier transformation on derived R-R intervals using Kubios software (Kubios HRV version 2.0, University of Kuopio, Finland) [10]. The power spectrum was divided into the very low frequency (0.0-0.04 Hz), low frequency (0.04-0.12 Hz) and high frequency (0.12-0.4 Hz) bands, which fluctuate under the influence of the sympathetic nervous system (very low frequency band), the parasympathetic nervous system (high frequency band) or both (low frequency band) [11-12].

Statistical analysis

All statistical analyses were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Values for the first and second autonomic function tests under standardised conditions and the test under non-standardised conditions are represented as median (IQR[range]) for the heart rate variability and as mean (SD) for the classical Ewing's tests. Test reproducibility was analysed by intraclass correlation coefficients (95% CI). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Autonomic function testing was performed in 20 healthy male subjects on three different occasions. In one subject, the re-test data were not further studied because of significant heart rhythm disturbances. All cardiovascular autonomic test values were within the reference ranges under both standardised and non-standardised test conditions (Table 1).

The reproducibility of autonomic function testing and heart rate variability under standardised test conditions is shown in Table 2. Analysis of the low frequency and high frequency band reproducibility during heart rate variability analysis showed good and moderate intraclass correlation coefficients (0.93 and 0.66, respectively; $P < 0.05$ for both). However, the reproducibility of the very low frequency band during heart rate variability analysis was poor (intraclass correlation coefficient 0.37; $P > 0.05$). Re-testing of deep breathing, Valsalva manoeuvres and the sustained handgrips under standardised conditions was associated with good intraclass correlation coefficient values (0.88, 0.89 and 0.81, respectively; $P < 0.05$ for all). The reproducibility of the blood pressure and heart rate responses during the quick standing test was, however, poor (intraclass correlation coefficients 0.32 and 0.34, respectively).

Table 1.
Test results of autonomic function tests under standardised and non-standardised conditions. Data are represented as median (IQR [range]) or mean (SD) for each test condition.

	Standard 1st test	Standard 2nd test	Non-standard test
HRV; VLF power spectrum (< 0.04 Hz); ms^2	1305 (850–2089 [394–4390])	962 (669–1349 [504–4198])	994 (452–1374 [325–4289])
HRV; LF power spectrum (0.04–0.12 Hz); ms^2	1037 (476–2041 [373–4505])	568 (344–1548 [174–2976])	769 (364–1109 [142–1679])
HRV; HF power spectrum (0.12–0.40 Hz); ms^2	1611 (709–2976 [412–8920])	874 (375–2456 [177–6876])	825 (451–1715 [103–5795])
Deep breathing; heart rate response ratio	1.29 (0.14)	1.28 (0.15)	1.31 (0.13)
Valsalva manoeuvre; heart rate response ratio	1.68 (0.33)	1.74 (0.37)	1.70 (0.41)
Sustained handgrip; blood pressure response; mmHg	22 (14)	19 (9)	18 (8)
Quick standing; blood pressure response; mmHg	–3 (9)	–1 (8)	–5 (8)
Quick standing; heart rate response ratio	1.49 (0.23)	1.45 (0.24)	1.42 (0.21)

HRV, heart rate variability; VLF, very low frequency; LF, low frequency; HF, high frequency.

The comparisons of autonomic function tests and heart rate variability under random and standardised test conditions are shown in Table 3. The three heart rate variability frequency bands (very low, low and high frequency) demonstrated a moderate-to-good reproducibility between standardised and non-standardised test conditions, with intraclass correlation coefficients of 0.65, 0.87 and 0.83, respectively (all $P < 0.05$). The classical autonomic function tests showed good correlation values for the deep breathing (intraclass correlation coefficient 0.89; $P < 0.05$), the Valsalva manoeuvre (intraclass correlation coefficient 0.76; $P < 0.05$) and the sustained handgrip (intraclass correlation coefficient 0.76; $P < 0.05$) for retesting under random and standardised test conditions. The two parameters associated with the quick standing test (blood pressure and heart rate responses) demonstrated a poor reproducibility (intraclass correlation coefficients 0.48 and 0.32, respectively) when standardised and non-standardised test conditions were compared.

Table 2.
Reproducibility of autonomic function testing under standardised test conditions. Data are represented as intraclass correlation (95% CI).

Standard–standard	Intraclass correlation	P value
HRV; VLF power (< 0.04 Hz)	0.37 (–0.60–0.75)	0.172
HRV; LF power (0.04–0.12 Hz)	0.93 (0.81–0.97)	< 0.001
HRV; HF power (0.12–0.40 Hz)	0.66 (0.12–0.87)	0.018
Deep breathing; heart rate response	0.88 (0.69–0.95)	< 0.001
Valsalva manoeuvre; heart rate response	0.89 (0.71–0.97)	< 0.001
Sustained handgrip; blood pressure response	0.81 (0.47–0.93)	0.001
Quick standing; blood pressure response	0.32 (–0.76–0.74)	0.212
Quick standing; heart rate response	0.34 (–0.88–0.76)	0.208

HRV, heart rate variability; VLF, very low frequency; LF, low frequency; HF, high frequency.

Table 3.
Reproducibility of autonomic function testing under standardised and non-standardised test conditions. Data are represented as intraclass correlation (95%CI).

Standard – non-standard	Intraclass correlation	P value
HRV; VLF power (< 0.04 Hz)	0.65 (0.14–0.86)	0.012
HRV; LF power (0.04–0.12 Hz)	0.87 (0.58–0.96)	< 0.001
HRV; HF power (0.12–0.40 Hz)	0.83 (0.56–0.94)	< 0.001
Deep breathing; heart rate response	0.89 (0.71–0.96)	< 0.001
Valsalva manoeuvre; heart rate response	0.76 (0.37–0.91)	0.002
Sustained handgrip; blood pressure response	0.76 (0.35–0.91)	0.002
Quick standing; blood pressure response	0.48 (–0.38–0.8)	0.092
Quick standing; heart rate response	0.32 (–0.78–0.74)	0.212

HRV, heart rate variability; VLF, very low frequency; LF, low frequency; HF, high frequency.

DISCUSSION

This study provides evidence that non-standardised cardiovascular autonomic function tests could be used as an alternative to standardised measurements for the detection of disturbances in cardiovascular autonomic function. Our data show that non-standardised cardiovascular autonomic function tests derived from an ECG-monitor and non-invasive blood pressure waveforms (obtained using a volume-clamp based monitor [9]) correspond well with standardised test conditions. The reproducibility of the deep breathing, Valsalva manoeuvre, and sustained handgrip tests were moderate-to-good under both standardised and non-standardised test conditions. Heart rate variability analysis showed moderate-to-good reproducibility of the low frequency and high frequency bands, but poor reproducibility of the very low frequency band, under standardised and non-standardised test conditions. These data suggest that autonomic function testing under non-standardised test conditions may provide a valuable alternative to those performed under standardised test conditions.

Ewing et al. described the classical cardiovascular screening tests to diagnose cardiovascular autonomic neuropathy [6, 13-14], with the parasympathetic nervous system being assessed by the heart rate responses

during deep breathing, Valsalva manoeuvre and quick standing tests, and the sympathetic nervous system being assessed by the blood pressure responses during sustained handgrip and quick standing tests. These tests continue to be used for the diagnosis of autonomic dysfunction [7, 8, 15].

A significant proportion of patients attending the preoperative assessment clinic suffer from complex comorbidities, which can affect autonomic function. Meticulous assessment and preparation of such patients for surgery is a vital component of efficient perioperative medical practice [16-17]. To date, cardiovascular autonomic function has not been routinely evaluated during preoperative assessment because of the complexity of the standardised test conditions. Interestingly, the results of our study show comparable reproducibility for autonomic function assessments performed under standardised and non-standardised conditions, suggesting that implementation of autonomic function testing in the preoperative assessment clinic may be feasible.

Whether such preoperative assessment of autonomic function is of value in reducing perioperative morbidity remains to be elucidated. However, it has been shown that perioperative haemodynamic stability and postoperative complications are influenced by the presence of cardiovascular autonomic neuropathy [1-4]. Other reports have shown that autonomic neuropathy is associated with the development of blood pressure instability and intraoperative hypothermia and can influence patient outcome [2-5]. The identification of such neuropathy during the preoperative period may therefore improve perioperative treatment of patients undergoing surgery and enhance risk stratification.

We used the classical cardiovascular autonomic functions tests [6-8] described by Ewing et al., which enable the analysis of heart rate and blood pressure responses to different stimuli of the autonomic nervous system. Data were obtained using a relatively novel non-invasive blood pressure measurement device (Nexfin HD) that provided a beat-to-beat arterial pressure waveform, which has been shown to have good accuracy and precision while tracking fast changes in blood pressure [9].

To comply with accepted standardised conditions [6-8], we required the study participants to attend for testing having fasted from midnight and having refrained from smoking and consuming caffeine-containing beverages. The autonomic function tests took place between 08:00 and 10:30 hours in a quiet environment with a room temperature of 19-22°C. Testing under non-standardised conditions took place in the same subjects without any restrictions with regard to oral intake. We found no significant differences in the test reproducibility and test results between

standardised and non-standardised test conditions.

A limitation of our study is that the study population consisted of healthy male volunteers; our findings may not be reproducible in populations with greater gender variation and in individuals with known autonomic dysfunction or other complex medical diseases. Future studies should address this limitation when examining the reproducibility of cardiovascular autonomic function tests under non-standardised conditions [8].

The reproducibility of the quick standing test for both blood pressure and heart rate responses was low. This finding was consistent for both standardised and non-standardised test conditions and with the findings of other studies that have showed a low reproducibility for the quick standing test [7]. Future investigations should explore whether this specific test condition is of value in detecting autonomic function disorders in preoperative patients.

In conclusion, our data show that cardiovascular autonomic function tests performed under non-standardised conditions correspond well with those obtained under standardised test conditions in healthy male volunteers. This suggests that autonomic function tests may be viably performed in settings such as the preoperative assessment clinic, where standardised conditions are difficult to reproduce. However, more research is needed to examine whether this conclusion can be extrapolated to broader patient groups, and whether the information gleaned from the tests can be used to influence perioperative outcome.

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