Converging methods in the assessment of sympathetic baroreflex sensitivity

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Aims
Abnormalities of the sympathetic baroreflex regulation are documented in various diseases. The recording of sympathetic nerve activity allows for the calculation of baroreflex gain but this is not available in practice. A non-invasive method based on blood pressure during the late phases of Valsalva manoeuvre (VM) was proposed. Sympathetic gain could be calculated from the pressure fluctuations following ventricular extrasystole or non-sustained ventricular tachycardia (NSVT).

Methods and results
We assessed both indices in 25 subjects with no significant cardiovascular disease. VM was performed at 40 mmHg for 12 s. Paced NSVT consisted of five to six cycles. The sympathetic gains were determined based on the recovery of mean arterial pressure (MAP, mmHg/s). The maximum slope of five consecutive MAP elevations occurring within a 15-cycle period after NSVT was calculated. This MAP turbulence slope (MAPTS) was expressed in mmHg/cycle. Five patients were excluded because of unacceptable VM. VM-derived sympathetic gain (SBRSvals) and the NSVT-derived gain (SBRSNSVT) correlated closely (R = 0.86, P < 0.001). Their mean difference was 3.2 ± 4.8 mmHg. Both SBRSvals and SBRSNSVT correlated closely with MAPTS (R = 0.77, P < 0.001 and R = 0.86, P < 0.001, respectively).

Conclusion
The sympathetically mediated arterial pressure recovery is an analogous process following both VM and NSVT. SBRSNSVT or MAPTS may be useful in the assessment of patients with implanted antiarrhythmic devices.

Keywords
Sympathetic baroreflex sensitivity • Valsalva manoeuvre • Non-sustained ventricular tachycardia

Introduction
Decreased cardiovagal baroreflex sensitivity along with abnormal heart rate variability parameters is a predictor of adverse outcome in certain cardiovascular diseases. Baroreflex-based and autonomic nervous system-mediated post-extrasystolic heart rate fluctuations (heart rate turbulence) have similar predictive capacity.1,2 Cardiovagal baroreflex sensitivity, however, characterizes only a part of the baroreflex, and not even the most important component.3 Baroreflex regulation of muscle sympathetic nerve activity (MSNA) exhibits well-known abnormalities in certain conditions, such as congestive heart failure, and essential hypertension.4–6 MSNA recording however is a time-consuming, invasive technique, which requires special skill and equipment. Recently, a simple sympathetic baroreflex index, derived from the blood pressure dynamics during the late phases of Valsalva manoeuvre (VM) was proposed.7,8 In the mean time, based on the relationship with heart rate turbulence slope, several groups introduced the idea of the post-extrasystolic blood pressure turbulence slope.9–11 Blood pressure turbulence slope may represent another sympathetic baroreflex gain. Our goal was to assess the relationship between these indices in subjects with no severe structural heart disease.

Methods
The subjects were recruited from patients who underwent cardiac electrophysiological study at our laboratory. The protocol was approved by our local ethical committee, the study complied with the Declaration of Helsinki and all patients gave written consent to the study. Twenty-five patients with normal left ventricular systolic function entered the study [ejection fraction (EF) >50%]. Patients

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with diabetes, Parkinson’s disease, or with a history of excessive alcohol consumption were not considered. In order to elicit blood pressure drops of similar magnitude by pacing and VMs, short ventricular runs (four to six beats), with a cycle length of $< 60\%$ of the prevailing sinus rhythm were applied instead of single extrasystole. $12$ VMs were repeated at $40 \text{mmHg}$ for $12 \text{s}$ until the first acceptable recording (by length, maintained pressure, and character of blood pressure recording) was obtained. $7$

The ECG and blood pressure signals were continuously measured with a Marquette bedside monitor and with a Finapres 2300 (Ohmeda) non-invasive blood pressure monitor. The signals were digitalized online, with $250 \text{Hz}$ by the Dataq/Windaq system. Data were analysed offline by the same system. Cardiac cycles were defined by RR intervals for both sinus-, and paced NSVT periods. The arterial pressure signal was integrated and averaged over each cardiac cycle. Since systolic pressure values could not be interpreted during pulseless NSVT periods, mean arterial pressure (MAP) was selected for comparison of the different tests.

Baseline MAP was determined from $20$ cardiac cycles immediately preceding the NSVT and the VM. The minimum MAP values, and the drops compared with baseline ($\Delta\text{MAP}$) were determined during phase $3$ of the VM and following the paced NSVT periods. The arterial pressure signal was integrated and averaged over each cardiac cycle. Since systolic pressure values could not be interpreted during pulseless NSVT periods, mean arterial pressure (MAP) was selected for comparison of the different tests.

Baseline MAP was determined from $20$ cardiac cycles immediately preceding the NSVT and the VM. The minimum MAP values, and the drops compared with baseline ($\Delta\text{MAP}$) were determined during phase $3$ of the VM and following the paced NSVT series (Figures 1 and 2). The MAP return times ($\Delta\text{time}$) were defined as the time elapsing from the onset of the cardiac cycle with the minimum MAP to the onset of the first cycle exceeding the baseline (Figures 1 and 2). The sympathetic BRS values were determined as the ratio of MAP drop and return time, expressed as mmHg/s. $\text{SBRS}_{\text{val}}$ was derived from a single VM. $\text{SBRS}_{\text{NSVT}}$ was defined as the average of gains, derived from two NSVT series. Within a $15$-cycle pressure recording, which immediately followed the NSVT, the maximum slope of five consecutive MAP elevation steps was also calculated, and expressed as MAP turbulence slope ($\text{MAP}_{\text{T5}}$) in the dimension of mmHg/cycle. Comparisons of the pressure responses and recovery time, as well as the baroreflex gains were performed by paired t-tests. The Wilcoxon-signed rank test was used for parameters showing skewed distribution. The relationship between the two baroreflex gains and the $\text{MAP}_{\text{T5}}$ was assessed by linear regressions. The agreement between $\text{SBRS}_{\text{val}}$ and $\text{SBRS}_{\text{NSVT}}$ was also assessed by Bland–Altman plot.

**Results**

The cardiac electrophysiology study was uneventful in all cases. Based on a preliminary assessment, five recordings were excluded from further analysis; two recordings because of the inability of the subject to perform acceptable VM, and frequent Valsalva-induced premature ventricular complex, preventing analysis in three other recordings.

Recordings of $20$ patients ($11$ female) entered the final analysis. Their mean age was $57 \pm 17$ years. Seventeen patients suffered from atrioventricular nodal re-entry tachycardia, one from paroxysmal atrial flutter, one from atrioventricular reentry tachycardia, and one from right ventricular outflow tract tachycardia. Co-morbidity included mild, controlled hypertension in $13$ cases.

The paced NSVT consisted of five to six cycles with a driving frequency of $184 \pm 40 \text{min}$ (range $120–270 \text{min}$). $\Delta\text{MAP}$ was slightly but significantly greater following NSVT than during the recovery phase of the VM ($37 \pm 18 \text{ vs. } 45 \pm 17 \text{mmHg}$).
Accordingly, the recovery time from NSVT was slightly longer (4.9 ± 3 vs. 6.2 ± 7 s, P = NS). The SBRS\textsubscript{NSVT} values were significantly higher than the SBRS\textsubscript{vals} values (12.5 ± 5 vs. 9.4 ± 7 mmHg/s, P < 0.008). Nevertheless, these parameters correlated closely (R = 0.86, P < 0.001). Their mean difference was 3.2 ± 4.8 mmHg. The Bland–Altman plot (Figure 3) also indicated a modest relationship.

With two exceptions MAP\textsubscript{TS} could be calculated over the first five post-NSVT cycles. Both SBRS\textsubscript{vals} and SBRS\textsubscript{NSVT} correlated closely with MAP\textsubscript{TS} (R = 0.77, P < 0.001 and R = 0.86, P < 0.001, respectively).

**Discussion**

It has long been noted that arterial pressure fluctuation following a premature ventricular contraction resembles the late phases of the VM. Blood pressure recovery from VM in patients with autonomic failure varies directly with the severity of adrenergic
impairment,14,15 and the sluggish blood pressure recovery following premature ventricular contraction is also characteristic of these patients.13 Furthermore, both abnormal responses could be reproduced in healthy subjects by Nn-nicotinic blockade.13,16 In spite of these similarities, important differences between the two responses could also be acknowledged. A premature ventricular beat with its compensatory pause results in a temporary decline in arterial pressure, triggering sympathetic response.17,18 Conflicting influences could be operational during ventricular tachycardia, which is accompanied by unloading of the arterial, and loading of the cardiopulmonary baroreceptors.19 Arterial baroreflex control predominates in mediating sympathoexcitation.19 Following ventricular extrasystole, or NSVT, the sympathetic activation generates arterial pressure elevation. The changes in stroke volume following a longer pause contribute significantly to the restoration of arterial pressure. The vagal withdrawal, which accompanies the temporary hypotension, may also interfere with the MAP recovery profile. Therefore, gains derived from the MAP recovery are not pure indices of sympathetic activity. During VM, complex interactions of mechanical and reflex responses occur.20,21 The arterial baroreflex activation during the early strain phase reflects opposing influences of different aortic and carotid baroreceptor stimulation.22 With prolonged straining, both the aortic cross-sectional area and the peripheral pressure decline. These changes are reflected by increased sympathetic muscle nerve activity. Post-straining arterial pressure elevation is proportional to (and probably caused by) the preceding increase of sympathetic activity.22 With regard to these discrepancies in their mechanisms, the correlation that we found between the Valsalva-derived and NSVT-derived sympathetic baroreflex indices is remarkably close.

Directly, or indirectly, both vagal and sympathetic systems contribute to the shaping of the postextrasystolic heart rate pattern. Therefore, it could be assumed that HRT TS provides information about both systems. The two systems, however, can be affected differently by various pathological conditions. Lieshout et al. reported misleading Valsalva heart rate responses of patients, who suffered form isolated efferent sympathetic neuropathy.23 One may object that such patients are very rarely encountered in real life, but this is not necessarily true. Contrary to the general belief, the sympathetic control of baroreflexes is often abnormal before parasympathetic dysfunction can be demonstrated in diabetic patients.14 The independent predictive value of a sympathetic baroreflex gain in large patient populations suffering from cardiac diseases is yet to be determined. By the analogy of HRT TS calculation recent publications have already demonstrated the feasibility of blood pressure turbulence analysis. Davies et al. introduced a systolic blood pressure turbulence parameter, defined as the slope of regression line over the five pulses corresponding to the RR interval series, which yielded the HRT TS.9 Systolic blood pressure TS was also assessed by Wichterle et al.11 Voss et al.10 determined maximal postextrasystolic mean blood pressure slopes, a method similar to our technique. Since the calculation of systolic-, or MAP slopes are not restricted to the period preceding the baseline crossing, perhaps these parameters provide more thorough information about the dynamics of arterial pressure recovery.

Importantly, a trend has been reported towards decreased blood pressure slopes among patients with heart failure,9,11 or with idiopathic dilated cardiomyopathy.10 The VM is dependent on several factors, and requires good cooperation of the subjects. The effects of the subject’s position, the magnitude and duration of straining, and the role of breathing pattern before and after the manoeuvre are well documented.21 Certain subjects, such as elderly patients with Parkinson’s disease, are unable to perform the test.24 The ‘square wave Valsalva response’, which was first described among patients with heart failure,25 could be recorded in healthy volunteers suffering from no apparent heart disease as well.26 In spite of these limitations, VM-derived SBRSsial remains a valuable non-invasive tool in assessing the sympathetic arterial baroreflex regulation.

Arterial pressure recoveries from VM- and VT-induced hypotension are analogous phenomena. While the VM is suitable for studies in the general populations, SBRSsNSVT could be incorporated into the cardiac electrophysiological protocols. Patients with implantable antiarrhythmic devices might also be investigated non-invasively, by external programming of NSVT-s, allowing standardized serial assessment of sympathetic arterial baroreflex regulation.

Conflict of interest: none declared.

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