The role of the autonomic reflex tests in arrhythmology

Ph.D. Thesis

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TABLE OF CONTENTS

1. Introduction ……5

2. Aims and hypotheses..... .9

3. Materials and Methods……..11

3.1 Ethical approval……...11

3.2 Patient populations……..11

3.3 Study equipment, monitors……12

3.4 Laboratory environment, data acquisition ……..12

3.5 Study protocols……13

3.6 Data analysis……...14

3.7 Statistical analyses……...22

4. Results ..... ……23

4.1 Hemodynamic and reflex responses to carotid artery stenting……...23

4.2 Hemodynamic and reflex responses to short-lasting paced VT and Valsalva maneuver……...25

4.3 Orthostatic responses of BRScv and HRT parameters……26

5. Discussion (Interpretations and Conclusions)……...29

5.1 Observations during carotid artery stenting……...29

5.2 A short comment on arterial baroreflex sensitivity indices…….33

5.3 New sympathetic baroreflex indices derived from pressure recovery from paced NSVT, and Valsalva maneuver…….33

5.4 Postural influences on BRScv and HRT parameters …….36

6. Limitations 42

7. Respective findings and future clinical implications……44

8. List of references……...46

1. INTRODUCTION

Cardiac rhythm is under strong autonomic regulation. The importance of the autonomic influences in the genesis of supraventricular- and ventricular arrhythmias, and in sudden death has been long recognized. (Waxman MB 1990, Eckberg DL and Sleight P 1992, Verrier RL 2004, Verrier RL 2009, Zipes DP 2006, Zipes DP 2008). Autonomic regulation is, however, not regularly studied in clinical arrhythmology. Notable exceptions are the group of neutrally mediated syncope.

The most common neutrally mediated syncope is vasovagal syncope, which - although intensively studied by our research team - is not included in the topics of the thesis. Another related syndrome is carotid sinus hyperaesthesia. The electrical device therapy of these syndromes is a topic of current debate (Connolly SJ 2003, Ryan DJ 2010). Besides the permanent device therapy, arrhythmologists are often asked to perform temporary device therapy in cases, where neutrally mediated bradycardia can occur as a consequence of medical intervention. Such intervention is carotid artery dilation and stenting, where longer lasting episodes of bradycardia have been reported (Yadav JS, 1997, Teitelbaum GP, 1998). Temporary pacemaker therapy, however, carries certain risks (Betts TR 2003). Therefore methods to assess the real hazard of the neutrally mediated reactions, thus minimalizing the iatrogenic complications, are needed.

It has been long recognized that various medical conditions are characterized by abnormalities of the cardiovascular autonomic regulation. There are well known sympathetic and parasympathetic reflex abnormalities in common diseases such as diabetes mellitus, obesity or hypertension (Ewing DJ 1980, Lengyel Cs 1998, Lénárd Zs 2005, Honzíková N 2009). Evaluation of the autonomic regulation in these entities is often part of the routine clinical work-up. A typical example is the assessment the reflex parameters in diabetic subjects, based on a series of well established simple tests, (i.e. the „Ewing panel") (Ewing DJ 1980). Association between autonomic abnormalities and poor prognosis, for example in diabetes, is also well documented (Ewing DJ 1980). Nevertheless, detection of reflex abnormalities in these conditions does not prompt specific therapeutic interventions. Recognizing the abnormal reflex responses, specialists who are in charge for these patients usually attempt to optimalize the medical therapy and urge the patients to observe medical directions, in order to achieve better control of the underlying disease. In contrast to the above

mentioned conditions, reflex abnormalities detectable in post-myocardial infarction state and congestive heart failure are more important for the arrhythmologists. Certain markers of the autonomic regulation do have the capacity to predict short- and long-term adverse outcome, including sudden cardiac death (LaRovere MT 1998, De Ferrari GM 2007, LaRovere MT 2008). Therefore an abnormal parameter may help to define patient subpopulations that could have benefit from more aggressive preventive therapy, such as ICD implantation (LaRovere MT 2008). In spite of their potential predictive capacity, autonomic markers have not yet qualified to serve as ICD implantation criteria (Epstein A 2008, Tung R 2009, Exner DV 2007, Bauer A 2010). This virtual paradox has a complex explanation. The most promising parameter, the cardiovagal baroreflex sensitivity (BRScv), requires arterial pressure recording. Predictive power of BRScv was demonstrated in the convincing ATRAMI trial, however, in that study intra-arterial pressure recording, and pharmacological baroreflex challenge (i.e. phenylephrine injection) were used (LaRovere MT 1998). Neither of them is suitable for routine clinical investigations, therefore no large scale prospective study was ever performed with this technique. Although noninvasive continuous blood pressure recorders are now available, and spontaneous, rather than pharmacological tests are in use (Kardos A 2001), the ATRAMI-based cut-off values have not yet been validated with the noninvasive methods. Recently a pair of promising new risk-predictor parameters, the heart rate turbulence onset (HRT onset) and slope (HRT slope) have emerged (Schmidt G 1999). These parameters are based on the RR interval fluctuations subsequent to a premature ventricular complex (PVC). (The definitions and calculations of these indices are given in details in the chapter of methods). Calculation of the HRT parameters does not require complicated instruments or software. HRT values could be easily derived from Holter recordings containing PVC-s in sufficient number. Nevertheless HRT interpretation needs further refinements. Physiological considerations suggest that Holter based HRT parameters are closely related to BRScv. Therefore, HRT - similar to the BRScv - could be subject to external influences. Delineation of these influences may help to put the Holter-based information into context.

Our attitude toward autonomic regulation is determined by the availability of the instruments used in the analysis. Cardiovagal parameters could be easily assessed. Pulse intervals are readily available and analyzable on ECG recordings, and commercially available Holter monitors are capable to calculate the well known time- and frequency domain HRV parameters. As it has been mentioned before, many of these parameters could indicate pathological conditions. It is possible that impaired vagal regulation is not only a marker, but

contributes directly to the adverse outcome, (e.g., in certain arrhythmias), however, the evidence supporting this theory is mostly circumstantial. In contrast, there is abundant evidence indicating that in advanced cardiac diseases the uncontrolled sympathetic activation contributes tremendously to the progress of the pathological process (Cohn JN 1984, Eckberg DL and Sleight P 1992, Mark A 1995, Esler M 1997, Karemaker JM 2008, Triposkiadis F 2009). Data related to longer-term regulation, such as the level of circulating catecholamines exemplify the role of sympathetic activation (Cohn JN 1984). Analyzability of the short-time sympathetic regulation in the clinical practice however is limited. For sympathetic reflexes both the input- and the output parameter are arterial blood pressure (or more precisely the distension of the arterial baroreflexive areas), trigger-response relationship could be scanned by only very short-lasting perturbations. Such perturbation can be provided by the cumbersome neck chamber technique (Eckberg DL and Sleight P 1992). The heavily criticized technique of balancing the low- and high frequency heart rate spectra (Eckberg DL 1997) was not used in our study, and therefore it is not discussed here. The vasomotor muscle sympathetic nerve activity (MSNA), recorded by direct microneurography, provides an independent output parameter in assessing the sympathetic baroreflex sensitivity (BRSsy) (Wallin G 1988, Eckberg DL and Sleight P 1992). Baroreflex regulation of muscle sympathetic nerve activity (MSNA) exhibits well-known abnormalities in conditions such as congestive heart failure and essential hypertension (Matsukawa T 1991, Ferguson DW 1992, Grassi G 1995). MSNA recording, however, is an invasive technique and requires special equipment and skill. A simple clinical test for BRSsym is badly needed in clinical cardiology. Such a simple sympathetic baroreflex index, derived from the blood pressure dynamics during the late phases of Valsalva maneuver, was recently proposed by the group of Philip Low (Huang CC 2007, Schrezenmaier C 2007). At the same time, arrhythmologists who studied the genesis of HRT introduced new parameters based on post-extrasystolic blood pressure fluctuations (Davies LC 2001, Voss A 2002, Wichterle D 2006). These “post-extrasystolic blood pressure turbulence slopes” are theoretically analogous to the pressure recovery slopes derived from the recovery phase of Valsalva maneuver. By confirming this analogy we could prove the convergence of the new techniques, allowing unification of methods, terms and concepts in studying various healthy and disease-stricken populations.

2. AIMS AND HYPOTHESES

The main goal of the thesis is to assess the genesis, modulations, and predictive power of certain noninvasive autonomic markers, which could allow us to screen the candidates for temporary- or permanent electrical device therapy.

- Temporary pacemaker therapy is frequently performed in patients undergoing carotid artery stenting. This procedure, however, presents a risk of complications, requires special equipment, and assistance of a specialist. Reducing preventive temporary pacing to a high risk subset of patients could be safe and cost-effective. Therefore, our aim was to test the feasibility, and accuracy of noninvasive BRS testing in predicting long (>3s) pauses, in a cohort of subsequent patients awaiting carotid artery stenting.

- HRT analysis is a new noninvasive tool in assessing autonomic heart rate control, thus predicting adverse outcome, including sudden death. This method has the potential to qualify as a screening tool for ICD implantation among patients with poor systolic cardiac function, both of ischemic- and non-ischemic origin. HRT, however, is usually derived from Holter tapes, thus the results are modified by unknown external influences. Therefore, our aim was to determine the postural influences on HRT parameters.

- Pulse derived, vagally mediated autonomic parameters are extensively used in clinical practice. The sympathetic activity - which also has a great impact on cardiovascular morbidity and mortality - is not readily assessable. Therefore, our goal was to assess a new sympathetic baroreflex marker, derived from the arterial pressure recovery subsequent to an episode of a short-lasting, paced ventricular tachycardia. Our aim was also to compare this new parameter to another sympathetic baroreflex index, which could be derived from the pressure responses of the Valsalva maneuver.

3. MATERIALS AND METHODS

3.1 Ethical approval

All the protocols included in the dissertation were approved by the local ethical committee of the Szeged University. The studies complied with the Declaration of Helsinki. Following a thorough briefing about the studies, all patients gave written consent to the investigations.

3.2 Patient populations

BRScv and HRV parameters, prior to and during carotid stent implantation, were studied in twenty-four consecutive patients (14 male, 10 female). Eleven patients (46%) had symptomatic stenosis. Eight patients (33%) had left-sided, ten (42%) had right-sided, and six (25%) had bilateral stenosis. Three patients (13%) had a history of contra-lateral stent implantation. Of the four patients (17%) who had previously undergone carotid endarectomy, 3 had stenting of post-endarterectomy restenoses, and one had a contralateral intervention. The presence of hypertension was noted in twenty-one patients (88%), diabetes in eleven (46%), hyperlipidemia in seven (29%), and ischemic heart disease in eight (33%) cases. Three patients (13%) had a history of peripheral arterial disease.

For the study, assessing the relationship between different sympathetic baroreflex parameters, 25 subjects were recruited from patients waiting for cardiac electrophysiological study. Only patients with preserved left ventricular systolic function were selected (ejection fraction (EF) >50%). Patients with diabetes, Parkinson's disease or with a history of excessive alcohol consumption were not considered.

For the study, where we assessed the postural effects on HRT and BRScv parameters, the participants were recruited from the pacemaker outpatient clinic of the University of Szeged. Subjects with ventricular pacemaker lead and predominant sinus rhythm were selected. No patients with sick sinus syndrome, left ventricular dysfunction (EF < 50%) or

congestive heart failure (NYHA III–IV) were included. Patients older than 80 years, and those with diabetes mellitus, Parkinson's disease or alcoholism were excluded.

3.3 Study equipment, monitors

In all studies included in the dissertation, continuous ECG monitoring was performed with a bedside Marquette Eagle monitor. ECG channels with high signal-noise ratio were selected, with well discernible positive R waves. Blood pressure was monitored non-invasively with a Finapress 2300 (Ohmeda) device. In the study on the effects of carotid artery stenting, the breathing was also traced as an uncalibrated signal, with an abdominal pneumobelt.

3.4 Laboratory environment, data acquisition

The study on the autonomic responses to carotid artery stenting was performed at the Department of Radiology of the University of Szeged. A 3-minute recording was performed in all patients, subsequent to arterial cannulation, but prior to any other interventions. This segment served as a baseline in the off-line analysis. Continuous recording was then performed throughout the whole stent implantation procedure.

The study, where Valsalva maneuver- and ventricular tachycardia-derived sympathetic baroreflex parameters were assessed, was performed in the electrophysiology laboratory of the University of Szeged. In the other study, where we assessed the postural effects on HRT and BRScv dynamics, the participating patients, subsequent to their routine pacemaker check-up, were transferred to the tilt table laboratory. In both studies sufficient adaptation periods were allowed and baseline recordings were taken. Continuous recordings were then performed throughout these studies.

In all of the studies included in the dissertation, analogous biological signals were recorded by DATAQ/WINDAQ® digitalizing system (DATAQ Instruments, Inc., Akron, OH, USA), at 250 Hz per channel (in the study on sympathetic baroreflex indices), or at 500 Hz per channel (in the other 2 studies included in the dissertation).

3.5 Study protocols

Patients, waiting for carotid artery stent implantation procedure, remained fasting but were well hydrated. Aspirin 100 mg plus clopidrogel 75 mg daily were started at least 72 hours prior to the intervention, and continued for a minimum of thirty days post-procedure. According to the protocol approved at the University of Szeged, antihypertensive and cardiac medications are not routinely discontinued before the intervention. The patients are not routinely sedated, and receive no preventive temporary pacemaker- or atropine therapy. The catheterization is performed in local anesthesia through a femoral arterial puncture site. Appropriately-sized self-expandable stents are implanted at 7-8 at. pressure with 5-10 second manual inflation. Episodes of hypotension are treated with rapid administration of 500 ml physiological saline; vasopressor therapy is not routinely administered. During the post-interventional period, adequate fluid intake is ensured, and vasoactive drugs are given as necessary (The American Society for Interventional and Therapeutic Neuroradiology 2001).

In the study on different sympathetic BRS indices, the subjects underwent cardiac electrophysiological diagnostic study before our measurements. Valsalva maneuvers were repeated at 40 mmHg for 12 s until the first acceptable recording (by length, maintained pressure, and character of blood pressure recording) was obtained (Huang CC, 2007). In order to elicit blood pressure drops of similar magnitude to that of the second phase of Valsalva maneuvers, short ventricular runs (4 to 6 beats), with a cycle length of <60% of the prevailing sinus rhythm were applied (Raj SR 2005).

In the study on postural effects on HRT and BRScv parameters, patients arriving to the laboratory assumed supine position on the tilt table. Following a few minutes of adaptation, the patients' prevailing average RR intervals were determined. Then, with the external pacemaker programmer, a pacing frequency was initiated corresponding to approximately 60% of the prevailing RR intervals. After the first captured paced beat, the pacemaker frequency was quickly switched back to the original low backup rate. This maneuver was repeated five times. Each captured paced beat was separated by at least 60 uninterrupted sinus cycles. After the series of the paced premature contractions had been completed, the patients had a few minutes of rest, then the tilt table was elevated to 70 degrees head-up tilt position.

In this position another 5-minute ECG and arterial pressure recording was taken. Subsequently the externally paced series of PVC-s was repeated.

3.6 Data analysis

For the off-line analysis of the recordings the Windaq® program (DATAQ Instruments, Inc., Akron, OH, USA) and theWinCPRS® software (Absolute Aliens Ay, 2000) were used (Rudas L 1999).

From the noise-free and extrasystole-free baseline recordings the parameters of blood pressure and heart rate variability, as well as the markers of cardiovagal baroreflex sensitivity were determined. The studied time-domain parameters of RR interval variability included the following (Kleiger RE 1995):

- Mean RR interval (**RR mean**): Σ RR-intervals / n

- RR interval standard deviation (**SDRR**): $\sqrt{\Sigma(X-X)^2 / (n-1)}$

- **PNN50**: Percent of difference between adjacent normal RR intervals that are greater than 50 msec.

- **RMSSD**: Root mean square successive difference. The square root of the mean of the sum of the squares of differences between adjacent normal RR intervals $\sqrt{\Sigma(X_i-X_{i-1})^2 / (n)}$.

BRScv in all studies was characterized by the method of spontaneous sequences (Bertinieri G 1988). Spontaneous sequences were defined as three or more cardiac cycles with continuous systolic blood pressure elevation or decrease accompanied by the unidirectional RR-interval changes. The minimum acceptable change in systolic pressure was set at one mmHg/cycle. Linear regression analysis between systolic blood pressure and RR interval transients was performed for each sequence, and only those with an R value of ≥ 0.8 were accepted for further analysis. The BRScv was defined as change in the R-R interval per unit

change in systolic blood pressure measured in units of ms/mmHg. Since the slopes of the regressions of increasing (up) and decreasing (down) sequences may differ significantly (Rudas 1999), in all studies the up and down sequences were assembled and averaged separately (**Figure 1**). At least three spontaneous up and three down sequences were required during the three-minute period in order to accept their average (up BRS and down BRS) as appreciable data.

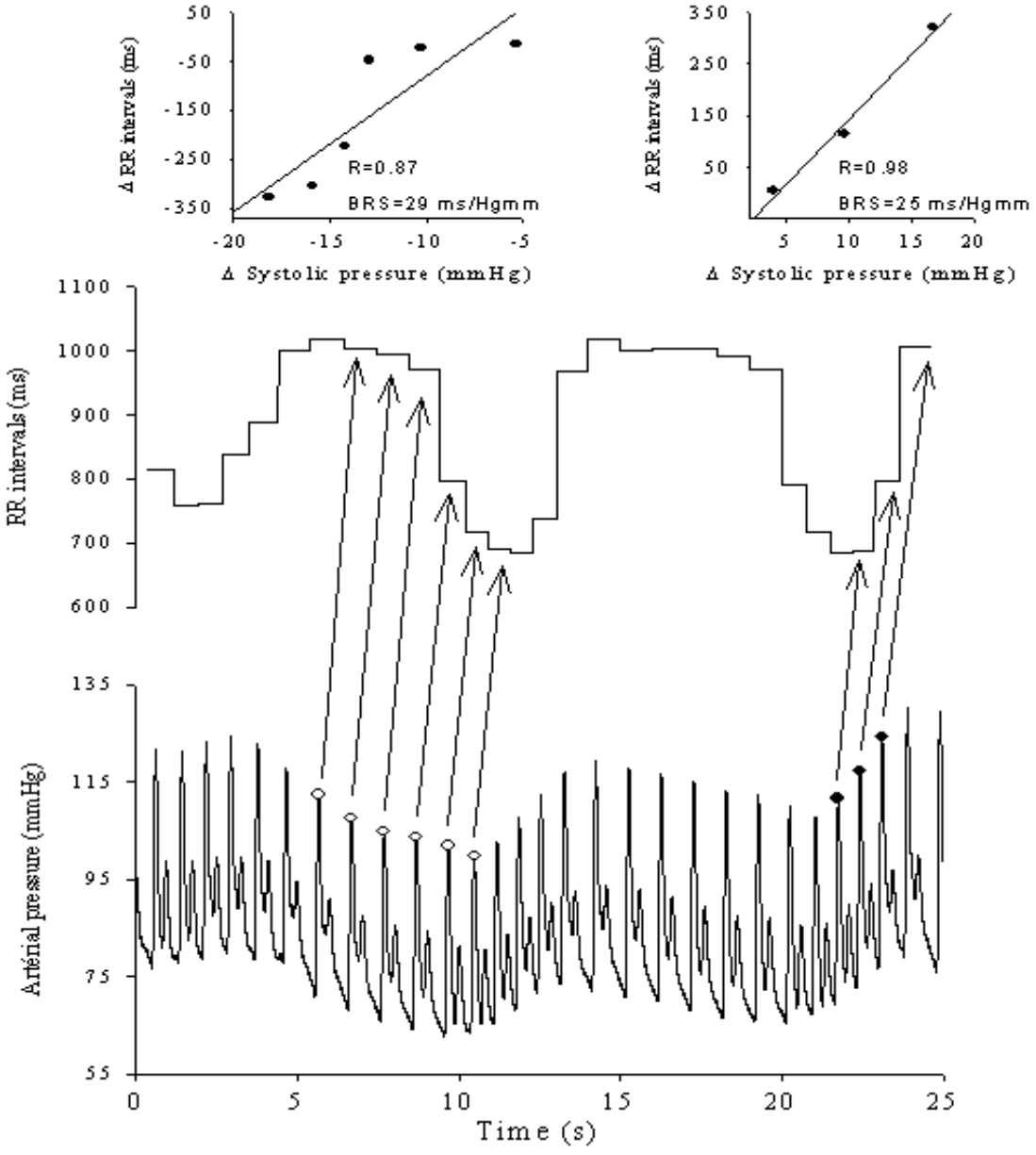

Figure 1.

Illustration of the spontaneous up and down cardiovagal BRS sequences. Open circles represent the down BRS segment, and closed circles represent the up BRS segment of the recording.

In the analysis of the recordings, which were taken at the time of stent deployment, duration of the longest induced RR pause was determined. A subgroup was formed on the analogy of carotid sinus hypersensitivity. Patients in the "pathological pause" (PP) subgroup exhibited a pause of ≥3 seconds (**Figure 2**).

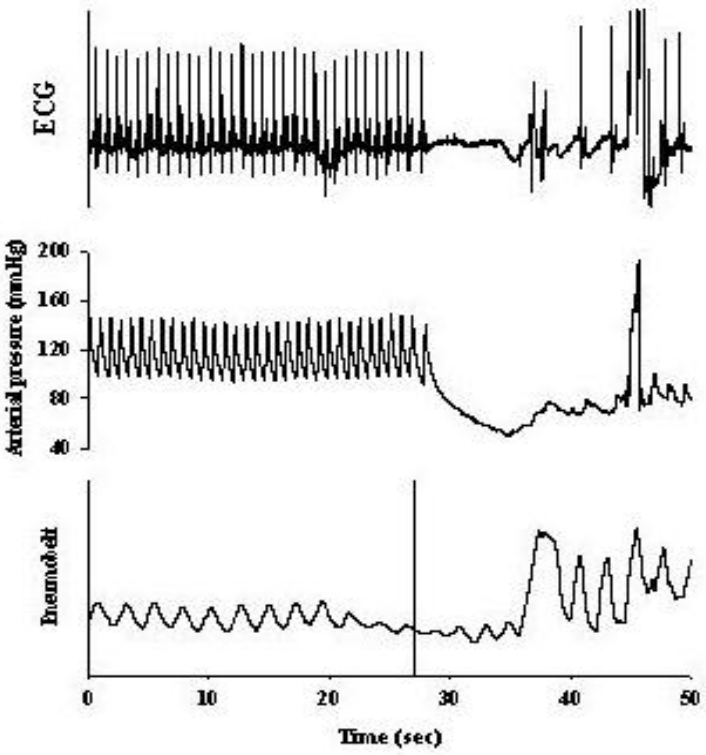

Figure 2.

57-year-old male. ECG, arterial blood pressure and breathing recordings. The vertical marker on the breathing panel shows the moment of dilatation of the carotid stent. (The same applies to Figures 3 and 7) The pause lasting more than 3 seconds is interrupted by junctional escape beats.

Data collected in the subgroup with PP were compared to the subgroup without pathological pauses (WP). The change of the systolic pressure was compared to a baseline, determined as an average of the last three systolic values prior to stent dilation. The minimum systolic blood pressure value was typically recorded during the first cycle following the pause in the asystolic subgroup (**Figure 3**).

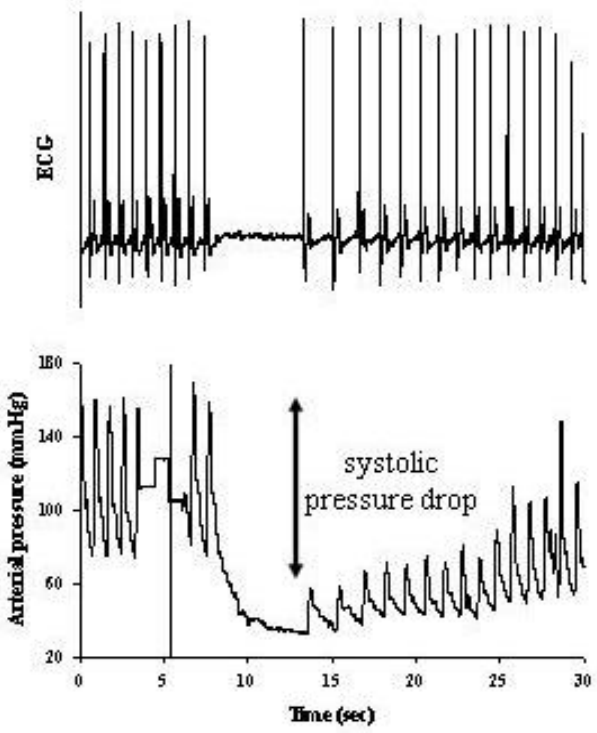

Figure 3.

74-year-old male. ECG and arterial blood pressure recordings. The double arrow indicates the magnitude of the systolic blood pressure drop.

In the study on different sympathetic baroreflex indices, 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 Valsalva maneuver. The minimum MAP values, and the drops compared to baseline (Δ MAP) were determined during phase 3 of the Valsalva maneuver and following the paced NSVT series (**Figures 4 and 5**). The MAP return times (Δtime) 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 4 and 5**). The sympathetic BRS values were determined as the ratio of MAP drop and return time, expressed as mmHg/s. SBRSvals was derived from a single Valsalva maneuver. $SBRS_{NSVT}$ was defined as the average of gains, derived from two NSVT series. Within a 15-cycle pressure recording, which followed immediately the NSVT, the maximum slope of 5 consecutive MAP elevation steps was also calculated, and expressed as MAP turbulence slope (MAP_{TS}) in dimension of mmHg/cycle.

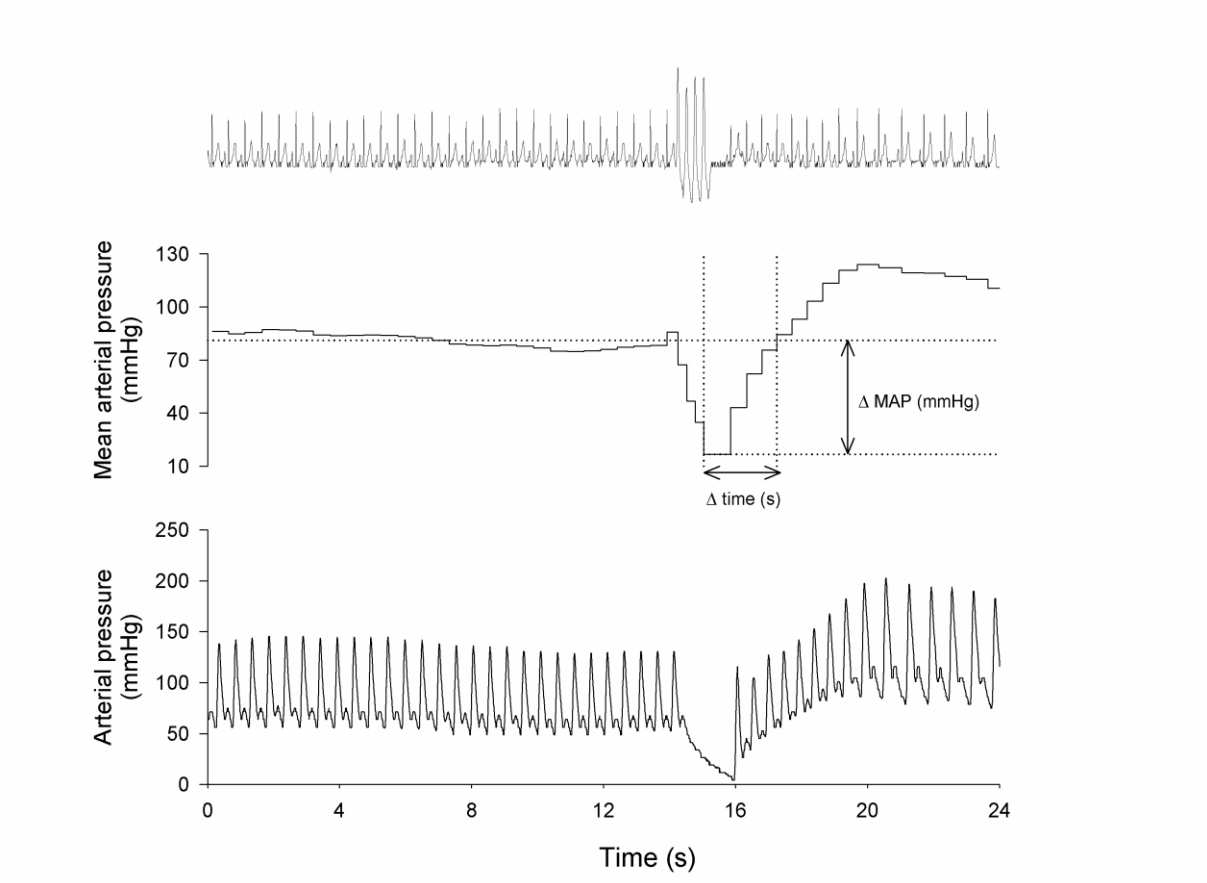

Figure 4.

A run of NSVT induces substantial drop in MAP. $SBRS_{NSVT}$ is defined as the ratio of the Δ MAP to recovery time.

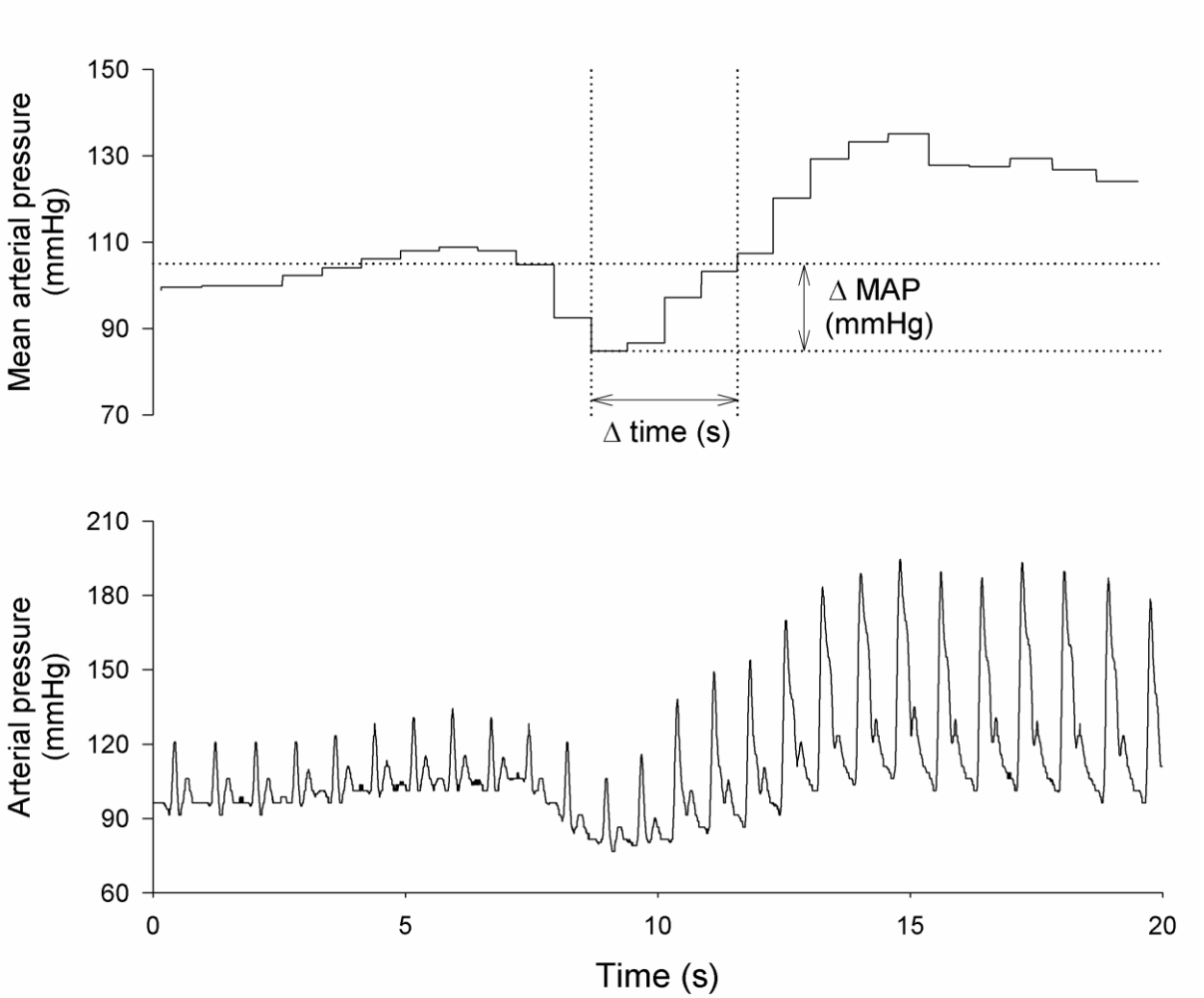

Figure 5.

Late phases (late 2, 3 and 4) of a Valsalva maneuver. $SBRS_{vals}$ is defined as the ratio of the Δ MAP to recovery time.

In the study on the postural HRT and BRScv indices, the RR interval parameters, the traditional time domain parameters of HRV and the spontaneous BRS values were determined as described above. Turbulence onset (TO) was defined as the difference between the mean of the first two sinus RR intervals following the paced PVC and the last two sinus RR intervals before the PVC, divided by the mean of the last two sinus RR intervals before the PVC (**Figure 6).** TS was defined as the maximum positive slope of regression line assessed over any sequence of five subsequent sinus rhythm RR intervals within the first 15 cycles after the paced PVC (**Figure 6)** (Schmidt G 1999). The average of supine and upright TO and TS parameters were calculated separately for each patient.

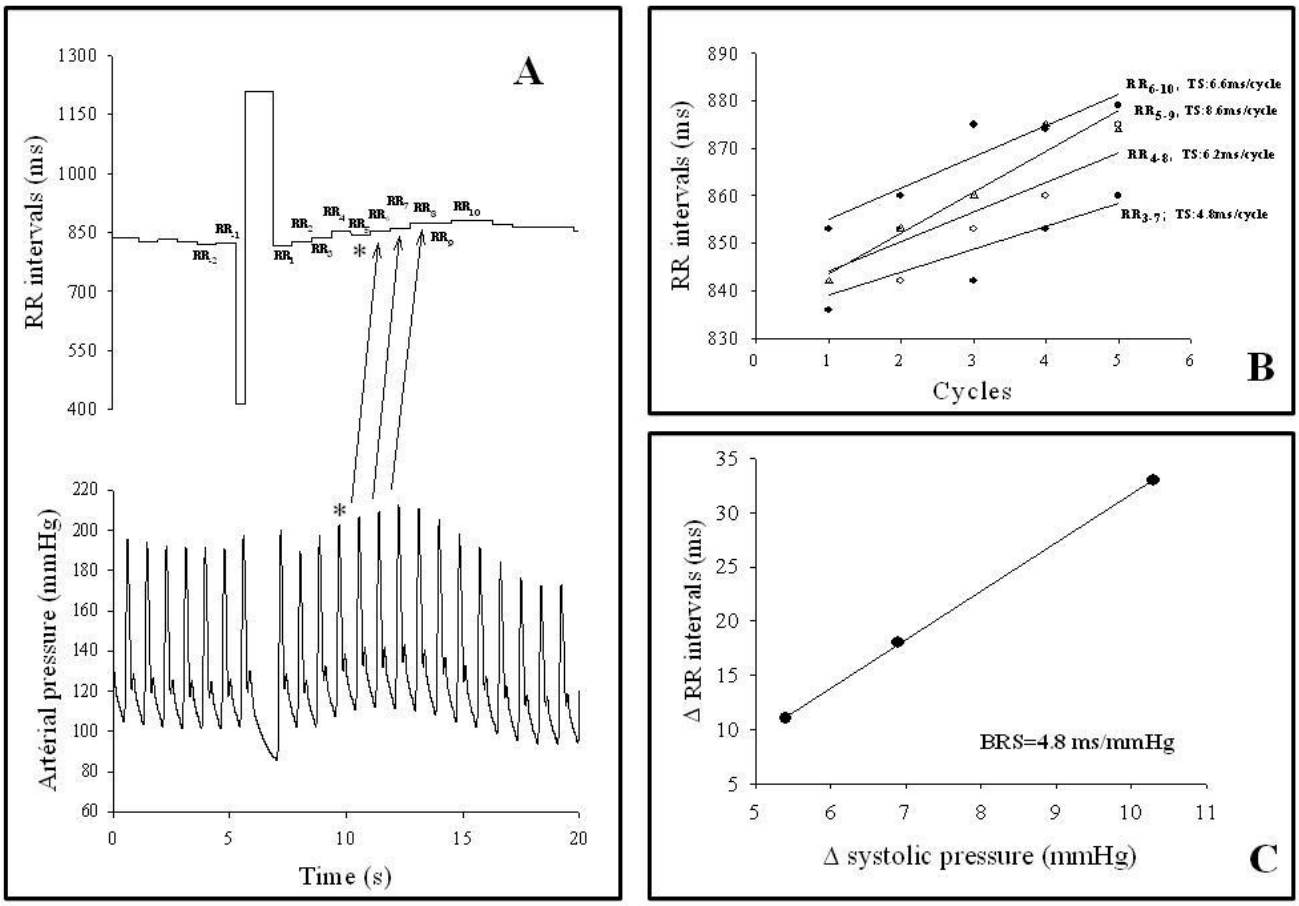

Figure 6.

Illustration of the HRT parameters. In panel "A" simultaneous RR interval tachogram and arterial pressure recordings are shown, taken at the occurrence of a single PVC. Heart rate TO is determined by the ratio of 2-2 cycles immediately preceding (RR_{-2}, and RR_{-1}) and following (RR_1 and RR_2) a premature ventricular complex. The TS is defined as the greatest slope of 5 consecutive, post-extrasystolic sinus RR intervals, occurring within the series of the first 15 cycles. In the illustrative recording, the greatest slope - given in the dimension of ms/cycle - was found between the fifth and ninth post-extrasystolic cycles (panel "B"). The arterial pressure recording reveals an increasing systolic pressure ramp, accompanied by gradual, uninterrupted RR interval lengthening, allowing the calculation of the gain; a BRScv value, expressed in ms/mmHg dimension (panel "C").

3.7 Statistical analyses

Unpaired T-test was used for the comparison of the heart-rate variability and baroreflex parameters between the subgroups with and without pathological pauses during carotid artery stenting.

Comparisons of the hemodynamic and reflex responses following paced ventricular tachycardia and Valsalva maneuver were performed by paired t tests. The Wilcoxon Signed Rank test was used for parameters showing skewed distribution. The relationship between the two baroreflex indices and the MAP_{TS} was assessed by linear regressions. The agreement between SBRSvals and $SBRS_{NSVT}$ was also assessed by Bland Altman plot.

Relationship between the BRS and HRT parameters were assessed by linear regression. Comparison of supine and upright data was performed using paired t test. Wilcoxon Signed Rank Test was used to compare supine and upright PNN50.

4. RESULTS

4.1 Hemodynamic and reflex responses to carotid artery stenting

Pause exceeding three seconds was seen in seven cases (29%), two of which were complicated by syncope. The average duration of the pauses was 7.2±3.0 seconds (range: 3.7-11.5 seconds). The systolic blood pressure drop in this PP group was 76±27 mmHg, whereas in the group without pause it was 34±29 mmHg ($p<0.003$). Seven (29%) patients were given atropine during the interventions due to asystole or significant bradycardia. During follow-up, two patients experienced transient ischemic attacks; one minor stroke and one major stroke occurred. One subject died within thirty days due to complications of a previously unknown cancer.

Assessment of baseline recordings was impeded by several factors. The heart rate variability analysis was precluded in one case by fixed pacemaker rhythm, in one case by atrial fibrillation; in another five cases by frequent ventricular or supraventricular extrasystoles. The parameters of heart-rate variability could be determined in seventeen cases. Motion artifacts precluded the blood pressure analysis in three cases. Some of the technically good records failed to show the minimally required sequence number. Therefore we were able to determine the baroreflex sensitivity index of increasing sequences in twelve cases, while that of decreasing sequences in nine cases. Data of the subgroups are shown in ***Table 1***.

There was no statistically significant difference between the heart rate variability and the baroreflex sensitivity indices in the two subgroups.

Table 1. Autonomic markers and hemodynamic responses of the PP and no PP subgroups.

	"PP"	no "PP"	p
Pause (s)	7.2±3	-	NS
MEAN RR (ms)	788±70	840±81	NS
SDRR (ms)	28±10	25±8	NS
RMSSD (ms)	13±8	14±5	NS
UP-BRS (ms/Hgmm)	3.4±2	3.3±2	NS
DOWN-BRS (ms/Hgmm)	3.7±1	4.4±2	NS
BASELINE SBP (Hgmm)	147±26	154±31	NS
MINIMUM SBP (Hgmm)	71±31	120±34	<0.003
dSBP (Hgmm)	76±27	34±29	<0.003

There was an incidental observation in connection with the monitoring of breathing with pneumobelt. We experienced deceleration of the breathing frequency and deepening of breathing in three cases. Two cases were from the PP group; their records are shown in **Figure 2** and **Figure 7**.

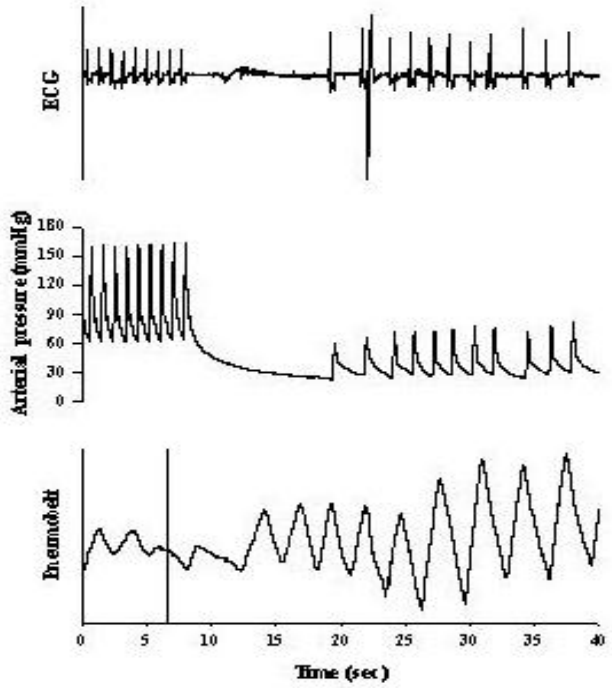

Figure 7.

72-year-old male. ECG, arterial blood pressure and breathing recordings. The non-calibrated breathing signal shows the increment in the breathing movements.

4.2 Hemodynamic and reflex responses to short-lasting paced VT and Valsalva maneuver

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 Valsalva maneuver and frequent Valsalva induced PVC-s, preventing analysis in three other recordings.

Recordings of 20 patients (11 female) entered the final analysis. Their mean age was 57±17 years. Seventeen patients suffered from atrioventricular nodal re-entry tachycardia, 1 from paroxysmal atrial flutter, 1 from atrioventricular re-entry tachycardia and 1 from right ventricular outflow tract tachycardia. Comorbidity included mild, controlled hypertension in 13 cases.

The paced NSVT consisted of 5-6 cycles with the driving frequency of 184±40/min (range 120-270/min). Δ MAP was slightly but significantly greater following NSVT than during the recovery phase of the Valsalva maneuver (37±18 vs. 45±17 mmHg, p<0.04). Accordingly, the recovery time from NSVT was slightly longer (4.9±3 vs. 6.2±7 s, P=NS). The $SBRS_{NSVT}$ values were significantly higher than the $SBRS_{vals}$ 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 8**) also indicated a modest relationship.

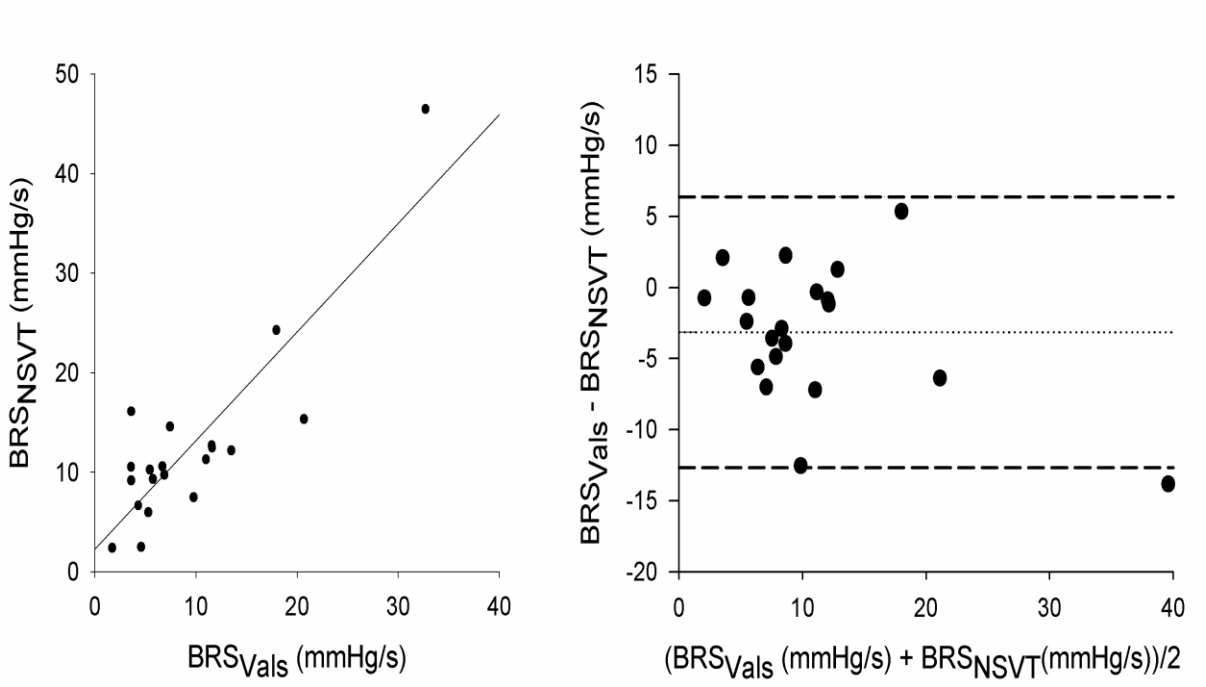

Figure 8.

Relationship of $SBRS_{NSVT}$ and $SBRS_{vals}$ illustrated by linear regression and Bland - Altman plot.

With two exceptions, MAP_{TS} could be calculated over the first five post-NSVT cycles. Both $SBRS_{vals}$, and $SBRS_{NSVT}$ correlated closely with MAP_{TS} ($R=0.77$, $p<0.001$ and $R=0.86$, $p<0.001$ respectively).

4.3 Orthostatic responses of BRScv ad HRT parameters

Twelve male subjects were recruited for the study. Their mean age was 61 ± 11 years. Indication for permanent pacemaker implantation was intermittent AV block in 11 cases, and carotid sinus syncope in one. In four instances the number of spontaneous BRS up or down sequences on the patient's baseline recording was less than 5; therefore, these patients were excluded from the further analysis. For the remaining eight subjects, the up- and down-BRS values showed very close correlation both in supine and in upright position ($R = 0.97$, $P < 0.001$ and $R = 0.98$, $P < 0.001$, respectively). The up-BRS values and the TS values correlated closely in the supine and upright positions ($R = 0.94$, $P < 0.001$ and $R = 0.96$, $P < 0.001$, respectively). Similarly, close relation was found between the down-BRS and TS values in the supine and upright positions ($R = 0.92$, $P < 0.001$ and $R = 0.94$, $P < 0.001$, respectively). TO and up-BRS negatively correlated both in supine and in upright posture ($R = - 0.5$ and $R = - 0.66$). However, the correlation did not reach statistical significance. Similarly, non-significant negative correlation was found between supine and upright down-BRS and TO ($R = - 0.57$ and $R = - 0.64$, respectively). TS and TO were significantly and negatively correlated both in laying and in tilted position ($R = -0.71$, $P = 0.05$ and $R = - 0.77$, $P = 0.03$, respectively). Compared to the supine rest position upright tilt resulted in significant RR interval shortening. The systolic arterial pressure remained unchanged and the diastolic pressure showed elevation; however, this did not reach statistical significance. No significant change was seen in SDRR, RMSSD and PNN50 (Table 1). Both the up- and down-BRS values showed significant decrease upon tilting. Similar significant decline was detected in the TS values (Table 2). The individual postural changes of baroreflex gains and TS values are shown in **Figure 9**. In contrast, the TO showed no significant postural decrease (**Table 2**).

Table 2. Hemodynamic, baroreflex and HRT responses to orthostasis

	Supine	Upright	*P*
Mean RR interval (ms)	820 ± 139	747 ± 120	0.005
SD RR (ms)	37 ± 21	37 ± 26	NS
RMSSD (ms)	29 ± 20	22 ± 13	NS
PNN 50 (ms)	7.1 ± 12	3.3 ± 7	NS
Mean systolic pressure (mm Hg)	125 ± 25	128 ± 18	NS
Mean diastolic pressure (mm Hg)	69 ± 17	76 ± 19	NS
Up BRS (ms/mm Hg)	7.8 ± 6.9	4.2 ± 3.7	0.02
Down BRS (ms/mm Hg)	6.8 ± 4.9	3.9 ± 3.3	0.003
TO (%)	−2.62 ± 4.9	−2.15 ± 2.6	NS
TS (ms/cycle)	21.6 ± 21.5	13.9 ± 19.6	0.02

Data are given as mean ± standard deviation

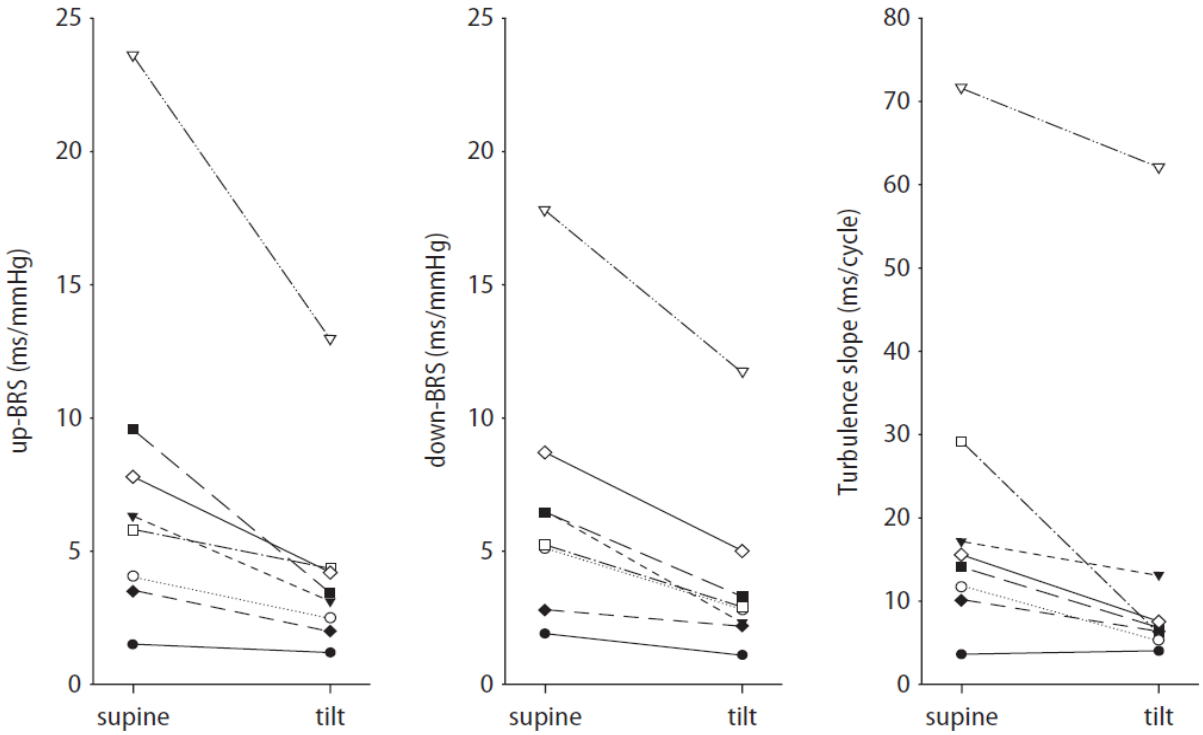

Figure 9. Individual up-BRS, down-BRS, and TS responses upon tilting

5. DISCUSSION (INTERPRETATIONS AND CONCLUSIONS)

5.1 Observations during carotid artery stenting

Swings of the arterial pressure from its resting point elicit immediate counter-regulation, mediated by arterial baroreflexes. Increasing blood pressure induces reduction of vasomotor tone and an increase in vagal activity; whereas decreasing the blood pressure leads to regulation in the opposite direction. Calculation of the slope of the regression between systolic pressure and RR interval changes is the base of several baroreflex sensitivity formulas, (which will be discussed in detail in the subsequent chapters) (Smyth HS, 1969, Eckberg DL 1976, Rudas L 1999). Human baroreceptors are located in the aortic arch and in the two carotid sinuses. It is not surprising that in the course of carotid endarterectomy or intravascular therapy, hemodynamic instability mediated by autonomic nervous mechanisms may occur. Earlier studies described two types of reactions following endarterectomy. The first type, most often an early reaction, involves bradycardia, hypotension, or both. These responses are due to an increased stimulation of carotid baroreceptors. The second type of reactions is similar to, and presumably shares mechanisms with carotid sinus deafferentation, which is characterized by widely fluctuating blood pressure, and severe hypertensive episodes (Ille O, 1995, Smit AAJ 2002). A common conclusion of several studies is that the early reactions with bradycardia and hypotension are relatively benign (Cafferata HT 1982, Margulies DR 1993, Wong JH 1997). Blood pressure rising, on the other hand, definitely increases the risk of adverse outcome, stroke and death (Hans SS 1995, Wong JH 1997).

Carotid stenting may also be accompanied by hemodynamic instability during or after the procedure. The stent dilation leads to immediate activation of stretch-sensitive mechanoreceptors (Mendelshon FO 1998). This results in a marked, immediate reaction, which however may persist post-procedurally (Qureshi AI 1999, Qureshi AI, Neurosurg 1999). Some publications have given account of cases where no preventive measures were used against bradycardia. In the report of Yadav et al. balloon inflation induced syncope in four cases; all of them were known to have complete occlusion of the contralateral carotid artery (Yadav JS, 1997). Teitelbaum et al. recorded bradycardia and asystole lasting less than three seconds during angioplasty and stent implantation, in a similar population. Bradycardia was controlled successfully in all of the instances by administering atropine or glycopyrrolat

(Teitelbaum GP 1998). Howel et al. have recently reported carotid stent implantation in sixty high-risk subjects. Only 15% of the patients required atropine administration. A relationship was found between transient hypotension and neurological complications (Howell M 2002). In this study greater blood-pressure drop was associated with preexisting hypertension. The role of this condition as a risk factor has been confirmed by other publications as well (Corson JDBB 1986, Towne JB 1980).

There are several reports documenting the use of preventive measures at the time of carotid angioplasty, to preclude bradycardia response. In two studies - Mendelshon et al. 1998 and Harrops et al. 2001 - the authors performed all of their procedures with temporary ventricular pacemaker (Mendelshon FO 1998, Harrop JS 2001). The ventricular "escape" frequency was set at 60/minute in both examinations. The term "bradycardia reaction" in these studies meant reaching the 60/min escape frequency. In Harrop's study, despite pacemaker treatment, hypotension occurred in a few cases (Harrop JS 2001). In these studies, according to our view, the hemodynamic and autonomic regulation could have been affected by the pacemaker itself. At the time of sinus bradycardia, ventricular stimulation might have resulted in atrioventricular asynchrony. Besides the immediate hemodynamic responses (due to the sudden loss of the atrial booster pump), atrioventricular dyssynchrony may induce rise in atrial strain initiating unexpected reflex responses.

The risk profile of the population in our study is comparable to that of Yadav's and Teitelbaum's. We avoided the loosely defined term of "bradycardia". Instead we defined episodes with pauses of three or more seconds as "pathological pauses". Actually both patients who suffered syncope in our study met this criterion. Iv. atropine was given in 29% of the cases in our study. This percentage, however, may not reflect the real need for vagolytic therapy. The drug administration itself takes a few seconds and by the time the atropine injection was completed, most of the asystolic episodes might have terminated spontaneously. Pauses reaching three seconds or more did not correlate with neurological complications. Transient hypotension, according to our experience, was quite a uniform reaction. Although the magnitude of the blood pressure drop in the subgroup with pathological pauses was greater, significant blood pressure drop was often seen in cases without pauses as well. Transient hypotension seemed to be a harmless phenomenon in our study.

The reduction in BRS indices and in other autonomic markers observed in our study could be related to the age of the subjects. The inverse correlation between the autonomic

markers and the age is well documented (Gribbin B 1971, Rudas L 1999, Kardos A 2001). Assessment of baroreflex data is particularly complex as the parameter shows significant scattering even in normal population (Kardos A 2001). Accompanying diseases such as coronary heart diseases, diabetes mellitus and hypertension may have also influenced the data.

Our methods had important technical limitations. Frequent rhythm disturbances often precluded even simple heart rate variability tests, whereas baroreflex sensitivity sequences could be determined in less than half of the patients. Significant extension of the sampling period could have assured extrasystole-free and noise-free periods in a greater proportion of the cases, but the time of data collection was limited in instrumented subjects awaiting catheter intervention. Our observations about the technical limitations corroborate other publications describing the difficulty of HRV or BRS measurements in elderly populations (Oka H 2003). The same limitation was found in one of our other studies, showing small number of assessable BRS sequences in patients suffering from intermittent AV-block.

The exaggerated autonomic responses shown by the patients upon carotid distension are in contrast with their baseline cardiovagal regulation. The situation resembles to that of "hypersensitive carotid syndrome" (HCS). HCS is a very common phenomenon among the elderly (Kerr SRJ 2006), and its clinical importance is overemphasized (Cole CR 2001, Kaufmann H 2001). The discrepancy between the baseline and induced responses are sufficiently explained by O'Mahony, and his theory could be applicable for the responses induced by carotid stenting. According to this theory, reduced carotid sinus compliance in elderly arteriosclerotic patients reduces afferent impulse traffic in the baroreflex pathway. The relative deafferentation may cause baroreflex postsynaptic hypersensitivity, mediated by up-regulation of the dominant postsynaptic alpha-2 adrenoceptors. Vigorous carotid sinus stimulation, such as massage, could thus cause an overshoot baroreflex efferent response, resulting in profound hypotension and bradycardia (O'Mahony D 1995).

An interesting observation in our study, which deserves a short comment, was the change in the breathing frequency and depth following carotid dilatation. It was already noted by Thomas Lewis in 1932 that breathing often slows down and deepens upon carotid compression (Lewis T 1932). The same change in breathing pattern was seen in some of our patients at the time of balloon inflation (**Figures 2 and 7**). In our view, this altered respiration is compatible with the so called "strained breathing" occurring in subjects who anticipate pain or injury (Fokkema DS 1999).

In conclusion, hemodynamic instability accompanying carotid artery dilatation is a transitory and benign phenomenon, which is not predictable from the subjects' baseline baroreflex markers. In elderly patients who suffer from accompanying diseases, the traditional heart rate variability and baroreflex markers reveal universally pathological and low values.

5.2. A short comment on arterial baroreflex sensitivity indices

As has been mentioned before, arterial baroreflex system stabilizes the arterial pressure. The efferent limbs of the regulation include efferent vagal-, and sympathetic activation. I have also indicated in the "Introduction" the importance of both vagal-, and sympathetic responses in health and disease. From the pulse rate responses, induced by arterial pressure changes, a baroreflex gain, i.e. the cardiovagal BRS could be derived. This BRScv in the cardiological practice and publications is often denoted as "BRS", without specification. This negligency deceives many readers, who believe that only one kind of baroreflex mechanism and one kind of baroreflex gain, the "BRS" exist. In fact, even the BRScv values can differ, depending on whether they were derived from increasing or decreasing sequences (up- and down-BRS) (Rudas L 1999). There is no generally accepted definition of sympathetic BRS. BRSsym could be calculated from the blood pressure induced muscle sympathetic nerve activity changes (Rudas L 1999, Studinger P 2009), or directly, from certain arterial pressure fluctuations. It was shown by previous publications, and is confirmed by our study - included into the present dissertation - that indices, derived from the arterial pressure changes of the Valsalva maneuver (BRSvals), and induced VT (BRSvt) are valid forms of BRSsym.

5.3 New sympathetic baroreflex indices derived from pressure recovery from paced NSVT, and Valsalva maneuver

It has been long noted that arterial pressure fluctuation following a premature ventricular contraction resembles to the late phases of the Valsalva maneuver (Goldstein DS. 2000). Blood pressure recovery from Valsalva maneuver in patients with autonomic failure varies directly with severity of adrenergic impairment (Ferrer MT 1991, Vogel ER 2005), and the sluggish blood pressure recovery following premature ventricular contraction is also

characteristic of these patients (Goldstein DS. 2000). Furthermore, both abnormal responses could be reproduced in healthy subjects by N_n-nicotinic blockade (Goldstein DS. 2000, Jordan J 1998). 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 (Welch WJ, 1989; Segerson NM 2007). Conflicting influences could be operational during ventricular tachycardia, which is accompanied by unloading of the arterial, and loading of the cardiopulmonary baroreceptors (Smith ML, 1999). Arterial baroreflex control predominates in mediating sympathoexcitation (Smith ML 1999). 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 Valsalva maneuver complex interactions of mechanical and reflex responses occur (Korner PI 1976, Bennaroch EE 1993). The arterial baroreflex activation during the early strain phase reflects opposing influences of different aortic and carotid baroreceptors stimulation (Smith ML 1996). 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 (Smith ML 1996). 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 post-extrasystolic 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 from isolated efferent sympathetic neuropathy (van Lieshout JJ 1989). 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 (Ferrer MT 1991). 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 5 pulses corresponding to the RR interval series, which yielded the HRT TS (Davies LC 2001). Systolic blood pressure TS was also assessed by Wichterle et al. (Wichterle D 2006). Voss et al. determined maximal post-extrasystolic mean blood pressure slopes, a method similar to our technique (Voss A 2002). Since the calculation of systolic- or MAP slopes is 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 toward decreased blood pressure slopes among patients with heart failure (Davies LC 2001, Wichterle D 2006), or with idiopathic dilated cardiomyopathy (Voss A 2002).

The Valsalva maneuver 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 maneuver are well documented (Bennaroch EE 1993). Certain subjects, such as elderly patients with Parkinson's disease are unable to perform the test (Oka H 2003). The "square wave Valsalva response", which was first described among patients with heart failure (Sharpey-Schafer EP 1955), could be recorded in healthy volunteers suffering from no apparent heart disease as well (Ten Harkel AD 1990). In spite of these limitations, Valsalva maneuver derived $SBRS_{vals}$ remains a valuable non-invasive tool in assessing the sympathetic arterial baroreflex regulation.

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

5.4 Postural influences on BRScv and HRT parameters

The capability of HRT parameters to predict adverse outcome was first documented by Schmidt et al. in 1999 (Schmidt G 1999). In their landmark study retrospective analysis was performed on Holter tapes of acute myocardial infarction survivors, who were enrolled in large-scale follow-up studies (MPIP and EMIAT trials) (Schmidt G 1999). Since 1999 HRT analysis has gained general acceptance in clinical cardiology (Watanabe MA 2004). The method has been also advertised in Hungary (Tomcsányi J 2001). Recently, a consensus statement, issued by the International Society for Holter and Noninvasive Electrophysiology (ISHNE) redefined its measurement standards and clinical use (Bauer A 2008). Subsequent to the initial report by Schmidt et al., numerous studies have been performed. The retrospective Holter-tape analysis of the ATRAMI trial population, which included low-risk post-myocardial infarction patients, confirmed the independent value of the new markers in predicting the risk of subsequent cardiac arrest (Ghuran A 2002). Barthel et al. in the ISAR HRT study extended the previous observations to myocardial infarction survivors who received routine reperfusion therapy (Barthel P 2003). In these studies HRT actually provided better risk prediction than any of the traditional ECG derived heart rate variability parameters. Recently, Exner and the REFINE investigators published their findings on noninvasive risk assessment, early after myocardial infarction (Exner DV 2007). They found that impaired HRT and „T-wave alternans" (TWA) beyond 8 weeks were better predictors of sudden cardiac death or resuscitated cardiac arrest during a 47 months follow-up than traditional HRV parameters and BRScv, determined by the phenylephrine injection method (Exner DV 2007). Bauer and coworkers in the ISAR-RISK study assessed noninvasive risk prediction during a 5 year follow-up in post-myocardial infarction subjects. They found that "severe autonomic failure", which included abnormal HRT variables along with abnormal heart rate deceleration capacity, identifies a high mortality risk population (Bauer A 2009). Moore et al. in their publication of 2006 confirmed the predictive power of TS in patients suffering from decompensated heart failure (Moore RKG 2006). Klingenheben and coworkers reported abnormal autonomic indices, including HRT parameters in a cohort of patients suffering from dilated cardiomyopathy, however, only phenylephrine injection based BRScv could predict ventricular tachyarrhythmic events during the follow-up (Klingenheben T 2008). In two ongoing investigations, in the REFINE ICD trial and in the ISAR-ICD trial, the benefit of ICD implantation will be tested in high risk patients, defined by (among other selection

criteria) abnormal HRT (Exner DV 2009, Bauer A 2010). The results of these trials may dramatically influence the future of HRT analysis.

Regardless of the results of the ongoing studies, it remains still important to define the potential modifiers and the limitations of the HRT method. We know that HRV and BRScv determinations could be influenced by several factors, including circadian variations, sleep-wake differences, and the influences of physical activity, emotions, post-prandial state and posture (Eckberg DL and Sleight P 1992). Circadian variation of the HRT parameters has been recently also noted (Chen HY 2010). As has been already documented for BRScv (Gribbin B 1971, Laitinen T 1998, Kardos A 2001), HRT parameters could be also influenced by the subjects' age (Bauer A 2008). Our study adds orthostasis to the list of proven confounders.

Orthostasis is an important determinant of cardiovascular autonomic regulation in humans. In quadrupleg mammals, about 70% of the blood volume is located above the level of heart. In contrast, in upright humans 70% of the blood volume is below the level of heart (Rowell LB 1993). Our orthostatic stability depends on strict baroreflex regulation. Our study indicates that TS values are subject to postural influences. The parallel changes of TS and BRScv in response to orthostasis further support their common mechanism (this will be discussed in detail later). Reduction of the BRScv in upright posture was already noticed by Pickering et al. (Pickering TG 1971) using the Oxford method. In subsequent studies, the same trend was confirmed using spontaneous BRS techniques (Kardos A 1997, Steptoe A 1990). The decrease in BRS could be explained by a leftward movement of subjects on their arterial pressure - vagal response relationship (Cooke WH 1999). Postural decline of Cardiovagal BRS was detected even among patients with diabetic neuropathy with already low baseline values (Lengyel Cs 1998). Therefore, postural factor should be always considered when assessing TS from Holter tapes; for instance, by performing separate analyses of recordings taken in supine and erect positions.

From the very first description of HRT parameters, the exact mechanism of post-extrasystolic RR interval changes has been a subject of debate. Schmidt et al. already suggested changes in autonomic tone, however, traction of the sinus node region, or transient fluctuation in the sinus node blood flow were also implicated (Schmidt G 1999). By now, most of the researchers are convinced that these RR interval responses are vagally mediated, as it has been shown that atropine administration could abolish them (Lin L-Y 2002, Marine JE 2002). Numerous studies investigated the relationship between baroreflex and HRT phenomenon (Davies LC, 2001, Ghuran A 2002, Iwasaki M 2005, Lin L-Y 2002, Lindgren

KS 2003, Wichterle D 2006). Although the degree of correlation varied with the different baroreflex techniques, all of these studies confirmed the relationship. Thus, HRT could be regarded as a special baroreflex technique, which requires no simultaneous arterial pressure recording. This idea is not entirely unprecedented. Davies et al. (Davies LC 2002) recently suggested baroreflex gain assessment by the analysis of RR interval oscillations of slow patterned breathing. Two factors should be considered when interpreting the results of HRT-BRS comparisons. The first is related to the time delay between the specific baroreflex test and the Holter recording which supplied material for HRT analysis. Baroreflex indices show some extent of day-to-day variation, even in well-controlled laboratory conditions (Zöllei É 2007). The time delay between BRS tests and Holter monitoring presumably varied even more widely in some of the above cited studies. The other factor which deserves comment is related to the methodology of BRS testing. In those studies which utilized vasoactive drug injection, or Valsalva maneuver, the BRS gain calculation was based on relatively large arterial pressure swings, which may extend to the flat portion of the sigmoid arterial pressure-RR interval relationship. Nevertheless, previous publications confirmed the relationship between HRT parameters and the baroreflex gain determined by bolus phenylephrine injection. One of these reports is related to the ATRAMI trial. Reanalysis of the Holter recordings of the patients included in the study indicated a moderate, but significant correlation between the HRT indices and the phenylephrine baroreflex gain (Ghuran A 2002). In another report, Iwasaki et al. (Iwasaki M, 2005) found good correlation between phenylephrine BRS and Holter-derived HRT parameters in acute infarction. The baroreflex gain, calculated from the blood pressure overshoot phase of the Valsalva maneuver, was studied by Lindgren et al. (Lindgren KS, 2003) in subjects with no structural heart disease. They reported a good correlation between the Valsalva BRS and the HRT values of spontaneous and paced PVCs. (Lindgren KS, 2003). Unlike the large pressure fluctuations with the above mentioned studies, the post-extrasystolic blood pressure fluctuations are usually moderate, confined to the vicinity of the resting set point. Actually this is also the range of the spontaneous sequences. This assumption was well substantiated by two recent studies, both performed in cardiac electrophysiological laboratories, utilizing paced PVC-s (Lin L-Y 2002, Roach D 2002).

Roach et al. (Roach D 2002) calculated spontaneous sequence gains of their patients both during sinus rhythm and following PVCs. They found that the values were not only closely correlated, but were practically identical. Lin et al. (Lin L-Y 2002) determined spontaneous baroreflex gain of their patients from 5-minute recordings of RR intervals and

arterial pressure, and then they determined the HRT parameters using pace-induced PVC-s. They documented good correlation between HRT- and BRS parameters. In a recent report, Wichterle et al. (Wichterle D 2006) calculated baroreflex gain from the five post-extrasystolic cycles, which also served for TS calculations. This gain showed good correlation not only with the TS, but also with another spontaneous baroreflex index, the transfer function modulus in the low frequency (0.05– 0.15 Hz) band. Davies et al. (Davies LC 2001) also reported a strong correlation between TS values and a spectral baroreflex gain, the low frequency alpha-index. Our present study, which documented close connection between the HRT parameters and the spontaneous sequence gain, is in line with that of Lin et al. Instead of invasive procedure we used non-invasive, externally programmed pacemaker stimuli - a method that was introduced by Raj et al. (Raj SH 2005) in patients with implanted ICD. Our present study extended the observation to an elderly population with atrioventricular conduction abnormalities.

6. LIMITATIONS

With regard to the close resemblance of HRT and sequence BRS values reported by others (Ghuran A 2002, Lin L-Y 2002, Roach D 2002), we selected this method for our analysis. Nevertheless, the sequence BRS method has limitations. Firstly, as indicated by our results, in many cases the method is unfeasible because of the lack of spontaneous sequences. The lack of spontaneous sequences is more common in certain patient populations, such as those with Parkinson's disease (Oka H 2003). In our study group the lack of sequences could be related to the patients' coexisting, previously unidentified sinus node disease (this might have had an impact on the results using alternative BRS techniques as well). Secondly, the high correlation limit for the spontaneous sequences may impose a selection bias. In order to mitigate selection bias toward higher BRS values, we set no RR interval limit. Thirdly, the validity of spontaneous baroreflex tests is the subject of an ongoing debate. Arterial baroreflex, in real life, acts within a closed loop system (Diaz T 2006). The oscillations of the blood pressure and pulse rate encompass both feedback (baroreflex) and feed forward relations (Diaz T 2006). The traditional human baroreflex tests, such as the vasoactive drug administration, the neck suction test, and the Valsalva maneuver, alter the arterial transmural pressure and briefly open part of the closed loop. In contrast, spontaneous indices, which are based on arterial pressure and heart period changes with no apparent external cause for their occurrence, may errantly suggest baroreflex involvement (Diaz T 2006). In this regard, the PVC-induced response may represent another example of ‘‘opening the loop.’’ Indeed, the hemodynamic responses to PVCs have a resemblance to that of Valsalva maneuver (Goldstein DS 2000). Finally, the somewhat different correlations and postural responses of the TS and TO parameters merit explanation. As discussed above in detail, both the BRS method of spontaneous sequences and HRT measurements are based on ramp-like arterial pressure fluctuations. Similarly, all the traditional BRS tests induce ‘‘ramp-like’’ changes in the stretch of arterial baroreceptive areas. The relationship between the stimulus (arterial pressure, neck chamber pressure, or carotid diameter) and the response (RR intervals) is characterized by calculating the gain between these variables. From the methodological limitation of the BRS tests, it might be erroneously concluded that baroreflex response requires several cardiac cycles to manifest. In reality, the vagally mediated pulse interval responses are very quick and could be short-lasting. Arterial pressure alterations may elicit perceptible RR interval changes within the prevailing cardiac cycle (Eckberg DL and Sleight P 1992). These minuscule

‘‘single beat’’ baroreflex events are usually not assessable with traditional tests, and their relationship to the pressure ramp-related parameters is not yet characterized. TO represents such brief baroreflex manifestation and in this capacity is a unique parameter. Another factor should also be considered. Unlike BRS and TS values, TO is a ‘‘normalized’’ parameter, expressing proportional, instead of absolute changes. With a faster baseline, as it is in upright posture, the different representation may contribute to the different behavior.

7. RESPECTIVE FINDINGS AND FUTURE CLINICAL IMPLICATIONS

- Our observations indicate that BRS and HRV values are generally depressed in elderly arteriosclerotic population, allowing no real prediction of bradycardia upon carotid artery stenting. These observations are supported by recent clinical studies (Huang CC 2010, Mense L 2010). On the other hand, our study confirmed that the episodes of intervention-related transient bradycardia are generally benign, requiring no temporary pacemaker insertion. This finding may help to avoid unnecessary costs and complications of the procedures.

- Our observation of the close association between BRScv and HRT indices is in line with the results of previous studies. The relationship is emphasized by the parallel behavior of these indices upon orthostasis. The latter finding may help to explain the documented day-night differences of HRT parameters, derived from Holter tapes. Besides changes resulting from wake-sleep differences, the postural decline of vagal heart rate regulation should be also considered. The results also exemplify the uncertainties arising from Holter recording based studies. In our publication we concluded that HRT parameters could be more reliably assessed during controlled laboratory conditions. We have even suggested that external induction of arrhythmia via programming implanted devices may serve as a tool for longitudinal studies in certain patient populations. Since the publication of our paper, studies have been started with similar rationale. In the ongoing DECIDE HF study (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00949676) HRT is calculated by implanted devices after spontaneous PVC-s or after device stimuli (Bauer A 2010).

- Our study on the arterial pressure recovery from paced NSVT-induced pressure decline indicates that this maneuver can serve as a tool in characterizing sympathetic baroreflex regulation. The indices derived from induced NSVT closely parallel an other, validated sympathetic gain, which is derived from the pressure responses of Valsalva maneuver. Confirmation of the converging nature of these techniques may allow uniformization of the methods used in healthy and sick populations.

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