Baroreflex Sensitivity And Autonomic Nervous System Function In Carotid Sinus Hypersensitivity

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Abstract

Syncope in the elderly may be caused by an apparent hypersensitivity in the high pressure baroreflex control of heart rate and blood pressure - carotid sinus hypersensitivity.

Previous studies have found ambiguous results regarding the baroreceptor sensitivity in patients with carotid sinus hypersensitivity ranging from reduced to increased sensitivity compared to controls. We wanted to establish whether measures of baroreflex sensitivity and autonomic function differed between patients diagnosed with carotid sinus hypersensitivity and age-matched controls.

We included 36 patients (12 women; 74 +/-10.2 years) with carotid sinus hypersensitivity and 26 controls (14 women; 72 +/-3.6 years). RR-intervals and blood pressures were measured continuously in the supine and head-up tilted position and during active change to the upright posture. The same parameters were measured during the Valsalva maneuver and deep breathing at 0.1 Hz. From these measurements we derived indices of baroreflex sensitivity and heart rate variability.

We found differences between groups with respect to the tachycardia ratio (p = 0.037) reflecting vagal withdrawal during the Valsalva maneuver and the adrenergic baroreflex sensitivity index (BRSa; p = 0.026) during the same maneuver. We could not demonstrate any significant difference between groups with respect to other measures of cardiovagal or adrenergic baroreceptor control and the response to head-up tilt was comparable between the two groups.

We conclude that only minor differences in autonomic baroreceptor control could be found between patients with carotid sinus hypersensitivity and their controls. Our findings seem to reflect the ambiguous results obtained by others and have led us to suggest that the signals behind the established parameters of cardiovagal baroreflex sensitivity may not follow the same neuronal pathways as those responding to the crude external pressures applied during carotid massage.

Keywords: Carotid sinus massage; Carotid sinus hypersensitivity; Syncope; Falls, Elderly; Baroreflex sensitivity


Introduction

Almost 30% of home-dwelling elderly fall each year with an age related increase reaching 50% in octogenarians [1] and syncope appears to be a common cause of falls with a 10-year incidence of almost 25 per cent in people older than 70 years [2]. Syncope in the elderly may be ascribed to an apparent hypersensitivity in the high pressure baroreflex control, carotid sinus hypersensitivity (CSH), characterized by at least 3 seconds of a systole and/or a drop in systolic blood pressure of 50 mmHg or more in response to carotid sinus massage (CSM). The prevalence of CSH in healthy older adults is estimated at 10% and is present in as much as 50% of the elderly suffering from falls [3].

The arterial baroreflex is a negative feedback system designed to buffer blood pressure fluctuations on a beat-by-beat basis and thereby minimizing random fluctuations in blood pressure. The baroreceptor afferents are tonically active, stretch-sensitive nerve endings situated in the vessel wall of both the proximal aorta and the carotid arteries. The baroreceptor sensitivity is entirely a function of dimensional alterations of the vessels secondary to changes in distension pressure or to external, mechanical stretch. Dimensional changes lead to changes in afferent firing rate and after central relaying of the signal through the nucleus of the solitary tract this will lead to changes in sympathetic and parasympathetic outflow. Changes in sympathetic outflow lead to changes in heart rate, cardiac contractility, and vascular tone, whereas changes in parasympathetic outflow primarily affect heart rate.

Increasing age is associated with changes in the arterial walls including increased intimal thickness, vascular smooth muscle hypertrophy, fragmentation of the internal elastic membrane and an increase in the amount of collagen and collagen cross linking [4]. The changes result in an increased stiffness of the arterial wall and may play a role in the pathophysiological changes resulting in CSH [5,6].

Baroreflex sensitivity (BRS) may be quantified by the heart rate response to blood pressure changes induced by vasoactive drugs with minimal effect on the sinus node. Non-interventional alternatives are mainly represented by forced changes in cardiac filling by the Valsalva maneuver (VM), by direct changes in external carotid pressures through the neck chamber technique, or by analysis of spontaneous variations of blood pressure and RR interval. In quantifying BRS a distinction is made between the effects on heart rate (cardiovagal BRS) and on the vascular system (adrenergic BRS).

Interestingly, the cardiovagal BRS is dampened with advancing age [6,7], but several studies have demonstrated a positive correlation between age and CSH [8,9]. The hypersensitive response has only been convincingly demonstrated during external, mechanical stimulation of the carotid sinus [10] whereas studies examining the association between CSH and spontaneous cardiovagal BRS have been equivocal with some studies demonstrating an association between CSH and increased [11] and others reduced spontaneous cardiovagal BRS [12]. On this background, we wanted to study if various measures of BRS and autonomic function differed between patients diagnosed with CSH and age matched healthy controls.

Materials and Methods

Subjects

We included 36 patients aged 53 to 92 years diagnosed with CSH in the last year before examination. All were referred to our syncope unit due to unexplained syncope or recurrent falls and a head-up-tilt test (HUT) including CSM was performed. The diagnosis of CSH was based on CSM for five seconds on the right side, followed by the left in the supine position, and repeated in the 60 degrees head-up tilted position. CSH was considered to be present if a systole of > 3 seconds (cardio inhibitory type) or reduction in systolic blood pressure of > 50 mmHg independent of heart rate slowing (vasodepressor type) or a combination of the two (mixed type) occurred in the supine position or at HUT. Twenty six healthy subjects aged 65-80 years recruited through The Copenhagen City Heart study served as controls. The Danish Data Protection Agency and the regional Ethical committee for the Capital Region of Denmark approved the study (No. H-4-2010-030, H-4-2010-031) and written informed consent was obtained from all participants.
Testing procedure

All tests were performed between 8 a.m. and 10 a.m. in the fasting state at standard room temperature. Clinical characteristics registered in the study included: Age, gender, height, weight and body mass index (BMI). Clinical blood pressure was measured by an automated sphygmanometer (Omron 705C, Kyoto, Japan) three times on the right arm after 5 minutes of rest in the sitting position and expressed as the mean value. RR-intervals and blood pressure were measured continuously from one precordial ECG-lead and by Finometer equipment (Finapres Medical Systems BV, Amsterdam, The Netherlands), respectively. The ECG was band-pass filtered with a lower and higher cut-off frequency of 0.5 and 40 Hz, respectively and the blood pressure data were low-pass filtered with a cut-off frequency of 40 Hz. RR-intervals were converted to instantaneous heart rate and systolic blood pressure was derived from the maximum value on the continuous blood pressure recording on a beat-by-beat basis. Data were sampled at 1.0 kHz and analyzed using commercial software (Lab Chart, AD Instruments Inc, Colorado Springs, CO, USA).

Baseline data were acquired during 10 minutes of supine rest, where the subjects refrained from speaking and from unnecessary movements. The subjects were then loosely strapped to an electrically driven tilt table and tilted to a 60 degree head up position within 3-4 seconds and stayed in this position for 10 minutes if intolerable symptoms did not appear.

The subjects then performed the VM in the sitting position. A mouthpiece was connected to a mercury manometer by a rubber hose with an air leak. The subjects were asked to inhale deeply and then exhale in to the mouthpiece maintaining a pressure of 40 mmHg for 15 seconds. The procedure was repeated until two identical responses were obtained [13]. Following the VM, the subjects were asked to breathe deeply at a rate of 6 min-1 following a stop-watch for two minutes in the seated position (deep breathing). Finally and after at least 5 minutes of sitting rest the subjects were asked to rise and stand for three minutes without moving or speaking (active stand).

Data analysis

Analysis of heart rate variability (HRV) was performed according to current guidelines [14] using share-ware (Kubios, vers. 2.0, http://kubios.uku.fi). Artefact and ectopic-free 5-minutes segments of supine and tilted rest were analyzed in the time domain as mean value of successive normal beats (meanNN), standard deviation of successive normal beats (SDNN), and numerical difference between successive normal beats (Root Mean Squared Successive Difference, RMSSD). Power spectral densities were calculated using the autoregressive method and total power as well as the power in the low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.40 Hz) bands were obtained and expressed as actual and normalized values (LFnu, HFnu) as well as by the ratio between low and high frequency components (LF/HF)[14].

Cardiovascular BRS was obtained as the beat-by-beat changes in HR in relation to the concomitant BP changes and analyzed using Nevrokard BRS software (Nevrokard BRS, Nevrokard, Izola, Slovenia). We used the sequence technique analyzing ectopic free segments of 5 minutes length of matching HR and blood pressure measurements – recorded during five minutes in the supine and head-up-tilted positions. In the sequence technique an event is present when the RR-interval length and blood pressure height change with a time lag of one beat for three or more beats. Changes of 1 mmHg for systolic blood pressure (SBP) and 6 ms for RR-interval were chosen as the minimal values. A linear correlation between changes in RR-interval and SBP was computed for each of the detected sequences and the slope of the regression line was calculated for those sequences having a correlation coefficient of 0.8 or more. Slopes resulting from events with increases in both parameters are denoted upBRS whereas events with decreases in both parameters are denoted downBRS. The average value of slopes from all regression lines are given as all BRS.

The hemodynamic response to the VM is divided in to four phases: Phase I is the early increase in blood pressure, being followed by a fall and subsequent rise in blood pressure during Phase II. Heart rate increases throughout these phases. Phase III describes the short decrease in blood pressure at the release of strain and is followed by a rapid increase in blood pressure above baseline and a fast reduction in heart rate – Phase IV. The index of cardiovascular BRS was calculated as the slope of the regression line of RR-intervals plotted against mean blood pressure in the early Phase II. (BRSv) [15-16]. Pressure recovery time (PRT) was calculated as the time interval between trough values of systolic blood pressure in Phase III and the return to baseline value of 30 seconds before the maneuver and was not calculated if the SBP in Phase III did not decrease below baseline [16]. Adrenergic baroreflex sensitivity (BRSa) was defined as
the SBP decrement associated with Phase III divided by the PRT. An alternative calculation (BRSa1) relates PRT to a combined decrease in BP during early Phase II and 0.75 of Phase III [16]. The Valsalva ratio is calculated as the ratio between the longest RR-interval following the maneuver by the shortest RR-interval during or immediately following the maneuver. Tachycardia ratio is calculated as the ratio between the shortest RR interval during strain and the mean RR interval before the test [17].

The results from the deep breathing session were expressed by the expiratory/inspiratory difference (E/I-difference) between the mean value of the slowest (HRmin) and fastest (HRmax) heart rate during six consecutive cycles.

The hemodynamic response to HUT was determined as HR, SBP and DBP measured as mean values during the last 30 seconds of supine rest before HUT, and 30 seconds during the 5th and 10th minute of HUT. The hemodynamic changes elicited were also calculated as changes relative to baseline values. The heart rate response to active stand was calculated as the ratio of the highest heart rate around the 15th beat and the lowest heart rate around the 30th heart beat after assumption of the upright posture (30:15 ratio).

Statistical analysis

Statistical analysis was done using SPPS 19 (SPSS inc. Chicago, IL, USA). Log normal transformation was used for non-normally distributed parameters. Comparisons between groups were made with Student’s T-test. ANCOVA analysis was done in order to adjust for the possible confounding effects of gender and BMI.

Results are expressed as means +/- standard deviations (SD) for non-transformed data and as means with 95% confidence intervals (CI) for transformed variables. A two-sided significance level of 0.05 was used unless otherwise indicated.

Results and Discussion

Results

A total of 36 CSH-patients (12 women, age 74 +/-10.2 years, range: 53-92 years) and 26 controls (14 women, age 72 +/-3.6 years, range: 66-79 years) were included in the study. The clinical characteristics are given in Table 1 and these did not differ significantly between groups except for a slight but significantly lower BMI in the patients.

<table>
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<tr>
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<th>Controls (n = 26)</th>
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<td>Weight (kg)</td>
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<td>HR (min$^{-1}$)</td>
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<td>63</td>
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<td>SBP (mmHg)</td>
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<td>150</td>
<td>0.951</td>
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<td>Hypertension</td>
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Table 1: Baseline characteristics.

Characteristics of patients with carotid sinus hypersensitivity (CHS) and control subject. Previous diagnosis of diabetes and treatment for hypertension are given. Comparisons between groups were made with Student’s T-test. And results are given as means +/- standard deviations (SD).

Measures of HRV could not be calculated in seven patients and three healthy subjects due to multiple ectopy. Indices of spontaneous BRS could not be calculated in eleven patients and seven healthy subjects due to multiple ectopy or technical difficulties in blood

pressure measurement. Values of spontaneous cardiovagal BRS tended to be smaller in CSH patients but this difference only reached significance for downBRS in the supine position (p = 0.034; Table 2).

![Table 2: Spontaneous baroreflex sensitivity in supine and head-up-tilted rest.](image)

Logarithmic transformation of indices of spontaneous baroreflex sensitivity (BRS) given as mean values with confidence intervals (CI) for positive changes (upBRS), negative changes (downBRS) and the combination (allBRS) in the supine and head-up tilted (HUT) positions. Comparisons between groups were made with Student’s T-test and results are expressed as means with 95% confidence intervals (CI).

The indices of spontaneous HRV did not differ significantly between CSH-patients and controls (Table 3).

![Table 3: Spontaneous heart rate variability in the supine and head-up-tilted positions.](image)

Heart rate variability measures in the time (MeanNN, SDNN, RMSSD) and frequency domain (Total Power (TP), Low Frequency Power (LF), and High Frequency Power (HF)) in the supine and head-up tilted position (HUT). Comparisons between groups were made with Student’s T-test. Results are expressed as means +/- standard deviations (SD) for non-transformed data and as means with 95% confidence intervals (CI) for transformed variables.

The response to deep breathing (E/I-difference) was significantly lower in the CSH-patients (p = 0.024) as was the tachycardia ratio (p = 0.034) obtained by the VM (Table 4). Neither the Valsalva ratio nor the 30:15-ratio derived from active stand differed between groups (Table 4).

<table>
<thead>
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<td>E/I-difference</td>
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<tr>
<td>TR</td>
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<tr>
<td>Active stand</td>
<td></td>
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<tr>
<td>30:15 ratio</td>
<td>1.14</td>
<td>1.12</td>
<td>0.629</td>
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**Table 4:** Measures of parasympathetic function obtained by deep breathing, Valsalva manoeuvre, and active stand.
Calculated heart rate changes during deep breathing at 0.1 Hz (maximal heart rate (HR<sub>max</sub>); minimal heart rate (HR<sub>min</sub>); ex-/inspiratory difference in heart rate (E/I-difference)) and in response to the Valsalva maneuver (Valsalva Ratio (VR), Tachycardia Ratio (TR)) and to active change to the upright posture (Active Stand(30:15 ratio)). Comparisons between groups were made with Student’s T-test and results are expressed as means +/- standard deviations (SD).

The indices of adrenergic baroreceptor function derived from the VM (PRT, BRSa and BRSa1) could not be calculated in six controls and in 12 CSH-patients as the SBP in Phase III did not decrease below baseline. BRSa was lower in CSH-patients, whereas the other parameters of adrenergic baroreceptor function did not differ between groups (Table 5). The index of cardiovagal baroreceptor function (BRSv) could not be calculated in seven controls and in nine CSH-patients and did not differ between groups (Table 5).

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<td>lnPRT</td>
<td>1.56</td>
<td>1.88</td>
<td>0.197</td>
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<tr>
<td>lnBRSa</td>
<td>2.25</td>
<td>2.16</td>
<td>0.013</td>
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<tr>
<td>lnBRSa1</td>
<td>2.48</td>
<td>2.05</td>
<td>0.059</td>
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<tr>
<td>lnBRSv</td>
<td>1.50</td>
<td>1.47</td>
<td>0.940</td>
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</table>

**Table 5:** Indices of baroreflex sensitivity derived from the Valsalva manoeuvre.
Logarithmic transformation of pressure recovery time (PRT), adrenergic baroreceptor indices (BRSa; BRSa1), and cardiovagal baroreceptor sensitivity (BRSv). Comparisons between groups were made with Student’s T-test and results are expressed as means with 95% confidence intervals (CI).

Blood pressure measured at the finger level during tilt testing showed lower supine values of SBP and lower values of both SBP and DBP both at the 5<sup>th</sup> and the 10<sup>th</sup> minute of HUT in CSH patients (Table 6), whereas HR did not differ between groups neither in the supine nor in the head-up tilted position. When adjusted for baseline values the two groups did not differ.

When adjusting for gender and BMI, the only parameters still showing statistical significant differences between controls and CSH patients were the tachycardia ratio (p = 0.037) and the adrenergic index BRSa (p = 0.026) both obtained during the VM.

This study compared a number of parameters reflecting different aspects of baroreflex control in patients with CSH and age matched controls. We found significant differences in two measures derived from the VM – the adrenergic baroreflex sensitivity and the tachycardia ratio reflecting cardiovagal control. We could not demonstrate any differences between our two groups with respect to spontaneous cardiovagal BRS or HRV.

Tan et al. found higher resting heart rates in patients with CSH combined with an increase in total and low frequent power of HRV and an increase in the low to high frequency power ratio (LF/HF) [18]. Apart from a non-significant trend towards increased LF/HF values in the CSH-patients compared to controls, we were unable to confirm any of the aforementioned findings in our patients. Previous studies have shown both lower [12] and higher [11] spontaneous cardiovagal BRS using a technique similar to ours. Madden, et al. [12] compared type-2 diabetic patients with or without carotid hypersensitivity, whereas only one in 54 patients had diabetes in the study by Tan, et al. [11]. In the latter study symptomatic patients had higher heart rates and were somewhat younger and adjusting for this removed all significant differences with respect to HRV. Baroreceptor sensitivity remained significantly elevated in the symptomatic group that included a significantly higher number of patients on statin treatment. Statin treatment has been shown to increase baroreceptor sensitivity and HRV in both human [19] and animal studies possibly through structural changes in the carotid arteries, leading to improved triggering of the mechanoreceptors [20]. In summary – our understanding of the age related changes in baroreflex function associated with CSH is still scarcely understood.

**Table 6:** Hemodynamic response to 60 degree head-up-tilt test. Absolute changes and changes relative to baseline values in heart rate (HR, min-1), systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) in response to head-up-tilt test (HUT) Comparisons between groups were made with Student’s T-test and results are expressed as means +/- standard deviations (SD).

When adjusting for gender and BMI, the only parameters still showing statistical significant differences between controls and CSH patients were the tachycardia ratio (p = 0.037) and the adrenergic index BRSa (p = 0.026) both obtained during the VM.

**Discussion**

This study compared a number of parameters reflecting different aspects of baroreflex control in patients with CSH and age matched controls. We found significant differences in two measures derived from the VM – the adrenergic baroreflex sensitivity and the tachycardia ratio reflecting cardiovagal control. We could not demonstrate any differences between our two groups with respect to spontaneous cardiovagal BRS or HRV.

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The VM is a validated test measuring autonomic adaptation to changes in venous return to the heart. The increase in intrathoracic pressure reduces venous return and hence stroke volume and arterial pressure. This is compensated by vagal withdrawal resulting in tachycardia quantified as the tachycardia ratio. It also elicits sympathetic activation to the vasculature resulting in vasoconstriction measured by the adrenergic BRS. At release of the increased intrathoracic pressure venous return and stroke volume are re-established resulting in an overshoot of blood pressure due to the previously induced vasoconstriction. The rise in pressure elicits a bradycardic response quantified by the Valsalva ratio and mediated almost exclusively by the parasympathetic branch of the baroreflex arch. Our study demonstrated a reduced tachycardia ratio possible due to a lower intrinsic heart rate or a defect withdrawal of vagal tone. However, other measures of cardiovagal function did not differ between CSH patients and controls and considering the number of statistical tests performed we cannot rule out that the finding may be due to mass significance.

We found a difference between groups with respect to blood pressures measured at the finger by photoplethysmography, but not when measured on the upper arm by the oscillometric technique. As the basal levels of both systolic and diastolic blood pressures and their difference (pulse pressure) were the same in the two groups, we cannot offer any explanation for this discrepancy. The blood pressure and heart rate responses to HUT did not differ between the two groups when adjustments were made for differences in baseline values, and this is compatible with a similar overall baroreceptor function in the CSH patients and the controls.

The reproducibility of a hypersensitive response to carotid sinus massage has only been the subject of relatively few studies [21-24]. The studies have found that neither the nature of the hypersensitive response (cardioinhibitory/vasodepressor) nor the side (right/left) or position of the patient (supine/upright) used to elicit the response are very reproducible. But carotid sinus hypersensitivity as such during CSM as well as the cardiovascular instability that it reflects are reproducible phenomena with a test-retest reliability of up to 90% [21].

We suggest that CSH should not be regarded as a disease entity as such with a specific pathophysiology but rather an indicator of an age-related mismatch between components of baroreflex function. This acquired instability in the cardiovascualr reflexes leaves the patient susceptible to syncope, falls and black outs and previous studies have demonstrated that CSH is associated with an enhanced prevalence of other forms of reflex syncope [8].

Based on the literature and on our results the findings with respect to baroreceptor and/or general autonomic dysfunction in patients with CSH are very few. In appraising this conclusion it may be worthwhile considering whether we are testing the right system response or not. Most – if not all – the cardiovagal parameters are based on signals carried in myelinated afferent fibres from mechanoreceptors with a low threshold to the nucleus tractussolitarius and relayed to the nucleus ambiguous and the efferent, myelinated part of the vagal nerve. This system seems to be essential for normal cardiovagal BRS [25]. It must be kept in mind that there are unmyelinated afferent fibres with a high threshold[26] also terminating in the nucleus tractussolitarius and most likely relayed in the dorsal vagal motor nucleus and from there carried in the unmyelinated part of the vagal nerve. It may be this system that responds to the rather crude mechanical pressure used in carotid sinus massage and that a lower than normal threshold in this system would explain the finding of CSH and the lack of relation to measures of “myelinated” baroreceptor function.

Age related changes in baroreflex function and sensitivity is a complex matter with the different components of the baroreflex arc and age related changes in these components interplaying in many known and surely also many yet unidentified ways. Our findings confirm the notion that further studies are warranted – preferably in larger study-populations.

Conclusion

Comparing a number of parameters reflecting different aspects of baroreflex control in patients with CSH compared to age matched controls we found significant differences in two measures derived from the Valsalva maneuver – the adrenergic baroreceptor sensitivity and the tachycardia ratio reflecting cardiovagal control. We could not demonstrate any differences between our two groups with respect to spontaneous cardiovagal BRS or HRV suggesting that only minor differences in autonomic baroreceptor control exist between patients with CSH and their controls.
Bibliography


