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HEALTHY AGING RESEARCH

Carotid sinus syndrome and cardiovagal regulation in elderly patients with suspected syncope-related falls

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Abstract

Background: Falls and syncope in the elderly may be caused by hypersensitivity in the high-pressure baroreflex control - carotid sinus syndrome (CSS). The pathophysiological process causing CSS remains poorly understood.

Methods: We studied the hemodynamic response to carotid sinus massage (CSM) and compared this to other measurements of autonomic cardiovascular control in patients suspected of syncope-related falls. One hundred patients (≥80 years-old) referred to our syncope unit due to recurrent falls or possible syncope participated. CSM was performed in the supine and head-up tilted (HUT) positions. A hypersensitive response was defined by current guidelines.

Results: In the supine position, heart rate (HR) and systolic blood pressure (SBP) decreased during CSM on the right side by 17.0 +/- 15.2 min^{-1} and 32.5 +/- 25.5 mmHg, and on the left side by 12.8 +/- 14.3 min^{-1} and 22.7 +/- 20.7 mmHg, respectively. Changes in SBP were greater in the head-up tilted position (right side; p=0.029, left side; p=0.007). Hypersensitive responses were elicited in 45 patients. We found orthostatic hypotension (OH) (r=-0.275, p=0.015), not CSS, to be inversely correlated to low frequency HR variability during HUT.

Conclusions: The hemodynamic response to CSM has a well-defined pattern and differs both with respect to the stimulus site and patient position. We suggest that CSS is not a distinct pathophysiological process or disease entity but rather an acquired cardiovascular instability due to age-related degeneration and following mismatch between different components of cardiovascular regulation.

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Introduction

Falls are the most common cause of accidents in older people and lead to substantial morbidity and mortality [1]. A common cause of falls in the elderly is syncope and, as such, the 10-year incidence is almost 25% in people over 70 years-old [2]. As syncope is often associated with retrograde amnesia [3], syncope-related falls are presumably under-reported.

Falls in the elderly due to syncope may be caused by hypersensitivity of the high-pressure baroreflex control of heart rate (HR) and blood pressure (BP) (carotid sinus hypersensitivity, CSH) and lead to carotid sinus syndrome (CSS), a condition in which the hypersensitive baroreflexes are accompanied by recurrent symptoms of dizziness, light-headedness or syncope.

Czermark was the first to observe that pressure applied externally to the carotid artery may cause a temporary cardiac arrest [4]. While he misattributed the reflex as being caused by a direct activation of the vagal nerve running in parallel with the carotid artery, this misconception was later clarified by Hering [5], who described that stimulation of the carotid baroreceptors produces reflex cardiac slowing and hypotension with the latter being independent on changes in HR.

The high-pressure baroreceptors are situated in both the aortic arch and the carotid sinus, but the threshold for stimulation is higher in the aortic arch. In effect, the carotid sinus is considered to be more important in blood pressure regulation at normal pressure levels [6]. Bedside testing of the carotid baroreflex can be achieved grossly by carotid sinus massage (CSM), which is performed by applying longitudinal digital pressure at the bifurcation of carotid artery for 5 seconds on either side in the supine and upright positions, which normally reduces HR and decreases BP. In some individuals, CSM elicits an exaggerated response of extreme bradycardia and/or severe hypotension indicating the presence of CSH, which is denoted CSS when symptomatic. Complications of CSM are most often neurological, and even though they are very rare (0.2-0.3%) [7,8], CSM is contraindicated in patients with transient ischemic attack or stroke within the past three months, or with carotid bruits, unless carotid Doppler studies have excluded significant stenosis.

Healthy aging has an effect on the autonomic control of the circulation, and the baroreflex-mediated vagal control of the heart has been shown to deteriorate with age [9], whereas baroreflex control of the vascular system is less affected by age [10]. Apositive correlation between advancing age and CSH and CSS has been demonstrated [11]. Therefore, it appears paradoxical that carotid hypersensitivity in the form of extreme bradycardia is more prevalent with advancing age, as it has been reported that vagal control of HR declines with age [9].

The actual pathophysiological process causing CSS remains poorly understood. CSS is associated with neurodegenerative diseases as Parkinson's disease, Lewy body dementia, and Alzheimer's disease [12] and it is unclear whether CSS is an actual disease entity or merely reflective of the overall age-related instability of cardiovascular control.

The aim of the current study was to quantify HR and BP changes in response to CSM and head-up-tilt (HUT) in patients aged 80 years or older consecutively referred for possible syncope-related falls. Secondly, we wanted to compare these hemodynamic changes in response to CSM and HUT to measurements of HR variability (HRV). Taken together, these aims attempt to address the aforementioned paradox of the increased prevalence of CSS but impaired cardiovagal regulation with age.

Methods

Patient cohort and testing

We did a retrospective analysis based on data obtained from a tilt table test and CSM from 100 patients aged 80 years or older who were consecutively referred to our syncope unit between January 2006 and August 2008 for tilt testing due to transient, unexplained loss of consciousness and/or unexplained falls. All tests were performed between 8 a.m. and 2 p.m. in the non-fasting state at standard room temperature. All patients included were required to have a normal baseline 12-lead ECG. Due to the retrospective nature of the study, approval by the authorities was not required

Carotid sinus massage (CSM) was performed after at least 10 minutes of rest in the supine position, initially on the right side and then repeated on the left side after 1 to 2 min. CSM was performed by applying firm pressure for 5-10 s at the anterior margin of the sternocleidomastoid muscle at the level of the cricoid cartilage according to current guidelines [13].

The patients were then tilted to the upright position within 3-4 s with the inclination of the table set at 60. They stayed in this position for at least 10 minutes unless they wanted the test aborted before due to orthostatic intolerance. If a definite pathological response had not been elicited in the supine position, CSM was repeated in the head-up tilted position (HUT) at 60 degrees.

RR-interval and blood pressure were measured continuously from one precordial ECG-lead and by photopletysmography (FinoMeter, Finapres Medical Systems B.V., Amsterdam, The Netherlands), respectively. Data were sampled at 1.0 kHz and analyzed using commercial software (Chart 5.59, AD Instruments Inc., Colorado Springs, USA). The ECG was band-pass filtered with cut-off frequencies of 0.5 and 40.0 Hz and the BP data were low-pass filtered with a cut-off frequency of 40.0 Hz. RR-intervals were converted to instantaneous HR and SBP was derived from the maximum value from the continuous blood pressure recording on a beat-by-beat basis.

Data analysis

Baseline values of instantaneous HR and SBP were derived as the mean value from the 30 s immediately preceding CSM. The following trough values for both HR and SBP were recorded (Fig. 1). Changes in HR and SBP in response to CSM were then defined as the difference between baseline and trough values.

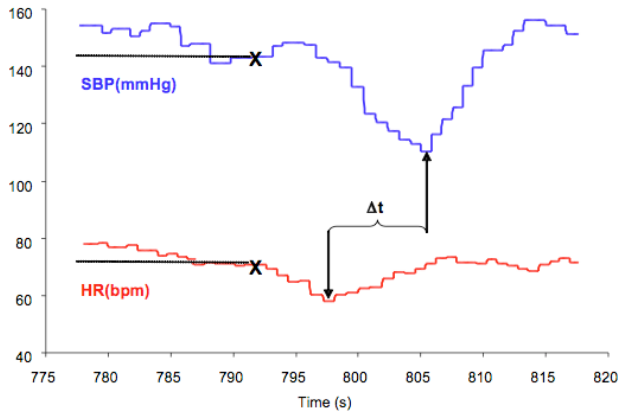

Figure 1. Quantification of hemodynamic changes during carotid sinus massage

Recording of systolic blood pressure (SBP, blue line) and heart rate (HR, red line) in response to carotid massage instituted at "**X**". Changes in SBP and HR were calculated as the differences between baseline values indicated by the broken line and the trough values indicated by arrows. Time difference between trough values is indicated (**Δt**)

Carotid sinus syndrome (CSS) was diagnosed based upon the occurrence of asystole lasting more than 3 s (cardioinhibitory type) or reduction in SBP of >50 mmHg independent of HR slowing (vasodepressor type) or a combination of the two (mixed type).

The hemodynamic response to HUT was quantified by calculating mean values of HR, SBP and DBP during 30 s obtained in the supine position before the first CSM and during the fifth minute of HUT. Orthostatic hypotension (OH) was defined as a decrease in SBP greater than 20 mmHg or in DBP of more than 10 mmHg from the supine to the head-up tilted position [13].

Heart rate variability (HRV) analysis was performed according to current guidelines [14] using share-ware (Kubios, vers. 2.0, [15]). Artifact- and ectopic-free five-minute segments from the resting supine and tilted positions were analyzed. Values derived in the time domain were: mean value of time period between normal beats (meanNN), standard deviation of time periods between normal beats (SDNN) and the numerical difference between successive normal beats (root mean squared successive difference, RMSSD). The power spectral densities were obtained by the autoregressive method, calculating the total power as well as power in the low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz) bands. The results were expressed both as absolute power (LF, HF, Total Power (TP)) and as normalized units (LFnu, HFnu). The ratio between low and high frequency variation was derived (LF/HF).

Statistical analysis was done using SPSS version 19 (SPSS inc. Chicago, IL). Comparison between groups was made with the χ^2 test for categorical data and Student's t-test for continuous data; results were expressed as mean values +/- standard deviation. Log normal transformation was used for data where a linear normal distribution could not be assumed (SDNN, RMSDD, TP, LF, HF and LF/HF values in both supine and tilted position) and results are given as geometric means with 95% confidence intervals. Correlations between parameters are given by Pearson's correlation coefficient. A two-sided significance of $p<0.05$ was used unless otherwise indicated.

Results

The clinical characteristics of the patients included are summarized in Table 1. A total of 100 patients (82 women, 18 men) were included in the study. The mean age was 84.5 (range: 80 – 96) years. In the resting supine position, HR was 69 +/-10 min^{-1} and systolic BP (SBP) and diastolic BP (DBP) were 132 +/- 31 mmHg and 58 +/- 18 mmHg, respectively. HRV-data could not be calculated in 19 patients in the supine position and in 21 patients in the tilted position due to multiple cardiac ectopies.

	Non-CSS			CSS				Combined		
	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD
Age (years)	55	84.1	3.4	45	85.3	3.8	0.112	100	84.5	3.6
HR (bpm)	55	69.1	10.4	45	69.5	9.7	0.832	100	69.3	10.1
SBP (mmHg)	55	131	34.2	45	134	25.2	0.559	100	132	30.9
DBP (mmHg)	55	57	18.4	45	59	17.3	0.609	100	58	17.9

Table 1. Clinical characteristics of included patients

characteristics given as mean +/- SD for patients with and without carotid sinus syndrome (CSS and non-CSS, respectively), separately and combined. P-values refer to comparisons between groups

Clinical characteristics given as mean +/- SD for patients with and without carotid sinus syndrome (CSS and non-CSS, respectively), separately and combined. P-values refer to comparisons between groups

Heart rate and BP responses to CSM (Table 2) were significantly greater on the right than on the left side both in the supine (HR: p=0.020, SBP: p=0.003) and head-up tilted (HR: p=0.001, SBP: p=0.011) positions. Heart rate response to CSM did not differ significantly between the supine and head-up tilted positions whereas the changes induced in SBP were greater during HUT.

The slowing of HR in response to CSM preceded the decrease in SBP and the time elapsing between the trough values did not differ between the right and left side or between supine position and HUT. Ten patients achieved the suggested cut-off point of asystole of 3 s or more and of these six occurred only in the head-up tilted position. Two episodes were elicited from the left side only, six from the right side only, and two from both sides. The mean duration of asystole was 4.5 s (range: 3.5 – 6.1 s) in the ten patients experiencing asystole of 3 s or more. A fall in SBP of more than 50 mmHg during CSM occurred in 24 of 100 patients in the supine and in 30 of 88 patients in the tilted position. In 12 cases this response was found only in the supine position and in 18 cases it occurred only during HUT. Forty-two patients responded to CSM with a fall in SBP of more than 50 mmHg and of these, seven also had asystole. All together, a total of 45 patients responded with CSS according to current guidelines. Three were diagnosed with CSS of the cardioinhibitory type, 35 were diagnosed with CSS of the vasodepressor type and seven were diagnosed with CSS of the mixed type. Only 4 subjects were symptomatic at the time of CSM – 3 of them with asystole of more than 3 s and one patient with a marked BP drop upon CSM. We were not able to demonstrate any age- or gender-related differences in the responses to CSM. Examples of the distribution of changes in HR and SBP in response to CSM are shown in Fig. 2 and 3, respectively.

	Supine	HUT	P-value
ΔHR, right (min^{-1})	17.0 (15.2)	17.9 (15.9)	0.109
ΔHR, left (min^{-1})	12.8 (14.3)*	11.9 (12.9)*	0.266
ΔSBP, right (mmHg)	32.5 (25.5)	38.8 (23.6)	0.029
ΔSBP, left (mmHg)	22.7 (20.7)*	28.9 (25.6)*	0.007
Δt, right (s)	7.3 (5.1)	7.9 (4.6)	0.315
Δt, left (s)	7.1 (4.6)	7.3 (4.1)	0.436

Table 2. Response to carotid massage in the supine position and during head up tilt (HUT)

Changes induced by carotid massage in the supine position and during head-up tilt (HUT) to 60 degrees in heart rate (ΔHR) and systolic blood pressure (ΔSBP) and the time difference between trough values for heart rate and systolic blood pressure (Δt). Values are given as the mean with standard deviation in parenthesis. P-value refers to differences between supine and head-up tilted values. * denotes significant differences ($p<0.05$) between values obtained on the right and left side, respectively.

In the 60-degree head-up tilted position HR was 73 +/- 10 min^{-1} and SBP and DBP were 136 +/- 35 mmHg and 68 +/- 19 mmHg, respectively. In response

to head-up tilt, HR increased by 4.9 +/- 5.8 min^{-1} and the mean increases in SBP and DBP were 3.5 +/- 24 mmHg and 9.8 +/- 12 mmHg, respectively. Of the three patients who requested abortion of the test before 10 minutes of HUT due to orthostatic discomfort, none were syncopal.

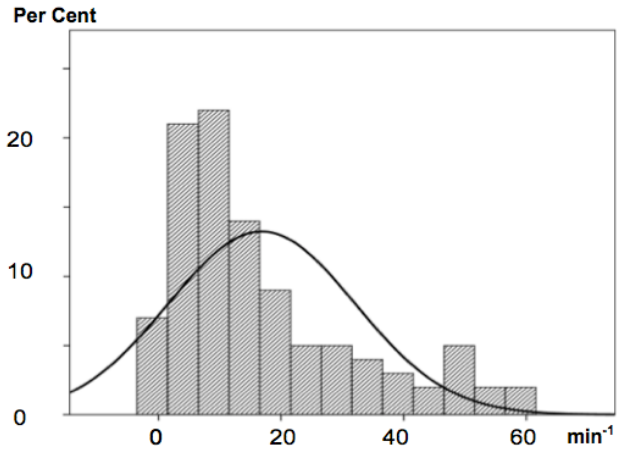

Figure 2. Distribution of heart rate response to carotid sinus massage (right side, supine position)

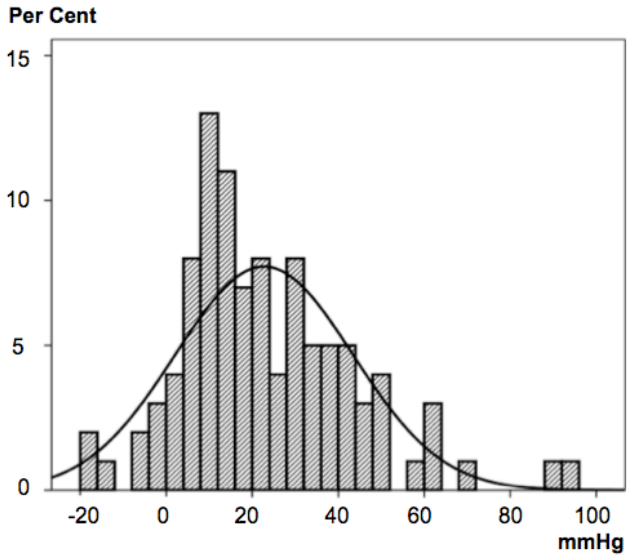

Figure 3. Distribution of systolic blood pressure response to carotid sinus massage (right side, supine position)

In total, 18 patients fulfilled the criteria for OH HUT and 11 patients fulfilled the diagnostic criteria for both OH and CSS. Presence of OH and CSS were not significantly correlated (r=0.152; p=0.132). Resting HR and BPs were independent of age in both the supine position and during HUT. HR was significantly higher in women compared to men both in the supine position (70+/-8.8 versus 63+/-8.7 min^{-1}; p = 0.005) and during HUT (69+/-11 versus 64+/-8.1 min^{-1}; p = 0.020), whereas the changes in HR in response to tilt did not differ between sexes. The responses in HR or BP to CSM did not differ between those with OH and those with a normal BP change during head-up tilt.

We found a significant, albeit weak, correlation between HR changes in response to HUT and to CSM on the right side in the supine position (r = 0.324; p=0.002; Fig. 4) whereas this could not be demonstrated with respect to changes in SBP (r = 0.184; p=0.066). There were no significant correlations between hemodynamic response to CSM in other positions (on the left side in the supine position and on both sides in tilted position) and the hemodynamic response to HUT.

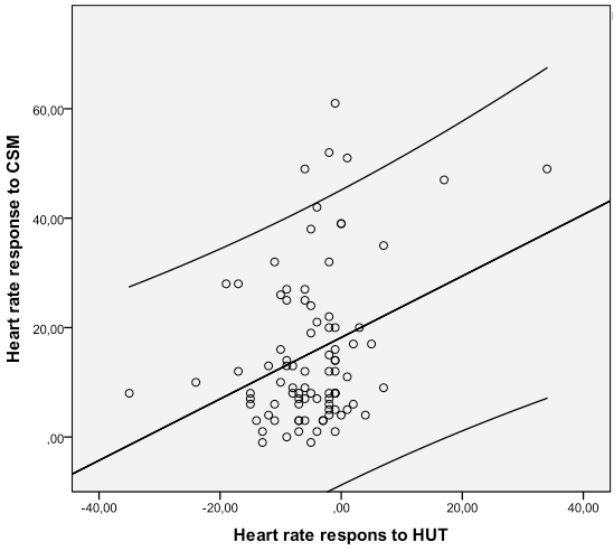

Figure 4. Heart rate response to head-up tilt and carotid massage

Heart rate response to head-up tilt (HUT) versus carotid sinus massage (CSM) (right side, supine position). The regression line is given (r^2=0.105) with 95% confidence intervals.

Values of HRV in the supine and head-up-tilted position are shown in Table 3. All measurements were significantly reduced in response to HUT except from the normalized values and the LF/HF-ratio. We did not find a significant correlation between measurements of HRV and the hemodynamic response to CSM or significant differences in HRV measurements between patients with or without CSS (Table 4).

	Supine (N=79)		HUT (N=79)		
	Mean	95% CI	Mean	95% CI	p-value
MeanNN	873	(850; 897)	827	(804; 850)	<0.0005
SDNN	14	(13; 16)	12	(10; 13)	0.001
RMSSD	13	(12 ; 15)	11	(9; 13)	0.004
LF	89	(69; 115)	57	(42; 78)	0.002
HF	52	(39; 68)	35	(24; 50)	0.017
Total	198	(152; 257)	103	(75; 141)	<0.0005
LF/HF	1.72	(1.43; 2.08)	1.55	(1.22; 1.96)	0.304
LFnu	61	(56; 65)	59	(54; 64)	0.417
HFnu	39	(35; 44)	41	(36; 46)	0.417

Table 3. Heart rate variability in the supine position and during head up tilt (HUT)

Values of heart rate variability and the changes in these indices induced by HUT given as geometric means with 95% CI. Statistics for each analysis are based on the cases with no missing data for any variable in the analysis giving the number N=79. LF: low-frequency; LFnu: LF normalized units; HF: high-frequency; HFnu: HF normalized units; MeanNN: mean value of time period between normal beats; RMSSD: root mean squared successive difference; SDNN: standard deviation of time period between normal beats

Patients with OH had the same magnitude of total HRV both in time and frequency in the supine positions as those not fulfilling the criteria except for significantly lower low-frequency variation (r=-0.232, p=0.037). Patients with OH had significantly lower absolute (r=-0.275, p=0.015), relative (r=-0.250, p=0.027) and normalized (r=-0.243, p=0.031) LF-values and higher normalized HF values (r=0.243, p=0.031) at HUT than patients not fulfilling the criteria.

	Non-CSS (N=44)		CSS (N=37)		
	Mean	95% CI	Mean	95% CI	p-value
Supine					
MeanNN	877	(875; 879)	866	(864; 868)	0.65
SDNN	15	(13; 17)	14	(12; 16)	0.57
RMSSD	14	(12; 16)	12	(10; 14)	0.34
LF	93	(91; 95)	77	(75; 79)	0.49
HF	56	(54; 58)	44	(41; 46)	0.37
LF/HF	1.66	(-0.55; 3.87)	1.76	(-0.61; 4.13)	0.78
LFnu	60	(55; 65)	62	(55; 69)	0.69
HFnu	40	(35; 45)	38	(31; 45)	0.69
Head-up tilt					
MeanNN	825	(823; 827)	829	(827; 831)	0.85
SDNN	11	(9; 13)	13	(10; 15)	0.32
RMSSD	10	(8; 13)	112	(9; 14)	0.47
LF	48	(46; 50)	70	(68; 73)	0.23
HF	32	(29; 34)	39	(37; 42)	0.56
LF/HF	1.51	(-0.79; 3.80)	1.61	(-0.76; 3.97)	0.79
LFnu	58	(52; 65)	59	(51; 67)	0.92
HFnu	42	(35; 48)	41	(33; 49)	0.92

Table 4. Heart rate variability in patients with and without carotid sinus syndrome (n=81)

Values of heart rate variability (HRV) in patients with and without carotid sinus syndrome (CSS) given as geometric means with 95% CI. LF: low-frequency; LFnu: LF normalized units; HF: high-frequency; HFnu: HF normalized units; MeanNN: mean value of time period between normal beats; RMSSD: root mean squared successive difference; SDNN: standard deviation of time period between normal beats

Discussion

This study has shown that HR and BP responses to CSM have a well-defined pattern of a slowing in HR followed by a fall in BP and that the magnitude of these changes depends both on the stimulus site and the position of the patient. The HR and BP responses to CSM were significantly more pronounced on the right than on the left side both in the supine and head-up tilted positions. Systolic blood pressure was significantly more reduced in the head-up tilted position in response to CSM. We found the distribution of HR and BP changes were skewed to the right, but otherwise even without obvious cut-off values (Figures 2 and 3). Using the standard cut-off values, we found a CSS prevalence of 45% in a

population of elderly people suffering from falls, which is in agreement with previous studies [7,16].

In a study of patients with known CSS, Krediet et al. [17] found that the distinct temporal pattern of HR and BP changes reflected the underlying vagal and sympathetic mechanisms. In their study, they concluded that even though the vagal and sympathetic withdrawal occurs simultaneously, the HR response is faster due to differences in neurocardial and neurovascular conduction lag times. The more pronounced BP response to CSM in the upright position observed both in their study and our present study most likely reflects a different ability to compensate for reductions in HR by increases in cardiac filling and thereby in stroke volume, as cardiac filling pressure is reduced in the upright position due to gravitational forces.

Our finding of a more pronounced response to massage of the right compared to the left carotid sinus is in accordance with previous studies [18,19]. These findings are most likely due to side differences in the innervation of the heart. The right atrium, in particular the sinus node, is primarily innervated by the right-sided vagal nerve, and selective stimulation of this nerve leads to greater changes in HR than stimulation on the left side [20]. Furthermore, blocking the stellate ganglion on the right side has a greater impact on HR variability than blocking the left side [21]. The difference between the hemodynamic response to CSM on the right and left side could also in part be ascribed to CSM always being performed on the right side first; if CSM was repeated on the left side too soon following the right-sided CSM, a proper baseline may not have been reached.

We did not find any correlations between measurements of HRV and CSS. In effect, we have not convincingly found the response to CSM to be reflected in measurements of HRV. This is surprising as CSS is thought to reflect an imbalance in autonomic cardiovascular regulation, which is expected to be mirrored in measurements of HRV. Our HRV measures are quantifications of the spontaneous variations in HR during supine and tilted rest. At rest, BP and HR spontaneously oscillate with a phase shift of 180 degrees, most likely reflecting baroreflex control. CSM is an external non-physiological stimulus, mechanically stretching the stretch-sensitive nerve endings in the carotid sinus mimicking an abrupt and marked increase in BP. Several studies have demonstrated that spontaneous measurements of baroreflex sensitivity derived from steady state conditions differ from measurements of baroreflex sensitivity obtained from transient and marked changes in BP even though they may be correlated [22]. This could explain the lack of difference in HRV between CSS and non-CSS patients. Our findings are in contrast to the findings by Tan et al. [18] who demonstrated significantly higher total supine HRV primarily in the low-frequency area in asymptomatic CSS-patients compared to a non-CSS control group. The control group in that study consisted of asymptomatic elderly people without a previous history of syncope or falls whereas our control group consisted of elderly patients referred for tilt table testing due to suspected syncope, which may explain the differences between the two studies.

We found that HRV declined with orthostatic stress. In younger subjects, head-up tilting leads to a reduction in the total HR variance with a pronounced shift towards the low frequency area, usually interpreted as vagal withdrawal and increased baroreceptor regulation [23,24]. In our group of elderly subjects, the total variation decreased, but this reduction was evenly distributed in the whole frequency area; the shift towards low frequent variation in the tilted position was missing, in agreement with the findings by Lipsitz et al. [2]. In accordance with others [25], we found OH to occur in 24% of patients with CSS, and there was a tendency for patients diagnosed with OH to have impaired HRV in the low frequency range in the tilted position.

Many studies have demonstrated an age-related decrease in the cardiovagal efferent part of the baroreflex arch whereas age-related changes in other aspects of baroreflex function, such as the vasoconstrictor response mediated by the efferent sympathetic nerves, are less well understood and investigated. Studies in both animals and humans have demonstrated that baroreceptor control of BP is quantitatively preserved in healthy aging, but the time course of the vascular response is prolonged with age [26,27].

In summary, we have demonstrated that aging is correlated to a dampened reactivity in the low frequency HRV, suggesting a functional decline in the baroreceptor-vasoconstrictor function. We have also demonstrated a relatively high prevalence of CSS in a cohort of elderly people suffering from falls and syncope. High prevalence of CSS has also been demonstrated in asymptomatic elderly with no history of dizziness, syncope and falls and therefore the clinical importance of CSS diagnoses is unclear, and it has been suggested that the current criteria are too sensitive [25,28]. Wieling et al. have proposed a stricter set of diagnostic criteria for CSS with cut off values of 6 s asystole for cardioinhibitory CSS and a drop in SBP of more than 75 mmHg or to values lower than 80 mmHg for vasodepressor CSS, both of which require reproduction of spontaneous symptoms [29]. Our findings underscores the importance of research into the pathophysiology behind CSS and are in agreement with Wieling et al. [29] in their suggestion to implement stricter diagnostic criteria in order to distinguish healthy aging and actual disease.

Our finding of non-significant differences in measurements of HRV between patients with and without CSS and a continuous distribution of the hemodynamic response to CSM suggest that CSS is an age-related instability in cardiovascular regulation rather than a separate disease entity. This is in line with previous findings showing that CSS can be elicited in up to 35% of asymptomatic elderly people [30].

Conclusions

Hyperreactivity in response to stimulation of the carotid sinus is common in the elderly suffering from falls, emphasizing the importance of performing CSM as part of the diagnostic work-up in these patients as recommended by European Task Force on Syncope [13]. Our findings demonstrate that the hemodynamic response to CSM has a well-defined pattern and differs both with respect to the stimulus site and to the position of the patient. To this end, our results emphasize the clinical importance of performing CSM in both the supine and tilted positions.

Our findings supports the notion that CSS is not a distinct pathophysiological process or disease entity but rather an age-related sign of cardiovascular instability due to an age related mismatch between different components of cardiovascular regulation.

Further studies are warranted in order to clarify the age-related changes in baroreflex mediated vascular control, as well as studies elucidating the functional role of these changes in the pathophysiology of CSS.

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