ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Symptomatic Presentation of Carotid Sinus Hypersensitivity Is Associated With Impaired Cerebral Autoregulation

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Background—Carotid sinus hypersensitivity (CSH) is associated with syncope, unexplained falls, and drop attacks in older people but occurs asymptomatically in 35% of community-dwelling elders. We hypothesized that impaired cerebral autoregulation is associated with the conversion of asymptomatic CSH to symptomatic CSH. We therefore conducted a case–control study evaluating individuals with CSH with and without the symptoms of syncope or unexplained falls, as well as non-CSH controls, to determine whether the blood pressure and heart rate changes associated with CSH are associated with symptoms only when cerebral autoregulation is altered.

Methods and Results—Bilateral middle cerebral artery blood flow velocities (BFV) were measured in consecutive patients with symptomatic CSH (n=22) and asymptomatic controls with (n=18) and without CSH (n=14) using transcranial Doppler ultrasonography during lower body negative pressure-induced systemic hypotension. Within-group comparisons revealed significantly lower cerebrovascular resistance index (CVR_i) at nadir for the asymptomatic CSH group (right, mean [95% CI]: 2.2 [1.8, 2.8] versus 2.6 [2.2, 3.0]; P=0.005; left: 2.8 [2.4, 3.3] versus 3.1 [2.7, 3.8]; P=0.016). Between-group comparisons showed higher mean BFV (right: estimated mean difference, B=5.49 [1.98, 8.80], P=0.003; left: 4.82 [1.52, 8.11], P=0.005) and lower CVR_i (right: B=0.08 [0.03, 0.12], P=0.003, left: B=0.07 [0.02, 0.12], P=0.006) in asymptomatic CSH versus symptomatic CSH groups. There were no significant differences in bilateral mean BFV or right CVR_i between the non-CSH and symptomatic CSH groups but differences were present for left CVR_i (B=0.07 [0.02, 0.013], P=0.015).

Conclusion—Cerebral autoregulation is altered in symptomatic CSH and therefore appears to be associated with the development of hypotension-related symptoms in individuals with CSH. **(*J Am Heart Assoc*. 2014;3:e000514 doi: 10.1161/JAHA.113.000514)**

Key Words: arrhythmia • autonomic nervous system • baroreceptors • cerebrovascular circulation • syncope

Carotid sinus hypersensitivity (CSH) is characterized by an asystolic or hypotensive response to carotid sinus massage (CSM) and is associated with syncope, unexplained falls, and drop attacks in older individuals.[1–3] CSH is rare before the age of 40 years, but is diagnosed with increasing frequency with advancing age.[4] Prodromal symptoms are absent in up to 93% of patients with carotid sinus syncope, and high serious injury rates have been reported, with 25% of patients sustaining fractures.[5]

The diagnostic yield of CSM in individuals with unexplained syncope or falls has been reported as 14% to 54% by various groups with varying case selection and methods of investigation.[4,6,7] However, a community study has found that CSH was also present in 35% of community-dwelling older individuals without any symptoms of syncope, falls or drop attacks.[8] This high prevalence of CSH in asymptomatic older individuals raises the question of the validity of a pathological role for CSH, particularly given recent data showing no benefit for pacing intervention in patients with CSH associated with unexplained falls[9,10] and further data questioning the causal role of CSH in syncope, falls, and drop attacks.[11] In contrast, CSH associated with syncope is a Class I indication for permanent pacing,[12,13] albeit with largely observational data and consensus supporting these recommendations.[14,15] Furthermore, real-time recording of patients with CSH using implantable loop recorders shows asystole during characteristic symptoms.[16] A recent study reporting the association between hypotension during head turning with the presence of CSH further adds

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Received August 29, 2013; accepted May 6, 2014.

validity to the pathological role of CSH. In addition, the authors observed a discrepancy between head-turning–induced hypotension and the presence of symptoms.[17] It is possible, therefore, that additional pathological factors exist that result in the conversion of individuals with asymptomatic CSH to symptomatic CSH (often labeled "carotid sinus syndrome" but termed symptomatic CSH here to avoid confusion).

We hypothesized that impaired cerebral autoregulation is one such converting factor and have previously shown altered cerebral autoregulation as measured by using transcranial Doppler ultrasonography (TCD) in patients with symptomatic CSH and controls whose CSH status was unknown.[18] In order to test this hypothesis more rigorously, we assessed cerebral autoregulation during controlled systemic hypotension induced by lower body negative pressure in individuals with symptomatic and asymptomatic CSH and in controls without CSH.

Methods

Consecutive patients with symptomatic CSH diagnosed following investigation with CSM for syncope, unexplained falls, and drop attacks at our specialist syncope facility were invited to participate in our study. Asymptomatic older people aged >65 years were recruited from an existing community-dwelling cohort investigated with CSM.[8] This latter group therefore composed 2 groups of individuals without any history of syncope, unexplained falls, or drop attacks: an asymptomatic CSH group and an asymptomatic control group without CSH. Carotid sinus massage was conducted using established protocols[19] with 5 to 10 seconds of bilateral, sequential CSM conducted at the point of maximal pulsation of the carotid arteries, right sided then left, in the supine position followed by 70° head-up tilt position.[19,20] Continuous ECG and beat-to-beat blood pressure (Taskforce; CNSystems) were recorded throughout. Carotid sinus hypersensitivity was defined as asystole of ≥3 seconds and/or systolic blood pressure (SBP) reduction of ≥50 mm Hg in response to CSM. Symptomatic CSH was defined as the presence of symptoms of syncope, falls, or drop attacks with a positive CSM. Potential participants were excluded if they had a permanent cardiac pacemaker or if they were unable to provide informed consent. Carotid Doppler ultrasound studies were conducted on all participants to rule out significant internal carotid artery stenosis, which can affect cerebral blood flow velocity measurements. The study was approved by the local research ethics committee, and all participants provided written informed consent.

Transcranial Doppler Ultrasound

Bilateral middle cerebral artery (MCA) blood flow velocities were measured continuously using TCD (Digilite; RIMED). The MCAs were insonated using 2-MHz TCD probes through the transtemporal windows, which were then fixed in position using a specially designed head gear. The TCD signals were then synchronized to beat-to-beat blood pressure measurements (Taskforce; CNSystems). End-tidal CO_2 was also recorded simultaneously using a nasal or oronasal cannula and infrared capnography (Oxi-pulse Capnograph System; SIMS-BCI) to monitor for hypocapnea with its potential to cause intracerebral arterial vasoconstriction.[21]

Lower Body Negative Pressure

We used graded lower body negative pressure (LBNP) to induce a controlled fall in SBP mimicking the reductions in SBP that would occur spontaneously in CSH. Cerebral autoregulation cannot be maintained below a critical SBP of around 50 mm Hg in most individuals.[22] Hence, real-time CSM-induced CSH would provide an inaccurate and misleading view of cerebral autoregulation in patients with CSH. In addition, comparable levels of blood pressure reduction cannot be achieved with CSM in individuals without CSH, because non-CSH individuals will have a smaller hypotensive response to CSM. Graded LBNP therefore allows us to compare the cerebral blood flow velocity between CSH and non-CSH individuals in response to an identical hypotensive insult.

Participants were asked to assume the supine position in a temperature-controlled, dimly lit, quiet room for 15 minutes prior to the procedure. A custom-built LBNP chamber was used to induce LBNP suction at −20 mm Hg for 8 minutes, followed by −40 mm Hg for an additional 8 minutes. The target reduction in SBP was 50 mm Hg from maximal recorded SBP and/or a 50% fall from maximal SBP. Lower body suction was discontinued as soon as the target SBP drop was achieved and/or hypotensive symptoms supervened.

Assessment of Cerebral Autoregulation

TCD has been used extensively in the assessment of cerebral autoregulation.[18,21,23,24] While this complex process cannot be directly assessed by using current technology, TCD measures of changes in cerebral arterial blood flow velocities provide an accurate surrogate measure of cerebral autoregulation. Systolic (SBFV), diastolic (DBFV), and mean (MBFV) cerebral blood flow velocities were determined at baseline and at SBP nadir. MBFV was determined by calculating the true mean within the spectral envelope. Baseline values were obtained by calculating the mean SBFV, DBFV, and MBFV for 20 beats immediately before the commencement of LBNP. Nadir was defined as the point at which SBP was lowest

during LBNP. The minimal SBFV, DBFV, and MBFV around this point were recorded. As the TCD signals were synchronized to continuous blood pressure measurements, corresponding values were obtainable for SBP, diastolic blood pressure, and mean arterial pressure (MAP) at baseline and nadir.

The cerebrovascular resistivity index (CVR_i) was then calculated for baseline and nadir by dividing the cerebral perfusion pressure (CPP) by the MBFV (CVR_i=CPP/MBFV). Cerebral perfusion pressure is assumed to approximate to MAP as intracranial pressure is considered negligible in our subjects who were assessed in the supine position. The CVR_i is a measure of the interrelationship between cerebral perfusion pressure and cerebral blood flow. In the absence of cerebral autoregulation, CVR_i will remain constant as cerebral blood flow changes commensurate with changes in CPP. Appropriate changes in CVR_i in response to alterations in CPP therefore indicate the presence of intact cerebral autoregulation.

Data Analysis

All data analyses were conducted with the use of anonymized data. Continuous variables were plotted as histograms and assessed by using the Komolgorov–Smirnov test to determine normal distributions. The CVR_i was non-normally distributed, and, hence, its inverted value cerebrovascular conductance (CVC_i=MBFV/CPP) was used for statistical analysis. The baseline characteristics of the 3 study groups were first compared with the use of ANOVA for continuous variables or χ^2 test for categorical variables to identify baseline differences between groups. Within-group comparisons for SBFV, MBFV, DBFV, and CVR_i for bilateral TCD measurements at baseline and nadir were then carried out with paired *t* tests.

Subsequent between-group analyses involved only 2 preplanned comparisons between the symptomatic CSH and asymptomatic CSH groups and the symptomatic CSH and non-CSH control groups. Linear regression methods were used to compare the values of MBFV and CVR_i at nadir using entry method for potential confounding variables to control for differences in baseline MBFV, baseline CPP, and nadir CPP. Adjustments for age and sex were considered, but it was decided to limit the covariates that were adjusted for due to the small sample size. All statistical analyses were conducted using the SPSS 15.0 statistical software package. A planned comparison based on 20 per group between, for example, the symptomatic versus asymptomatic group using the 2-sample *t* test would result in 80% power to detect an effect size of 0.9 (for any comparison between 2 groups on a continuous outcome measure).

Results

Baseline Characteristics

Fifty-four participants were recruited to the study: 22 in the symptomatic CSH group, 18 in the asymptomatic CSH group, and 14 in the non-CSH control group. The baseline characteristics of each group are summarized in Table 1. There were no significant differences in any of the baseline demographics, medical history, medications, and hemodynamic indices

Table 1. Baseline Characteristics of Participants

Characteristics	Symptomatic CSH (n=22)	Asymptomatic CSH (n=18)	No CSH (n=14)
Age (y), mean (SE)	73.0 (2.0)	77.7 (2.1)	76.6 (1.3)
Male sex, n (%)	11 (50)	14 (78)	8 (57)
Cardioinhibitory subtypes	8 (36)	9 (50)	
ΔSBP <50 mm Hg	4 (18)	1 (6)	
ΔSBP ≥50 mm Hg	4 (18)	8 (44)	
Vasodepressor subtype	14 (64)	9 (50)	
Medical history, n (%)			
Arthritis	6 (27)	9 (50)	8 (57)
Asthma/COPD	3 (14)	3 (17)	3 (21)
Hypertension	9 (41)	9 (50)	5 (36)
Angina	5 (23)	5 (28)	4 (29)
Myocardial infarction	2 (9)	4 (22)	4 (29)
Medications, n (%)			
Antiplatelets or anticoagulants	13 (59)	6 (33)	5 (36)
β-Adrenoceptor antagonists	2 (9)	2 (11)	5 (26)
ACE inhibitors	7 (32)	1 (6)	4 (29)
Angiotensin II antagonists	2 (9)	2 (11)	1 (7)
Calcium channel antagonist	5 (23)	6 (33)	4 (29)
Diuretics	6 (27)	4 (22)	3 (21)
Lipid-lowering drugs	13 (59)	4 (22)	4 (29)
Proton pump inhibitors	5 (23)	3 (17)	2 (14)
Baseline heart rate, bpm†‡	72 (2)	62 (2)	63 (4)
Baseline SBP, mm Hg†	124 (2)	133 (4)	131 (17)
Baseline DBP, mm Hg†	78 (3)	80 (3)	77 (5)
Baseline CPP, mm Hg†	90 (2)	95 (3)	95 (5)
Baseline end-tidal CO_2, kPa†	4.5 (0.2)	4.6 (0.1)	4.3 (0.3)

ACE indicates angiotensin-converting enzyme; bpm, beats per minute; CPP, cerebral perfusion pressure; COPD, chronic obstructive pulmonary disease; CSH, carotid sinus hypersensitivity; DBP, diastolic blood pressure; SBP, systolic blood pressure. †During 10 minutes' supine rest, ‡P<0.05.

between the 3 groups apart from the use of lipid-lowering medications and resting heart rate. End-tidal CO_2 levels between the 3 groups were not significantly different at both baseline and nadir (Tables 1 and 2). Five subjects did not have adequate transtemporal windows from which to obtain meaningful cerebral blood flow measurements and were excluded from subsequent analyses. Only right-sided measurements were available from 2 subjects and only left-sided measurements were available from 2 subjects. There were no significant differences in MAP at SBP nadir and maximal reduction in SBP between the 3 groups (Table 2).

Within-Group Comparisons

The Figure demonstrates the relationship between in MAP and MBFV in an individual with symptomatic CSH and impaired cerebral autoregulation. Paired comparisons were conducted between baseline and nadir cerebral blood flow values (Table 3). The SBFV, DBFV, and MBFV at the right MCA was significantly lower at nadir compared with baseline for all 3 groups, suggesting that reductions in CBFV are observed with reductions in blood pressure. CVC_i rather than CVR_i was calculated to obtain a normal distribution. CVR_i was not significantly different between baseline and nadir for the right MCA for both the symptomatic CSH group and the non-CSH control group. No change in CVR in response to changes in CPP suggests that cerebral autoregulation is impaired. The asymptomatic CSH group, however, had significantly lower CVR_i at nadir compared with baseline at the right MCA, indicating the presence of appropriate and intact cerebral autoregulation. The left MCA also demonstrated significant reductions in SBFV, DBFV, and MBFV between baseline and nadir in all 3 groups. Similarly, CVR_i was not significantly different between baseline and nadir for the left MCA for the symptomatic CSH or the non-CSH control group, while the asymptomatic CSH group, however, had significantly lower CVR_i at nadir compared with baseline in the left MCA measurements.

Mean Blood Flow Velocity

For right MCA measurements, using linear regression to adjust for potential confounders, MBFV was significantly lower in the symptomatic CSH group compared with the asymptomatic CSH group ($P<0.05$), with no significant differences in MBFV between the symptomatic CSH group and the non-CSH control group. For the left side, however, MBFV remained significantly lower in the symptomatic CSH group compared with the asymptomatic CSH group ($P<0.01$), however, the MBFV between the symptomatic CSS group and the non-CSH control group approached borderline significance ($P=0.088$) (Table 4).

Table 2. Hemodynamic, Carotid Doppler Flow, and End-Tidal CO_2 Characteristics at Nadir*

Characteristics	Symptomatic CSH (n=22)	Asymptomatic CSH (n=17)	Non-CSH Controls (n=10)	*P* Value†
Nadir CPP, mm Hg, mean (SE)	72 (2)	73 (2)	75 (5)	0.841
Nadir end-tidal CO_2, kPa, mean (SE)	4.6 (0.1)	4.8 (0.2)	4.4 (0.2)	0.439
Maximal ΔSBP, mm Hg, mean (SE)	50 (2)	51 (2)	41 (4)	0.067

CPP indicates cerebral perfusion pressure; CSH, carotid sinus hypersensitivity; SBP, systolic blood pressure.
*Nadir is defined as the point of the minimal SBP during lower body negative pressure.
†ANOVA.

Table 3. Differences Between Cerebral Blood Flow Velocities and Cerebrovascular Resistance at Baseline and Nadir

Characteristics, Mean Difference (SE)	Symptomatic CSH	Asymptomatic CSH	Non-CSH Controls
Right MCA	n=21	n=17	n=9
SBFV, cm/s	15.17 (2.05)	11.38 (3.05)	10.29 (3.84)
P value*	<0.001‖	0.002§	0.028‡
DBFV, cm/s	−7.39 (1.51)	−3.41 (1.03)	−6.49 (1.22)
P value*	<0.001‖	0.005§	0.001§
MBFV, cm/s	8.88 (1.47)	4.75 (1.52)	6.33 (2.37)
P value*	<0.001‖	0.007§	0.028‡
CVC_i†, cm/s per mm Hg	0.038 (0.017)	−0.060 (0.018)	0.014 (0.026)
P value*	0.121	0.005§	0.629
Left MCA	n=19	n=17	n=10
SBFV, cm/s	14.01 (1.86)	8.12 (1.40)	8.97 (2.57)
P value*	<0.001‖	<0.001‖	0.007§
DBFV, cm/s	7.60 (1.40)	5.28 (1.11)	2.07 (1.33)
P value[a]	<0.001‖	<0.001‖	0.156
MBFV, cm/s	8.12 (1.23)	3.36 (1.25)	4.35 (1.01)
P value[a]	<0.001‖	0.016‡	0.002§
CVC_i,† cm/s per mm Hg	0.037 (0.019)	−0.043 (0.017)	−0.033 (0.029)
P value*	0.060	0.025‡	0.288

CSH indicates carotid sinus hypersensitivity; CVC_i, cerebrovascular conductance index; DBFV, diastolic blood flow velocity; MBFV, mean blood flow velocity; MCA, middle cerebral artery; SBFV, systolic blood flow velocity.
*Paired *t* tests.
†Derived from the inverse value of CVR_i ($CVC_i=1/CVR_i$).
‡$P<0.05$, §$P<0.01$, ‖$P<0.001$.

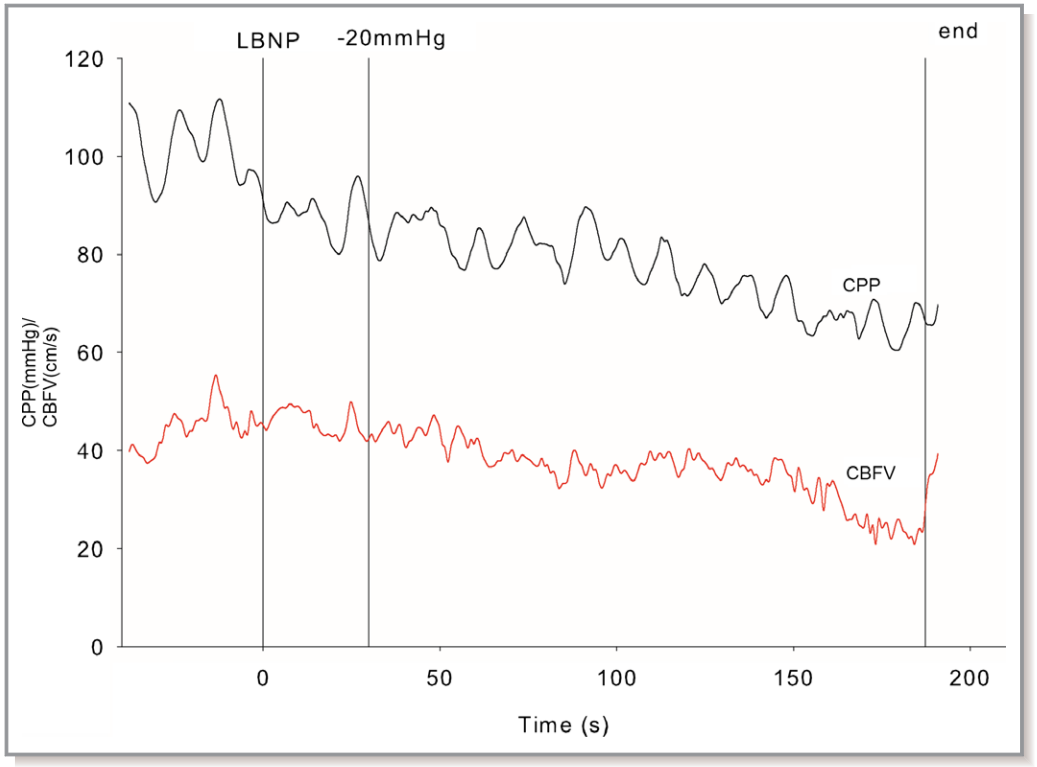

Figure. Mean arterial pressure and cerebral blood flow in response to lower body negative pressure. This is a time-series plot demonstrating the relationship between mean arterial pressure (MAP) and cerebral blood flow velocity (MBFV) in an individual with symptomatic carotid sinus syndrome. A marked reduction in MAP was observed with lower body negative pressure, with typical sinusoidal fluctuations over time. Cerebral blood flow velocity should remain relatively constant in response to changes in MAP but fluctuated with MAP, and fell rapidly with the fall in MAP in response to lower body negative pressure. This suggests marked impairment in cerebral autoregulation. CPP indicates cerebral perfusion pressure; LBNP, lower body negative pressure.

Cerebrovascular Resistive Index

The CVR_i at nadir for both right-side and left-sided measurements were significantly higher in the symptomatic CSH group compared with the asymptomatic CSH group ($P<0.05$). There was no significant difference between the symptomatic CSH group and the non-CSH controls for the right MCA, but the differences between the 2 groups

Table 4. Linear Regression Analysis for Mean Cerebral Blood Flow and Reciprocal of Cerebrovascular Resistance at Nadir

	Non-CSH Controls vs Symptomatic CSH		Asymptomatic CSH vs Symptomatic CSH	
	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Right middle cerebral artery				
Mean cerebral blood flow velocity,* cm/s	−0.749 (−5.40 to 3.90)	0.747	4.07 (0.34 to 7.80)	0.033§
Cerebrovascular conductance,†,‡ cm/s per mm Hg	0.011 (−0.05 to 0.08)	0.737	0.08 (0.03 to 0.14)	0.003‖
Left middle cerebral artery				
Mean cerebral blood flow velocity,* cm/s	3.35 (−0.17 to 7.31)	0.088	4.49 (1.52 to 8.11)	0.009‖
Cerebrovascular conductance,†,‡ cm/s per mm Hg	0.06 (0.02 to 0.15)	0.043§	0.06 (0.01 to 0.11)	0.026‖

B indicates parameter estimate (represents the estimated mean difference between groups); CSH, carotid sinus hypersensitivity.
*Linear regression adjusted for baseline cerebral perfusion pressure (CPP), nadir CPP, baseline mean cerebral blood flow velocity.
†Adjusted for baseline CPP, nadir CPP, cerebrovascular conductance at baseline.
‡Cerebrovascular conductance=1/cerebrovascular resistance.
§$P<0.05$, ‖$P<0.01$.

achieved statistical significance for the left MCA (P=0.043) (Table 4).

Discussion

Cerebral autoregulation is a complex mechanism through which intracranial blood flow is maintained in response to variations in systemic blood pressure. This process is influenced by various metabolic factors as well as the autonomic nervous system. For many years, scientists have reported that cerebral blood flow remains constant within an "autoregulatory range," as demonstrated by experiments using xenon diffusion methods.[25] However, with the advent of TCD, cerebral blood flow can now be assessed in real time with every heartbeat.[26] It has since become apparent that cerebral blood flow does fluctuate alongside fluctuations in systemic blood pressure, and cerebral autoregulation appears to "buffer" the changes in cerebral blood flow leading to a lower coherence between MAP and cerebral blood flow.

Our study has demonstrated that individuals with symptomatic CSH have lower cerebral blood flow than do asymptomatic individuals with CSH in response to comparable reductions in systemic blood pressure. This suggests that symptomatic individuals have an increased susceptibility to syncope or falls compared with individuals with asymptomatic CSH due to a lower ability to maintain cerebral blood flow in the face of a hypotensive challenge. The derived measure of CVR_i takes into account changes in MAP as well as cerebral blood flow. Cerebral autoregulation is therefore intact if a reduction in CVR_i is observed in response to a reduction in MAP. This was the case for the asymptomatic CSH group in our study in the within-group comparisons, in contrast to no changes in CVR_i from baseline to nadir in the symptomatic group.

There was no significant difference in CVR_i between the symptomatic CSH group and the non-CSH control group. This may indicate that cerebral autoregulation may also be impaired in our control group without CSH. The asymptomatic groups of community-dwelling older individuals were not necessarily healthy controls but were individuals without the symptoms of syncope, falls, or drop attacks. These individuals remain spared of symptoms of syncope or recurrent falls in the absence of the heart rate or blood pressure abnormalities observed in individuals with CSH. There were borderline significant differences in MBFV and CVR_i in the left, dominant hemisphere but no differences in MBFV in the right, nondominant hemisphere between the symptomatic CSH group and the non-CSH control group. While the symptomatic CSH and non-CSH control groups may be due to a type II error, it also supports the theoretical supposition that the lack of statistical significance has been confounded by the presence of impaired cerebral autoregulation in some of the individuals in the non-CSH control group. In addition, the difference between right and left also raises the concept of differential cerebral autoregulatory capacity between the 2 cerebral hemispheres, with protective relative sparing of the dominant hemisphere in the non-CSH control group, which will be an interesting topic for future studies.

Cerebral autoregulation in CSH had been evaluated in 3 previous small studies. Lefteriotis et al[27,28] measured cerebral blood flow in patients with cardioinhibitory CSH in 2 similar studies during CSM with OOO and DDD pacing in 9 and 11 individuals, respectively. The authors drew the conclusion that cerebral autoregulation was preserved in individuals with CSH through an estimation of the lower limit of autoregulation and rate of recovery of cerebral blood flow without comparisons with a control group. They had, however, documented large increases in cerebrovascular resistance following CSM with no pacing (OOO), but attributed this to the CPP dropping below the lower limit of autoregulation.[27,29] A subsequent study by our group suggested that cerebral autoregulation is impaired in symptomatic CSH[18] through the observation of an overall reduction in cerebral blood flow velocity and increase in cerebrovascular resistance in subjects with symptomatic CSH compared with healthy older controls whose CSH status was unknown. These previous studies had not considered individuals with asymptomatic CSH.

This potential mechanism for impaired cerebral autoregulation was not evaluated in this study. The complex mechanisms underlying cerebral autoregulation remain poorly understood. Cerebral blood flow is said to remain constant at around 60 mL/100 g per minute through a wide range of blood pressure. This is achieved through cerebral blood flow self-regulation (cerebral autoregulation), which is controlled by local metabolic factors that include myogenic responses to transmural pressure,[30] nitric oxide,[31] CO_2,[32] H^+ concentrations, potassium, adenosine, and calcitonin gene–related peptide.[33] Factors such as hypocapnia are known to stimulate cerebral vasoconstriction and have been found to contribute to the reduction in cerebral blood flow seen experimentally in subjects with orthostatic intolerance and neurally mediated syncope.[21,32] However, there was no significant difference in end-tidal CO_2 among the 3 groups in our study, suggesting that hypocapnia does not explain the reduction in cerebral blood flow during induced hypotension in individuals with symptomatic CSH. Because impaired cerebral autoregulation is only present in the symptomatic CSH group, the mechanism for impaired cerebral autoregulation is likely to differ from the underlying mechanisms for CSH, which has been shown to be associated with resting sympathetic overactivity and increased baroreflex sensitivity.[34]

Limitations

The ability to perform TCD studies is reliant on the availability of an adequate bone window, because ultrasound conducts poorly through bone, which is not possible in up to 10% of subjects.[35] In addition, several assumptions are made in the estimation of cerebral blood flow velocity. First, laminar flow exists in the center of the vessels, as velocity changes out of proportion to flow in the unlikely situation of nonlaminar flow.[36] Second, the angle of insonation and the diameter of the blood vessels remain constant. The large cerebral arteries are capacitance rather than resistance vessels, and hence changes in arterial pressure should have negligible effects on vessel diameter. This assumption has been substantiated by direct observations during craniotomy,[37] magnetic resonance imaging during orthostatic stress simulated by LBNP, and xenon clearance studies.[38,39] The magnitude of SBP reduction in the non-CSH group was smaller than the 2 CSH groups, but this observed difference was not statistically significant. Only 30% of non-CSH participants achieved the target SBP drop of >50 mm Hg compared with 67% of CSH participants, as the CSH and non-CSH participants appeared to have different hemodynamic response patterns to LBNP. However, similar MAP at nadir was achieved for all 3 groups, and BP changes achieved in the symptomatic and asymptomatic groups were similar. These potential differences were also adjusted for statistically. The significant difference in MBFV and CVR_i was noted between the 2 CSH groups, but not between non-CSH controls and the symptomatic CSH group. The statistical power of this study is also limited by its small sample size, which was unavoidable due to the specific nature of its recruitment criteria.

Implications of the Study

Our results show a clear association between impaired cerebral autoregulation and the symptomatic presentation of CSH. Normal cerebral autoregulation in the asymptomatic CSH group provides further evidence that it is the abnormality in cerebral autoregulation that is the proximate cause of syncope, unexplained falls, and drop attacks associated with CSH rather than the hypersensitive response per se. This may help explain why there is so little in the literature regarding the pathophysiology of CSH, with the only tested hypothesis to date, that of central α-adrenoceptor upregulation,[40] failing to withstand experimental scrutiny.[41] There is increasing evidence that CSH is associated with autonomic dysfunction, with neuropathological studies showing increased neurodegenerative substrates within key medullary autonomic nuclei[42] and physiological studies demonstrating sympathetic hyporesponsiveness[4,43,44] in individuals with symptomatic CSH. The role of the autonomic nervous system in the regulation of cerebral blood flow has previously been described,[45] and our results provide further circumstantial evidence suggesting that symptomatic CSH is the ultimate expression of a more generalized autonomic disorder. This has important implications for potential therapies in symptomatic CSH; permanent pacing appears to be effective in the cardioinhibitory subtype associated with syncope, but vasodepressor CSH has no specific therapy. Our work suggests that less invasive measures could help ameliorate the disorder, with important implications for future pathophysiological, prevention, and treatment studies.

Conclusion

Cerebral blood flow is lower during LBNP in patients with symptomatic CSH than in asymptomatic older individuals with CSH, with corresponding increases in CVR_i, indicating that the symptomatic presentation of CSH is associated with impaired cerebral autoregulation. These clear differences in MBFV and CVR_i were, however, not observed between the non-CSH control and symptomatic CSH groups. Non-CSH controls remain asymptomatic in the absence of CSH, while CSH controls remain asymptomatic in the absence of altered cerebral autoregulation. Autonomic dysfunction may be the ultimate site of the pathological underpinning of symptomatic CSH, providing an important target for further explanatory and therapeutic studies.

Sources of Funding

Dr Tan's salary was funded by the Royal College of Physicians/Dunhill Medical Trust joint research fellowship. The TCD equipment was purchased with a grant from the Newcastle Hospitals Charitable Trusts. This study was also supported by the United Kingdom National Institute for Health Research, Biomedical Research Centre for Ageing and Age-related disease awarded to the Newcastle upon Tyne Foundation Hospitals National Health Service Trust. Dr Tan is currently the recipient of the University of Malaya Research Grant (RP-010-2012), the Ministry of Science, Technology and Innovation Sciencefund (SF017-2013), and the University of Malaya-Department of Higher Education High Impact Research Grant (UM.C/625/1/HIRMOHE/ASH/02).

Disclosures

None.

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