

Carotid Sinus Hypersensitivity in Asymptomatic Older Persons

Implications for Diagnosis of Syncope and Falls

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Background: Carotid sinus hypersensitivity is the most commonly reported cause of falls and syncope in older persons. Recent guidelines recommend 5 to 10 seconds of carotid sinus massage in supine and upright positions with beat-to-beat monitoring. The aim of this study was to determine the prevalence of carotid sinus hypersensitivity in (1) an unselected community sample of older people and (2) a subsample with no history of syncope, dizziness, or falls using recently standardized diagnostic criteria.

Methods: One thousand individuals older than 65 years were randomly sampled from a single general practice register; 272 participants underwent supine and upright carotid sinus massage with continuous heart rate and phasic blood pressure monitoring. Carotid sinus hypersensitivity was defined as asystole of 3 seconds or greater and/or a drop in systolic blood pressure of 50 mm Hg or greater.

Results: Carotid sinus hypersensitivity was present in 107 individuals (39%); 24% had asystole of 3 seconds or greater during carotid sinus massage; and 16% had symptoms (including syncope) with carotid sinus hypersensitivity. Age (odds ratio, 1.05; 95% confidence interval, 1.00-1.09) and male sex (odds ratio, 1.71; 95% confidence intervals, 1.04-2.82) were the only predictors of carotid sinus hypersensitivity. In 80 previously asymptomatic individuals, carotid sinus hypersensitivity was present in 28 (35%) and accompanied by symptoms in 10. The 95th percentile for carotid sinus massage response was 7.3 seconds' asystole and a 77-mm Hg drop in systolic blood pressure.

Conclusions: Carotid sinus hypersensitivity is common in older persons, even those with no history of syncope, dizziness, or falls. The finding of a hypersensitive response should not necessarily preclude further investigation for other causes of syncope.

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CAROTID SINUS HYPERSENSITIVITY (CSH) is a well-recognized cause of syncope and falls in older persons,¹ responsible for up to a third of symptoms in patients referred to tertiary care.² Carotid sinus hypersensitivity is an age-related phenomenon, rarely diagnosed in patients with syncope younger than 50 years and increasing in prevalence as a cause of syncope with advancing years.^{3,4}

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It is characterized by prolonged heart rate slowing or a profound drop in systolic blood pressure (SBP) in response to carotid sinus massage.⁴ Cardiac pacing dramatically reduces symptoms in those with diagnostic heart rate slowing.⁵⁻⁷ Consequently, cardioinhibitory CSH is a class I indication for

cardiac pacing in syncope.⁸ Recent recommendations for the diagnosis of CSH include phasic blood pressure monitoring (to capture the frequently occurring hypotensive response) and evaluation in the supine and

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upright positions (because one third of patients only have a positive response when upright).⁹ Some previously published studies have described the prevalence of CSH in different populations. Results range from 0% to 62%.^{3,10-24} The varied responses are due to differences in methods of recruitment of participants, in settings, in comorbidity, in duration of carotid sinus massage (CSM), and in definitions of abnormal responses. Clarification of the prevalence of CSH, consistent with the methods recommended by the guidelines, is relevant for

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the correct diagnosis and management of patients with syncope.

The purpose of this study was to determine the prevalence of CSH in (1) an unselected community sample of people older than 65 years and (2) a nested subsample of older persons with no history of falls, syncope, or dizziness.

METHODS

The study was approved by County Durham and Darlington Local Research Ethics Committee, England. Participants were recruited from a single urban general practice of 9200 patients between April 2002 and October 2003. Persons in residential and nursing homes were excluded. The baseline population of 1517 subjects older than 65 years was stratified into 4 groups by age and sex: men aged 65 to 74 years (n=389); women aged 65 to 74 years (n=499); men 75 years and older (n=252); and women 75 years and older (n=377). The median age of the baseline population was 73 years (range, 65-99 years) and 641 (42%) were male.

A total of 250 individuals were randomly sampled from each strata and contacted by letter. Interested individuals were seen for an introductory visit. The introductory visit and subsequent assessments were carried out in a small community hospital in close proximity to the general practice to maximize recruitment and compliance. Written informed consent for the study was obtained from each participant. In particular, the ethics committee required participants to be informed of the risk of possible neurological complications associated with CSM; reported complication rates vary from 0.17%²⁵ to 0.9%.²⁶ Permission for data collection from computerized general practitioner notes was obtained from all in-scope persons, including those who declined participation in the study to enable clinical and demographic comparisons of participants and nonparticipants.

Baseline clinical assessment of previous and extant symptoms of syncope, falls, and dizziness; cognitive assessment (Mini-Mental State Examination)²⁷; full clinical examination; and 12-lead electrocardiograms were performed.

Syncope was defined as a rapid onset of transient and self-limited loss of consciousness usually associated with falling, with complete and spontaneous recovery.⁹ A fall was defined as coming to rest on the ground or any other lower level without loss of consciousness.²⁸ Dizziness included unsteadiness, light-headedness, rotational symptoms, and postural nonrotational symptoms.

CAROTID SINUS MASSAGE

Carotid sinus massage was performed between 9 AM and 1 PM. Surface electrocardiogram was recorded using lead 1 or lead 2 to obtain a clear signal. Beat-to-beat SBP was recorded noninvasively by means of a digital photoplethysmographic device (Portapres; TNO, Amsterdam, the Netherlands). Physical function enabled intermittent calibration. The data obtained were digitized and stored on a notebook computer for subsequent analysis. Contraindications to CSM were myocardial infarction in the preceding 3 months, stroke or transient ischemic attack in the preceding 3 months, any history of ventricular tachyarrhythmia and carotid bruits, or established atrial fibrillation.

After 10 minutes' supine rest, carotid sinus massage was performed for 5 seconds over the point of maximal carotid pulsation (usually at the level of the upper border of the cricoid cartilage). Blood pressure and heart rate responses were monitored throughout. Right-sided supine CSM was followed by left-sided CSM after an interval of 1 minute. Right- and left-sided CSM were then repeated in the upright position (foot-plate assisted tilt bed

to 70°). Each participant underwent a maximum of 4 episodes of CSM. In the event of persistent symptoms or persistent hypotension (SBP <100 mm Hg), the procedure was aborted. After each episode of CSM, participants were questioned about dizziness, presyncope, and syncope.

DEFINITION OF CSH

Cardioinhibitory CSH was defined as asystole of 3 seconds or more with a drop in SBP of less than 50 mm Hg. Vasodepressor CSH was defined as a drop of 50 mm Hg or more in SBP and mixed CSH was a combination of cardioinhibitory CSH and vasodepressor CSH.⁹

STATISTICAL ANALYSIS

Statistical analysis of the data was carried out using SPSS version 10.0 (SPSS Inc, Chicago, Ill). Comparison of participants with nonparticipants was made using the Pearson χ^2 test for categorical data and the Mann-Whitney test for continuous data.

The absolute variables included in the analysis were the presence or absence of CSH, the presence or absence of CSH accompanied by symptoms of dizziness, presyncope, or syncope. The heart rate and blood pressure response to CSM was also analyzed using continuous variables. The continuous variables included in the analysis were the maximum RR interval and minimum SBP during CSM, the change in RR interval between baseline and maximum post-CSM (delta RR interval), and the change in SBP from baseline to minimum SBP nadir after CSM. The maximum value of each was calculated for each subject.

As heart rate (RR interval) data were skewed, they are presented as medians and (minimum-maximum) ranges. Mean values and standard deviations are presented for the BP data, which were normally distributed. The impact of explanatory variables on CSH and CSH in association with symptoms of dizziness, presyncope, and syncope was estimated using (univariate and multivariate) logistic regression. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported. Explanatory variables included in the models were age; sex; current smoking history; falls; syncope; dizziness in the preceding 12 months (as a composite and individually); history of myocardial infarction, angina, ischemic heart disease, hypertension, congestive cardiac failure, peripheral vascular disease, any cardiovascular diagnosis, diabetes, hyperlipidemia, and cerebrovascular disease; and use of psychotropic medications, cardioactive medications, and antihypertensives (as a composite and individually for angiotensin-converting enzyme inhibitors, β -blockers, α -blockers, calcium channel blockers, angiotensin II receptor blockers, and thiazide diuretics).

RESULTS

PATIENT RECRUITMENT

One thousand patients were sampled (median age, 75 years [range, 65-99 years]); 500 (50%) were male. Of the 1000 patients, 784 replied to the initial invitation to participate, 185 did not reply, and 31 died during this time. A total of 444 patients declined CSM, and 68 patients had contraindications to CSM: carotid bruits (n=32), transient ischemic attack or stroke in preceding 3 months (n=2), atrial fibrillation or frequent ectopic activity (n=29), persistent systolic hypotension (n=2), implantable defibrillator in situ (n=1), and permanent pacemaker in situ (n=2).

Table 1. Characteristics of Study Population and Subsample With No Prior Symptoms*

Characteristic	Study Group (n = 272)	Subsample With No Prior Falls, Syncope, or Dizziness (n = 80)
Age, median (range), y	71 (65-92)	70 (65-86)
Male	154 (57)	54 (68)
Current smoker	23 (9)	8 (10)
Falls, syncope, or dizziness in last year		
Falls	75 (28)	0
Syncope	7 (3)	0
Dizziness	128 (47)	0
Medical history		
Myocardial infarction	26 (10)	6 (8)
Angina	31 (11)	9 (11)
Ischemic heart disease	35 (13)	11 (14)
Hypertension	88 (32)	20 (25)
Congestive cardiac failure	21 (8)	4 (5)
Diabetes	15 (6)	3 (4)
Cerebrovascular disease	16 (6)	4 (5)
Baseline medication†		
Antihypertensive medication	113 (42)	28 (35)
Cardioactive medication	124 (46)	31 (39)
Psychotropic medication	43 (16)	7 (9)

*Data are given as number (percentage) of patients unless otherwise specified.

†Antihypertensive medications include any of the angiotensin-converting enzyme inhibitors, α -blocker, β -blocker, calcium channel blocker, angiotensin type 2 receptor blocker, and thiazide diuretic; cardioactive medications include any antihypertensive agents, antianginal (nitrate) medications, antiarrhythmics, fludrocortisone acetate, or midodrine hydrochloride; psychotropic medications include any typical neuroleptic, atypical neuroleptic, anticholinergic, cholinesterase inhibitor, tricyclic antidepressant, selective serotonin reuptake inhibitor, other antidepressant agent, or antiparkinson or other psychotropic medication.

A total of 272 subjects (median age, 71 years [range, 65-92 years]) underwent CSM, of whom 154 (57%) were male, 35 (13%) had ischemic heart disease, and 124 (46%) were taking cardioactive medication (**Table 1**). Of those taking cardioactive medications, 53 (20%) were taking β -blockers; 33 (12%), angiotensin-converting enzyme inhibitors; 42 (15%), calcium channel blockers; 54 (20%), diuretics (loop or thiazide); and 36 (13%), antianginal medication (Table 1).

PARTICIPANTS VS NONPARTICIPANTS

To assess whether recruited participants accurately represented the baseline population, baseline characteristics on general practitioner notes review were compared with those of 445 individuals from the baseline population who declined participation but agreed to notes review. Participants were younger (70 years [range, 65-92 years] vs 76 years [range, 65-96 years]; $P < .001$) and more likely to be male (57% vs 47%; $P = .01$); less likely to have ischemic heart disease (22% vs 32%; $P = .006$), congestive cardiac failure (5% vs 12%; $P = .003$), hypertension (34% vs 43%; $P = .02$), or cerebrovascular disease (7% vs 17%; $P < .001$); and less likely to be taking cardioactive (16% vs 66%; $P < .001$) or psychotropic (16% vs 30%; $P < .001$) medications compared with nonparticipants.

Table 2. Prevalence of CSH in Study Group and Subsample With No Prior Falls, Syncope, or Dizziness*

Variable	Study Group (n = 272)	Subsample With No Prior Falls, Syncope, or Dizziness (n = 80)
CSH	107/272 (39)	28 (35)
Cardioinhibitory CSH	6/107 (6)	2/28 (7)
Vasodepressor CSH	42/107 (39)	8/28 (29)
Mixed CSH	59/107 (55)	18/28 (64)
Symptoms with CSH	43/107 (40)	10/28 (36)
Syncope	18/43 (42)	4/10 (40)
Presyncope/dizziness	25/43 (58)	6/10 (60)
RR interval post-CSM, median (range), ms	1701 (633-11264)	1676 (633-8637)
Maximum delta RR, median (range), ms	766 (29-10021)	783 (29-7798)
SBP nadir, mean \pm SD, mm Hg	83 \pm 28	85 \pm 27
Maximum fall in SBP during CSM, mean \pm SD, mm Hg	47 \pm 20	45 \pm 17

Abbreviations: CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; ms, milliseconds; SBP, systolic blood pressure.

*Data are given as number/total number (percentage) of patients unless otherwise specified.

CAROTID SINUS HYPERSENSITIVITY

Carotid sinus hypersensitivity was present in 107 (39%) of the study group (**Table 2**). The median age of the 107 subjects with CSH was 73 years (range, 65-92 years), and 69 (65%) were male. Male sex (OR, 1.71; 95% CI, 1.04-2.82; $P < .04$) and age (OR, 1.05; 95% CI, 1.00-1.09; $P < .04$) were the only variables that predicted a hypersensitive response. Both remained independent predictors after multivariate analysis ($P < .03$). Syncope, falls, or dizziness in the preceding 12 months (individually or as a composite) did not predict CSH, nor did a history of cerebrovascular disease or ischemic heart disease or prescription of cardiovascular or psychotropic medications.

Thirty-one participants (29% of those with CSH) had a hypersensitive response only when upright. Overall, 60 had symptoms of syncope, presyncope, or dizziness during CSM. No one experienced a stroke or transient ischemic attack as a result of CSM.

Forty-three participants (40% of those with CSH) had dizziness, presyncope, or syncope during CSM in conjunction with the hypersensitive response. Syncope was present in 18 (17%) and dizziness or presyncope in 25 (23%). After multivariate analysis, age was the only factor to affect the odds of a hypersensitive response being accompanied by dizziness, presyncope, or syncope (OR, 1.06; 95% CI, 1.01-1.12; $P = .03$).

SUBGROUP WITH NO PRIOR FALLS, SYNCOPE, OR DIZZINESS

Eighty participants (mean age, 70 years [range, 65-86 years]) had no history of falls, syncope, or dizziness and normal cognitive function (Mini-Mental State Examination score of ≥ 24 to ensure accurate history of previous symptoms).

The subgroup was younger and had a higher proportion of men compared with the total participant group (Table 1). The prevalence of CSH was 35% (28/80) (Table 2). Of these, 2 (7%) had cardioinhibitory CSH, 18 (64%) had a mixed subtype, and 8 (29%) had vasodepressor CSH. Male sex was the only predictor of a hypersensitive response of those with CSH: 10 participants (36% of the CSH-positive group) described either dizziness, presyncope, or syncope in association with a hypersensitive response. Four (14%) had syncope (Table 2). Previous myocardial infarction (OR, 9.57; 95% CI, 1.65-56.74; $P = .01$) was the only predictor of symptomatic CSH.

SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUE OF CSM

For those with any history of falls, syncope, or dizziness and defining a positive response as CSH, the sensitivity of CSM was 41% (78/191); specificity was 64% (52/81), positive predictive value was 73% (78/107), and negative predictive value was 32% (52/165). When CSH was accompanied by symptoms of syncope, presyncope, or dizziness, the sensitivity was 17% (32/191), specificity was 86% (70/81), positive predictive value was 74% (32/43), and negative predictive value was 31% (70/229).

DERIVATION OF A NORMAL RANGE FROM THE ASYMPTOMATIC SUBSAMPLE

The 97.5th percentile was 8292 milliseconds (ms) for heart rate response and 82 mm Hg for SBP vasodepressor response. The 95th percentiles were 7277 ms and 77 mm Hg, respectively. Applying these normal ranges to all participants revealed that 4 (1.5%) had a maximum RR value above 8292 ms, and 13 (5%) had a value above the 95th percentile value. Sixteen (6%) had a maximum blood pressure drop above the 97.5th percentile (82 mm Hg), while 22 (8%) had a value above the 95th percentile value.

In the supine position, the 97.5th percentile for maximum RR interval and systolic vasodepression were 7433 ms and 77 mm Hg, respectively. The 95th percentiles are 7083 ms and 74 mm Hg.

For CSM performed upright, the 97.5th percentiles for maximum RR interval and systolic vasodepression are 6897ms and 80 mm Hg, respectively. The 95th percentiles are 5530 ms and 75 mm Hg.

COMMENT

To our knowledge, this is the first study of heart rate and phasic blood pressure responses to CSM in supine and upright positions, using recommended standardized methods,⁹ in an unselected community sample of older persons. Carotid sinus hypersensitivity was common in older people—39% of an unselected cohort and 35% of older people with no history of symptoms traditionally associated with a hypersensitive response (syncope, falls, and dizziness). No clinical characteristics predicted a hypersensitive response with the exception of age and male sex, although for both variables the 95% CIs included variables close to 1. This prevalence is much higher than that

previously reported. In previous reports, the prevalence in asymptomatic subjects was on average 14%. However, participants were recruited from hospital in-patient^{12,16,17} or tertiary referral outpatient settings,^{10,21} which is unrepresentative of community cohorts. The technique of CSM was not standardized: in some, CSM was carried out for 30 seconds or longer^{18,19}; in most, CSM was performed in the supine position only,^{13,15-17,21,24} and the vasodepressor response was not reported.^{13,16,17,19,22,24}

Syncope occurs at some stage in 40% of the population, and its prevalence increases with advancing years. The prevalence of CSH and other comorbid causes of syncope also increase with advancing age.²⁹ Given the high prevalence of CSH in asymptomatic older persons, it is clear that rigor and caution must be exercised when assuming an attributable cause for syncope in older persons who have CSH. The clinical relevance of a finding of CSH remains unclear. Ongoing prospective follow-up of this group will help to clarify whether it is predictive of future symptoms or merely an age-related physiological response.

Symptoms of dizziness, presyncope, or syncope were present in 40% of the unselected sample with a hypersensitive response and 36% of the asymptomatic subgroup with a hypersensitive response. Only a small proportion of patients experienced syncope during CSM: 6.6% of the entire population (17% of those with CSH) and 5% of the subsample (14% of those with CSH)—none had a history of syncope. This emphasizes the importance of symptom reproduction in the context of the investigation of syncope as clearly stated in European Society of Cardiology guidelines.⁹

Falls are a common age-related symptom: 30% of individuals older than 65 years fall at least once per year, and fall rates rise exponentially with advancing physical and cognitive frailty.³⁰ Because recent guidelines have recommended that the comprehensive assessment of fallers includes CSM, the procedure is increasingly being carried out by geriatricians and general physicians.³⁰⁻³³ Our findings are thus relevant to a wider medical community than to cardiologists only. Recommended treatments for CSH include cardiac pacing⁶ and medications such as midodrine hydrochloride.³⁴ Both are effective in correctly selected patients although neither has been subject to large double-blind randomized control studies.^{6,34} Given the high prevalence of CSH in nonsyncopal cases, it is important that careful consideration is given to attribution of cause or the widespread misinterpretation of CSM could result in inappropriate cardiac pacing and medication use.

The study raises the critical question of causality in common and heterogeneous symptoms such as dizziness, syncope, and falls. Although the results suggest that CSH may be a physiological age-related finding of marginal significance with low sensitivity and specificity, there is also strong evidence from many studies of a causal association between cardioinhibitory CSH and/or CSS, syncope, and nonaccidental falls.^{5,6,35} It may be that age-related changes in cerebral autoregulation may “convert” asymptomatic CSH to symptomatic CSH. We have recently reported abnormal static and dynamic cerebral autoregulation in symptomatic CSS.³⁶

The present study was limited to a single general practitioner practice to maximize participation and facilitate assessment of participants in their local environment. Only those older than 65 years were asked to participate as symptomatic CSH is an age-related disorder. Only 27% of those sampled participated in the study. The principal reason cited for unwillingness to participate was the possibility of neurological complications as a consequence of CSM (although no participant experienced a neurological complication). Participants were compared with nonparticipants (including those in whom CSM was contraindicated) when consent for general practitioner notes review was given. Participants were less frail than nonparticipants. Thus, it is likely that the prevalence was underestimated and not overestimated.

A new normal range was derived from the asymptomatic subsample, which differed greatly from traditional thresholds. Applying this new range to the whole cohort dramatically reduced the numbers of individuals with CSH. There is no accurate documentation of how the traditional cutoff levels for CSH were derived. Although 3 seconds is the traditional cutoff for cardioinhibitory CSH diagnosis,^{4,23} many patients have much longer pauses, and it may be that redefinition of the upper limit is appropriate. When considering the cardioinhibitory response, for which the most effective treatment is available, if one applied a normal range derived from the subsample to the whole cohort, at the 97.5th percentile (8.3 seconds) 1.5% had cardioinhibitory CSH and mixed CSH, and at the 95th percentile 5% had cardioinhibitory CSH or mixed CSH (7.2 seconds) compared with 24% of the unselected cohort and 25% of the asymptomatic cohort using traditional thresholds (cardioinhibition, ≥ 3 seconds). It may be that these ranges are more accurate for discriminating for symptomatic CSH, but this should be tested in a prospective intervention trial.

In conclusion, CSH is common in a community sample of older individuals, even those without prior symptoms of syncope, falls, or dizziness. In men, CSH is more common and the heart rate, and blood pressure responses are more pronounced. The finding of CSH does not necessarily preclude other causes of syncope. Further prospective studies of the prevalence of CSH in patients with other attributable causes of syncope will better inform interpretation of a hypersensitive response in symptomatic patients.

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