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ORIGINAL RESEARCH

Asymptomatic Asystolic Carotid Sinus Hypersensitivity Predicts Asystolic Events During ILR Monitoring in Reflex Syncope Patients

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ABSTRACT

BACKGROUND The diagnosis of carotid sinus syndrome requires the reproduction of spontaneous symptoms during carotid sinus massage (CSM) alongside clinical features indicative of a reflex mechanism. In contrast, the significance of asymptomatic asystolic carotid sinus hypersensitivity (CSH) remains uncertain, as it is frequently observed in older adults without syncope.

OBJECTIVES This study aimed to evaluate the correlation between asymptomatic asystolic CSH and spontaneous events documented via implantable loop recorder (ILR).

METHODS In this study, 92 reflex syncope patients with an asymptomatic pause >3 seconds during CSM (average 4.9 ± 1.7 seconds) received an ILR and were followed for a median of 23.1 months. The control group consisted of reflex syncope patients with negative CSM drawn from a historical ILR population and matched with the propensity score method to the CSH group based on clinical variables.

RESULTS During the observation period, 38 (41.3%) CSH patients had recurrence of syncope, which was associated with asystole of 8.0 seconds (95% CI: 5.3-13.5 seconds) in 29 (76.3%) cases. Although the actuarial rate of total syncope recurrence in CSH group was similar to that in the control group (HR: 1.22; $P = 0.40$), CSH patients showed a higher rate of asystolic syncope (HR: 2.13; $P = 0.011$) and asystolic pauses (HR: 2.06; $P = 0.009$).

CONCLUSIONS Patients with asymptomatic asystolic CSH were more likely to experience spontaneous asystolic syncope than those without CSH. Among CSH patients who experienced a recurrence of syncope documented by an ILR, the positive predictive value of an asystolic pause detected during CSM was 76.3%.
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ABBREVIATIONS AND ACRONYMS

CSH = carotid sinus hypersensitivity

CSM = carotid sinus massage

CSS = carotid sinus syndrome

ESC = European Society of Cardiology

ILR = implantable loop recorder

The diagnosis of carotid sinus syndrome (CSS) requires the reproduction of spontaneous symptoms during carotid sinus massage (CSM) alongside clinical features indicative of a reflex mechanism of syncope.[1] According to most recent guidelines of the European Society of Cardiology (ESC) on cardiac pacing,[2] cardioinhibitory (asystolic) CSS, defined previously, is a class I indication for permanent cardiac pacing.

In contrast, the significance of asymptomatic asystolic carotid sinus hypersensitivity (CSH) remains unclear.[3] Indeed, it is frequently observed in older adults with no history of syncope[4,5] and has been hypothesized that CSH may be an aging-related process.[6] Among patients with recurrent falls and nonspecific symptoms who exhibited cardioinhibitory CSH, no association was found between this diagnosis and spontaneous asystolic episodes.[7] Consequently, the guidelines were unable to give recommendations on management of CSH.

This study aimed to evaluate the correlation between asymptomatic asystolic CSH and spontaneous events documented via an implantable loop recorder (ILR) in patients with a diagnosis of likely reflex syncope.

METHODS

The SUP3 (Syncope Unit Project 3) trial was a multicenter, prospective observational study which was performed in 10 experienced syncope units. Patients with a clinical diagnosis of likely reflex syncope who had an asymptomatic asystolic response to CSM were enrolled and were observed by means of an ILR. The CSH study group was compared with a control group selected from a historical ILR population of patients with reflex syncope and a negative response to CSM. The study was approved by the Ethical Committees of participating centers.

INCLUSION CRITERIA. The inclusion criteria were the following. The first was clinical diagnosis of likely reflex syncope. In compliance with the criteria of the ESC syncope guidelines,[1] clinical diagnosis of likely reflex syncope was diagnosed in patients who had clinical features consistent with reflex syncope in whom alternative diagnoses had been excluded. The second was induction of cardioinhibitory CSH during CSM, defined as an asystolic pause >3 seconds that was either asymptomatic or caused nonsyncopal symptoms that were not recognized by the patients as being similar to the spontaneous symptoms. The third was age >40 years. The fourth was at least 2 syncopal episodes during the previous year or 3 episodes during the previous 2 years

EXCLUSION CRITERIA. The exclusion criteria were the following. The first was CSS (ie, reproduction of spontaneous symptoms during CSM). The second was nonsyncopal causes of real or apparent transient loss of consciousness that may have been incorrectly diagnosed as syncope (eg, accidental falls, epilepsy, psychogenic pseudo syncope).[1] The third was established or suspected cardiac syncope, defined in compliance with the criteria of the ESC syncope guidelines.[1] Specifically, these were the patients with: 1) suspected cardiac arrhythmic syncope (inadequate sinus bradycardia [<50 beats/min] or sinoatrial block, second-degree Mobitz I atrioventricular block, second-degree Mobitz II or third-degree atrioventricular block, paroxysmal tachyarrhythmia or ventricular tachycardia, bundle branch block); and 2) severe structural heart disease and/or significant electrocardiographic abnormalities, as defined in Table 2 of the previously mentioned guidelines.[1]

CAROTID SINUS MASSAGE. As recommended by the ESC guidelines,[8] CSM was performed during continuous electrocardiography and noninvasive beat-to-beat blood pressure monitoring in supine and standing positions, on both right and left sides, for 10 seconds in each position. Thus, each patient underwent 4 massages.

ENDPOINTS. The primary endpoint was the occurrence of an asystolic syncope documented by an ILR during the observation period.

The secondary endpoints were the recurrence of any syncope, the occurrence of any asystolic pauses >3 seconds regardless of symptoms, and the electrocardiography pattern of asystolic pauses. The pattern of asystolic events was classified according to the ISSUE classification:[8,9] type 1A (sinus arrest), type 1B (sinus bradycardia plus arteriovenous block), type 1C (arteriovenous block), and type 1 (undefined pause).

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Characteristics of the CSH and Control Groups After Matching

	CSH Group (n = 92)	Control Group (n = 178)	*P* Value
Age, y	71.5 ± 10.3	71.7 ± 11.4	0.85
Male	65 (70.1)	125 (70.2)	1.00
Total number of syncopes	4.1 ± 2.8	4.7 ± 2.5	0.11
Syncopes last 2 y	3.0 ± 1.6	3.3 ± 1.4	0.14
Structural cardiac abnormalities	34 (37.0)	72 (40.4)	0.60

Values are mean ± SD or n (%).
CSH = carotid sinus hypersensitivity.

CONTROL GROUP. The control group was selected from a historical ILR population of 1,046 patients with reflex syncope and a negative response to CSM.[10] This cohort was created by combining raw data from 4 studies.[11-14] The control population was matched 2:1 by means of the propensity score method to the study group based on 5 clinical variables: age, sex, total number of syncopal episodes, number of syncopes in the previous 2 years, and the presence of structural heart disease or electrocardiography abnormalities. Nearest-neighbor matching (without replacement) was used for propensity score matching.

FOLLOW-UP. Follow-up started at the time of ILR implantation. After ILR implantation, heart rhythm was monitored remotely and clinical outcomes were assessed at quarterly visits. Follow-up ended at the first syncope recurrence whatever it was and, in absence of syncope recurrence, at the time of ILR battery exhaustion or study termination.

STATISTICAL METHOD. Sample calculation. Among 1,046 historical ILR patients, asystolic events were observed in 19% of them.[15] We hypothesized that if the study group had a doubled event rate of asystolic events (38%) with similar syncope recurrence, a sample sizes of 87 for the study group and 174 for control subjects would have been necessary to show a bilateral *t* test ($\alpha = 0.05$) with 80% power.

Statistical analysis. Continuous data were presented as mean ± SD or median (Q1-Q3) as appropriate. Normality was checked using the Kolmogorov-Smirnov method. Categorical data were reported using absolute and relative frequencies. Comparisons of continuous variables were performed using unpaired Student's *t* test or Wilcoxon test for non-normally distributed variables. Proportions were compared using Fisher exact test.

To evaluate differences between individuals in the CSH group and those in the control group, Kaplan-Meier survival curves were constructed for each outcome of interest: asystolic syncope, recurrent syncope, and asystolic pauses.

Furthermore, for each outcome, a proportional hazards model was employed to estimate HRs and 95% CIS for CSH, with adjustments made for the following covariates: age, sex, total number of syncopal episodes, number of syncopes in the preceding 2 years, and the presence of structural heart disease or electrocardiographIC abnormalities. The proportional hazards assumption was evaluated using the Schoenfeld test. Finally, to verify the robustness of our results, several sensitivity analyses were performed: 1) the Fine and Gray model treating recurrence of syncope without asystole and recurrence of asystole without syncope as competing events;[16] 2) a stratified Cox model by matched set;[17] 3) a Cox model with robust sandwich variance estimator[18], and 4) a Cox model weighted for the inverse probability of censoring weighting.[19] All tests were 2-tailed, and statistical significance was set at the 0.05 level.

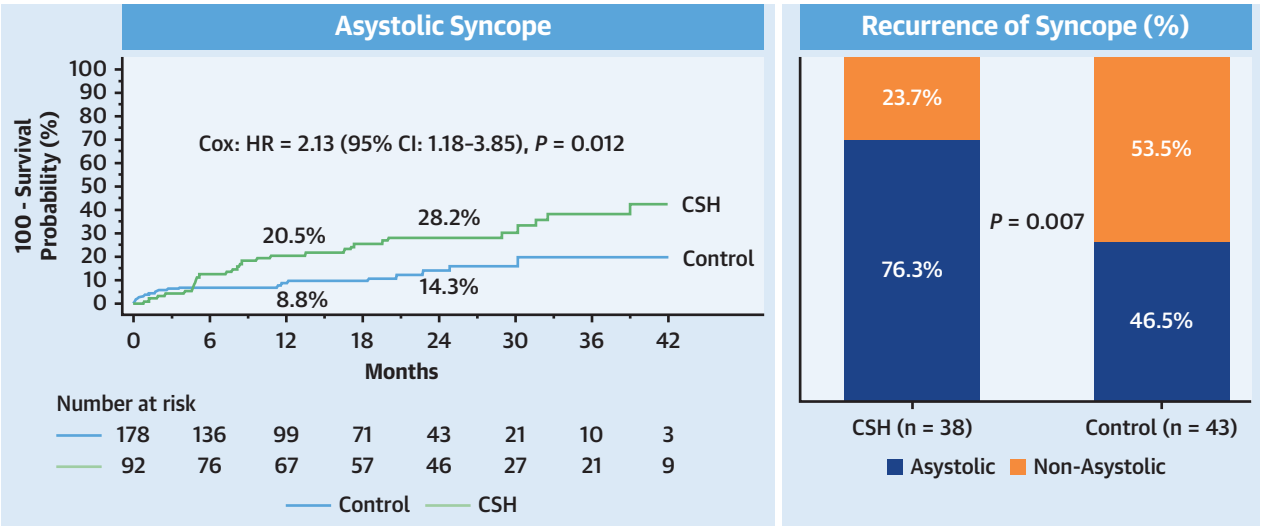
RESULTS

CHARACTERISTICS OF THE POPULATION. The study population included 92 CSH patients and 178 matched control subjects with similar clinical characteristics (Table 1). During CSM, the CSH patients had a mean asystolic pauses of 4.9 ± 1.7 seconds. The longest pause was achieved in the supine position in 71% of cases and in the standing position in 29% of cases, and on the right side in 71% of cases and on the left side in 29% of cases. The mean fall in systolic blood pressure was 47 ± 25 mm Hg.

OUTCOME. CSH patients were followed for a median of 24.0 months. During the observation period, 38 (40.9%) CSH patients experienced a recurrence of syncope, which was associated with asystole of 8.0 seconds (95% CI: 5.3-13.5 seconds) in 29 (76.3%) cases. Among the subjects in the control group, 43 had recurrence of syncope which was associated with asystole of 7.0 seconds (95% CI: 4.4-6.3 seconds) in 20 (46.5%) ($P = 0.007$ vs CSH group) (Central Illustration, right). In patients who did not have syncope recurrence, asymptomatic asystolic episodes >3 seconds were observed in 9 CSH patients and in 4 control subjects.

The estimated occurrence rate of asystolic syncope was 20.5% (SE 4.3%) at 1 year and 28.2% (SE 4.9%) at

CENTRAL ILLUSTRATION **Asymptomatic Asystolic Carotid Sinus Hypersensitivity Predicts Asystolic Syncope**



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Rates of recurrence of asystolic and nonasystolic syncope in the two groups (right) and actuarial estimate of recurrence of asystolic syncope (left) in the carotid sinus hypersensitivity (CSH) and control groups. The results of comparison between groups, as determined by the Cox proportional hazards model, is also shown. The Fine and Gray model was applied, treating recurrence of syncope without asystole and recurrence of asystole without syncope as competing events.

2 years of follow-up in the CSH group compared with 8.8% (SE 2.3%) at 1 year and 14.3% (SE 3.5%) at 2 years of follow-up, respectively, in the control group (Central Illustration). The Cox regression model showed that the CSH group had a higher rate of asystolic syncope (HR: 2.13; 95% CI: 1.18 to 3.85; $P = 0.012$). All other clinical and sociodemographic covariates were not statistically significant. The assumption of proportional hazards was respected using the global Schoenfeld test ($P = 0.28$). Moreover, sensitivity analyses confirmed this finding ($HR_{Fine\ and\ Gray}$: 2.42; 95% CI: 1.36-4.29; $HR_{stratified}$: 2.08; 95% CI: 1.06-4.10; $HR_{sandwich}$: 2.16; 95% CI: 1.22-3.83; and $HR_{inverse\ probability\ of\ censoring\ weighting}$: 2.23; 95% CI: 1.24-4.02).

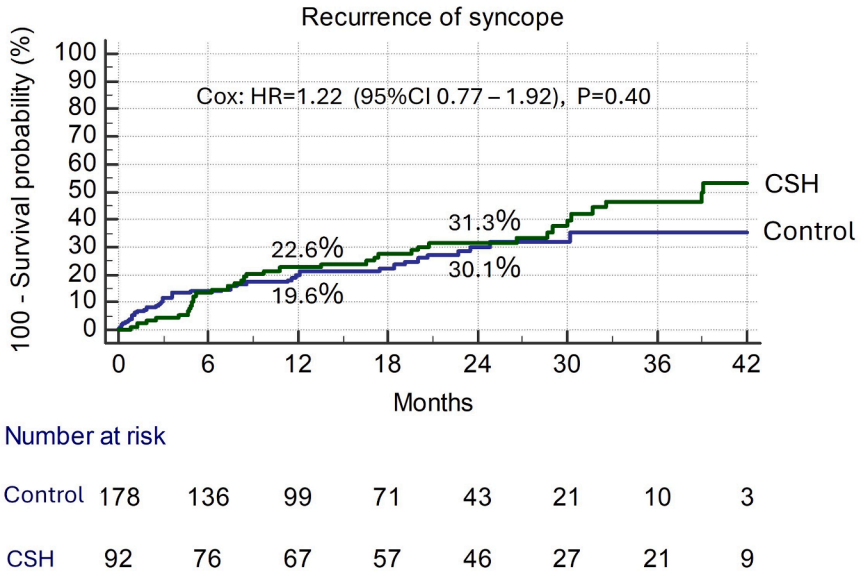
Concerning the secondary endpoints, the actuarial rate of any syncope recurrence in the CSH group was similar to that of the control group (HR: 1.22; 95% CI: 0.77-1.92; $P = 0.40$) (Figure 1). Overall, asystolic pauses (asymptomatic or symptomatic) were observed in 35 CSH patients and in 24 control subjects during the follow-up. The most frequent type of pause was type 1A (sinus arrest) in both groups, but it was more frequent in the CSH group (82.8%) than in the control group (41.6%) ($P = 0.001$) (Figure 2). The CSH group showed a higher rate of asystolic pauses (HR: 2.06; 95% CI: 1.21-3.53; $P = 0.009$) (Figure 3).

DISCUSSION

We found that most patients with a clinical diagnosis of reflex syncope, who had an asymptomatic pause >3 seconds induced during CSM (ie, CSH), later experienced a spontaneous asystolic syncope documented by ILR during follow-up more frequently than in those without CSH. The positive predictive value of asymptomatic asystolic CSH for asystolic syncope was 76.3% (95% CI: 63%-87%). Asystolic syncope and total asystolic pauses occurred approximately twice the rate in patients with asystolic CSH compared with control subjects, despite similar overall syncope, recurrence rates were similar. This indicates that pauses longer than 3 seconds during CSM are clinically relevant for diagnosing bradycardic spontaneous reflex syncope and helps inform patient management.

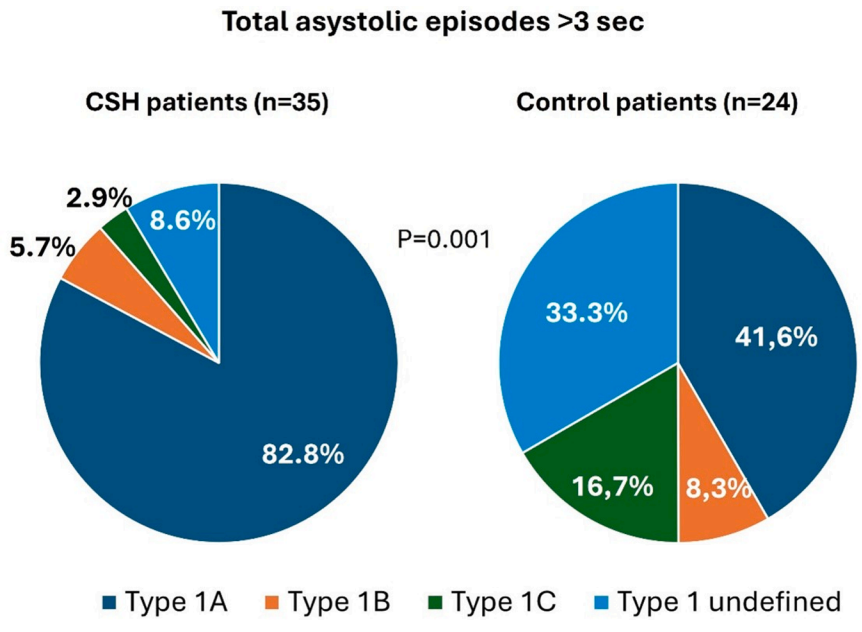
How can these study results be reconciled with previous findings suggesting that asymptomatic CSH,

FIGURE 1 **Actuarial Estimate of Recurrence of Syncope in the CSH and Control Groups**



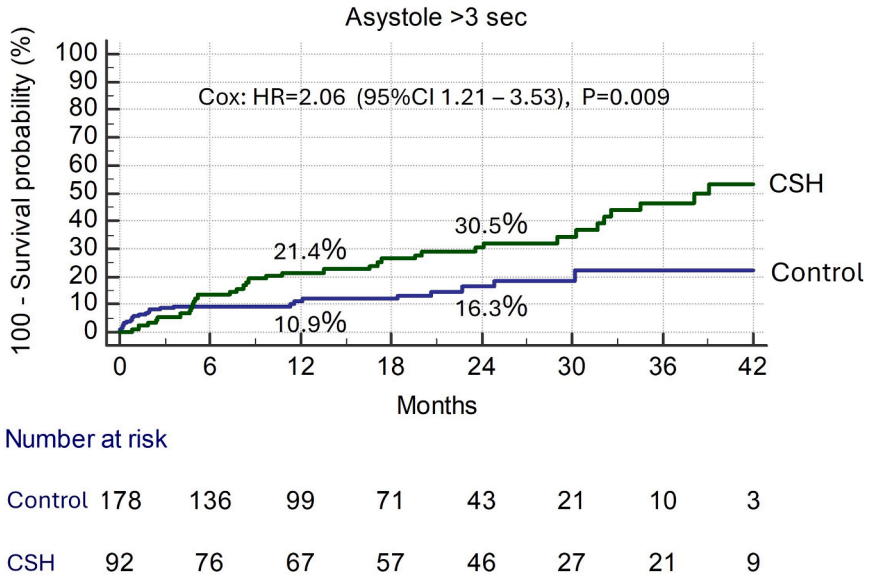
The results of comparison between groups, as determined by the Cox proportional hazards model, is shown. CSH = carotid sinus hypersensitivity.

FIGURE 2 **Total Asystolic Pauses (Asymptomatic and Symptomatic) in the CSH and Control Groups**



The pattern of asystolic pause was classified according to the ISSUE classification:[8,9] type 1A (sinus arrest), type 1B (sinus bradycardia plus atrioventricular block), type 1C (AV block), and type 1 (undefined pause). CSH = carotid sinus hypersensitivity.

FIGURE 3 Actuarial Estimate of Recurrence of Asystolic Pause >3 Seconds in the CSH and Control Groups



The results of comparison between groups, as determined by the Cox proportional hazards model, is shown. CSH = carotid sinus hypersensitivity.

which is often observed in older adults without syncope, has low specificity and uncertain significance?[4-6] For example, in the Safepace 2 trial,[7] no association was found between spontaneous asystolic episodes and asystolic CSH in patients with recurrent falls and nonspecific symptoms. Among 48 ILR activations (only 4 of which were for syncope), the electrocardiography tracing showed the absence of any arrhythmia except for 2 cases of bradycardia. In the present study, the diagnosis of reflex syncope was established using rigorous guideline-based clinical criteria for proper patient selection (see inclusion/exclusion criteria). Here, CSM was used to characterize the phenotype of syncope in cases that were already identified as probably having a reflex origin, whereas earlier studies used CSM with the intention of making a new etiological diagnosis. Thus, the pretest probability of a spontaneous asystolic events was higher in the present study than in the others. We may suppose that cardioinhibitory CSH has high predictive value for identifying asystolic events in patients with likely reflex syncope. This predictive value may not apply to patients with a history of falls, minor symptoms, or syncope whose characteristics differ from those with reflex mechanism. This is in accordance with the indication to perform CSM only in patients with recurrent syncope after the initial evaluation when a reflex mechanism is suspected.

Recently, the approach of phenotyping reflex syncope mechanisms has been used to support personalized treatment strategies aimed at preventing recurrence in patients with severe, recurrent syncopes.[20] CSM was included among essential cardiovascular autonomic tests that help identify patients with bradycardic or mixed phenotypes. The present study extends the results of recent literature suggesting that cardioinhibitory CSH should be included among conditions potentially associated with a bradycardic phenotype of syncope.

The positive predictive value of asystolic CSH found in this study (76.3%) is similar to the positive predictive value of 70% found in patients with asystolic tilt testing who had subsequently an ILR-documented syncope.[21] Thus, also the clinical implications may be similar. The positivity rate of asystolic syncope induced during tilt testing decreased with age, from 31% in patients under 60 years of age, to 12.1% in patients 61 to 72 years of age, and to 11.1% in patients over 73 years of age.[21] Conversely, in the same study, the rate of spontaneous asystolic syncopes recorded by ILR occurred more frequently and remained constant at a value around 50% of total syncope recurrences. In the

present study, the rate of spontaneous asystolic syncope documented by ILR in CSH patients, 71.6 years of age, was 31.5% (ie, 29 of 92), approximately 3 times greater than that of the corresponding tilt tertiles. It is well known that CSM is usually negative in younger patients and that the positivity rate increases with age.[6,22] Thus, different mechanisms responsible for asystolic reflex syncope, evidenced by CSM, are present in older compared with younger adults (in whom vasovagal syncope is more frequent).[23,24] This may explain a higher prevalence of asystolic syncope than that expected based on decline in vagal tone with advancing age and explains why, contrary to what is commonly believed, the rate of the spontaneous asystolic form of documented by ILR is constant at any age >40 years. This observation confirms the complementary importance of CSM and tilt testing in phenotyping reflex syncope.[20]

STUDY LIMITATIONS. A direct comparison of the predictive value between patients with asystolic syncope during CSM (cardioinhibitory CSS) and those with an asymptomatic asystolic response to CSM (cardioinhibitory CSH) is not feasible. This is due to the standard practice of treating CSS patients with cardiac pacing soon after diagnosis, which restricts the ability to observe their natural progression.

The follow-up concluded at the point of the first syncope recurrence, as extending follow-up and postponing treatment was not permitted by ethical guidelines. As a result, it remains possible that some patients who experienced nonasystolic syncope recurrence may have subsequently developed asystolic syncope.

The reproducibility of CSM results across different days was not evaluated in this study. A review of 7 prior studies indicated that reproducibility rates varied between studies from 43% to 100%.[25]

CONCLUSIONS

The patients with a clinical diagnosis of reflex syncope and asymptomatic asystolic CSH were more likely to experience spontaneous asystolic events and asystolic syncope compared with those without CSH. Among patients who had a recurrence of syncope documented by an ILR, the positive predictive value of an asystolic pause detected during CSM was 76.3%. On the other hand, a failure to predict an asystolic syncope was present in a quarter of patients, thus questioning the benefit of an immediate indication to cardiac pacing that will not prevent recurrence of syncope in such circumstances. Delaying cardiac pacing after a ILR documentation of a spontaneous asystolic event is likely to reduce greatly the risk of failure but exposes the patient at risk of severe traumatic recurrences. An individual risk/benefit assessment is warranted.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The patients with a clinical diagnosis of reflex syncope and asymptomatic asystolic CSH are more likely to experience spontaneous asystolic events and asystolic syncope compared with the patients with reflex syncope without CSH. This finding contrasts with the prevailing view that asymptomatic asystolic CSH is characterized by low specificity and uncertain clinical significance. The most probable explanation pertains to pretest probability. In this study, the diagnosis of reflex syncope was determined through the application of stringent, guideline-based clinical criteria to ensure appropriate patient selection. CSM was used here to clarify the mechanism of syncope in cases likely caused by reflexes, unlike earlier studies that used CSM to identify an etiological causes. Thus, the pretest probability of a spontaneous asystolic events was higher in the present study than in the others. We may suppose that cardioinhibitory CSH has high predictive value for identifying asystolic events in patients with likely reflex syncope. This predictive value may not apply to patients with a history of falls, minor symptoms, or syncope whose characteristics differ from those with reflex mechanism.

TRANSLATIONAL OUTLOOK: How do we translate this new knowledge into clinical practice? Can a pacemaker implantation be justified by the finding of an asystolic pause >3 seconds during CSM? The positive predictive value for detecting asystolic pauses during CSM was 76.3%, indicating that in about 25% of cases, asystolic syncope was not predicted. This challenges the usefulness of immediate cardiac pacing, as recurrence of syncope may still occur. On the other hand, delaying cardiac pacing after a ILR documentation of a spontaneous asystolic event is likely to reduce greatly the risk of failure but exposes the patient at risk of severe traumatic recurrences. An individual risk/benefit assessment is warranted.

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KEY WORDS carotid sinus hypersensitivity, carotid sinus massage, carotid sinus syndrome, implantable loop recorder, syncope