



Original Article

Prevalence and One-year Outcome of Carotid Sinus Hypersensitivity in Unexplained Syncope: A Prospective Cohort Study from South India

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ABSTRACT

Background: Carotid sinus syndrome accounts for one third of patients who presents with unexplained syncope. Prevalence of carotid sinus hypersensitivity (CSH) in Indians has not been studied till now.

Objectives: To assess the prevalence and associations of CSH in symptomatic patients above 50 years and to study its prognostic significance pertaining to sudden cardiac death, syncope, recurrent pre syncope and falls on 1 year follow up.

Methods: Patients above 50 years who presented with unexplained syncope, recurrent syncope or falls were considered cases and those without these symptoms were considered as controls. All the patients underwent carotid sinus massage and their responses noted. All symptomatic patients were followed up and observed for events like sudden cardiac death, syncope, recurrent pre syncope and falls during 1 year follow up. Patients with recurrent syncope and predominant cardioinhibitory syncope were advised permanent pacemaker implantation.

Results: A total of 252 patients were screened, 130 patients constituted cases and 49 patients constituted controls. CSH was demonstrable in 32% (n = 42) of cases as compared to 8% (n = 4) in controls (p < 0.001). Cardioinhibitory response was the predominant response (88%, n = 38) followed by mixed response (12%, n = 4). CSH was associated with advancing age, male gender (93%, n = 39, p < 0.001) and history of smoking (63%, n = 27, p = 0.009). Composite outcomes of sudden cardiac death, syncope, recurrent pre syncope and falls were significantly higher in patients with symptomatic CSH than in those without it (45%, n = 16 vs. 6.8%, n = 6; p < 0.001).

Conclusions: In conclusion, the prevalence of CSH in patients above 50 yrs with unexplained syncope was high in our population. Patients with CSH and baseline symptoms developed recurrent syncope during follow up. Carotid sinus massage should be a part of routine examination protocol for unexplained syncope.

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1. Introduction

Carotid sinus hypersensitivity (CSH) is a frequently overlooked cause of syncope in elderly and accounts for one-third of patients with unexplained syncope^{1,2}. CSH is an age-related phenomenon, rarely seen in patients younger than 50 years and increasing in prevalence with advancing age³. Studies from the western population have reported high prevalence (17–45%^{4,5}) of CSH in symptomatic patients older than 50 years of age. There are no studies on the prevalence and outcomes of CSH from India.

Carotid sinus massage (CSM) performed with monitoring of heart rate and blood pressure can reliably diagnose CSH. However, CSM to bring out CSH as a possible cause of symptoms is not a routine practice in the evaluation of patients with syncope. Patients with pure or predominantly cardioinhibitory response on CSM with reproduction of symptoms during massage are likely to benefit from pacemaker therapy⁶. We hypothesized that the prevalence of CSH in symptomatic patients in our population is as high as in the western reports. The aims of this study were to estimate the prevalence of CSH in patients older than 50 years with syncope, presyncope, or unexplained falls and one-year composite outcome of death, syncope, presyncope in these patients.

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2. Patients and methods

A prospective cohort study from Government Medical College Hospital, Kozhikode, Kerala, during the period from August 2013 to August 2014, we included all consecutive patients aged or older than 50 years with symptoms such as syncope, recurrent presyncope, or unexplained fall within 6 months of inclusion. They constituted the study group. Patients with ischemic stroke in the past 3 months, carotid bruit or known carotid stenosis, arrhythmias such as type II or III degree atrio ventricular (AV) block, sinus node dysfunction (spontaneous bradycardia of <40 bpm or sinus pause >2.5 s on Holter recording) and patients who have a permanent pacemaker, sustained ventricular tachyarrhythmia, and structural heart disease which can cause syncope or refusal to give consent were excluded from the study. The control group comprised patients older than 50 yrs who were referred for Holter recording for reasons other than syncope, presyncope, or falls.

Approval for the study was obtained from the Ethics Committee, Government Medical College, Calicut. A written informed consent was obtained from all patients enrolled in the study. The study conformed to the principles laid down by the Helsinki Declaration.

A full demographic and clinical characterization was performed at study entry for both the study and control groups. Rate-altering drugs were, if any, discontinued 48 h before Holter recording. Cardiovascular evaluation including supine and standing blood pressure, 12-lead electrocardiogram, transthoracic echocardiogram, and Holter recording were performed in all patients.

CSM was performed by a single operator, while Holter recording was performed in a facility equipped with a cardiac defibrillator, transcutaneous pacemaker, and all items required to perform cardiopulmonary resuscitation. Longitudinal massage was applied for 5–10 s over the point of maximal carotid pulse, just above the thyroid cartilage and below the angle of the jaw. Right CSM was performed in the supine position followed by, if negative, left CSM. If the test is still negative, CSM was repeated sequentially on both sides in sitting posture. On occurrence of symptoms, CSM was terminated and the patient was returned to the supine position immediately. Heart rate and blood pressure were measured by continuous cardiac monitor and noninvasive sphygmomanometer every 2 min. In the event of persistent symptoms or persistent hypotension (systolic blood pressure, SBP < 90 mmHg), the procedure was terminated. After each episode of CSM, symptoms such as presyncope and syncope, if any, were noted. Those patients who had recurrent syncope and a cardioinhibitory response during CSM were advised permanent pacemaker implantation in accordance to the American Heart Association (AHA) 2012 pacing guidelines.⁷

2.1. Follow-up

Patients in the study group were followed up for one year by personal interviews or telephone calls at 6 months and one year after the procedure. Participants were asked to attend the clinic at 6 months and 1 year for a follow-up; those who could not attend personally were contacted over the telephone. They were queried on recurrence of syncope, presyncope, and unexplained falls. Mortality data were also recorded. Primary endpoint was composite outcomes of sudden cardiac death, syncope, recurrent (>2 episodes) presyncope, and unexplained falls during a 1-year follow-up. Individual events constituted secondary endpoints.

2.2. Statistical analysis

2.2.1. Sample size

Sample size was calculated using the formula, $n = 4 \times p \times q/d^2$, where N was the sample size, p was the expected prevalence, q was

$100 - p$, and d was the precision index. Based on a previous study with 35% prevalence, a sample size of 130 patients was required to provide adequate power for the study.⁸

2.2.2. Statistical methods

Normally distributed continuous variables were expressed as mean $\pm$ standard deviation. Proportions were expressed as counts and percentages. Statistical analysis of the data was carried out using SPSS, version 18.0. Comparison was made using the Chi-squared test for categorical data and paired t -test for continuous data. A p value less than 0.05 was defined as statistically significant.

2.3. Definitions

CSH was classified into cardioinhibitory, vasodepressor, or mixed. Cardioinhibitory CSH was defined as asystole of ≥ 3 s without significant fall in blood pressure. Vasodepressor CSH was defined as a drop of 50 mm Hg or more in SBP without significant asystole, and mixed CSH was a combination of cardioinhibitory CSH and vasodepressor CSH.

Carotid sinus syndrome was defined as syncope or presyncope in combination with a ventricular pause lasting 3 s or more and a fall in SBP of 50 mmHg or more from the baseline value in response to carotid sinus stimulation. Patients were classified as having diabetes mellitus, hypertension, and hypercholesterolemia as per standard definitions^{9–11}

3. Results

A total of 498 patients were referred for Holter recording from August 2013 to August 2014 for various symptoms such as palpitation, syncope, dizziness presyncope, or recurrent unexplained falls. Among 252 patients who were older than 50 years, 130 patients constituted the study group after exclusion. All patients were in sinus rhythm. Fifty-two patients were excluded from our study because of rhythm disorders. This includes 30 patients who had sinus pause for more than 2.5 s, 14 patients with complete heart block and type 2 mobitz, 4 patients with non sustained ventricular tachycardia (NSVT), 2 patients with persistent atrial fibrillation, and 2 patients with baseline heart rate less than 40 beats per minute. This has been depicted in our flow chart. There were 49 patients in the control group (Fig. 1)

3.1. Clinical characteristics

Baseline parameters among the study and control groups were comparable (Table 1). Among 30 patients on rate-altering drugs, 26 patients were on cardioselective beta blockers such as atenolol (8 patients) and metoprolol (18 patients) and 4 patients were on calcium channel blockers such as verapamil (2 patients) and diltiazem (2 patients). As our study was performed during a Holter study, all patients were advised to withhold such drugs 48 h before the study. Prevalence of CSH was significantly higher in symptomatic patients as compared with the controls (32% vs. 8%; $p = 0.001$). Among the 42 patients with CSH, 93% had cardioinhibitory response ($n = 39$), 7% had a mixed response, ($n = 3$) whereas none had isolated vasodepressor response. Patients who had cardioinhibitory response developed sinus pause (Fig. 2) in 88% ($n = 37$), whereas 7% ($n = 3$) revealed a high-grade AV block (Fig. 3). Eighty-eight percent of these patients developed presyncope during massage. CSM revealed a mean pause of $4.6 \text{ sec} \pm 0.6 \text{ s}$ and mean BP fall of $18 \text{ mmHg} \pm 12$. None of the patients developed complications during massage (Table 2).

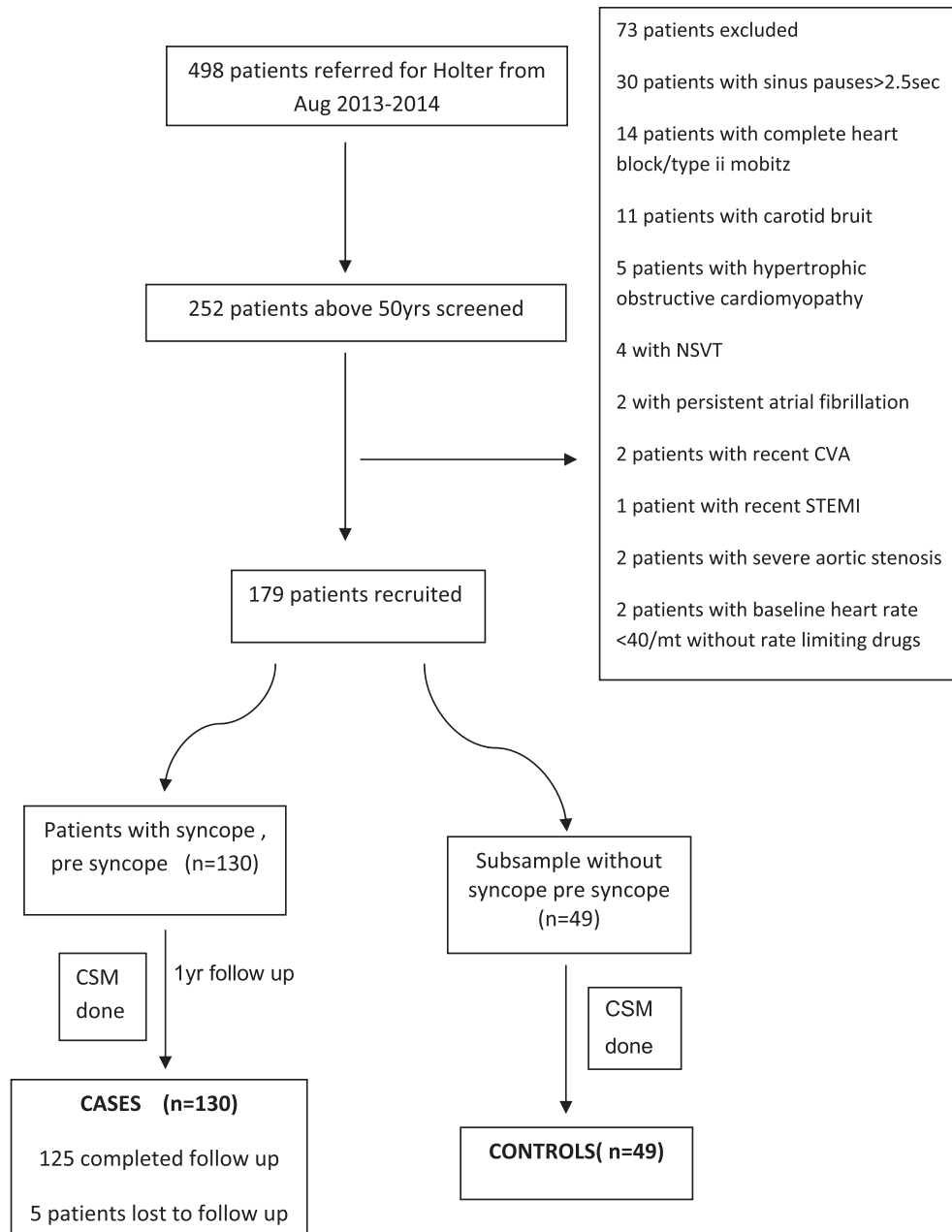


Fig. 1. The study flow chart. CSM, carotid sinus massage; CVA, cerebrovascular accident; STEMI, ST elevation myocardial infarction.

Table 1
Comparison of the baseline characteristics between cases and controls.

Baseline parameters	Total (n = 179)	Case (n = 130)	Control (n = 49)	P value Sig <0.05
Age	63 ± 7	68 ± 8.1	62 ± 9	0.12
Men	123(68.7%)	93(71%)	30(61%)	0.10
Hypertension	96(53.8%)	72(55.4%)	24(48.7%)	0.46
Type 2 diabetes mellitus	40(22.3%)	31(23%)	9(18%)	0.43
History of smoking	81(45.2%)	62(47%)	19(38%)	0.06
Stroke	10(5.5%)	8(6%)	2(4%)	0.81
Coronary artery disease	45(25.1%)	35(27%)	10(20%)	0.42
Hypercholesteremia	81(45.2%)	62(47%)	19(38%)	0.31
Rate-altering drugs	40(22.3%)	30(19.2%)	10(20.4%)	0.26
Peripheral arterial disease	2(1.1%)	2(1.5%)	0	0.43

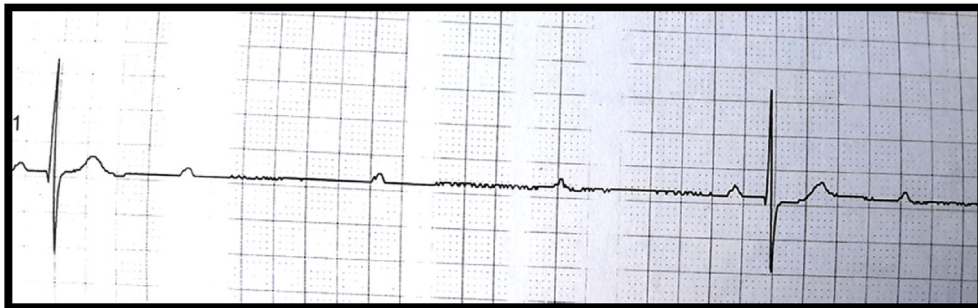


Fig. 2. A 4.2-s high-grade AV block induced by left-sided carotid sinus massage.

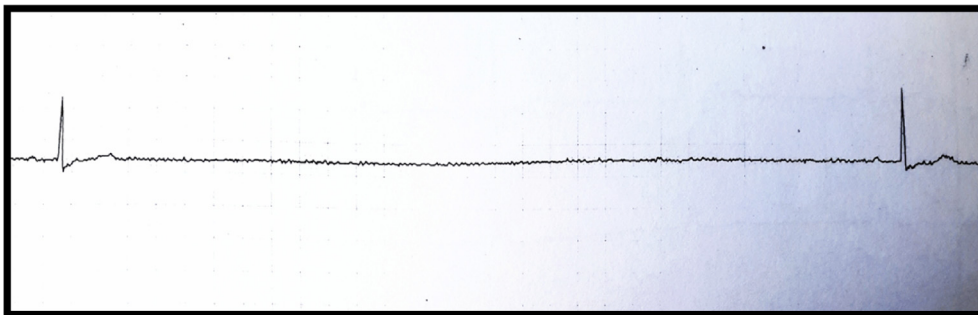


Fig. 3. A 7.1-s sinus pause induced by right-sided carotid sinus massage.

Prevalence of CSH was more common in men (93%,*p* < 0.01), smokers, and elderly; the prevalence was 45% in patients aged or older than 70. Symptoms of CSH were precipitated by neck movements in 43% of cases. Recurrent syncope and falls were common in patients with CSH, whereas vertigo was a predominant symptom in those without CSH (Table 3).

3.2. Pacemaker patients

Permanent pacemaker insertion was advised to 18 patients who presented with recurrent syncope and a predominant cardioinhibitory response during CSM. But only seven patients underwent permanent pacemaker implantation. Choice of pacemaker was decided by the treating physician, and the predominant mode of pacing used in this study was ventricular paced ventricular sensed pacemaker (VVI).

3.3. Follow-up

Of 130 symptomatic patients in the study group, follow-up data were available for 123 (94.6%) patients. During the 1-year follow-up, it was noticed that there were greater events in those with CSH as compared with those without CSH (42.8% vs. 6.8%; *p* < 0.001). Both syncope and recurrent syncope were significantly higher in the CSH group (Table 4). There was no significant difference in mortality among the two groups. Patients who underwent pacemaker insertion did not have syncope during the follow-up. As pacemaker insertion might alter the follow-up outcomes, they were considered as a separate group and were excluded from the final analysis.

4. Discussion

This was the first Asian study which assessed the prevalence of CSH in patients above 50 years of age with unexplained syncope.

Table 2
Comparison of prevalence and responses during carotid sinus massage between cases and controls.

Responses	Cases (n = 130)	Controls (n = 49)	Total (n = 179)	P value (<0.05)
Carotid sinus hypersensitivity	42(32.3%)	4(8%)	46(25.6%)	0.001
Types of response				
Cardioinhibitory	39(93%)	4(100%)	43(24%)	0.58
Vasodepressor	0	0		
Mixed	3(7%)	0	3(1.7%)	
Symptoms during massage				
Syncope	0	0	0	0.013
Presyncope	37(88%)	1(33.3%)	38(22.4%)	
Asymptomatic	5(12%)	3(61.2%)	8(4.1%)	
Types of cardioinhibitory response				
Sinus pause	39(92.9%)	4(100%)	42(24.2%)	0.58
AV block	3(7.1%)	0	3(1.7%)	
Complications	Nil	Nil		
Mean sinus pause(duration in seconds)	4.6 ± 0.6	4.3 ± 0.4		
Mean BP fall (mmhg)	18 ± 17	14 ± 10		

BP, blood pressure.

Table 3

Comparing the clinical profile of symptomatic patients (cases) with carotid sinus hypersensitivity (CSH).

Patient characteristics	CSH+ve (n = 42)	CSH–ve (n = 88)	Total (n = 130)	P Value (<0.05)
Age				
50–59	8(21%)	30(79%)	38(29%)	0.12
60–69	20(32.8%)	41(67.2%)	61(47%)	
>70	14(48%)	15(51.7%)	29(22.3%)	
Male gender	39(93%)	54(61%)	93(71.5%)	<0.001
Risk factors				
Hypertension	20(47.6%)	52(59%)	72(55.4%)	0.21
Type 2 diabetes mellitus	8(19%)	23(26%)	31(23.8%)	0.37
History of smoking	27(64.3%)	35(40%)	62(47.7%)	0.009
Stroke	3(7%)	5(5.7%)	8(6.2%)	0.74
Coronary artery disease	11(26.2%)	24(27.3%)	35(26.9%)	0.89
Peripheral arterial disease	1(2.4%)	1(1.1%)	2(1.5%)	0.59
Hypercholesteremia	23(54.8%)	39(44.3%)	67(42.7%)	0.26
Precipitating factors				
Prolonged Standing	10(23.8%)	20(23%)	30(23.3%)	0.91
Neck Movement	18(43%)	9(10%)	27(20.8%)	<0.001
Exercise	6(14.3%)	11(12.5%)	17(13.1%)	0.77
Presenting symptoms				
Recurrent presyncope	39(93%)	86(97%)	125(96.2%)	0.177
Syncope	23(54.6%)	37(42%)	60 (46%)	0.1
Recurrent syncope	18(75%)	6(25%)	24(18.4%)	0.001
History of fall	5(12%)	2(2.3%)	7(5.4%)	0.023
Vertigo	4(9.5%)	22(25%)	26(20%)	0.039

Table 4

Comparison of outcomes between CSH +ve and CSH–ve cases during the 1-yr follow-up.

Outcomes	CSH+ve ^a (n = 35)	CSH–ve (n = 88)	p value (sig.<0.05)
Composite outcomes	15(42.8%)	6(6.8%)	<0.001
Syncope	4(11.4%)	0	0.02
Recurrent presyncope	10(29.4%)	6(6.8%)	0.01
Fall	0	0	1.0
Sudden cardiac death	1(2.8%)	0	0.11

CSH, carotid sinus hypersensitivity.

^a 7 patients who underwent pacemaker implantation were excluded from this analysis.

Even though the guidelines recommend CSM for patients older than 40 years, majority of the international studies regarding CSH were carried out in patients older than 50 years. Humm et al had demonstrated that the yield of CSM was negligible below the age of 50 years.³ Hence, we selected patients older than 50 years, for a better diagnostic yield during CSM. Because recollecting symptoms of an event which had occurred more than six months might be difficult, we included only patients who presented within six months of the symptomatology. Among 130 symptomatic patients (cases), 42 patients had CSH. Thus, the prevalence of CSH was 32%. But among 42 patients, only 37 patients had symptoms during massage. So the probable prevalence of carotid sinus syndrome was 28%. CSH was significantly higher in symptomatic patients with syncope and presyncope as compared with the control patients without these symptoms. This was in accordance with multiple studies from western countries which revealed a varying prevalence from 17% to 45% in patients with unexplained syncope^{4,5,7}.

Our study revealed that CSH was more prevalent with male gender, smoking, and advancing age. We were able to demonstrate an increasing prevalence of CSH with advancing age with maximum prevalence seen in patients older than 70 years. Similar associations of age and male sex with CSH were demonstrated by Kerr et al⁷. The major precipitating factor for symptoms was neck movements; this was in accordance with previous studies.¹²

Predominant response to CSM was cardioinhibitory (93%) followed by mixed variety (7%) in our study. Even though old studies

demonstrate this trend,¹² recent published trials show a predominant mixed and vasodepressor response when compared with cardioinhibitory response.^{4,5,7} This difference can be explained by the lack of tilt table testing in this study. Among the presenting symptoms, recurrent syncope and falls were more common in patients with CSH. High-grade AV block was observed in 7% of the patients similar to a previous study.¹³

Symptomatic patients were advised against extreme neck movements, avoidance of tight collars, adequate hydration, and to withhold rate-altering drugs such as calcium channel blockers, beta blockers, and so on during their follow-up. Composite outcomes and individual outcomes such as syncope and recurrent presyncope were significantly higher in patients with CSH. Brignole et al had demonstrated that untreated patients with CSH had recurrent symptoms.¹⁴ Eighteen patients who presented with recurrent syncope were advised pacemaker insertion, but only 7 of them underwent the procedure. During the 1-year follow-up, none of these patients had recurrent syncope. This was in accordance with a study by Claesson et al¹⁵ who demonstrated that pacing decreased symptom recurrence in patients with CSH. There was no significant difference in mortality between the two groups in our study. Hampton et al¹⁶ in a large 12-yr retrospective study with 1500 patients demonstrated that patients with CSH had no survival difference when compared with age-matched general population.

5. Study limitations

A major limitation of our study was the lack of tilt table testing which could have given a better yield of vasodepressor response and inducible syncope during massage. Blood pressure measurement would have been more accurate if beat-to-beat measurement was performed with digital artery photoplethysmography. CSM repeated after giving parenteral atropine would have been an ideal method to assess mixed or vasodepressor responses as asystole itself can produce transient hypotension. The small sample size and our choice of VVI mode as the default pacemaker were also limitations of this study. Even though there are no randomized trials that compared dual chamber pacing and dual chamber sensing (DDD) pacemakers over VVI in CSH, the benefit of DDD pacemakers were demonstrated based on various meta-analysis. As our study

was conducted in a government medical college, we preferred VVI pacemaker over DDD pacemakers due to financial constraints.

6. Conclusion

In conclusion, our study showed that the prevalence of CSH in patients older than 50 yrs with unexplained syncope was high in our population. It was more prevalent in elderly, men, and smokers. Patients with CSH and baseline symptoms developed recurrent syncope during follow-up. Permanent pacemaker implantation prevented recurrence of symptoms. CSM should be a part of routine examination protocol for unexplained syncope.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2019.01.004>.

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