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Cardioinhibitory carotid sinus hypersensitivity predicts an asystolic mechanism of spontaneous neurally mediated syncope

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Aims We correlated the finding of cardioinhibitory carotid sinus hypersensitivity (CSH) with that observed during a spontaneous syncopal relapse by means of an implantable loop recorder (ILR).
Methods and results We included 18 consecutive patients with suspected recurrent neurally mediated syncope and positive cardioinhibitory response during carotid sinus massage (max pause 5.5 ± 1.6 s) who had subsequent documentation of a spontaneous syncope by means of an ILR. They were compared with a 2:1 age- and sex-matched group of 36 patients with a clinical diagnosis of recurrent neurally mediated syncope and negative response to carotid sinus massage, tilt testing and ATP test. Asystole >3 s was observed at the time of the spontaneous syncope in 16 (89%) of CSH patients and in 18 (50%) of the control group ($P = 0.007$). Sinus arrest was the most frequent finding among CSH patients but not among controls (72 vs. 28%, $P = 0.003$). After ILR documentation, 14 CSH patients with asystole received dual-chamber pacemaker implantation; during 35 ± 22 months of follow-up, 2 syncopal episodes recurred in 2 patients (14%), and pre-syncope occurred in another 2 patients (14%). Syncope burden decreased from 1.68 (95% confidence interval 1.66 − 1.70) episodes per patient per year before to 0.04 (0.038–0.042) after pacemaker implant (98% relative risk reduction).
Conclusions In patients with suspected neurally mediated syncope, the finding of cardioinhibitory CSH predicts an asystolic mechanism at the time of spontaneous syncope and, consequently, suggests a possible benefit of cardiac pacing therapy.

Introduction

The correlation of spontaneous syncopal episodes with a cardiac rhythm documented by an implantable loop recorder (ILR) can be regarded as a reference standard when an arrhythmia is suspected to have a role in the genesis of syncope. Therefore, the observations at the time of syncope have become the reference standard to evaluate the diagnostic yield of several diagnostic tests in patients with and without structural heart disease.[1–8] In particular, the predictive value of tilt testing and adenosine triphosphate test has been investigated in patients affected by neurally mediated syncope and a weak or lack of correlation was found between the responses to these tests and the mechanism of spontaneous neurally mediated syncope.[6–8] This somewhat unexpected finding raises concern on the predictive value of carotid sinus hypersensitivity (CSH), which is the oldest and most frequently used test for the diagnosis of neurally mediated syncope. In all previous ILR studies, the patients affected by CSH were excluded from evaluation.

In this study, we prospectively evaluated whether a cardioinhibitory CSH was correlated (and therefore could predict) the clinical outcome and the mechanism of ILR-documented spontaneous syncope.

Methods

Between 1998 and 2006, 35 patients with a clinical diagnosis of suspected neurally mediated syncope and a cardioinhibitory CSH had received an ILR implantation in the hospitals of Lavagna and Reggio Emilia in order to assess the contribution of bradycardia before embarking on cardiac pacing. Of these, 18 patients had a syncopal recurrence documented by ILR and formed the study group. These latter had a maximum pause of 5.5 ± 1.6 s (range

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3.6 − 8.5 s) during the carotid sinus massage. The carotid sinus massage was performed during electrocardiographic and systemic blood pressure monitoring on the right side and on the left side, with the patient in the supine and upright positions. The massage was continued for 10 s. The test was defined as positive if, during the massage, the spontaneous symptoms were reproduced in association with cardioinhibition (with or without concomitant vasodepression). Cardioinhibitory CSH was defined as a maximum ventricular pause >3 s.

The CSH patients were compared with a control group of 36 patients affected by neurally mediated syncope and negative carotid sinus massage, matched 2:1 for age and sex, selected from the ISSUE 2 database[5,6] among those with a negative response to tilt testing and adenosine triphosphate test who had a syncopal recurrence documented by ILR

Both in CSH and controls, in accordance with current guidelines,[9,10] neurally mediated syncope was considered likely when, on the initial evaluation, the following observations were excluded: (1) suspected or definite structural heart disease suggesting a high likelihood of cardiac syncope, i.e. syncope during exercise; overt heart failure; ejection fraction ≤40%; myocardial infarction; hypertrophic cardiomyopathy; dilated cardiomyopathy; significant valvular disease; sinus bradycardia <50 bpm or sino-atrial block; Mobitz I second degree atrioventricular block; Mobitz II second or third degree atrioventricular block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; right bundle branch block pattern with ST-elevation in leads V1–V3 (Brugada syndrome); negative T waves in right pre-cordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia; (2) symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; (3) non-syncopal loss of consciousness (e.g. epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischaemic attack, intoxication, and cataplexy); (4) subclavian steal syndrome.

After ILR implantation, patients and controls were followed quarterly until the first electrographically (ECG) documented syncope. The mechanism of syncope was assigned according to the ISSUE classification[11] by the End-point Committee members who analysed the records of all episodes (MB, CM, RS, AM).

Statistical methods

Comparison between groups was performed with the non-parametric '*U*' test of Mann–Whitney for continuous variables and with Fisher's exact test for proportions, as appropriate. All reported *P*-values are two-tailed and the value <0.05 was considered significant. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves, which were compared using the log-rank test.

Results

The clinical characteristics of 18 CSH patients and 36 controls are listed in *Table 1*.

Asystole >3 s was observed at the time of the spontaneous syncope in 16 (89%) of CSH patients (average longest pause of 9 s[8–18]) and in 18 (50%) of the control group ($P = 0.007$). Sinus arrest (type 1A pattern of the ISSUE 2 classification) was the most frequent finding among CSH patients but not among controls (72 vs. 28%, $P = 0.003$) (*Table 2*). Conversely, controls had a higher prevalence of patterns different from type 1 (*Table 2*). Thus, correlation between induced and spontaneous asystole was 89% (95% confidence interval, 65–99%).

Compared with controls, CSH patients had a short history of syncope, higher prevalence of pre-syncope, hospitalization and cardiac abnormalities. The median time to first syncope recurrence after ILR implantation was longer in CSH patients than in controls (*Figure 1*). There was no difference in length of the asystole documented by ILR between groups.

Follow-up

After ILR documentation of spontaneous syncope, 14 CSH patients with asystole received dual-chamber pacemaker implantation; during 35 ± 22 months of follow-up, a single syncopal episode recurred in 2 patients (14%) after 12 and 23 months respectively and pre-syncope in another 2 patients (14%). One of the two patients who had syncope recurrence was found to have pacemaker malfunction due to ventricular lead fracture. The corresponding actuarial estimate of syncope recurrence was 8% at 1 year and 20% at 5 years. Syncope burden decreased from 1.68 (95% confidence interval 1.66–1.70) episodes per patient per year observed before enrolment to 0.04 (95% confidence interval 0.038–0.042) episodes per patient per year during the 3 years after the pacemaker implant (relative risk reduction 98%, $P < 0.001$).

Two other patients with documented asystole received education on how to avoid recurrences and one of these had pre-syncopal recurrences. One patient with documented high rate atrial fibrillation was treated with drugs and had multiple syncopal recurrences. Finally, one patient with documented sinus tachycardia had no syncope during 82 months of follow-up. Two patients had strokes, one of these was fatal.

Discussion

Electrocardiographic findings in patients with cardioinhibitory CSH

This study shows that a long asystole, mainly due to sinus arrest, is the most frequent finding at the time of spontaneous syncope in patients with cardioinhibitory CSH. In patients with a clinical diagnosis of suspected neurally mediated syncope, the finding of a cardioinhibitory response during carotid sinus massage predicts, with a probability of 89%, that a long asystolic reflex is also present at the time of spontaneous syncope. The finding of progressive sinus bradycardia followed by ventricular asystole (type 1A and 1B of the ISSUE classification[11]) is consistent with the aetiology of neurally mediated syncope.

In the absence of cardioinhibitory CSH, the electrocardiographic findings at the time of spontaneous neurally mediated syncope are heterogeneous with bradycardia or asystole accounting for only approximately one-half of the syncope events. Indeed, a prevalence around 50% was constantly found either in the control patients of this study as well in previous studies in neurally mediated patients including those with positive response to tilt testing or adenosine triphosphate test.[1,5,6]

The relationship between cardioinhibitory CSH and the mechanism of spontaneous, otherwise unexplained, syncope was inferred in an old study[12] where, in patients implanted with a pacemaker designed to detect asystolic episodes, long pauses (≥6 s) were detected in 53% of the patients during 2 years of follow-up.

Table 1 Characteristics of CSH patients and controls at enrolment

	CSH $n = 18$	Control $n = 36$	*P-value*
Mean age, year	68 ± 13	68 ± 12	–
Male gender, *n* (%)	12 (67%)	24 (67%)	–
Syncope events			
Total lifetime episodes	81	312	–
Syncope, median (interquartile range)	4 (3–6)	5 (4–9)	0.07
Interval between first and last episode, median year (interquartile range)	3 (2–5)	5 (4–10)	0.001
Syncope burden, episodes per patient/year (interquartile range)	1.4 (1.0–5.3)	1.1 (0.8–1.4)	0.11
Age at first syncope	68 (54–77)	63 (43–72)	0.31
History of pre-syncope, *n* (%)	13 (72%)	16 (44%)	0.05
Hospitalization for syncope, *n* (%)	13 (72%)	16 (44%)	0.05
Injuries related to fainting, *n* (%)	11 (61%)	21 (58%)	0.54
No warning at the onset of the attack (last and/or previous episode), *n* (%)	12 (67%)	16 (44%)	0.10
Normal electrocardiogram, *n* (%)	12 (67%)	32 (89%)	0.05
No structural heart disease, *n* (%)	12 (67%)	30 (83%)	0.05
Medical history, *n* (%)			
Cardiac disease	6	6	
Hypertension	12	22	
Diabetes	2	3	

We observed some differences in the clinical features of the two groups. CSH patients had a short history of syncope, higher prevalence of pre-syncope, more hospitalizations and cardiac abnormalities. Owing to the fact that the control patients were matched with CSH patients in respect of age and sex, these differences also separate CSH on clinical grounds from the other forms of neurally mediated syncope. The reason for a different time to first syncope recurrence is uncertain.

The effect of cardiac pacing in CSH patients

The finding of asystolic syncope during spontaneous episodes forms the background for the potential benefit of cardiac pacing in CSH patients. Indeed, in this study, cardiac pacing resulted in a 98% reduction of the syncope burden during the following 3 years of follow-up. The effect of pacing in CSH patients measured as syncope burden (0.04 episodes per patient per year) was very similar to that observed in patients without CSH (0.05 episodes per patient/year) in the ISSUE 2 study,[5] suggesting that the efficacy of therapy is similar in the two different clinical situations once the documented spontaneous episode is shown to be due to the same mechanism, i.e. an asystolic pause.

Until now, little evidence of efficacy of cardiac pacing exists despite cardiac pacing being widely used in patients with syncope and CSH. Some pre-post comparisons showed fewer recurrences of syncope after pacemaker implant.[13–16] One non-randomized comparative study of patients receiving a pacemaker and untreated patients showed syncope recurrence rates to be lower in paced than non-paced patients.[17] In the only randomized small open study,[18] 32 patients were assigned to the pacemaker arm and 28 to the 'no treatment' group. After a mean follow up of 36 ± 10 months, syncope recurred in 9% of pacemaker group vs. 57 % in the untreated patients ($P < 0.0002$).

The results of this study apply to a population of patients with a high likelihood of being affected by neurally mediated syncope who were identified by relatively straightforward initial evaluation and clinical features, in accordance with the recommendations of current guidelines.[9,10] The diagnosis of neurally mediated syncope was largely unrelated to the finding of CSH which was used to evaluate the role of the cardioinhibitory component of the reflex. It is possible that, when the diagnosis of neurally mediated syncope is less certain or syncope is unexplained, also the predictive value of CSH might be lower. It is well known that specificity of carotid sinus massage is suboptimal and that abnormal responses are also frequently observed in subjects without syncope. For example, an abnormal response was observed in 17–20% of asymptomatic patients affected by various types of cardiovascular diseases,[19] and in 38% of asymptomatic patients with severe narrowing of the carotid arteries.[20] Moreover, in patients with accidental falls and CSH,[21] syncope recurrence burden after pacemaker implant was 0.32 episodes per year, i.e. a frequency of eight times higher than that observed in this study.

Limitations

This study shows that syncope is difficult to predict and about half of the patients with CSH who had undergone ILR implantation, did not have recurrence during the follow-up period. This finding is consistent with the natural history of neurally mediated syncope which shows that even severely symptomatic patients remain asymptomatic for long periods due to an unpredictable recurrence rate. For example, a 33% recurrence rate at 1 year was observed in ISSUE 2 population.[5] Therefore, a longer follow-up would probably have been helpful in order to determine the mechanism of syncope in these other patients. Longer follow-up was limited by the battery longevity of the present ILR generation. Theoretically, these late-recurrent patients could have mechanisms different

Table 2 The mechanism of syncope documented by ILR in 18 CSH patients and 36 controls assigned according to the ISSUE classification[11]

	CSH $n = 18$	Control $n = 36$	*P-value*
Type 1, Asystole. RR pause/s $\geq$3 s	16 (89%)	18 (50%)	0.004
Type 1A, sinus arrest: progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest.	13 (72%)	10 (28%)	0.003
Type 1B, Sinus bradycardia plus AV block: Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate	3 (17%)	3 (8%)	0.31
Type 1C, AV block: sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate	0 (0%)	5 (14%)	0.11
Asystole duration:			
Longest pause (interquartile range), s	9 (8–18)	10 (6–15)	0.72
Total asystolic period (interquartile range), s	18 (12–21)	19 (12–30)	0.89
Type 2, Bradycardia. Decrease of heart rate >30% or <40 bpm for >10 seconds	0 (0%)	3 (8%)	0.54
Type 3, No or slight rhythm variations. Variations of heart rate <30% and heart rate >40 bpm	0 (0%)	8 (22%)	0.04
Type 4, Tachycardia. Increase of heart rate >30% to >120 bpm	2 (11%)	7 (19%)	0.70

from the early-recurrent. However, the baseline characteristics of the patients who did not have ILR recurrence were not significantly different from those who had; in particular, their maximum pause during the carotid sinus massage was 6.7 $\pm$ 2.4 s ($P = 0.12$ vs. ILR positive patients). Moreover, the larger ISSUE 2 study[5] showed no difference between the patients with and without syncopal recurrence.

The study correlated one test with the first ILR documented episode. Reproducibility of spontaneous episodes was not evaluated.

On average, in our departments the carotid sinus massage is performed every year in 375 patients affected by syncope; of these, 97 (26%) are positive, and 45 (12%) show a cardioinhibitory response.[22] Thus, the study group is a selected population representing less than 10% of the total patients with cardioinhibitory CSH evaluated in our departments. Severe carotid sinus syndrome is a widely accepted indication for cardiac pacing and an electrocardiographic documentation is not required in the clinical practice.[9,10] Reasons for implanting an ILR before embarking on cardiac

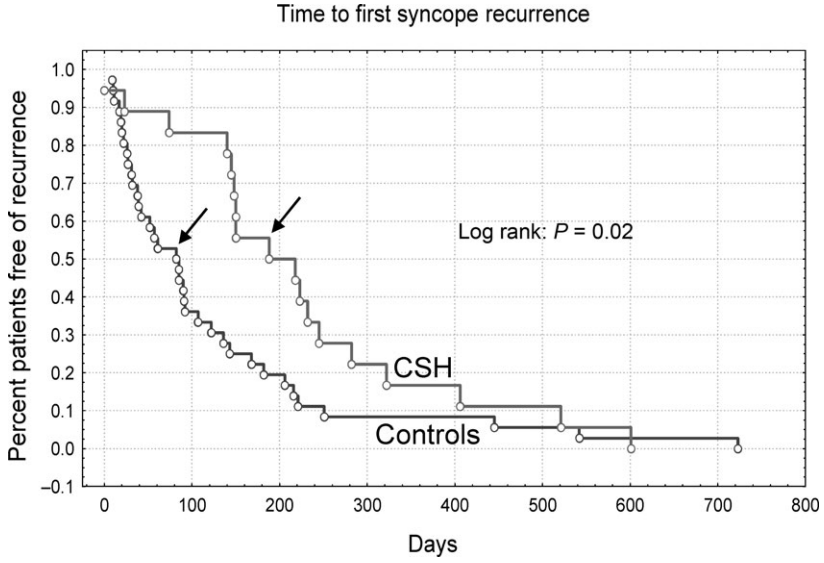

Figure 1 Actuarial estimate (Kaplan–Meier curve) of syncope recurrence in the 18 patients affected by CSH and in the 36 control patients. The arrow indicates the median time to syncope recurrence in the 2 groups which was 188 (interquartile range 142–263) days for CSH patients, and 82 (27–143) days for controls ($P = 0.04$).

pacing in these selected patients included uncertainty of the physician for the clinical diagnosis due to competing abnormalities (i.e. hypotensive syncope) and/or comorbidities and reluctancy of the patient to implant a pacemaker without a definite confirmation of the asystolic nature of the symptoms. Thus, the studied population could not be fully representative of the patients affected by CSH who usually undergo a pacemaker implant.

Conclusions and perspectives

In patients with suspected neurally mediated syncope, the finding of cardioinhibitory CSH predicts an asystolic mechanism at the time of spontaneous syncope. While these data are supportive of the value of carotid sinus massage in the selection of patients who may benefit from permanent pacemaker, only a formal randomized clinical trial should be able to confirm and quantify the exact effect of pacing in these patients.

Conflict of interest: R. Sutton reports having served as a consultant for Medtronic Inc. during the period of this investigation. N. Grovale is employee of Medtronic Italy.

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