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Incidence and predictors of syncope recurrence after cardiac pacing in patients with carotid sinus syndrome☆

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ABSTRACT

Background: Cardiac pacing is the treatment of choice for cardioinhibitory carotid sinus syndrome (CSS), but syncope recurrence occurs in up to 20% of patients within 3 years. The present study aims at assessing incidence and identifying predictors of syncope recurrence in patients receiving pacing therapy for CSS.
Methods: The Syncope Clinics of two large regional hospitals in Northern Italy, both following European Syncope Guidelines, combined to perform this study. Retrospective analysis of 3127 consecutive patients undergoing carotid sinus massage (CSM) was performed 2004–2014. Ten-second supine and standing CSM was systematically assessed in patients aged >40 years with suspected reflex syncope as part of the initial evaluation. Syncope recurrence was investigated in those paced for CSS having >6 months' available follow-up. Data were collected from clinical records and patient interviews.
Results: CSS was diagnosed in 261 patients (8.3%). Pacemakers were implanted in 158, with follow-up data available in 112: 19 (17%) experienced 73 syncope recurrences during a mean follow-up of 89 ± 42 months, yielding an incidence of 0.5 episodes per patient/year. Prodrome, predisposing situations preceding syncope and chronic nitrate therapy were more frequent in patients reporting recurrence. Prodrome and predisposing situations remained independent predictors of post-implantation recurrence on multivariable analysis.
Conclusions: CSS is a frequent cause of syncope, if CSM is performed during the initial evaluation. Most patients treated by pacing remain asymptomatic during long-term follow-up. In those who have recurrence, its incidence is very low. Prodrome and predisposing situations are predictors of post-implantation recurrence, suggesting presence of hypotensive susceptibility.

1. Introduction

Carotid sinus syndrome (CCS) is defined as reproduction of spontaneous syncope by means of carotid sinus massage (CSM) associated with asystole >3 s and/or a fall in systolic blood pressure (BP) of >50 mm Hg or more [1]. CSS is different from carotid sinus hypersensitivity (CSH) in which asystole or BP fall are demonstrated on CSM but the patient is asymptomatic. A highly variable prevalence of CSS is reported in the literature, ranging from 0% up to 40% [2], due to different patient selection, timing of CSM or failure to perform CSM during the work-up.

Cardiac pacing is the treatment of choice for cardioinhibitory (CI) and mixed forms and is a Class IIA recommendation in the European Society of Cardiology (ESC) syncope guidelines [1]; nevertheless, there is still controversy as to the efficacy of this treatment. The evidence supporting this recommendation is considered to be weak, with only four randomized controlled trials [3–6] and a single randomized, double-blind, placebo-controlled trial [7] ever reported, presenting conflicting results. Moreover, syncope recurrence is expected to occur in up to 20% of patients after pacemaker (PM) implantation [8]. According to the available literature, mixed CSS and a positive response to Tilt Testing (TT) are associated with a higher risk of recurrence [9,10], suggesting a hypotensive underlying mechanism.

The aim of the present study was to assess incidence and identify predictors of syncope recurrence in patients receiving pacing therapy for CSS when CSM was performed in patients aged >40 years with suspected reflex syncope as part of the initial evaluation, as recommended by the ESC guidelines on syncope [1]. Two large regional

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hospitals in Northern Italy participated, both following ESC guidelines collected the patients who had been referred for investigation of syncope.

2. Methods

The study population consisted of patients who had received cardiac pacing therapy because of mixed or cardioinhibitory CSS. We retrieved electronic records concerning 3127 consecutive patients who had undergone CSM in the Syncope Units of Careggi Hospital, Florence, and Ospedali del Tigullio, Lavagna, Italy in the period 2004–2014. Patients were referred to the Syncope Unit from the Emergency Department, as inpatients or from out-of-hospital services, because of syncope, pre-syncope or unexplained falls. All patients were evaluated according to the ESC guidelines protocol [1] and CSM was performed in patients aged >40 years with suspected reflex syncope after initial evaluation (which consisted of clinical history, physical examination, standard 12 lead electrocardiogram, blood pressure measurement in supine and upright positions). Clinical history was aimed at assessing characteristics of spontaneous episodes, including presence of vasovagal prodrome (blurring/clouded vision, light-headedness, loss of balance, pallor, sweating, etc.) and the following predisposing situations for reflex syncope: hot and crowded environment, emotional distress (including intense pain, blood and instrumentation), prolonged standing, typical trigger for situational syncope (micturition, defaecation, cough, post-exercise and post-prandial).

CSM was performed according to the ESC guidelines technique [1]: longitudinal massage was applied for 10 s over the point of maximum carotid impulse (between the angle of the jaw and the cricoid cartilage, on the anterior margin of the sternocleidomastoid muscle), on the right and then left side. Patients had supine and then erect CSM, using a motorized footplate tilt table with an angle of 60°. The time interval between massages had to be long enough for baseline heart rate (HR) and BP to be restored. In accordance with the "Method of Symptoms" [11], CSH was diagnosed if CSM elicited abnormal cardioinhibition (asystole ≥3 s) and/or vasodepression (systolic BP fall ≥50 mm Hg); if spontaneous symptoms were reproduced in the presence of CSH, CSS was diagnosed. Asymptomatic CSH was not considered diagnostic owing to its low specificity [12]. A transient ischaemic attack, stroke or a myocardial infarction over the previous three months was a contraindication to CSM. In case of carotid bruit, patients were referred for a Doppler ultrasound; if a carotid stenosis >70% was detected, CSM was not performed. In order to investigate the susceptibility to orthostatic stress, the evaluation was completed by means of TT performed according to the Italian protocol [13]; positive responses were defined according to the VASIS classification (Vasovagal Syncope International Study) [14]. CSM and TT were performed under continuous electrocardiogram and BP monitoring (Task Force® monitor, CNSystems Medizintechnik AG, Graz, Austria). Written informed consent for the procedures was obtained from each participant.

2.1. Treatment and follow-up

Enrolled patients had received a dual-chamber pacemaker. Outcome of the study was recurrence of syncope after pacemaker implantation. Syncopal recurrence was investigated by retrieving clinical records and patient interviews, by telephone or during clinic visits.

2.2. Statistical analysis

Data are reported as a mean ± standard deviation, median with interquartile range or as percentage, as appropriate. The Fisher exact text was used to compare dichotomous variables; the Student *t*-test for unpaired data was used to compare continuous data with normal distribution; the non-parametric Mann–Whitney test for unpaired data was used to compare continuous data with not normal distribution. A multivariable analysis by Cox logistic regression of predictors of syncope recurrence was performed among those variables listed in Table 1 that had a *P* value ≤0.1 at univariable analysis. The hazard

Table 1
Comparison between paced patients with and without syncope recurrence during a 3.8 ± 3.4 year follow-up (min >6 months).

	All patients (n = 112)	Recurrence (n = 19)	No recurrence (n = 93)	*P*
Mean follow-up, months ± SD	71 ± 43	89 ± 42	68 ± 43	0.06
Mean age, years ± SD	77.1 ± 9.7	78.3 ± 6.5	76.9 ± 10.2	0.6
Male sex, n (%)	77 (69)	10 (53)	67 (72)	0.09
Number of syncope before PM, median (IQR)	2 (1;3)	3 (1;3.5)	2 (1;3)	0.3
Number of syncope episodes in the 2 years before evaluation, median (IQR)	2 (1;2)	2 (1;3)	1 (1;2)	0.5
Incidence of syncope episodes in the 2 years before evaluation, n/year	0.91/year	1.03/year	0.88/year	
History of syncope (years), median (IQR)	1 (0.5;4)	1 (1;5.5)	1 (0.5;4)	0.9
Hypertension, n (%)	52 (46.4)	9 (47.4)	43 (46.2)	0.9
Diabetes, n (%)	23 (20.5)	3 (15.8)	20 (21.5)	0.6
Falls, n (%)	21 (18.8)	4 (21.1)	17 (18.9)	0.8
Orthostatic hypotension, n (%)	35 (31.2)	5 (26.3)	30 (32.3)	0.6
Heart disease, n (%)	37 (33.0)	7 (36.8)	30 (32.3)	0.7
Presyncope, n (%)	45 (40.2)	7 (36.8)	38 (40.9)	0.7
Prodrome, n (%)	72 (64.3)	16 (84.2)	56 (60.2)	0.04
Prodrome >10 s, n (%)	29 (25.9)	9 (47.4)	20 (21.5)	0.02
Prodrome <10 s, n (%)	43 (38.4)	7 (36.8)	36 (38.7)	0.9
Predisposing situations for VVS, n (%)	20 (17.9)	6 (31.6)	14 (15.1)	0.08
Hospitalization for syncope, n (%)	29 (25.9)	3 (15.8)	26 (28.0)	0.3
Injuries, n (%)	39 (34.8)	5 (26.3)	34 (36.6)	0.4
Digitalis, n (%)	6 (5.4)	1 (5.3)	5 (5.4)	0.9
ACEi/ARB, n (%)	51 (45.5)	11 (57.9)	40 (43.0)	0.2
β-Blockers, n (%)	24 (21.4)	6 (31.6)	18 (19.4)	0.2
Calcium channel antagonists, n (%)	18 (16.1)	5 (26.3)	13 (14.0)	0.2
Alpha-receptor blockers, n (%)	18 (16.1)	2 (10.5)	16 (17.2)	0.5
Nitrates, n (%)	7 (6.3)	3 (15.8)	4 (4.3)	0.05
Diuretics, n (%)	27 (24.1)	6 (31.6)	21 (22.6)	0.4
Antiarrhythmic drug, n (%)	3 (2.7)	1 (5.3)	2 (2.15)	0.4
Other hypotensive drugs, n (%)	15 (13.4)	3 (15.8)	12 (12.9)	0.7
Abnormal ECG, n (%)	58 (51.8)	10 (52.6)	48 (51.6)	0.9
Atrial fibrillation, n (%)	12 (10.7)	1 (5.3)	11 (11.8)	0.4
Left bundle branch block, n (%)	8 (7.1)	3 (15.8)	5 (5.4)	0.1
Right bundle branch block alone, n (%)	10 (8.9)	1 (5.3)	9 (9.7)	0.3
Right and anterior fascicular block, n (%)	12 (10.7)	1 (5.3)	11 (11.8)	0.7
I degree atrio-ventricular block, n (%)	18 (16.1)	1 (5.3)	17 (18.3)	0.2
Cardioinhibitory CSS, n (%)	81 (72.3)	14 (73.7)	67 (72.0)	0.8
Mixed CSS, n (%)	31 (27.8)	5 (26.3)	26 (28.0)	0.8
Asystole duration, seconds ± SD	7.0 ± 2.5	6.8 ± 1.6	7.1 ± 2.7	0.9
Tilt table test: performed, pts. n (%)	89 (79%)	17 (89%)	72 (77%)	0.3
– of whom positive responses, pts. n (%)	44 (49.4)	9 (53)	35 (48.6)	0.5
– VASIS I, n (%)	19 (21.3)	4 (23.5)	15 (20.8)	0.6
– VASIS II (A + B), n (%)	8 (8.9)	0 (0.0)	8 (11.1)	0.11
– VASIS III, n (%)	17 (19.1)	5 (29.4)	12 (16.6)	0.3

SD, standard deviation; PM, pacemaker; VVS, vasovagal syncope; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor antagonists; CSS, carotid sinus syndrome; ECG, electrocardiogram.