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Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study

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Aims The aim of this study was to determine the long-term effects and determinants of success of cardiac pacing in patients affected by reflex syncope enrolled in the Syncope Unit Project 2 (SUP 2) study. Initial results have validated the effectiveness of a standardized guideline-based algorithm which can be used in clinical practice in order to select suitable candidates for cardiac pacing.

Methods and results In this prospective, multicentre, observational study, patients aged >40 years, affected by severe unpredictable recurrent reflex syncope, underwent carotid sinus massage (CSM), followed by tilt testing (TT) if CSM was negative, followed by implantation of an implantable loop recorder (ILR) if TT was negative. Those who had an asystolic response to one of these tests received a dual-chamber pacemaker. Of 281 patients who met the inclusion criteria, 137 (49%) received a pacemaker and were followed up for a mean of 26 ± 11 months: syncope recurred in 25 (18%) of them. At 3 years, the actuarial syncope recurrence rate was 20% [95% confidence interval (CI) 12–30] and was significantly lower than in 142 patients who did not receive a pacemaker and were observed by means of an ILR [43% (95% CI 29–57), $P = 0.01$]. The 3-year recurrence rate was not different among 78 CSM+, 38 TT+, and 21 ILR+ patients, whereas it was lower in 20 patients with negative TT [5% (95% CI 0–15)] than in 61 patients with positive TT [24% (95% CI 10–38)].

Conclusion The benefit of cardiac pacing is maintained at 3 years, irrespective of the index diagnostic test, and is maximum in patients with negative TT.

Clinical trial registration URL: http://www.clinicaltrials.gov. Unique identifier: NCT01509534.

Keywords Syncope • Cardiac pacing • Reflex syncope • Neurally mediated syncope • Carotid sinus syndrome • Tilt testing • Implantable loop recorder

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What's new?

- Initial results of SUP 2 study have validated the short-term effectiveness of a standardized guideline-based algorithm which can be used in clinical practice in order to select suitable candidates for cardiac pacing. According to that algorithm, cardiac pacing can be offered to patients who have an asystolic response with CSM or with TT or the documentation of an asystolic pause by means of an ILR.
- The present study showed that the effectiveness of the guideline-based algorithm and the benefit of cardiac pacing are maintained up to 3 years. The benefit of pacing was irrespective of the index diagnostic test but it was influenced by the results of TT.
- In patients with negative TT, the recurrence rate was very low, being 5% at 3 years. In patients with a positive TT, the probability of recurrence of syncope within 3 years was 23% in patients with asystolic tilt and 27% in patients with mixed or vasodepressor tilt response, but was lower than in patients who did not receive a pacemaker who showed a recurrence rate of 43%.

Introduction

The aim of this study was to determine the long-term effects and determinants of success of cardiac pacing in patients affected by asystolic reflex syncope enrolled in the Syncope Unit Project 2 (SUP 2) study. Initial results[1] have validated the effectiveness of a standardized guideline-based algorithm which can be used in clinical practice in order to select suitable candidates (see 'Methods' section); the algorithm proved able to identify those patients (about half) who can benefit from cardiac pacing.

Methods

The multicentre, prospective observational SUP 2 study was conducted in 10 Italian structured syncope units[2] selected among those of the network of syncope units certified by the Gruppo Italiano Multidisciplinare per lo studio della Sincope (GIMSI, www.gimsi.it). Patient recruitment started in January 2012 and ended in December 2014. Follow-up ended in June 2015. The study protocol was approved by each Institutional Review Board.

Patient selection

The study included consecutive patients aged ≥40 years affected by severe, unpredictable, recurrent, reflex syncope. Syncopes were defined as 'severe' when they impaired the patient's quality of life (because of high frequency) and their occurrence was 'unpredictable', in that they occurred without, or with very short (<10 s) prodromes (thus exposing patients to risk of trauma). Syncopes were defined as 'recurrent' when the patient had had at least two episodes during the previous year (including the index episode) or three episodes during the previous 2 years (including the index episode). In accordance with the guidelines of the European Society of Cardiology,[3] reflex syncope was considered likely when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Specifically, we excluded patients with: (i) suspected cardiac arrhythmic syncope [inadequate sinus bradycardia (<50 b.p.m.) 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]; (ii) severe structural heart disease and/or significant electrocardiogram (ECG) abnormalities, as defined in *Table 2* of those guidelines[3]; (iii) orthostatic hypotension; and (iv) non-syncopal causes of transient loss of consciousness. Moreover, we excluded patients with (v) reflex syncopes due to reversible causes, e.g. vasoactive drugs, concomitant diseases, etc.

Study protocol

Eligible patients underwent the following sequential algorithm, which was drawn up in accordance with the recommendations of the European Society of Cardiology's guidelines on syncope.[3,4]

- Initially, patients underwent carotid sinus massage (CSM) according to the 'method of symptoms'[3,5,6]; if a diagnosis of cardio-inhibitory (CI) carotid sinus syndrome (CSS) was made, a dual-chamber pacemaker was proposed and follow-up immediately started. In accordance with the 'method of symptoms', CI-CSS was established when spontaneous symptoms (syncope or pre-syncope) were reproduced in the presence of an asystolic pause >3 s. Thus, an asymptomatic CI reflex was not considered sufficient to establish a diagnosis, as this is a frequent finding in the general older population[7]; these patients proceeded to the next step.
- If CSM was negative or the response was vasodepressor (VD), the patient underwent tilt testing (TT) according to the Italian protocol[8]; if a diagnosis of CI form [i.e. Vasovagal Syncope International Study (VASIS) 2B form] was made, a dual-chamber pacemaker was proposed and follow-up immediately started. The Italian protocol[8] consists of 60–70° passive tilting for 20 min or until syncope occurs. Hypotension or pre-syncope is not criteria for tilt-down. If the passive tilt phase did not induce syncope, 0.3 mg sublingual nitroglycerine was administered while the table was maintained in the same position; the test was continued for 15 min after pharmacological challenge. Tilt testing was considered positive if syncope occurred in the presence of hypotension, with or without bradycardia. Positive responses were classified according to the New VASIS classification[9]; VASIS 2B form was defined when an asystole ≥3 s was induced.
- If TT was negative or the response was VD, the patient underwent implantable loop recorder (ILR) implantation and was followed up until a diagnosis was made or the study ended; if a diagnosis of CI form [i.e. type 1 of the International Study on Syncope of Uncertain Etiology (ISSUE) classification[10]] was made during the study period, a dual-chamber pacemaker was proposed and follow-up continued. A diagnosis of CI form was established when patients had syncopal recurrence with a documented asystolic pause >3 s at the time of syncope, or asymptomatic or pre-syncopal episodes with documentation of an asystolic pause >6 s.[11,12]

When a pacemaker was indicated, investigators were advised to use a dual-chamber device with rate hysteresis (allowing minimal ventricular pacing).

Data management and follow-up

Baseline data and data from periodic follow-up examinations were recorded on electronic clinical report forms created by means of the SyncopeWeb platform, which was available to the GIMSI syncope units. SyncopeWeb (D.I.T., ASL 4, Chiavari, Italy), an upgrade of the EGSYS software utilized in previous studies,[13] is a web-based online interactive decision-making system developed to help the physician to follow the diagnostic pathway and the recommendations of the ESC guidelines.

Follow-up visits were performed every 6 months with additional unscheduled visits upon patients' request in case of symptom occurrence.

Objectives

The present study had two primary objectives: to assess the effectiveness of the above pacing algorithm in preventing syncopal recurrences during a follow-up period extended to 3 years and to identify the clinical factors responsible for syncopal recurrences.

Statistical analysis

Continuous data are shown as means ± SDs or medians (25–75th percentile), as appropriate, whereas absolute and relative frequencies were used to describe categorical data. The method of Kolmogorov and Smirnov was used to check the normality of distributions. Continuous variables were compared by one-way ANOVA or a non-parametric Kruskal–Wallis test with post-test, depending on data distribution. Heterogeneity among centres was tested by means of a stratified Cox model. The χ^2 test was used to compare multiple proportions. The differences with a two-sided $P < 0.05$ were indicated. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves, which were compared by means of the log-rank test. Analyses were performed by means of the MedCalc® software (Mariakerke, Belgium).

Results

Of 281 patients who met the inclusion criteria, 137 (49%) finally received a dual-chamber pacemaker (with rate-drop feature in 101 of cases); of these, 78 (57%) had CI-CSS, 38 (28%) had asystolic VASIS 2B response during TT, and 21 (15%) had documentation of an asystolic pause during ILR observation. In CI-CSS, the mean pause was 9.5 ± 6.2 s; this was obtained in the standing position in 65% of cases and supine in 35%. In asystolic (VASIS 2B) TT, the longest pause was 22 ± 16 s; this was obtained during the passive phase in 18 patients and during the nitroglycerine phase in 20 patients. In ILR-documented CI type 1 events, syncopal episodes were found in 17 patients and non-syncopal episodes in the other 4 patients: the longest pause was 13 ± 7 s. Finally, the group of 142 patients who had received an ILR served as a control group. With few exceptions, the populations had fairly similar baseline clinical features. Clinical characteristics are summarized in *Table 1* and the Supplementary material online, *Table*.

Table 1 Clinical baseline characteristics of patients who underwent cardiac pacing

Characteristics	Total (*n* = 137)	Recurrence (*n* = 25)	No recurrence (*n* = 112)
Age, mean (SD), year	73 (11)	72 (14)	73 (10)
Male gender, *n* (%)	82 (60)	15 (60)	67 (60)
Syncope events			
Total events, median (IQR)	4 (3–5)	5 (3–5)	4 (3–5)
Syncopes in the previous year, median (IQR)	2 (2–3)	2.5 (2–3)	2 (2–3)
Syncopes in the last 2 years, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)
Age at first syncope, mean (SD), year	65 (19)	65 (19)	66 (18)
Interval between first and last episode, median (IQR), year	3.3 (1–6)	3.3 (2–5)	3.3 (1–8)
Syncopes without or with prodromes <10 s, *n* (%)	116 (85)	21 (84)	95 (85)
History of pre-syncope, *n* (%)	51 (37)	8 (32)	43 (38)
Hospitalization for syncope, *n* (%)	71 (52)	9 (36)	62 (55)
Injuries related to fainting, *n* (%)			
Major injuries (fractures, brain concussion)	18 (13)	3 (12)	15 (13)
Minor injuries (bruises, contusion, haematoma)	83 (61)	14 (56)	69 (62)
Medical history, *n* (%)			
Structural cardiac abnormalities	28 (20)	7 (28)	21 (19)
ECG abnormalities	27 (20)	6 (24)	21 (19)
Hypertension	69 (50)	12 (48)	57 (51)
Diabetes	24 (18)	1 (4)	23 (20)
Neurological/psychiatric disorders	15 (11)	4 (16)	11 (10)
Concomitant medications, *n* (%)	90 (66)	16 (64)	74 (52)
Angiotensin-converting enzyme inhibitors	45 (33)	7 (28)	38 (34)
Angiotensin-receptor blocker	17 (12)	2 (8)	15 (13)
Beta-blockers	16 (12)	3 (11)	13 (12)
Calcium antagonists	20 (15)	4 (16)	16 (14)
Alpha-antagonists	7 (5)	0 (0)	7 (6)
Diuretics	18 (13)	2 (8)	16 (14)
Nitrates	4 (3)	1 (4)	3 (3)
Psychiatric	7 (5)	0 (0)	7 (6)

IQR, interquartile range.

Table 2 Estimated recurrence rate of syncope, analysed by means of Kaplan–Meier survival curves, in paced and in control patients

Characteristics	Total population with Pm ($n = 137$)	CSS ($n = 78$)	Asystolic (VASIS 2B) TT ($n = 38$)	ILR-documented asystolic episodes ($n = 21$)	Control (no pacing) ($n = 142$)
1-Year recurrence rate (95% CI)	8 (4–12)	9 (3–15)	3 (0–9)	11 (0–25)	21 (13–29)
2-Year recurrence rate (95% CI)	18 (10–26)	16 (6–26)	17 (3–31)	24 (2–46)	33 (23–43)
3-Year recurrence rate (95% CI)	20 (12–30)	16 (6–26)	23 (5–41)	24 (2–46)	43 (29–57)

Overall, TT was performed in 223 patients (81 who subsequently received a pacemaker and 142 controls) and was positive in 118 (53%) patients. In paced patients, in addition to the 38 patients with a VASIS 2B response, 23 patients had a mixed (M) or VD response: these belonged to the CSS group (#11) and the asystolic ILR subgroup (#12); as per protocol, 56 CSS patients did not undergo TT.

Outcome

During the subsequent mean follow-up of 26 ± 11 months, syncope recurred in 25 of 137 patients (18%) who had received a pacemaker. No heterogeneity among centres was found. Pre-syncope occurred in 26 patients. Overall, syncope and/or pre-syncope recurred after pacing in 44 patients (32%). The total number of syncopes decreased from 206 in the year before enrolment (excluding the index episode) to 16 in the year after pacemaker implantation; 39 syncopes occurred during the total follow-up period. Syncope recurrence rates were similar among the CSS, VASIS 2B tilt response, and ILR positive subgroups, but significantly lower than in the 142 patients who did not receive a pacemaker and were observed by means of an ILR; syncope recurred in 43 of these latter during 18 ± 12 months of follow-up (*Table 2* and *Figure 1*). No baseline clinical variable was able to predict syncope recurrence among paced patients (*Table 1*). The probability of recurrence of syncope was lower among patients who had had a negative response during TT than in those who had had a positive response (asystolic or not asystolic) or those who had not undergone TT (*Table 3* and *Figure 2*).

During follow-up, four pacemaker recipients died and one suffered a stroke. No patient had serious adverse events secondary to syncope recurrence. No patient in the ILR group died or suffered major adverse clinical events.

Discussion

The main results of this study are that the effectiveness of the guideline-based algorithm and the benefit of cardiac pacing are maintained up to 3 years. The benefit is irrespective of the index diagnostic test, but is maximum in patients with negative TT.

In TT-negative asystolic reflex syncope patients in this study, the recurrence rate after cardiac pacing was very low, being around 5% at 3 years. A similarly low rate had also been observed in TT-negative patients in the ISSUE 3 sub-study[14]; these rates are similar to that observed in patients paced for intrinsic AV block.[15] Thus, pacemaker therapy can be offered to these patients with the same confidence as it can in patients with intrinsic AV block.

A positive response during TT has recently been interpreted as a marker of hypotensive susceptibility to reflex syncope; this susceptibility, which involves both reduced pre-load and after-load, renders cardiac pacing less effective.[16] In the ISSUE 3 sub-study (Supplementary material online, Table),[14] the recurrence rate in TT-positive asystolic reflex syncope patients was 40% [95% confidence interval (CI) 21–67] at 18 months and was similar to that found in un-paced control patients. In the present study, TT-positive asystolic reflex syncope patients had a better outcome, the recurrence rate at 18 months being 12% (95% CI 4–20), which falls outside the range of confidence of the two studies. In the ISSUE-3 sub-study,[14] the 14 TT-positive patients with an asystolic VASIS 2B response had a recurrence rate of 35% (95% CI 13–75) at 12 months and of 57% (95% CI 24–93) at 21 months; in the present study, the corresponding figures were much lower, outside the range of confidence, being 3% (95% CI 0–6) at 12 months and 17% (95% CI 3–31) at 21 months. The reasons for these contrasting findings are uncertain: a type II error due to the small populations of both studies and/or important differences in inclusion criteria might explain such strikingly different results. Indeed, the SUP 2 population was older than that of ISSUE 3 (73 vs. 64 years), more frequently had the absence of prodromes (85 vs. 54%) and included subgroups (i.e. CSS and VASIS 2B patients) that were not included in ISSUE 3. However, these contrasting results suggest caution in their interpretation. The results of these studies cannot be extended to the general population of patients affected by reflex syncope, and any inference regarding indications for cardiac pacing in different patients should be avoided. A larger randomized trial[17] is currently assessing the real benefit of cardiac pacing in patients with asystolic VASIS 2B response.

The patients who did not perform TT (belonging to the CSS group as per protocol) had an intermediate recurrence rate because we can estimate that about a half of these patients would have had a positive TT and the other half a negative TT response. This finding confirms the utility of performing TT in all CSS patients candidates to cardiac pacing in order to better stratify their risk of recurrence of syncope, as previously suggest by Gaggioli *et al.*[18]

From a practical perspective, when pacing is being considered, the patients with a positive TT should be informed of the probability of recurrence of syncope within 3 years: i.e. 23% in TT-positive VASIS 2B patients and 27% in TT-positive asystolic reflex syncope patients. Nevertheless, we believe that cardiac pacing may still be a clinically

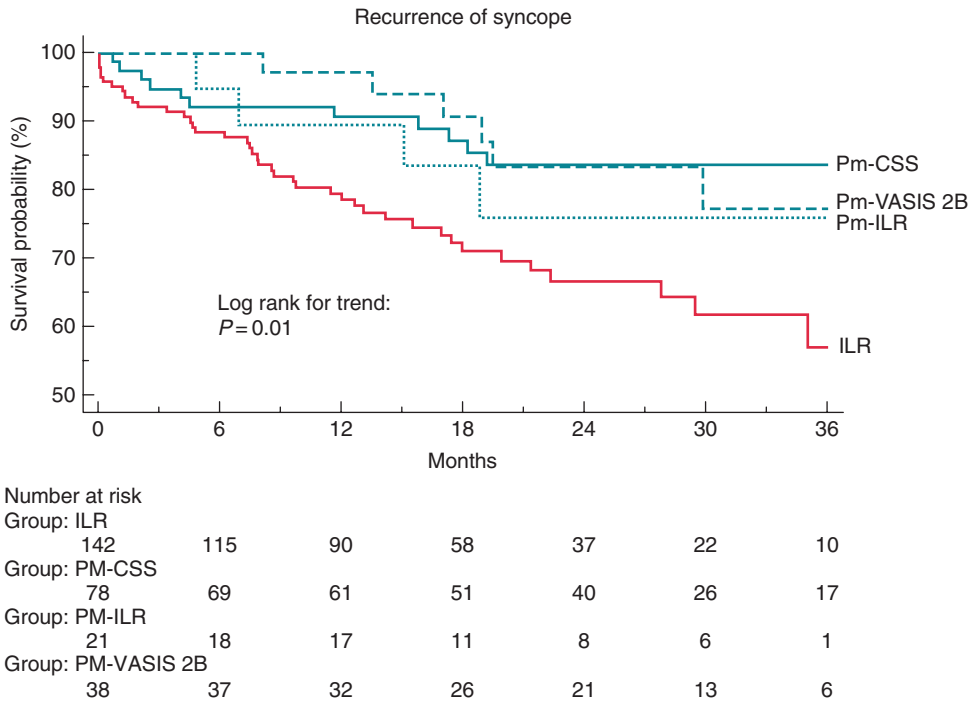


Figure 1 Time to first recurrence of syncope in the three pacemaker subgroups and in the ILR group. Pm-CSS and Pm-VASIS 2B subgroups reached statistical significance compared with the ILR group ($P = 0.003$ and $P = 0.04$, respectively); Pm-ILR subgroup did not ($P = 0.28$). Pm, pacemaker; ILR, implantable loop recorder; CSS, carotid sinus syndrome; VASIS 2B, class 2B of the VAsovagal Syncope International Study classification.

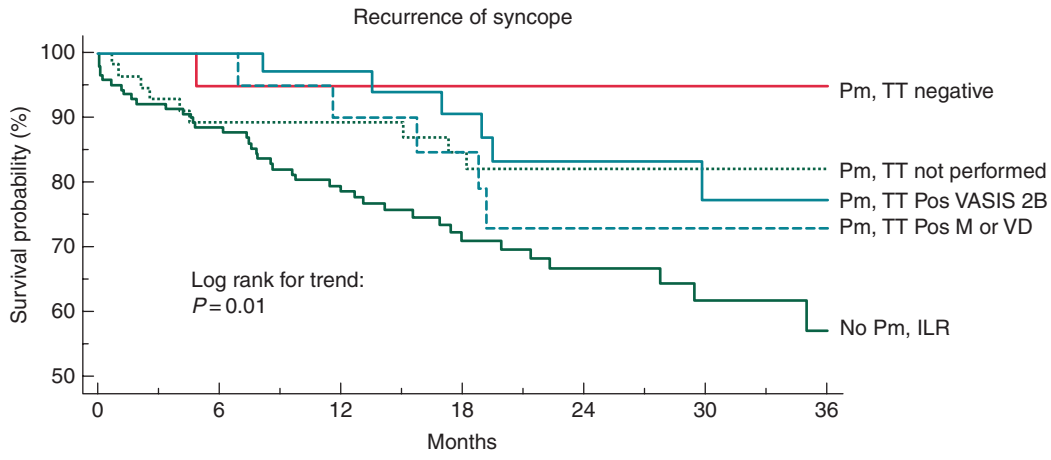
Table 3 Estimated recurrence rate of syncope, analysed by means of Kaplan–Meier survival curves, in paced patients according to TT findings

Characteristics	TT− ($n = 20$)	TT+ VASIS 2B ($n = 38$)	TT+ M or VD forms ($n = 23$)	TT not performed
1-Year recurrence rate (95% CI)	5 (0–10)	3 (0–9)	10 (0–24)	11 (3–19)
2-Year recurrence rate (95% CI)	5 (0–10)	17 (3–31)	27 (7–47)	20 (8–32)
3-Year recurrence rate (95% CI)	5 (0–10)	23 (5–41)	27 (7–47)	20 (8–32)

acceptable solution because the above figures are still much lower than the 43% rate observed in patients who did not receive a pacemaker, provided that pacing is offered to older patients with severe recurrent syncopes with no or minimal prodromes, and that hypotensive susceptibility is counteracted as much as possible. A not too different recurrence rate was observed in paced patients affected by sick sinus syndrome and syncope in the DANPACE trial.[19] Regarding hypotensive susceptibility in TT-positive patients, there is a strong rationale for discontinuing or reducing the dose of hypotensive medications and adopting measures to increase systemic blood pressure. Although large trials are lacking, some small studies[20–22] have shown that TT-positive hypertensive patients with syncope benefit from the withdrawal of hypotensive medication in addition to cardiac pacing. Unfortunately, the present study was not designed to assess the effect of hypotensive medications.

Despite the minimal age for inclusion in the study was 40 years, the actual mean age of paced patients was much higher and only 18 patients (22%) were <65 years old. Contrary to classical vasovagal syncope, the mean age at the first syncope of our patients was 65 years, meaning that the severe forms with atypical presentation with no or short prodromes—which constituted our inclusion criteria—appear in more advanced ages. However, we cannot exclude some patient/physician's reluctance to accept pacemaker implantation in younger ages.

The present study was designed as a pragmatic study, i.e. it was aimed at determining the effects of an intervention in the usual conditions in which it will be applied.[23] The final result of this pragmatic study was that syncopal events decreased from 206 in the year before enrolment (excluding the index episode) to 16 in the year after pacemaker implantation, with 39 events occurring during the total follow-up period. In other words, even the patients with recurrences had no more than one or two episodes during the 26 months following pacemaker implantation, none of which caused serious adverse events. It is likely that other mechanisms, in addition to cardiac



Number at risk

Group: ILR						
142	115	90	58	37	22	10
Group: Negative						
20	18	17	12	11	6	4
Group: not performed						
56	49	43	35	28	18	12
Group: Pos M or VD						
23	20	18	15	9	8	2
Group: Pos VASIS 2B						
38	37	32	26	21	13	6

Figure 2 Probability of recurrence of syncope based on TT response (from lowest to highest probability): pacemaker (Pm) and negative TT, irrespective of their inclusion group; Pm and TT VASIS 2B; Pm and TT M or VD response. In green, patients who did not undergo TT and unpaced control patients (No Pm, ILR) are superimposed. Compared with the No Pm ILR group, both the Pm and negative TT and Pm and positive TT subgroups reached statistical significance ($P = 0.02$ and 0.03, respectively).

pacing, contributed to this reduction. Indeed, a regression-to-the-mean effect was probably involved.[24,25] It is known that syncopal recurrence is not constant, but rather fluctuates over time, peaking at the time of evaluation. Moreover, we cannot exclude some placebo effect of device implantation. However, whatever the causes of the reduced syncopal burden, the study showed the effectiveness of the proposed strategy, which is in accordance with the concept of pragmatic trials.[23]

Conclusion

In conclusion, this study shows the long-term effectiveness of a practical guideline-based diagnostic algorithm which can be used in clinical practice in order to select patients affected by asystolic reflex syncope in whom cardiac pacing is a reasonable solution.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: none declared.

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EP CASE EXPRESS

Twiddler's syndrome with a baroreflex stimulator device

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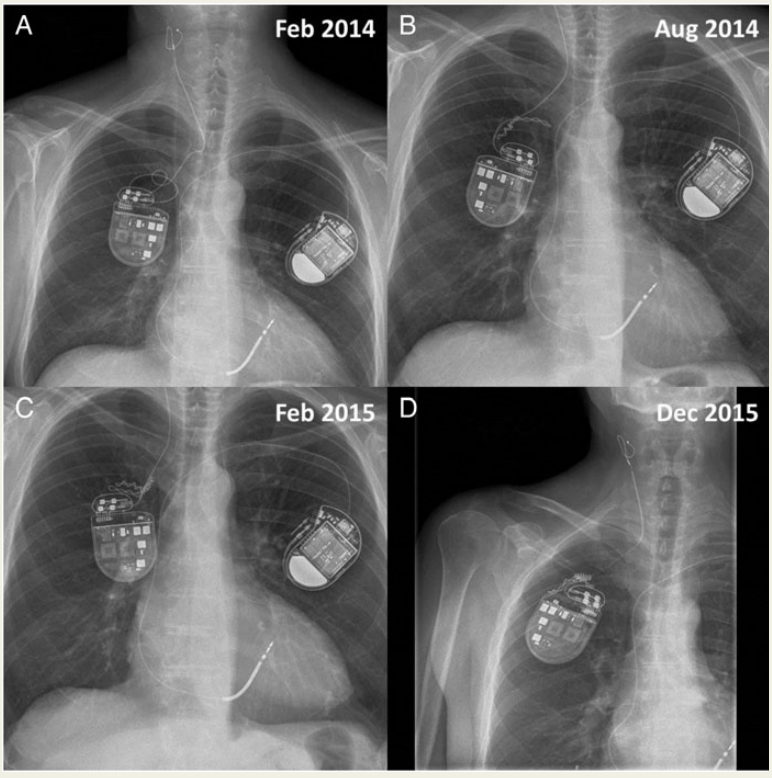
A 48-year-old man with a biventricular ischaemic cardiomyopathy with severe left ventricular ejection fraction impairment (20%) and narrow QRS complexes underwent a single-chamber implantable cardioverter-defibrillator (ICD) implantation for secondary prevention. In December 2014, despite optimal medical therapy, the patient remained symptomatic (NYHA III). An implantation of right baroreflex stimulation device (CVRx®, Barostim neo) was performed to improve the clinical status of the patient by positive action on the autonomic tone. Subsequent chest X-ray successively revealed device and lead twisting on the left and right sides due to Twiddler's syndrome. Curiously, ICD lead and device presented no abnormalities. The patient did not want to confess conscious manipulation of the device and reported 'spontaneous' rotation of the stimulator. Interrogations of the device initially revealed a normal function of the lead, and the patient was asked to stop manipulating the stimulator. Unfortunately, he kept manipulating the device, eventually leading to a lead fracture revealed by elevated lead impedance. The patient declined reintervention. The images illustrate the uncommon phenomenon of Twiddler's syndrome which is not only limited to cardiac pacemaker or defibrillators.



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