Original Article

Benefit of Pacemaker Therapy in Patients With Presumed Neurally Mediated Syncope and Documented Asystole Is Greater When Tilt Test Is Negative

An Analysis From the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)

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Background—In the Third International Study on Syncope of Uncertain Etiology (ISSUE-3), cardiac pacing was effective in reducing recurrence of syncope in patients with presumed neurally mediated syncope (NMS) and documented asystole but syncope still recurred in 25% of them at 2 years. We have investigated the role of tilt testing (TT) in predicting recurrences.

Methods and Results—In 136 patients enrolled in the ISSUE-3, TT was positive in 76 and negative in 60. An asystolic response predicted a similar asystolic form during implantable loop recorder monitoring, with a positive predictive value of 86%. The corresponding values were 48% in patients with non–asystolic TT and 58% in patients with negative TT (P=0.001 versus asystolic TT). Fifty-two patients (26 TT+ and 26 TT–) with asystolic neurally mediated syncope received a pacemaker. Syncope recurred in 8 TT+ and in 1 TT– patients. At 21 months, the estimated product-limit syncope recurrence rates were 55% and 5%, respectively (P=0.004). The TT+ recurrence rate was similar to that seen in 45 untreated patients (control group), which was 64% (P=0.75). The recurrence rate was similar between 14 patients with asystolic and 12 with non–asystolic responses during TT (P=0.53).

Conclusions—Cardiac pacing was effective in neurally mediated syncope patients with documented asystolic episodes in whom TT was negative; conversely, there was insufficient evidence of efficacy from this data set in patients with a positive TT even when spontaneous asystole was documented. Present observations are unexpected and need to be confirmed by other studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01463358.

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Key Words: arrhythmias, cardiac ■ autonomic effect ■ baroreflexes ■ biological pacemakers ■ cardiology ■ nervous system ■ syncope ■ tilt-table test

The randomized, double-blind, Third International Study on Syncope of Uncertain Etiology (ISSUE-3) showed that dual-chamber permanent pacing was effective in reducing the recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope (NMS) documented by implantable loop recorder (ILR).[1] Nevertheless, patients who had received pacing therapy had an estimated syncopal recurrence rate of 25% at 2 years. Previous randomized controlled trials[2–6] enrolled patients with a positive tilt testing (TT). In ISSUE-3, only about half of the patients had a positive test. Because of its sequential design, the study lacked the power

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to make any subgroup analysis. The aim of this study was to investigate the role of TT response in predicting syncopal recurrence in the whole ISSUE-3 population.

Methods

Patient Selection

The multicenter, prospective ISSUE-3 study included patients ≥40 years who had experienced ≥3 syncopal episodes with a clinically assessed neurally mediated mechanism (presumed) in the previous 2 years. NMS was defined as reflex syncope, with the exception of carotid sinus syndrome, with a sufficiently severe clinical presentation to warrant specific treatment. These individuals received an ILR and were followed up. In accordance with the guidelines of the European Society of Cardiology,[7] NMS was diagnosed when the clinical history was consistent with NMS and competing diagnoses had been excluded. Detailed inclusion criteria and study protocol have been published previously.[1,8]

TT was recommended, but its result was not taken into account in the subsequent management. The Italian protocol[9] was recommended, which consists of 60° to 70º passive tilting for 20 minutes or until syncope occurs. If the passive tilt phase did not induce syncope, 0.4-mg sublingual nitroglycerine spray was administered to the patient while the table was maintained in the same position; the test was continued for 15 minutes after pharmacological challenge. TT 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[10] as an asystolic or VASIS 2B form (those with an asystole ≥3 s) or mixed or vasodepressor forms (all the other forms without asystole). TT was considered negative if syncope did not occur.

Study Protocol

After ILR implantation, all patients were followed up quarterly until the first documented syncopal recurrence, occurrence of a diagnostic arrhythmic event, or the end of the study. Events were classified according to the ISSUE classification[11] as: type 1 (asystole >3 s), type 2 (bradycardia), type 3 (slight or no rhythm variations), and type 4 (tachycardia).

For the purpose of this study, the selected group consisted of those patients who had performed a TT and had a diagnosis established by means of ILR documentation. Those with asystolic episodes received a DDD pacemaker that was programmed in rate drop response pacing mode (lower rate of 40/min, drop size of 20 beats with a drop rate of 50/min within a detection window of 1 minute) and were followed up quarterly for 24 months or up to the first episode of recurrence of syncope. The control group consisted of those patients who, despite an established diagnosis, did not receive active treatment; there were 31 asystolic NMS patient (29 of whom assigned to inactive pacemaker arm of the randomized trial) and 14 not asystolic NMS.

The protocol was approved by a research ethics board at each center and each patient provided signed informed consent.

Statistical Analysis

Continuous data are shown as averages±SDs or medians (25th–75th percentile), as appropriate, whereas absolute and relative frequencies were used to describe categorical data. The Shapiro–Wilk test was performed to check the skewness of distribution. Continuous variables were compared by unpaired Student *t* test or the nonparametric Mann–Whitney test, depending on data distribution. Fisher exact test was used to compare proportions. Differences with a P value <0.05 were indicated. The time to the first recurrence of syncope was analyzed by means of Kaplan–Meier survival curves, which were compared using the log-rank test. Analyses were performed by means of SAS version 9.3 (Cary, NC).

Results

Study participants were enrolled from July 2006 to November 2010 and follow-up was concluded in November 2012. During the observation period, 162 of 504 patients had a presumed diagnosis of NMS documented by ILR, which showed an ECG pattern consistent with a reflex mechanism (ie, types 1, 2, and 3 of the ISSUE classification).[11] In another 25 patients, the ILR documented an event that was inconsistent with the diagnosis of NMS (eg, persistent atrioventricular block, brady-tachy syndrome, atrial or ventricular tachyarrhythmias); these patients were therefore excluded from the analysis.

Among the 162 patients with presumed NMS, TT was positive in 76 (during the passive phase in 22 and during drug challenge in 54) and negative in 60 (not performed in 26). Their clinical characteristics are listed in Table 1. Patients with positive and negative TT had similar characteristics; apart from TT response, the 2 groups were indistinguishable. An asystolic response (type 2B of the VASIS classification) predicted a similar asystolic form during ILR monitoring (type 1 of the ISSUE classification), with a positive predictive value of 86% (95% confidence interval [CI], 70%–95%; Figure 1). The corresponding values were 48% in patients with non–asystolic TT (P=0.001 versus asystolic TT) and 58% in patients with negative TT (P=0.001 versus asystolic TT).

Fifty-two patients (26 TT+ and 26 TT–) with asystole documented by ILR received a pacemaker (Figure 2). Apart from TT response, the 2 groups had similar clinical characteristics (Table 2). Syncope recurred in 8 (31%) TT+ and in 1 (4%) TT– patients: it occurred in standing or sitting positions in all and was preceded by a prodrome in 8. At multivariable analysis, TT+ and total number of events were the only independent predictor of syncope recurrence (Table I in the online-only Data Supplement). At the 21st month, the estimated product-limit syncope recurrence rates were 55% (95% CI, 29–85) and 5% (95% CI, 1–32), respectively (P=0.004). The recurrence rate in TT+ patients was similar to that seen in 45 untreated controls (Table 2; Figure I in the online-only Data Supplement), which was 64% (95% CI, 48–80; P=0.75). The 14 TT+ 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; these rates were similar to those observed in 12 non–asystolic TT+ patients (P=0.53). There was a trend toward a longer median time to first syncope recurrence in the 4 asystolic TT+ patients who had syncopal recurrence than in the 4 non–asystolic TT+ patients who had syncopal recurrence: 8 (4–15) and 2 (0–4) months (P=0.1; Figure 3). Finally, 10 patients who had not performed TT had asystole documented by ILR and received a pacemaker: 1 had syncopal recurrence (estimated product-limit syncope recurrence rate at 21 months of 14% [95% CI, 2–67]).

Discussion

The study was able to provide some insight into pacing failure observed in a quarter of patients in the double-blind, randomized, ISSUE-3 trial. Indeed, we found that the benefit of pacemaker therapy in patients with presumed NMS and documented asystole was not substantial in those with a positive TT. Syncope recurrence was independent from the type of response during TT. Although an asystolic response during TT predicted spontaneous asystole, we were unable to show a benefit greater than in patients with non–asystolic responses. Therefore, we speculate that pacing failure was because of hypotensive syncope (either vasodepressor NMS or orthostatic hypotension), which is disclosed by TT susceptibility and which cannot be prevented by cardiac pacing. It is commonly accepted that hypotension

AQ11 **Table 1. Baseline Characteristics and ILR Findings**

Characteristics	Tilt, all (n=136)	Tilt+ (n=76)	Tilt– (n=60)	Tilt Not Performed (n=26)
Age, mean (SD), y	64±13	64±13	64±14	64±15
Men, n (%)	60 (44)	29 (38)	31 (52)	14 (54)
Syncope events				
Total events, median (IQR)	8 (5–14)	10 (5–15)	6 (5–11)	6 (5–10)
≥8 episodes, n (%)	74 (54)	46 (61)	28 (47)	9 (35)
Events in the past 2 y, median (IQR)	4 (3–7)	4 (3–7)	4 (3–7)	4 (3–5)
pisodes, n (%)	90 (66)	48 (63)	42 (70)	17 (65)
Events in the past 2 y without prodromes, median (IQR)	2 (0–4)	2 (0–4)	2 (0–4)	2 (0–4)
Age at first syncope, mean (SD), y	46±23	43±24	51±21	55±17
Interval between first and last episode, median (IQR), y	9 (3–25)	10 (4–35)	9 (3–20)	4 (1–16)
History of presyncope, n (%)	75 (55)	44 (58)	31 (52)	14 (54)
Hospitalization for syncope, n (%)	54 (40)*	29 (38)	15 (25)	14 (54)*
Injuries related to fainting, n (%)				
Major injuries (fractures, brain concussion)	13 (10)	10 (13)	3 (5)	3 (12)
Minor injuries (bruises, contusion, and hematoma)	64 (47)	39 (51)	25 (42)	11 (42)
Typical vasovagal presentation, n (%)	71 (52)	43 (57)	28 (47)	9 (35)
Typical situational presentation, n (%)	27 (20)*	17 (22)	10 (17)	1 (4)*
Without prodromes	73 (54)	39 (51)	34 (57)	14 (54)
Medical history, n (%)				
Structural cardiac abnormalities	15 (11)	5 (7)	10 (17)	4(15)
Atrial tachyarrhythmias	6 (4)	4 (5)	2 (3)	2 (8)
Hypertension	63 (46)	34 (45)	29 (48)	13 (50)
Diabetes mellitus	13 (7)	6 (8)	7 (12)	3 (12)
Neurological/psychiatric disturbances	7 (5)	2 (3)	5 (8)	0 (0)
Concomitant medications, n (%)				
Antihypertensive	65 (48)	32 (42)	33 (55)	12 (46)
Psychiatric	19 (14)	12 (16)	7 (12)	4 (15)
Any other	35 (26)	16 (21)	19 (32)	9 (35)
Mean number of drugs per patient, n (SD)	1.2±1.3	1.1±1.3	1.4±1.3	1.4±1.4
Baseline mean heart rate (SD), beats per minute	69±9	68±9	69±9	71±9
Supine arterial blood pressure (SD), mm Hg	130±18	131±20	129±15	134±16
Standing arterial blood pressure	119±20†	118±22	121±17	128±17†
Echocardiogram				
Left ventricular ejection fraction (SD), %	62±6	62±8	62±6	61±8
Left ventricular diastolic diameter (SD), mm Hg	49±7	48±6	51±8	49±3
Left ventricular systolic diameter (SD), mm Hg	33±7	32±7	34±6	28±5
Any abnormality, n (%)	9 (7)	3 (4)	6 (10)	4 (15)
Tilt testing: positive, n (%)	76 (56)	...	...	...
Asystolic response (VASIS 2B form), n (%)	28 (21)	28 (37)	...	...
Asystole duration in VASIS 2B form (IQR), s	14 (8–24)	14 (8–24)	...	...
Non–asystolic response	48 (79)	48 (63)	...	...
ILR findings				
Time to diagnosis median (IQR), mo	6 (2–12)	6 (2–14)	5 (1–11)	6 (1–11)
ISSUE classification, n (%)				
Type 1 (asystole)	82 (60)	47 (62)	35 (58)	17 (65)
Type 2 (bradycardia)	16 (12)	12 (16)	4 (7)	4 (15)
Type 3 (no/slight rhythm variations)	38 (28)	17 (22)	21 (35)	5 (19)
Asystole duration (IQR), s	10 (6–18)	10 (6–17)	8 (6–19)	7 (4–13)

ILR indicates implantable loop recorder and IQR, interquartile range.
*P=0.05 and
†P=0.06.

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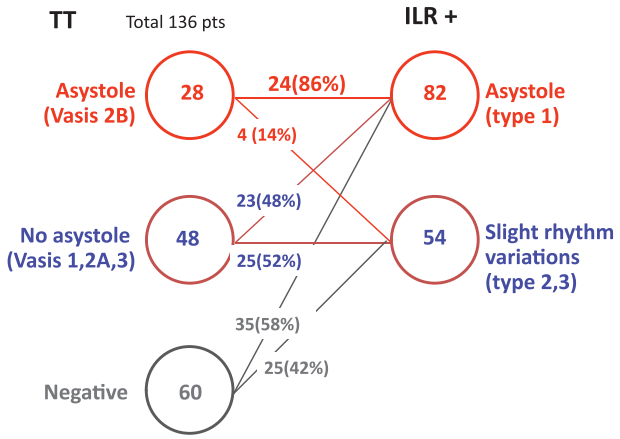

Figure 1. Correlation between tilt test (TT) responses and the mechanism of syncope, as documented by implantable loop recorder (ILR).

plays a major role in all forms of TT-induced NMS and that it precedes (and perhaps triggers) bradycardia and syncope in the vast majority of patients even in those with cardioinhibitory syncope according to the modified VASIS classification.[12,13]

TT+ and TT– patients had similar clinical characteristics, similar outcomes, and similar ECG patterns when an episode was documented by ILR (Table 1). These findings had already emerged from the ISSUE 1 and ISSUE 2 studies[14,15] and other studies in the literature.[16–19] Although the 2 groups were indistinguishable in terms of clinical characteristics, the different effect of pacing prompts us to infer that the underlying mechanism of syncope is different, that is, that a vasodepressive mechanism is dominant in TT+ patients, whereas a cardioinhibitory mechanism is dominant in TT– patients. Thus, the use of TT shifts from that of a tool for clinical diagnosis to a tool for pathophysiological classification, with obvious therapeutic implications. Before the ISSUE-3 trial, cardiac pacing for NMS had only been evaluated in randomized trials which enrolled patients with TT+,[2–6] TT being considered the standard means of diagnosing NMS; no indication for pacing in TT– NMS patients existed. ISSUE-2 enrolled both TT+ and TT– patients but the outcome was not considered separately.[15] ISSUE-3 included both TT+ and TT– patients, and clinical history and initial evaluation were regarded as the standard for diagnosis. By showing that TT– NMS patients are those who benefit most from cardiac pacing, the present study inverts previous knowledge on indications for pacing.

In this subanalysis of ISSUE-3 study, pacemaker therapy in TT+ patients showed no benefit, despite the documentation of a long asystole at the time of a spontaneous event; the syncopal recurrence rate was also similar to the 37% and 57% rates observed at 1 and 2 years in the pacemaker-off arm of ISSUE-3. This result was largely unexpected as previous 5 major multicenter, randomized, controlled trials[2–6] performed on TT+ showed some efficacy of pacing even in the absence of documentation of spontaneous asystole. When pooled together, the 5 trials evaluated 318 patients; syncope recurred in 21% of the paced patients and in 44% of unpaced patients ($P<0.001$). A meta-analysis suggested a nonsignificant 17% reduction in syncope in the double-blind studies and a 84% reduction in the studies in which the control group did not receive a pacemaker.[20] Our study group was small and the confidence interval of the probability of recurrence of syncope at 21st month ranged from 29% to 85%. We cannot therefore exclude a type II error; some benefit of pacing may still be possible, especially in patients with an asystolic TT+ response. What we have observed here in NMS patients is similar to what was observed in patients paced for carotid sinus syndrome. In the study of Gaggioli et al,[21] patients with carotid sinus syndrome and TT+ had a 2.7-fold increased risk of syncopal recurrence compared with carotid sinus syndrome and TT–: at a mean follow-up of 33 months, syncope recurred in 21% of 70 patients versus 9% of 99 patients ($P=0.02$); positive TT was the only independent predictor of syncopal recurrence. Solari et al,[22] in 141 patients affected by carotid sinus syndrome, found that a mixed or vasodepressor response to TT was the only independent predictor of syncopal recurrence (hazards ratio, 1.8; $P=0.01$). In conclusion, in the light of the present study and of the above literature, it is clear that cardiac pacing is effective when TT is negative, whereas syncope can frequently recur when TT is positive.

Limitations

As discussed above, the study group was small with a large confidence interval of the probability of recurrence of syncope.

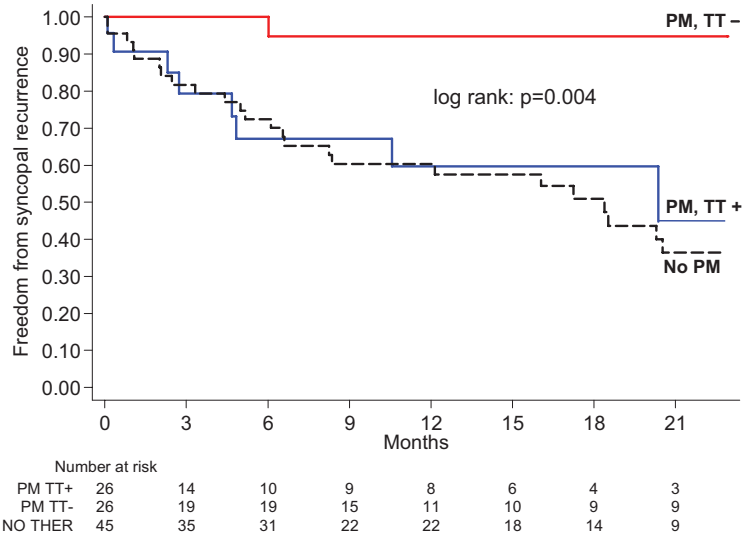

Figure 2. Kaplan–Meier freedom from syncope recurrence after pacemaker therapy in tilt-negative asystolic neurally mediated syncope (NMS) and in tilt-positive asystolic NMS patients. The curve of a control group of untreated patients is also superimposed.

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Table 2. Baseline Characteristics of the 52 Patients With Asystole Documented by ILR Who Received an Active Pacemaker and of 45 Control Patients Who Did Not

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Characteristics	PM, All (n=52)	PM, TT+ (n=26)	PM, TT– (n=26)	Control (n=45)
Age, mean (SD), y	62 (13)	63 (13)	61 (13)	65 (13)
Men, n (%)	27 (50)	10 (38)	17 (65)	15 (33)
Syncope events				
Total events, median (IQR)	7 (4–12)	10 (5–14)	6 (4–10)	8 (5–10)
≥8 episodes, n (%)	25 (48)	17 (65)*	8 (31)*	24 (53)
Events in the past 2 y, median (IQR)	4 (3–5)	4 (3–6)	4 (3–5)	4 (3–6)
≥4 episodes, n (%)	33 (63)	16 (62)	17 (65)	30 (67)
Events in the past 2 y without prodromes, median (IQR)	3 (1–4)	2 (0–4)	3 (1–4)	2 (0–4)
Age at first syncope, mean (SD), y	45 (24)	42 (24)	48 (24)	47 (23)
Interval between first and last episode, median (IQR), y	8 (3–31)	13 (3–38)	6 (2–17)	10 (3–30)
History of presyncope, n (%)	29 (56)	15 (58)	14 (54)	25 (56)
Hospitalization for syncope, n (%)	36 (69)	18 (69)	18 (69)	28 (62)
Injuries related to fainting, n (%)				
Major injuries (fractures, brain concussion)	4 (8)	2 (8)	2 (8)	9 (20)
Minor injuries (bruises, contusion, and hematoma)	22 (42)	11 (42)	11 (42)	21 (47)
Typical vasovagal presentation, n (%)	26 (50)	11 (42)	15 (58)	25 (56)
Typical situational presentation, n (%)	10 (19)	6 (23)	4 (15)	13 (29)
Without prod	27 (52)	11 (42)	16 (62)	29 (64)
Medical history, n (%)				
Structural cardiac abnormalities	6 (12)	1 (4)	5 (19)	4 (9)
Atrial tac ythmias	4 (8)	2 (8)	2 (8)	2 (4)
Hypertension	20 (38)	9 (35)	11 (42)	23 (51)
Diabetes mellitus	5 (10)	1 (4)	4 (15)	5 (11)
Neurological/psychiatric disturbances	3 (6)	0 (0)	3 (12)	0 (0)
Concomitant medications, n (%)				
Antihypertensive	22 (42)	9 (35)	13 (50)	11 (24)
Psychiatric	8 (15)	5 (19)	3 (12)	10 (22)
Any other drugs	12 (23)	5 (19)	7 (27)	4 (9)
Mean number of drugs per patient (SD)	1.3 (1.4)	1.1 (1.3)	1.5 (1.5)	1.0 (1.1)
Baseline mean heart rate (SD), beats per minute	67 (10)	67 (10)	67 (10)	71 (9)
Supine arterial blood pressure (SD), mm Hg	131 (18)	131 (21)	131 (15)	133 (18)
Standing arterial blood pressure	120 (21)	118 (23)	122 (20)	123 (20)
Echocardiogram				
Left ventricle ejection fraction (SD), %	62 (5)	60 (3)	63 (6)	60 (6)
Left ventricle diastolic diameter (SD), mm Hg	50 (8)	52 (5)	49 (10)	50 (6)
Left ventricle systolic diameter (SD), mm Hg	33 (6)	34 (7)	33 (6)	31 (5)
Any abnormality, %	4 (8)	2 (8)	2 (8)	3 (7)
Tilt testing: performed, n (%)	52 (100)	...	...	37 (82)
Positive of those performed, n (%)	26(50)	...	...	24 (65)
Asystolic response (VASIS 2B form), n (%)	14 (27)	14 (54)	...	9 (24)
Asystole duration in VASIS 2B form (IQR), s	17 (12–26)	17 (12–26)	...	15 (10–15)
Non–asystolic response	12 (23)	12 (23)	...	15(41)
ILR findings				
ISSUE classification, n (%)				
Type 1A (asystole because of sinus arrest)	31 (60)†	13 (50)	18 (69)	16 (36)†

(Continued)

Table 2. Continued

Characteristics	PM, All (n=52)	PM, TT+ (n=26)	PM, TT– (n=26)	Control (n=45)
Type 1B (asystole because of sinus brady+AV block)	9 (17)	5 (19)	4 (15)	7 (16)
Type 1C (asystole because of AV block)	7 (13)	4 (15)	3 (12)	7 (16)
Type 1, undefined asystole	5 (10)	4 (15)	1 (4)	1(2)
No type 1 (no asystole)	0 (0)‡	0 (0)	0 (0)	14 (31)‡
Asystole duration (IQR), s	8 (6–13)	10 (6–18)	8 (6–14)	10 (6–20)

AV block indicates atrioventricular block; ILR, implantable loop recorder; IQR, interquartile range; and ISSUE, International Study on Syncope of Uncertain Etiology.
*P=0.02; †P=0.05; and ‡P=0.001.

Some benefit of pacing may still be possible in patients with positive TT response. For example, we observed a 4-fold longer median time to syncope recurrence (8 versus 2 months) in asystolic than in non–asystolic TT+ patients with pacemaker treatment. The same finding was observed in the SYNPACE trial,[6] in which the time to the first syncope recurrence was longer on pacemaker therapy than on placebo in patients who had shown an asystolic (ventricular pause of 13±8 s) response during tilt table testing: 97 versus 11 days (P=0.06). We did not evaluate the effect of cardiac pacing in asystolic TT+ patients who did not achieve the end point of an ILR event documentation; theoretically, these patients could have a better outcome with a pacemaker.

It is not completely clear that all of patients had NMS. It is important to acknowledge that the ISSUE-3 population is by no means the typical NMS type of patients. Many ISSUE-3 patients were old and had atypical presentation with no or subtle prodrome and lack of recognizable triggers. NMS could not be confirmed by TT which was negative in half of the patients. It is possible that these patients simply had an intermittent form of extreme bradycardia (ie, asystole) different from NMS. A great overlap between extrinsic sinus node dysfunction and dysautonomic conditions exists.[23,24] Idiopathic paroxysmal atrioventricular block has been described recently as a different cause of unexplained syncope in patients without structural heart disease.[25]

Compared with TT–, TT+ patients treated with a pacemaker had a longer history of more syncopal episodes during life (but not in the past 2 years) and fewer were men. Albeit marginal, these differences could indicate a different susceptibility to NMS and partly influence pacing results.

Finally, this study suggests a strategy of pacing indication largely based on the result of TT, despite TT being regarded as having questionable diagnostic accuracy and reproducibility.[17,19]

For all the above reasons, the findings of the present study cannot be taken as conclusive; the largely unexpected prompt future studies may show similar results to ours.

Conclusions

In the present study, cardiac pacing was effective in NMS patients with documented asystolic episodes in whom TT was negative; conversely, there was insufficient evidence of efficacy from this data set in patients with a positive TT even when spontaneous asystole was documented. Present observations are unexpected and need to be confirmed by other studies.

Disclosures

Dr Brignole reports receiving modest consultancy fees from Medtronic and being a direct shareholder of F2 solutions. R. Sutton is a consultant to Medtronic, receiving modest fees, and is a paid lecturer for St Jude Medical. Dr Moya reports receiving modest consultancy fees from Medtronic. Dr Deharo reports receiving limited consultant fees

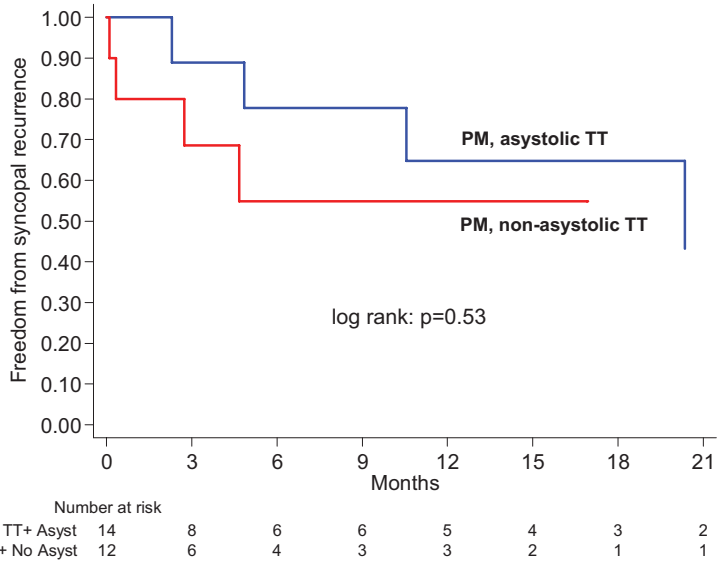

Figure 3. Kaplan–Meier freedom from syncope recurrence after pacemaker therapy in patients who had had an asystolic response during tilt testing (TT; VASIS 2B) and in those who had not.

from Medtronic. Dr Beiras reports receiving limited consultant fees from Medtronic and St Jude Medical. S. Giuli and A. Gentili are em-
AQ15 ployees of Medtronic. The other authors report no conflicts.

References

1. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R; International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation*. 2012;125:2566–2571.
2. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. *Circulation*. 2000;102:294–299.
3. Connolly SJ, Sheldon R, Roberts RS, Gent M. Vasovagal pacemaker study investigators. The North American vasovagal pacemaker study (VPS): a randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol*. 1999;33:16–20.
4. Ammirati F, Colivicchi F, Santini M; Syncope Diagnosis and Treatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation*. 2001;104:52–57.
5. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, MorilloC, Gent M. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II). *JAMA*. 2003;289:2224–2229.
6. Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M. The vasovagal syncope and pacing trial (Synpace). A randomized placebo-controlled study of permanent pacing for treatment of recurrent vasovagal syncope. *Eur Heart J*. 2004:25:1741–1748.
7. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Thomsen PE, Gert van Dijk J, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Masotti G, Moya A, Raviele A, Sutton R, Theodorakis G, Ungar A, Wieling W, Priori SG, Garcia MA, Budaj A, Cowie M, Deckers J, Burgos EF, Lekakis J, Lindhal B, Mazzotta G, Morais J, Oto A, Smiseth O, Menozzi C, Ector H, Vardas P. Guidelines on management (diagnosis and treatment) of syncope—Update 2004. *Europace*. 2004;6,467–537.
8. The Steering Committee of the ISSUE 3 Study. International study on syncope of uncertain aetiology 3(ISSUE 3): pacemaker therapy for patients with asystolic neurally-mediated syncope: rationale and study design. *Europace*. 2007;9:25–30.
9. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, Menozzi C, Raviele A, Sutton R. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace*. 2000;2:339–342.
10. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. *Europace*. 2000;2:66–76.
11. Brignole M, Moya A, Menozzi C, Garcia-Civera R, Sutton R. Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. *Europace*. 2005;7:14–18.
12. Schroeder C, Tank J, Heusser K, Diedrich A, Luft FC, Jordan J. Physiological phenomenology of neurally-mediated syncope with management implications. *PLoS One*. 2011;6:e26489.
13. Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W. Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. *Heart Rhythm*. 2008;5:1695–1701.
14. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D; International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation*. 2001;104:1261–1267.
15. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P. Early application of an Implantable Loop Recorder allows a mechanism-based effective therapy in patients with recurrent suspected neurally-mediated syncope. *Eur Heart J*. 2006;27:1085–1092.
16. Grimm W, Degenhardt M, Hoffman J, Menz V, Wirths A, Maisch B. Syncope recurrence can better be predicted by history than by head-up tilt testing in untreated patients with suspected neurally mediated syncope. *Eur Heart J*. 1997;18:1465–1469.
17. Sheldon R, Rose S, Koshman ML. Comparison of patients with syncope of unknown cause having negative or positive tilt-table tests. *Am J Cardiol*. 1997;80:581–585.
18. Sheldon R, Rose S, Connolly S, Ritchie D, Koshman ML, Frenneaux M. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J*. 2006;27:344–350.
19. Sheldon R. Tilt table testing and implantable loop recorders for syncope. *Cardiol Clin*. 2013;31:67–74.
20. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med*. 2007;120:54–62.
21. Gaggioli G, Brignole M, Menozzi C, Devoto G, Oddone D, Gianfranchi L, Gostoli E, Bottoni N, Lolli G. A positive response to head-up tilt testing predicts syncopal recurrence in carotid sinus syndrome patients with permanent pacemakers. *Am J Cardiol*. 1995;76:720–722.
22. Solari D, Maggi R, Oddone D, Sola[illegible]Croci F, Donateo P, Brignole M. Clinical context and outcome of c[illegible]sinus syndrome diagnosed by means of the "method of symptoms." ~~September 20, 2013. *Europace*. 2013.~~ AQ16
23. Brignole M, Menozzi C, Gianfranchi L, Oddone D, Lolli G, Bertulla A. Neura[illegible]iated syncope detected by carotid sinus massage and head-up tilt test. *Am J Cardiol*. 1991;68:1032–1036.
24. Alboni P, Menozzi C, Brignole M, Paparella N, Lolli G, Oddone D, Dinelli M. An abnormal neural reflex plays a role in causing syncope in sinus bradycardia. *J Am Coll Cardiol*. 1993;22:1130–1134.
25. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L, Ruf J, Guieu R. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. *J Am Coll Cardiol*. 2011;58:167–173.

CLINICAL PERSPECTIVE

Before the International Study on Syncope of Uncertain Etiology (ISSUE-3) trial, cardiac pacing for neurally mediated syncope (NMS) had only been evaluated in patients with a positive tilt test response; no indication for pacing in patients with negative tilt testing existed. The results of the ISSUE-3 trial show that cardiac pacing is effective in presumed NMS patients in whom an asystolic event has been documented and the tilt test is negative (tilt-negative asystolic NMS). The observed AQ17 5% recurrence rate at 21 months with pacing is similar to that observed in patients paced for intrinsic bradycardia. Thus, pacemaker therapy can be offered to these patients with the same confidence as it can in patients with sick sinus syndrome or atrioventricular block. However, caution should be exercised before such therapy is offered to patients with a positive tilt test even if they have had an asystolic response during the test, and asystole has been documented during a spontaneous event (tilt-positive asystolic NMS). Although some benefit may still be possible in terms of reduced syncopal burden, patients should be informed that they will likely have some recurrence of syncope, despite cardiac pacing. Finally, tilt test should no longer be regarded as a test aimed at the diagnosis of NMS, but rather as a useful tool for risk stratification for pacemaker therapy.

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