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CLINICAL RESEARCH

Cardiac pacing in patients with neurally mediated syncope and documented asystole: effectiveness analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) Registry

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Aims 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, probably neurally mediated syncope (NMS), documented by implantable loop recorder (ILR). Analysis in ISSUE-3 was performed according to the intention-to-treat principle. In the present study, we performed an on-treatment analysis, which included additionally those non-randomized patients followed up in the ISSUE registry to evaluate in a better manner the effectiveness of cardiac pacing therapy.

Methods and results Initially, 504 patients received an ILR, 162 (32%) patients had a diagnosis consistent with NMS within a mean observation period of 15 ± 11 months: 99 (19%) patients had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope. Sixty patients affected by asystolic NMS received cardiac pacing therapy and 86 (33 asystolic and 53 non-asystolic NMS) were untreated; 16 patients were lost to follow-up. Paced and unpaced groups had similar clinical characteristics. During subsequent follow-up, syncope recurred in 10 paced (17%) and in 40 non-paced (46%) patients. At 21 months, the estimated product-limit syncope recurrence rates were 27% [95% confidence interval (CI) 15–47] and 54% (95% CI 43–67), respectively ($P = 0.01$). With cardiac pacing, the risk of recurrence was reduced by 57% (hazard ratio = 0.43, 95% CI = 0.2–0.8). Complications of pacemaker therapy were haemothorax at implantation in one patient and lead dislodgement that required correction in two patients.

Conclusion Permanent cardiac pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic possible NMS with a few complications. The study shows that 61% of patients with a diagnosis of NMS made by ILR received a pacemaker but 5.1 ILRs had to be implanted to find one patient who finally had a pacemaker implanted.

Keywords Loop recorder • Syncope • Neurally- mediated syncope • Pacemaker • Cardiac pacing

† The investigators in the ISSUE-3 study are listed in the online supplementary appendix.

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What's new?

- Further proof of the value of pacing in the older neurally-mediated syncope (NMS) patient.
- An indication of the number of implantable loop recorders needed to identify an NMS patient who will benefit from pacing.

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, probably neurally mediated syncope (NMS), documented by implantable loop recorder (ILR).[1,2] Consistent with the rigorous rules of double-blind randomized trials, the analysis was performed according to the intention-to-treat principle and some patients were excluded because they (or their attending physician) refused randomization.

In the present study, we performed an on-treatment analysis, which included additionally all non-randomized patients who were followed up in the ISSUE registry to evaluate in a better manner the effectiveness of cardiac pacing therapy in the overall population. The goal was to give a clinical perspective on the effectiveness of the ILR strategy in NMS patients that the randomized trial could not.

Methods

Patient selection

The multicentre, prospective Third International Study on Syncope of Uncertain Etiology (ISSUE-3) Registry included patients ≥40 years old, who had suffered ≥3 syncopal episodes of possible NMS aetiology in the previous 2 years. Neurally mediated syncope was defined as any form of reflex syncope, with the exception of carotid sinus syndrome, and 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,[3,4] NMS was considered possible when the clinical history was consistent with NMS and competing diagnoses were excluded. Patients with positive and negative tilt table test responses were included. Patients were excluded if they had one or more of the following features: (i) cardiac abnormalities which suggested cardiac syncope (overt heart failure; ejection fraction <40%; old or recent myocardial infarction; hypertrophic or dilated cardiomyopathy; clinically significant valvular disease; sinus bradycardia <50 b.p.m. or sino-atrial block; Mobitz I second-degree atrioventricular (AV) block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; Brugada syndrome; arrhythmogenic right ventricular cardiomyopathy); (ii) symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; (iii) non-syncopal loss of consciousness (e.g. epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischaemic attack, intoxication and cataplexy).

Study protocol

After ILR implantation, all the 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[5] as: type 1 (asystole >3 s), type 2 (bradycardia), type 3 (slight or no rhythm variations), and type 4 (tachycardia).

The following ILR findings were considered consistent with a diagnosis of NMS:

- Asystolic syncope >3 s (possible NMS)
- Non-syncopal asystole >6 s (possible NMS)
- Syncope and progressive intermittent bradycardia (possible mixed NMS)
- Syncope and no or slight rhythm variations (possible hypotensive NMS or orthostatic hypotension).

The patients with NMS were subdivided into two distinct groups: those with asystolic NMS who received cardiac pacing therapy, and a control group consisting of those patients who did not receive cardiac pacing therapy for any reason (e.g. asystolic NMS patients assigned to the inactive pacemaker arm of the randomized study, patient's or physician's refusal of pacemaker treatment and non-asystolic forms of NMS). The patients were followed up quarterly for 24 months or up to the first episode of recurrence of syncope.

The protocol was approved by a research ethics board at each centre and each patient provided signed informed consent. The full study protocol has been previously published,[6] along with the results of the randomized trial.[1]

Statistical analysis

Continuous data are shown as averages ± SDs or medians (25th–75th percentile), as appropriate, while absolute and relative frequencies were used to describe categorical data. The Shapiro–Wilk test was performed to check the skewness of distributions. The unpaired Student's *t* or the non-parametric Mann–Whitney *U* tests were used to compare continuous variables, depending on data distribution. Fisher's exact test was used to compare proportions. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves, which were compared by using the log-rank test. After testing the proportional hazard assumption, the risk of syncope recurrence was calculated by hazard ratio (HR) obtained by using the univariate Cox model. Analyses were conducted by means of SAS 9.3.

Results

Study participants were enroled from July 2006 to November 2010 and follow-up was concluded in November 2012. Over a mean observation period of 15 ± 11 months, 162 of 504 (32%) patients had a diagnosis consistent with NMS and 99 patients (19%) of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope, thus meeting the ISSUE-3 criteria for cardiac pacing. This shows that 61% of patients with a diagnosis of NMS received a pacemaker but 5.1 ILRs had to be implanted to find one patient who finally had a pacemaker implanted.

Outcome

Follow-up was available for 60 patients affected by asystolic NMS (type 1 of ISSUE classification) treated with cardiac pacing (38 of the randomized ON arm, 8 who crossed-over from the randomized OFF arm, and 14 who refused randomization and had a pacemaker implanted) and for 86 not paced patients (31 of the randomized OFF arm, 2 who refused a pacemaker, and 53 with non-asystolic ILR findings); 16 patients were lost to follow-up. The two groups had similar clinical characteristics (*Table 1*). During follow-up, syncope recurred in 10 paced (17%) and in 40 non-paced (46%)

Table 1 Characteristics of NMS patients who received cardiac pacing therapy and those who did not

Characteristics	Cardiac pacing $n = 60$	No cardiac pacing $n = 86$
Age, mean (SD), and year	63 (13)	64 (13)
Men, no. (%)	30 (48)	35 (41)
Syncope events		
Total events, median (IQR)	7 (5–12)	8 (5–15)
≥8 episodes, no. (%)	28 (45)	49 (57)
Events in the last 2 years, median (IQR)	4 (3–5)	5 (3–8)
≥4 episodes, no. (%)	38 (61)	60 (70)
Events in the last 2 years without prodrome, median (IQR)	2 (0–4)	2 (0–5)
Age at first syncope, mean (SD), and year	47 (23)	48 (21)
Interval between first and last episode, median (IQR), and year	8 (3–24)	9 (3–24)
History of pre-syncope, *n* (%)	35 (56)	46 (53)
Hospitalization for syncope, *n* (%)	41 (66)	49 (57)
Injuries related to fainting, *n* (%)		
Major injuries (fractures, brain concussion)	5 (8)	10 (12)
Minor injuries (bruises, contusion, haematoma)	25 (40)	42 (49)
Typical vasovagal presentation, *n* (%)	28 (45)	44 (51)
Typical situational presentation, *n* (%)	6 (10)	17 (20)
Without prodromes	30 (48)	50 (58)
Medical history, *n* (%)		
Structural cardiac abnormalities	9 (15)	9 (10)
Atrial tachyarrhythmias	4 (6)	4 (5)
Hypertension	25 (40)	43 (50)
Diabetes	5 (8)	9 (10)
Neurological/psychiatric disturbances	3 (5)	1 (1)
Concomitant medications, no. (%)		
Anti-hypertensive	27 (44)	42 (49)
Psychiatric	7 (11)	15 (17)
Any other drugs	20 (32)	18 (21)
Mean number of drugs per patient	1.3 (1.4)	1.2 (1.2)
Baseline mean heart rate, b.p.m.	67 (10)	70 (9)
Supine arterial blood pressure (SD), mmHg	133 (18)	130 (17)
Standing arterial blood pressure	123 (22)	121 (18)
Echocardiogram		
Left ventricle ejection fraction (SD), %	62 (8)	62 (6)
Left ventricle diastolic diameter (SD), mmHg	49 (8)	49 (6)
Left ventricle systolic diameter (SD), mmHg	32 (7)	32 (7)
Any abnormality, %	8 (13)	5 (6)
Tilt testing: performed, no. (%)	51 (82)	73 (85)
Positive of those performed, no. (%)	26 (51)	43 (59)
ILR findings (according to ISSUE classification), no. (%)		
1A	35	17
1B	12	7
1C	7	8
1 undefined	6	1
2	0	13
3	0	38
4A	0	2
Asystole duration in type 1 patients (SD), s	12 ± 10	14 ± 11

IQR, interquartile range.

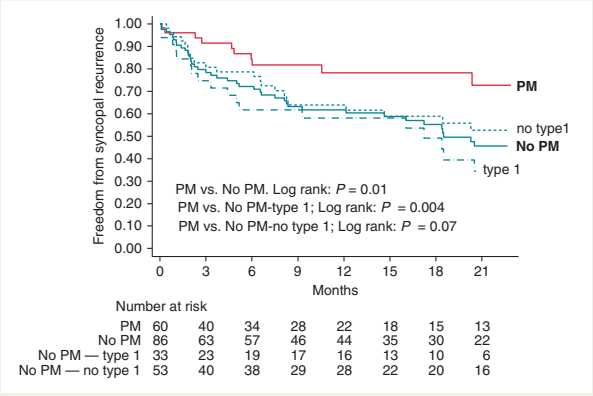

Figure 1 Kaplan–Meier freedom from syncope recurrence in pacemaker therapy (PM) and no pacemaker therapy (No PM) groups. The curve of No PM group is also divided into two curves (intermittent lines) of patients with asystolic NMS (type 1 of ISSUE classification) and with non-asystolic NMS (no type 1).

patients. At 21 months, the estimated product-limit syncope recurrence rates were 27% [95% confidence interval (CI) 15–47] and 54% (95% CI 43–67), respectively ($P = 0.01$) (*Figure 1*).

With cardiac pacing, the risk of recurrence was reduced by 57% (HR = 0.43, 95% CI = 0.2–0.8). In a subgroup analysis, the risk of syncope recurrence in the paced group was reduced by 64% compared with the 33 non-paced patients with asystolic (type 1 of ISSUE classification) NMS [HR = 0.34, (95% CI = 0.15–0.7, $P = 0.004$)] and by 49% compared with the 53 non-paced patients with non-asystolic (no type 1) NMS [HR = 0.51 (95% CI = 0.24–1.07, $P = 0.07$)].

Complications of pacemaker therapy were haemothorax at implantation in one patient and lead dislodgement that required correction in two patients. During the period of the study, two patients died, one per group. Atrial tachyarrhythmias developed in two non-paced patients and AV block in one non-paced patient.

Discussion

This study shows that cardiac pacing maintained similar efficacy in the larger total population of patients enroled in the ISSUE registry than that observed in the randomized double-blind trial:[1] absolute risk reduction of 27% in the present study vs. 32% in the randomized trial and a risk reduction by HR of 57 and 57%, respectively. Pacemaker therapy was well tolerated with a few complications. The benefit of cardiac pacing therapy is reinforced by the finding of an even greater risk reduction compared with the subgroup of patients with asystolic NMS patients who did not receive active pacing therapy despite these patients having received a sham pacemaker. This finding was also observed in the ISSUE-2 study[7] and argues against a placebo effect of the pacemaker, which was supported by other authors.[8–10]

By analysing the overall population, the registry allows the drawing of some clinical perspectives on the effectiveness of the ILR strategy in NMS patients that the randomized trial could not. The use of the ILR to select patients, who could benefit from a pacemaker implantation, is limited by the high number of ILR implants necessary due to the inherent variability of syncope recurrence, itself subject to the principle of regression to the mean. Indeed, patients are systematically more likely to present for medical care when they are at their worst, and many inevitably fluctuate back to a less severe state over time. Consequently, in our study, 61% of patients with a diagnosis of NMS had pacemaker indications but 5.1 ILRs had to be implanted to find a pacemaker indication during an observation period of up to 3 years. Finally, the treatment effect of cardiac pacing in NMS was estimated to be a 57% risk reduction in the recurrence of syncope, thus doubling the number of ILRs needed for the prevention of syncope recurrence in comparison with the number needed to establish a pacemaker indication.

Despite the above limitations, no alternative therapeutic strategy exists. The strategy of implanting a pacemaker in all NMS patients after initial evaluation without waiting for ILR diagnosis would have brought to implant 405 useless pacemakers (342 in patients without syncope recurrence and 63 in patients with hypotensive syncope). This 'shot-gun approach' has failed in two randomized blind trials.[8,9] Apart from a diagnosis of asystolic NMS necessary for selection of good candidates for cardiac pacing, the ILR strategy permits establishment of different diagnoses;[11] in addition to the diagnosis of hypotensive NMS mentioned above (potentially manageable with specific vasoactive therapy), ILR proved to be able to identify 11% of ISSUE-3 patients affected by cardiac arrhythmic syncope, which were mistakenly initially diagnosed as NMS.[12]

The above considerations suggest that ILR use should be restricted to those patients who potentially can benefit most, such as ISSUE-like patients: i.e. those of a relatively high mean age who have a history of recurrent syncope beginning in middle or older age and who suffer frequent injuries, probably owing to the lack of prodrome. Such patients match those defined by the European Society of Cardiology guidelines[4] as high-risk or high frequency of recurrence patients. Young patients, who usually have a more prolonged prodrome before loss of consciousness, were not included in the ISSUE population. Other therapies, e.g. physical counter-pressure manoeuvres,[13] are more desirable in young patients.

Conflict of interest: M.B. reports receiving modest consultancy fees from Medtronic and being a direct shareholder of F2 solution; R.S. is a consultant to Medtronic, receiving modest fees, and is a paid lecturer for St Jude Medical; A.M. reports receiving modest consultancy fees from Medtronic; X.B. reports receiving limited consultancy fees from Medtronic and St Jude Medical; H.H.E. reports being a limited paid lecturer or tutor for Medtronic, St Jude, Boston, Sorin and conducting advisory board activity for MSD; S. Giuli is an employee of Medtronic; the other authors have no financial disclosures to make.

Supplementary material

A full list of investigators is available as supplementary material online.

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