Pacemaker Therapy in Patients with Neuorally-Mediated Syncope and Documented Asystole. Third International Study on Syncope of Uncertain Etiology (ISSUE-3): A Randomized Trial

Running title: Brignole et al.; PM for asystolic reflex syncope

Michele Brignole, MD1; Carlo Menozzi, MD2; Angel Moya, MD3; Dietrich Andresen, MD4; Jean Jacques Blanc, MD5; Andrew D. Krahn, MD6; Wouter Wieling, MD7; Xulio Beiras, MD8; Jean Claude Deharo, MD9; Vitantonio Russo, MD10; Marco Tomaino, MD11; Richard Sutton, DSc12 on behalf of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) investigators*

1Dept of Cardiology, Ospedali del Tigullio, Lavagna; 2Dept of Cardiology, Arcispedale S, Maria Nuova, Reggio Emilia, Italy; 3Dept of Cardiology, Hospital Universitario Vall d’Hebron, Barcelona, Spain; 4Dept of Cardiology, Vivantes Klinikum Am Urban, Berlin, Germany; 5Dept of Cardiology, Hopital de la Cavale Blanche, Brest, France; 6Dept of Cardiology, University of Western Ontario, London, Canada; 7Dept of Cardiology, Academisch Medisch Centrum, Amsterdam, The Netherlands; 8Dept of Cardiology, Hospital Xeral de Vigo, Vigo, Spain; 9Dept of Cardiology, Hopital La Timone Adultes, Marseille, France; 10Dept of Cardiology, Ospedale di Manduria, Taranto; 11Dept of Cardiology, Ospedale di Bolzano, Bolzano, Italy; 12Dept of Cardiology, St. Mary’s Hospital, Imperial College Healthcare NHS Trust, London, UK

*The investigators in the ISSUE-3 study are listed in the Appendix

Correspondence:
Michele Brignole MD
Arrhythmologic Centre, Department of Cardiology
Ospedali del Tigullio
16033 Lavagna, Italy
Tel: +39 0185 329569
Fax: +39 0185 306506
E-mail: mbrignole@ASL4.liguria.it

Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs; [120] Pacemaker; [33] Other diagnostic testing
Abstract:

**Background** - The efficacy of cardiac pacing for prevention of syncopal recurrences in patients with neurally-mediated syncope (NMS) is controversial. We wanted to determine if pacing therapy reduces syncopal recurrences in patients with severe asystolic NMS.

**Methods and Results** - Double-blind, randomized placebo-controlled study conducted in 29 centers in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial. Patients were ≥40 years, had suffered ≥3 syncopal episodes in the prior 2 years. Initially, 511 patients, received a ILR; 89 of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope within 12±10 months and met criteria for pacemaker implantation; 77 of 89 patients were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. The data were analyzed on intention-to-treat principle. There was syncope recurrence during follow-up in 27 patients, 19 of whom had been assigned to pacemaker (Pm) OFF and 8 to PmON. The 2-year estimated syncope recurrence rate was 57% (95% CI: 40-74) with Pm OFF and 25% (95% CI: 13-45) with Pm ON (log rank: p=0.039 at the threshold of statistical significance of 0.04). The risk of recurrence was reduced by 57% (95% CI: 4-81). Five patients had procedural complications: lead dislodgment in 4 requiring correction and subclavian vein thrombosis in 1 patient.

**Conclusions** - Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic NMS. The observed 32% absolute and 57% relative reduction in syncope recurrence support this invasive treatment for the relatively benign NMS.

**Clinical Trial Registration Information** - ClinicalTrials.gov; Identifier: NCT00359203.

**Key words**: pacemakers; syncope; implantable loop recorder
The efficacy of pacemaker therapy for prevention of syncopal recurrences in patients affected by neurally-mediated syncope (NMS) was questioned after two randomized double-blind controlled trials failed to prove superiority of cardiac pacing over placebo of unselected patients with positive tilt testing. The prospective, observational Second International Study on Syncope of Uncertain Etiology (ISSUE-2) showed that the mechanism of spontaneous NMS syncope, documented by Implantable Loop Recorder (ILR), was heterogeneous with asystolic syncope accounting for approximately one-half of the syncope events. While pacing may be potentially effective when asystole is documented at the time of syncope, there is no rationale for the use of pacing in patients without asystole in whom the likely mechanism is a dominant hypotensive reflex. The mechanism of spontaneous NMS documented by ILR is reproducible within patients. In ISSUE-2, the patients with asystolic NMS treated with pacemaker showed a >80% relative risk reduction of syncopal recurrence compared with untreated groups. However ISSUE 2 was not a formal controlled double-blind trial. Consequently, ISSUE 3 was designed to assess the apparent pacing benefit observed in ISSUE 2, but in a randomized controlled trial.

Methods

The International Study on Syncope of Uncertain Etiology (ISSUE-3) was a multi-center, prospective, randomised, double-blind study evaluating the effectiveness of pacing therapy for preventing syncope recurrence in patients with documented spontaneous asystolic NMS.

Patients selection

Patients included in this study were ≥40 years and had suffered, in the prior 2 years, ≥3 syncopal episodes of likely NMS etiology. In this study NMS was defined as any form of reflex syncope, with the exception of carotid sinus syndrome, and a sufficiently severe enough clinical
presentation to warrant specific treatment. These individuals received an ILR and were followed-up (pre-study screening phase).

In accordance with the guidelines of the European Society of Cardiology \(^5,6\), NMS was considered likely when the clinical history was consistent with NMS and competing diagnoses were excluded. Patients with positive and negative tilt table testing were included. Patients were excluded if they had one or more of the following features: (1) 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 bpm or sino-atrial block; Mobitz I second degree atrioventricular block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; Brugada syndrome; arrhythmogenic right ventricular cardiomyopathy); (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 ischemic attack, intoxication, cataplexy). Patients with carotid sinus syndrome and documented symptomatic bradycardia during carotid sinus massage were also excluded because this is an accepted indication for cardiac pacing \(^5,6\). The assessment of the severity of the clinical presentation was based on the definitions of high frequency or high risk provided by those guidelines \(^5,6\). In particular, syncope was defined as very frequent when it altered the quality of life of the patient and at high risk when syncope was unpredictable (absence of premonitory symptoms), thus not being amenable to prevention by standard measures (i.e., physical maneuvers, sitting, squatting, etc) and exposing patients to risk of trauma or occurring during the performance of a ‘high risk’ activity (e.g., driving, machine operation, etc).

**Study design**
Eligible patients for the Pacemaker (Pm) trial (study phase) were those who, during the pre-study screening phase, had syncopal recurrence with documented asystolic pause (sinus arrest or AV block) ≥3 s at the time of syncope, or asymptomatic or presyncopal episodes with documentation of asystolic pause (sinus arrest or AV block) ≥6 seconds (type 1 of the ISSUE classification\(^7\)). Eligible patients underwent dual-chamber pacemaker implantation.

The protocol was approved by a research ethics board at each center and each patient provided signed informed consent. The full study protocol has been previously published\(^8\).

**Randomization and Programming**

Immediately after implantation of a dual-chamber pacemaker, patients were randomized 1:1 to dual-chamber pacing (DDD) with an AV delay sufficient to minimize unnecessary ventricular pacing or sensing without pacing (ODO) with default diagnostic functions. Randomization was made centrally and was assigned automatically to each patient via Internet. The randomization list was blocked per center, with randomly varying block sizes of 2 and 4. The centers were not aware of the block sizes. The pacemaker was programmed by the implanting physician or technician, who were not blinded, whereas treatment allocation was kept blind to patient and clinical follow-up physician. In addition to RCT, eligible patients who for any reasons were not randomized entered into a registry and were followed-up as well as randomized patients in order to have a complete picture of the outcome of eligible patients.

Patients randomized to DDD were programmed in rate drop response pacing mode, a feature of the pacemaker that instituted rapid DDD pacing if the device detected a rapid decrease in heart rate. Based on a post-hoc analysis of spontaneous asystolic episodes documented by ILR in the ISSUE-2 study (9), the protocol specified that the initial rate drop response parameters should be a lower rate of 40/min (for 2 beats) or a drop size of 20 beats with a droprate of 50/min
within a detection window of 1 min and an intervention rate of 90/min for 1 minute.

Outcomes

After pacemaker implantation, all patients were followed-up quarterly for 24 months or up to the first episode of recurrence of syncope by a physician who was blind to the pacemaker mode. The primary study outcome was the comparison of the number of patients with syncopal recurrence in the two study arms according to the intention-to-treat principle. Patients were requested to report syncope episodes as soon as possible after the event occurred. Evidence of syncope was collected from pacemaker and ILR interrogation.

Statistical Analysis

Based on the ISSUE 2 results, this study was designed to have 80% power to detect a 1-year absolute reduction of 25% in the risk of recurrence of first syncope in the treatment arm applying a log-rank test with a two-sided significance level of 0.05 (alpha <0.01 at ad-interim and alpha <0.04 at final analysis). At inception, the study was designed with one-sided significance in keeping with the VPS II trial. At the implementation stage, the Steering committee decided to use two sided testing to increase the rigor of the study design. With a sequential design, the study was planned to be stopped when a total of 27 primary end-point events, irrespective of the study arms, would be reached. An ad-interim analysis was pre-defined at the time of 20 primary end-point events (75% of the total). No center was allowed to recruit more than 10% of the total number of the study population.

During the follow-up, the cumulative number of patients with the primary end-point, but not the relative distribution of these episodes between the two randomized arms was made available to the End-point Committee. Statistical analysis was performed by an independent statistician, who was not involved in the study. Neither the End-point Committee, nor the
Steering Committee were informed of the results before study closure. The primary analysis of the study was planned as a comparison of the cumulative risk of syncope between the 2 treatment groups using a log-rank test. The risk of syncope recurrence was based on hazard ratio obtained by means of the univarate Cox model, using the Breslow method for ties. All randomized patients were analyzed according to the intention-to-treat principle. Thus, all outcomes were attributed to the randomly assigned treatment groups regardless of compliance to assigned treatment.

Results

Screening phase

Initially, 511 patients met the inclusion criteria for the pre-study screening phase and received an ILR implantation. During a mean observation of 12±10 months, syncope recurred in 185 (36%) patients and was documented by the ILR in 141 (28%) patients. Events were classified according to the ISSUE classification as: type 1 (asystole) in 72, type 2 (bradycardia) in 16, type 3 (slight or no rhythm variations) in 37 and type 4 (tachycardia) in 16. Moreover, ECG documentation of non-syncopal (asymptomatic or pre-syncopal) asystolic events of ≥6 seconds was made in 17 patients. Thus, in total 89 patients with asystolic events were eligible for the randomized Pm trial (Figure 1). They had a mean asystolic pause of 11±4 s (range 3-44 s). The patients with syncope had an asystolic pause of 12±10 s and those without syncope an asystolic pause of 10±6 s.

Patients

Study participants were enrolled from April 2007 to April 2011 and follow-up concluded in August 2011. A total of 77 patients of the 89 eligible were randomized from 29 hospitals in Italy (#12 hospitals), Spain (#6), Germany (#3), Canada (#2), United Kingdom (#2), Austria (#1),
France (#1), The Netherland (#1) and Switzerland (#1). Of these patients, 38 were assigned to the Pm ON arm, and 39 were assigned to the Pm OFF arm. Reasons for non-randomization in the remaining 12 patients were: investigator’s decision to implant a pacemaker because of severity of syncope in 6 cases; and patient’s refusal to be randomized in 6 cases. These patients were followed up in the ISSUE registry (Figure 1). The patients’ characteristics were well matched in the randomized arms and in the registry group (Table 1). During follow-up, in the absence of occurrence of the primary end-point, 8 patients assigned to the Pm OFF arm had their Pm reprogrammed to DDD (6 cases) or to VVI 40 bpm (2 cases) because of ILR-documentation of prolonged non-syncopal asystole in 2 patients and investigator/patient’s decision (because of patients’ high risk activity) in the other cases. According to the intention-to-treat principle these patients were analyzed in the Pm OFF arm.

Outcome

A total of 27 patients out of 77 had syncope recurrence during follow-up: of these, 19 patients had been assigned to Pm OFF and 8 to pm ON. The estimated product-limit syncope recurrence rate based on the intention-to-treat analysis was 37% (95% CI: 24-55) at 1 year and 57% (95% CI: 40-74) at 2 years in Pm OFF arm and 25% (95% CI: 13-45) at 1 year and 25% (95% CI: 13-45) at 2 years in the Pm ON arm (log rank: p=0.039 at the threshold of statistical significance of 0.04)(Figure 2). Based on this hazard ratio, the risk of syncope recurrence at 2 years was reduced by 57% (95% CI: 4-81). Asystolic pauses were documented during the study period in 8 patients assigned to Pm OFF arm and in 2 of these the documented pauses were responsible for syncope.

None of the 9 patients who refused randomization whose follow-up was available had syncope during 14±8 months of observation.
Adverse events

One patient died due to cancer. Five patients had procedure-related complications: right ventricle lead dislodgment in 2 patients, right atrial lead dislodgment in 2 patients and subclavian vein thrombosis in 1 patient. No patient had severe adverse events as consequence of recurrence of syncope.

Discussion

The main finding of this study is that dual-chamber permanent pacing is effective in reducing the recurrence of syncope in severe NMS patients ≥40 years in whom a long asystolic pause (11 s mean) has previously been documented by use of ILR. The observed 32% absolute and 57% relative reduction in syncope recurrence support the use of this invasive treatment for the relatively benign NMS in this circumstance. The overall strategy of using an ILR, with the consequent relatively certainty regarding mechanism, likely contributed to the positive findings.

In the ISSUE-2 study, the estimated 2-year syncope recurrence rate was 12% in pacemaker patients and 41% in untreated patients with an absolute risk reduction of 29% and a relative risk reduction of 80% (95% CI 45–93). The results of the present study are comparable in the magnitude of pacing benefit and are more convincing given the double-blind randomized controlled nature of the current study compared to the observational results in ISSUE2.

A comparison of this study with previous randomized double-blind trials is somewhat difficult because of important differences in study design, largely focused on patient selection. The Second Vasovagal Pacemaker Study (VPS II) included 100 unselected patients with a typical history of vasovagal syncope and a positive tilt test; follow-up was shorter. The relative risk reduction in syncope recurrence with DDD pacing was 30% (95% CI: −33 to 63; p=0.14)
compared with 57% in the present study. VPS II was designed and conducted at the beginning of
the ILR era when the mechanism of spontaneous NMS was not completely understood. Since we
know from ILR experience that about half of spontaneous neurally-mediated episodes are
asystolic in nature, we can expect that the relative risk reduction observed in VPS II would have
been doubled up to 60% if only the patients with asystolic syncope were included as was the case
in ISSUE-3. The 60% figure is comparable to what we found in ISSUE-3. The SYNPACE trial\(^2\)
enrolled 29 unselected patients with positive tilt table testing. The trial was prematurely
interrupted and greatly underpowered. Although SYNPACE was unable to show a benefit of
pacemaker over placebo, the time to first syncope recurrence was longer with pacemaker therapy
than with placebo in the 15 patients who had shown an asystolic (ventricular pause of 13 ± 8 s)
response during tilt table testing: 97 vs 11 days, \( p = 0.06 \). No difference was found in the patients
with a non-asystolic response. Therefore, in the light of the ISSUE trials results, our
interpretation of the above findings is that the efficacy of pacemaker therapy has been hampered
by the difficulty in identifying the relative contributions of vasodepression and
bradyacardia/asystole in patients with undocumented spontaneous syncope. ISSUE-2 and now
ISSUE-3 demonstrate that when spontaneous syncope is documented to be associated with
asystole, pacemaker therapy is beneficial. However, even in this situation, the importance of an
associated hypotensive component is suspected in those patients since 25% of Pm ON arm had
syncopal recurrence despite pacemaker therapy.

In the randomized open-label VASIS-PM\(^{10}\) and SYDIT\(^{11}\) trials NMS patients were
selected on the basis of a positive cardioinhibitory (mostly asystolic) response during tilt table
testing. Apart from the use of tilt-table induced bradycardia to select subjects, the population of
these 2 open trials had characteristics that were similar to those of the present study. In the
VASIS-PM study, syncopal recurrence rate in the no treatment arm was 50% at 2 years, which is similar to the 57% observed in the present study. The control patients in the SYDIT trial were treated with beta-blockers. Syncopal recurrence at 2 years in pacemaker arm was 6% in VASIS-PM and 7% in SYDIT, much lower than that observed in the present study. Any open-label trial has the potential for bias in reporting and assessment of outcomes. However, in light of the ISSUE-3 trial results, it seems that the induction of an asystolic NMS during tilt table testing can predict the efficacy of pacemaker therapy albeit to a lesser extent than that expected from VASIS-PM results. Overall, the value of bradycardia induced during tilt-table testing in predicting pacing benefit must remain uncertain pending future studies.

Finally in the randomized open-label pilot VPS I 12, which included unselected patients with a typical history of vasovagal syncope and a positive tilt table test, syncope recurred in 22% of paced and 70% of non-paced patients with most episodes occurring within the first 6 months. This speaks to a combination of physiologic effect as demonstrated in the blinded portion of the study, and the expectation effect that may be an aspect of open labeled studies 13.

The fact that pacing is effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be undertaken in the clinical context of a benign condition (in terms of mortality), which frequently affects young patients. Thus, cardiac pacing should be a last choice in highly selected patients affected by severe NMS. In this regard, the ISSUE studies focused on NMS subjects with a relatively high mean age, a history of recurrent syncope beginning in middle or older age and frequent injuries probably due to lack of prodrome. The ISSUE-like patients match those defined by ESC guidelines as high-risk or high-frequency. 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 maneuvers\textsuperscript{14}, are more desirable in young patients. ISSUE patients were also quite different from the populations in VPS I and II\textsuperscript{1,12}. For example, in these trials, the patients were younger (40-46 years in VPS I and 48-51 years in VPS II) and had a higher lifetime burden of syncope (a median of 14-35 in VPS I and a median of 15-20 in VPS II).

How many NMS patients will be candidates for pacemaker therapy based on findings in ISSUE-3? Although a screening log was not kept for the ISSUE 3 trial, we estimated that the patients who met the ISSUE 3 inclusion criteria were 9\% of all patients affected by NMS referred for evaluation\textsuperscript{8}. In the present study, 18\% of these had an asystolic pause $\geq$3 s with syncope or $\geq$6 s without syncope after a mean observation of 12 months and therefore were eligible for pacing therapy. Based on the patient flow shown in Figure 1, 255 patients needed to have an ILR implanted and 38 of them needed to have a pacemaker in order to prevent syncope recurrence in 11 patients. The critical role played by the ILR in screening, albeit in a large number of patients, was the ability to document the cardiac rhythm during spontaneous syncope which would otherwise have been unavailable. Since ILR diagnostic yield is a function of the length of observation, this rate will probably increase by prolonging the ILR follow-up. Indeed, in a recent study\textsuperscript{15}, the diagnostic yield of asystolic events on ILR rose to 40\% when the observation period was prolonged to 4 years.

Limitations

Similarly to all previous trials, we used DDD pacemakers with rate hysteresis algorithms. We are unable to evaluate if the rate-drop response algorithm used in this trial provided an additional benefit to that of a DDD pacemaker without this feature. In an ISSUE-2 substudy\textsuperscript{9} we estimated that the same rate-drop response parameters would have been able to anticipate the onset of intervention pacing in 58\% of patients by a median of 5.7 s.
While first event occurrence is optimal for single or rare serious outcomes, e.g., death or hospitalization, it is not optimal for repetitive relatively benign events such as NMS recurrence. Nevertheless, all randomized trials considered first syncope as the primary outcome of the study. In the case of syncope trials, syncope burden would likely give a better picture of the clinical benefit of pacemaker therapy. For example, in the ISSUE-2 trial, paced patients had only 0.05±0.15 episodes of syncope per year with a relative risk reduction of 87% compared with pre-treatment period. In the study of Sud et al, syncope burden decreased from 2.17 per year to 0.45 per year in patients with likely reflex syncope and from 4.57 per year to 0 per year in the patients in whom intrinsic AV block was most likely the cause of symptoms.

Finally, owing to its sequential design, the study is underpowered to make any subgroup analysis. Future and ongoing studies will investigate whether subgroups of patients benefit more from a pacemaker.

**Sources of Funding:** The study was funded by Medtronic Bakken Research Center. The sponsor had no access to the database until the primary analysis of the study was completed.

**Conflict of Interest Disclosures:** M. Brignole reports receiving modest consultancy fee from Medtronic and being direct shareholding of F2 solutions; R. Sutton is a Consultant to Medtronic receiving modest fees and a paid lecturer for St Jude Medical; A. Moya reports receiving modest consultancy fee from Medtronic; Dr. Blanc reports receiving limited consultant fee from Medtronic and St Jude Medical; Dr. Deharo reports receiving limited consultant fees from Medtronic; Dr. Beiras reports receiving limited consultant fee from Medtronic and St Jude Medical.

**References:**


Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pm ON n=38</th>
<th>Pm OFF n=39</th>
<th>Registry n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (14)</td>
<td>63 (12)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>20 (53)</td>
<td>16 (41)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Syncope events:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total events, median (IQR)</td>
<td>7 (4-12)</td>
<td>8 (5-10)</td>
<td>7 (5-13)</td>
</tr>
<tr>
<td>- Events in the last 2 years, median (IQR)</td>
<td>4 (3-5)</td>
<td>5 (3-6)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>- Events in the last 2 years without prodrome, median (IQR)</td>
<td>3 (1-4)</td>
<td>3 (0-5)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>- Age at first syncope, mean (SD), y</td>
<td>48 (25)</td>
<td>45 (23)</td>
<td>41 (23)</td>
</tr>
<tr>
<td>- Interval between first and last episode, median (IQR), y</td>
<td>8 (3-29)</td>
<td>8 (3-24)</td>
<td>17 (7-43)</td>
</tr>
<tr>
<td>- History of presyncope, n (%)</td>
<td>19 (50)</td>
<td>22 (56)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>- Hospitalization for syncope, n (%)</td>
<td>24 (63)</td>
<td>25 (64)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>- Injuries related to fainting, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major injuries (fractures, brain concussion)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>- Minor injuries (bruises, contusion, hematoma)</td>
<td>15 (39)</td>
<td>18 (46)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>- Typical vasovagal/situational presentation, n (%)</td>
<td>18 (47)</td>
<td>16 (41)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>- Atypical presentation (uncertain), n (%)</td>
<td>20 (53)</td>
<td>23 (59)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>ILR documentation (eligibility criteria):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Syncope and asystole ≥3 s, No. (%)</td>
<td>30 (79)</td>
<td>32 (82)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>- Non-syncopal pause ≥6 s, No. (%)</td>
<td>8 (21)</td>
<td>7 (18)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>- Length of asystole, mean (SD)</td>
<td>10 (9)</td>
<td>12 (9)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Tilt testing: performed, No (%)</td>
<td>33 (87)</td>
<td>32 (82)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>- Positive of those performed, No. (%)</td>
<td>14 (42)</td>
<td>23 (72)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Structural heart disease</td>
<td>5 (13)</td>
<td>4 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>19 (50)</td>
<td>19 (49)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>4 (11)</td>
<td>4 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Concomitant medications, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anti-hypertensives</td>
<td>18 (47)</td>
<td>12 (31)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>- Psychiatric</td>
<td>4 (11)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Anyotherdrugs</td>
<td>10 (26)</td>
<td>10 (25)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Patients’ flow.

Figure 2. Time to first recurrence of syncope according to the intention-to-treat analysis. The p value was calculated at the threshold of statistical significance of 0.04.
Screening phase

511 met inclusion criteria and received an ILR

Study phase

89 had ECG documentation of:
- syncopal recurrence with asystole ≥3 s (#72)
  or
- non-syncopal asystole ≥6 s (#17)

77 randomized

38 assigned and received Pm ON
39 assigned and received Pm OFF

8 had Pm reprogrammed DDD/VVI in absence of primary end-point

12 refused randomization
3 lost to follow-up
9 followed-up (registry):
  6 implanted Pm
  3 no therapy

38 analysed
39 analysed
9 analysed
Circulation

Freedom from syncopal recurrence

log rank: p = 0.039

Number at risk

<table>
<thead>
<tr>
<th>Pm OFF</th>
<th>39</th>
<th>31</th>
<th>25</th>
<th>21</th>
<th>21</th>
<th>18</th>
<th>15</th>
<th>12</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pm ON</td>
<td>38</td>
<td>32</td>
<td>27</td>
<td>22</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>
Pacemaker Therapy in Patients with Neurally-Mediated Syncope and Documented Asystole. Third International Study on Syncope of Uncertain Etiology (ISSUE-3): A Randomized Trial

Michele Brignole, Carlo Menozzi, Angel Moya, Dietrich Andresen, Jean Jacques Blanc, Andrew D. Krahn, Wouter Wieling, Xulio Beiras, Jean Claude Deharo, Vitantonio Russo, Marco Tomaino and Richard Sutton

Circulation. published online May 7, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/05/07/CIRCULATIONAHA.111.082313

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2012/05/07/CIRCULATIONAHA.111.082313.DC1
http://circ.ahajournals.org/content/suppl/2013/10/14/CIRCULATIONAHA.111.082313.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
Supplemental Material

Appendix

The following centers and investigators participated in the ISSUE-3 trial:


**Steering committee**: Michele Brignole (Chairman), Dietrich Andresen, David Benditt, Jean Jacques Blanc, Roberto Garcia-Civera, Andrew Krahn, Carlo Menozzi, Angel Moya, Richard Sutton, Panos Vardas, Wouter Wieling.

**End-point committee**: Michele Brignole, Richard Sutton, Carlo Menozzi, Angel Moya.
**Statistical analysis:** Erik Cobo, Universitat Politecnica de Catalunya, Spain; Tiziana De Santo, Medtronic Italia

**Overall study management responsibilities:** Nicoletta Grovale, Silvia Giuli, Medtronic Italy.

**Data management:** electronically web-based by an external company (DEMIURG Clinical Technologies, S.L.L., Barcelona, Spain).
신경매개성 실신 환자 중 무수축을 보이는 환자에서는 심박동기 치료가 효과적이다: ISSUE-3 연구

최 기 준 교수 서울아산병원 심장내과

Summary

배경
신경매개성 실신(neurally mediated syncope) 환자에서 실신의 재발을 예방하기 위한 심박동기의 효과에 대해서는 아직도 이견이 많다. 저자들은 이러한 신경매개성 실신 환자 중 심한 무수축을 보였던 환자들에서 심박동기 치료의 효과를 평가해 보고자 하였다.

방법 및 결과
ISSUE-3 (the Third International Study on Syncope of Uncertain Etiology) 연구는 29개의 센터에서 40세 이상이면서 지난 2년 동안 3번 이상의 실신을 경험하였던 환자를 대상으로 이중맹검 무작위 대조군 연구로 시행되었다. 처음에 511명의 환자에게 삽입형 사변기록기(implantable loop recorder)를 삽입하여 12±10개월 동안 3초 이상의 무수축과 실신을 보였거나 실신을 동반하지 않은 6초 이상의 무수축이 기록되어 심박동기 삽입의 적응증이 되었던 89명을 대상으로 하였다. 89명의 환자들 중, 이 중 77명의 환자를 심박수 하강반응 기능의 양심강(dual-chamber) 조율군과 심박조율 기능을 꺼놓고 감지만 시행한 군으로 무작위 배정하여 intention-to-treat 방법으로 분석하였다.

관찰 기간 동안 27명의 환자에서 실신이 재발하였는데, 이 중 19명이 심박조율을 작동하지 않은 군에서 발생하였고, 8명만이 심박조율군에서 발생하였다. 2년 후의 분석에서 실신의 재발률은 심박조율을 작동하지 않은 군에서 57%, 심박조율군에서는 25%였다 (P=0.039). 결국, 심박수 하강반응 기능을 이용한 심박조율이 실신의 재발을 57% 감소시켰다. 5명의 환자에서 시술 관련 합병증이 있었는데, 4명에서 조율선의 위치 변경으로 교정을 필요로 했고 1명에서는 쇄골하정맥에 혈전이 발생하였다.

결론
양심강 심박조율은 40세 이상이면서 신경매개성 실신과 심한 무수축을 보인 환자에서 실신의 재발을 줄이는 데 효과적이었다. 심박조율의 절대적 위험도 감소율은 32%, 상대적 위험도 감소율은 57%로 신경매개성 실신 환자에서 이러한 치료 방법의 효율성을 입증하였다.
Commentary

과거 2000년대 중반에 두 개의 이중맹검 무작위배정 연구인 VPS II(Second Vasovagal Pacemaker Study)와 Synpace(thes vasovagal Syncope and pacing) 연구에서 는 경사테이블 검사에서 양성을 보인 신경매개성 실신 환자에서의 심실 예방에 대한 심박동기의 유용성을 입증하는 데 실패하였다. 반면 전향적 관찰연구인 ISSUE-2 연구에 따르면 신경매개성 실신 환자에서 삽입형 사건기록기 결과를 보면 절반 정도의 환자에서 실신과 동반된 무수축 소견을 보였고, 이러한 실신의 기전은 같은 환자에서 반복적으로 재현성 있게 관찰되었다. 그리고 ISSUE-2 연구에서 무수축과 동반된 실신 환자에서는 심박동기 치료로 실신의 재발률을 80% 정도 감소시켰다. 하지만 ISSUE-2 연구는 이중맹검 연구가 아니기에 전향적 이중맹검 무작위배정 연구인 ISSUE-3 연구를 시행하게 되었다.

이번 ISSUE-3 연구 결과, 양심강 심박조율을 40세 이상의 신경매개성 실신 환자 중에 삽입형 사건기록기를 이용하여 심한 무수축이 관찰된 환자에서 심실의 재발률을 줄이는 데 효과적인 결과를 보여주었다. 또한, 최근 발표된 다른 연구에서는 원인을 밝히지 않은 실신 환자에서(대부분이 신경매개성 실신 환자일 가능성이 높음) ATP 테스트를 시행하여 10초 이상의 심정지를 보인 환자군에서 심박동기 치료가 실신 재발을 75% 정도 줄이는 아주 효과적인 치료방법으로 보고되었다. 따라서 신경매개성 실신 환자에서의 심박동기 치료의 유용성은 환자군을 어떻게 선별할지에 효과 여부를 결정하는 데 중요하다는 결론을 내릴 수 있다. 단순히 경사테이블 검사에서 양성인 실신 환자군에서는 심박동기 치료가 실신 재발의 예방 효과를 보이지 못했고, 본 연구에서와 같이 삽입형 사건기록기를 이용하여 심한 무수축을 보였거나, 다른 연구에서 보고된 것처럼 ATP 테스트를 시행하여 10초 이상의 심정지를 보인 환자군에서의 심박동기 치료는 실신 재발을 75-80% 정도 줄이는 효과적인 치료방법으로 나타났다. 그러므로 신경매개성 실신 환자 중 삽입형 사건기록기나 ATP 테스트를 이용하여 환자군을 잘 선별한다면 심박동기 치료가 도움이 되는 환자군을 선택할 수 있었다. 또한, 이러한 결과는 VASIS-PM(Vasovagal Syncope International Study) 연구나 SYDIT(Syncope Diagnosis and Treatment study) 연구에서 경사테이블 검사 양성 환자군 중 cardioinhibitory 유형의 양성 환자군에서는 심박동기 치료가 대조군에 비해 실신의 재발을 줄일 수 있었다는 연구 결과와도 어느 정도 공통점을 보여준다.

하지만 본 연구에서도 25%의 환자에서는 심박동기 치료에도 불구하고 실신이 재발하였는데, 이는 심박동기 치료만으로는 서맥이나 심정지와 동반되는 혈압_drop을 예방하지 못하기 때문으로 설명할 수 있다.

References


Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole

Third International Study on Syncope of Uncertain Etiology (ISSUE-3)

A Randomized Trial

Michele Brignole, MD; Carlo Menozzi, MD; Angel Moya, MD; Dietrich Andresen, MD; Jean Jacques Blanc, MD; Andrew D. Krahn, MD; Wouter Wieling, MD; Xulio Beiras, MD; Jean Claude Deharo, MD; Vitantonio Russo, MD; Marco Tomaino, MD; Richard Sutton, DSc; on behalf of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators

Background—The efficacy of cardiac pacing for prevention of syncopal recurrences in patients with neurally mediated syncope is controversial. We wanted to determine whether pacing therapy reduces syncopal recurrences in patients with severe asystolic neurally mediated syncope.

Methods and Results—Double-blind, randomized placebo-controlled study conducted in 29 centers in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial. Patients were ≥40 years, had experienced ≥3 syncopal episodes in the previous 2 years. Initially, 511 patients, received an implantable loop recorder; 89 of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope within 12±10 months and met criteria for pacemaker implantation; 77 of 89 patients were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. The data were analyzed on intention-to-treat principle. There was syncope recurrence during follow-up in 27 patients, 19 of whom had been assigned to pacemaker OFF and 8 to pacemaker ON. The 2-year estimated syncope recurrence rate was 57% (95% CI, 40–74) with pacemaker OFF and 25% (95% CI, 13–45) with pacemaker ON (log rank: \( P = 0.039 \) at the threshold of statistical significance of 0.04). The risk of recurrence was reduced by 57% (95% CI, 4–81). Five patients had procedural complications: lead dislodgment in 4 requiring correction and subclavian vein thrombosis in 1 patient.

Conclusions—Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope. The observed 32% absolute and 57% relative reduction in syncope recurrence support this invasive treatment for the relatively benign neurally mediated syncope.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359203.

(Circulation. 2012;125:2566-2571.)

Key Words: pacemakers • syncope • implantable loop recorder

The efficacy of pacemaker therapy for prevention of syncopal recurrences in patients affected by neurally mediated syncope (NMS) was questioned after 2 randomized, double-blind, controlled trials failed to prove superiority of cardiac pacing over placebo of unselected patients with positive tilt testing.\(^1\,\,^2\) The prospective, observational Second International Study on Syncope of Uncertain Etiology (ISSUE-2)\(^3\) showed that the mechanism of spontaneous NMS syncope, documented by implantable loop recorder (ILR), was heterogeneous with asystolic syncope accounting for
approximately one-half of the syncope events. Although pacing may be potentially effective when asystole is documented at the time of syncope, there is no rationale for the use of pacing in patients without asystole in whom the likely mechanism is a dominant hypotensive reflex. The mechanism of spontaneous NMS documented by ILR is reproducible within patients. In ISSUE-2, the patients with asystolic NMS treated with pacemaker showed a >80% relative risk reduction of syncopal recurrence in comparison with untreated groups. However, ISSUE-2 was not a formal controlled double-blind trial. Consequently, ISSUE-3 was designed to assess the apparent pacing benefit observed in ISSUE-2, but in a randomized controlled trial.

Clinical Perspective on p 56

Methods
The International Study on Syncope of Uncertain Etiology (ISSUE-3) was a multicenter, prospective, randomized, double-blind study evaluating the effectiveness of pacing therapy for preventing syncope recurrence in patients with documented spontaneous asystolic NMS.

Patients Selection
Patients included in this study were ≥40 years and had experienced, in the previous 2 years, ≥3 syncopal episodes of likely NMS etiology. In this study, NMS was defined as any form of reflex syncope, with the exception of carotid sinus syndrome, and a sufficiently severe enough clinical presentation to warrant specific treatment. These individuals received an ILR and were followed up (prestudy screening phase).

In accordance with the guidelines of the European Society of Cardiology, NMS was considered likely when the clinical history was consistent with NMS and competing diagnoses were excluded. Patients with positive and negative tilt table testing were included. Patients were excluded if they had one or more of the following features: cardiac abnormalities that 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 bpm or sinoatrial block; Mobitz I second-degree atrioventricular (AV) block; bundle-branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; preexcited QRS complexes; prolonged QT interval; Brugada syndrome; arhythmogenic right ventricular cardiomyopathy); symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy). Patients with carotid sinus syndrome and documented symptomatic bradycardia during carotid sinus massage were also excluded because this is an accepted indication for cardiac pacing. The assessment of the severity of the clinical presentation was based on the definitions of high frequency or high risk provided by those guidelines. In particular, syncope was defined as very frequent when it altered the quality of life of the patient and at high risk when syncope was unpredictable (absence of premonitory symptoms), thus not being amenable to prevention by standard measures (ie, physical maneuvers, sitting, squatting, etc) and exposing patients to risk of trauma or occurring during the performance of a high-risk activity (eg, driving, machine operation, etc).

Study Design
Eligible patients for the Pacemaker (Pm) trial (study phase) were those who, during the prestudy screening phase, had syncopal recurrence with documented asystolic pause (sinus arrest or AV block) ≥3 s at the time of syncope, or asymptomatic or presyncopal episodes with documentation asystolic pause (sinus arrest or AV block) ≥6 s (type 1 of the ISSUE classification). Eligible patients underwent dual-chamber pacemaker implantation.

The protocol was approved by a research ethics board at each center, and each patient provided signed informed consent. The full study protocol has been previously published.

Randomization and Programming
Immediately after implantation of a dual-chamber pacemaker, patients were randomly assigned 1:1 to dual-chamber pacing (DDD) with an AV delay sufficient to minimize unnecessary ventricular pacing or sensing without pacing with default diagnostic functions. Randomization was made centrally and was assigned automatically to each patient via Internet. The randomization list was blocked per center, with randomly varying block sizes of 2 and 4. The centers were not aware of the block sizes. The pacemaker was programmed by the implanting physician or technician, who were not blinded, whereas treatment allocation was kept blind to patient and clinical follow-up physician. In addition to randomized controlled trial, eligible patients who for any reason were not randomly assigned entered into a registry and were followed-up, and patients who had been randomly assigned, as well, to have a complete picture of the outcome of eligible patients.

Patients randomly assigned to DDD were programmed in rate drop response pacing mode, a feature of the pacemaker that instituted rapid DDD pacing if the device detected a rapid decrease in heart rate. Based on a post hoc analysis of spontaneous asystolic episodes documented by ILR in the ISSUE-2 study, the protocol specified that the initial rate drop response parameters should be a lower rate of 40/min (for 2 beats) or a drop size of 20 beats with a drop rate of 50/min within a detection window of 1 minute and an intervention rate of 90/min for 1 minute.

Outcomes
After pacemaker implantation, all patients were followed up quarterly for 24 months or up to the first episode of recurrence of syncope by a physician who was blind to the pacemaker mode. The primary study outcome was the comparison of the number of patients with syncopal recurrence in the 2 study arms according to the intention-to-treat principle. Patients were requested to report syncope episodes as soon as possible after the event occurred. Evidence of syncope was collected from pacemaker and ILR interrogation.

Statistical Analysis
Based on the ISSUE-2 results, this study was designed to have 80% power to detect a 1-year absolute reduction of 25% in the risk of recurrence of first syncope in the treatment arm applying a log-rank test with a 2-sided significance level of 0.05 (\( \alpha = 0.01 \) at ad interim and \( \alpha = 0.04 \) at final analysis). At inception, the study was designed with 1-sided significance in keeping with the Second Vasovagal Pacemaker Study (VPS II) trial. At the implementation stage, the Steering Committee decided to use 2-sided testing to increase the rigor of the study design. With a sequential design, the study was planned to be stopped when a total of 27 primary end point events, irrespective of the study arms, would be reached. An ad interim analysis was predefined at the time of 20 primary end point events (75% of the total). No center was allowed to recruit >10% of the total number of the study population.

During the follow-up, the cumulative number of patients with the primary end point, but not the relative distribution of these episodes between the 2 randomized arms, was made available to the End Point Committee. Statistical analysis was performed by an independent statistician who was not involved in the study. Neither the End Point Committee, nor the Steering Committee were informed of the results before study closure. The primary analysis of the study was planned as a comparison of the cumulative risk of syncope between the 2 treatment groups with the use of a log-rank test. The risk of syncope recurrence was based on hazard ratio obtained by means of the univariate Cox model, with the use of the Breslow method for ties. All randomly assigned patients were analyzed according to the intention-to-treat principle. Thus, all outcomes were attributed to the randomly assigned treatment groups regardless of compliance to assigned treatment.
Screening Phase

Initially, 511 patients met the inclusion criteria for the pre-study screening phase and received an ILR implantation. During a mean observation of 12 ± 10 months, syncope recurred in 185 (36%) patients and was documented by the ILR in 141 (28%) patients. Events were classified according to the ISSUE classification as type 1 (asystole) in 72, type 2 (bradycardia) in 16, type 3 (slight or no rhythm variations) in 37, and type 4 (tachycardia) in 16. Moreover, ECG documentation of nonsyncopal (asymptomatic or presyncopal) asystolic events of ≥6 s was made in 17 patients. Thus, in total, 89 patients with asystolic events were eligible for the randomized Pm trial (Figure 1). They had a mean asystolic pause of 11 ± 4 s (range, 3–44 s). The patients with syncope had an asystolic pause of 12 ± 10 s and those without syncope had an asystolic pause of 10 ± 6 s.

Patients

Study participants were enrolled from April 2007 to April 2011 and follow-up concluded in August 2011. A total of 77 patients of the 89 eligible patients were randomly assigned from 29 hospitals in Italy (12 hospitals), Spain (6 hospitals), Germany (3 hospitals), Canada (2 hospitals), United Kingdom (2 hospitals), Austria (1 hospital), France (1 hospital), The Netherlands (1 hospital), and Switzerland (1 hospital). Of these patients, 38 were assigned to the Pm ON arm, and 39 were assigned to the Pm OFF arm. Reasons for nonrandomization in the remaining 12 patients were as follows: investigator’s decision to implant a pacemaker because of severity of syncope in 6 cases, and patient’s refusal to be randomly assigned in 6 cases. These patients were followed up in the ISSUE registry (Figure 1). The patients’ characteristics were well matched in the randomized arms and in the registry group (Table). During follow-up, in the absence of occurrence of the primary end point, 8 patients assigned to the Pm OFF arm had their Pm reprogrammed to DDD (6 cases) or to VVI 40 bpm (2 cases) because of ILR documentation of prolonged nonsyncopal asystole in 2 patients and investigator/patient’s decision (because of patient’s high-risk activity) in the other cases. According to the intention-to-treat principle, these patients were analyzed in the Pm OFF arm.

Outcome

A total of 27 of 77 patients had syncope recurrence during follow-up: of these, 19 patients had been assigned to Pm OFF and 8 to Pm ON. The estimated product-limit syncope recurrence rate based on the intention-to-treat analysis was

---

### Table. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pm ON n = 38</th>
<th>Pm OFF n = 39</th>
<th>Registry n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (14)</td>
<td>63 (12)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>20 (53)</td>
<td>16 (41)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Syncope events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events, median (IQR)</td>
<td>7 (4–12)</td>
<td>8 (5–10)</td>
<td>7 (5–13)</td>
</tr>
<tr>
<td>Events in the last 2 y, median (IQR)</td>
<td>4 (3–5)</td>
<td>5 (3–6)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>Events in the last 2 y without prodrome, median (IQR)</td>
<td>3 (1–4)</td>
<td>3 (0–5)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Age at first syncope, mean (SD), y</td>
<td>48 (25)</td>
<td>45 (23)</td>
<td>41 (23)</td>
</tr>
<tr>
<td>Interval between first and last episode, median (IQR), y</td>
<td>8 (3–29)</td>
<td>8 (3–24)</td>
<td>17 (7–43)</td>
</tr>
<tr>
<td>History of presyncope, n (%)</td>
<td>19 (50)</td>
<td>22 (56)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Hospitalization for syncope, n (%)</td>
<td>24 (63)</td>
<td>25 (64)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Injuries related to fainting, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major injuries (fractures, brain concussion)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Minor injuries (bruises, contusion, hematoma)</td>
<td>15 (39)</td>
<td>18 (46)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Typical vasovagal/situational presentation, n (%)</td>
<td>18 (47)</td>
<td>16 (41)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Atypical presentation (uncertain), n (%)</td>
<td>20 (53)</td>
<td>23 (59)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>ILR documentation (eligibility criteria)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope and asystole ≥3 s, n (%)</td>
<td>30 (79)</td>
<td>32 (82)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Nonsyncopal pause ≥6 s, n (%)</td>
<td>8 (21)</td>
<td>7 (18)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Length of asystole, mean (SD)</td>
<td>10 (9)</td>
<td>12 (9)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Tilt testing: performed, n (%)</td>
<td>33 (87)</td>
<td>32 (82)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Positive of those performed, n (%)</td>
<td>14 (42)</td>
<td>23 (72)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>5 (13)</td>
<td>4 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (50)</td>
<td>19 (49)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (11)</td>
<td>4 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Concomitant medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>18 (47)</td>
<td>12 (31)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>4 (11)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any other drugs</td>
<td>10 (26)</td>
<td>10 (25)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

Pm indicates pacemaker; IQR, interquartile range; and ILR, implantable loop recorder.
37% (95% CI, 24–55) at 1 year and 57% (95% CI, 40–74) at 2 years in the Pm OFF arm and 25% (95% CI, 13–45) at 1 year and 25% (95% CI, 13–45) at 2 years in the Pm ON arm (log rank; \( P = 0.039 \) at the threshold of statistical significance of 0.04) (Figure 2). Based on this hazard ratio, the risk of syncope recurrence at 2 years was reduced by 57% (95% CI, 4–81). Asystolic pauses were documented during the study period in 8 patients assigned to the Pm OFF arm, and, in 2 of these patients, the documented pauses were responsible for syncope.

None of the 9 patients who refused randomization whose follow-up was available had syncope during 14±8 months of observation.

**Adverse Events**

One patient died of cancer. Five patients had procedure-related complications: right ventricle lead dislodgment in 2 patients, right atrial lead dislodgment in 2 patients, and subclavian vein thrombosis in 1 patient. No patient had severe adverse events as a consequence of recurrence of syncope.

**Discussion**

The main finding of this study is that dual-chamber permanent pacing is effective in reducing the recurrence of syncope in severe NMS patients ≥40 years in whom a long asystolic pause (mean, 11 s) has previously been documented by use of ILR. The observed 32% absolute and 57% relative reduction in syncope recurrence support the use of this invasive treatment for the relatively benign NMS in this circumstance. The overall strategy of using an ILR, with the consequent relatively certainty regarding mechanism, likely contributed to the positive findings.

In the ISSUE-2 study,\(^3\) the estimated 2-year syncope recurrence rate was 12% in pacemaker patients and 41% in untreated patients with an absolute risk reduction of 29% and a relative risk reduction of 80% (95% CI, 45–93). The results of the present study are comparable in the magnitude of pacing benefit and are more convincing given the double-blind randomized controlled nature of the current study in comparison with the observational results in ISSUE2.

A comparison of this study with previous randomized double-blind trials is somewhat difficult because of important differences in study design, largely focused on patient selection. The Second Vasovagal Pacemaker Study (VPS II) trial\(^1\) included 100 unselected patients with a typical history of vasovagal syncope and a positive tilt test; follow-up was shorter. The relative risk reduction in syncope recurrence with DDD pacing was 30% (95% CI, −33 to 63; \( P = 0.14 \)) in comparison with 57% in the present study. VPS II was designed and conducted at the beginning of the ILR era when the mechanism of spontaneous NMS was not completely understood. Because we know from ILR experience that about half of spontaneous neurally mediated episodes are asystolic in nature, we can expect that the relative risk reduction observed in VPS II would have been doubled up to 60% if only the patients with asystolic syncope were included, as was the case in ISSUE-3. The 60% figure is comparable to what we found in ISSUE-3. The vasovagal syncope and pacing trial (SyNPACE)\(^2\) enrolled 29 unselected patients with positive tilt table testing. The trial was prematurely interrupted and greatly underpowered. Although SYNPACE was unable to show a benefit of pacemaker over placebo, the time to first syncope recurrence was longer with pacemaker therapy than with placebo in the 15 patients who had shown an asystolic (ventricular pause of 13±8 s) response during tilt table testing: 97 versus 11 days, \( P = 0.06 \). No difference was found in the patients with a nonasystolic response. Therefore, in the light of the ISSUE trials results, our interpretation of the above findings is that the efficacy of pacemaker therapy has been hampered by the difficulty in identifying the relative contributions of vasodepression and bradycardia/asystole in patients with undocumented spontaneous syncope. ISSUE-2 and now ISSUE-3 demonstrate that when spontaneous syncope is documented to be associated with asystole, pacemaker therapy is beneficial. However, even in this situation, the importance of an associated hypotensive component is suspected.
in those patients because 25% of Pm ON arm had syncopal recurrence despite pacemaker therapy.

In the randomized open-label Vasovagal Syncope International study (VASIS-PM) and Syncope Diagnosis and Treatment Study (SYDIT) trials, NMS patients were selected on the basis of a positive cardioinhibitory (mostly asystolic) response during tilt table testing. Apart from the use of tilt table–induced bradycardia to select subjects, the population of these 2 open trials had characteristics that were similar to those of the present study. In the VASIS-PM study, syncopal recurrence rate in the no treatment arm was 50% at 2 years, which is similar to the 57% observed in the present study. The control patients in the SYDIT trial were treated with β-blockers. Syncopal recurrence at 2 years in pacemaker arm was 6% in VASIS-PM and 7% in SYDIT, much lower than that observed in the present study. Any open-label trial has the potential for bias in reporting and assessment of outcomes. However, in light of the ISSUE-3 trial results, it seems that the induction of an asystolic NMS during tilt table testing can predict the efficacy of pacemaker therapy albeit to a lesser extent than that expected from VASIS-PM results. Overall, the value of bradycardia induced during tilt table testing in predicting pacing benefit must remain uncertain pending future studies.

Finally, in the randomized open-label pilot VPS I, which included unselected patients with a typical history of vasovagal syncope and a positive tilt table test, syncope occurred in 22% of paced and 70% of nonpaced patients with most episodes occurring within the first 6 months. This speaks to a combination of physiological effects, as demonstrated in the blinded portion of the study, and the expectation effect that may be an aspect of open-label studies.

The fact that pacing is effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be undertaken in the clinical context of a benign condition (in terms of mortality), which frequently affects young patients. Thus, cardiac pacing should be a last choice in highly selected patients affected by severe NMS. In this regard, the ISSUE studies focused on NMS subjects with a relatively high mean age, a history of recurrent syncope beginning in middle or older age, and frequent injuries probably due to lack of prodrome. The ISSUE-like patients match those defined by European Society of Cardiology guidelines as high risk or high frequency. Young patients, who usually have a more prolonged prodrome before loss of consciousness, were not included in the ISSUE population. Other therapies, eg, physical counterpressure maneuvers, are more desirable in young patients. ISSUE patients were also quite different from the populations in VPS I and II. For example, in these trials, the patients were younger (40–46 years in VPS I and 48–51 years in VPS II) and had a higher lifetime burden of syncope (a median of 14–35 in VPS I and a median of 15–20 in VPS II).

How many NMS patients will be candidates for pacemaker therapy based on findings in ISSUE-3? Although a screening log was not kept for the ISSUE 3 trial, we estimated that the patients who met the ISSUE 3 inclusion criteria were 9% of all patients affected by NMS referred for evaluation. In the present study, 18% of these had an asystolic pause ≥3 s with syncope or ≥6 s without syncope after a mean observation of 12 months and therefore were eligible for pacing therapy. Based on the patient flow shown in Figure 1, 255 patients needed to have an ILR implanted, and 38 of them needed to have a pacemaker to prevent syncope recurrence in 11 patients. The critical role played by the ILR in screening, albeit in a large number of patients, was the ability to document the cardiac rhythm during spontaneous syncope, which would otherwise have been unavailable. Because ILR diagnostic yield is a function of the length of observation, this rate will probably increase by prolonging the ILR follow-up. Indeed, in a recent study, the diagnostic yield of asystolic events on ILR rose to 40% when the observation period was prolonged to 4 years.

Limitations

Similarly to all previous trials, we used DDD pacemakers with rate hysteresis algorithms. We are unable to evaluate whether the rate drop response algorithm used in this trial provided an additional benefit to that of a DDD pacemaker without this feature. In an ISSUE-2 substudy, we estimated that the same rate drop response parameters would have been able to anticipate the onset of intervention pacing in 58% of patients by a median of 5.7 s.

Although first-event occurrence is optimal for single or rare serious outcomes, eg, death or hospitalization, it is not optimal for repetitive, relatively benign events such as NMS recurrence. Nevertheless, all randomized trials considered first syncope as the primary outcome of the study. In the case of syncope trials, syncope burden would likely give a better picture of the clinical benefit of pacemaker therapy. For example, in the ISSUE-2 trial, paced patients had only 0.05±0.15 episodes of syncope per year with a relative risk reduction of 87% in comparison with pretreatment period. In the study of Sud et al, 22% of patients, was the ability to document the cardiac rhythm during spontaneous syncope, which would otherwise have been unavailable. Because ILR diagnostic yield is a function of the length of observation, this rate will probably increase by prolonging the ILR follow-up. Indeed, in a recent study, the diagnostic yield of asystolic events on ILR rose to 40% when the observation period was prolonged to 4 years.

Sources of Funding

The study was funded by Medtronic Bakken Research Center. The sponsor had no access to the database until the primary analysis of the study was completed.

Disclosures

Dr Brignole reports receiving modest consultancy fee from Medtronic and being direct shareholding of F2 solutions; Dr Sutton is a Consultant to Medtronic receiving modest fees and a paid lecturer for St Jude Medical; Dr Moya reports receiving modest consultancy fee from Medtronic; Dr Blanc reports receiving limited consultant fee from Medtronic and being direct shareholding of F2 solutions; Dr Sutton is a Consultant to Medtronic receiving modest fees and a paid lecturer for St Jude Medical; Dr Deharo reports receiving limited consultant fees from Medtronic; and Dr Beiras reports receiving limited consultant fee from Medtronic and St. Jude Medical.

References

We evaluated a treatment strategy based on early application of the implantable loop recorder in patients ≥40 years with a certain or highly likely diagnosis of neurally mediated syncope based on clinical evaluation. In our patients, therapy was delayed until documentation of a spontaneous prolonged (mean, 11 s) asystolic event was obtained by implantable loop recorder. In this highly selected population, which we estimated to be 9% of neurally mediated syncope patients referred for evaluation, cardiac-pacing therapy is effective in reducing syncopal recurrences. We found that ≈1 of 3 pacemaker patients will benefit from pacing therapy within the subsequent 2 years.