The North American Vasovagal Pacemaker Study (VPS)
A Randomized Trial of Permanent Cardiac Pacing for the Prevention of Vasovagal Syncope

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Objectives. This study was done to evaluate pacemaker therapy for severe recurrent vasovagal syncope.

Background. Nonrandomized studies have suggested that permanent pacing might help control the symptoms of recurrent vasovagal syncope. The study goal was to evaluate the effect of permanent pacemaker implantation on syncope in patients with frequently recurrent vasovagal syncope.

Methods. Patients with ≥6 lifetime episodes of syncope and with a tilt-table test that induced syncope or presyncope, as well as a relative bradycardia, were randomized to receive a dual-chamber pacemaker or not. The pacemaker prevented bradycardia and provided high-rate pacing if a predetermined drop in heart rate occurred (rate-drop response). The primary outcome was the first recurrence of syncope. Patients also completed a detailed diary recording presyncopal episodes.

Results. A total of 284 patients was originally planned and a pilot study of 60 patients was initiated. At the planned first formal interim analysis of efficacy of the pilot study, an unanticipated large treatment effect was observed which fulfilled the prespecified criteria for early termination of the study. At that time, there were 54 patients enrolled, randomized evenly to no pacemaker or to pacemaker. In the no-pacemaker and pacemaker groups the mean ages were 40 and 46 years; 74% and 70% patients, respectively, were female. The baseline tilt-table test showed a slowest heart <60/min or longest heart period >1000 ms in 60% of no-pacemaker patients and 72% of pacemaker patients. There was a marked reduction in the postrandomization risk of syncope in pacemaker patients (relative risk reduction 85.4%, 95% confidence interval 59.7% to 94.7%; 2p = 0.000022).

Conclusions. Dual-chamber pacing with rate-drop response reduces the likelihood of syncope in patients with recurrent vasovagal syncope.

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Vasovagal or neurally mediated syncope is a common condition caused by inappropriate reflex vasodilation and bradycardia. Recently, the increased use of tilt-table testing to elicit vasovagal syncope has confirmed a high prevalence of relative bradycardia at the time of fainting and has heightened interest in the use of pacemaker therapy (1–8). The usefulness of cardiac pacing has, however, been questioned owing to the observation that vasodilation usually accompanies bradycardia at the time of fainting. Several observational nonrandomized studies (6–8) have suggested a possible benefit from pacing but no randomized controlled trial has been done. The goal of this study (9) was to perform a randomized controlled trial of pacemaker therapy in vasovagal syncope. The pacemaker used for this study not only provided bradycardia support by dual-chamber pacing but also had rate-drop responsiveness. With this feature, the pacemaker can be programmed to detect a small, rapid drop of heart rate through a prespecified range, then pace at a relatively high rate to provide chronotropic support during a time of presumed vasodilation. The primary hypothesis was that a decision to implant a pacemaker would reduce the risk of syncope compared to not implanting a pacemaker.

Methods

Patient eligibility. The study protocol was published previously (9). Patients were eligible for inclusion if they had had at least six syncopal spells in order to provide a probability of a recurrence of ≥50% in 1 year (10). Patients also had to have had a positive tilt-table test with syncope or presyncope and with relative bradycardia. Relative bradycardia was defined as

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Syncope was defined as a transient state of unconsciousness characterized by spontaneous recovery. Pre-syncopal sensation was defined as a state of lightheadedness usually associated with one or more symptoms of decreased vision, the sensation of hearing voices distinctly, slow response times to verbal stimuli, nausea, vomiting, or partial loss of postural tone.

Randomization and follow-up. Patients were randomized centrally by telephone either to receive a permanent pacemaker or not. Patients randomized to receive a pacemaker did so at the earliest possible date, and the protocol specified that the pacemaker be implanted within a week of randomization. The pacemaker used was the Medtronic Thera DR dual-chamber pacemaker with rate-drop response. The rate-drop response algorithm and pacing parameters were activated within 24 h of implant and prior to the patient leaving hospital. A minimum pacing rate of 60 beats/min was programmed in all patients. The initial rate-drop response parameters were programmed to detect a “rate drop” if there was a fall in heart rate of 5 to 15 beats/min over a sequence of 20 to 40 beats that remained below the lower rate for at least three beats. If this occurred, a pacing response of 100 beats/min for 2 min would occur. Patients in both groups were permitted to receive any medical or nonmedical treatment, according to the judgment of their treating physicians, but none was required. Following discharge, patients completed a daily diary of all presyncopal and syncopal spells. In addition, the patients were either contacted by telephone or seen every 2 months by study nurses.

Study design. The goal of the study was to test the hypothesis that the decision to implant a dual-chamber pacemaker with rate-drop response would reduce the risk of a first recurrence of syncope compared to no pacemaker. We elected not to implant a pacemaker in control patients (which would not be activated) because, in 1995 when the trial was designed, the evidence in support of pacing was sufficiently scant that we wanted to minimize the number of patients who received this invasive therapy.

Outcome measures. The primary outcome measure of the study was the first recurrence of syncope. This was chosen because the time to the first recurrence of syncope has been shown to correlate very well with the eventual frequency of syncope (11), and the frequency of syncope in turn correlates with the diminution of quality of life in patients with frequent vasovagal syncope (12). Once a patient had a recurrence of syncope, formal study participation ended.

The verification of syncope was done by careful documentation of the features of the syncopal spell as reported by the patient, by obtaining collateral history from bystanders witnesses, and by examination of the patient for signs of physical trauma such as abrasions or contusions. All patients were given diaries to record their symptoms of presyncope and syncope, and were instructed to grade their presyncope symptoms daily on a 10-point scale, ranging from 0 (no symptoms) to 10 (syncope). Patients were interviewed in the clinic or by telephone within 1 week of any syncopal spell. Each investigator decided whether an outcome event had occurred based upon whether complete loss of consciousness had happened, and whether the loss of consciousness was similar to previous vasovagal syncope.

Statistical methods. Because patients were followed for varying lengths of time and the primary outcome event, recurrence of syncope, could occur at any time postrandomization, survival analysis techniques were used. The cumulative risk of syncope over time was estimated within each treatment group using the Kaplan-Meier procedure (13), and the two survival curves were formally compared using a Mantel-Haenszel test (14). The treatment effect and its associated 95% confidence interval were represented by a relative risk reduction and computed with a Cox proportional hazards model (15). The Cox model was also used to adjust for baseline imbalances in a predetermined set of potentially important prognostic factors and to investigate possible subgroup interactions.

Because we anticipated a 1-week delay in pacemaker implantation for those patients allocated to receive a pacemaker, the protocol specified that, for the primary analysis of efficacy, no outcome events would be counted until the eighth postrandomization day. All analyses were based on the intention-to-treat principle.

The assumptions for the sample size calculation were that the no-pacemaker group would have a cumulative risk of recurrent syncope at 1 year of 60%. We calculated that a total of 286 patients would yield 80% power to detect a 30% relative reduction in risk of recurrent syncope (based on a one-sided type I error of 5%).

A pilot study of 60 patients was initiated in June 1995. Formal interim analysis of efficacy was specified in the protocol (9) for both the pilot and main studies with early study termination for p < 0.001. The study was approved by the Institutional Review Boards of all participating sites.

Results

Early termination for efficacy. The study began to enroll patients in June 1995 and the first formal interim analysis of efficacy was carried out on April 30, 1997. Although 54 patients had been enrolled at that time, follow-up data for interim analysis were available from 46 patients in whom a treatment effect in favor of pacing was observed (p = 0.0007). In consultation with the External Safety and Efficacy Monitor, a decision was made to terminate enrollment and follow-up, and to report the study results as of May 2, 1997. An unknown number of patients...
were screened and found to be eligible for the study; of the 54 who gave consent and were enrolled, 27 were assigned to receive no pacemaker and 27 were assigned to receive a pacemaker.

**Baseline characteristics.** Table 1 shows the clinical characteristics of the two groups. The mean age of patients was 43 years, and almost three-quarters were female. There was a low incidence of diabetes mellitus, systemic hypertension and lung disease. Patients had a heavy burden of prior syncope, with median lifetime history of 35 episodes (no pacemaker) and 14 episodes (pacemaker). The median number of episodes in the year preceding enrollment was 6 (no pacemaker) and 3 (pacemaker). The mean time between the most recent episode of syncope and randomization was 6.3 days (no pacemaker) and 3 days (pacemaker). Beta-blocker therapy had been used in 130 days (no pacemaker) and 92 days (pacemaker). The mean time from randomization to pacemaker implantation was 6.7 days with a range of 1 to 22 days. Eighteen patients (69%) allocated to receive a pacemaker had it implanted within 7 days of randomization. All patients were initially programmed into the dual-chamber pacing mode with a minimum rate of 60/min, with the rate-drop response function programmed on. One patient was subsequently programmed to rate responsive dual-chamber pacing with the rate-drop response programmed off.

**Recurrent syncope.** The protocol specified that events would only be included in the primary analysis if they occurred at least 7 days after randomization to allow time for pacemaker implantation. Figure 1 shows the cumulative rate of recurrent syncope (excluding the first 7 days after randomization) in the no-pacemaker and pacemaker groups. There was a reduction in risk of syncope of 85.4% (relative risk reduction 85.4%, 95% confidence interval, 59.7% to 94.7%; $p = 0.000022$). Recurrent syncope occurred in 19/27 (70%) of no-pacemaker patients and in 6/27 (22%) of pacemaker patients. The mean time from randomization to syncope was 54 days in the no-pacemaker group and 112 days in the pacemaker group. The syncope episode was witnessed in 6 of the 19 no pacemaker patients and in 3 of the 6 pacemaker patients. There was evidence of injury in 4 of the no-pacemaker patients with syncope (bruises) and none of the pacemaker patients with syncope. During follow-up, 2/27 (7%) of patients in both treatment groups received a beta-blocking drug; disopyramide was used by one patient in the no-pacemaker group. No other drugs were prescribed for the treatment of syncope or presyncope. During the first 7 days after randomization, six patients in the no-pacemaker group and none in the pacemaker group had syncope.

**Presyncope.** All patients were instructed to maintain a daily diary of presyncope episodes that was reviewed by the study nurse. As shown in Table 2, there was no significant effect of pacing on the occurrence of presyncope. At least one episode of presyncope was reported by 7/27 (41%) no-pacemaker patients and 6/27 (33%) pacemaker patients. Episodes of presyncope were rated by patients on a numeric scale.

**Table 1.** Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>No-Pacemaker Group</th>
<th>Pacemaker Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>40 ± 18</td>
<td>46 ± 18</td>
</tr>
<tr>
<td>Female (%)</td>
<td>19 (70)</td>
<td>18 (74)</td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes (%)</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension on therapy (%)</td>
<td>3 (11)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Chronic lung disease (%)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Syncope episodes lifetime, mean (IQR)</td>
<td>35 (20–100)</td>
<td>14 (8–35)</td>
</tr>
<tr>
<td>Syncope episodes last year, median (IQR)</td>
<td>6 (3–40)</td>
<td>3 (2–12)</td>
</tr>
<tr>
<td>Mean days from most recent syncope episode to randomization (±SD)</td>
<td>63 ± 130</td>
<td>92 ± 126</td>
</tr>
<tr>
<td>Prior therapy for syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>11 (41)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Disopyramide (%)</td>
<td>3 (11)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Fludrocortisone (%)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Baseline tilt-table test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol used (%)</td>
<td>18 (67)</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Syncope induced (%)</td>
<td>17 (63)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Lowest heart rate &lt;60/min or longest RR &gt;1000 ms</td>
<td>17 (63)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Lowest heart rate &lt;40/min or longest RR &gt;1500 ms</td>
<td>7 (26)</td>
<td>5 (19)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; SD = standard deviation.
There was one pacemaker lead dislodgement. Five patients had more syncopal episodes in the year preceding randomization. There was a trend for no-pacemaker patients to have had fewer lifetime episodes of syncope and none for the no-pacemaker patients. Before pacing, 13 patients had syncope, and only 5 after pacing; however, syncope persisted in all but one patient.

**Presyncope Characteristics**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No-Pacemaker Group</th>
<th>Pacemaker Group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with presyncope in follow-up</td>
<td>20/27 (74%)</td>
<td>17/27 (63%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Average rate of presyncope, episodes/100 days</td>
<td>10.0</td>
<td>4.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Number of patients with frequency of presyncope episodes &gt;10/100 days</td>
<td>9/25* (36%)</td>
<td>6/27 (22%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Number of patients with any severe presyncope (≥8 on 1–10 scale)</td>
<td>12/25* (48%)</td>
<td>10/27 (37%)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Data not available on two patients.

(1 to 10, in increasing severity). At least one presyncope event of severity ≥8 was reported by 48% of no-pacemaker patients and by 37% of pacemaker patients. A rate of presyncope of >10 episodes/100 days was reported by 36% of no-pacemaker and by 22% of pacemaker patients. The average rates of presyncope episodes per 100 days were 10.0 for no-pacemaker patients and 4.5 for pacemaker patients.

**Adjusted analysis and subgroup effects.** With a relatively small study, there is scope for baseline imbalances in potentially important prognostic factors to occur, despite randomization. There was a trend for no-pacemaker patients to have had more syncopal episodes in the year preceding randomization than pacemaker patients. To determine if any baseline characteristics were predictive of recurrent syncope and to determine if observed baseline imbalances might have had an impact on the relative risk reduction, an adjusted analysis was performed. The baseline factors considered were age (<40 years, ≥40 years), number of syncopal events in the past year (<4, ≥4), lifetime syncopal events (<20, ≥20), days since most recent syncope (<37, >37), tilt-test minimum heart rate of <40 beats/min or maximum heart period >1500 ms (yes/no), tilt-test syncope (yes/no) and tilt-test seizure-like activity (yes/no). When included together in a Cox model, none of these variables were significantly predictive of recurrent syncope. Therefore, when the estimate of pacemaker efficacy was adjusted for the observed differences between the groups in these baseline factors, the estimated treatment effect was unchanged (relative risk ratio = 90.8%, 95% confidence interval 71.0% to 97.1%, 2p = 0.000045). Thus, it is highly unlikely that baseline differences between the patient groups explains any of the observed effect on syncope.

To explore the possibility that the pacemaker treatment effect varied in the presence or absence of any of these baseline characteristics, treatment–covariate interactions were evaluated in the Cox model. None of these interactions were statistically significant, even without allowance for multiple testing.

**Adverse effects.** Seven adverse events were reported for the pacemaker patients and none for the no-pacemaker patients. There was one pacemaker lead dislodgement. Five patients reported at least one episode of palpitations, and one patient reported pacemaker activity at rest.

**Discussion**

This was the first randomized controlled trial of pacemaker therapy in vasovagal syncope. It demonstrated that in patients who are severely symptomatic from vasovagal syncope, permanent pacing markedly reduces the likelihood of a recurrence of syncope. In contrast, pacing has little effect on the occurrence of presyncope, which was common in these patients.

**Mechanism of action.** The pacemaker could have benefited these patients in at least two ways. By providing a minimum heart rate of 60 beats/min, the pacemaker prevented extreme bradycardia and asystole, which has been observed to occur with vasovagal syncope in many patients. A second mechanism of potential benefit was the rate-drop response feature, which automatically provided high rate (usually 100 to 120 beats/min) dual-chamber pacing if an abrupt drop in heart rate was detected. This intervention might prevent an episode of vasovagal syncope by augmenting cardiac output at the initiation of a vasovagal episode. This study was not designed to determine the mechanism of pacemaker effectiveness. Prevention of bradycardia, rate-drop response, both interventions or other mechanisms of benefit may be responsible for the observed effect.

This study design cannot exclude a bias in assessment of outcome as the treatment was unblinded. There was, however, objective verification of many syncope episodes. Of the 25 syncope episodes that were reported by patients and determined to be outcome events, 36% were witnessed and 16% were associated with documented minor injury. As the study was unblinded and patients knew whether they were receiving the experimental therapy or not, there is some potential for a placebo-type effect or psychological benefit from receiving a pacemaker. An imbalance in events reported during the first week after randomization when some pacemaker patients had not yet received a device suggests that some psychological effect may have occurred. Conversely, if the large reduction in syncope that was observed was due to a placebo or psychological mechanism, one would have expected this to carry over into the area of presyncope, yet there was no significant effect of pacing on presyncope.

A reduction in syncope without effect on presyncope actually corresponds closely with the known pathophysiology of vasovagal syncope, which includes both bradycardia and vasodilation. Pacing will prevent bradycardia but is unlikely to prevent vasodilatation. Thus, a patient with a pacemaker experiencing a vasovagal episode might well be expected to continue to have vasodilatation, which would explain the persistence of presyncope. The observation that pacemaker therapy has an effect on syncope but not on presyncope has been previously reported by Sra et al. (2) in a study of 22 vasovagal syncope patients undergoing tilt-table testing before and after pacemaker therapy. In that study, 18 patients had syncope before pacing and only 5 after pacing; however, presyncope persisted in all but one patient.

**Adjusted analysis.** Despite randomization, there was a trend for pacemaker patients to have had fewer lifetime
episodes of syncope and fewer episodes in the past year. Although one might be concerned that a chance baseline imbalance might have exaggerated the treatment effect, this appears unlikely. Syncope burden prior to randomization was not a predictor of recurrent syncope, and when the relative risk reduction is adjusted for differences in baseline variables, it remains essentially unchanged.

One might argue that the time to recurrence of syncope is less important than the total burden of syncope. We have, however, previously shown that the time to first recurrence of syncope is closely correlated with total syncope episodes in the year following diagnostic tilt-table testing of vasovagal syncope (11). Furthermore, there was a practical reason to choose first recurrence of syncope as the primary outcome measure. We expected that patients not receiving a pacemaker would be unwilling to persist in the study after they had experienced a recurrence.

Unanswered questions. There are several remaining questions not addressed by this study. It is not known to what extent the rate-drop response function is required to obtain a benefit from pacemaker therapy. A randomized comparison of dual-chamber pacing with and without rate-drop intervention would be useful. The patients enrolled in this study were highly selected. They had a substantial burden of previous syncope and they had relative bradycardia demonstrated on a tilt-table test. It is unknown to what extent other patients with vasovagal syncope would benefit from pacing, especially those with less frequent syncope or those without bradycardia or symptoms at the time of tilt-table testing. We did not determine whether pacemaker therapy improved the quality of life in patients with vasovagal syncope in this study. However, in a recent two-period study we have shown that quality of life improved markedly and significantly in patients with vasovagal syncope who received a dual-chamber pacemaker (8).

Patients with recurrent vasovagal syncope can be severely disabled. They may seriously injure themselves on occasion and they may not be able to drive a car or to perform their jobs. Beta-blocking drugs, disopyramide and fludrocortisone have been used to treat vasovagal syncope but none have been demonstrated in randomized trials to prevent syncope. The findings of this study provide strong evidence that pacemaker therapy can help some patients with vasovagal syncope.

A study in which all patients receive a pacemaker with subsequent blinded randomization to pacemaker on or pacemaker off would provide even stronger evidence that pacemaker therapy helps these patients. At present a reasonable management strategy for patients with highly frequent and symptomatic vasovagal syncope would be to provide counseling about lifestyle modification and increased dietary salt; then to discuss with the patient whether to try empiric pharmacological therapy. It would then be reasonable to consider implanting a pacemaker in patients with highly symptomatic, frequent vasovagal syncope who also have a relative bradycardia on tilt-table testing.

Appendix

Members of the Vasovagal Pacemaker Study Investigators

Clinical Sites and Investigators: University of Calgary, Calgary: Robert Sheldon, Mary Lou Koshman; McMaster University, Hamilton: Stuart Connolly, Mariane Menard; Cleveland Clinic Foundation, Cleveland: Fred Jaeger, Bruce Wilkoff, Fethnat Fouad, Donald Holmes; Institut de Cardiologie de Montreal, Montreal: Mario Talajic, Denis Roy, Danielle Beaudoin; St. Michael's Hospital, Toronto: David Newman, Minye Paquette, Paul Dorian, Jane Lasglop; Hospital du Sacre-Coeur, Montreal: T. Kuo, Ginette Gaudelet; University Hospital, Kingston: H. Abdollah; Medical College of Virginia Hospital, Richmond: Kenneth Ellenbogen, Carlos Morillo, Cheryl Dietrich; University of Ottawa Heart Institute, Ottawa: Martin Green, Anthony S. L. Tang, Clare Carey; University Hospital, London: Raymond Yee, George Klein, Marilyn Braney; Laval Hospital, Saint-Foy: Francois Philippon, Marcel Gilbert, Gilles O'Hara, Johanne Rompere; Temple University School of Medicine, Philadelphia: Alfred Buxton, Henry Hsia, Nancy Adelizzi; Lansing, Michigan: Rajan Thakur, Terry Mangum; Sacramento, California: Gearoid O’Neill, Arjun Sharma, Anne Skadsen; Canton, Ohio: Raquel Martin, James Maloney, Ladyne Miller; Bowman Gray Medical Centre, Winston-Salem, North Carolina: George H. Crossley, Kathleen Davis-O’Brien.


References