Permanent Cardiac Pacing Versus Medical Treatment for the Prevention of Recurrent Vasovagal Syncope
A Multicenter, Randomized, Controlled Trial

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Background—This clinical investigation was performed to compare the effects of permanent dual-chamber cardiac pacing with pharmacological therapy in patients with recurrent vasovagal syncope.

Methods and Results—Patients from 14 centers were randomized to receive either a DDD pacemaker provided with rate-drop response function or the β-blocker atenolol at the dosage of 100 mg once a day. Inclusion criteria were age ≥35 years, ≥3 syncopal spells in the preceding 2 years, and positive response to tilt table testing with syncope occurring in association with relative bradycardia. The primary outcome was the first recurrence of syncope after randomization. Enrollment started in December 1997, and the first formal interim analysis was performed on July 30, 2000. By that time, 93 patients (38 men and 55 women; mean age, 58.1 ± 14.3 years) had been enrolled and randomized, although follow-up data were available for all patients (46 patients in the pacemaker arm, 47 patients in the pharmacological arm). The interim analysis showed a significant effect in favor of permanent cardiac pacing (recurrence of syncope in 2 patients [4.3%] after a median of 390 days) compared with medical treatment (recurrence of syncope in 12 patients [25.5%] after a median of 135 days; OR, 0.133; 95% CI, 0.028 to 0.632; P = 0.004). Consequently, enrollment and follow-up were terminated.

Conclusions—DDD pacing with rate-drop response function is more effective than β-blockade for the prevention of syncopal recurrences in highly symptomatic vasovagal fainters with relative bradycardia during tilt-induced syncope. (Circulation. 2001;104:52-57.)

Key Words: syncope • pacing • β-blockers

Vasovagal syncope represents a common disorder of the autonomic cardiovascular regulation.1,2 Even if this condition is not life threatening, patients with recurrent vasovagal syncope may show a substantial physical and psychosocial morbidity.3,4 Consequently, highly symptomatic subjects with excessive lifestyle difficulties are usually considered for a specific treatment.4,5 In general, the available therapeutic options for vasovagal syncope can be broadly classified as long-term pharmacological therapy and permanent dual-chamber cardiac pacing.5–6 Although medical therapy should be effective in preventing the development of the vasovagal reflex, cardiac pacing is expected to contrast the reflex just after its appearance. In particular, many pharmacological agents have been proposed as effective in the prevention of vasovagal syncope, even if only 3 drugs—atenolol, midodrine, and paroxetine—have shown some efficacy in ≥1 prospective, randomized, controlled clinical trial.7–9 As a matter of fact, in clinical practice, β-blockers currently represent the most widely prescribed drug class in patients with recurrent vasovagal spells.5,6 On the other hand, after several observational studies,10,11 2 randomized, controlled trials have suggested that cardiac pacing may represent a reasonable therapeutic alternative in highly symptomatic vasovagal fainters.12,13 However, despite the existence of substantial literature on both pharmacological and pacing treatment, the relative efficacy of any specific option in patients with recurrent vasovagal spells is still a matter of dispute.4–6

Accordingly, this clinical investigation was designed and undertaken to compare the effects of medical therapy and cardiac pacing in patients with recurrent vasovagal syncope. The β-blocker atenolol was considered the pharmacological agent, whereas a dual-chamber pacemaker with rate-drop response (RDR) function was chosen for pacing treatment.

Methods

Patients
The study cohort consisted of 93 patients (38 men and 55 women; mean age, 58.1 ± 14.3 years) with recurrent vasovagal syncope. These patients were recruited from consecutive subjects referred to...
the 14 participating centers from December 1997 to April 2000 for the evaluation of unexplained syncope. Syncope was defined as a sudden transient loss of consciousness with inability to maintain postural tone and with spontaneous recovery. In each patient, the cause of syncope was established according to a standardized diagnostic workup and by adhering to previously reported diagnostic criteria. In fact, all patients were considered to have been affected by vasovagal syncope when presenting with the following features: (1) no clinical or laboratory evidence of any cardiac, neurologic, or metabolic cause for the recurrent syncopal spells and (2) positive response to head-up tilt testing.

The preliminary diagnostic evaluation included history, physical examination, full routine laboratory tests, 12-lead ECG, exercise ECG, Doppler echocardiography, 24-hour ECG monitoring, carotid sinus massage, EEG, and duplex ultrasound scanning of the carotid arteries. When clinically indicated, CT scans and MRI of the central nervous system and cardiac electrophysiological study were also performed. When this diagnostic workup could not establish the cause of syncope, the patient underwent tilt table testing according to a previously described protocol. All patients were also questioned about the occurrence of trauma during syncopal spells. Syncope-related traumatic injuries were classified as previously described; major trauma (any fracture, head injury, or internal organ damage requiring hospital admission and surgical treatment) and minor trauma (any bruise, cut, and soft tissue injury).

Head-Up Tilt Testing

The test was performed in the morning in patients in a fasting state. An electronically controlled tilt table with a footboard for weight-bearing and restraining belts was used for the procedure. Continuous ECG monitoring of heart rate and rhythm was performed, whereas blood pressure was noninvasively measured beat to beat by means of an Ohmeda Finapress 2300 photoplethysmographic device. In 8 centers, such a device was not available, and blood pressure was measured by a standard mercury sphygmomanometer at 5-minute intervals throughout the test. Subjects were initially tilted at 60° for 30 minutes (control phase). Subsequently, if no symptoms occurred, participants received 1.25 mg isosorbide dinitrate sublingually and continued to be tilted for an additional 15 minutes (pharmacological phase). The test was considered positive if syncope occurred in association with hypotension, bradycardia, or both. In case of syncope, the procedure was terminated by rapidly lowering the tilt table to the horizontal position.

Patient Eligibility

To be included in the study, patients with recurrent vasovagal syncope had to fulfill the following criteria: age >35 years; ≥3 syncopal spells in the preceding 2 years, with the last episode occurring within 6 months of enrollment; and positive response to tilt table testing with syncope occurring in association with relative bradycardia. Relative bradycardia was defined as a trough heart rate ≤60 bpm as previously described. All enrolled patients provided written informed consent to take part in the investigation. Patients were excluded if a cause of syncope other than vasovagal was known or even suspected. Patients were also excluded in case of any historical, clinical, or laboratory evidence of cardiac, neurologic, or metabolic disease. Other exclusion criteria included the need for any concomitant chronic pharmacological treatment for any cause and patient refusal to participate in the study.

Study Design

The study was planned as a multicenter, prospective, randomized, controlled trial with parallel groups. The main goal of the study was to compare the effects of pharmacological β-blockade and permanent dual-chamber cardiac pacing in the prevention of the recurrence of vasovagal syncope. The study protocol was approved by the ethics committee of all participating institutions. Eligible patients were assigned to 1 of the 2 study arms according to a central computer-generated randomization list: (1) treatment with atenolol at the dosage of 100 mg once a day and (2) implantation of a DDD pacemaker with RDR function (Medtronic Thera-I, model 7960, Medtronic Inc).

Pharmacological Treatment

Pharmacological therapy was started immediately after randomization at the dosage of 50 mg once a day. Subsequently, the drug was titrated up to the full dosage of 100 mg once a day within 2 to 3 days. Titration increments in atenolol to 50 mg/d were allowed during follow-up in case of side effects. Compliance with pharmacological therapy was assessed by pill counting. Patients who dropped out owing to intolerable side effects, adverse reactions, or lack of adequate response to treatment were taken as complete cases for the intention-to-treat analysis.

Pacemaker Implantation and Programming

Pacemaker implantation was performed immediately after randomization in all cases. The parameters of the RDR algorithm were programmed after implantation and before discharge from the hospital. The RDR programming was performed on the basis of heart rate behavior during head-up tilt testing in every single patient as previously described. In addition, all pacemakers were programmed with a lower rate at 40 bpm and a minimum AV delay of 200 ms to avoid inappropriate pacing and to favor spontaneous cardiac rhythm.

Follow-Up and Outcome Measures

All subjects were asked to immediately note any syncope recurrence. In addition, a clinical follow-up visit, including physical examination and a 12-lead ECG, was scheduled on a 3-month basis. The primary end point of the study was the first recurrence of syncope during follow-up. This outcome measure was chosen because the time to first recurrence of syncope has been shown to correlate with the eventual frequency of syncopal spells in vasovagal fainters. For all included patients, formal study participation ended in case of recurrence of syncope.

As in previous studies, recurrences of minor symptoms such as presyncope, dizziness, or lightheadedness were neither collected nor considered in the analysis. In fact, syncope represents a memorable and easily quantifiable event, whereas other minor disturbances are far more difficult to define in terms of severity, duration, and clinical relevance.

Statistical Analysis

The primary analysis of all outcomes was by intention to treat. Moreover, an on-treatment analysis of the primary end point was also performed. The recurrence of syncope in the 2 treatment groups was tested with the OR of the 2-binomial proportion analysis. The cumulative risk of recurrence of syncope within each group was estimated by means of the Kaplan-Meier method. The survival curves of the 2 different treatment groups were then formally compared by use of the log-rank test.

Mean±SD and medians were calculated for continuous variables, and frequencies were measured for categorical variables. Differences between groups were analyzed by unpaired Student’s t test for continuous variables and χ² for categorical variables; a value of \( P<0.05 \) was considered significant.

Sample size calculation was based on an expected 15%/y syncopal recurrence rate in the pharmacological arm and on an expected 5%/y recurrence rate in the pacemaker arm. Consequently, with an α level of 0.05 and a test power of 0.80, the resulting sample size was 60 patients in each treatment group.

Results

Enrollment was started in December 1997, and the first formal interim analysis was performed on July 30, 2000. By that time, 93 patients had been enrolled, and follow-up data were available for all patients. The interim analysis showed a significant effect in favor of permanent cardiac pacing com-
The baseline characteristics of the 2 groups were similar and are shown in Table 1. Before enrollment, patients had a median of 7 (range 3 to 130) syncopal spells. During the preliminary workup, all patients had a negative response to the carotid sinus massage. In addition, 41 patients (44.0%) showed a positive response to head-up tilt testing in the control phase, whereas in the remaining 52 patients (56.0%), tilt-induced syncope followed the pharmacological provocation. A pure cardioinhibitory response to head-up tilt testing (syncope in association with an asystolic pause >3 seconds) was present in 56 patients (60.2%). Forty-seven patients (50.5%) had ≥1 syncopal-related traumatic injury in their clinical histories. In 10 patients, the severity of physical injuries had determined ≥1 hospital admission and surgical treatment (major trauma). Patients with and without syncope-related trauma showed a similar prevalence of asystolic response to tilt testing (61.7% versus 58.7%).

**Primary End Point**

In the intention-to-treat analysis, syncope recurred in 2 patients (4.3%) in the pacemaker arm after a median of 390 days (interquartile range, 360 to 420 days) and in 12 patients (25.5%) in the pharmacological arm after a median of 135 days (interquartile range, 15 to 250 days). The difference was found to be highly significant (P=0.004) (Table 2). The Kaplan-Meier actuarial estimates of first recurrence of syncope after 6, 12, 24, and 36 months were 0%, 3.3%, 7.2%, and 7.2% in the pacemaker arm and 14.1%, 24.1%, 33.9%, and 33.9% in the pharmacological arm (Figure 1). In the on-treatment analysis, similar results were found (Table 2). The Kaplan-Meier actuarial estimates of first recurrence of syncope by on-treatment analysis are shown in Figure 2.

**Side Effects and Adverse Events**

No local or systemic complications related directly to pacemaker implantation were reported in any patient during the study. Five patients (10.8%) in the pacemaker group reported ≥1 episode of palpitations, possibly related to inappropriate pacemaker intervention. Twelve patients (26.0%) in the pharmacological group reported mild to moderate side effects such as fatigue, depression, anxiety, and impotence. These symptoms were considered to be directly related to the atenolol treatment. A titration decrement to 50 mg was then

### TABLE 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pacemaker (n=46)</th>
<th>Drug (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±13</td>
<td>55±15</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (43)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Syncopal episodes in clinical history, median (minimum–maximum)</td>
<td>8 (3–80)</td>
<td>7 (3–130)</td>
</tr>
<tr>
<td>Syncopal episodes in last 6 months, median (minimum–maximum)</td>
<td>2 (1–20)</td>
<td>2 (1–12)</td>
</tr>
<tr>
<td>Reported prodromes, n (%)</td>
<td>35 (76)</td>
<td>40 (86)</td>
</tr>
<tr>
<td>Mean duration of prodromes, s</td>
<td>51±54</td>
<td>46±54</td>
</tr>
<tr>
<td>Asystolic response during tilt testing, n (%)</td>
<td>28 (61)</td>
<td>28 (60)</td>
</tr>
<tr>
<td>Mean duration of asystole, s</td>
<td>16±18</td>
<td>18±11</td>
</tr>
<tr>
<td>Syncope-related trauma, n (%)</td>
<td>25 (55)</td>
<td>17 (36)</td>
</tr>
<tr>
<td>Major syncope-related trauma, n (%)</td>
<td>7 (15)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

pared with medical treatment (P=0.004). Consequently, in accordance with the Study Safety and Efficacy Monitor, a decision was made to terminate enrollment and follow-up. The study results were than reported as of August 13, 2000.

During the recruitment period, 1743 potentially eligible patients were initially screened. Among these 1743 patients, 93 (5.3%; 38 men and 55 women; mean age, 58.1±14.3 years) met all inclusion and exclusion criteria, provided informed consent, and were randomized to 1 of the 2 treatment groups. Forty-seven patients were assigned to pharmacological treatment with atenolol, and 46 patients were assigned to receive a pacemaker. All patients were informed consent, and were randomized to 1 of the 2 treatment groups. Forty-seven patients were assigned to pharmacological treatment with atenolol, and 46 patients were assigned to receive a pacemaker. All patients were followed up for ≥60 days after randomization, with a mean follow-up of 520±266 days. No patient was lost to follow-up. During follow-up, 2 patients were not assessable by on-treatment analysis. In fact, 1 patient in the pacemaker arm refused pacemaker implantation just after randomization, and a patient in the pharmacological arm discontinued treatment owing to intolerable side effects. Thus, the on-treatment analysis was performed on a total of 91 patients.

### Baseline Characteristics

The baseline characteristics of the 2 groups were similar and are shown in Table 1. Before enrollment, patients had a median of 7 (range 3 to 130) syncopal spells. During the preliminary workup, all patients had a negative response to the carotid sinus massage. In addition, 41 patients (44.0%) showed a positive response to head-up tilt testing in the control phase, whereas in the remaining 52 patients (56.0%), tilt-induced syncope followed the pharmacological provocation. A pure cardioinhibitory response to head-up tilt testing (syncope in association with an asystolic pause >3 seconds) was present in 56 patients (60.2%). Forty-seven patients (50.5%) had ≥1 syncope-related traumatic injury in their clinical histories. In 10 patients, the severity of physical injuries had determined ≥1 hospital admission and surgical treatment (major trauma). Patients with and without syncope-related trauma showed a similar prevalence of asystolic response to tilt testing (61.7% versus 58.7%).

### TABLE 2. Primary and Secondary Outcome Events in the Study Population

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Pacemaker</th>
<th>Drug</th>
<th>OR (95% CI), Pacemaker/Drug</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in analysis, n</td>
<td>46</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncopal recurrence, n (%)</td>
<td>2 (4.3)</td>
<td>12 (25.5)</td>
<td>0.133 (0.028–0.632)</td>
<td>0.004</td>
</tr>
<tr>
<td>Median time to first recurrence (interquartile range), d</td>
<td>390 (360–420)</td>
<td>135 (15–250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>34.4</td>
<td>37.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per year</td>
<td>0.06</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in analysis, n</td>
<td>45</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncopal recurrence, n (%)</td>
<td>2 (4.4)</td>
<td>12 (26.1)</td>
<td>0.132 (0.028–0.629)</td>
<td>0.004</td>
</tr>
<tr>
<td>Median time to first recurrence (interquartile range), d</td>
<td>390 (360–420)</td>
<td>135 (15–250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>32.04</td>
<td>35.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per year</td>
<td>0.05</td>
<td>0.32</td>
<td></td>
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</tbody>
</table>

...
required in 9 patients (19.5%). Only 1 patient required premature pharmacological treatment discontinuation owing to intolerable side effects.

No deaths or major syncope-related traumatic injuries occurred during the investigation. Four patients had minor syncope-related traumatic injuries (1 in the pacemaker group and 3 in the pharmacological group).

Discussion
In clinical practice, the long-term therapeutic approach to vasovagal syncope markedly differs among patients. The only interventions warranted in case of sporadic spells are represented by reassurance and education regarding the avoidance of known triggering events and the awareness of evasive, protective actions. Additional therapies are deemed necessary when frequent recurrences impair quality of life, threaten employment, and impart an increased risk of traumatic injuries.4–6,23 In general, pharmacological treatment is usually considered the first option for the prevention of recurrent vasovagal episodes, even if the evidence in favor of such an approach is scarce.5,6 Moreover, long-term compliance with drug therapy is far from satisfactory, with side effects or adverse reactions causing frequent withdrawals.5,6 Conversely, recent studies have suggested that cardiac pacing may significantly relieve symptoms in specific subsets of highly symptomatic vasovagal fainters.4,12,13

This study represents the first randomized, controlled trial to allow comparison of the effects of medical treatment and pacemaker therapy in patients with recurrent vasovagal syncope. The main finding of this clinical investigation is that in highly symptomatic vasovagal fainters with relative bradycardia during tilt-induced syncope, dual-chamber cardiac pacing is more effective than β-blockers in reducing the likelihood of a recurrence of syncope. Indeed, although pacemaker therapy was associated with a 93% actuarial probability of remaining free of syncopal recurrences after 3 years, in medically treated patients, this probability was reduced to <67% after the same period of time.

Pacemaker therapy was found to be more effective in this trial than in several previous studies.10,12 However, the effects of pacing in this study are comparable to those reported in the recently published Vasovagal Syncope International Study (VASIS), which included patients with similar baseline clinical features.13 As for medical treatment, the effect of β-blockade in preventing recurrences of syncope in this trial was comparable to that reported in previous observational studies addressing the same issue.24 Overall, β-blockers have been associated with a likelihood of recurrence of syncope of 10%/y to 20%/y, depending on the symptom burden of treated patients. Moreover, in patients with cardioinhibitory vasovagal syncope, β-blockers may occasionally worsen the tendency toward syncope (the so-called “prosyncope” phenomenon),17 even if such an adverse event has rarely been reported and has never been noted in large series.24

This clinical trial further contributes to the emerging evidence in favor of cardiac pacing for the prevention of recurrence of vasovagal syncope. Most practicing clinicians tend to consider pacing therapy as a “no-return” approach,
which should be the last resort for severely symptomatic patients refractory to conventional medical therapy. However, the impact of medical treatment on the symptom burden of recurrent vasovagal syncope has not been clearly demonstrated.4,5 Conversely, cardiac pacing is consistently showing an unexpected efficacy in the specific subset of patients with a high recurrence rate.

**Study Limitations**

As in the recently published VASIS, the results of the present study may have been influenced by a lower-than-expected recruitment rate of potentially eligible patients.13 In fact, as in VASIS, a bias in encouraging and favoring the acceptance of randomization, as well as the subsequent pacemaker implantation, by older, highly symptomatic patients with an asystolic response to tilt testing (considered the worst or most severe cases) might have been possible. In fact, the proportion of randomized patients to potentially eligible subjects and the mean age and baseline clinical characteristics of the study populations in this investigation and in VASIS are similar.

Despite randomization, there was a trend for pacemaker patients to be older and to have had more syncope-related traumatic injuries. However, both variables have never been found to influence the recurrence rate of syncope in patients with vasovagal fainting. In addition, all other baseline characteristics were well balanced (Table 1).

As in previous studies,13 no data concerning the recurrences of presyncope or lightheadedness in the study population were collected. However, although cardiac pacing therapy is known to be less effective in reducing such minor symptoms,12 no data are available as to the effects of medical treatment on these events. Moreover, these symptoms are often nonspecific and notably difficult to define and quantify in the long term.22

The study was not blinded. Consequently, a bias in the assessment of outcome cannot be excluded, even if most of the outcome events were witnessed (8 of 14, 57.1%) or were associated with minor injuries (4 of 14, 28.5%).

Finally, patients knew the therapy, and the pharmacological group did not undergo a surgical procedure with its consequent psychological impact. Accordingly, part of the benefit of pacing therapy may derive from a possible “pacemaker placebo” effect.22

**Conclusions**

Dual-chamber cardiac pacing provided with the RDR function is more effective than pharmacological β-blockade in reducing the likelihood of recurrence of syncope in patients showing a relative bradycardia during tilt-induced syncope. However, because patients included in this study showed a mean age >50 years and a high prevalence of asystolic response to tilt testing, according to the results of this trial, pacing treatment should probably be reserved for the subset of older, highly symptomatic vasovagal fainters with clear evidence of tilt-induced cardioinhibition. Further investigations are needed to define the specific indications and possible deleterious long-term effects of pacing therapy in patients with recurrent vasovagal syncope.

**Appendix**

**Study Investigators**

The Syncope Diagnosis and Treatment (SYDIT) Study Investigators were as follows (the number of randomized patients is given in parentheses): D. Cornacchia, Ospedale degli Infermi, Faenza (2); G. Pulitano, Policlinico Madonna della Consolazione, Reggio Calabria (6); M. Del Greco, Ospedale S. Chiara, Trento (1); S. Orazi, Ospedale Provenziale, Rieti (11); C. Pignalberi, Policlinico Campus Biomedico, Roma (8); M. Mariani, Ospedale Parodi-Delfino, Colleferro (7); C. Bianchi, Ospedale CTO, Roma (8); F. Ammirati and F. Colivicchi, Ospedale S. Filippo Neri, Roma (14); M. Rolloni, Ospedale Santissimo Gonfalone, Monterotondo (6); E. Falettra, Aurelia Hospital, Roma (7); G. Limongelli, Ospedale Villa Betania, Roma (5); M. Modica, Ospedale IDI, Roma (4); A. Ammirati, Ospedale Bambino Gesù, Presidio di Padiglione, Roma (6); and P. Gelfo, Ospedale S. Maria Goretti, Latina (8). The Organizing Committee was made up of M. Santini (chairman), F. Ammirati, F. Colivicchi, S. Orazi, and C. Pignalberi. The External Safety and Efficacy Monitor was M. Zoni Berisso.

**Acknowledgment**

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