

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Dual-Chamber Pacing in the Treatment of Neurally Mediated Tilt-Positive Cardioinhibitory Syncope : Pacemaker Versus No Therapy: A Multicenter Randomized Study

Richard Sutton, Michele Brignole, Carlo Menozzi, Antonio Raviele, Paolo Alboni, Paolo Giani and Angel Moya

Circulation 2000;102;294-299

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2000 American Heart Association. 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/cgi/content/full/102/3/294>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

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

Dual-Chamber Pacing in the Treatment of Neurally Mediated Tilt-Positive Cardioinhibitory Syncope

Pacemaker Versus No Therapy: A Multicenter Randomized Study

Richard Sutton, DSc Med; Michele Brignole, MD; Carlo Menozzi, MD; Antonio Raviele, MD; Paolo Alboni, MD; Paolo Giani, MD; Angel Moya, MD;
for the Vasovagal Syncope International Study (VASIS) Investigators

Background—This study was performed to compare implantation of a DDI pacemaker with rate hysteresis with no implant in respect to syncopal recurrences in patients with severe cardioinhibitory tilt-positive neurally mediated syncope.

Methods and Results—Forty-two patients from 18 European centers were randomized to receive a DDI pacemaker programmed to 80 bpm with hysteresis of 45 bpm (19 patients) or no pacemaker (23 patients). Inclusion criteria were ≥ 3 syncopes over the last 2 years and a positive cardioinhibitory (Vasovagal Syncope International Study types 2A and 2B) response to tilt testing. The median number of previous syncopal episodes was 6; asystolic response to tilt testing was present in 36 patients (86%) (mean asystole, 13.9 ± 10.2 seconds). All patients were followed up for a minimum of 1.0 years and a maximum of 6.7 years (mean, 3.7 ± 2.2). One patient (5%) in the pacemaker arm experienced recurrence of syncope compared with 14 patients (61%) in the no-pacemaker arm ($P=0.0006$). In the no-pacemaker arm, the median time to first syncopal recurrence was 5 months, with a rate of 0.44 per year. On repeated tilt testing performed within 15 days after enrollment, positive responses were observed in 59% of patients with pacemakers and in 61% of patients without pacemakers ($P=NS$).

Conclusions—In a limited, select group of patients with tilt-positive cardioinhibitory syncope, DDI pacing with hysteresis reduced the likelihood of syncope. The benefit of the therapy was maintained over the long term. Even in untreated patients, the syncopal recurrence burden was low. A negative result of tilt testing was not a useful means to evaluate therapy efficacy. (*Circulation*. 2000;102:294-299.)

Key Words: syncope ■ nervous system, autonomic ■ pacemakers

The usefulness of cardiac pacing for prevention of syncopal recurrences in patients affected by tilt-positive neurally mediated syncope has been questioned owing to the observation that the vasodepressor component often seems to play a dominant role compared with the cardioinhibitory component. In a tilting study,¹ syncope was not prevented by atropine or pacing. A few observational, nonrandomized studies²⁻⁴ have suggested a possible benefit from pacing, but syncope recurred in 18% to 50% of patients over a follow-up ranging from 6 to 50 months. In a recent randomized, controlled trial,⁵ there was an 84% reduction in risk of syncope in pacemaker patients compared with patients without pacemakers, but syncope still recurred in 22% of patients during a 2-month follow-up. Pacemaker therapy was more effective in a small series of tilt-positive patients who had the fortuitous ECG documentation of a spontaneous asystolic syncope.⁶ We formed the hypothesis that the greater the

cardioinhibitory component of the reflex is, the higher the likelihood is that pacing therapy may be effective. The pacemaker protocol of the Vasovagal Syncope International Study (VASIS) was designed to investigate whether dual-chamber pacing is able to prevent syncopal recurrences in patients with severe cardioinhibitory tilt-positive responses. Results of the drug (Etilefrine) protocol of the VASIS study have recently been published.⁷

Methods

Study Protocol

This was a prospective, controlled, multicenter study with central randomization: therapy versus no therapy. The study tested the hypothesis that a decision to implant a DDI pacemaker with rate hysteresis would reduce the risk of recurrence of syncope compared with not implanting a pacemaker. The study protocol was previously published.⁸ The main aim of the study was to evaluate the ability of the active therapy to reduce the interval to first recurrence of

Received November 3, 1999; revision received January 21, 2000; accepted February 14, 2000.

From the Departments of Cardiology of Royal Brompton Hospital, London, UK (R.S.); Ospedali Riuniti, Lavagna, Italy (M.B.); Ospedale S Maria Nuova, Reggio Emilia, Italy (C.M.); Ospedale Umberto I, Mestre, Italy (A.R.); Ospedale Civile, Cento, Italy (P.A.); Ospedale Bolognini, Seriate, Italy (P.G.); and Hospital Vall d'Hebron, Barcelona, Spain (A.M.).

A complete list of investigators appears in the Appendix.

Correspondence to Michele Brignole, MD, Via A Grilli 164, 16041 Borzonasca, Italy. E-mail brignole@omninet.it

© 2000 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

syncope. Secondary aims were to investigate whether pacing is able to reduce the total burden of syncopal recurrences, to evaluate the natural history of tilt-induced cardioinhibitory neurally mediated syncope, to evaluate the short-term effect of pacemaker therapy during tilt testing, and to test the utility of the VASIS classification of tilt-induced syncope⁸⁻¹⁰ to identify patients who may benefit from pacing therapy. The study protocol was approved by the ethics committee of each participating center. All enrolled patients gave written, informed consent.

Patient Eligibility

To be included in the study, the patients affected by neurally mediated syncope had to fulfill the following 3 conditions: ≥ 3 syncopal episodes in the last 2 years, with the last episode occurring within 6 months of enrollment and with an interval between the first and the last episode of >6 months; positive VASIS type 2A or 2B cardioinhibitory response to head-up tilt testing (definitions in the Tilt Test Protocol Section); and age >40 years or, if <40 years, proven refractoriness to conventional drug therapy. Eligible patients who refused to participate in the pacemaker study were allowed to enter the Etilerfrine arm of the study. The diagnosis of neurally mediated syncope was based, in addition to a positive tilt test result, on the exclusion of all other possible causes of syncope by means of a systematic workup as previously described.^{7,8} Patients were excluded if a cause of syncope other than vasovagal was known or suspected.⁸ Other exclusion criteria included recent (<6 months) myocardial infarction, severe heart failure (NYHA class III or IV), concomitant severe chronic diseases (eg, diabetes mellitus, neurological diseases, terminal diseases, and neoplasia), and patient refusal to participate in the study.

Tilt Test Protocol

The Westminster protocol,^{8,11-13} ie, tilting to 60° for 45 minutes, was used. It was highly recommended that we use noninvasive continuous monitoring of arterial pressure; a sphygmomanometer cuff was permitted, rendering subclassification into VASIS 2A and 2B categories difficult. Beginning in November 1996, sublingual nitroglycerin provocation¹⁴ was added. If syncope did not develop during the initial passive phase, 300 μg nitroglycerin was administered sublingually, and patients continued to be tilted for an additional 20 minutes. Overall, 3 patients (1 in the pacemaker arm and 2 in the no-pacemaker arm) were enrolled because of a positive response to nitroglycerin provocation.

The end point of the test was reproduction of syncope. For the purposes of the study, only type 2 positive responses of the VASIS classification⁸⁻¹⁰ were eligible for inclusion. Type 2A (cardioinhibitory) response is defined as the heart rate rising initially then falling to a ventricular rate <40 bpm for >10 seconds or asystole occurring for >3 seconds, with blood pressure rising initially then falling before the heart rate falls. Type 2B (cardioinhibitory) response is defined as the heart rate rising initially then falling to a ventricular rate <40 bpm for >10 seconds or asystole occurring for >3 seconds, with blood pressure rising initially and only falling to hypotensive levels <80 mm Hg systolic at or after the onset of rapid and severe heart rate fall.

Study Design

Eligible patients were assigned, according to a central computer-generated randomization list, to 1 of the 2 study arms. Immediately after randomization, treatment arm patients received a dual-chamber pacemaker with rate hysteresis (Paragon III or Trilogy DC, St Jude Medical) programmed as follows: DDI, 80 bpm; hysteresis, 45 bpm; and AV interval, 150 ms. Patients in the no-pacemaker arm received no specific therapy. In both groups, any other treatment for syncope (drugs or elastic compression stockings) was forbidden. Six patients were receiving medication for syncope before enrollment, but the medications were discontinued because of obvious inefficacy. Any other vasoactive treatment already in progress (eg, digitalis, diuretics, or antihypertensives) was allowed to continue, with the recommendation that their doses not be modified during follow-up.

A further head-up tilt test was performed within 15 days of enrollment in the patients in both groups (no therapy for the control arm and activated pacemaker for the pacemaker arm).

During follow-up, patients were monitored either clinically or by telephone interview with the patient or the physician. The primary study end point was recurrence of syncope. Recurrence of presyncope, dizziness, and other minor events were not collected or considered for analysis.

Statistical Methods

For the primary analysis, all outcomes were analyzed on the intention-to-treat principle. A second analysis of efficacy (on-treatment analysis was made primarily to demonstrate the natural history of neurally mediated syncope (secondary end point).

The recurrence of syncope in the 2 treatment groups was tested by using the odds ratio of the 2-binomial proportion analysis. Moreover, the time to the first syncopal recurrence was analyzed by means of Kaplan-Meier survival curves, and the curves were compared by means of the log-rank test.

The assumption for the sample size calculation was that the no-pacemaker arm would have a cumulative risk of recurrence of syncope of 20%/y. We anticipated that a total of 60 patients would have to be followed up for an average of 2 years to yield an 80% power to detect a 75% reduction of risk of recurrence of syncope in the active treatment arm with $P=0.05$. Owing to the lower-than-expected recruitment rate, enrollment ceased in May 1998. In October 1998, an analysis was performed in which a treatment effect in favor of pacing was observed; thus, a decision was made to complete a minimum 1-year follow-up for all patients.

Results

Patient Characteristics

Screening logs were not maintained throughout the trial, but we used data from tilt laboratory records to calculate that during the study recruitment period, ≈ 1200 potentially eligible patients were initially screened. Of these, 42 patients (3.5%) met all inclusion and exclusion criteria, gave informed consent, were randomized and assigned to pacemaker or no-pacemaker groups, and were followed up until the end of the study according to the intention-to-treat principle. Enrollment started in April 1992 and ended in May 1998.

All the patients were followed up for a minimum of 1.0 years and a maximum of 6.7 years (mean \pm SD, 3.7 ± 2.2 years). Follow-up was completed in May 1999. No patient was lost to follow-up.

Three patients assigned to the no-pacemaker group requested a pacemaker implant within 1 month of randomization before any recurrence of syncope. The reason for 1 patient was recurrence of presyncope. In the on-treatment analysis, these patients were assigned to the pacemaker group. Five other patients in the no-pacemaker group received a pacemaker after the time of the primary end point because of the recurrence of ≥ 1 syncopal episodes. In the on-treatment analysis, their follow-up was censored at time of pacemaker implantation (Figure 1).

The baseline characteristics of patients in the 2 groups were broadly similar, but pacemaker group patients were older (Table 1). Before enrollment, the patients had had a median of 6 syncopal episodes. A severe cardioinhibitory response to tilt testing causing a prolonged asystolic pause >3 seconds was present in 36 of 42 patients (86%), with a mean ventricular pause of 13.9 ± 10.2 seconds (median, 11.5 seconds; range, 3 to 34 seconds).

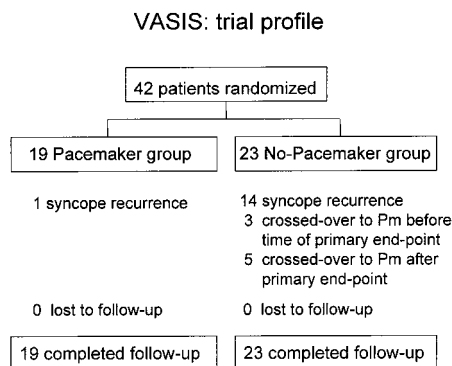


Figure 1. Flow diagram of trial. Pm indicates pacemaker.

Primary End Point

In the intention-to-treat analysis, syncope recurred in 1 patient (5%) in the pacemaker arm after 15 months and in 14 patients (61%) in the no-pacemaker arm after a median of 5 months (interquartile range, 2 to 20; Table 2); the difference was highly significant ($P=0.0006$). The Kaplan-Meier actuarial estimates of first recurrence of syncope after 1, 3, and 5 years were 0%, 6%, and 6% in the pacemaker group and 39%, 50%, and 75% in the no-pacemaker group (Figure 2).

Secondary End Points

The natural history of untreated patients was evaluated by on-treatment analysis. Syncope recurred in 70% of untreated patients (Table 2). The Kaplan-Meier actuarial estimates of first recurrence of syncope after 1, 3, and 5 years were 45%, 57%, and 78% (Figure 3). Overall, only 24 episodes (mean, 1.7 ± 0.9 per patient) occurred during a total follow-up of 54.7 years, yielding a rate of 0.44 episodes per year. As expected, the comparison with the treated patients was even higher with the on-treatment analysis than with intention-to-treat analysis. In no case did syncopal relapse cause injury.

On repeat tilt testing performed within 15 days of enrollment, pacemaker treatment was not superior to no therapy in preventing tilt-induced syncope (Table 2). In the no-pacemaker arm, overall reproducibility of positive responses between the first and second tests was 61% (11 of 18); of type 2 responses, 50% (9 of 18); and of asystolic responses, 41% (7 of 17 cases). In the pacemaker arm, the tilt test was repeated with the pacemaker programmed at a rate of 80 bpm with a hysteresis rate of 45 bpm. There were 10 of 17 positive responses (59%). In 5 patients, the heart rate never decreased below 45 bpm, so the pacemaker remained inactive; in 5 patients, syncope occurred despite activation of pacing therapy. Of the 7 negative cases, the pacemaker was activated and possibly prevented syncope in only 1 patient.

Three patients developed stable or paroxysmal second-degree AV block during follow-up. There were 2 deaths in the pacemaker arm, 1 caused by stroke and 1 by cancer.

Discussion

This study shows that dual-chamber permanent pacing markedly reduces the likelihood of a recurrence of syncope in patients with severe cardioinhibitory response to tilt testing to about 1%/y. The benefits of pacing treatment are maintained

TABLE 1. Baseline Clinical Characteristics

	Pacemaker (n=19)	No Pacemaker (n=23)
Age, y	64±11*	56±14*
Male, n (%)	11 (58)	13 (57)
Syncope episodes in lifetime, n, median (interquartile range)	5 (3–12)	6 (3–10)
Syncope episodes in last 2 y, n, median (interquartile range)	3 (3–4)	3 (3–4.5)
Duration of symptoms, y, median (interquartile range)	4 (2–14)	5 (2.5–12)
Presyncope, n (%)	12 (63)	16 (70)
Presyncope episodes in last 2 y, n, median (interquartile range)	4 (1–10)	6 (5–30)
Trauma secondary to syncope, n (%)	8 (42)	10 (43)
Previous drug treatment, n (%)	2 (11)	4 (17)
History of suspected vasovagal or situational syncope, n (%)	10 (53)	13 (57)
Associated cardiovascular disorders, n (%)	9 (47)	7 (30)
Hypertension on therapy, n	4	4
Atherosclerotic, n	4	3
Valvular, n	1	1
ECG abnormalities, n (%)	3 (16)	4 (17)
Echocardiographic abnormalities, n (%)	6 (32)	6 (26)
Response to baseline tilt testing		
Type 2A, n (%)	8 (42)	8 (35)
Type 2B, n (%)	8 (42)	11 (48)
Type 2 (undefined), n (%)	3 (16)	4 (17)
Asystolic, n (%)	15 (79)	21 (91)
Mean asystole, s	15.2±12.0	13.0±8.9

* $P=0.05$.

for ≥ 5 years. If left untreated, about half the patients would have had recurrence of syncope within 1 year and about two thirds within 5 years, as can be presumed by the results observed in the control group.

Pacemaker therapy was more effective than in other studies^{2–5} in which syncope recurred in 18% to 50% of patients. We think that a possible explanation for these better results was the different selection of patients. Indeed, all our patients had had a severe cardioinhibitory response of type 2A or 2B during tilt testing, and almost all had a very long ventricular pause at the time of induced syncope. This suggests that when asystole is part of the mechanism of the vasovagal response, pacing is likely to be effective and that this good result could be predicted by a cardioinhibitory response to tilt testing. In this respect, the study validates the usefulness of our protocol of tilt testing and of the VASIS classification.

The results may have been influenced by the lower-than-expected recruitment rate. It is likely that only the “worst” or “most severe” cases were included. It seems clear that all enrolled patients had to have extensive discussions before becoming ready to accept the notion of pacemaker implantation before randomization; indeed, no patient who was randomized to a pacemaker subsequently refused, and 3

TABLE 2. Primary and Secondary Outcome Events by Group

Outcome Event	Pacemaker	No Pacemaker	Risk Ratio (95% CI)	P
Intention-to-treat analysis				
Patients in analysis, n	19	23		
Syncopal recurrence, n (%)	1 (5)	14 (61)	0.04 (0.005–0.3)	0.0006
Total syncope episodes, n	2	26		
Mean per patient, n	2	1.9±1.2		
Median time to first recurrence, mo (interquartile range)	15	5 (2–20)		
Follow-up, y	72.2	75.9		
Rate per year	0.03	0.34		
On-treatment analysis				
Patients in analysis, n	22	20		
Syncopal recurrence, n (%)	1 (5)	14 (70)	0.02 (0.003–0.2)	0.0001
Total syncope episodes, n	2	24		
Mean per patient, n	2	1.7±0.9		
Median time to first recurrence, mo (interquartile range)	15	5 (2–20)		
Follow-up, y	77.8	54.7		
Rate per year	0.03	0.44		
Acute effect (repeated positive tilt testing), n (%)	10/17 (59)*	11/18 (61)*	0.84 (0.19–4.3)	0.84

*Control tilt testing not performed in 5 and 2 patients in the pacemaker and no-pacemaker groups, respectively, because of patient refusal.

patients randomized to no treatment required the implantation of a pacemaker soon after randomization. Thus, the “decision” process was a prerequisite for all candidates. The decision to accept a “no-return” treatment severely restricted the patients who accepted to be enrolled much more than, for example, when a drug was proposed.⁷ We do not exactly know the reasons other than the predefined inclusion and exclusion criteria that made investigators include or exclude a patient. There are some possible explanations. First, patients with long asystolic responses were preferred for inclusion over those with cardioinhibition without asystole. Indeed, the percentage of asystolic forms observed in the present study—86% of all type 2 responses—is higher than that observed in 2 unselected populations, 48% and 65% respectively.^{15,16} Second, the clinical judgment of disease severity is largely individual and is based on the patient’s and the physician’s perceptions of the disease in that patient. These concepts can

hardly be defined in a study protocol but may play an important role in the selection of more severely ill patients. For these reasons, caution must be used when the results of this study are applied to a general population of patients presenting with cardioinhibitory response to tilt testing.

Comparison With the North American Vasovagal Pacemaker Study

Our results substantiate those of the other existing randomized prospective study, ie, the North American Vasovagal Pacemaker Study.⁵ In both studies, the control group did not include the implantation of a device; thus, the studies were not blinded. We therefore cannot exclude a bias in assessment of outcome, and there is some potential for a “placebo effect” of psychological benefit from receiving a pacemaker. Thus, more precisely, the conclusion of the study should be that the decision to implant a pacemaker was better than no treatment.

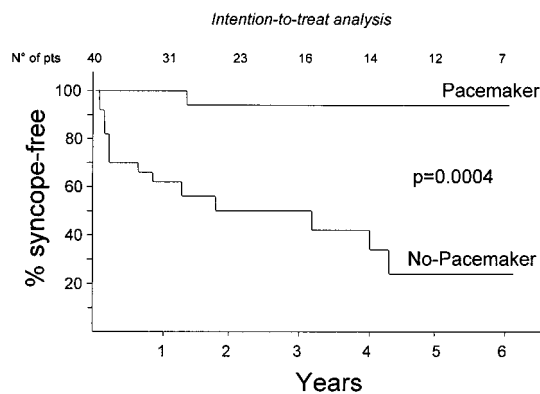


Figure 2. Kaplan-Meier estimates of probability of remaining free of syncopal recurrences in 19 patients in pacemaker arm and 23 patients in no-pacemaker arm in intention-to-treat analysis.

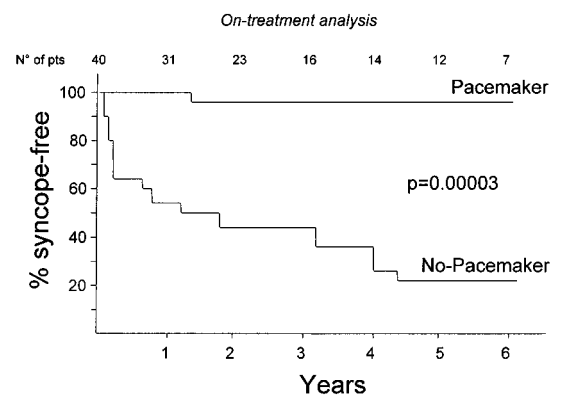


Figure 3. Kaplan-Meier estimates of probability of remaining free of syncopal recurrences in 22 patients in pacemaker arm and 20 patients in no-pacemaker arm in on-treatment analysis.

When the study was planned in 1992, we decided not to control for the implantation itself because at that time we knew very little of the natural history of severe vasovagal syncope and because device implantation was not justified in all candidates. However, it is unlikely that a placebo can account for all the dramatic reduction in syncopal recurrences. For example, in the VASIS Etilefrine Study,⁷ the placebo arm yielded a recurrence rate of syncope of 24% at 1 year, which remains much higher than that observed with pacemakers activated. Moreover, the very long duration of the follow-up makes it unlikely that a pacemaker that was switched off could have prevented syncopal relapses.

There are some important differences between the 2 studies. Apart from the different tilt protocols—long passive phase versus isoproterenol challenge—that have already been discussed, the clinical characteristics of the 2 populations seem quite different. In the North American Pacemaker Study, patients were younger (mean age, 43 years); had had more episodes of syncope both during their lifetimes and during the last year (median, 3 to 6 episodes during the last year); and in those randomized to no pacemaker, the mean time from randomization to first syncopal relapse was shorter (only 54 days). Even though in the untreated arm the rate of recurrence of syncope was similar to that of our study, these differences could partially explain the different outcome of the treated patients. Unfortunately, in the American study, data were censored to the time of the first syncopal recurrence, so a comparison with the total burden of syncope cannot be made. We used a conventional pacemaker programmed to prevent extreme bradycardia and asystole, whereas in the other study, a specifically designed device with a rate-response feature and a higher pacing rate (100 bpm) was implanted. Given the good results, in our population, these features may not add significant benefit. This is in contrast to some published data.¹⁷

Natural History

In the untreated group, the total burden of syncope was lower than expected, with a syncopal recurrence rate of 0.44%/y during a follow-up of >3 years. Because this rate was lower than that observed in the 2 years before enrollment, there was a spontaneous decrease in syncopal episodes even in the absence of any active or placebo treatment. This fact had already been observed in previous studies evaluating the outcome of patients after diagnostic tilt testing.^{18–20} The reason is unclear. One could argue that the simple fact that a patient was evaluated and diagnosed has a therapeutic effect, probably because the patient learns to recognize the onset of syncopal symptoms and to avoid loss of consciousness. Another explanation may be that syncopal episodes occur in clusters, with the maximum number of episodes at the time of evaluation.²⁰ Anyway, the low recurrence rate and the low risk of related injury we observed suggest that the use of pacemaker therapy could be restricted only to those patients who have frequent relapses, after diagnostic evaluation, or are at risk of associated injuries.

Value of Repeated Tilt Testing

Previous studies have shown that the reproducibility of passive tilt testing is ≈60% to 80%.^{13,18,21} When subjects

were given a placebo, the reproducibility rate decreased to 55% in the VASIS Etilefrine Study.⁷ The present study confirms that the same reproducibility applies to the cardioinhibitory forms. Moreover, pacemaker therapy was unable to prevent syncopal recurrences during tilt testing, as shown by Sra et al¹ in a short-term study. The present result indicates that short-term studies cannot predict the long-term outcome.

Study Limitations

Despite randomization, pacemaker patients were older than non-pacemaker patients. It is unlikely that the age imbalance could have modified results substantially because no data in the literature show that the recurrence rate of syncope is different between young and old patients. Moreover, the 2 groups were well balanced for all other baseline characteristics (Table 1). As discussed, the study was not blinded, with no device implantation in the control arm. Recurrences of presyncope and dizziness were not collected, but there were no differences between the 2 groups at enrollment (Table 1). It is possible that pacemaker therapy aborted syncope in many patients, but they were still symptomatic with dizziness or presyncope. However, presyncope and dizziness are less easy to define than syncope and are difficult to evaluate in a long follow-up study. Furthermore, for a syncopal patient to be converted to presyncope could be regarded as a benefit because the symptoms are less severe and falls with injury will not occur. Finally, a longer follow-up is necessary to assess any potential deleterious effect of long-term pacing in the same cohort of patients.

Conclusions

Dual-chamber pacing at a rate of 80 bpm reduces the likelihood of syncope in patients with tilt-positive cardioinhibitory syncope, and the benefits are maintained for several years. Because in untreated patients the syncopal recurrence rate is low and the outcome benign for many years, further studies are required to define the indications for this therapy. Currently, it seems prudent to limit pacemaker use to a few select, severely symptomatic patients who are particularly predisposed to injury or accidents or have frequent relapses.

Appendix

VASIS Participating Centers and Investigators

The number of patients is given in parentheses.

Italy

Ospedale S. Maria Nuova, Reggio Emilia: Lolli Gino (8); Ospedali Riuniti, Lavagna: Oddone Daniele (4); Ospedale Civile, Imperia: Musso Giacomo (3); Ospedale Civile Ferrari, Casarano: Pettinati Giacinto (3); Ospedale S. Andrea, Vercelli: Gronda Maurizio (2); Ospedale S. Agostino, Modena: Moracchini Pier Vittorio, Giuliani Mauro (2); Ospedale Civile, Desenzano sul Garda: Ziacchi Vigilio (2); Ospedale S. Gerardo, Monza: Vincenti Antonio (2); Ospedale S. Spirito, Roma: Carunchio Alessandro (2); Ospedale Bolognini Seriate: Giudici Vittorio, Leoni Giuseppe (1); Ospedale Civile, Mirano: Sartori Federico (1); and Ospedale Umberto I, Mestre: Giada Franco (1).

Sweden

Sahlgrenska Hospital, Gothenburg: Edvardsson Nils (4); and University Hospital, Umea: Rask Peter (2).

United Kingdom

Chelsea and Westminster Hospital, London: Richard Sutton (1); and Royal Victoria Infirmary, Newcastle-on-Tyne: Kenny Rose Anne (1).

Poland

University Hospital, Gdansk: Kozłowski Dariusz (2).

Spain

Valme University Hospital, Seville: Vazques Rafael (1).

Organizing Committee (Steering Committee)

R. Sutton (chairman), P. Alboni, M. Brignole, P. Giani, C. Menozzi, A. Moya, and A. Raviele.

Liaison Committee

R. Sutton, M. Brignole, and A. Raviele.

External Monitoring and Safety Committee

D. Benditt, J.J. Blanc, J. Perrins, and E. Piccolo.

Acknowledgment

The study was supported by a grant from St Jude Medical, CRM Division, Järfälla, Sweden.

References

- Sra JS, Jazayeri MR, Avital B, et al. Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl Med*. 1993;328:1085–1090.
- Petersen ME, Chamberlain-Webber R, Fitzpatrick AP, et al. Permanent pacing for cardioinhibitory malignant vasovagal syncope. *Br Heart J*. 1994;71:274–281.
- Sheldon R, Koshman ML, Wilson W, et al. Effect of dual-chamber pacing with automatic rate-drop sensing on recurrent neurally mediated syncope. *Am J Cardiol*. 1998;81:158–162.
- Benditt D, Sutton R, Gammage M, et al. Clinical experience with Thera DR rate-drop response pacing algorithm in carotid sinus syndrome and vasovagal syncope. *Pacing Clin Electrophysiol*. 1997;20(pt II):832–839.
- Connolly S, Sheldon R, Roberts R, et al. The North American Vasovagal Pacemaker Study (VPS): a randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol*. 1999;33:16–20.
- Brignole M, Menozzi C. Methods other than tilt testing for diagnosing neurocardiogenic (neurally mediated) syncope. *Pacing Clin Electrophysiol*. 1997;20:795–780.
- Raviele A, Brignole M, Sutton R, et al. Effect of Etilefrine in preventing syncopal recurrence in patients with tilt-induced vasovagal syncope: a double-blind, randomized, placebo-controlled trial. *Circulation*. 1999;99:1452–1457.
- Is dual-chamber pacing efficacious in treatment of neurally mediated tilt positive cardioinhibitory syncope? Pacemaker vs no therapy: a multi-center randomized study. *Eur J Cardiac Pacing Electrophysiol*. 1993;3:169–172.
- Sutton R, Petersen M, Brignole M, et al. Proposed classification for tilt induced vasovagal syncope. *Eur J Cardiac Pacing Electrophysiol*. 1992;2:180–183.
- Benditt D, Petersen ME, Lurie K, et al. Cardiac pacing for prevention of recurrent vasovagal syncope. *Ann Intern Med*. 1995;122:204–209.
- Kenny RA, Bayliss J, Ingram A, et al. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet*. 1986;1:1352–1354.
- Fitzpatrick A, Sutton R. Tilting towards a diagnosis in recurrent unexplained syncope. *Lancet*. 1986;1:658–660.
- Fitzpatrick A, Theodorakis G, Vardas P, et al. Methodology of head-up tilt testing in unexplained syncope. *J Am Coll Cardiol*. 1991;17:125–130.
- Raviele A, Menozzi C, Brignole M, et al. Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol*. 1995;76:267–272.
- Kurbaan AS, Franzén AC, Bowker TJ, et al. Usefulness of tilt test-induced patterns of heart rate and blood pressure using a two-stage protocol with glyceryl trinitrate provocation in patients with syncope of unknown origin. *Am J Cardiol*. 1999;84:665–670.
- Brignole M, Menozzi C, Del Rosso A, et al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification: analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. *Europace*. 2000;2:66–76.
- Ammirati F, Colivicchi F, Toscano S, et al. DDD pacing with rate drop response function versus DDI with rate hysteresis pacing for cardioinhibitory vasovagal syncope. *Pacing Clin Electrophysiol*. 1998;21:2178–2181.
- Brignole M, Menozzi C, Gianfranchi L, et al. A controlled trial of acute and long-term medical therapy in tilt-induced neurally mediated syncope. *Am J Cardiol*. 1992;70:339–342.
- Sheldon R, Rose S, Flanagan P, et al. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. *Circulation*. 1996;93:973–981.
- Natale A, Geiger MJ, Maglio C, et al. Recurrence of neurocardiogenic syncope without pharmacologic interventions. *Am J Cardiol*. 1995;77:1001–1003.
- Blanc JJ, Mansourati J, Maheu B, et al. Reproducibility of a positive passive head-up tilt test at a seven day interval in patients with syncope. *Am J Cardiol*. 1993;72:469–471.