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Clinical research

A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE)

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Aims Recently, some studies revealed the efficacy of pacemaker implantation in decreasing recurrences in patients with vasovagal syncope. As these studies were not blinded or placebo-controlled, the benefits observed might have been due to a bias in the assessment of outcomes or to a placebo effect of the pacemaker. We performed a randomized, double-blind, placebo-controlled study in order to ascertain if pacing therapy reduces the risk of syncope relapse.

Methods and results Twenty-nine patients (53 ± 16 years; 19 women) with severe recurrent tilt-induced vasovagal syncope (median 12 syncopes in the lifetime) and 1 syncopal relapse after head-up tilt testing underwent implantation of a pacemaker, and were randomized to pacemaker ON or to pacemaker OFF.

During a median of 715 days of follow-up, 8 (50%) patients randomized to pacemaker ON had recurrence of syncope compared to 5 (38%) of patients randomized to pacemaker OFF (p=n.s.); the median time to first syncope was longer in the pacemaker ON than in pacemaker OFF group, although not significantly so (97 [38–144] vs 20 [4–302] days; $p = 0.38$). There was also no significant difference in the subgroups of patients who had had a mixed response and in those who had had an asystolic response during head-up tilt testing.

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Conclusion Our data were unable to show a superiority of active pacing versus inactive pacing in preventing syncopal recurrence in patients with severe recurrent tilt-induced vasovagal syncope.

Introduction

Though vasovagal syncope does not directly cause death, it is often associated with severe trauma and, when recurrent, significantly impairs the patient's quality of life. Indeed, patients with frequent fainting fits suffer severe functional and psychological limitations.[1]

The treatment of vasovagal syncope generally involves reassurance, education and behavioural measures for all patients, drug therapy for those who are most symptomatic, and pacemaker implantation in a few selected subjects.[2] However, placebo-controlled drug studies have yielded disappointing results.[3–7] Moreover, as all pacemaker studies, except for one, have not been double-blind or placebo-controlled,[8–14] it is not possible to exclude a methodological bias in outcomes assessment or a placebo effect of pacemaker implantation. Thus, pharmacological and electrical therapies for vasovagal syncope are still controversial. Other possible therapeutical approaches, such as tilt training[15] and counter-pressure manoeuvres[16,17] have only recently been proposed and need to be further evaluated.

The aim of the vasovagal SYNcope and PACing (SYNPACE) trial was to ascertain whether, in patients with recurrent tilt-induced vasovagal syncope, the implantation of a dual-chamber, pacemaker programmed to ON, reduced the number of patients suffering syncopal relapses and/or prolonged the time to the first recurrence in comparison with the implantation of a pacemaker programmed to OFF.

Methods

Study design

This clinical trial was a multi-centre, prospective, double-blind, randomized, placebo-controlled study. Its main aim was to compare the efficacy of an active dual-chamber pacemaker with that of an inactive pacemaker in reducing syncopal relapses in patients suffering from recurrent vasovagal syncope. The study protocol had been published previously.[18] The primary end-point of the study was the first recurrence of syncope. The number of patients who experienced syncope during follow-up, and the time to the first recurrence were taken as parameters for measuring the primary end-point. On reaching the primary clinical end-point, or at the end of the study period, all patients had their pacemaker programmed to ON. The study protocol was approved by the ethics committee of each participating centre, and all patients gave written, informed consent.

Patient eligibility

To be enrolled, all patients had to meet the following criteria: frequently recurrent syncopes and positive head-up tilt testing with asystolic or mixed response (see below), at least 6 syncopal events in the patient's lifetime, the last occurring no more than 6 months before enrolment; at least one recurrence within 12 months following positive head-up tilt testing, exclusion of any other cause of syncope after a complete work-up, age more than 18 years. These criteria were selected in order to provide a study population with a high probability of syncopal recurrence during follow-up.[5,19] Moreover, the requirement for a significant cardioinhibitory component was based on the assumption that pacemaker implantation is effective in preventing new syncopal episodes only in patients with bradycardia/asystole during tilt-induced syncope.

Definitions

Syncope was defined as sudden complete loss of consciousness associated to the inability to maintain postural tone, followed by spontaneous recovery. Pre-syncope was defined as the appearance of specific symptoms typical of imminent syncope (nausea, clouding of vision, weakness, sweating, dizziness) associated with partial loss of tone, without complete loss of consciousness.

Head-up tilt testing

Head-up tilt testing was carried out in accordance with the ''Italian protocol'':[20,21] 20 min at 60° without drug potentiation, followed by 15 min at the same inclination after sublingual administration of 400 μg of nitroglycerin spray.

A positive head-up tilt test response was defined as reproduction of the patient's spontaneous syncope in association with hypotension, bradycardia, or both. The positive response to head-up tilt testing was classified as follows: *asystolic response*: development of asystole $\geqslant$ 3 s; *mixed response*: development of bradycardia <60 beats per minute for at least ten beats, but without asystole $\geqslant$ 3 s; *vasodepressor response*: development of marked hypotension with no or only a slight decrease in heart rate.

Randomisation and pacemaker programming

Enrolled patients were divided into two groups on the basis of their haemodynamic response during tilt-induced syncope: *Asystolic group* and *Mixed group*. Patients from both groups underwent implantation of a dual-chamber pacemaker, and were immediately randomized in a double-blind fashion to pacemaker ON in the active (DDD) mode with rate-drop response (RDR), or pacemaker OFF in the inactive (OOO) mode. Randomisation was centralized and was based on two tables, one for the Asystolic group, and the other for the Mixed group.

The device used was the Vitatron Clarity DR dual-chamber pacemaker. Programming of PM ON was as follows: DDD-RDR mode; lower rate 60 beats per minute; long atrio-ventricular delay in order to facilitate ventricular activation through the normal conduction pathways; rate drop parameters with detection at an RR interval prolongation $\geqslant 200$ ms with respect to the mean value, three confirmation beats, intervention rate 100—110 beats per minute, and spontaneous rhythm recovery ON. In each hospital there was only one person responsible for programming the pacemaker.

Follow-up

Patients were asked to keep a clinical diary, specifying the number, severity and time of syncopal and pre-syncopal events, the circumstances in which they occurred and any associated traumas. During the study period, the use of drugs to prevent vasovagal syncope was not allowed. The clinical follow-up was performed by an investigator who was unaware of the randomisation applied.

Statistical analysis

The primary analysis of the results of the study was by intention-to-treat but we also made an on-treatment analysis. Differences between pacemaker ON and pacemaker OFF patients in the total population were tested for statistical significance by means of Student's *t*-test, Wilcoxon's test, and Fisher's exact test, as appropriate. Differences within the Asystolic and Mixed groups were assessed by ANOVA and v^2-test. The time to the first syncopal recurrence was analysed by using the Kaplan—Meier curves, and compared using the log-rank test. The COX proportional-hazards model was used to identify clinical variables independently associated with the risk of syncopal recurrence. The accepted value for significance was $p < 0.05$.

Sample size calculation was based on the following assumptions.[18] According to data in the literature[5,19,22] we hypothesised a risk of syncope recurrence of 70% after one year in our patient population. We estimated that, owing to its placebo effect, pacemaker implantation per se would have decreased this risk by 20%. Furthermore, we anticipated a further 80% reduction in syncope recurrence produced by the therapeutic effect of pacemaker treatment.[11,12] Based on these data, we calculated a 50% syncopal rate after one year in patients randomized to pacemaker OFF, versus 10% in patients randomized to pacemaker ON.[18] Consequently, with an *a* error level of 0.05 and a test power of 0.90, the resulting sample size was 25 patients for each group.

Results

Early termination of the study

Enrolment started in April 2000. As planned, the first formal interim analysis was undertaken after >50% of the expected number of patients were enrolled, in September 2002; 29 patients had been randomized by that time. The analysis showed no superiority of active pacing over inactive pacing. Moreover, in the same period the results of the Vasovagal Pacemaker Study (VPS) II[14] were announced that demonstrated inability of pacing to reduce the risk of syncope recurrence significantly, making the prosecution of the enrolment unethical. Thus, in consultation with the Data and Safety Monitoring Board, a decision was made to terminate enrolment and follow-up, and to report study results as of October 2002.

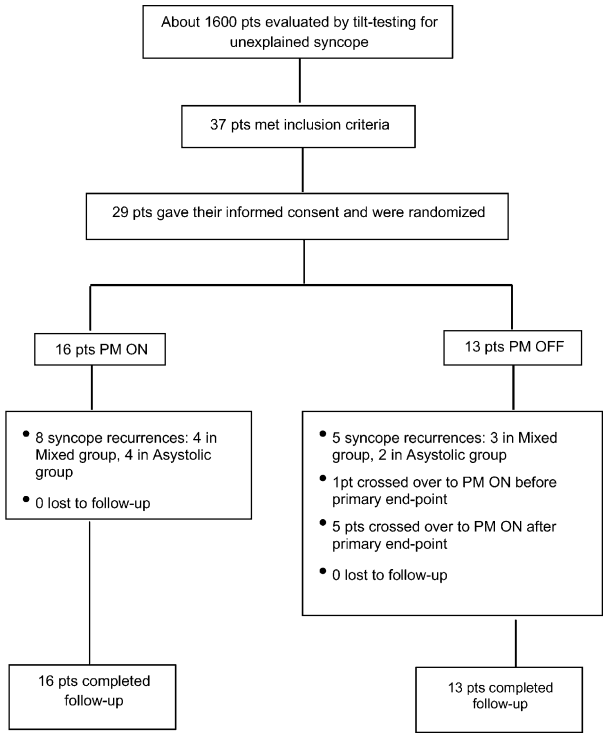

Fig. 1 Trial profile.

Patient characteristics

Screening logs were not maintained throughout the study, but we used data from the head-up tilt testing laboratory to calculate the trial profile (Fig. 1). During the recruitment period, about 1600 patients with unexplained syncope were referred for head-up tilt testing evaluation, and 37 of these (approximatively 2.3%) met all inclusion criteria. Only 29 of the eligible patients gave informed consent and took part in the study (about 1.8% of the source population). Of the 29 patients enrolled, 16 were randomized to pacemaker ON (Asystolic group, 8; Mixed group, 8), and 13 to pacemaker OFF (Asystolic group, 7; Mixed group, 6).

Patients were followed up for a minimum of 4 months, with a median of 715 days (interquartile range 302—785 days). No patient was lost to follow-up. One patient with mixed response, assigned to the pacemaker OFF group, underwent reprogramming to pacemaker ON before the primary end-point, 100 days after randomisation, because of frequent presyncopal recurrences. In the on-treatment analysis, this patient was assigned to pacemaker ON. Five other patients randomized to pacemaker OFF (three Mixed group, and two Asystolic group) had their pacemaker programmed to ON after the first syncopal recurrence. Their follow-up was censored at the time of pacemaker activation. However, they were followed up until the end of the study period.

Table 1 Baseline clinical characteristics

	Total population (n = 29)		Mixed group (n = 14)		Asystolic group (n = 15)	
	PM ON (n = 16)	PM OFF (n = 13)	PM ON (n = 8)	PM OFF (n = 6)	PM ON (n = 8)	PM OFF (n = 7)
Age, years (mean ± SD)	52 ± 19	54 ± 18	53 ± 17	56 ± 9	50 ± 21	52 ± 15
Female gender, n (%)	12 (69)	7 (54)	4 (50)	5 (83)	8 (100)	2 (19)[a]
Cardiovascular disorders, n (%)	6 (37)	5 (38)	3 (37)	3 (50)	3 (37)	2 (29)
Hypertension on therapy, n	3	2	1	1	2	1
Mitral valve prolapse, n	3	3	2	2	1	1
Syncope episodes lifetime, n (median, IQR)	14 (9–30)	10 (6–23)	23 (10–32)	18 (10–105)	12 (8–27)	7 (6–12)
Syncope episodes in the last 6 months, n (median, IQR)	4 (3–6)	2 (1–4)	4 (3–5)	3 (2–12)	4 (2–9)	2 (1–4)
Duration of symptoms, years (median, IQR)	6 (4–25)	12 (3–27)	5 (1–20)	11 (3–33)	18 (5–35)	24 (2–27)
Pre-syncope episodes lifetime, n (median, IQR)	3 (0–10)	2 (0–10)	3 (0–10)	6 (0–10)	3 (0–9)	2 (0–10)
Major syncope-related trauma, n (%)	4 (25)	5 (38)	3 (38)	2 (33)	1 (13)	3 (43)
Prior ineffective drugs for syncope, n (mean ± SD)	1.4 ± 0.8	1.5 ± 1.1	1.3 ± 1.1	1.8 ± 1.3	1.5 ± 0.5	1.1 ± 0.9
Time from last syncope to randomisation, days, (mean ± SD)	17 ± 10	21 ± 15	19 ± 11	17 ± 10	16 ± 9	24 ± 18

IQR: interquartile range; PM: pacemaker; SD: standard deviation.
[a] PM OFF vs PM ON in the Asystolic group: p = 0.01.

The baseline clinical characteristics of patients randomized to pacemaker ON were broadly similar to those of patients randomized to pacemaker OFF (Table 1). However, in the Asystolic group, fewer males were assigned to pacemaker ON than to pacemaker OFF. Before enrolment, patients had had a median of 12 syncopes in their lifetime (interquartile range 7–25), and all had unsuccessfully tried at least one drug for vasovagal syncope. Nine patients (31%) had a positive head-up tilt-test response during the drug-free phase of the test, and 24 patients (69%) after nitroglycerin administration. An asystolic response was present in 15 patients (52%), with a mean ventricular pause of 13 ± 8 s (range 4–30 s; pause >10 s in 8 cases) and a mixed response was present in 14 patients (48%).

Primary end-point

After pacemaker implantation, syncope recurred in 13 (45%) of the 29 patients. In the intention-to-treat and on-treatment analyses, no statistically significant differences in recurrences emerged between the patients with pacemaker ON and those with pacemaker OFF (Table 2). In patients randomized to pacemaker ON, syncope recurred in 8 (50%): 4 (50%) in the Mixed group and 4 (50%) in the Asystolic group. Three of these last patients had had a pause >10 s during baseline head-up tilt testing. In patients randomized to pacemaker OFF, syncope recurred in 5 (38%): 3 (50%) in the Mixed group and 2 (29%) in the Asystolic group. Two (40%) of the 5 patients who suffered syncopal recurrence with pacemaker OFF continued to have recurrences even after pacemaker reprogramming to ON.

In the intention-to-treat and on-treatment analyses the median time to the first syncopal recurrence was about five times longer in the pacemaker ON than in pacemaker OFF group, though not significantly so (97 [38–144] vs 20 [4–302] days, p = 0.38). This overall difference was due to a longer time to syncope in the Asystolic group (97 [50–140] vs 11 [2–20] days, p = 0.064) whereas no difference was observed in the Mixed group (88 [13–387] vs 100 [7–505] days, p = 0.56) (Table 2).

The Kaplan–Meier actuarial estimates of the first syncopal recurrence by intention-to-treat analysis and by on-treatment analysis showed that the probability of remaining free of syncopal events, at one year, was similar between patients with active pacing and patients with inactive pacing both in the total population and in the Mixed and Asystolic groups (by intention-to-treat, 44% vs 31%, 37% vs 33%, and 50% vs 29%, respectively, p=ns) (Fig. 2).

Secondary end-points

Considering the 29 patients as a whole, the syncopal rate was significantly lower in the post-implantation period than in the period before pacemaker implantation (0.06 ± 0.11 syncopes/month vs 0.72 ± 0.68 syncopes/months, $p < 0.001$). By contrast, no differences

Table 2 Outcome events

	Total population		Mixed group		Asystolic group	
	PM ON	PM OFF	PM ON	PM OFF	PM ON	PM OFF
Intention-to-treat analysis						
Patients in analysis, *n*	16	13	8	6	8	7
Syncopal recurrence, *n* (%)	8 (50)	5 (38)	4 (50)	3 (50)	4 (50)	2 (29)
Time to first recurrence, days, (median, IQR)	97 (38–144)	20 (4–302)	88 (13–387)	100 (7–505)	97 (50–140)	11 (2–20)
Syncopal rate, *n*/month (mean ± SD)	0.04 ± 0.06	0.08 ± 0.15	0.04 ± 0.06	0.13 ± 0.20	0.05 ± 0.07	0.04 ± 0.09
Pre-syncopal recurrence, *n* (%)	12 (75)	5 (38)	7(87)	2 (33)	5 (62)	3 (43)
Total pre-syncope episodes, *n* (median, IQR)	1 (0–4)	0 (0–4)	1 (0–4)	1 (0–11)	1 (0–4)	0 (0–1)
Follow-up, days (median, IQR)	563 (355–825)	730 (247–785)	562 (385–872)	722 (228–763)	630 (267–745)	780 (255–820)
On-treatment analysis						
Patients in analysis, *n*	17	12	9	5	8	7
Syncopal recurrence, *n* (%)	8 (47)	5 (42)	4 (44)	3 (60)	4 (50)	2 (29)
Time to first recurrence, days, (median, IQR)	97 (38–144)	20 (4–302)	88 (13–387)	100 (7–505)	97(50–140)	11 (2–20)
Syncopal rate, *n*/month (mean ± SD)	0.05 ± 0.06	0.09 ± 0.19	0.04 ± 0.06	0.19 ± 0.27	0.05 ± 0.07	0.04 ± 0.09
Pre-syncopal recurrence, *n* (%)	12 (71)	5 (42)	7 (78)	2 (40)	5 (62)	3 (43)
Total pre-syncope episodes, *n* (median, IQR)	1 (0–4)	0 (0–2)	1 (0–4)	0 (0–6)	1 (0–4)	0 (0–1)
Follow-up, days (median, IQR)	575 (360–800)	745 (244–788)	575 (400–865)	715 (216–767)	630 (267–745)	780 (255–820)

IQR: interquartile range; PM: pacemaker; SD: standard deviation.

were found in the syncopal rate after pacemaker implantation between patients with pacemaker ON and those with pacemaker OFF, either in the total population or in the Mixed and Asystolic groups (Table 2).

In the intention-to-treat and on-treatment analyses, no significant differences between pacemaker ON and pacemaker OFF patients were seen in the percentages of patients with pre-syncopal recurrences, and in the total number of pre-syncopal events, either in the total population or in the Mixed and Asystolic groups (Table 2).

Variables predictive of syncopal recurrence

In order to assess the value of baseline clinical characteristics in predicting the risk of syncopal recurrence, the data of all 29 patients enrolled were analysed together. The following variables were examined in a Cox model: age, female gender, hypertension, number of syncopes in the lifetime, and duration of symptoms. Among these variables, only the number of syncopes in the lifetime (hazard ratio=1.24, 95% confidence interval = 1.04–1.47, $p = 0.02$) was significantly predictive of syncopal recurrence.

Adverse events

No deaths or severe syncope-related trauma occurred during the study. One pacemaker OFF patient suffered a minor syncope-related injury during follow-up. Six pacemaker ON patients reported mild palpitations, possibly related to inappropriate device intervention. The only complications of pacemaker implantation were 2 cases of generator-related pain, one requiring repositioning of the device.

Discussion

Main findings

The main finding of the SYNPACE study is that a high percentage of patients with recurrent tilt-induced vasovagal syncope continue to have syncopal relapses despite active cardiac pacing and that this percentage is similar to that observed in patients with inactive pacing. Although there is a trend in favour of active pacing in prolonging the time to first recurrence, especially for those patients who had had an asystolic response during head-up tilt testing, the high proportion of patients who experienced syncopal relapses makes the usefulness of pacemaker therapy questionable on a clinical ground.

The present negative results of pacemaker implantation in patients with vasovagal faints are probably due both to an inefficacy of active pacing in preventing syncopal recurrence in our patient population and to a placebo effect of inactive pacing.

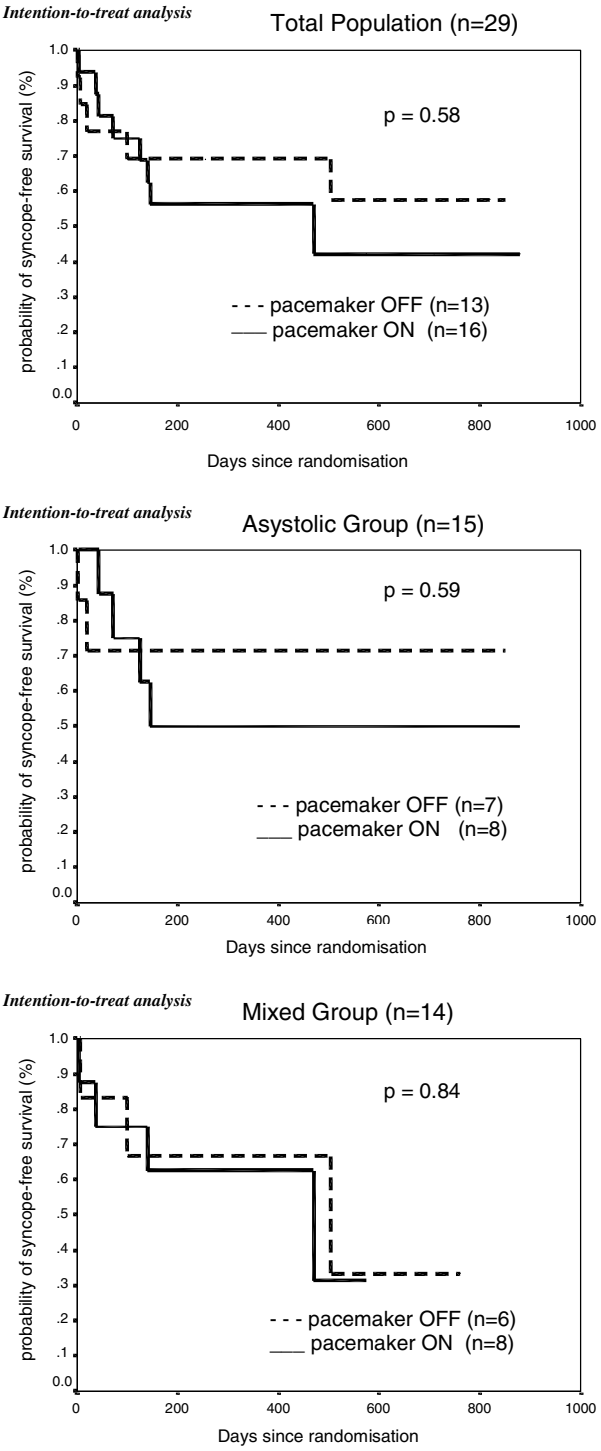

Fig. 2 Kaplan–Meier estimates of the probability of remaining free of syncopal recurrences in patients with pacemaker ON and in patients with pacemaker OFF, in the total population, and in the Asystolic and Mixed groups (Intention-to-treat analysis).

Comparison with previous studies

Many studies have been performed in the past to evaluate the role of permanent cardiac pacing in the treatment of vasovagal syncope. Non-randomized observational studies have shown that single-chamber VVI mode pacing is ineffective,[9] while dual-chamber pacing is associated to a significant decrease in syncopal recurrences.[8,10] Positive results have also been reported by three randomized open studies performed in the last few years.[11–13] This contrasts with the data of the very recently published VPS II trial,[14] a randomized, double-blind, placebo-controlled study that, like the present one, has been unable to confirm the efficacy of electrical therapy in patients with recurrent vasovagal syncope. In VPS II trial,[14] the incidence of syncopal recurrence during the follow-up was not significantly different between patients randomized to pacemaker ON and those randomized to pacemaker OFF (33% vs 42% at 6 months, respectively). The most likely explanation for the difference in results encountered in the VPS II trial compared to previous trials is the unblinded nature of open studies and the absence of a placebo arm in them. Thus, it is possible that the reported benefit of pacemaker implantation in these studies is attributable to a bias in outcomes assessment and to the psychological or emotional effect related to receiving a device by means of an invasive procedure. This, in effect, may favourably condition the patients by giving them a sense of security and protection. The occurrence of a placebo effect in our cases is suggested by the lower than expected one-year incidence of syncopal recurrence in patients programmed to pacemaker OFF (31% vs 70%), and by the same decrease of the incidence of syncope after pacemaker implantation in pacemaker ON and pacemaker OFF patients (see Table 2).

The rationale for cardiac pacemaker implantation in patients with recurrent vasovagal syncope lies in the fact that some degree of bradycardia is frequently noted during syncopal episodes induced by head-up tilt testing or occurring spontaneously.[2] However, the inefficacy of active pacing in our study, as well as in the VPS II trial, is not surprising and is probably justified by the inability of electrical cardiac stimulation to counteract the vasodepressor component of the vasovagal reflex that is present in practically all subjects during syncopal episodes and usually precedes cardioinhibition and bradycardia.

There are other possible reasons to explain the differences encountered between uncontrolled and placebo-controlled studies regarding the value of pacemaker implantation in patients with vasovagal syncope. First, in the uncontrolled studies the percentage of patients with syncopal recurrence after pacemaker implantation was significantly lower than that observed in the VPS II and in SYNPACE studies (4.3% to 22%, versus 33% to 50%).[11–14] This probably means a less severe syncopal burden of the patients enrolled in the open studies that may have accounted for the best outcome observed. Second, the trials with the best results in favour of pacing were those with the highest average age (60 years in Vasovagal Syncope International Study — VASIS — and 58 years in Syncope Diagnosis and Treatment study — SYDIT)[12,13] which raises the question of whether neurally-mediated syncope in older individuals has a different pathophysiological mechanisms requiring different treatments. This observation also seems to indicate that

implantation of pacemaker for vasovagal syncope is especially contraindicated in young patients.

Minor findings

In the present study, the number of patients with syncopal recurrence after pacemaker implantation was similar in both the Asystolic and Mixed groups. Thus, the presence of a marked cardioinhibitory component during tilt-induced syncope is not able to identify patients who are likely to benefit from permanent pacing. These results confirm previous observations regarding the poor value of head-up tilt testing in predicting the efficacy of a given therapeutic intervention.[4,5]

Apart from the number of syncopes in the lifetime, none of the baseline clinical variables significantly correlated with syncopal recurrence after pacemaker implantation.

Limitations

In this study, the enrolled patients were highly selected and were estimated to be only 1.8% of the source population; they had had a much higher number of syncopal spells in their lifetime than the average of patients affected by vasovagal syncope. This proportion is not so different from that of previous studies in which less strict selection criteria were used (from 3.6% in VASIS to 5.3% in SYDIT).[12,13] This means that patients with vasovagal syncope who theoretically may benefit from pacemaker implantation represent only a small number of subjects compared to the whole population of patients suffering from this condition. We do not know if patients with different (less severe) forms of vasovagal syncope or those with negative head-up tilt testing, would have had the same results.

This study was carried out on a relatively small sample of patients. A trend toward a prolonged time to first syncopal relapse was observed in the active pacing arm; with a higher number of patients the difference could have become significant. The outcome measurement used in the study, namely the time to first recurrence of syncope, could be not sufficiently sensitive in detecting differences of efficacy between active and control treatments. It is possible that a different outcome measurement, i.e. the total burden of syncope, could have been able to detect a reduction of total number of episodes in the active arm despite a similar percentage of patients with recurrences in both groups. However, we decided to interrupt the study because the high proportion of patients continuing to have syncopal relapses and the results of the VPS II made the continuation of the trial unethical.

Future perspectives

One of the most important limitations of pacing in vasovagal syncope is the timely detection of the onset of the neurally-mediated reaction and triggering of pacing. RDR, like the other algorithms utilized in the previous studies, is a sensing modality based on heart-rate reduction. It is possible that the use of different sensing modalities, such as those based on cardiac contractility[23] or respiratory changes,[24] might yield better results in preventing syncopal relapse.

Conclusions

Although pacemaker implantation in patients with severe vasovagal syncope seems to restore quality of life to a normal level[10] and offer an attractive cost-effectiveness ratio,[25] to date there is no proven efficacy of electrical therapy for the treatment of recurrent vasovagal syncope. Caution should therefore be exercised before invasive treatment, including device therapy, is prescribed in patients with a benign syndrome that is known not to affect survival nor to increase morbidity.

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Appendix. SYNPACE Participating Centres and Investigators (the number of randomized patients is reported in brackets)

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References

1. Linzer M, Pontinen M, Gold DT et al. Impairment of physical and psychosocial function in recurrent syncope. *J Clin Epidemiol* 1991;**44**:1037—43.
2. Brignole M, Alboni P, Benditt D et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;**22**:1256—306.
3. 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—42.
4. Morillo CA, Leicht JW, Yee R et al. A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993;**22**:1843—8.
5. Raviele A, Brignole M, Sutton R et al. Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope. A double-blind, randomized, placebo-controlled trial. *Circulation* 1999;**99**:1452—7.
6. Madrid AH, Ortega J, Rebollo J et al. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 2001;**37**:554—9.

7. Flevari P, Livanis EG, Theodorakis G et al. Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patient's well-being. *J Am Coll Cardiol* 2002;**40**:499—504.
8. Petersen MEV, Chamberlain-Webber R, Fitzpatrick AP et al. Permanent pacing for cardioinhibitory malignant vasovagal syndrome. *Br Heart J* 1994;**71**:274—81.
9. Benditt DG, Petersen M, Lurie KG et al. Cardiac pacing for the prevention of recurrent vasovagal syncope. *Ann Intern Med* 1995;**122**:204—9.
10. 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—62.
11. Connolly SJ, Sheldon R, Roberts RS 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**:6—20.
12. Sutton R, Brignole M, Menozzi C et al. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope. Pacemaker versus no therapy: a multicentre, randomized study. *Circulation* 2000;**102**:294—9.
13. Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope. *Circulation* 2001;**104**:52—7.
14. Connolly SJ, Sheldon R, Thorpe KE et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope (VPS II): a randomized trial. *JAMA* 2003;**289**:2224—9.
15. Ector H, Reybrouck T, Heidbuchel H et al. Tilt training: a new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. *Pacing Clin Electrophysiol* 1998;**21**: 193—6.
16. Krediet CT, van Dijk N, Linzer M et al. Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. *Circulation* 2002;**106**:1684—9.
17. Brignole M, Croci F, Menozzi C et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal sincope. *J Am Coll Cardiol* 2002;**40**:2053—9.
18. Raviele A, Giada F, Sutton R et al. The vasovagal syncope and pacing (Synpace) trial: rationale and study design. *Europace* 2001;**3**:336—41.
19. Sheldon RS, Rose S, Flanagan P et al. Multivariate predictors of syncope recurrence in drug-free patients following a positive tilt table test. *Circulation* 1996;**93**:973—81.
20. Raviele A, Giada F, Brignole M et al. Comparison of diagnostic accuracy of sublingual nitroglycerin test and low-dose isoproterenol test in patients with unexplained syncope. *Am J Cardiol* 2000;**85**:1194—8.
21. Bartoletti A, Alboni P, Ammirati F et al. ''The Italian protocol'': simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;**2**:339—42.
22. Malik P, Koshman ML, Sheldon R. Timing of first syncope recurrence predicts syncope frequency following a positive tilt table test. *J Am Coll Cardiol* 1997;**29**:1284—9.
23. Deharo JC, Peyre JP, Chalvidian T et al. Continuous monitoring of an endocardial index of myocardial contractility during head-up tilt test. *Am Heart J* 2000;**139**:1022—30.
24. Kurbaan AS, Erikson M, Petersen MEV et al. Respiratory changes in vasovagal syncope. *J Cardiovasc Electrophysiol* 2000;**11**:607—11.
25. Milton CR, Rose MS, Koshman MI et al. Cost-utility analysis of pacemakers for the treatment of vasovagal syncope. *Am J Cardiol* 1999;**84**:1356—9.