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Should we treat severe vasovagal syncope with a pacemaker?

R. Sutton

From the Imperial College, National Heart & Lung Institute, London, UK

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Cardiac pacing for vasovagal syncope (VVS) addresses the cardioinhibitory component of the reflex but cannot directly affect vasodepression, which occurs in every reflex even when hidden by dominant cardioinhibition. The randomized controlled trials of pacing in VVS have, after almost 2 decades, determined that a small number of patients can benefit because their vasodepressor component is not severe. Early studies compared pacing with no therapy yielding highly significant benefits. Subsequently, all study patients had implanted devices with half being switched off. No benefit was seen. The ISSUE-3 study found significant benefit ($P < 0.039$) in prevention of syncope recurrence in older patients. A sub-study later showed those with negative tilt tests, otherwise indistinguishable from tilt-positives, had 5% recurrence in 21 months ($P < 0.004$). There is acceptance that pacing must be dual chamber, but the question of how pacing is delivered remains open. Relying on falling heart rate is insufficient, probably because it occurs too late. Other algorithms which indirectly detect neuroendocrine changes earlier than heart rate fall may have useful application. In clinical terms, the patient to be considered for pacing should not be young and have severe symptoms. Ideally, tilt testing should be negative implying vasodepression of lesser severity and, therefore, yielding fewer syncope recurrences. When selecting pacing, additional concern must be given to regression to the mean of symptoms, severe to less severe. Patients seek help when they are at their worst. Moreover, many years of pacing are unlikely to be free of complications related to implanted hardware.

Keywords: cardioinhibition, dual-chamber cardiac pacing, pacemaker algorithms, pacemaker complications, regression of symptoms to the mean, vasodepression, vasovagal syncope.

Introduction

At first sight, pacing might seem to be a logical approach to treat the bradycardia of the vasovagal reflex. However, vasovagal syncope (VVS) is a combination of bradycardia and vascular effects, known as vasodepression, which begins before bradycardia and often dominates over bradycardia [1]. Thus, for an expensive therapy and possibly lifelong, complicated therapy, which will almost certainly be less than a total solution, great care in patient selection must be exercised.

It is often stated that VVS is a benign condition. If this were the case, caution in selecting this therapy should be emphasized. Today, the benign nature of VVS is questioned [2–4], but as we know nothing of a possible role for pacing in the amelioration of mortal and morbid associations of VVS, we must allow its presently considered benign nature to be included in decision-making for pacing therapy.

Methods

This review of pacing in VVS has been based on a PubMed search of 'Pacing – Vasovagal syncope', from the ESC database related to the 2009 Guidelines on management of VVS [5] and the author's own database hand-searched. In the PubMed search, 297 articles were found. After discarding reviews older than 10 years, case reports, commentaries and those not in the English language, 27 relevant articles remained. These, therefore, form the basis of this review.

The review will cover the historical development of cardiac pacing in the treatment for VVS, ultimately to set the scene for drawing conclusions on when and for whom should pacing be offered.

Historical development – studies

My, at the time novel, treatment philosophy in the late 1970s and early 1980s was to view pacing as successful therapy for atrioventricular block and to speculate about its potential for a wider application to other causes of syncope. The first focus was on carotid sinus syndrome (CSS), another reflex syncope, which yielded some success [6]. Our interest in the aetiology of this condition led us serendipitously to find that there was overlap between CSS and VVS and, further, that patients with syncope, in the same older age group as those with CSS, at that time going without a diagnosis, could have their syncope reproduced by prolonged head-up tilt. This serendipitous finding resulted in the first paper on the clinical value of tilt in revealing the cause of syncope in many patients [7]. Years of work followed to attempt to treat the bradycardia of VVS, initially exposed by tilt testing, with pacing and the best way of delivering the pacing therapy.

An early patient series of recipients of pacing was published in 1994 [8]. This pacing policy had been encouraged by acute tilt studies showing promising results [9]. The series included 37 patients with intractable symptoms and syncope with evidence of cardioinhibition (heart rate <60 bpm) on tilt, over an 8-year period allowing follow-up of 50.2 months (±23.9). The patients were of mean age 61 years (±15.6) range 33–89, they had experienced a mean of six episodes of syncope. The collective syncope burden was reduced by pacing from 136/year to 11/year, and 62% were asymptomatic. The features, which predicted a better outcome in terms of syncope recurrence, were relative youth, male gender and fewer episodes of syncope before pacing. The mode of pacing was dual chamber (DDI with rate hysteresis) in 35 and VVI in two, one of whom had permanent atrial fibrillation. The pacing mode DDI with rate hysteresis was chosen because it was thought to be a mode that could be programmed to avoid unnecessary pacing and intervene effectively with 'physiological' (i.e. dual chamber) pacing when needed. The results were quite encouraging but examined in retrospect they predict the outcome of later, larger studies quite closely. These predictions were notably the lack of complete elimination of syncope and the high level of symptoms prompting consideration of pacing in an older population compared with those who suffer from typical VVS. The report concluded that a randomized controlled trial (RCT) was justified.

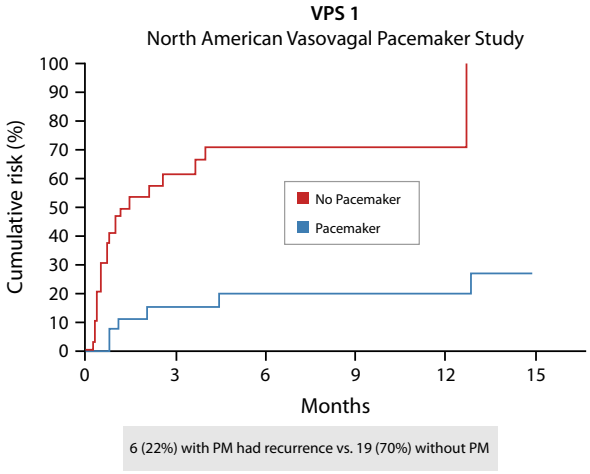

Fig. 1 *VPS-1: Comparison of syncope recurrence in patients with paced and unpaced vasovagal syncope [10] after VPS-1 results. VPS, vasovagal pacemaker study; cumulative risk (%), percentage cumulative risk of recurrence of syncope.*

The first and second such trials were published in 1999 and 2000 [10, 11] Figs 1 and 2, Table 1. The designs of these two trials were similar in that a comparison was made between dual-chamber pacing with a special rate hysteresis mode called rate-drop response (Medtronic) in VPS-1 [10] or standard rate hysteresis in VASIS [11] and a 'control' group which continued present medication, if any. Thus, the treated group received an

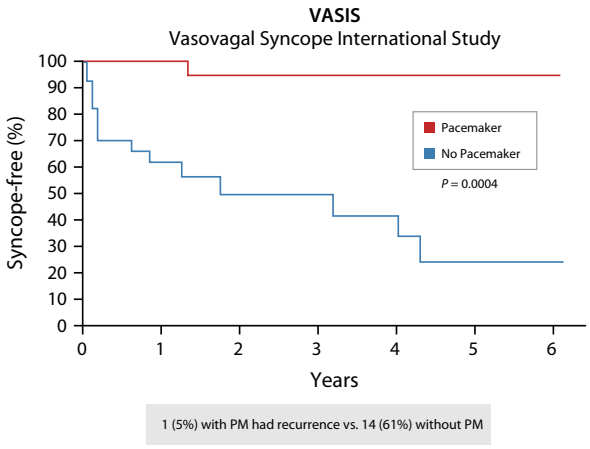

Fig. 2 *VASIS: Vasovagal syncope international study: comparison of percentage free of syncope over 6 years between those paced and those unpaced: after VASIS results [11]. PM, pacemaker.*

Table 1 *Data from randomized controlled trials of pacing in vasovagal syncope*

Trial	Patients	m-Age (years)	Pacing modes	Follow-up (month)	Outcome	Significance
VPS1 1999 [10]	54	43	DDR + RDR versus no PM	12	Benefit PM 22% rec No PM 70% rec	$2P = 0.000022$
VASIS 2000 [11]	42	60	DDD + RH versus no PM	72	Benefit PM 5% rec PM 61% rec	$P = 0.0004$
SYDIT 2001 [12]	93	58	DDD + RDR versus Atenolol & no PM	36	Benefit PM 4% rec No PM 26% rec	$P = 0.0032$
VPS-2 2003 [13]	100	49	DDD + RDR versus ODO	6	No benefit PM 33% rec No PM 42% rec	P = ns
SYNPACE 2004 [27]	29	53	DDD + RDR versus ODO	36	No benefit	$P = 0.58$
INVASY 2004 [27]	59	59	DDD + CLS versus DDI @30bpm	36	Benefit PM 0% rec No PM 80% rec	$P < 0.0001$
ISSUE-3 2012 [20]	78	63	DDD + RDR versus ODO	24	Benefit PM 25% rec No PM 57% rec	$P < 0.039$

All trials had 1 : 1 randomization except INVASY where randomization was 5 : 1 in favour of pacing. All trials had an approximate 1 : 1 gender distribution. The ISSUE-2 registry has not been included as it was not a controlled trial. For each trial, the year of publication is given and the reference in the text. For trial details, see text. m-Age, mean age; PM, pacemaker; DDD, DDI, ODO are programmable pacemaker modes; RDR, rate-drop response; RH, rate hysteresis; CLS, closed-loop stimulation; bpm, beats per minute; rec, recurrence of syncope.

implant and the controls did not. The outcome of the two trials was very similar with a highly significant benefit in favour of pacing. The differences between the trials were the ages of subjects being older in VASIS, the evidence in favour of cardioinhibition was stronger in VASIS, and VASIS patients were more symptomatic. These differences well reflected the different clinical practices in North America (VPS-1) and Europe (VASIS). The data seemed so convincing in VPS-1 for the data monitoring and safety board to terminate the study early with only 54 patients included versus the target of 284. Both trials recruited very slowly perhaps because referring physicians held strong views on the relevance, or lack of it, of pacing in this indication. These two trials were considered by many to have revealed only a placebo effect of implantation of a device in treatment for reflex syncope, which can be much influenced by cortical input, for example in the donation of blood where VVS is quite common. The VASIS was backed-up in 2001 [12] by another European trial comparing dual-chamber pacing with Atenolol 100 mg daily, again showing a highly significant benefit for pacing in a very similar patient group to that of VASIS. The same criticism was offered as before on grounds of there being no implant in the drug-treated group.

These trials were followed by two more, one from North America, VPS-2 [13], Fig. 3, and the other from Europe, SYNPACE [14], Table 1. These trials overcame the earlier reservations by implanting devices in all and programming the untreated patients to sensing-only modes. However, the patient selection in both trials was less rigorously favouring cardioinhibition. Neither trial showed a benefit for the active pacing mode. Both trials were flawed: in VPS-2 only 6-month follow-up was made, which is too short for VVS, occurring in

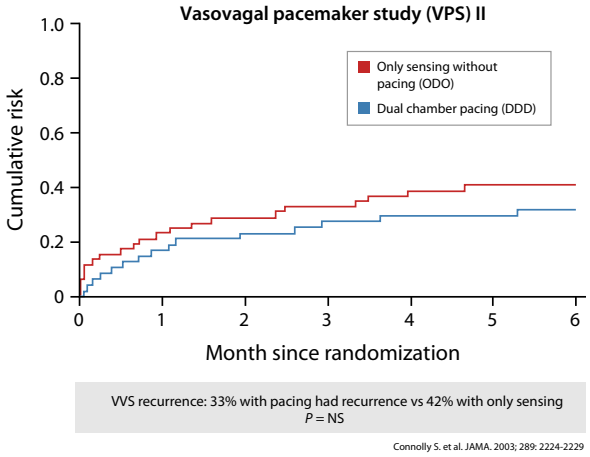

Fig. 3 *VPS-2: Comparison between active pacing mode and sensing mode only in patients with vasovagal: after VPS-2 results [13]. DDD and ODO are pacemaker modes; NS, nonsignificant.*

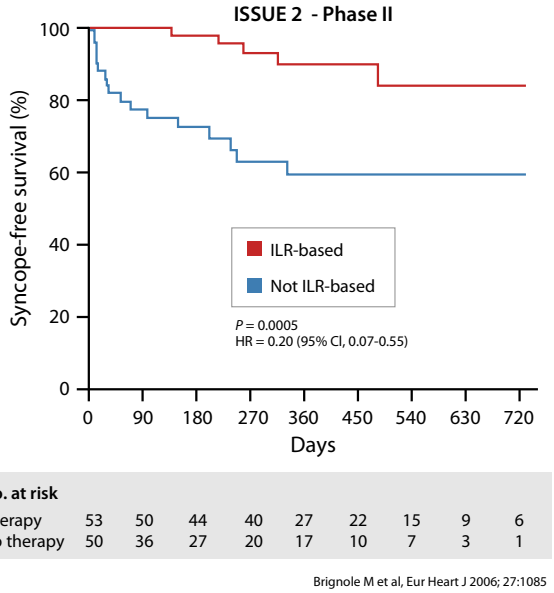

Fig. 4 *ISSUE-2: Results of registry comparison of syncope-free survival between patients treated on the basis of implantable loop recorder findings and those not treated on this basis (Kaplan–Meier curves): after ISSUE-2 results [19]. ILR, implantable loop recorder; HR, hazard ratio; CI, confidence interval.*

great severity at six times per year and severe cardioinhibtion was not evident in all subjects included in SYNPACE. These trials were considered to have answered the question of the utility of pacing for VVS, in the negative, for the majority of cardiologists [15].

Some of those involved in the first set of ISSUE studies [16–18] and in VASIS remained convinced that pacing had value for some patients, and that the failure of VPS-2 and SYNPACE to demonstrate this benefit could be attributed to patient selection. From this background, the ISSUE-2 and ISSUE-3 studies were borne. The ISSUE-2 reported in 2006 [19], Fig. 4, a registry involving recruitment of patients with clinically identified VVS of an older age group (>40 m, age 67 years). All of them received an implantable ECG loop recorder (ILR) after baseline testing including a tilt test. A recurrence of syncope was awaited and was well documented on ECG in the ILR in 103 of the 392 patients included. The registry format of the study allowed for the event with its ECG documentation to be provided to the caring clinician who would decide how to manage the patient in the light of the new information. Approximately half decided in favour of pacing when cardioinhibition was revealed with the other half electing not to change treatment. Follow-up continued, and at 1-year and later, there was a highly significant difference in favour of treating documented cardioinhibition by pacing. These findings were interpreted by the trialists as a justification for another RCT using a methodology similar to VPS-2/SYNPACE for the trial and a selection process identical to ISSUE-2. ISSUE-3 [20] commenced in 2006 and reported in 2012. A tilt test was not mandatory but was performed in the majority of included patients. The result was a significant reduction in syncope recurrence in those with dual-chamber pacemaker switched on compared with those for whom it was switched off. The benefit was a 57% relative reduction in syncope recurrence over 2 years of follow-up, Fig. 5, Table 1. As in the early series [8], pacing was not a panacea but offered a tangible and worthwhile improvement in outcome.

When further follow-up and inclusion of ISSUE-3 registry patients, those who declined randomization, became available, a striking finding was noted [21]. Patients who had a negative tilt in the initial investigation phase demonstrated a very low recurrence of syncope 5% in just under 2 years whilst those whose tilts were positive had outcomes in terms of syncope recurrence not significantly different from those who were not paced (device

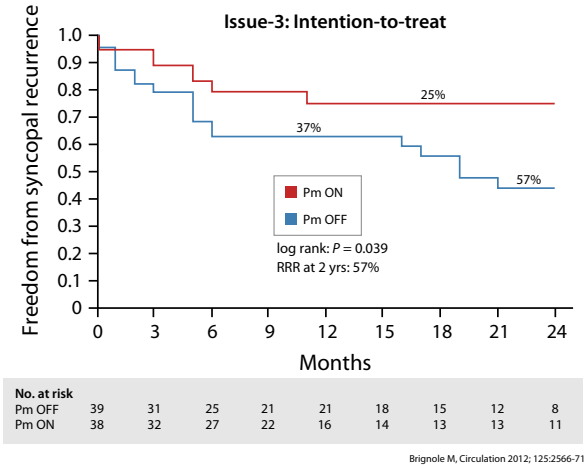

Fig. 5 *ISSUE-3: Comparison of freedom from syncope recurrence between paced and unpaced (sensing-only mode) (Kaplan–Meier curves: after ISSUE-3 [20]. Pm, pacemaker; RRR, relative risk reduction.*

switched off or no pacemaker). This observation called for a new assessment of tilt test results in this type of patient and more widely for the utility of tilt testing. Sutton and Brignole's analysis [22] implies that tilt reveals the vasodepressor component even when cardioinhibition is apparently dominant and tilt test results can be considered a predictor of syncope recurrence, or risk stratification tool, with a positive test pointing to a much higher rate than in those who are tilt-negative. It is important to state that the patients with positive and negative tilts were otherwise, on clinical grounds, indistinguishable with similar presentations, physical and electrocardiographic findings. Thus, the investigators were convinced that they were not treating sinus node disease or paroxysmal atrioventricular block. It is also, perhaps, worth emphasizing that the early study of 37 patients also showed this same pattern [8].

Subsequent data from the SUP-2 study in Italian Syncope Clinics [23, 24] offered support for the above ISSUE-3 observations. Using a decision algorithm for older patients with syncope, involving first, carotid sinus massage and treating CSS if found, followed by a tilt test and treating the findings, if positive, and finally, implanting an ILR if both preliminary tests were negative, provided some succour for the tilt-positive patients as results for them were better in longer follow-up than for patients with unpaced VVS.

Historical developments – pacing algorithms

Concurrently with these developments, attempts were being made to optimize pacemaker behaviour to address the special challenges of VVS. As has been mentioned above, the first trial to commence (although the second to report) was VASIS [11] where the pacing mode chosen was DDI with standard rate hysteresis. In the early 1990s, an idea was put forward to Medtronic for a sensing system, which paid particular attention to the slow heart rate fall that is typical of most VVS [25]. At the same time, the proposed algorithm should not ignore a rapid rate fall, such as may occur in sudden onset atrioventricular block but, simultaneously, also attempting to ignore the very gradual heart rate falls that occur naturally with relaxation or onset of sleep, for example.

This idea was translated into the rate-drop response and has been very widely used with some encouraging clinical results [26] and copied by other device companies. It is flawed by two important aspects: first, it can only sense an impending VVS by detecting a heart rate fall which may be too late for effective introduction of pacing. Secondly, it has proved not to be discreet from natural heart rate falls in everyday life resulting in much unnecessary pacing. This mode was used in VPS-1 [10], VPS-2 [13] and SYNPACE [14], Table 1. VPS-2 [13] set out to compare the rate-drop response with standard hysteresis which explains why only a 6-month follow-up was planned for the main trial. The results of this comparison have not been published and must lead one to conclude that there was no significant difference.

From this discussion, it may be obvious that a different sensed parameter, other than heart rate, may offer earlier triggering of pacing which could be more effective. It is generally accepted that in VVS, the central blood volume is reduced [1]. Detecting this in the right ventricle might be the ideal parameter. Biotronik had already developed this sensing system, called closed-loop stimulation (CLS) for rate-responsive pacing in the late 1980s and it seemed logical to apply it to detection of VVS. Interest in this idea emerged in Denmark in the 1990s, where a RCT was designed but, as for all trials in VVS, recruitment was slow. Specialists from the UK were invited to contribute patients, but the internationalization of this trial led to its cancellation by Biotronik's main office in Berlin. In 2004, a RCT using the CLS device of Biotronik in

all subjects was published. A small, not very scientifically strong trial demonstrated quite striking benefit of the CLS device programmed to dual-chamber mode in comparison with DDI mode at 30 bpm [27]. Subsequently, other data have supported these findings [28, 29]. Finally, a trial has been designed, BIOPACE, strongly supported by Biotronik, and is under way in several European countries with a sound protocol. Results are not expected until 2018/9.

Other work in this field examined right ventricular (RV) pressure, RV dp/dt and pre-ejection interval [30]. The most promising of these parameters was RV dp/dt which rose as arterial pressure was beginning to fall, but dp/dt fell at 2 min before syncope in the nine patients studied. This was not pursued immediately but was revisited in 2007 with a new 'black box' which attempted, using an algorithm based on systolic blood pressure and heart rate, to predict the onset of VVS offline in >1100 recorded tilt tests. This approach was successful yielding >90s of warning [31]. A follow-up study using the same algorithm prospectively in tilt-tested patients has proved similarly successful Virag (unpublished data). Application of this algorithm in a device will be delayed until a good device-based surrogate of systolic blood pressure is available. Thus, currently the best alternative to the rate-drop response is the CLS.

Clinical context of pacing in vasovagal syncope

Pacing is an invasive therapy with many long-term clinical and social implications. These considerations were the main determinants of the choice to study older rather than young people in ISSUE-2 & 3 [19, 20]. A lifetime pacing system is difficult to envisage without some form of device-related complication when multiple generator and even lead changes must be anticipated. Further, patients who have a pacemaker implantation have reduced employment possibilities and may be excluded from other social and professional activities.

Secondly, VVS is an occasional phenomenon and in a severe form may present six times per year. It is also known to present in clusters. In the same vein is the important consideration that patients will present for the consideration of pacing at their worst and that there is likely to be a regression to the mean following implantation or even no implantation [32]. Pacing cannot be considered until basic measures including adequate fluid intake, adequate salt intake, counter-pressure manoeuvres employed and medication (fludrocortisone or midodrine) have demonstrably failed [5].

Clinical features which may prompt consideration of pacing are lack of warning leading to falls with injury, frequent attacks 2–6+/year, prolonged

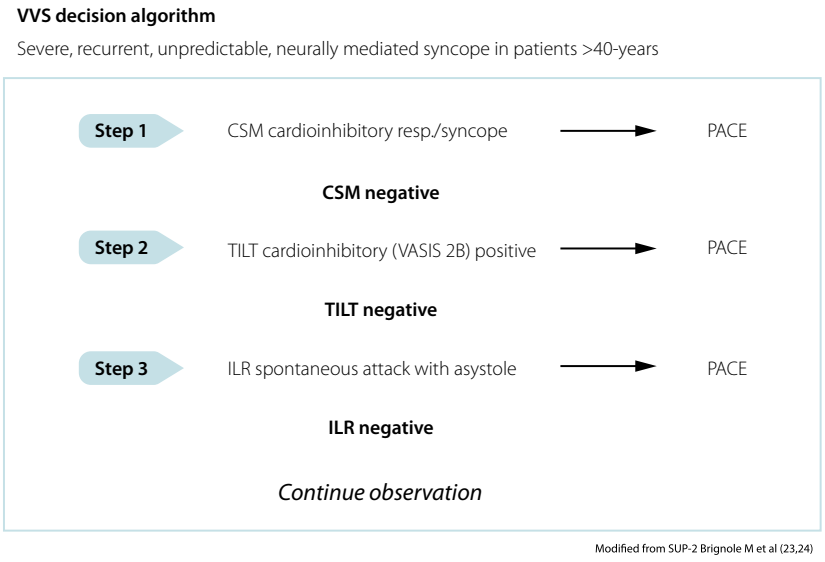

Fig. 6 *Vasovagal syncope decision algorithm; modified from SUP-2 [23, 24]. VVS, vasovagal syncope; CSM, carotid sinus massage [37]; Resp., response; VASIS, vasovagal syncope international study; ILR, insertable/implantable ECG loop recorder.*

attacks, sufficiently so to be associated with abnormal movements and incontinence, possible continuation of driving a motor vehicle, if successfully paced. Such patients with VVS are quite rare and constitute about 1% of those attending a specialist syncope facility each year (depending on referral pattern).

Evidence exists that VVS changes through life [33, 34] and may be a disease in later life [35]. So it is for older people, who seem more commonly to be unaware of the onset of VVS [36] that pacing is likely to offer most benefit.

In older patients, a clinical approach has been described and applied in a group of 10 Italian specialized syncope clinics. Patients, at first, undergo routine assessment as advised in the European guidelines [5]. If no diagnosis is reached but the clinical presentation is compatible with neurally mediated syncope, patients undergo carotid sinus massage [37]. If positive with cardioinhibitory syncope, they receive a dual-chamber pacemaker and, if negative, they are subjected to tilt testing. If positive with VASIS type 2B cardioinhibition [5], again they receive a dual-chamber pacemaker and, if negative, they receive an insertable ECG loop recorder and a further attack is awaited. Those who show cardioinhibition in a recorded spontaneous attack receive a dual-chamber pacemaker (Fig. 6). This is the SUP-2 (Syncope Unit Project) study [23, 24] which has shown encouraging results in applying pacing to patients with older neurally mediated syncope with the greatest possible benefit. One-hundred and thirty-seven patients (49% of the total) received a dual-chamber pacemaker and were followed for mean 26 ± 11 months. Syncope recurred in 18%. The actuarial syncope recurrence rate at 3 years was calculated to be 20% (95% confidence interval [CI] 12–30) and was significantly lower than in 142 patients who were not paced because their tests were all negative, remaining under observation by ILR. The 3-year recurrence rate was not different in the three positive groups, but it was lower in 20 patients with negative tilt tests (5% [CI 0–15]) than in 61 patients with positive TT (24% [CI 10–38]). This study provides a clinically useful approach that is recommended.

Conclusion

Pacing is for a tiny minority of patients with VVS, who have a very common condition, bearing in mind that around 40% of the population will experience VVS in their lives [38]. Pacing remains a complicated therapy and has been demonstrated so far to be relatively unsuited to the vasovagal challenge. Despite these drawbacks, research will continue to strive for greater success in managing this debilitating condition, when appropriate.

Conflict of interest statement

Richard Sutton serves as a consultant to Medtronic Inc., Minneapolis, MN, USA, is a member of Speakers' Bureau, St Jude Medical Inc., St Paul, MN, USA, and is a shareholder in the following companies: Boston Scientific Inc; Edwards LifeSciences Inc; Shire PLC; and AstraZeneca PLC.

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Correspondence: Professor Richard Sutton, Department of Cardiology, Hammersmith Hospital, Ducane Road, London W12 0NN, UK.
(e-mail: r.sutton@imperial.ac.uk)

