Implications of mechanism of bradycardia on response to pacing in patients with unexplained syncope

Sachin Sud, George J. Klein, Allan C. Skanes, Lorne J. Gula, Raymond Yee, and Andrew D. Krahn*

Division of Cardiology, University of Western Ontario, London Health Sciences Centre, University Campus, C6-113 339 Windermere road, London, Ontario N6A 5A5, Canada

Received 10 August 2006; accepted after revision 7 January 2007; online publish-ahead-of-print 21 March 2007

Aims

Asystole > 3 s or sinus bradycardia with a ventricular rate < 40 in association with complete heart block or sinus node dysfunction are considered to be Class 1 indications for permanent cardiac pacing. Nevertheless, these phenomena may be observed in symptomatic patients with neurocardiogenic syncope, who may not respond to pacing therapy. We hypothesized that the pattern of spontaneous bradycardia in symptomatic patients would distinguish patients with sinus node dysfunction or conduction system disease who would benefit from pacing from patients with neurally-mediated syncope who would derive lesser benefit.

Methods and results

Patients with symptomatic spontaneous bradycardia during long-term monitoring for unexplained syncope who underwent pacemaker implantation were classified according to the ISSUE classification system and followed for recurrent syncope. Follow-up included review of medical records, pacemaker clinic visits, and telephone interviews. Loop recorder tracings were reviewed to identify characteristics potentially predicting a favourable response to pacing. Thirty-three patients (21 male; age, 70 ± 14) were followed for 3.56 ± 1.71 years. Six patients had a recurrence of syncope during the follow-up. All patients with recurrent syncope despite pacing demonstrated a Type 1A (n = 5) or 1B (n = 1) pattern with gradual onset of bradycardia at baseline, suggesting a neurocardiogenic mechanism. There was no difference in the severity of bradycardia or duration of asystole in baseline loop recorded events in responding and non-responding patients. Multivariate analysis using stepwise logistic regression revealed that the ISSUE classification and the absence of structural heart disease were the only independent predictors of treatment failure of cardiac pacing in patients with spontaneous symptomatic bradycardia.

Conclusion

Patients with syncope associated with abrupt bradycardia displayed a better response to cardiac pacing therapy than those with gradual onset bradycardia.

KEYWORDS

Syncope; Bradycardia; Pacemaker; Diagnosis; Monitoring

Introduction

Syncope affects 12–48% of the population at some point in their lives. The diagnosis is established in 50% of cases that present to a physician’s office or an emergency department. Bradycardia causing syncope is often intermittent and typically requires long-term cardiac monitoring with an external loop recorder or implanted loop recorder (ILR) to detect. The use of an external loop recorder or ILR has been shown to increase the diagnostic yield in the evaluation of patients with unexplained syncope. The most common diagnoses after prolonged monitoring are ‘primary’ bradycardia or vasovagal syncope. Asystole > 3 s or bradycardia < 40 in association with complete heart block or sinus node dysfunction are considered to be Class 1 indications for cardiac pacing. These phenomena, however, may also be observed in patients with neurally-mediated syncope, and it is left to the clinician to distinguish patients with reflex bradycardia from those with primary bradycardia on the basis of the clinical history. Several randomized studies have examined the role of pacing in neurally-mediated syncope. Recently, the efficacy of pacemaker therapy for prevention of neurally-mediated syncope has been questioned after two randomized controlled trials failed to prove superiority of cardiac pacing over sham pacing of unselected patients with positive tilt testing. A classification scheme was proposed by the ISSUE Investigators that assigned the mechanism of syncope according to the pattern of bradycardia recorded during spontaneous syncope (Table 1). The utility of this classification scheme in identifying patients with syncope who will respond to cardiac pacing has not been studied. We classified loop recorder tracings in a cohort of patients with recurrent syncope, and observed the recurrence of syncope during long-term follow-up.

*Corresponding author. Tel: +519 663 3746; fax: +519 663 3782. E-mail address: akrahn@uwo.ca
Methods

Patient selection

Patients with recurrent unexplained syncope who received single- or dual-chamber pacemakers after documentation of spontaneous bradycardia by external loop recorder or ILR were identified from a syncope database. All patients underwent consultation with the Arrhythmia Service at the London Health Sciences Center, and testing at the discretion of the attending physician prior to prolonged monitoring with an external loop recorder or ILR. All patients underwent a minimum of 48 h of Holter or in-patient monitoring and cardiac imaging. Patients were included in the present study if they received a pacemaker for bradycardia as a result of prolonged monitoring. Patients were excluded if they had a left ventricular ejection fraction (LVEF) <35%, or if they received a pacemaker for any other reason such as AV node ablation. Carotid sinus massage was performed at the time of tilt table test in select patients, where there was suspicion of carotid sinus sensitivity. Patients from the RAST12 and MAST27 trials who met inclusion criteria were included. Pacemaker configuration was chosen at the discretion of the implanting physician after review of the relevant clinical data. In general, pacemakers were implanted without rate-drop features activated at implant to increase battery longevity unless syncope recurred.

Data collection

Hospital charts were reviewed to obtain relevant baseline clinical details, including the results of baseline electrocardiogram (ECG), telemetry or Holter monitoring, tilt testing, electrophysiological testing, and echocardiography. Records were reviewed to assess clinical outcomes through yearly visits to pacemaker clinics, or physician-requested and patient-requested clinic visits. Diagnostic printouts from all symptomatic events recorded during loop recorder follow-up were reviewed and classified according to the ISSUE classification of loop recorder events.26 Patients were contacted when details or follow-up could not be assessed from the patient chart. A previous history of ischaemic heart disease was not considered to be 'active' if the patient had been revascularized and free of symptoms at the time of enrolment. Structural heart disease was defined as a known history of cardiomyopathy, severe systolic LV dysfunction (LVEF <40%), ischaemic heart disease, severe left ventricular hypertrophy or severe valvular or aortic root disease.

The primary outcome measure was the recurrence of syncope. Secondary outcome measures included the time to first recurrence of syncope and injury secondary to syncope.

Statistical analysis

Continuous outcomes variables were analysed using the Student's t-test. Dichotomous outcomes were analysed using a chi-squared test or Fisher's exact test. The endpoint of time to recurrent syncope after pacemaker implantation was analysed using Kaplan-Meier survival curves. Clinical parameters including age, gender, ejection fraction, baseline ECGs, previous cardiac surgery, previous myocardial infarction, structural heart disease, antihypertensive medication use, syncope burden prior to monitoring, injury associated with syncope, complete loss of consciousness vs. presyncope, syncopal episodes without bradycardia, duration of asystole, lowest heart rate, and ISSUE classification were recorded for each subject. Continuous variables were rendered dichotomous using cut-points equal to the mean for normally distributed variables and equal to the median for skewed variables. In some cases, clinically relevant cut-points were also used (e.g. asystole <3 s or ejection fraction <50%). A univariate analysis using the chi-squared test for each variable was performed to identify potential variables which might predict recurrence of syncope after pacing. Since we anticipated small numbers in our study, a more liberal level of significance (P < 0.25) in identifying variables for the multivariate analysis was used so that more subtle interactions between variables would not be missed. Finally, a multivariate analysis was performed using step-wise logistic regression to identify independent predictors of failure to respond to pacing therapy. A likelihood ratio test P < 0.10 was used as the threshold to enter the model and P > 0.10 as threshold to leave the model. The model was further evaluated using the Hosmer-Lemeshow goodness of fit test, which compares the estimated probability of an outcome of interest based on the multivariable model to the observed probability in the sample population, and the R2 statistic, which reflects the percentage of the variance in

<table>
<thead>
<tr>
<th>Classification</th>
<th>Sinus rate</th>
<th>AV node</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asystole (RR &gt; 3 s)</td>
<td>Arrest</td>
<td>Normal</td>
<td>Progressive sinus bradycardia until sinus arrest, probably vasovagal</td>
</tr>
<tr>
<td>1A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>Bradycardia</td>
<td>AV block</td>
<td>AV block with associated sinus bradycardia, probably vasovagal</td>
</tr>
<tr>
<td>1C</td>
<td>Normal or tachycardia</td>
<td>AV block</td>
<td>Abrupt AV block without sinus slowing suggests intrinsic AV node disease</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Decrease &gt;30%</td>
<td>Normal</td>
<td>Probably vasovagal</td>
</tr>
<tr>
<td>2A</td>
<td>Heart rate &lt;40 for &gt;10 s</td>
<td>Normal</td>
<td>Probably vasovagal</td>
</tr>
<tr>
<td>Minimal heart change</td>
<td>&lt;10% variation</td>
<td>Normal</td>
<td>Suggests non-cardiac cause: unlikely vasovagal</td>
</tr>
<tr>
<td>3A</td>
<td>Heart rate increase or decrease 10–30%, not &lt;40 or &gt;120 bpm</td>
<td>Normal</td>
<td>Suggests vasovagal</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Progressive tachycardia</td>
<td>Normal</td>
<td>Sinus acceleration suggests orthostatic intolerance or non-cardiac cause</td>
</tr>
<tr>
<td>4A</td>
<td>Not applicable</td>
<td>Normal</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>4B</td>
<td>N/A</td>
<td>Normal</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>4C</td>
<td>N/A</td>
<td>Normal</td>
<td>Ventricular tachycardia</td>
</tr>
</tbody>
</table>

AV, atrioventricular.
the dependent variable explained by the independent variable. A P value < 0.05 was considered significant.

Results

Patient selection: a database of 122 patients who received an ILR was reviewed for potential candidates for inclusion. Of these, 33 patients received pacemakers for bradycardia and met the inclusion criteria for the present study. The baseline characteristics of patients included in this study are described in Table 2.

ISSUE classification

All patients had symptomatic events during monitoring, which were classified according to the ISSUE classification scheme (Table 3). Eleven patients had progressive sinus bradycardia associated with sinus arrest (1A), three patients had progressive sinus bradycardia associated with complete heart block (1B), 13 patients had abrupt complete heart block without slowing of the sinus rate (1C), and three patients had sinus bradycardia with heart rate < 40 for at least 10 s (2B). Three patients had bradycardia that could not be classified according to the ISSUE system due to the presence of atrial fibrillation.

Recurrent syncope

Six of the 33 patients had recurrent syncope during 3.56 ± 1.71 years of follow-up. No recurrent syncope occurred after cardiac pacing in patients with a baseline 1C, 2B, or unclassified pattern of bradycardia compared with recurrent syncope in five patients (45%) classified as 1A and 1 patient (33%) classified as 1B, [RR = 0.00 (95% CI 0.00–0.39), P = 0.003, Figure 1]. The median time to

Table 2 Patient characteristics

<table>
<thead>
<tr>
<th>Spontaneous symptomatic bradycardia (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at insertion of pacemaker</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Structural heart disease</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Previous CABG</td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>Previous atrial fibrillation</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td>Lifetime syncopal episodes</td>
</tr>
<tr>
<td>Syncope in year before ILR</td>
</tr>
<tr>
<td>Positive HUT</td>
</tr>
<tr>
<td>Electrophysiological study</td>
</tr>
</tbody>
</table>

Loop recorder characteristics

- ILR: 32
- External loop recorder: 1
- Heart rate < 40 on ILR: 20
- Ventricular asystole > 3 s: 24
- Ventricular asystole > 5 s: 18
- AV block: 11
- Previous injuries with syncope: 9
- Major injuries: 0
- Syncope while driving: 2
- Cardiac pacemaker
  - Single chamber: 14
  - Dual chamber: 19
  - Beta blocker: 10
  - Other vasoactive medicationsa: 18

*Other vasoactive medications included angiotensin converting enzyme inhibitor, angiotensin receptor blocker, nitrates, diuretics, and alpha blockers.

CABG, coronary artery bypass grafting; HUT, head up tilt test; MI, myocardial infarction; AV, atrioventricular.

Table 3 Classification of loop recorder events

<table>
<thead>
<tr>
<th>Classification of loop recorder events</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>11</td>
</tr>
<tr>
<td>1B</td>
<td>3</td>
</tr>
<tr>
<td>1C</td>
<td>13</td>
</tr>
<tr>
<td>2A</td>
<td>0</td>
</tr>
<tr>
<td>2B</td>
<td>3</td>
</tr>
<tr>
<td>3A</td>
<td>0</td>
</tr>
<tr>
<td>3B</td>
<td>0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3a</td>
</tr>
</tbody>
</table>

*These patients’ tracings showed bradycardia that could not be classified because of atrial fibrillation.

Figure 1 Syncope frequency per year (with 95% CI) before (grey) and after (black) permanent cardiac pacemaker. Syncope burden decreased in both after the insertion of a cardiac pacemaker. In the 1A or 1B group syncope, burden decreased from 2.17 per year [95% CI 1.04–3.29] to 0.45 per year [95% CI 0.17–1.09], P = 0.02. In non-1A non-1B patients, syncope burden decreased from 4.57 per year [95% CI 1.99–7.14] to 0 per year [95% 0.00–0.00], P = 0.0015.

Symptomatic events during monitoring included both complete syncope and presyncope (i.e. impending loss of consciousness without frank syncope). Twenty-three patients experienced only complete syncope associated with bradycardia during monitoring, compared with 10 patients who experienced episodes of presyncope associated with bradycardia.
syncope in patients with ISSUE Class 1A or 1B syncope was 1706 days after pacemaker implantation (Figure 2). No patient who had recurrent syncope sustained significant injury with recurrence, compared with two patients who reported injury associated with syncope prior to receiving a pacemaker [RR = 0.00 (95% CI 0.00–1.62), P = 0.227].

Four patients with recurrent syncope either had their pacemaker reprogrammed or had the rate drop response feature activated. Three of these patients continued to have recurrence of syncope despite reprogramming, and the remaining patient has not had recurrent syncope over 7 months of follow-up. One patient, who originally received an AAI pacemaker and had subsequent recurrence of syncope was upgraded to DDD and had no further episodes of syncope. All other patients with recurrence of syncope had a dual chamber pacemaker (DDI or DDD) at the time of pacemaker implantation.

When patients were analysed with regards to whether they had syncope and presyncope at baseline, patients with syncope alone had a trend towards a lower rate of recurrent syncope after cardiac pacing compared with those who experienced episodes of both syncope and presyncope, however, this difference did not reach significance [3/23 vs. 3/10, RR = 0.43 (95% CI 0.11–1.71), P = 0.34]. Conversely, patients with only prior syncope experienced a shorter time to recurrent syncope compared with patients with presyncope and syncope [371 days (95% CI 364 to 378) vs. 1462 days (95% CI 1076 to 1848), P = 0.34 by log-rank test, Figure 3].

Clinical characteristics of responders and non-responders

The minimum heart rate and longest RR interval on the loop recorder tracing did not differ significantly between responders and non-responders to pacing therapy (Table 4). There was also no difference in terms of age, gender, or ejection fraction in responders or non-responders to cardiac pacing. There was a trend towards a higher incidence of structural heart disease in patients who responded to pacing therapy (11/27 vs. 0/6, P = 0.077). The univariable analysis identified four variables that were potential independent predictors of recurrent syncope: absence of structural heart disease (P = 0.077); ISSUE Class 1A or 1C (P = 0.0027); normal ECG (0 = 0.065); and dual chamber pacemaker (P = 0.20). After multivariate analysis, the only independent predictors of failure to respond to pacing therapy were ISSUE Class 1A or 1B, and the absence of structural heart disease (likelihood ratio test P = 0.0002 and 0.056, respectively, R² = 0.63, goodness of fit test P = 0.995). Manual stepwise regression using all clinical variables from the univariate analysis generated an identical result.

Figure 2  Kaplan-Meier plot of syncope free survival. The median time to syncope in patients in the 1A or 1B group was 1706 days (95% CI 347–3065) and the mean time to syncope was 1233 days (95% CI 860–1605). The median survival time was not reached in patients with non-1A non-1B syncope. The Kaplan-Meier estimate of the probability of remaining syncope free was 43% for the 1A or 1B group vs. 100% for non-1A non-1B groups (P = 0.0035 by log-rank test).
One interesting observation was that despite a higher rate of recurrent syncope, patients with 1A or 1B bradycardia experienced a long phase of remission before recurrence (median time >4.5 years). This suggests that these patients experience a benefit from pacemaker therapy, but is not conclusive in the absence of a 1A or 1B control group who did not receive a pacemaker. Furthermore, three patients with 2B bradycardia, which is also thought to be neurally mediated,26 experienced no syncopal recurrence after cardiac pacemaker therapy. However, possible explanations for these observations might include a pacemaker placebo effect or the prevention of bradycardia in some patients with neurally-mediated syncope,28 or the inability of the pacemaker to counteract the vasodepressor component in other patients with dramatic hypotensive episodes.

We also analysed patients with respect to syncope with or without presyncope during baseline loop recorder monitoring. We reasoned that patients who had presyncope, would be either likely to represent a less severe disease burden, or patients who were likely to have a vasovagal mechanism of syncope. Patients with presyncope had a higher rate of recurrent syncope after pacing, but a longer median time to recurrent syncope. These differences, however, did not reach significance and given the small numbers in our study, we refrain from making any conclusions in these subgroups.

Two patients with 1C or unclassifiable pattern of bradycardia on loop recorder demonstrated a vasodepressor response on tilt table testing, suggesting that although their loop recorder tracings demonstrated a pattern most consistent with a primary bradycardia, they may also have had some component of vasovagal syncope. These patients may represent a ‘mixed’ picture of primary bradycardia and neurally-mediated syncope. Interestingly, none of these patients reported recurrence of syncope after pacing therapy, raising the possibility of a benefit in patients where intrinsic electrical disease and neurally-mediated bradycardia coexist, and that tilt table testing may not reliably identify responders and non-responders to pacing. Patients with a positive tilt table test may still respond to cardiac pacing when the mechanism of syncope is primarily due to conduction system disease, and patients with symptomatic tilt negative bradycardia may have a poor response to pacing therapy because of a falsely negative tilt table test result.

In previous studies of neurally-mediated syncope, patients with cardioinhibitory vasovagal syncope were identified by history and response to tilt table testing.18,19,21,23 Response to tilt table testing may not reflect the physiological events that occur during a spontaneous episode.29 This was best illustrated in the ISSUE study, where recurrence of syncope in the context of presumed vasovagal syncope was not affected by the results of tilt testing.29 The use of tilt table testing in the work-up of patients with bradycardia is thus somewhat questionable, as in the tilt negative syncope may still be neurally mediated and tilt positive syncope may still be due to primary bradycardia. This is particularly problematic in an elderly population, where the two problems may coexist such as in the current study. In these patients, assigning the mechanism of syncope based on rhythm-symptom correlation obtained during monitoring with a loop recorder or telemetry may be preferable. In the recent ISSUE 2 study, patients with syncope who received an

### Table 4 Loop recorder characteristics of responders and non-responders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n = 27)</th>
<th>Non-responders (n = 6)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest RR interval (s)</td>
<td>7.93 ± 7.10</td>
<td>11.5 ± 13.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Minimum heart rate (bpm)</td>
<td>39.37 ± 18.95</td>
<td>35.0 ± 6.66</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Discussion**

The current study suggests that pacemaker implantation after documentation of spontaneous symptomatic bradycardia with an external loop recorder or ILR dramatically reduces or eliminates syncope. Moreover, when patients are classified according to the pattern of bradycardia, which predicts the natural history of syncope due to spontaneous bradycardia after cardiac pacing, better than the duration of asystole or lowest heart rate. In particular, patients who demonstrated a pattern of progressive sinus bradycardia associated with sinus arrest or complete heart block were more likely to have recurrent syncope compared with patients who did not. Patients with abrupt AV block with concomitant increase in the sinus rate did not have recurrent syncope after cardiac pacing.

This finding suggests that the ISSUE classification correctly discriminates between vasovagal syncope and ‘primary’ bradycardia. Patients with vasovagal syncope have been shown to be less responsive to cardiac pacing because pacing is unable to address the vasodepressor component of neurally-mediated syncope, although a surgical placebo effect may be expected in these patients. On the other hand, patients with primary bradycardia would be expected to have a curative response to pacing therapy, a finding confirmed in the present study.

**Discussion**

The current study suggests that pacemaker implantation after documentation of spontaneous symptomatic bradycardia with an external loop recorder or ILR dramatically reduces or eliminates syncope. Moreover, when patients are classified according to the pattern of bradycardia, which predicts the natural history of syncope due to spontaneous bradycardia after cardiac pacing, better than the duration of asystole or lowest heart rate. In particular, patients who demonstrated a pattern of progressive sinus bradycardia associated with sinus arrest or complete heart block were more likely to have recurrent syncope compared with patients who did not. Patients with abrupt AV block with concomitant increase in the sinus rate did not have recurrent syncope after cardiac pacing.

This finding suggests that the ISSUE classification correctly discriminates between vasovagal syncope and ‘primary’ bradycardia. Patients with vasovagal syncope have been shown to be less responsive to cardiac pacing because pacing is unable to address the vasodepressor component of neurally-mediated syncope, although a surgical placebo effect may be expected in these patients. On the other hand, patients with primary bradycardia would be expected to have a curative response to pacing therapy, a finding confirmed in the present study.

One interesting observation was that despite a higher rate of recurrent syncope, patients with 1A or 1B bradycardia experienced a long phase of remission before recurrence (median time >4.5 years). This suggests that these patients experience a benefit from pacemaker therapy, but is not conclusive in the absence of a 1A or 1B control group who did not receive a pacemaker. Furthermore, three patients with 2B bradycardia, which is also thought to be neurally mediated, experienced no syncopal recurrence after cardiac pacemaker therapy. However, possible explanations for these observations might include a pacemaker placebo effect or the prevention of bradycardia in some patients with neurally-mediated syncope, or the inability of the pacemaker to counteract the vasodepressor component in other patients with dramatic hypotensive episodes.

We also analysed patients with respect to syncope with or without presyncope during baseline loop recorder monitoring. We reasoned that patients who had presyncope, would be either likely to represent a less severe disease burden, or patients who were likely to have a vasovagal mechanism of syncope. Patients with presyncope had a higher rate of recurrent syncope after pacing, but a longer median time to recurrent syncope. These differences, however, did not reach significance and given the small numbers in our study, we refrain from making any conclusions in these subgroups.

Two patients with 1C or unclassifiable pattern of bradycardia on loop recorder demonstrated a vasodepressor response on tilt table testing, suggesting that although their loop recorder tracings demonstrated a pattern most consistent with a primary bradycardia, they may also have had some component of vasovagal syncope. These patients may represent a ‘mixed’ picture of primary bradycardia and neurally-mediated syncope. Interestingly, none of these patients reported recurrence of syncope after pacing therapy, raising the possibility of a benefit in patients where intrinsic electrical disease and neurally-mediated bradycardia coexist, and that tilt table testing may not reliably identify responders and non-responders to pacing. Patients with a positive tilt table test may still respond to cardiac pacing when the mechanism of syncope is primarily due to conduction system disease, and patients with symptomatic tilt negative bradycardia may have a poor response to pacing therapy because of a falsely negative tilt table test result.

In previous studies of neurally-mediated syncope, patients with cardioinhibitory vasovagal syncope were identified by history and response to tilt table testing.18,19,21,23 Response to tilt table testing may not reflect the physiological events that occur during a spontaneous episode.29 This was best illustrated in the ISSUE study, where recurrence of syncope in the context of presumed vasovagal syncope was not affected by the results of tilt testing.29 The use of tilt table testing in the work-up of patients with bradycardia is thus somewhat questionable, as in the tilt negative syncope may still be neurally mediated and tilt positive syncope may still be due to primary bradycardia. This is particularly problematic in an elderly population, where the two problems may coexist such as in the current study. In these patients, assigning the mechanism of syncope based on rhythm-symptom correlation obtained during monitoring with a loop recorder or telemetry may be preferable. In the recent ISSUE 2 study, patients with syncope who received an
ILR, and subsequently demonstrated symptomatic bradycardia for which a pacemaker was inserted, had a significantly reduced burden of syncope compared with patients who did not receive a pacemaker. Our study further suggests that the pattern of bradycardia demonstrated on ILR during syncope may predict response to pacemaker therapy. The current study had the benefit of recording spontaneous bradycardia during episodes of syncope with a loop recorder to select a group of patients most likely to respond to pacing. Nonetheless, comparisons made between patients who had recurrent syncope and those who remained syncope free during the follow-up did not reveal any obvious difference in the duration of asystole, minimum heart rate during index monitoring, or other baseline clinical characteristic. This suggests that while there are patients with syncope who achieve a lasting remission after the implantation of a pacemaker, the severity of bradycardia or asystole experienced during episodes of syncope does not predict a better response to pacemaker therapy, but rather the mechanism of the bradycardia. Multivariate analysis of clinical parameters recorded during this study revealed that the only independent predictors of treatment failure were an absence of structural heart disease (which presumably increases the likelihood of neurally-mediated syncope) and ISSUE classification 1A or 1B. In the recently published ISSUE 2 study, however, hypertension, age, and the absence of pacemaker therapy were most predictive of recurrent syncope (after pacemaker insertion). These differences may be explained by minor differences in methodology; all patients in our study received a pacemaker, and the analysis was based on the mechanism of syncope according to a classification of loop recorder events. Validation of the current findings in the ISSUE 2 database and prospective assessment of response to pacing in the currently enrolling ISSUE 3 study should provide further insight into the role of pacing in the population with spontaneous bradycardia. Despite the modest number of patients in the current study, the findings stem from the underlying physiology leading to syncope, and suggest that clinicians, therefore, should consider both the pattern of documented symptomatic bradycardia if available and the presence of structural heart disease when assessing patients for pacing. Furthermore, our results stress the importance of obtaining rhythm-symptom correlation before considering pacing.

Our study also suggests that the use of the ISSUE Classification of Loop Recorder Events is a useful means of identifying candidates for pacing therapy after ILR. When used retrospectively in conjunction with the clinical history, the ISSUE classification identified patients with primary bradycardia in whom pacemaker implantation would lead to the elimination of syncope, and patients with neurally-mediated syncope who will experience a decrease in syncope burden with pacing therapy. The ISSUE classification system appears useful in interpreting the clinical significance of spontaneous symptomatic bradycardia and as a means for standardizing patients for future pacemaker trials.

Study limitations
This retrospective study was susceptible to potential biases in patient selection and outcome. The natural history of patients who have vasovagal syncope or primary bradycardia and received no pacing therapy is not addressed. Furthermore, the study may have been underpowered to detect other parameters in the multivariate analysis. Nonetheless, the current study reflects clinical decision-making based on documented bradycardia, and the response to the pacing intervention over a sufficient duration of follow-up to expect that the placebo effect of pacing would have markedly diminished. Although the results are drawn from a selected patient population, they may identify candidates for pacing, and provide the basis for advice on expected outcome.

Conclusion
Patients with syncope associated with abrupt bradycardia display a better response to pacing therapy than those with gradual onset bradycardia, consistent with the underlying mechanism of bradycardia.

References


