Response of a Closed-loop Sensor during Head-Up Tilt Table Testing: Impact of CLS in Patients with Recurrent Syncope after Pacemaker Implantation for Bradycardia

ATUL PRAKASH, MD, RAHUL KUMAR, MD and SANTOSH BHASKARABHATLA, BA, MBS

University of Medicine and Dentistry of New Jersey, Clifton, NJ, USA

ABSTRACT. Patients who have pacemakers implanted for bradycardia do sometimes present with recurrent syncope. This may be due to a coexisting vasodepressor response. Numerous pacing algorithms have been developed for this phenomenon. We sought to determine the response of the closed loop sensor (CLS) in this cohort of patients, both during a head-up tilt table test (HUTT) and in clinical follow-up. Programming the CLS sensor to a more aggressive setting mimicked the normal chronotropic physiologic response in patients who did not have hypotension with head-up tilt testing, and helped in preventing recurrent syncope after pacemaker implantation. We submit that a coexisting vasodepressor response should be considered in patients who have syncope and bradycardia, and that CLS pacing can attenuate vasodepressor syncope.

KEYWORDS. bradycardia, closed-loop sensor, syncope, tilt table testing, vasodepressor.

Introduction

Background and hypothesis

Patients with a bradycardia indication for permanent pacemaker may continue to have symptoms of syncope and presyncope despite rate support. This incidence of recurrent syncope post pacemaker implantation for bradycardia along with its etiology has remained controversial, though a vasodepressor component has been implicated. The efficacy of permanent pacing in neurocardiogenic syncope has been suboptimal. This has been mainly attributed to either a predominant vasodepressor response, or a pacing intervention which comes well after this response. Different algorithms including ‘hysteresis’ and a rate drop response have been studied for these patients. However a closed-loop sensor (CLS) has not been well studied in this cohort. During myocardial contraction, the impedance continuously increases, reaching its maximum in late systole. This impedance increase is thought to correlate with right ventricular contractility, and, thus, with the inotropic state of the heart. The CLS responds to a change in myocardial contractility by measuring localized cardiac impedance, and translating this information to an appropriate rate response. This increase in contractility may precede a drop in blood pressure and even bradycardia with resulting syncope. Thus a CLS may allow early pacing intervention with an increase in rate, and may attenuate the drop in blood pressure and improve symptoms of syncope in these patients.

The purpose of this study was to evaluate the benefit and efficacy of the CLS in patients with recurrent syncope after receiving a permanent pacemaker for bradycardia. Comparison of a physiologic heart rate response and the CLS response during head-up tilt table testing (HUTT) was performed. In addition, the impact of reprogramming the CLS sensor to respond more aggressively in patients exhibiting a concomitant vasodepressor response during HUTT was assessed.
Methods

Inclusion criteria and study design

Consecutive patients with symptoms of syncope or presyncope and a standard bradycardia indication for permanent pacing were included in this study. Patients underwent pacemaker implantation with a Biotronik, Inc. Cylos permanent Pacemaker (DR-T). This pacemaker is equipped with a closed loop sensor (CLS). For standardization purposes, these pacemakers were initially programmed to a DDDR mode with the CLS left to a minimal response. Patients were seen within 1–3 weeks post pacemaker implantation. Those patients who continued to have persistent symptoms of syncope or presyncope underwent HUTT. Based on the response during HUTT, patients were divided into two groups. Group 1 consisted of patients with a significant drop in blood pressure associated with reproducible symptoms. Group 2 included patients with a smaller or no drop in blood pressure without any symptoms. The pacemaker was reprogrammed with the CLS sensor responding more aggressively in all patients in Group 1 and only in those patients in Group 2 who exhibited a drop in blood pressure. The remaining patients who did not exhibit a drop in blood pressure did not have their pacemaker settings modified and were investigated for other reasons of syncope (see Figure 1 for study design and outcomes).

Tilt testing protocol

After obtaining informed consent, patients underwent standardized head upright tilt testing at 70 degrees. Baseline carotid sinus massage was performed and the patient remained in the tilt position for 15 min. Isoproterenol was then infused for 10 min, from 1 to 3 \( \mu g/min \). Blood pressure and heart rate were measured every minute in all patients. In addition, patients were monitored for development of any symptoms. Beat-to-beat blood pressure monitoring was performed in two patients. A positive response was defined as a drop of at least 20 mmHg in systolic blood pressure with symptoms.

Analysis

The implanted pacemakers were configured to capture beat-to-beat measurements of the impedance data during the tilt table tests for 25 min. Rate support was set to DDD-CLS, with the CLS rate response parameters set to minimum values. The recorded impedance information was then downloaded from the pacemaker, and processed through the CLS algorithm. This information was then utilized to show the different pacing support scenarios that CLS is capable of processing offline and analyzed in detail.

The proportion of patients with a standard bradycardia indication for permanent pacing who continued to have symptoms of syncope/presyncope was analyzed. The impact of reprogramming the CLS sensor to be more aggressive in a cohort of patients who exhibited a symptomatic drop in blood pressure during HUTT testing was measured. The correlation of the CLS response to a drop in blood pressure and a comparison of this response within the two groups were analyzed.

Results

Patient population

A total of 101 patients were included in this analysis, of which 59 patients were male. Table 1 summarizes the baseline clinical characteristics of the study population. The mean age of these patients was 75.2 years (SD \( \pm \) 13.0 years). Twenty-six patients had heart disease. Indications for pacemaker implantation were sick sinus syndrome (including symptomatic bradycardia) in 73 patients, atrioventricular (AV) conduction disease in 26 patients, and carotid sinus hypersensitivity in eight patients. Six patients in this cohort had both sick sinus syndrome and AV conduction disease.

All patients had syncope or presyncope prior to pacemaker implantation. Patients had a mean of 1.8 syncopeal episodes (interquartile range 2–4) prior to pacemaker implantation. Thirteen patients had coexisting atrial fibrillation, while two had supraventricular tachycardia. Neurological causes had been excluded as a mechanism for syncope in patients with a clinical suspicion for such a mechanism. Patients who were at high risk for ventricular tachycardia (VT) and met the criteria for implantable cardioverter-defibrillator implantation were not included in this study. After pacemaker implantation, episodes of VT that could have been contributing to symptoms of syncope and presyncope were excluded by pacemaker interrogation.

Drug therapy

Forty-two patients were on \( \beta \)-blockers. Calcium antagonists were used in 23 patients, and ACE inhibitors in 12 patients. Drug therapy was used for concomitant heart disease, hypertension, and/or heart failure. Midodrine and fludrocortisone were used in 14 patients who had a positive tilt prior to pacemaker implantation but continued to have symptoms despite drug therapy.

Outcome after pacemaker implantation

After pacemaker implantation, 67 of 101 patients had no further episodes at first follow-up at 2–4 weeks post implantation and continued to have no further episodes during the course of the study. Twenty-nine patients (29%) continued to have symptoms of presyncope or syncope on subsequent visits (1–12 months).

Tilt testing results

Of the patients who continued to have presyncope or syncope, a total of 27 had tilt table testing as described.
Two patients did not undergo tilt testing for unspecified reasons. Group 1 (13 out of the 27 patients) had reproducible clinical symptoms during HUTT, indicating a positive test. In five patients isoproterenol was required to achieve a positive response. A positive vasodepressor response was defined as a decrease in...
systolic pressure by 20 mmHg. The drop in systolic blood pressure in Group 1 ranged from 20 to 40 mmHg, occurring from 2 to 15 min after head up tilt. An increase in intrinsic heart rate of 10–80 bpm occurred in these 13 patients an average of 2 min after the initial drop in blood pressure that caused the positive tilt table test. Group 2 (14 of the 27 patients) did not have symptoms during HUTT. Figure 1 shows the clinical outcomes of the patients in graphic form.

Closed-loop stimulation sensor

CLS is a unique rate response sensor in pacemakers by Biotronik Inc. CLS works by driving the pacing rate by measuring and calculating impedance changes utilizing the right ventricular lead. This localized cardiac impedance provides an assessment of the myocardial wall motion changes around the ventricular lead tip. When CLS is turned on, the accelerometer determines whether the patient is at rest. Once this is established, a reference waveform is built, which reflects a resting state of the patient. This is built by taking eight sets of measurements during every cardiac cycle from 50 ms to 300 ms after every paced cycle (Figure 2). Once this reference resting waveform is determined, CLS compares the current impedance signals to this reference waveform during every cardiac cycle. As there is a change in inotropy, which reflect changes in contractility, the waveform that is measured changes. This change with respect to the reference waveform is calculated, and translated to a pacing rate (Figure 3).

Analysis of the CLS response

The CLS data that had been recorded were used to plot the “predicted CLS rate.” This rate is the rate the pacemaker would have paced if programmed to “High” given the input signal collected from the patient. In the 13 Group 1 patients (positive tilt table test with symptoms), the resulting “predicted” CLS rate increased from 20 to 50 bpm (mean of 21 bpm, SD ± 10.5 bpm). This increase in “predicted CLS rate” occurred in the range of 58 to 112 s before, to 40 s after the initial start of the drop in blood pressure. The drop in blood pressure ranged from 10 to 50 mmHg (mean 32.5 ± 9 mm Hg). The drop in blood pressure was seen consistently and within the magnitude of the deviation noted in patients with and without isoproterenol infusion. Figure 4 illustrates the CLS response in a patient with a positive tilt test. The 14 patients in Group 2 did not have symptoms corresponding with a drop in blood pressure. The drop in blood pressure was between 18 and 25 mm Hg (mean 23 ± 2.7 mm Hg). The “predicted CLS rate” increased from 10 to 35 bpm (mean 13 bpm, SD ± 7 bpm) in response to the blood pressure drop during the tilt table test. For all 14 patients that were classified as tilt table negative (absence of symptoms), the “predicted CLS rate” increase corresponded very well to the increase in intrinsic rates of the patient as seen in Figure 5, with an R² value ranging from 0.8 to 0.95. Referring to Figure 4, in positive tilt table test patients, there is a smaller deviation in average heart rate, which indicates increased vasodepressor response when compared with the negative tilt patients. However, there are increased inotropic changes in the positive tilt table patients as seen by the increased average and deviation of the “predicted CLS” patients. The lack of intrinsic heart rate response in these patients with positive HUTT implicates some degree of chronotropic incompetence in these patients.

In two patients, the data collected could not be used for analysis as the CLS initialization occurred during tilt testing, which meant that the baseline CLS used for calculating the pacing rate was incorrect, as seen in Figure 6. This incorrect initialization meant that the CLS response was exaggerated, and therefore these data were not used.

Management of patients with recurrent syncope

In the 13 patients with a positive tilt test, CLS reprogramming was done in all. The CLS was reprogrammed to “high” in all patients. This was done to allow the CLS to respond more aggressively to smaller changes in the measured signal. Seven patients (54%) had no further symptoms after reprogramming alone, while six patients continued to have some symptoms.

Table 1: Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects (n = 101)</th>
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<tbody>
<tr>
<td>Male, N (%)</td>
<td>59 (58)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>75.2 (13.0)</td>
</tr>
<tr>
<td>Prevalence of heart disease (CAD, structural heart abnormalities), N (%)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Indication for pacemaker</td>
<td>73 (72)</td>
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<tr>
<td>Sick sinus syndrome, N (%)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>AV node disease, N (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other, i.e. carotid hypersens, N (%)</td>
<td></td>
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<tr>
<td>Prevalence of atrial fibrillation, N (%)</td>
<td></td>
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<tr>
<td>Medical therapy</td>
<td></td>
</tr>
<tr>
<td>β-Blockers, N (%)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Calcium antagonists, N (%)</td>
<td>42 (42)</td>
</tr>
<tr>
<td>ACE inhibitors, N (%)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Midodrine or fludrocortisone, N (%)</td>
<td>12 (12)</td>
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despite CLS reprogramming, albeit the patients felt qualitatively better. One patient required adjuvant drug therapy with midodrine in addition to the reprogramming. Two patients were intolerant to a high CLS setting and had to be reprogrammed to medium. Diet adjustments and stockings were recommended to all 13 patients.

In the 14 patients with a negative tilt test, CLS was also reprogrammed to “High” in 10 patients, four of whom had no further symptoms. Medications were added or the dose was increased in six patients and four patients underwent electrophysiology studies. Patients who continued to have symptoms despite these interventions were referred for neurology evaluation.

Discussion

Syncope and bradycardia

Patients presenting with syncope and bradycardia often have other additional mechanisms persisting that result in recurrent symptoms despite pacing rate support. These include use of multiple vasodilatatory drugs, postural hypotension, and a concomitant vasodepressor mechanism in addition to bradycardia and chronotropic incompetence. Our finding of persistent syncope in 29% of the patients with a bradycardia mechanism suggests a need for evaluation of patient’s drugs, measuring orthostatic blood pressures, and HUTT testing. Tilt table testing may help to manifest a concomitant latent vasodepressor response which may explain persistent syncope. Tilt testing should therefore be considered after pacemaker implantation in all patients with bradycardia and recurrent syncope.

Pacing in neurocardiogenic syncope and role of CLS

Permanent pacing in neurocardiogenic syncope has yielded mixed results.5,8–10 The relative ineffectiveness of pacing may be either because pacing intervention is delivered too late after blood pressure dropping or because a vasodepressor response is the dominant response. The Vasovagal Pacemaker Study multicenter trial has shown that dual-chamber pacing with a rate-drop response reduces the likelihood of syncope in patients with recurrent vasovagal syncope, although a follow-up randomized trial produced different results.11,12 A sensor which could allow pacing intervention early during a syncopal event associated with a mixed response of bradycardia and a drop in blood pressure could alleviate

Figure 2: The reference waveform is constructed at rest using eight sets of impedance measurements at specified time intervals from 50 to 300 ms after each paced beat. This represents an index of the intropic state of the right ventricle at baseline.
Figure 3: A change in perfusion pressure can result in alteration in the inotropic state of the right ventricle (i.e., a drop in blood pressure leads to increase in ventricular contractility as a compensatory mechanism). This in turn can be measured by impedance changes at the right ventricular pacemaker lead tip. If an impedance change that suggests hypotension is recorded, the CLS increases heart rate to attenuate the drop in blood pressure.

Figure 4: "Would-be CLS rate" and intrinsic heart rate versus blood pressure measurements for positive tilt table response.
an episode. Different algorithms have been tried in these patients. These include rate drop response and hysteresis.\(^5\)

A recent retrospective study showed that dual-chamber CLS pacing was more effective than dual-chamber pacing with conventional algorithms for syncope prevention in preventing bradycardia-related syncope in patients with a cardioinhibitory response to HUTT.\(^13\)

In this study, we have shown that the CLS sensor responds appropriately, quickly, and accurately to a drop in blood pressure seen during HUTT. This suggests

**Figure 5:** “Would-be CLS rate” and intrinsic heart rate versus blood pressure measurements for negative tilt table response with isoproterenol infusion at time 13 min.

**Figure 6:** “Would-be CLS rate” and intrinsic heart rate versus blood pressure measurements for negative tilt table response with isoproterenol infusion. Note the horizontal “would-be CLS rate” during the first 4 min of the tilt. This indicates that the initialization of CLS occurred during the tilt.
that an increase in contractility occurs in patients with a blood pressure drop during tilt table testing. The response was seen to occur before a drop in blood pressure, suggesting an increase in contractility may occur before a drop in blood pressure. Interestingly, patients without symptoms had an intrinsic heart rate increase that mimics that of the CLS sensor. This implies that many of these patients with syncope after permanent pacemaker implantation had not only a vasodepressor component but also an element of insufficient chronotropic response that contributed to their symptom complex. Reprogramming the CLS sensor to respond more aggressively led to an alleviation of patient symptoms. Additionally, this suggests that increasing the pacing rate in response to a drop in blood pressure may attenuate the vasodepressor response. 

The HUTT protocol employed in this study involved the use of isoproterenol in order to increase sensitivity and yield over a passive tilt test. The most recent update of the Newcastle protocols includes the use of either sublingual nitroglycerin or isoproterenol, or simply passive tilt testing. Evidence corroborating the validity of using isoproterenol to elicit a positive response is extensive, although sublingual nitroglycerin is also a legitimate option. In this particular study, where patients already had permanent pacemakers and a hypotensive response was sought, sublingual nitroglycerin could have increased sensitivity of the HUTT at the cost of some specificity.

The CLS sensor has been previously investigated in clinical studies, both in the context of vasovagal syncope and in everyday activities. The PROVIDE study showed that the CLS sensor was more sensitive to mental stress and was preferred to a greater extent by patients than the traditional accelerometer sensor. The effectiveness of the CLS sensor in completing moderate physical tasks has also been noted. For patients with vasovagal syncope, small and medium size studies have shown that CLS pacemaker implantation prevents recurrence of symptoms. Furthermore, the INVASY study showed that CLS pacing resulted in fewer episodes of vasovagal syncope due to a cardioinhibitory response than DDI pacing. Of note, the indication for permanent pacing in these studies was malignant vasovagal syncope and not degenerative conduction system disease. In addition, comparison across the levels of CLS programming was not performed as part of these analyses nor was a comparison of appropriate physiologic heart rate response and CLS response.

Conclusion

A significant proportion of patients with syncopal symptoms and bradycardia continue to have symptoms despite adequate pacing rate support. A proportion of these patients exhibit a vasodepressor response during HUTT. This suggests the coexistence of this mechanism, in addition to bradycardia, as an explanation for symptoms. The results of this study convey that this cohort represents a different set of patients. This cohort, in fact, may be far greater as some patients may have been improved by the CLS program at onset and/or with the addition of drugs like ß-blockers, florinef, and proamatine. The study also demonstrates an appropriate response of the CLS sensor to a drop in blood pressure with an increase in heart rate in almost all patients, which resulted in improvement of symptoms. This heart rate response was noted to closely mimic the physiologic heart rate in patients without symptoms during HUTT. It is therefore perceivable that the CLS sensor may translate into additional benefit in the overall population of patients in whom these symptoms exist despite pacing support. To our knowledge, this is the first analysis of the CLS sensor performance in vasovagal syncope in which the original indication of permanent pacing was sinus or AV node dysfunction. In addition, this is the first study to present offline analysis of the CLS sensor and to show that when programmed to “High,” the CLS rate closely mimics intrinsic physiologic heart rate in patients without symptoms.

Limitations

This is an observational, cohort study which has limitations to statistical analysis and establishing temporality. Several other study limitations are also applicable in terms of bias and generalizability. For example, CLS programming may have undermined the true incidence of symptoms after pacemaker implantation (prior to tilt testing). In addition, the use of drugs, vasoactive or antihypertensive, was not appropriately controlled. There are also limitations on implication of age and other demographic variables, which may require further examination and control. For example, the use of the CLS sensor remains to be tested in a population of younger patients with representation of different ethnic backgrounds. A randomized, larger study comparing different rate response sensors and CLS is needed and is warranted for further evaluation.

References