DEVICE THERAPY

COMPLEX CASE STUDY

A Long-term Follow-up on the Use of Closed-loop Cardiac Pacing in Patients with Refractory Neurocardiogenic Syncope

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ABSTRACT. There have been reports on the use of inotropy-based permanent pacemaker therapy using a closed-loop system (CLS; Biotronik Inc., Lake Oswego, OR) in patients with neurocardiogenic syncope (NCS); however there are few data on the long-term efficacy of this therapy in patients with NCS. In this retrospective study, patients were identified from the cohort of patients who were referred to us for their refractory NCS and underwent implantation of pacemakers utilizing closed-loop technology. The data about the patient symptoms were collected both before and after the implantation during follow-up clinic visits. Sixty-four patients aged 16–73 years (mean 44 years, 52 females) were identified to be eligible for this observational study. Thirty-three patients (51.6%) had recorded asystole or severe bradycardia from an implantable loop recorder. Ten patients (15.6%) had a documented syncope episode and hypotension associated with asystole or bradycardia during the tilt table test, and 21 patients (32.8%) had documented asystole or severe bradycardia from an event recorder of an electrocardiogram during syncope. During the follow-up period (3.81 ± 1.9 years), 30 patients (47%) had no syncope episode after CLS implantation. Twenty-three patients (36%) had significant reduction (>50% in syncope frequency) in syncope episodes after CLS implantation. Eleven patients (17%) did not have a significant reduction in syncope. Permanent pacemaker placement using a CLS system provides a potentially effective way of treating refractory NCS.

KEYWORDS. closed-loop stimulation, head-up tilt test, neurocardiogenic syncope, pacemaker

Introduction

Neurocardiogenic syncope (NCS) is the most common cause of syncope. Recurrent and severe NCS can result in serious physical injuries and psychological consequences, which often times are difficult to manage.

The efficacy of dual-chamber pacemaker placement using a rate drop response algorithm for treatment of NCS showed mixed results in four randomized double-blind, controlled trials. However, the results from the ISSUE 3 trial demonstrated significant reduction in syncope in patients who demonstrated a significant asystole on a loop monitor. However, pacemakers with a rate drop algorithm intervene only when the heart rate falls below the preset values and in NCS a fall in blood pressure usually precedes a decline in heart rate. Ergo an episode is often well underway before the device can sense its occurrence, and by the time pacing begins it is often “too little too late.”
Closed-loop pacing offers a form of rate adaptive pacing using right ventricular (RV) impedance. Figure 1 illustrates RV impedance ($Z_3$) as being constantly measured at the interface of the RV lead and the myocardium by a closed-loop stimulation pacemaker.

When the right ventricle is full of blood there is a smaller fraction of myocardium that interfaces with the lead tip, and hence the impedance ($Z_3$) is low. In contrast, when there is less blood in the ventricular cavity the proportion of myocardium at the interface increases, resulting in a higher impedance ($Z_3$) (Figure 2). The high impedance triggers the closed-loop system (CLS) algorithm and starts pacing the heart at a preset CLS intervention rate.

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**Figure 1:** Right ventricular (RV) impedance ($Z_3$) being constantly measured at the interface of the RV lead and the myocardium by a closed-loop stimulation pacemaker.

**Figure 2:** When there is less blood in the ventricular cavity the proportion of myocardium at the interface increases, resulting in a higher impedance ($Z_3$). The high impedance triggers the closed-loop system (CLS) algorithm and starts pacing the heart at a preset CLS intervention rate.

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**Methods**

The study was conducted in a retrospective fashion and was approved by our local Institutional Review Board at the University of Toledo Medical Center.

**Patient selection**

Patients were included in the study if they were suffering from recurrent NCS and met all of the following criteria:

1. they had suffered at least two syncopal episodes in the preceding 6 months;
2. they were refractory to (or intolerant of) all conventional, non-pharmacological, or pharmacological treatments;
3. they had documented evidence of asystole (>6 s) or severe bradycardia (heart rate <30 bpm) on an implantable loop recorder or during the head-up tilt test (HUTT) recorded during an actual syncopal episode.

**Programming algorithm**

The programming parameters we used in this cohort have been published previously,6 but, briefly, we prefer resting rate control (RRC) to the “off” mode. Under normal circumstances the RRC would limit heart rate migration to base rate plus 20 pulses per minute (ppm) as a default if the patient is not currently moving enough to trigger the accelerometer. Programming the RRC to Off allows the CLS algorithm to vary the rate response in the device from base rate to the maximum programmed CLS rate based on the current contraction dynamics that are being measured. When the device is programmed in this manner the algorithm intervenes much earlier in the neurocardiogenic (vasovagal) reflex, thereby increasing the patient’s cardiac output (CO) much sooner. Earlier intervention has been shown to decrease the number of syncopal events, or alternatively to provide a prodromal warning for the patient that was not noted before CLS implantation. We also program the base rate to between 60 and 65 ppm with a maximum CLS rate between 130 and 140 ppm. This is the maximum rate at which the device can drive the heart rate. The CLS response is usually programmed to “high” or “very high.” This setting determines the aggressiveness of the CLS response over time. We program the atrioventricular (AV) delay so as to minimize ventricular pacing whenever the patient has intact intrinsic conduction through the use of the AV hysteresis function in the device.

**Data collection**

Patients were identified by searching University of Toledo Medical Center Syncope and Autonomic Disorder Center database for patients who had a CLS pacemaker implanted between January 2005 and June 2013. Information was collected from patient charts and correspondence from physicians. The frequency of syncope before and after device implantation was determined for each patient, as well as the characteristics of events (aura/prodrome). We also used syncope burden (number of syncope over a period of 6 months) before and after pacemaker implantation as a measure of success. Permanent pacing was termed successful if any of the following criteria were met:
1. there was no syncope after CLS pacemaker implantation;
2. if the syncope burden (frequency) declined by ≥50%;
3. if pacing provided the patient with a consistent aura/prodrome where none had been present previously, thus converting a black-out spell (without warning) to a gray-out spell (with warning).

### Statistical analysis

The continuous data are presented as means and standard deviation. Categorical data are presented as percentages or ratios.

### Results

#### Patient characteristics

An extensive search of our center database for patients with a CLS pacemaker implanted between January 2005 and June 2013 identified 64 patients meeting the above criteria. All 64 patients received a CLS unit (Cylos, Biotronik). The baseline characteristics of patients are summarized in Table 1. Out of 64 patients, 52 are female (81.3%) and 12 are male (18.8%). Their age ranged from 16 to 73 years, with a mean age of 44 years.

Prior to inclusion in the study, patients had undergone extensive education regarding NCS, had been advised to avoid predisposing factors (i.e., heat, prolonged standing), and had been instructed in using physical counter maneuvers (such as leg crossing and leg and arm tensing). All patients had been advised to consume at least 2 l of fluids per day and 6–10 g of sodium per day. All patients were either refractory to or intolerant of therapy with fludrocortisone, midodrine, methylphenidate, serotonin re-uptake inhibitors, β-blockers, and pyridostigmine. None of the above-mentioned therapies had changed the frequency or severity of these syncopal events. Patients originated from throughout the United States and all over the world and had been referred to our syncope center for management of refractory NCS.

#### Treatment results

The mean follow-up was 3.81 ± 1.9 years. Thirty-three out of 64 patients (51.6%) had a record of asystole or severe bradycardia from an implantable loop recorder. Ten patients (15.6%) had a documented syncope episode and hypotension associated with asystole or bradycardia from the tilt table test. The remainder of patients had documented asystole or severe bradycardia on an event recorder.

All patients underwent dual-chamber pacemaker implantation after an overnight fast.

Thirty patients (47%) had no syncope episode after CLS implantation. Twenty-three patients (36%) had a significant reduction (>50%) in syncope episodes after CLS implantation. A total of 53 patients (73%) were deemed to have successful treatment. Eleven patients (17%) did not have a significant reduction in syncope episodes (nine female patients and two male patients) (Table 1 and Figure 3).

Of 64 patients, 25 patients had previously received a standard conventional pacemaker (with rate drop), but didn’t have a satisfactory response to it. Out of these 25 patients, 21 had a good response to a CLS pacemaker: either no syncope or significant reduction in syncope attack.

### Discussion

There are certain observations that are worth noting from this study with a long-term follow-up.

#### Reduction in syncope burden

There has been no FDA-approved therapy for NCS, which represents the most common cause of syncope. Most of the clinical trials of pharmacotherapy in NCS have shown little benefit over placebo. One potential reason could be that most of these trials were flawed to begin with or the endpoints of the study were not reasonable. Most of these clinical trials looked at the

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**Table 1: Baseline characteristics of patients with refractory neurocardiogenic syncope**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>64</td>
</tr>
<tr>
<td>Age</td>
<td>44 ± 13.6</td>
</tr>
<tr>
<td>Female</td>
<td>81.3%</td>
</tr>
<tr>
<td>Follow up period (months)</td>
<td>45.8 ± 22.9</td>
</tr>
<tr>
<td>Number of patients received</td>
<td>25 (39.1%)</td>
</tr>
<tr>
<td>conventional pacemaker before closed-loop system (CLS) implantation</td>
<td></td>
</tr>
<tr>
<td>Number of patients with documented asystole on implantable loop recorder</td>
<td>33 (51.6%)</td>
</tr>
<tr>
<td>Number of patients with documented asystole on tilt table test</td>
<td>10 (15.6%)</td>
</tr>
<tr>
<td>Patients without syncope after CLS implantation</td>
<td>30 (47%)</td>
</tr>
<tr>
<td>Patients with 50% reduction in syncope or prodrome following CLS pacemaker implantation</td>
<td>23 (36%)</td>
</tr>
<tr>
<td>Patients with no improvement</td>
<td>11 (17%)</td>
</tr>
</tbody>
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**Figure 3:** Response rate to closed-loop system pacemaker in patients with refractory neurocardiogenic syncope.
“time to first syncope,” which may not be a reasonable end point to assess success of any therapy. NCS should be considered, as a chronic condition like other chronic diseases where the aim of the therapy should be to decrease the recurrence of syncope rather than complete elimination of syncope. In this study, one of our endpoints was reduction in syncope burden. We observed that there was a significant reduction in the syncope burden in patients when they received a CLS pacemaker. We believe that there is a need for using reasonable endpoints like “syncope burden” when devising new clinical trials. In future, we hope to see more data on the management of NCS. Although we did not formally collect the data on quality of life in this retrospective cohort, we believe patients who had a significant reduction in their syncope burden would have enjoyed better quality of life.

Converting “black-out” spells to “gray-out” spells

Patients with recurrent NCS can display profound bradycardia or asystole and/or hypotension during their syncopal events. Some of these patients will experience little or no warning prior to their syncope, thereby exposing them to an enhanced risk of injury related to sudden falls that can accompany the syncopal event. The usual dual-chamber pacemakers utilizing the rate drop algorithm are capable of sensing heart rate alone. Our current understanding of NCS suggests that, in many patients, the fall in blood pressure precedes the fall in heart rate. Thus, a rate drop algorithm that possesses rate-only sensing may be able to sense the occurrence of a syncopal episode only after it is well underway, thereby offering, as was alluded to earlier, “too little too late.” While rate drop and surge hysteresis functions may enhance the efficacy of conventional pacing, it is often limited by the aforementioned constraints. On the other hand, the CLS pacemaker used in this study (Cylos, Biotronik Inc., Lake Oswego, OR) is capable of measuring changes in blood pressure. It measures the right ventricular impedance between the electrode tip and right ventricular myocardium on a beat-to-beat basis. As blood pressure declined, so would the return of blood to the right ventricle. The deceased amount of blood in the right ventricle, caused by the blood pressure drop, would cause an impedance increase that the CLS pacemaker was capable of detecting. So the device is capable of sensing drops in blood pressure in a patient with hypotensive syncope and starts pacing in an attempt to increase blood pressure or provides a reliable prodrome for patients to respond with evasive actions such as sitting down or lying down. Indeed, the preliminary observations reported herein confirm this concept.

Efficacy of CLS pacing at a long-term follow-up

One of the important observations from this study was that patients who received CLS pacing demonstrated continued efficacy in terms of reduction in syncope burden and/or the occurrence of warning symptoms prior to presyncope or syncope at a mean follow-up of 8 years.

Conclusion

Permanent pacemakers with a CLS algorithm offer long-term efficacy in terms of reduction in syncope burden and converting black-out spells (without warning) to “gray-out” spells with warning. These observations will need to be confirmed by prospective double blind trials to further evaluate the utility of this approach.

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References