Preliminary observations on the use of closed-loop cardiac pacing in patients with refractory neurocardiogenic syncope

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Abstract

Background In many patients with recurrent neurocardiogenic syncope (NCS), a significant fall in blood pressure precedes any appreciable decline in heart rate. Closed-loop pacing (CLS) employs a sensing system that measures myocardial contractility, thereby providing a potential way to detect the onset of NCS at a much earlier point in time than that provided by standard pacing systems.

Methods Patients were included in the study if they suffered 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) Patients were refractory to (or intolerant of) all conventional, non-pharmacological, or pharmacological treatments. (3) They had evidence of asystole (>10 s) or severe bradycardia (heart rate <30 bpm) on implantable loop recorder or during head-up tilt test (HUTT).

Results Thirty five patients meeting the above criteria received 44 devices. Twelve patients received a standard unit (with rate drop or rate hysteresis response) and 32 patients received a CLS unit (Cylos, Biotronik). The pacemaker implantation was termed successful if there was no recurrence of syncope, if the syncope burden decreased by ≥50%, if only presyncope occurred, or if the syncope occurred but with significant warning symptoms. Thirty-five patients, 29 females and six males, age 41±11, with refractory NCS underwent pacemaker implantation. Mean follow-up was 9±3 months. Out of 32 patients who received CLS, nine had a conventional pacemaker implanted in the past. Recurrence (59% vs 83%), reduction in syncope burden and pacemaker success (84% vs 25%, P=0.002), and occurrence prodrome/warning signs (40% vs 16%) were much better in the closed-loop group.

Conclusion These preliminary observations suggest that dual-chamber CLS pacing may be promising therapy for refractory NCS. Further randomized trials will be needed to better determine the role of this therapy in refractory NCS.

Keywords Closed-loop pacing · Neurocardiogenic · Syncope · Pacemaker

1 Introduction

Permanent cardiac pacing has been a controversial therapy for the prevention of recurrent episodes of neurocardiogenic syncope (NCS) [1]. While early-published reports suggested that permanent pacing was useful in preventing NCS [2–8], subsequent trials did not support the concept [9, 10]. However, the investigations employed pacemakers that were only capable of sensing heart rate. In many patients with recurrent NCS, a significant fall in blood pressure precedes any appreciable decline in heart rate [1]. Thus, during an episode of NCS, standard pacing systems may only detect a change in heart rate once the event is well under way and, therefore, be unable to fully prevent (or retard) its occurrence. Close-loop pacing (CLS) employs a sensing system that measures myocardial contractility,
thereby providing a potential way of detecting the onset of NCS at a much earlier point in time than that provided by standard pacing systems. Earlier detection would then allow for pacing to be employed at an earlier point in the syncopal process, potentially enhancing its ability to either prevent (or significantly modify) the syncopal process [11, 12]. In this paper, we report our initial findings using a CLS pacemaker for the prevention of recurrent severe NCS.

2 Methods

The study was conducted in a retrospective analysis fashion and was approved by our Institutional Review Board. Patients were included in the study if they were suffering from recurrent NCS and met all of the following criteria:

- Had suffered at least two syncopal episodes in the preceding 6 months.
- Patients were refractory to (or intolerant of) all conventional, non-pharmacological, or pharmacological treatments.
- Had an evidence of asystole (>10 s) or severe bradycardia (heart rate <30 bpm) on implantable loop recorder or during head-up tilt test (HUTT).

An extensive search of our syncope center database identified 35 patients meeting the above criterion and who, between them, had received a total of 44 devices. Twelve patients had received a standard unit (with rate drop or rate hysteresis response) and 32 patients received a CLS unit (Cylos, Biotronik). Out of these 32 patients, nine had already received a standard unit in the past. Information was collected from patient charts, correspondence from physicians, and patient inquiry. The occurrence rate of syncope after device implantation was determined for each patient, as well as the characteristics of events (aura/prodrome, duration of loss of consciousness, presence or absence of convulsive activity, and the time to complete recovery) both before and after pacemaker implantation.

Permanent pacing was termed successful if any of the following criteria were met:

1. There was no syncope.
2. If the syncope burden (frequency) declined by ≥50%.
3. If only presyncpe occurred rather than complete syncpe.
4. If pacing provided the patient with an aura/prodrome where none had been present previously.

3 Statistics

The continuous data are presented as means and standard deviation. Categorical data are presented as percentages or ratios. T test for comparison of means and chi-square or Fishers exact test was used to test the variables for statistical significance. The statistical significance was reached at P values less than 0.05.

4 Results

A total of 35 patients were identified for inclusion in the study. Of these, 32 had CLS pacemakers implanted at our institution and three underwent conventional dual-chamber pacemaker implants. Of the 32 patients who received CLS pacemakers, nine (29%) had previously undergone conventional pacemaker implantation, yet had experienced no change in the frequency or severity of their syncopal episodes. Thus, the effects of a total of 44 pacemakers were evaluated in a group of 35 patients.

Of the patients included in the study, there were five (15%) men and 30 (85%) women. Their age ranged from 30 to 52, with a mean age of 41±11 years. The mean syncopal frequency prior to inclusion was 5±2 episodes in the preceding 6 months. Twelve patients (35%) had no identifiable prodrome to warn them of impending loss of consciousness. Sixteen patients (46%) had suffered from bodily trauma during syncope, and in seven patients (20%), the trauma was considered severe (subdural hematoma, mandibular fracture, orbital fracture, dislocation of the shoulder, and fracture of the legs, wrist, and pelvis). Prior to inclusion in the study, the 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 a 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, beta-blockers, and pyridostigmine. Sixteen (46%) patients had tried “tilt training” with no effect and 29 (60%) had syncope despite the use of waist-high elastic compression hoses. Twelve patients (35%) had undergone conventional dual-chamber pacemaker placement with units possessing either “rate drop” or “rate hysteresis” function. None of the above-mentioned therapies had changed the frequency or severity of these syncopal events. Patients originated from throughout the USA and had been referred to our syncope center for management of refractory NCS. Twenty patients (57%) had either lost their employment or had to stop college due to recurrent syncope and were considered functionally disabled. Patients were followed for a mean of 9±3 months. The effects of CLS pacing were compared to those of conventional pacing. Table 1 summarizes the baseline clinical characteristics of the study population.
5 Syncope recurrence and burden

Syncope was reported to have occurred in 19 of the 32 patients (59%) who received CLS pacemakers and in 10/12 patients (83%) of the patients who received conventional pacemakers ($P=$NS) (Fig. 1). The syncope burden (defined as the frequency of the syncopal events) was decreased by >50% in 27/32 patients (84%), who received CLS pacing as compared to 3/12 (27%) of patients who received standard dual-chamber pacemakers ($P=0.002$) (Fig. 2).

6 Prodrome/warning symptoms

There were a total of 20 patients who experienced sudden loss of consciousness with no discernable warning of the impending event. All of these patients had suffered bodily trauma due to their syncopal events, and all of these patients had lost employment or had to discontinue educational pursuits. Fourteen of these patients had received CLS devices and six had received conventional pacing systems. After implantation, 14/14 patients who received CLS pacemakers reported having a clear prodrome or warning symptoms (lightheadedness and palpitations) that preceded a syncopal event, which afforded them the opportunity to perform evasive maneuvers (such as muscle tensing and recumbency) that allowed them to avoid falling. In the conventional pacing group, only 2/6 reported the appearance of a prodrome or warning symptoms after implantation (Fig. 3).

7 Success of pacing

Using the four criteria for success set forth previously, pacing was successful in the treatment of NCS in 84% (27/32) and in 3/12 (25%) of patients who received conventional units ($P=0.002$). While we did not employ a formal quality-of-life questionnaire, 29 of the 32 patients (90%) who received CLS pacemakers reported experiencing a dramatic improvement in their overall quality of life attributed to a reduction in their syncopal frequency and/or severity. One patient had been so disabled by the frequency and severity of her syncopal events that she was forced to enter an extended care facility. After implantation of a CLS pacemaker, the frequency and severity of her episodes

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Table 1 Baseline characteristics of our study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>41±11</td>
</tr>
<tr>
<td>Females</td>
<td>30 (85%)</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>9±3</td>
</tr>
<tr>
<td>Total No: of patients</td>
<td>35</td>
</tr>
<tr>
<td>Total No: of devices Implanted</td>
<td>44</td>
</tr>
<tr>
<td>Number of patients receiving Cylos</td>
<td>32</td>
</tr>
<tr>
<td>Number of patients receiving conventional pacing</td>
<td>12</td>
</tr>
<tr>
<td>Number of patients in Cylos group with prior conventional implants</td>
<td>9</td>
</tr>
<tr>
<td>Mean syncopal frequency prior to implant (in preceding 6 months)</td>
<td>5±2</td>
</tr>
<tr>
<td>Number of patients with no identifiable prodrome prior to implant</td>
<td>20 (45%)</td>
</tr>
</tbody>
</table>

Fig. 1 Recurrence rates in close loop versus conventional pacing

Fig. 2 Pacemaker success and reduction in syncope burden (>50%) in close loop vs conventional pacing
decreased to such an extent that she has left the facility and resumed independent living, as well as active employment.

8 Discussion

Recurrent unpredictable episodes of loss of consciousness due to NCS can have devastating effects on both the physical and emotional health of the individual. Several studies have demonstrated a dramatically reduced quality of life in patients with recurrent NCS [13–17].

Therapy for these individuals is often challenging. While some patients respond to non-pharmacologic modalities such as avoidance of provocative stimuli, hydration, salt loading, support hose, muscle tensing, and tilt training, there are some in whom these are ineffective. In some patients, pharmacotherapies such as beta-blockade, midodrine, fludrocortisone, serotonin reuptake inhibitors, and pyridostigmine have been reported to be effective in preventing NCS; however, there are some in whom these treatments are either ineffectual or poorly tolerated.

A subgroup of patients with recurrent NCS will display profound bradycardia or asystole during their syncopal events. Based on these observations, permanent cardiac pacing was explored as a potential therapeutic modality [3, 18]. While early trials of pacing in NCS showed promise [2–8], subsequent controlled trials failed to show a potential benefit [9, 10]. However, these studies were hampered by the fact that the pacemakers employed were traditional dual-chamber units that were only capable of sensing heart rate alone [1]. Our current understanding of NCS suggests that, in many patients, the fall in blood pressure precedes the fall in heart rate. Thus, conventional pacemakers that possess rate-only sensing may be able to sense the occurrence of a syncopal episode only after it is well underway, thereby offering “too little too late.” While rate drop and surge hysteresis functions may enhance the efficacy of standard pacing, it is often limited by the aforementioned constraints.

The concept of measuring changes in right ventricular impedance as a surrogate marker of changes in blood pressure was first explored over a decade and a half ago. At that time, a special lead was employed that had two right ventricular recording electrodes that measured impedance to an electrical field generated between them. As blood pressure declined, so would the return of blood to the right ventricle. This would cause an impedance increase that the pacemaker was capable of detecting. Our group published a report [18, 19] demonstrating that the device was capable of sensing drops in blood pressure in a patient with hypotensive syncope with tachypacing sufficient to prevent syncope. The device, however, was never brought to the market.

The CLS system that was used in this study (Cylos, Biotronik) is capable of measuring right ventricular impedance on a beat-to-beat basis by creating an electrical field between the electrode tip and the pulse generator [11, 12, 20, 21]. When the ventricle is full of blood during diastole, the impedance is less than that during systole [20, 21]. The unit can be programmed to pace at higher rates when the impedance suddenly rises. Thus, the unit can potentially detect the sudden drop in right ventricular return that occurs in NCS and pacing can be initiated much earlier in the process [22, 23]. Indeed, the preliminary observations reported herein confirm this concept.

In our study, we found CLS pacing to be an effective therapeutic modality in a select group of patients with recurrent severe NCS refractory to standard treatment modalities. When compared against standard pacing systems, CLS appeared to offer these patients a much greater degree of symptomatic relief.

All the CLS devices were programmed to a level of “high” sensitivity in order to catch the initial drop in venous return occurring in NCS. In addition, pacing rates were programmed to reach a rate of 130 ppm when impedance criterion were met (by contrast, the maximum programmable rate standard units could achieve was 120 ppm).

One of the most notable findings of our study was that CLS pacing provided prodrome/warning symptoms in each patient who had none prior to implant. Patients with no prodrome are particularly prone to injury from falls brought on by NCS. Each of the patients in this group was extremely pleased that the device provided them with a prodrome, thereby allowing time to take evasive actions to avoid injury.

Fig. 3 Effect on prodrome and warning symptoms in close loop versus conventional pacing

![Graph](https://example.com/graph.png)
9 Limitations

There were several important limitations to our study. The data were observational and were collected in a retrospective fashion. Patients often served as their own controls when comparing standard and CLS pacing systems. The patients studied suffered from an unusually severe forms of NCS, having come to our center from across the USA, and, thus, may not be representative of the average NCS patients. While all of the patients reported here had documented periods of severe bradycardia or asystole during their episodes, many patients with NCS do not.

Despite these limitations, the data presented herein suggest that CLS pacing may be an effective therapy in refractory NCS. These finding would seem to justify larger prospective randomized trials to better determine the utility of CLS pacing in patients with severe NCS.

10 Conclusion

These preliminary observations suggest that dual-chamber CLS pacing may be promising therapy for refractory NCS. Further randomized trials will be needed to better determine the role of this therapy in refractory NCS.

References