Baroreflex activation therapy in patients with pre-existing implantable cardioverter-defibrillator: compatible, complementary therapies

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Aims

The Neo™ System (CVRx) is an implantable device, CE certified for the treatment of resistant hypertension and investigationally used to treat systolic heart failure by electrical stimulation of the carotid baroreceptors. It is unknown whether interaction might exist between the Neo System and implantable cardioverter-defibrillators (ICDs).

Methods and results

Compatibility of the Neo device was tested in seven consecutive patients with pre-existing ICDs. Intra- and post-operative testing was completed with ICD and Neo settings programmed to provoke interaction. Intracardiac electrograms were printed to determine interaction with the ICD. Interaction testing during implantation and follow-up showed that there was no device–device interaction. No interaction was observed at maximum atrial and ventricular sensitivity settings and maximum Neo output settings.

Conclusion

Combined therapy with the Neo device and at least in this study reported that transvenous ICD systems can be performed safely.

Keywords

Resistant hypertension • Heart failure • Carotid baroreceptor • Implantable cardioverter-defibrillator

Introduction

Electrical stimulation of carotid sinus baroreceptors evokes coordinated reductions in sympathetic traffic to the heart, vasculature, and kidneys, as well as augmented parasympathetic activity. A new surgically implantable device (Neo System, CVRx, Inc.) has been developed to administer baroreflex activation therapy (BAT) via electrical stimulation of the carotid baroreceptors. Baroreflex activation therapy is applied by implanting a stimulator similar to a pacemaker, along with one or more leads attached to the carotid sinus.

With indications for implantation of carotid baroreceptor stimulators (CBSs) expected to expand from resistant hypertension to heart failure (HF), the number of patients with coindications for CBS and an implantable cardioverter-defibrillator (ICD), or pre-existing ICD, will be considerably increasing.

Coexistence of CBS and ICD is particularly frequent and important in the ongoing Barostim neo HF Study, an international, multi-centre, randomized evaluation of BAT in patients with New York Heart Association classification (NYHA) Class III HF and left ventricular ejection fraction (EF) < 35%. The trial will randomize 140 patients with and without ICD in a 1:1 fashion to receive either medical management alone or medical management plus BAT. Efficacy will be assessed by the improvement relative to baseline of EF at 6 months for the group receiving BAT vs. those patients receiving medical management alone. Secondary endpoints will include improvement in the quality of life, 6 min hall walk distance, and serum levels of amino terminal pro-B-type natriuretic peptide.

Due to the advanced state of HF in these patients and a high probability of a pre-existing ICD, there are understandable concerns about potential device–device interaction. Previous reports have provided evidence of the safety of the combined use of a first-generation CBS and a permanent pacemaker with the precaution of thorough intraoperative and careful follow-up tests. However, it is unknown whether interaction might exist between the Neo

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System and conventional ICDs. This report documents the safe coexistence of the Neo System and automatic ICDs in seven consecutive patients who had ICDs for underlying cardiac rhythm disturbances in place at the time of implantation of the Neo System in our heart centre.

**Methods**

**Neo system**
The Barostim Neo System for BAT consists of an implantable programmable pulse generator providing unipolar stimulation without a sensing circuit and one miniaturized electrode designed to be placed at the right carotid bulb.

The NEO device is using a continuous stimulation in which the pulse amplitude (programmable in milliampere), the pulse width (programmable in microseconds), and the frequency (programmable in Hertz) can be adapted. In addition, the device is programmable in a circadian manner to adapt to the patient’s need for therapy in regards to different outputs for different time windows.

**Intraoperative**
The Neo pulse generator was implanted in the upper pectoral region contralateral to the defibrillator device (Figure 1). Implantation of the unipolar lead involved unilateral exposure of the right carotid artery bifurcation using standard surgical techniques of oblique or vertical incision and tunnelling the components then subcutaneously. The lead was placed on the carotid sinus at various locations to map the best response to Neo therapy (Figure 2). Prior to testing the carotid sinus lead positions, the ICD was programmed to provoke oversensing. These programmed settings represent the highest possible sensitivity programmable in each device (atrial sensing parameters 0.15–0.25 mV, ventricular sensing parameters 0.18–0.25 mV). Changes to the ICD and assessment of appropriate function were managed by technicians of each ICD manufacturer. Furthermore, implantations were done on a regular basis with an experienced field support employee of CVRx Inc. who had electrophysiological and ICD programming know-how due to former duties.

During testing of the carotid sinus lead positions, 12-lead electrocardiogram as well as real-time intracardiac electrograms (EGMs) were telemetered from the ICD to document any oversensing (Figure 3A–C).

**Results**

Demographic information of the patients is provided in Table 1. During testing, the Neo devices were programmed to deliver therapy at 6 mA, 125 μs pulse width, and 40 Hz frequency. The stimulation was increased to a maximum of 12 mA or until a protocol-determined haemodynamic stop value was reached (systolic blood pressure <90 mmHg, diastolic blood pressure <50 mmHg, dbp <30 mmHg).
Figure 3 (A–C). Intracardiac ICD sensing with Neo device output at 109 µs, 8 mA, 60 Hz (A) and 300 µs, 8 mA, 80 Hz (B); ICD sensitivity at 0.15–0.25 mV (intraoperative tracing). No oversensing was observed at any voltage, pulse width, or frequency setting. Intraoperative 12-lead electrocardiogram showing Neo device stimulation spikes during testing (C).

Table 1 Demographic data (n = 7)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>EF</th>
<th>Indication for ICD implantation</th>
<th>ICD device</th>
<th>ICD age at Neo implant (months)</th>
<th>Neo follow-up (months)</th>
<th>Condition (NYHA)</th>
<th>Recorded VT/VF episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Men</td>
<td>29</td>
<td>35 Primary prophylaxis</td>
<td>BSC Teligen VR</td>
<td>33</td>
<td>20</td>
<td>III→III</td>
<td>Ø</td>
</tr>
<tr>
<td>2</td>
<td>Men</td>
<td>57</td>
<td>25 Primary prophylaxis</td>
<td>BSC Teligen VR</td>
<td>63</td>
<td>17</td>
<td>III→II</td>
<td>Slow VTs (self-limiting)</td>
</tr>
<tr>
<td>3</td>
<td>Men</td>
<td>69</td>
<td>35 Secondary prophylaxis</td>
<td>BSC Teligen DR</td>
<td>52</td>
<td>4</td>
<td>III→III</td>
<td>Ø</td>
</tr>
<tr>
<td>4</td>
<td>Women</td>
<td>59</td>
<td>30 Primary prophylaxis</td>
<td>BSC Confient</td>
<td>29</td>
<td>14</td>
<td>III→II</td>
<td>Ø</td>
</tr>
<tr>
<td>5</td>
<td>Men</td>
<td>59</td>
<td>25 Primary prophylaxis</td>
<td>MDT GEM VR</td>
<td>47</td>
<td>14</td>
<td>III→III</td>
<td>Ø</td>
</tr>
<tr>
<td>6</td>
<td>Men</td>
<td>56</td>
<td>35 Secondary prophylaxis</td>
<td>MDT Protecta VR</td>
<td>16</td>
<td>10</td>
<td>III→HTX</td>
<td>3× VTs (self-limiting)</td>
</tr>
<tr>
<td>7</td>
<td>Men</td>
<td>55</td>
<td>20 Secondary prophylaxis</td>
<td>BSC Vitality DR</td>
<td>57</td>
<td>3</td>
<td>III→III</td>
<td>Ø</td>
</tr>
</tbody>
</table>

EF, ejection fraction; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association classification; VT, ventricular tachycardia; VF, ventricular fibrillation; BSC, Boston Scientific; MDT, Medtronic.
HR < 40 b.p.m.). Additional testing was conducted with the pulse width increased up to 250 μs and the frequency up to 100 Hz. No oversensing was observed at any electrical output, pulse width, or frequency setting during stimulation (Figure 3A and B). At maximal output, which would never be clinically applied because of significant discomfort for the patient, intermittent signals in the atrial and ventricular channel of the ICD have been documented. The amplitudes were 0.05–0.2 mV and have not been annotated by the ICD as sensed events despite maximum sensitivity. Maximal sensitivity is especially given in the situation when the auto-sensing function of the ICD is working in the condition of permanent pacing. In the given example (Boston Scientific Teligen™), the maximum sensitivity is reached for 150 ms before the next ventricular stimulus.

For ICD oversensing detection, we consciously selected a paced rhythm for visualization. Due to automatic sensitivity control algorithms in today’s ICDs, this allows to reach the highest programmed sensitivity after the paced beat. This was done for atrium and ventricle. As even in these settings with two safety margins (ICD more sensitive than chronic programming and barostim device with higher output than chronic programming) no oversensing occurred, it is unlikely that discrimination algorithms might be impacted by the CBS.

During follow-up of 6 months, all patients underwent the standard ICD follow-up schedule. To date (mean follow-up 11.7 ± 6.4 months, range, 3–20 months, 82 cumulative months of combined Neo system treatment) no oversensing/undersensing episodes occurred and no device-device interaction was noted. In two patients of this cohort, there have been four episodes of self-limiting ventricular tachycardia (VT) in the device memories so far (Figure 4). None of them had a documented shock delivery. During follow-up one patient underwent successful heart transplantation.

**Discussion**

Because of the expanding prophylactic indications, the number of patients receiving an ICD has been steadily growing. With BAT being pursued as a novel treatment for HF as part of an ongoing trial, the number of patients having two devices implanted is considerably increasing.

The combination of CBS and ICD in HF patients may be particularly beneficial and synergistic. Implantable cardioverter-defibrillators

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**Figure 4** (A and B) Intracardiac electrogram of the same patient recorded by the ICD device during BAT with self-limiting VT (A) and after tachycardia episode (B).
therapy addresses life-threatening arrhythmias that arise despite medical therapy. Baroreflex activation therapy may potenti ate conventional therapies by reducing central sympathetic outflow, thereby reducing myocardial automaticity and inducing natriuresis and peripheral vasodilation to reduce cardiac workload and myocar dial oxygen consumption. Furthermore, restoring autonomic balance may have some beneficial arrhythmia suppression, thereby leading to reduced number of shocks. If the use of CBS in chronic HF proves beneficial, the coincidence of CBSs and ICDs becomes an increasingly likely possibility, thus raising justified concerns regarding possible device–device interactions.

Previous reports have reiterated the precautions needed for the safe and simultaneous use of pacemakers and CBS. Specifically, extensive intraoperative and close post-operative testing of the integrity of each system and search for device interference have been emphasized. However, no experience involving ICD and CBS has been reported. This study provides preliminary evidence that the combination of cardiac defibrillators and CBSs can be safe. We found no device–device interaction between the patient’s ICD and CBS intraoperatively at elevated Neo output settings and sensitive ICD parameters. Continued assessment at scheduled follow-up will occur at protocol-specified intervals to document the safe coexistence of these electronic devices.

Limitations
Evaluating every ICD along with BAT is almost impossible. In the current study, only patients with Boston Scientific and Medtronic ICDs were included. Therefore, because of the varying sensitivity threshold algorithms of other manufacturers, it is not possible to generalize the safety of coexistent ICDs with CBS. However, this study shows that across this small sample size, the theoretical prediction that it was low risk for interaction was supported. However, our results do not eliminate the need for studies with large numbers.

Conclusions
Concomitant use of CBS and ICD is becoming increasingly frequent. The present study provides further evidence that CBSs can be safely used in patients with the ICDs reported in the study. However, extensive perioperative testing is advisable to check the integrity of each system and to avoid device interference. Long-term testing with ICDs from other manufacturers is required to increase the understanding of potential issues that may arise when these devices are concomitantly implanted. The ongoing Barostim Neo HF trial is expected to yield evidence on the use of CBS in patients with NYHA Class III reduced-EF HF, including a large body of information supporting the safe combination of CBS and ICD.

Conflict of interest
N.M. is presently a paid consultant/advisor of CVRx, Inc. R.V. is an employee of CVRx, Inc.

References