Closed-loop cardiac pacing vs. conventional dual-chamber pacing with specialized sensing and pacing algorithms for syncope prevention in patients with refractory vasovagal syncope: results of a long-term follow-up

Pietro Palmisano*, Maria Zaccaria, Giovanni Luzzi, Frida Nacci, Matteo Anaclerio, and Stefano Favale

Department of Emergency and Organ Transplantation, Cardiology Unit, University of Bari, Pietro Palmisano, Piazza Giulio Cesare 11, 70124 Bari, Italy

Received 18 September 2011; accepted after revision 16 December 2011; online publish-ahead-of-print 13 January 2012

Aims

Closed-loop stimulation (CLS) pacing has shown greater efficacy in preventing the recurrence of vasovagal syncope (VVS) in patients with a cardioinhibitory response to head-up tilt test (HUTT) compared with conventional pacing. Moreover, there is no conclusive evidence to support the superiority of CLS over the conventional algorithms for syncope prevention. This study retrospectively evaluated the effectiveness of CLS pacing compared with dual-chamber pacing with conventional specialized sensing and pacing algorithms for syncope prevention in the prevention of syncope recurrence in patients with refractory VVS and a cardioinhibitory response to HUTT during a long-term follow-up.

Methods and results

Forty-one patients (44% male, 53 ± 16 years) with recurrent, refractory VVS (26% with trauma) and a cardioinhibitory response to HUTT who had undergone pacemaker implantation were included in the analysis. Twenty-five patients received a dual-chamber CLS pacemaker (CLS group) and 16 patients received a dual-chamber pacemaker with conventional algorithms for syncope prevention (conventional pacing group): 9 patients with Medtronic rate drop response algorithm and 7 patients with Guidant-Boston Scientific sudden brady response algorithm. During the follow-up (mean 4.4 ± 3.0 years, interquartile range 2.2–7.4 years) one patient (4%) in the CLS group and six (38%) in the conventional pacing group had syncope recurrences ($P = 0.016$). The Kaplan–Meier actuarial estimate of first recurrence of syncope after 8 years was 4% in the CLS group and 40% in the conventional pacing group ($P = 0.010$).

Conclusions

The results of this retrospective analysis show that, in order to prevent a recurrence of VVS in patients with a cardioinhibitory response to HUTT, dual-chamber CLS pacing was more effective than dual-chamber pacing with conventional algorithms for syncope prevention in preventing bradycardia-related syncope.

Keywords

Vasovagal syncope • Cardioinhibitory • Pacemaker • Closed-loop stimulation • Rate drop response • Head-up tilt test

Introduction

Vasovagal syncope (VVS) is a common disorder of the autonomic cardiovascular regulation. Significant bradycardia or prolonged asystole and concomitant hypotension in patients with recurrent, severe, cardioinhibitory VVS can result in serious physical injuries and psychological impairment, including substantial limitations to their social and working life. Some initial, uncontrolled, follow-up studies as well as subsequent, randomized, controlled trials have suggested that,
when VVS is refractory to conventional measures and/or pharmacological treatment, permanent pacing may induce clinical benefit with a reduction in syncope recurrence.

Small and large controlled studies have shown that dual-chamber pacing, incorporating algorithms that monitor the heart for faster detection of a significant rate drop and respond by pacing at a high rate, reduces syncope in patients with severe forms of neurocardiogenic syncope\(^{8,12,14–17}\) and may be preferable to the DDI pacing mode with rate hysteresis.\(^{18}\)

Closed Loop Stimulation\(^9\) (CLS) function, performed by INOS\(^2\), PROTOS, CYLOS, and EVIA CLS dual-chamber pacemakers (by Biotronik GmbH & Co., Germany), is a form of rate-adaptive pacing which responds to myocardial contraction dynamics by measuring variations in right ventricular intracardiac impedance.\(^{19}\)

During an incipient VVS it could increase paced heart rate and avoid bradycardia, arterial hypotension, and syncpe.\(^20\) The prospective, controlled, randomized, single-blind, multicentric INVASY study showed that the dual-chamber CLS pacing was more effective than the DDI pacing [without the rate drop response (RDR) function or rate hysteresis] in preventing a recurrence of VVS in patients with a cardioinhibitory response to head up tilt test (HUTT) during a mean follow-up period of 19 months.\(^21\)

It is generally accepted that the natural history of VVS is variable with long, recurrence free periods and that the clinical benefit of CLS pacing in the long term is unknown. Moreover, there is no conclusive evidence to support the superiority of CLS over conventional algorithms for syncope prevention.

This study retrospectively evaluated the efficacy of DDD pacing with conventional sensing and pacing algorithms for syncope prevention in the prevention of syncope recurrence in patients with refractory VVS and a cardioinhibitory response to HUTT during a long-term follow-up.

**Methods**

**Patient selection**

The study group included 41 consecutive patients who had undergone dual-chamber pacemaker implantation for recurrent, severe, cardioinhibitory VVS at our institute between January 2001 and October 2010. The clinical and pacemaker records and the test results for all patients were reviewed.

The inclusion criteria were a history of recurrent unpredictable syncope (≥2 in the year prior to pacemaker implantation) with significant limitation of social and working life, a positive type 2A or 2B (according to the VASIS classification) cardioinhibitory response to HUTT, refractoriness to conventional drug therapy, and/or tilt training. In addition to a positive HUTT result, the diagnosis of VVS was based on a complete systematic cardiac and neurological evaluation to exclude all other possible causes of syncope.

The exclusion criteria included second- or third-degree atrioventricular block, sinus node disease, carotid sinus hypersensitivity, tachyarrhythmia, an obstructive cardiac pathology, severe valvular heart disease, pulmonary hypertension, severe heart failure or severe neurological or psychiatric disorders found during clinical assessment, and conventional investigation.

Before pacemaker implantation resting electrocardiography, conventional 24 h Holter electrocardiogram (ECG) monitoring, transthoracic echocardiography, and carotid sinus massage in the supine position had been performed on all patients. Exercise tests were performed in 15% when clinically indicated. Cardiac catheterization with coronary angiogram was performed in 2% to exclude coronary disease and ischaemia-driven arrhythmias.

**Tilt test protocol**

Head-up tilt test had been performed according to current guidelines.\(^{22}\) The tests were performed between 9:00 and 11:00 a.m. in a temperature-controlled room (23°C) by an experienced nurse supervised by a physician. Electrocardiogram and systolic and diastolic blood pressure were continuously monitored and recorded using a Task Force Monitor (CNSystems, Graz, Austria). After 10 min of supine rest, the patients were tilted to 70° using an electronically operating tilt-table with a footboard. If VVS had not occurred after 20 min, 300 μg of nitroglycerin was administered sublingually, and the test was continued for a further 20 min.\(^{23}\) Fourteen patients were included after a positive response to nitroglycerine. Based on the modified Vasovagal Syncope International Study (VASIS) classification, syncope was classified as type 1 (mixed), type 2A (cardioinhibition without asystole), type 2B (cardioinhibition with asystole), or type 3 (vasodepressive).\(^{24}\)

**Pacemaker programming**

Twenty-five patients had received a dual-chamber pacemaker with CLS function (CLS group), 16 a dual-chamber conventional pacemaker programmed in DDD mode with the RDR function activated (conventional pacing group). Table 1 lists the pacemaker models implanted in each model.

In the CLS group the device had been programmed in DDD–CLS mode with a lower rate limit (LRL) of between 40 and 60 b.p.m. and a maximum, sensor-driven pacing rate of between 100 and 120 b.p.m. The CLS algorithm initializes automatically. This pacing system tracks the variations in intracardiac impedance measured between the ventricular electrode tip and the pacemaker case during the systolic phase of the cardiac cycle on a beat-to-beat basis.\(^{19}\) Changes in intracardiac impedance are closely correlated with both right and left ventricular contractility.\(^{25}\) Inotropic regulation affects

| Table 1 Pacemaker models implanted in the two groups and the algorithms for syncope prevention in each model |
|-----------------|-----------------|------------------|
| Pacemaker model | Patients, n (%) | Algorithm for syncope prevention |
| CLS group       | 25 (61)         | Biotronik CLS    |
| BIOTRONIK INOS  | 6 (15)          | Biotronik CLS    |
| BIOTRONIK CYLOS | 18 (44)         | Biotronik CLS    |
| BIOTRONIK EVIA  | 1 (2)           | Biotronik CLS    |
| Conventional pacing group | 16 (39) | Medtronic RDR    |
| MEDTRONIC KAPPA 700 | 7 (17) | Guidant-Boston Scientific SDR |
| GUIDANT INSIGNA I PLUS | 2 (5) | Guidant-Boston Scientific SDR |
| GUIDANT INSIGNA I ULTRA | 4 (10) | Guidant-Boston Scientific SDR |
| BOSTON SCIENTIFIC ALTRUA | 3 (7) | Guidant-Boston Scientific SDR |
myocardial contractility, which consequently reflects information about the haemodynamic state and requirements. Based on that relationship, CLS transfers the detected changes in myocardial contraction dynamics into individual pacing rates. In the very first days following programme implementation, CLS is adjusted to each individual patient: a reference curve is created and continuously updated with beat-to-beat impedance measurements. Starting from the programmed LRL, the system is designed to change rate dynamics within the full range between the lower and the upper rates.

In the conventional pacing group the device had been programmed in DDDR mode with an LRL of between 40 and 60 b.p.m. and a maximum sensor-driven pacing rate of between 100 and 120 b.p.m.

In this group, nine patients had received a pacemaker implemented with Medtronic RDR algorithm (Medtronic Inc., Minneapolis, MN, USA) and seven patients received a pacemaker with Guidant-Boston Scientific sudden brady response (SBR) algorithm (Boston Scientific Corp., Place Natick, MA, USA).

The operation of these algorithms is similar. The device monitors the heart for rate drops to detect any significant changes, it then intervenes when the ventricular rate drops by a specified number of beats per minute to below a specified heart rate within a specified period of time or when the atrium is paced at the LRL for the number of consecutive beats. When a rate drop is detected the device paces the heart at a programmable rate for a programmable time interval. When this is complete, the device gradually reduces the pacing rate until the sinus rate or LRL or sensor-indicated rate is reached. The algorithm parameters had been programmed in each patient according to the rate behaviour during HUTT, the underlying cardiac disease, and the constitution of the patient.

Follow-up
All patients were followed up until March 2011. Follow-up consisted of twice-yearly pacemaker interrogation, outpatient clinic visits, and telephone contact. At the time of implantation and follow-up, no patients in either group received medication for syncope. Other drug treatments in progress were continued in both groups without significant dosage modification. During follow-up no significant changes in pacemaker programming were performed.

Definitions
Syncope was defined as a transient loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery.

Pre-syncope was defined as any of the various premonitory signs and symptoms of imminent syncope (e.g. severe weakness or light headedness).

Data collection
The complete record of personal details, symptoms, and test results before implantation, implantation details, and symptoms after implantation were obtained for all patients from a review of the hospital and outpatient notes and pacemaker records and supplemented, where necessary, by additional patient interview.

Statistical analysis
Continuous variables were expressed as mean values ± standard deviation and frequencies were expressed as the number and percentage of patients. Categorical variables were compared between groups using the χ² or Fisher’s exact test as appropriate. Other between-group comparisons were made using the Student’s t-test. The event and event-free curves were based on Kaplan–Meier analyses, stratified by study group, and compared using the log-rank test. P values of <0.05 were considered statistically significant.

The data were analysed using the statistical software package Statistics version 6.1 (StatSoft Inc., Tulsa, Oklahoma).

Results

Patient characteristics
Forty-one patients who had been implanted at our centre between January 2001 and October 2010 were included in the analysis. Twenty-five were in the CLS group and 16 in the conventional pacing group. The baseline characteristics of patients are summarized in Table 2.

Fourteen patients (34%) had significant anomalies at resting electrocardiography: sinus bradycardia (eight patients), nonspecific ST-T wave abnormalities (four patients), and ECG signs of left ventricular hypertrophy (two patients). Four patients (10%) showed anomalies at transthoracic echocardiography, the most frequent (three patients, 75%) was a mild left ventricular systolic dysfunction. Of the patients who had undergone exercise tests or coronary angiogram, those with significant coronary disease and/or ischaemia-driven arrhythmias were excluded. Twenty-two of the 25 patients in the CLS group (88%) and 12 of the 16 patients in the conventional pacing group (75%) had a severe cardioinhibitory response to HUTT, causing a prolonged asystolic pause >3 s (VASIS 2B). The clinical characteristics of the two groups did not differ significantly.

Follow-up
The mean follow-up was 4.4 ± 3.0 years (interquartile range 2.2–7.4 years) and was similar in both groups (4.3 ± 3.2 years in the CLS group and 4.5 ± 2.9 years in the conventional pacing group; P = 0.819).

During the follow-up period, 1 of the 25 patients (4%) in the CLS group experienced syncopal recurrence only 22 days after pacemaker implantation. The patient was a 36-year-old woman with a history of numerous syncopal episodes occurring in the year preceding implantation. She had already had a cardioinhibitory response to HUTT, with an asystolic pause of 16 s, performed before implantation. After implantation the patient continued to have frequent syncopal episodes (three to four per month) none with trauma. Closed-loop stimulation algorithm activation was not found in any of the repeated device interrogations performed with the manufacturer’s technical support. A later, neuropsychiatric evaluation diagnosed a conversion disorder. The patient began psychological and antidepressant drug therapy with a consequently significant reduction in syncopal episodes.

In the conventional pacing group, 6 of 16 patients (44%) experienced syncopal recurrence after a mean period of 11 months (range 5–47 months). There were no cases of physical injury due to the syncopal recurrences. The difference in the syncopal recurrence rate between the two groups was significant (P = 0.016). The Kaplan–Meier actuarial estimates of first recurrence of syncope after 1, 3, 5, and 8 years were 4, 4, 4, and 4% in the CLS group and 25, 31, 40, and 40% in the control group, respectively (Figure 1). In the conventional pacing group, no significant...
A difference was found in syncopal recurrence rate in patients who had received a pacemaker with Medtronic RDR algorithm compared with those who had received a pacemaker with Guidant-Boston Scientific SBR algorithm (Figure 2).

During follow-up, 3 of 34 patients without syncopal recurrences (7%) reported at least one episode of pre-syncopal symptoms [2 of 24 patients (8%) in the CLS group and 1 of 10 patients (10%) in the control group (P = 0.876)] without any impairment to daily life.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 41)</th>
<th>CLS group (n = 25)</th>
<th>Conventional pacing group (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± standard deviation</td>
<td>53 ± 16</td>
<td>54 ± 15</td>
<td>52 ± 18</td>
<td>0.649</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (44)</td>
<td>9 (36)</td>
<td>9 (56)</td>
<td>0.202</td>
</tr>
<tr>
<td>Syncope episodes in lifetimes, median (range)</td>
<td>3 (2–12)</td>
<td>6 (3–12)</td>
<td>2 (2–7)</td>
<td>0.142</td>
</tr>
<tr>
<td>Syncope episodes in last 1 year, median (range)</td>
<td>2 (2–5)</td>
<td>3 (2–5)</td>
<td>2 (2–3)</td>
<td>0.373</td>
</tr>
<tr>
<td>Duration of symptoms, median (range)</td>
<td>5 (2–20)</td>
<td>5 (3–20)</td>
<td>3 (1–17)</td>
<td>0.143</td>
</tr>
<tr>
<td>Pre-syncope, n (%)</td>
<td>15 (37)</td>
<td>6 (24)</td>
<td>7 (44)</td>
<td>0.185</td>
</tr>
<tr>
<td>Pre-syncope episodes in last 1 year, median (range)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>1 (0–6)</td>
<td>0.119</td>
</tr>
<tr>
<td>Trauma secondary to syncope, n (%)</td>
<td>11 (26)</td>
<td>7 (28)</td>
<td>4 (25)</td>
<td>0.833</td>
</tr>
<tr>
<td>Previous drug treatment, n (%)</td>
<td>4 (10)</td>
<td>2 (8)</td>
<td>2 (13)</td>
<td>0.636</td>
</tr>
<tr>
<td>Previous tilt training, n (%)</td>
<td>5 (12)</td>
<td>3 (8)</td>
<td>2 (13)</td>
<td>0.962</td>
</tr>
<tr>
<td>Associated cardiovascular disorders, n (%)</td>
<td>23 (56)</td>
<td>11 (44)</td>
<td>12 (75)</td>
<td>0.051</td>
</tr>
<tr>
<td>Hypertension on therapy, n</td>
<td>18</td>
<td>7</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Atherosclerotic, n</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Valvular, n</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ECG abnormalities, n (%)</td>
<td>14 (34)</td>
<td>9 (36)</td>
<td>5 (21)</td>
<td>0.754</td>
</tr>
<tr>
<td>Echocardiographic abnormalities, n (%)</td>
<td>4 (10)</td>
<td>3 (12)</td>
<td>1 (6)</td>
<td>0.545</td>
</tr>
<tr>
<td>Response to baseline tilt testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2A, n (%)</td>
<td>7 (17)</td>
<td>3 (12)</td>
<td>4 (25)</td>
<td>0.281</td>
</tr>
<tr>
<td>Type 2B, n (%)</td>
<td>34 (83)</td>
<td>22 (88)</td>
<td>12 (75)</td>
<td>0.281</td>
</tr>
<tr>
<td>Asystole, s, mean ± standard deviation, median, range</td>
<td>15 ± 8, 14, 5–35</td>
<td>14 ± 7, 15, 5–35</td>
<td>12 ± 4, 10, 8–18</td>
<td>0.338</td>
</tr>
<tr>
<td>Nitroglycerin provocation, n (%)</td>
<td>14 (34)</td>
<td>9 (36)</td>
<td>5 (31)</td>
<td>0.754</td>
</tr>
</tbody>
</table>

Figure 1 Kaplan–Meier estimates of probability of remaining free of syncopal recurrences in 25 patients in closed-loop stimulation group (blue line) and 16 patients in control group (red line).

Figure 2 Kaplan–Meier estimates of probability of remaining free of syncopal recurrences in seven patients who received a pacemaker with Medtronic rate drop response algorithm (blue line) and nine who received a pacemaker with Guidant-Boston Scientific sudden brady response algorithm (red line).


Discussion

The results of this retrospective analysis show that, in order to prevent a recurrence of VVS in patients with a cardioinhibitory response to HUTT, dual-chamber CLS pacing was more effective than dual-chamber pacing with conventional algorithms in preventing bradycardia-related syncope. The benefit was maintained for up to 8 years. In the group of patients treated with dual-chamber CLS pacing, only one case of syncopal recurrences was reported. However, according to the patient clinical history, these were probably related to a psychiatric disorder.

Vasovagal syncope is an abnormal cardiovascular reflex characterized by an inappropriate reduction in heart rate and systemic hypotension caused by arteriolar vasodilatation.

In patients with severe, recurrent VVS and a prevalent cardioinhibitory response to HUTT, permanent pacing that prevents the important bradycardia and/or asystole induces clinical benefit with a reduction in syncope recurrence. Moreover, several studies have shown that VVS may not be completely prevented by conventional cardiac pacing. These suboptimal results are probably justified by the inability of conventional electrical cardiac stimulation to counteract the vasodepressor component of thevasovagal reflex present in almost all subjects during syncopal episodes and usually precedes cardioinhibition and bradycardia.

Closed-loop stimulation is an algorithm which provides the pacing rate modulation that integrates information for heart rate optimization from myocardial contraction dynamics by measuring right ventricular intracardiac impedance. After initialization of the CLS pacing mode, the pacemaker system not only initiates the rate modulating function automatically, but also permanently compensates for long-term drifts of the input signal. In the first stage of VVS, CLS detects increased myocardial contractility by measuring the intracardiac impedance and activates a high-rate atrioventricular sequential pacing that may anticipate withdrawal of sympathetic tone and counterbalance the increase in vagal tone, thus preventing arterial hypotension, bradycardia, and possibly syncope.

According to this rationale, previous studies have used CLS pacing in patients with cardioinhibitory VVS to prevent syncope during HUTT and daily life, with good results. However, several studies have shown that VVS may not be completely prevented by conventional cardiac pacing. These suboptimal results are probably justified by the inability of conventional electrical cardiac stimulation to counteract the vasodepressor component of the vasovagal reflex present in almost all subjects during syncopal episodes and usually precedes cardioinhibition and bradycardia.

More dedicated algorithms associated with pacing for a better prevention of VVS have been developed, such as the Medtronic RDR algorithm and the Guidant-Boston Scientific SBR algorithm in the control group of this study. These algorithms have been designed for the early detection of an insidious drop in heart rate and short-lasting intervention pacing at a high rate. Several studies have shown that, in patients with severe VVS, these algorithms are more effective than conservative treatments in the reduction of syncopal episodes. Moreover, in a small study, DDD pacing with RDR function was more effective than DDI pacing with rate hysteresis in cardioinhibitory VVS. These algorithms were not compared with CLS pacing in any other previous experiences.

This study compared the efficacy of CLS pacing with dual-chamber pacing with conventional algorithms in preventing bradycardia-related syncope in a selected population of patients with severe, recurrent VVS. Closed-loop stimulation pacing maintained over a long-term follow-up was shown to be significantly superior.

Our results do not provide a definite explanation, we may only suggest that the interactions between electrical cardiac pacing and the neuroendocrine mechanisms of the vasovagal reflex may explain the better results of the CLS pacing reported from our experience.

In pacemakers with conventional algorithms for syncope prevention, the high-rate pacing therapy is triggered by a sudden drop in heart rate. Therefore, the pacing may be delivered late in the afferent phase vasovagal reflex, when an excessive vagal activity is triggered by the signals from the ventricular mechanoreceptors. This delay may lead to hypotension becoming prominent and pacing may be inadequate to prevent syncope.

On the other hand, by detecting the variations in myocardial contractility, CLS may react quickly in the early phase of vasovagal reflex when the sudden reduction of central blood volume induces a compensatory increase in the sympathetic discharge, with an increase in the inotropic state of the myocardium. This timely intervention may suppress the resultant bradycardia and counterbalance the hypotension of decreased venous return by maintaining cardiac output.

This analysis confirms the results of the INVASY study which reported an extremely low, or no syncope episodes, in the CLS-treated patients.

Study limitations

This is an observational, retrospective study. The patients included in the analysis were implanted over a period of 10 years, and therefore they received different pacemaker models with different technological features. Moreover, despite the long-term mean follow-up of the entire study population, the follow-up duration was very heterogeneous (range 0.4–10.2 years). On the basis of these considerations, the results of this study should be interpreted with caution as confounding factors may not be entirely excluded.

The total population evaluated in the study was relatively low as patients in the conventional pacing group received pacemakers with two different algorithms. In this study no significant difference was found between the two algorithms. Due to the small number of cases evaluated in these two subgroups, this evidence is not conclusive. Moreover, the outcome measurement used in the study, namely the time to first recurrence of syncope, was not sufficiently sensitive in detecting differences in efficacy between these two subgroups. It is possible that a different outcome measurement, i.e. the total burden of syncope, would have been better able to detect the efficacy of the two algorithms evaluated.

Vasovagal syncope and pacemaker implantation can have important psychological consequences. Unfortunately, this study did
not assess the impact of the two pacing systems on the perceived quality of life.

**Conclusions**

The data of this retrospective experience suggest that dual-chamber CLS pacing is more effective than DDD pacing with conventional specialized sensing and pacing algorithms for syncope prevention in preventing syncope recurrence in patients with refractory VVS and a cardioinhibitory response to HUTT, and that this benefit may be long term.

Further prospective, large population studies are needed to confirm these results. If this evidence is confirmed, CLS pacing may be considered as the optimal treatment for patients with recurrent VVS, refractory to conventional measures, and/or pharmacological treatment.

**Conflict of interest:** none declared.

**References**


