Clinical research

Impact of Closed-Loop Stimulation, overdrive pacing, DDDR pacing mode on atrial tachyarrhythmia burden in Brady-Tachy Syndrome

A randomized study

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Aims Atrial overdrive pacing algorithms increase Atrial Pacing Percentage (APP) to reduce Atrial Tachyarrhythmia (AT) recurrences in patients with Brady-Tachy Syndrome (BTS). This study aimed to compare AT burden and APP in BTS patients treated with conventional DDDR pacing, DDD+ overdrive or Closed-Loop Stimulation (CLS).

Methods and results One hundred and forty-nine BTS patients were included (72 male, mean age 74±9), who received a dual chamber pacemaker (Philos DR or Inos 2+CLS, Biotronik GmbH, Berlin, Germany) programmed in DDD at 70 min⁻¹. At 1-month follow-up, DDDR, DDD+ or CLS algorithms were activated according to randomization. Follow-up visits for data collection were performed at 4 and 7 months. Non parametric statistical tests (Kruskal–Wallis H-test, Dunn test, Spearman coefficient) were used to analyse not-normally-distributed samples. At 7 months, AT burden was significantly lower in CLS group (20.3±63.1 min/day, P<0.01) compared to DDDR (56.0±184.0 min/day) and DDD+ group (63.1±113.8 min/day). APP was higher in CLS (89.0±13.2%) and in DDD+ group (97.9±2.7%) than in DDDR group (71.1±26.7%, P<0.001). The correlation found between AT burden and APP was very weak: at 7-month follow-up the Spearman coefficient was −0.29 (P=NS) in CLS, −0.52 (P<0.01) in DDD+, −0.22 (P=NS) in DDDR.

Conclusions CLS pacing was associated with a significantly lower AT burden, compared to the other pacing algorithms. Moreover APP was significantly higher in DDD+ and in CLS mode, than in DDDR. APP weakly correlated with AT burden only in DDD+ mode, though the lowest AT burden level was obtained in the CLS group where no significant correlation was found.

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KEYWORDS

Atrial tachyarrhythmia burden;
Brady-Tachy Syndrome;
Atrial overdrive pacing;
Atrial pacing percentage
Introduction

In patients with Sick Sinus Syndrome, atrial pacing has been shown to be associated with a lower incidence of atrial fibrillation, as compared to ventricular pacing.\(^1\)\(^-\)\(^3\)

In a subset of patients in whom atrial tachyarrhythmias are most likely to occur under bradycardia or long sinus pauses,\(^3\)\(^-\)\(^4\) atrial pacing has a beneficial effect in preventing atrial fibrillation recurrences.

Several mechanisms, such as overdrive suppression of ectopic foci\(^5\)\(^-\)\(^6\) or reduction of bradycardia-induced temporal dispersion of atrial refractoriness,\(^7\) are involved in the preventive effect of atrial pacing. The increase of atrial pacing percentage and the contemporary stabilization effect of cardiac rhythm, provided by specific pacing algorithms or rate responsive functions, may add incremental benefit in preventing atrial fibrillation occurrences.\(^8\)\(^-\)\(^9\)

This study was planned to test the hypothesis that, in Bradycardia-Tachycardia Syndrome (BTS) patients, the restoration of a physiological modulation of heart rate to beget atrial pacing overdrive, might have a valuable effect in reducing Atrial Tachyarrhythmia (AT) burden. In order to verify that hypothesis, three pacing algorithms were compared in this study: the Closed-Loop Stimulation (CLS) which is a physiological-sensor-based rate responsive system, with no specific functions addressed to AT trigger suppression; the so-called DDD+ overdrive algorithm, which strictly over-paces the spontaneous sinus rhythm, without supplying any rate responsive function; a conventional accelerometric-sensor-based DDDR pacing.

Methods

Patient selection and study protocol

The study was approved by the institutional board and a witnessed informed consent form was obtained from each patient.

Patients who were indicated to DDDR pacemaker implantation due to BTS and had had at least one documented AT episode within six months prior to implant, were eligible for the study. Exclusion criteria were angina, congestive heart failure, chronic atrial fibrillation, left atrium size greater than 50 mm, prior atrio-ventricular node ablation, life expectancy less than one year, pregnancy.

Enrolled patients were randomized at implant to be treated with CLS pacing mode, overdrive DDD+ algorithm, or accelerometric-sensor-based DDDR mode. The study flow-chart is shown in Fig. 1. The randomization procedure was planned to provide a balanced distribution of the treatment groups in each participating centre. Patients randomized in the CLS arm received a pacemaker Inos 2+CLS (Biotronik GmbH, Berlin, Germany), the remaining patients a Biotronik Philos DR pacemaker. The major features of both the pacemaker models are comparable, especially in terms of input stage signal processing and mode switch algorithm. Before activating the preventive pacing algorithms, an observational period of one month was required by the study protocol after pacemaker implant. In that period, patients were all paced in DDD mode with a basic rate of 70 min\(^{-1}\), while any antiarrhythmic drug therapy was allowed without limitations. As the 1-month observational period expired, the preventive pacing algorithms were switched on, according to randomization, and the best antiarrhythmic pharmacological treatment found at that moment was kept fixed during the following six months. Any change in antiarrhythmic therapy after the 1-month follow-up was considered a

![Study flow-chart](image-url)

Fig. 1 Study flow-chart
drop-out criterion. Data were retrieved at the follow-up visits scheduled for four and seven months after implant. The assigned time window for valid scheduled follow-ups was the target date±3 days.

The primary end-point of the study was to collect and compare AT burden and atrial pacing percentage (APP), evaluating any linear correlation between them, in each treatment group. Since at time of protocol formulation no data were available about CLS application in atrial fibrillation prevention, it was assumed that a minimal difference in AT burden among groups of at least 70% of the observed variance would have been clinically relevant and, in order to detect it with a statistical power of 90%, a sample size of 50 patients in each group was needed.

Methods of measuring AT burden and APP

AT burden was calculated as the cumulative duration (expressed in minutes per day) of periods with atrial rate at or above 150 min⁻¹ (unless longer cycle atrial tachycardia were documented); APP as the atrial paced event rate in the AT free periods. Data were derived from the Mean Atrial Rate Histogram provided by the pacemakers. To ensure an optimal pacemaker functioning and a reliable detection of atrial events during AT, all the patients were implanted with an atrial bipolar tined or screw-in lead positioned in right atrial appendage, and a P-wave amplitude of at least 2 mV was necessary to fulfil the protocol implant criteria. A uniform parameter setting was also required by the protocol in all the patients, including atrial bipolar sensing and 0.5 mV atrial sensitivity threshold. The basic rate was always programmed at 70 min⁻¹; the maximum CLS, DDD+, DDDR pacing rates were set at 130 min⁻¹, while the upper tracking rate at 140 min⁻¹ and the mode switch intervention rate at 150 min⁻¹, unless slower atrial tachycardia occurred, requiring specific reprogramming.

Description of the pacing algorithms used

CLS is a rate responsive pacing system. It is based on an indirect monitoring of the myocardial contractility, which is a function of the neurovegetative tone. That monitoring is obtained via a permanent sampling of the intraventricular impedance signal by a high frequency sub-threshold pulse train: an increase of the neurovegetative tone. That monitoring is obtained via a physiological rate responsive system. 12,13 It should be highlighted here that CLS functioning actively interacts with the autonomic regulation process of cardiac output, occurring under any condition of daily life, not only exercise-related stresses. 10

On that basis, it was tested in this study whether CLS can also provide an effective atrial overdrive pacing, while maintaining a physiological modulation of heart rate, independent of the spontaneous sinus rhythm, which in turn is simply over-paced immediately above.

DDD+ pacing mode was used in a control patient group. The rate responsive function was provided by a standard accelerometric sensor nominally programmed.

Data analysis

This was a prospective study with three treatment groups, with no crossover. So unpaired tests were used for multiple comparisons, in order to evaluate differences among groups. Unfortunately, AT burden samples remarkably deviated from normal distributions in the three treatment groups, so a more conservative non-parametric approach was preferred in all statistical tests involving that variable: specifically, Kruskal–Wallis rank test was used to evaluate differences among groups, Dunn test for multiple comparisons, and the Spearman correlation coefficient was calculated. On the other hand, for APP samples, the normal distribution hypothesis could be assumed, so that parametric F-test, and SNK tests were carried out. χ²-test or Fisher exact tests were performed on some categorical data. Kaplan–Meier method and the logrank test were used to obtain the study survival curves. Type I error level was set at 0.05, for statistical significance, in all the tests used. Data are presented as means±SD, even if median and percentiles should be preferred, as far as AT burden is concerned. Anyway, in these cases median values were always reported.

Results

Population

One hundred and forty-nine patients were enrolled from March 2001 to July 2002 in seventeen Italian centres: 52 were randomized in the CLS group, 49 in DDD+ group, 48 in the DDDR group. All the patients underwent echocardiographic examination at baseline. The clinical characteristics of the study population are presented in Table 1.

Of the 149 patients enrolled, 143 patients reached the 1-month follow-up, 126 the 4-month follow-up, 98 the 7-month follow-up (Table 2 reports the number of case report forms available within each treatment group at each follow-up and the number of drop-outs between two consecutive follow-ups). During the study, 51 patients dropped out, mostly due to occurrence of persistent or chronic atrial fibrillation or non-compliance with the protocol requirements, as is shown in Table 3. Three patients in the CLS group and two patients in the DDD+ group complained of intolerance to the pacing mode and/or of palpitation: in these cases the pacing algorithms were switched off and the pacemakers reprogrammed. The estimated survival at 7 months was 69.2% in the CLS group, 55.1% in DDD+ group and 72.9% in DDDR group (P=0.13, NS).

The protocol did not allow any change in the antiarrhythmic drug therapy after the 1-month follow-up. That requirement could not be fulfilled in three patients, who dropped out. At 1-month follow-up, 86 patients (60.1%) were under antiarrhythmic therapy. That percentage did not significantly change in the 126 patients who reached the 4-month follow-up (57.9%), and in the 98 patients who reached the 7-month follow-up.
There was no statistical evidence of an unbalanced distribution of patients under antiarrhythmic therapy among the three treatment groups. Table 4 shows the antiarrhythmic therapy of the patient population at 1-month follow-up.

### AT burden and atrial pacing percentage

The cumulative duration of atrial tachyarrhythmias was downloaded from the pacemaker memory in all the patients who reached the 4- and 7-month follow-up. Data collected were worked out to obtain the AT burden expressed in minutes per day. The lowest AT burden was observed in the CLS arm with both 4- and 7-month follow-up data (Fig. 2). At 4-month follow-up, AT burden data were available from 126 patients and the analysis showed that CLS group patients spent on average 21.1±71.6 min/day (median 0.14 min/day) with ATs, while DDD+ patients 213.5±535.6 min/day (median 5.29 min/day) and DDDR group patients 94.8±240.5 min/day (median 0.61 min/day). AT burden collected from 98 patients at 7-month follow-up was 20.3±63.1 min/day (median 0.11 min/day) in the CLS group, 63.1±113.8 min/day (median 10.9 min/day) in the DDD+

### Table 1 Clinical characteristic of study population

<table>
<thead>
<tr>
<th></th>
<th>CLS (n=52)</th>
<th>DDD+ (n=49)</th>
<th>DDDR (n=48)</th>
<th>Total population (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>74±9</td>
<td>75±8</td>
<td>74±9</td>
<td>74±9</td>
</tr>
<tr>
<td>Male gender</td>
<td>24 (46.1%)</td>
<td>23 (46.9%)</td>
<td>25 (52.1%)</td>
<td>72 (48.3%)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>1.4±0.6</td>
<td>1.5±0.5</td>
<td>1.5±0.6</td>
<td>1.5±0.6 (1–3)</td>
</tr>
<tr>
<td>LV ejections (%)</td>
<td>54.8±10.1</td>
<td>54.0±10.3</td>
<td>52.4±10.6</td>
<td>54.0±10.3 (27–80)</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>42.5±4.5</td>
<td>44.0±4.5</td>
<td>43.3±4.8</td>
<td>43.2±4.6 (28–50)</td>
</tr>
</tbody>
</table>

Underlying heart disease
- None
- Hypertension
- Coronary artery disease
- Valvular
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Other

*Twelve patients had more than 1 disease.

### Table 2 Enrolled patients and follow-ups

<table>
<thead>
<tr>
<th>Group</th>
<th>Recruitment/Implant</th>
<th>1 month</th>
<th>Drop-outs</th>
<th>4 months</th>
<th>Drop-outs</th>
<th>7 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLS</td>
<td>52</td>
<td>1</td>
<td>51</td>
<td>5</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>DDD+</td>
<td>49</td>
<td>1</td>
<td>48</td>
<td>6</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>DDDR</td>
<td>48</td>
<td>4</td>
<td>44</td>
<td>6</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>6</td>
<td>143</td>
<td>17</td>
<td>126</td>
<td>28</td>
</tr>
</tbody>
</table>

*Number of case report forms available in each treatment group for each follow-up. The number of patients who dropped out between two consecutive follow-ups is also reported.

### Table 3 Drop-out causes in each treatment group

<table>
<thead>
<tr>
<th>Drop-out causes</th>
<th>CLS group (n=52)</th>
<th>DDD+ group (n=49)</th>
<th>DDDR group (n=48)</th>
<th>Total population (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5 (3.3%)</td>
</tr>
<tr>
<td>Antiarrhythmic therapy change</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>12 (8.0%)</td>
</tr>
<tr>
<td>Implant revision</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Intolerance to the pacing algorithm</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5 (3.3%)</td>
</tr>
<tr>
<td>Non compliance</td>
<td>7</td>
<td>12</td>
<td>2</td>
<td>21 (14.1%)</td>
</tr>
<tr>
<td>Non compliance</td>
<td>16 (30.1%)</td>
<td>22 (44.9%)</td>
<td>13 (27.1%)</td>
<td>51 (34.2%)</td>
</tr>
</tbody>
</table>

*Percentages in the last column are relative to the total population.

Percentages in the last row are relative to the total number of patients in each group.
In the DDD group, 56.0±184.0 min/day (median 0.21 min/day) in the DDDR group. Both at 4- and 7-month follow-up, the AT burden in the CLS group was significantly lower compared to the DDD+ group (P<0.01) and the DDDR group (P<0.01). Differences between DDD+ and DDDR AT burden were not statistically significant at 4-month follow-up, nor at 7-month follow-up (Table 5). Persistent or chronic atrial fibrillation occurred in 12 patients: 3 patients in the CLS group, 5 in the DDD+ group, 4 in the DDDR group. Of these patients, 1 from the CLS group, 5 from DDD+, and 2 from DDDR, experienced persistent atrial fibrillation after the activation of the pacing algorithms. AT burden data of those 8 patients were retrieved and used in the analysis until persistent atrial fibrillation occurrence.

No statistical difference was found between the CLS and DDD+ groups in terms of APP (Fig. 3). CLS and DDD+ respectively exhibited a mean APP of 87.2±17.0% and 94.8±14.0% (P=NS) at 4 months, and 89.0±13.2% and 97.9±2.7% (P=NS) at 7 months. On the other hand, APP obtained in CLS and in DDD+ were both significantly higher than in DDDR, the latter being 71.4±26.1% at

**Table 4** Antiarrhythmic (AA) therapy distribution in the whole population and within each treatment group, at 1-month follow-up

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total</th>
<th>CLS group</th>
<th>DDD+ group</th>
<th>DDDR group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AA drug*</td>
<td>57 (39.9%)</td>
<td>21 (41.2%)</td>
<td>21 (43.7%)</td>
<td>15 (34.1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>34 (23.8%)</td>
<td>16 (31.4%)</td>
<td>11 (22.9%)</td>
<td>7 (15.9%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Propaphenone</td>
<td>15 (10.5%)</td>
<td>3 (5.9%)</td>
<td>4 (8.3%)</td>
<td>8 (18.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Sotalol</td>
<td>10 (7.0%)</td>
<td>4 (7.8%)</td>
<td>5 (10.4%)</td>
<td>1 (2.3%)</td>
<td>0.26</td>
</tr>
<tr>
<td>β-blockers</td>
<td>7 (4.9%)</td>
<td>1 (2.0%)</td>
<td>3 (6.2%)</td>
<td>3 (6.8%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Other</td>
<td>24 (16.8%)</td>
<td>6 (11.8%)</td>
<td>4 (8.3%)</td>
<td>14 (31.8%)</td>
<td></td>
</tr>
</tbody>
</table>

*Two AA drug were administered in 4 patients.

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**Fig. 2** AT burden in each treatment group at 4- and 7-month follow-up. Histograms of the Atrial Tachyarrhythmia (AT) burden expressed in minutes/day in each treatment group, at the 4-month follow-up (A), and at the 7-month follow-up (B). CLS group was always associated with a lowest AT burden (P<0.01), as a result of multiple comparisons among groups.

**Table 5** AT burden expressed in minutes per day at 4- and 7-month follow-ups in each group

<table>
<thead>
<tr>
<th>Mean±SD</th>
<th>Median</th>
<th>25th–75th percentiles</th>
<th>Kruskal–Wallis test</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-month follow-up (n=126)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLS*</td>
<td>21.1±71.6 min/day</td>
<td>0.14 min/day</td>
<td>0.01–4.05 min/day</td>
</tr>
<tr>
<td>DDD+</td>
<td>213.5±535.6 min/day</td>
<td>5.29 min/day</td>
<td>0.14–54.63 min/day</td>
</tr>
<tr>
<td>DDDR</td>
<td>94.8±240.5 min/day</td>
<td>0.61 min/day</td>
<td>0.05–19.03 min/day</td>
</tr>
<tr>
<td>7-month follow-up (n=98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLS*</td>
<td>20.3±63.1 min/day</td>
<td>0.11 min/day</td>
<td>0.01–0.98 min/day</td>
</tr>
<tr>
<td>DDD+</td>
<td>63.1±113.8 min/day</td>
<td>10.91 min/day</td>
<td>0.43–59.62 min/day</td>
</tr>
<tr>
<td>DDDR</td>
<td>56.0±184.0 min/day</td>
<td>0.21 min/day</td>
<td>0.02–8.70 min/day</td>
</tr>
</tbody>
</table>

*Multiple comparisons were performed with Dunn Q test. CLS group AT burden was significantly lower compared either to the DDD+ group (P<0.01) or DDDR group (P<0.01), both at the 4- and the 7-month follow-up. Difference between the DDD+ and DDDR group was not statistically significant at the 4-month follow-up, nor at the 7-month follow-up. AT=Atrial Tachyarrhythmia.
4 months ($P<0.001$), and 71.1±26.7% at 7 months ($P=0.001$). While APP significantly increased in CLS and DDD+ pacing, mean heart rates were not notably different among the groups, resulting in 80.9±4.2 min⁻¹ in CLS, 83.8±9.6 min⁻¹ in DDD+, 78.8±6.6 min⁻¹ in DDDR at 4 months, and 80.9±3.9 min⁻¹ in CLS, 81.6±6.0 min⁻¹ in DDD+, 79.9±7.0 min⁻¹ in DDDR at 7 months. Multiple comparisons among groups only detected a slight but significant difference between DDD+ and DDDR at 4 months ($P<0.05$). No persistent upper rate atrial pacing or other adverse events related to non-consistent algorithm functioning were documented.

Interestingly, although CLS and DDD+ algorithms both reached a high APP with no statistical difference detected between them, CLS pacing was associated with a significantly lower AT burden as compared to DDD+ overdrive. The Spearman correlation coefficient ($r_S$) was calculated to test the correlation between APP and AT burden at each follow-up data set, in each treatment group. The results are displayed in Table 6, while Fig. 4 shows the correlation plots of 7-month follow-up data. A very low correlation level was always found: the absolute value of correlation coefficients never exceeded 0.30 in the CLS and DDDR groups, standing very far from statistical significance. In spite of the statistical significance obtained in the DDD+ group, yet the correlation found was still very weak: $r_S$ was −0.54 at 4-month follow-up and −0.52 at 7-month follow-up.

**Discussion**

**Main findings**

The development and evaluation of different and specific pacing algorithms currently represent one of the major challenges in the prevention of AT recurrences in BTS. At present, more than a dozen atrial pacing algorithms are available, each of them addressed to the suppression or the prevention of specific electrophysiologic triggers through different action mechanisms. Most of the pacing algorithms are still under evaluation, though preliminary data appeared contradictory and could confirm further benefits, as compared to conventional DDDR pacing, only in few and small-sized studies. This study evaluated the hypothesis that an optimal preventive algorithm functioning should not leave out a physiologically correct modulation of heart rate in Sick Sinus Syndrome patients, whose spontaneous sinus activity is by definition partially or completely spoilt. The results of this study seemed to confirm such a hypothesis: patients treated with CLS pacing mode, which provides a rate responsive feature based on an indirect analysis of a physiologic autonomic nervous system signal and no specific AT trigger suppression functions, spent on average a shorter time

![Fig. 3 Atrial Pacing Percentage (APP) in the three treatment groups at 4- and 7-month follow-up. DDDR pacing mode had the lowest APP, while no difference was detected between CLS and DDD+.

![Fig. 4 Spearman correlation coefficients ($r_S$) between AT\* burden and APP\* and their significance level, obtained with each pacing algorithm in each follow-up.](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAIAAgMABJRU5ErkJggg==)

**Table 6**

<table>
<thead>
<tr>
<th></th>
<th>4-month follow-up</th>
<th>7-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n=126$)</td>
<td>($n=98$)</td>
</tr>
<tr>
<td>$r_S$</td>
<td>$P$</td>
<td>$r_S$</td>
</tr>
<tr>
<td>CLS</td>
<td>−0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>DDD+</td>
<td>−0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>DDDR</td>
<td>−0.21</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\*AT=Atrial Tachyarrhythmia.  
\*APP=Atrial Pacing Percentage.  
$r_S$=Spearman correlation coefficient.
with atrial tachyarrhythmias, as compared to patients treated with DDD+ persistent overdrive algorithm and conventional DDDR pacing mode.

This benefit could not be explained by a high APP level. Both CLS and DDD+ algorithms provided a higher APP, compared to the DDDR pacing mode, but no statistical difference was observed between them. This represents the major result of this study: the statistical power available was insufficient to detect any difference, between CLS and DDD+, in the efficacy of maintaining a high APP level, while it was sufficient to find a statistical difference in their AT prevention capabilities. This suggests that there might be a difference between CLS and DDD+ that is comprised in their own specific functioning and does not exclusively depend on the APP level reached by them.

Moreover, within the range of the high APP globally obtained with the pacing algorithms used (the 25th–75th percentile intervals at 7 months were 82.2%–98.9% with CLS, 97.5%–99.3% with DDD+, 52.5%–93.6% with DDDR), unexpectedly a further negative linear correlation with AT burden was very weakly detectable, or was not detectable at all. That may suggest that the equation: the more the atria are paced, the more the sinus rhythm is maintained, is not completely representative of the relationship between atrial pacing and AT burden reduction. In other words, when a satisfying APP is guaranteed, efforts should be then more effectively focused to understand how to maximise the preventive effect by pacing rate modulation.

The study protocol did not prohibit the use of antiarrhythmic therapy during the follow-up period, the only restriction being that this did not change between the 1- and the 7-month follow-ups. Therefore, a more or less synergistic interaction between preventive pacing and antiarrhythmic therapy should be considered. However, no statistical evidence of an unbalanced distribution of one or more antiarrhythmic drugs could be found among the study arms. Nevertheless, a slightly higher percentage of patients (16.7%, 8 patients) in the DDD+ group received either β-blockers or sotalol, compared to the CLS group (9.8%, 5 patients) and the DDDR group (9.1%, 4 patients). It has been recently shown that a more favourable outcome with atrial overdrive algorithms may be obtained by prohibiting the use of β-blockade. However, again there was no evidence that these drugs were predominantly used in the DDD+ group, as the difference of β-blockade-treated patient rate among groups was not statistically significant (P=0.48).

Furthermore, it is unlikely that relatively small differences (3 patients from the DDD+ group vs the CLS group and 4 patients vs the DDDR group) could have had a relevant effect on the AT burden evaluation of the whole DDD+ population: qualitatively, the median of AT burden of these eight sotalol- or β-blocker-treated patients in the DDD+ group was 6.26 min/day at 4 months and 5.21 min/day at 7 months. These values do not remarkably stand out from those of the entire DDD+ population, reported in Table 5.

A relatively high drop-out rate (34.2%) was observed in the study. The major cause of drop-outs was non-compliance with the study procedures (21 of 51 drop-outs), mainly due to invalid follow-up visits performed out of the very narrow time windows assigned.
(7 days). This resulted in well time-defined AT burden samples, that is crucial in studies on prevention of atrial fibrillation, whose time evolution in each individual may introduce biasing effects. On the other hand, it also caused a rather high number of drop-outs. However, no statistical difference was found among the survival estimates at 7 months. Furthermore, 7-month follow-up data confirmed the 4-month follow-up results, when the drop-out rate was remarkably lower (15.4%). CLS stimulation was repeatedly and consistently associated with a lower AT burden, compared to the other pacing algorithms, during the entire observation period of the study.

Possible mechanisms

Many authors have recently assessed the existence of a relation between atrial fibrillation onset and autonomous nervous system, identifying fluctuation of sympatho-vagal balance with variables shifting towards specific patterns of autonomic imbalance few minutes before AT initiation. The detailed mechanism still has not been completely assessed: Bettoni and Zimmermann observed that the occurrence of atrial fibrillation in 77 patients with and without structural heart disease, is characterized by a primary increase in adrenergic tone until 10 min before the episode onset, followed by a clear shift toward vagal predominance; the study by Huang JL et al. had found consistent results only in patients with idiopathic paroxysmal atrial fibrillation, while in patients with structural heart disease, an increase of the sympathetic drive was more frequently evident from 8 min before episode onset.

Such evidence may represent a starting point for a possible explanation of the low AT burden observed in CLS-paced patients. CLS pacing system furnishes a rate responsive function basing on a permanent monitoring of the contractility, prevalently controlled by the neurovegetative tone. It thus may be advanced the hypothesis that a modulation of the sympatho-vagal balance before AT onset, could induce a corresponding modulation in the CLS atrial pacing rate, in the critical time frame of few minutes before AT. The variation of the neurogenic drive preceding the onset of atrial fibrillation is expected to be reflected in the contractility. CLS may accordingly react, providing an early pacing modulation, that might play an active role in this process, possibly affecting it before atrial fibrillation raging. Admittedly, no data are presently available to confirm such hypothesis, which should be assessed by specific tests.

AT burden measurement

In the present study, AT burden was measured basing on atrial interval data stored in the pacemaker memory. Atrial intervals were included in the calculation if the mean atrial rate of the last four consecutive intervals was equal or higher than 150 min⁻¹. As a result of this rapid detection criterion and the relatively low rate cut off, atrial fibrillation episodes, as well as other slower sustained or non-sustained atrial tachycardias, contributed to the final measured AT burden values. Indeed, also the presence of oversensing events and, in general, false-positive episodes could not be excluded.

Actually, this is a critical issue in studies on pacing prevention of atrial fibrillation. Reliability of AT detection algorithms of implantable devices is still a controversial subject, bearing on a continuous technological development. Seidl et al. suggested that a detection rate of 220 min⁻¹, onset number beats 10, and termination number beats 20, provide a reliable arrhythmia detection with a sensitivity of 98% and a specificity of 100%. But this could only be assessed by comparing simulated pacemaker diagnostic reports with available electrocardiographic recordings of atrial arrhythmias. Pollak et al., comparing 2.3-second EGM recordings with the corresponding episode information digitally stored by the pacemaker, concluded that a high correlation (89%) can be found only with high rate (>250 min⁻¹) and/or long duration (>5 min) episodes. The correlation was measured analysing a relatively small number of EGM recordings (58 high rate episodes and 18 long lasting episodes). Indeed, using these criteria as guidelines for optimal detection programming may result in a valuable loss of information. Certainly, slow tachyarrhythmias with atrial rate below 250 min⁻¹ cannot be detected, possibly increasing the distortion effect of false-negative episodes. Israel et al., analysing 824 AT episode EGM recordings, found that almost 44% of them appeared highly organized and with a cycle length within 200 and 360 ms at onset, maintaining these characteristics over 1 min in 73%. Lee et al. using a 12-beat-sample-count-based detection algorithm, measured a positive predictive accuracy of 99.9% on 17018 EGM stored episodes and observed that almost one half of the AT episodes logged in the device memory had a duration of less than 1 min. Incidentally, it should be noted that accuracy of detection strongly depends on the specific algorithm used and the input stage circuitry of the device: programming recommendation should always refer to them.

These considerations may be helpful when evaluating the clinical impact on individuals of device-collected diagnostic information concerning high rate atrial events. However, a limited amount of false positive episodes can be tolerated, if the relative difference among treatment groups is the information of interest, as in the present study, more then the absolute value of AT burden.

Limitations of the study

Three major comments should be reported possibly limiting the results of this study:

1. The main result of this study is that CLS pacing system was associated with a lower AT burden compared to the other pacing algorithms used. But no data are available concerning the reduction rate of total duration of atrial tachyarrhythmia, with respect to the other pacing systems. This limitation should be resolved by a crossover design study, which was practically prevented by the fact that not all the pacing algorithms evaluated in this study were available in one pacemaker model. Further...
technological developments are expected to overcome this practical limitation.

2 The use of two different pacemaker models prevented further data reporting and comparisons concerning both the effect of pacing algorithms on the incidence of premature atrial contractions, and AT episode validation.

3 In this study the so-called CLS-AxVp algorithm was used. This algorithm version requires a persistent right ventricular capture in order to provide a correct rate responsive function. Thus the mean ventricular pacing percentage in the CLS group was 98.6±2.9% at 7 months, significantly higher than in DDD+ (96.4±6.0%, P<0.05), and in DDDR (91.6±15.5%, P<0.05). This could have resulted in a haemodynamic disadvantage, possibly affecting and limiting the AT prevention efficacy of CLS. Further technological development towards this objective are needed and expected.

Conclusions

In the patient population selected in this study, CLS pacing mode was associated with a lower AT burden, as compared to DDD+ persistent overdrive algorithm, and conventional accelerometer-sensor-based DDDR pacing mode, nominally programmed. CLS and DDD+ algorithms could provide an effective atrial overdrive with an APP significantly higher than in DDDR. Within the range of APP values found in each treatment group, an evident negative linear correlation between AT burden and APP was never observed, suggesting that APP is not the only parameter that should be considered in the pacing prevention mechanisms. These results need to be confirmed by a larger size cross-over-designed study, measuring the efficacy of CLS algorithm in reducing AT burden. Further analysis on premature atrial beat reduction are needed, while a technological development is expected to make CLS independent of right ventricular capture.

Appendix A

Participating centres:

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References


