The role of pacemaker in hypersensitive carotid sinus syndrome

Ricardo Lopes*, Alexandra Gonçalves, Júlio Campos, Cecília Frutuoso, Anabela Silva, Cristina Touguinha, João Freitas, and Maria Júlia Maciel

Aims
About 15% of patients with the hypersensitive carotid sinus syndrome (CSS) have no clinical improvement after permanent pacemaker implantation. We aimed to assess the outcome of patients with CSS treated with pacemaker and to determine predictors of symptoms’ recurrence.

Methods and results
A retrospective analysis of 138 patients in whom pacemaker was implanted for CSS was carried out from February 1990 to October 2008. Data were collected from clinical records. Mean age was 69 ± 10.7 years and 104 patients (75.4%) were men. Mean follow-up period was 4.9 ± 4.4 years. Twenty-one (15.2%) patients presented mixed CSS and 117 (84.8%) cardioinhibitory CSS. The head-up tilt test (HUTT) was performed in 93 patients (67.4%). After pacemaker implantation, 115 (83.3%) patients had no further symptoms, 8 (5.8%) presented minor symptoms and in 15 (10.9%), the symptoms remained unchanged. Among patients with symptoms’ recurrence, 8 (38.1%) had mixed CSS and 15 (12.8%) cardioinhibitory CSS. Mixed CSS was the only independent predictor of symptoms’ recurrence in total population \( \text{hazard ratio (HR) 2.84 [95\% confidence intervals (CI) 1.20–6.71]; } P = 0.017 \) and in patients who performed HUTT \( \text{[HR 1.84 (95\% CI 1.01–3.35); } P = 0.045 \). Although the HUTT result was not related to symptoms’ recurrence, patients with mixed CSS were more likely to present a vasodepressor response (61.9 vs. 19.4%; \( P,0.001 \) ) and a reproduction of spontaneous symptoms (28.6 vs. 2.8%; \( P = 0.001 \)) on HUTT.

Conclusions
Permanent pacemaker is an effective treatment for CSS. However, the recurrence of symptoms was two- to three-fold more frequent in patients with mixed CSS, probably due to the persistence of vasodepressor component.

Keywords
Carotid sinus syndrome • Pacing • Autonomics • Vagal syndromes

Introduction
The hypersensitive carotid sinus syndrome (CSS) is defined as syncope or presyncope resulting from an extreme reflex response to the carotid sinus stimulation.1 It affects 35–40 patients/million persons/year and is responsible for 1–20% of permanent pacemaker (PP) implantations2 and for 20–45% of unexplained falls or syncope in older patients.3–5 The CSS is more common in males (4:1), and in patients with diabetes and atherosclerosis.2 Diagnosis is made when an asystole >3 s and/or a fall in systolic blood pressure (SBP) >50 mmHg occurs during the carotid sinus massage (CSM), with reproduction of spontaneous symptoms.6 The CSS has two independent components: the cardioinhibitory, which results from increased vagal tone; and the vasodepressor, resulting from sympathetic activity withdrawal.1 The underlying cause of CSS is still unclear; however, current evidence supports the hypothesis of baroreceptor disturbance2 and more recently, Miller et al.7 suggested a medullary degeneration in CSS genesis.

Permanent pacemaker implantation is recommended for pure or predominant cardioinhibitory types of CSS in patients with recurrent syncope or presyncope, unexplained or caused by inadvertent carotid sinus stimulation, that is reproduced during CSM.1,6,8 However, these recommendations are based on two small, randomized, non-blinded, controlled trials9,10 and supported by pre–post-comparative and observational studies.11–17 Moreover, the first randomized, double-blind, placebo-controlled trials found no benefit of PP in decreasing the number of falls and syncope in older patients with CSS18,19.
In fact, syncope persists in ~15% of patients after PP implantation and up to 50% continue to present presyncope or minor symptoms, such as dizziness and orthostatic hypotension. Furthermore, few studies have addressed the predictors of symptoms’ recurrence, such as mixed CSS, positive response to the head-up tilt test (HUTT), and ventricular demand inhibited (VVI) pacemaker mode.

In this study, we aimed to assess the outcome of patients with CSS treated with PP and to determine predictors of symptoms’ recurrence.

Methods

We performed a retrospective analysis of 138 patients in whom a PP was implanted for cardioinhibitory or mixed CSS, from February 1990 to October 2008. Data were collected from clinical records.

All patients had clinical suspicion of CSS, and to confirm it, CSM was performed for 10 s in both supine and upright positions (the latter when the HUTT was performed too), on both sides and with blood pressure (BP) monitoring (continuously, using a Finapress system when performed during HUTT; and intermittently, using the auscultatory or an automatic method of BP measurement in all other cases). We considered a positive response to CSM when asystole >3 s and/or a fall in SBP >50 mmHg occurred, with reproduction of spontaneous symptoms. The type of CSS was defined as follows: cardioinhibitory type, when asystole >3 s occurred during CSM, with reproduction of spontaneous symptoms; mixed type, when asystole >3 s and fall in SBP >50 mmHg occurred during CSM, with reproduction of spontaneous symptoms.

The HUTT was performed in about two-thirds of our patients, with continuous BP monitoring (Finapress®), following the protocol of 5 min in supine position, 30 min head-up tilting to 70° followed by sublingual nitroglycerin, and continued tilting for more than 15 min. We considered a positive response to HUTT when asystole >3 s and/or a fall in SBP >50 mmHg occurred, independently of symptoms.

Data are described as mean (standard deviation) for quantitative variables and counts (proportions) for categorical variables. The characteristics that might predict symptoms’ recurrence were compared between patients, using the χ2 test for categorical variables and Student’s t-test for quantitative variables. All P-values are two-sided, and the significance level was 5%. The associations were quantified by odds ratios, which are presented with 95% confidence intervals (95% CI). All significant associations found with χ2 test or Student’s t-test were analysed considering time to outcome with the Cox regression and are expressed as hazard ratio (HR) and 95% CI. The analysis was completed with a multivariate logistic regression, including the independent variables associated with symptoms’ recurrence. Statistical analysis was performed using SPSS 16 software.

Table 1: Autonomic function tests results

<table>
<thead>
<tr>
<th>Test and type of response</th>
<th>Symptomatic (%)</th>
<th>Asymptomatic (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic function tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic massage</td>
<td>138 (100)</td>
<td>–</td>
<td>138 (100)</td>
</tr>
<tr>
<td>Cardioinhibitory</td>
<td>117 (84.8)</td>
<td>–</td>
<td>117 (84.8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>21 (15.2)</td>
<td>–</td>
<td>21 (15.2)</td>
</tr>
<tr>
<td>Head-up tilt test</td>
<td>8 (8.6)</td>
<td>85 (91.4)</td>
<td>93 (100)</td>
</tr>
<tr>
<td>Negative</td>
<td>–</td>
<td>66 (71.0)</td>
<td>66 (71.0)</td>
</tr>
<tr>
<td>Vasodepressor</td>
<td>5 (5.4)</td>
<td>13 (14.0)</td>
<td>18 (19.4)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (3.1)</td>
<td>6 (6.5)</td>
<td>9 (9.6)</td>
</tr>
</tbody>
</table>

Data are described as counts (proportions).
Syncope recurrence rate in our patients (10.9%) after PP implantation for mixed or cardioinhibitory CSS was lower than that reported previously. Mixed CSS was present in 15.2% of our patients, which is considerably lower than the 40–50% reported in previous studies. This highly selected population, composed predominantly of patients with cardioinhibitory CSS, may explain the lower rate of syncope recurrence. Furthermore, a placebo effect of PP may have also contributed to this result.

The rate of minor symptoms/presyncope recurrence in our population (5.8%) was also much lower than that reported previously. The reduced number of patients with mixed CSS and of patients treated with VVI pacemaker mode (with consequently less pacemaker syndrome) are possible explanations for this lower rate. We must also consider a probable underestimation of minor symptoms in those patients without syncope recurrence after PP implantation.

Nevertheless, 16.7% of patients still present syncope or minor symptoms/presyncope. Persistence of the vasodepressor component has been implicated in symptoms’ recurrence after PP implantation, and probably it was also the cause of symptoms’ recurrence in our population. Furthermore, the presence and contribution of vasodepression for symptoms were probably underestimated in our patients, since continuous BP monitoring was performed in only two-thirds of them and CSM after atropine or temporary pacemaker was not performed.

Mixed CSS was associated with a two- to three-fold increased risk of symptoms’ recurrence after PP implantation, being the only independent predictor of symptoms’ recurrence in our population, which is in accordance with the previous descriptions. Although the HUTT result was not a predictor of outcome as demonstrated by others, mixed CSS was a weaker predictor of symptoms’ recurrence in the 93 patients who underwent HUTT compared with the total population (two-fold in HUTT patients vs. three-fold in all patients). These HUTT patients were probably better selected to PP implantation due to a better vasodepression evaluation. Furthermore, it has been reported that ~50% of patients with CSS have a mixed type, which makes the assessment of the vasodepressor component even more important in the management of these patients.

Permanent pacemaker in VVI mode was not a predictor of outcome in our population. The pacemaker syndrome has been implicated in symptoms’ recurrence in patients with CSS who implanted a VVI PP, which may result in increased vasodepression. In our population, VVI mode PP was only implanted in patients with atrial fibrillation, without postural hypotension and/or without significant ventriculoatrial conduction. Thus, the probability of pacemaker syndrome development was reduced, and VVI PP was not associated with symptoms’ recurrence.

Dual-chamber pacemaker with ‘rate-drop response’, which allows for the rapid detection of a sudden decrease in heart rate, has shown good results in the reduction of syncope in patients with CSS and vasovagal syncope. However, there are no randomized trials comparing DDD mode with DDD ‘rate-drop response’ mode; so we did not use the latter in our patients.

The more frequency of positive and symptomatic HUTT results in patients with mixed CSS reinforces the hypothesis that CSS and neurocardiogenic syncope may have some common mechanisms.

### Discussion

Permanent pacemaker significantly reduces syncope in patients with pure or predominant cardioinhibitory CSS. However, ~15% of patients with CSS do not experience clinical improvement and up to 50% have minor symptoms or presyncope after PP implantation. It is also known that the mixed type of CSS is less responsive to PP implantation.

### Table 2 Symptoms’ recurrence predictors

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms’ recurrence predictors (all patients: n = 138)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.99–1.03</td>
<td>0.110</td>
</tr>
<tr>
<td>Mixed CSS</td>
<td>2.84</td>
<td>1.20–6.71</td>
<td>0.017</td>
</tr>
<tr>
<td>Symptoms’ recurrence predictors (HUTT patients: n = 93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.02–1.15</td>
<td>0.011</td>
</tr>
<tr>
<td>Mixed CSS</td>
<td>4.01</td>
<td>1.40–11.70</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

All significant associations found with χ² test or Student’s t-test were analysed considering time to outcome with the Cox regression and are expressed as hazard ratio and 95% confidence interval. CSS, carotid sinus syndrome; HUTT, head-up tilt test.

### Table 3 Symptoms’ recurrence predictors—Cox regression analysis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms’ recurrence predictors (all patients: n = 138)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.96</td>
<td>1.38–9.30</td>
<td>0.009</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.83</td>
<td>0.69–4.78</td>
<td>0.330</td>
</tr>
<tr>
<td>Syncope at presentation</td>
<td>0.62</td>
<td>0.07–5.37</td>
<td>1.000</td>
</tr>
<tr>
<td>Mixed CSS</td>
<td>4.09</td>
<td>1.41–11.70</td>
<td>0.011</td>
</tr>
<tr>
<td>Positive HUTT</td>
<td>0.76</td>
<td>0.44–1.33</td>
<td>0.34</td>
</tr>
<tr>
<td>Symptomatic HUTT</td>
<td>0.94</td>
<td>0.29–3.01</td>
<td>0.91</td>
</tr>
<tr>
<td>Pacemaker mode (DDD/VVI)</td>
<td>3.55</td>
<td>0.45–28.24</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Characteristics that might predict symptoms’ recurrence were compared between patients using the χ² test for categorical variables and Student’s t-test for quantitative variables. All P-values are two-sided and the significance level was 5%. The associations were quantified by odds ratio (OR), which are presented with 95% confidence interval (95% CI). CSS, carotid sinus syndrome; HUTT, head-up tilt test.
Although they have different afferent pathways, the overlap between CSS and positive HUTT in 21–45% of patients suggests a common central abnormality.\textsuperscript{21,22,24–26} Findings of similar clinical features between CSS syncope and HUTT-induced syncope suggest similar autonomic system activation.\textsuperscript{26} Moreover, the significant increase in the diagnostic yield of CSM with orthostatic stress further supports this hypothesis.\textsuperscript{27}

Study limitations

This study has the limitations of being a retrospective analysis with a limited sample size. Furthermore, concomitant morbidities and medications were not assessed. Thus, we assumed that symptoms’ recurrences were due to CSS and we did not consider other possible conditions that could cause syncope. The CSM was not repeated after intravenous atropine or temporary pacemaker and continuous BP monitoring during CSM was not performed in all patients.

Conclusions

Permanent pacemaker is an effective treatment for patients with carotidoinhibitory CSS. In mixed CSS, PP implantation may be an effective treatment; however, there is an increased risk of symptoms’ recurrence. Every effort should be done to evaluate the contribution of vasodepressor component to patients’ symptoms. The CSS and neurcardiogenic syncope might have some common mechanisms—the overlap between them being more frequent than previously thought. We suggest that for patients with CSS suspicion, physicians should perform HUTT to optimize patient selection for PP implantation. Powered, blinded, randomized trials are currently needed to improve the management of patients with CSS.

Conflict of interest: none declared.

References


