Less syncope and milder symptoms in patients treated with pacing for induced cardioinhibitory carotid sinus syndrome: a randomized study

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Aims The aim of this study was to examine the effect on symptoms in patients with induced cardioinhibitory carotid sinus syndrome (ICSS) when treated or not treated with a pacemaker.

Methods and results Sixty patients with a history of syncope or pre-syncope and ICSS were randomized to receive a permanent pacemaker (P group, n = 30) or no pacing (NP group, n = 30). ICSS was defined as a ventricular pause (i.e. asystole) lasting 3 s or more in response to carotid sinus stimulation. The patients were seen at 3 and 12 months and at symptoms. At 12 months, the rate of syncope in the NP group was 40% (n = 12) compared with 10% (n = 3) in the P group (P = 0.008). The majority (11 of 12) of the syncope recurrences in the NP group occurred during the first 3 months. Pre-syncope occurred in two patients (7%) in the NP group and in eight (27%) in the P group. Ten patients (33%) with recurrent syncope in the NP group later crossed-over to receive pacemaker implant.

Conclusions A history of syncope or pre-syncope, plus ICSS, was a strong predictor of subsequent syncope or pre-syncope. Most of the new symptoms occurred within 3 months. Pacemaker treatment effectively reduced syncope and/or resulted in milder symptoms.

KEYWORDS
Carotid sinus syndrome; Unexplained syncope; Pacemaker

Introduction

Carotid sinus syndrome is rare before the age of 40 and the prevalence increases with age and cardiovascular, cerebrovascular, and neurodegenerative co-morbidity.1–4 Spontaneous carotid sinus syndrome is considered to account for ~1% of all causes of syncope.5 Carotid sinus syndrome can frequently be induced and is found in 26–60% of patients affected by unexplained syncope.3,4,6–9 The relationship between carotid sinus syndrome and spontaneous, otherwise unexplained, syncope has been demonstrated in comparative studies, controlled trials, and a prospective observational study.10 Recurrence of syncope in patients treated with pacing has been studied in non-randomized comparisons11,12 that showed fewer recurrences in patients with pacemaker implants. Cardiac pacing appears to be beneficial in carotid sinus syndrome and is the treatment of choice when bradycardia has been documented.13–20 However, there is still controversy as to the frequency with which carotid sinus syndrome is responsible for syncopal episodes and to the efficacy of permanent pacemaker treatment. The aim of this study was to examine the effect on symptoms in patients with induced cardioinhibitory carotid sinus syndrome (ICSS) when treated with pacemaker or without this treatment.

Methods

Sixty patients with a history of syncope or pre-syncope and with ICSS participated in randomized pacemaker treatment vs. no pacing in a comparative study approved by the Ethics Committee of Göteborg University (L116-99). Patients were enrolled from October 1999 to February 2005 in a Swedish county hospital serving 250 000 inhabitants. Written and verbal informed consent were obtained after a positive carotid sinus stimulation test. At least one episode of syncope or pre-syncope and an ICSS were required for eligibility for randomization. Enrolment took place on an as consecutive a basis as possible. Two patients with four and six previous syncopal attacks were not enrolled for geographical reasons. Less than 10 patients were considered ineligible due to diminished cognitive functions, but otherwise all patients with a positive test were given study information. All informed patients were willing to participate and were included. Patients whose tests were negative were not recorded. Thirty patients were randomized to receive a...
permanent pacemaker (P group) and 30 patients were randomized to no pacing (NP group). The latter patients were allowed to cross-over to pacemaker implantation if syncope or pre-syncope re-occurred. The randomization was made using 30 cards of each with P and NP prints, put in envelopes with dark coloured insides. After sealing the envelopes shuffling was made 21 times and after that the envelopes were numbered 1–60. Medical history was recorded and a physical examination, 12-lead electrocardiogram, orthostatic test, head-up tilt test, and 24 h ambulatory Holter recording were done before randomization. All out-patient follow-up visits, scheduled at 3 months and 1 year, were carried out by the J.-E.C. All patients were also instructed to call for an extra visit if they experienced symptoms of syncope or pre-syncope.

Definitions

Syncope was defined as a transient, self-terminating loss of consciousness usually leading to falling.10 The onset of syncope is relatively rapid, and the subsequent recovery is spontaneous, complete, and usually prompt.21–23 Pre-syncope or near-syncope refers to the state in which patients feel that syncope is imminent. Symptoms associated with pre-syncope may be relatively non-specific and tend to overlap with those associated with the premonitory phase (e.g. light-headedness, nausea, sweating, weakness, and visual disturbances) of true syncope.10 Carotid sinus syndrome was defined as syncope or pre-syncope in combination with a ventricular pause lasting 3 s or more and a fall in systolic blood pressure of 50 mmHg or more from the baseline value in response to carotid sinus stimulation.24 Cardioinhibitory carotid sinus syndrome is diagnosed in patients with an abnormal response to carotid sinus stimulation and may be accepted as being present even though a close relationship between manipulation of carotid sinuses and the occurrence of syncope is not demonstrated.10 In the present study, ICSS was defined as a ventricular pause (i.e. asystole) lasting 3 s or more in response to carotid sinus stimulation and an otherwise negative work-up for syncope.10 Carotid sinus stimulation was done by applying firm pressure to the carotid sinus without any movement of the fingertips for 5 s in the supine position, first on the right side and then, if needed, on the left side.10

Orthostatic test protocol

Heart rate (HR) and blood pressure (BP) measurements were made after 10 min in the supine position. Continuous electrocardiographic monitoring was used. Measurements of HR and BP were made after 30 s and 1 min of standing and continued every minute for 8 min. A decrease in systolic blood pressure >20 mmHg or a decrease in systolic blood pressure to <90 mmHg after at least 1 min in the erect posture was defined as orthostatic hypotension regardless of whether symptoms occurred.25

Head-up tilt test protocol

After 10 min in the supine position, the patients were tilted at an inclination of 70°. Continuous electrocardiographic monitoring was utilized during the complete procedure.

Heart rate and BP measurements were made after 10 min in the supine position and continued after 30 s of tilting and every minute during the first 10 min and thereafter every 5 min throughout the following 30 min. No drug provocation was done. A positive response (vasovagal) was defined as pre-syncope or syncope that was related to hypotension and/or bradycardia.26

Statistical analysis

The statistical analyses were made using SPSS 14.0 for Window. Where appropriate, data are provided as mean and standard deviation. Parametric data were compared using the t-test. Fischer’s exact test was used to compare the syncope recurrence rate in the P and NP groups. Logistic regression analyses were made to analyze whether there were any significant correlations between syncope/pre-syncope, asystole duration, orthostatic hypotension, vasovagal hypotension, or randomization. A difference of \( P < 0.05 \) was considered significant.

Results

Clinical characteristics

The clinical characteristics before randomization in the NP and P groups are listed in Table 1. Syncope was the presenting symptom in 59 patients and pre-syncope in one patient (randomized to the NP group). The mean ventricular pause after carotid sinus stimulation in the entire group was 5.3 ± 2.1 s (range: 3.1–12.9 s), in the NP pacing group 5.2 ± 2.2 s (range: 3.1–12.9 s), and in the P group 5.5 ± 2.0 (range: 3.2–11.0 s). The mean ventricular pauses at baseline, subdivided according to the subsequent symptoms during follow-up, were: 5.3 ± 2.3 s (range 3.1–12.1 s) in 35 patients with no symptoms, 5.4 ± 2.0 s (range 3.2–10.0 s) in 16 patients with syncope, and 5.4 ± 1.5 s (range 3.2–7.7 s) in nine patients with pre-syncope.

Thirteen patients had a positive orthostatic test, four patients in the NP group, and nine patients in the P group. Twelve patients had a positive head-up tilt test, four patients in the NP group, and eight patients in the P group. Pacemaker indicating events were not found in the NP or P groups during 24 h ambulatory Holter recording.

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics at randomization</th>
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<tbody>
<tr>
<td>Age (mean ± 1SD)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Asystole (s) (mean ± 1 SD)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Vasovagal hypotension</td>
</tr>
<tr>
<td>Sinus rhythm</td>
</tr>
<tr>
<td>Sinus, AV-block I</td>
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<tr>
<td>Sinus, LAH</td>
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<tr>
<td>Sinus, BBB</td>
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<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Atrial fibrillation, BBB</td>
</tr>
<tr>
<td>Ectopic atrial rhythm</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Calcium inhibitors</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>ACE-I/ARB combinations of two</td>
</tr>
<tr>
<td>or more of the above and/or</td>
</tr>
<tr>
<td>digoxin and alfa 1-inhibitors</td>
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</tbody>
</table>

CSS, carotid sinus syndrome; AV, atrioventricular; BBB, bundle branch block (LBBB, RBBB, or RBBB+LAH); ACE-I, angiotensin converting enzyme-inhibitors; ARB, angiotensin II-receptor 1-blockers.
Table 2  Follow-up results at 12 months (intention-to-treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>No pacing (n = 30)</th>
<th>Pacing (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>16 (53)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (40)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Pre-syncope</td>
<td>2 (7)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Cross-over</td>
<td>10 (33)</td>
<td>0</td>
</tr>
</tbody>
</table>

Cardiovascular drugs

Twenty-six (43.3%) patients had no cardiovascular drugs before randomization, 14 (46.7%) in the NP group and 12 (40%) in the P group. The cardiovascular drugs at randomization are listed in Table 1.

Pacemaker treatment

Patients randomized to the P group (n = 30) received a DDDR \((n = 24)\), VVIR \((n = 5)\), or AAIR \((n = 1)\) pacemaker. The choice of pacing mode was made according to hospital routine. Four patients with atrial fibrillation and one patient with atrial fibrillation and right bundle branch block in combination with left anterior hemiblock received VVIR pacemakers. One patient with sinus rhythm and no conduction disturbances at implantation received an AAIR-pacemaker.

The follow-up results

The follow-up results in the P and NP groups up to 12 months from enrolment in the study are listed in Table 2. The first event was documented. In the group that was randomized to no pacing, 16 patients (53%) were asymptomatic compared with 19 patients (63%) in the group randomized to primary pacemaker implant. The rate of syncope recurrence in the NP group was 40% \((n = 12)\) compared with 10% \((n = 3)\) in the P group \((P = 0.008)\). The majority (11 of 12) of the syncope recurrences in the NP group occurred during the first 3 months. Pre-syncope occurred in two patients (7%) in the NP group and in eight (27%) in the P group. Ten patients (33%) with recurrent syncope in the NP group later crossed-over to receive a pacemaker implant, and eight of these 10 patients were asymptomatic at the 12-month follow-up. One patient in the NP group had a fall and fracture during syncope and was scheduled to have a pacemaker but died at home, probably of cardiovascular causes, before a pacemaker was implanted. Another patient in the NP group had planned to have a pacemaker implant but for personal reasons decided to have this operation after the end of the follow-up period. One patient in the NP group that crossed-over to pacemaker implant had a recurrence of syncope at 12 months due to AV nodal re-entry tachycardia. Three deaths were observed during follow-up; two cardiovascular deaths, (suspected AMI and sudden cardiac death) occurred in the NP group and one cardiovascular death (ruptured abdominal aortic aneurysm) occurred in the P group.

Discussion

The rate of syncope at the 12-month follow-up was significantly lower in the P group than in the NP group. Eleven of 12 patients had syncope in the NP group already at 3-month follow-up. Ten of them crossed-over to pacemaker implant, and eight of these 10 patients were asymptomatic at the 12-month follow-up. Three patients in the P group had a recurrence of syncope at follow-up, one of whom had a positive response in the head-up tilt test and probably had recurrences of syncope due to a vasodepressive or mixed type of carotid sinus syndrome. Between 3 and 12 months only three patients had new symptoms, all syncope. The reasons for the great difference in events between the first 3 and the subsequent 9 months are unknown, but one may be that those who had already been free of symptoms for 3 months had demonstrated a pattern of having long intervals between symptoms. A detailed pre-randomization history of the time intervals between the last few events might have given some indication about who would experience a relapse soon, but a history of this kind with reliable time intervals would have been difficult or impossible to obtain based on the patient’s memory alone.

A majority of the patients with pre-syncope in the two groups had vasovagal syncope/orthostatic hypotension and was treated with more cardiovascular drugs when compared with the total population. Vasovagal syncope episodes are frequently related to treatment with cardiovascular drugs. In the present study, the ventricular asystole in response to carotid sinus stimulation was 5.2 \(\pm 2.4\) s in patients \((n = 26)\) with no cardiovascular drugs when compared with 5.5 \(\pm 1.8\) s in patients \((n = 34)\) treated with cardiovascular drugs.

Brignole et al.\(^{14}\) observed in a randomized study of patients with severe spontaneous carotid sinus syndrome a recurrence of syncope in 57% in the untreated group vs. 9% in the pacing group \((P < 0.0002)\). Carotid sinus stimulation was performed for 10 s in both the supine and upright positions on a tilt table, and patients with vasodepressive and mixed type of carotid sinus syndrome were also included in the study. In the present study, the carotid sinus stimulation was performed in the supine position and stimulation was applied for no more than 5 s. Continuous BP measurement during carotid sinus stimulation was not used, and the vasodepressive or mixed type of carotid sinus syndrome was an exclusion criterion. Carotid sinus syndrome may be misdiagnosed in about one-third of cases if stimulation is not done in both the supine and upright positions.\(^{29,30}\) The importance of performing upright stimulation has to do with the better possibility of reproducing symptoms.\(^{10}\) However, a vasodepressive response to carotid sinus stimulation is present in most patients with ICSS.\(^{31}\) Logistic regression analyses were performed. None of the variables of asystole duration, orthostatic hypotension, or vasovagal syncope was significantly correlated to the events of syncope or pre-syncope in the P or the NP group.

In the present study, no pacemaker-indicating events were found during the pre-study 24 h ambulatory Holter recordings. In an overview\(^{32}\) of the results of eight studies of ambulatory monitoring in syncope, only 4% of the patients had a correlation of symptoms with arrhythmia. With implantable loop recorders\(^{33}\) a correlation between...
syncope or pre-syncope and ECG findings was achieved in 59% of 85 patients within a mean of 10 months. For this reason, it is likely that implantable monitors will be anticipated in the routine diagnostic work-up in unexplained syncope instead of or before the 24 h ambulatory telemetry recording. In one study\textsuperscript{15} with a 2-year follow-up in patients with carotid sinus syndrome with a pacemaker designed to detect asystolic episodes, long pauses (≥6 s) were detected in 53% of the patients, suggesting that a positive response to carotid sinus stimulation predicts the events of spontaneous asystolic episodes. Long pauses are, however, also a common finding in patients without syncope or pre-syncope, and the correlation between symptoms and documented rhythm disturbances must be confirmed before pacemaker treatment is considered.

The head-up tilt test may be useful, but a negative test does not exclude that the patient could have a symptomatic carotid sinus syndrome. Its reproducibility is highly variable and, in our study, a positive tilt test at baseline was a poor predictor of subsequent syncope or pre-syncope during follow-up in both the P and NP groups. Again, it seems that an implantable loop recorder might have provided more useful information than the tilt test did in the present study. Likewise, the correlation between a positive orthostatic test and subsequent symptoms in the NP group was low.

In contrast, the simple ICSS test in the present study induced symptoms and signs that were predictive of a high likeliness of recurrence of spontaneous syncope and/or pre-syncope. Altogether, 37 patients had negative orthostatic and head-up tilt tests but a positive carotid stimulation response, 16 of whom were randomized to pacing and 21 to no pacing. During follow-up, four of the 16 paced patients had symptoms (25%, one syncope, three pre-syncope). More importantly, in patients with no pacing, 10 of 21 had symptoms during follow-up (48%, nine syncope, one pre-syncope). Pre-syncope occurred during follow-up in eight paced patients (27%) when compared with only two non-paced patients (7%). Therefore, pre-syncope during pacing in these patients could be interpreted as an aborted syncope that was prevented by pacing.

The carotid stimulation test was used in the same way in patients with sinus rhythm and atrial fibrillation at baseline. One study\textsuperscript{34} in patients with chronic atrial fibrillation patients with sinus rhythm and atrial fibrillation at baseline. In these patients could be interpreted as an aborted paced patients (7%). Therefore, pre-syncope during pacing syncope. Pre-syncope occurred during follow-up in eight paced patients (27%) when compared with only two non-paced patients (7%). Therefore, pre-syncope during pacing in these patients could be interpreted as an aborted syncope that was prevented by pacing.

The carotid stimulation test was used in the same way in patients with sinus rhythm and atrial fibrillation at baseline. One study\textsuperscript{34} in patients with chronic atrial fibrillation showed that vagal hyperactivity due to carotid sinus syndrome can induce prolonged ventricular asystole that may be responsible for syncope and/or pre-syncope, as observed in patients in sinus rhythm with carotid sinus syndrome. It is not clear what duration of an induced pause is the best predictor of recurrence of symptoms. We did not find that, in pauses above 3 s, a longer duration within the range of 3–12.1 s was a better predictor. This applied both to patients in sinus rhythm and in atrial fibrillation.

Limitations of the study are the absence of double-blind design and not using a placebo control arm. Since syncope may present with falls causing fractures, contusions etc., which eventually turned out to be the case in this study, too, we felt that a true placebo arm, was unethical. As the patients were informed of P and NP group procedure, and no ‘placebo’ pacemakers were implanted, this ruled out blinding of the patients. All patients were seen by few people who ensured a uniform treatment of patients and interpretation of symptoms and signs. However, the differentiation between syncope and pre-syncope rests on the patient descriptions and since the border between these two conditions may sometimes be difficult to define, a blinded design would have made the study less sensitive to retrospective misdiagnosis or biased interpretation.

We conclude that there are clinical advantages of pacemaker treatment in patients with a history of syncope or pre-syncope and with an ICSS induced by carotid sinus stimulation, irrespective of results of commonly used methods during investigation such as 24 h Holter monitoring, orthostatic test, or head-up tilt test.

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