CLINICAL INVESTIGATION

Prevalence of positive carotid sinus massage and related risk of syncope in patients with Alzheimer’s disease

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Aims The prevalence of positive carotid sinus massage (CSM) in asymptomatic elderly persons and related risk of syncope are poorly known.

Methods and results We examined the ability of CSM to predict the risk of profound bradycardia or syncope in 30 patients with Alzheimer’s disease (AD) and no history of syncope, before treatment with cholinesterase inhibitors. Carotid sinus massage was repeated at 1, 2 and 8 months after onset of cholinergic therapy. The long-term incidence of syncope was observed over a 20-month follow-up. Among the study patients (mean age $\pm$ 6 years, 83% women), 10 had positive CSM, with prolonged ventricular standstill in two of them (6.7%). The response to CSM was not predictive of an increased risk in bradycardia-mediated syncope, though syncope occurred in three patients during long-term follow-up, related to orthostatic hypotension in one and to undetermined causes in the others. Cholinergic therapy in all patients, or drugs that slow cardiac conduction, administered to 40% of the responders to CSM and 45% of the non-responders, or the presence of a bundle branch block did not affect the response to CSM or incidence of syncope.

Conclusions A positive CSM was (i) observed in 30% of elderly persons with AD and no history of syncope, and (ii) not predictive of an increased risk of bradycardia-mediated syncope.

KEYWORDS
Carotid sinus massage; Syncope; Ageing; Cholinesterase inhibitor

Introduction
Carotid sinus massage (CSM) is a common diagnostic manoeuvre performed during the evaluation of syncope. In patients $>40$ years of age presenting with unexplained syncope and carotid sinus hypersensitivity, permanent cardiac pacing may be appropriate. However, a positive CSM may be observed in up to 4% of healthy individuals, and is frequently observed in patients with cardiovascular disorders in the absence of syncope. Depending on the methodology and definition used, carotid sinus hypersensitivity has been observed in 35% of asymptomatic persons $>65$ years of age, and elderly patients with histories of syncope have rates of positive response to CSM ranging between 20 and 60%. Little is known regarding the prevalence of positive CSM and associated risk of syncope in elderly persons who have no history of pre-syncope or syncope.

Cholinesterase inhibitors (CI) are pharmaceutical agents prescribed to slow the progression of Alzheimer’s disease (AD). Although they exert their therapeutic effects at the level of the central nervous system, CI produce vagally mediated peripheral adverse effects, which are the main reason for discontinuing therapy. Besides bradycardia, light-headedness, syncope and seizures have been reported in patients suffering from AD treated with CI, and a relationship may exist between CI and profound bradycardia and its clinical consequences. Our initial study objective was to determine whether CSM might reproduce the vagally mediated effects of CI, and identify before the beginning of cholinergic therapy patients at high long-term risk of profound drug-induced bradycardia. Since no bradycardia-mediated syncope was observed, CSM appeared non-contributory with respect to our hypothesis. However, the follow-up was extended for 12 additional months, and we present the prevalence of positive CSM in this elderly population without the history of pre-syncope or syncope, and its prognostic value with respect to the long-term risk of profound bradycardia or syncope.

Methods
We prospectively studied 30 consecutive patients presenting with early to moderately advanced AD. No patient was being treated with CI before inclusion in the study, and all had undergone evaluations by dementia experts who had confirmed the indication for cholinergic therapy. Patients who had a history of syncope or...
orthostatic hypotension were excluded from the study. No electrocardiographic (ECG) abnormality was a cause of exclusion from the study, including AV block and bundle branch block. Syncope was defined as sudden, complete and transient loss of consciousness and postural tone, with spontaneous recovery. Our study protocol was in compliance with the guidelines of the Human Research Committee of our institution, and all participants were included in the study after they had granted their written informed consent.

The study protocol has been described elsewhere. Briefly, after the baseline recordings of blood pressure, ECG and results of CSM, the patients were placed on a regimen of donepezil, 5 mg/day for 1 month, followed by 10 mg/day for 7 months, as tolerated. The patients were re-examined at 1, 2 and 8 months of follow-up. The baseline observations were compared with those made during follow-up, and interim clinical events were recorded. Carotid sinus massage was repeated at all time points during follow-up.

**Carotid sinus massage and interpretation of tests**

After a 15-min period of rest in the supine position under continuous ECG and blood pressure monitoring (Accutorr Plus, Datascope Corp.), Paramus, NJ, USA), right-sided CSM was performed by applying increasingly firm massage for 5–10 s at the site of most perceptible carotid pulsation, usually the anterior margin of the sterno-cleido-mastoid muscle, at the level of the cricoid cartilage. In absence of response, CSM was repeated on the left side 1 min later. No massage was performed in the upright position. In a first step, carotid sinus hypersensitivity was diagnosed when CSM caused a 3-s ventricular pause, a 50 mmHg fall in systolic blood pressure, or both, associated with pre-syncope or syncope according to usual definitions. In the course of the study, we broadened the definition of a positive CSM by applying the following criteria not used in prior studies: (i) development of a sinus rate < 40 bpm, (ii) > 30% decrease in heart rate, or (iii) both (i) and (ii), with or without associated symptoms. We expanded the definitions because we observed a distinct difference between patients who have no or only subtle heart rate response to CSM vs. patients with distinct manifestations of carotid sinus hypersensitivity other than heart block or fall in blood pressure.

When non-conducted P-waves occurred during CSM, the ‘heart rate at CSM’ was calculated from the cycle lengths of the last three QRS complexes preceded by a P-wave immediately before the first non-conducted P-wave. A positive CSM was then observed in 10 patients. Among these 10 patients, performed a Valsalva manoeuvre and, finally, underwent simultaneous CSM and Valsalva manoeuvre. All patients were capable of performing a satisfactory Valsalva manoeuvre. The deliberate duplication of these manoeuvres was to ascertain that vagal activity could be stimulated despite the absence of a positive response to CSM. However, neither more profound bradycardia nor more prominent hypotension were elicited by the Valsalva manoeuvre than by CSM, and both manoeuvres simultaneously never elicited a more prominent response than CSM alone.

At baseline, the examination ended with a search for orthostatic hypotension. The patient was instructed to assume an upright from a supine position, the systemic blood pressure was measured at 1-min intervals for 5 min, and the lowest measurement was retained. Orthostatic hypotension was diagnosed in the presence of a ≥20 mmHg decrease in systolic blood pressure, or a ≥10 mmHg decrease in diastolic blood pressure, or both, in association with syncope or presyncope within 3 min of assuming an upright posture.

After the eighth month, the development of pre-syncope or syncope was monitored by telephone communications with the patients and caregivers for an additional 12-month follow-up, while treatment with donepezil continued. The primary physicians were requested to refer the patients for further evaluation of pre-syncope or syncopal episodes.

**Statistical analyses**

Grouped results are presented as means ± SD. Student’s t-test was used for the comparisons of measurements made before treatment with donepezil in patients with positive CSM vs. the measurements made in patients without positive CSM. A P-value < 0.05 was considered to indicate statistical significance.

**Results**

The mean age of the study population was 80 ± 6 years, mean body weight 64 ± 11 kg, and 25 patients (83%) were women. A 20-month follow-up was completed by 28 patients. One patient was lost to follow-up, and another died of pneumonia at 12-month follow-up. Both patients had negative baseline CSM. Among 10 patients with positive CSM, two patients were treated with a reduced dose of donepezil (5 mg/day) because of gastro-intestinal adverse effects, and another discontinued treatment after 3 weeks because of vomiting. Follow-up information was, nevertheless, complete for these 10 patients.

**Carotid sinus massage**

**Positive CSM group**

Carotid sinus massage was positive in 10 of the 30 patients, and carotid sinus hypersensitivity was observed in two (6.7%) of the 30 patients (Figure 1). The clinical characteristics and ECG observations in the 10 patients with a positive CSM are shown in Table 1. Antiarrhythmic drugs were administered in four patients. Heart rate decreased by a mean of 32%, from 64 ± 9 at baseline to 43 ± 8 bpm during CSM.

**Negative CSM group**

Among the 20 patients with negative CSM, nine (45%) were treated with antiarrhythmic drugs. Their heart rate decreased by a mean of 13%, from 67 ± 8 at baseline to 58 ± 7 bpm during CSM. This group of patients included five men, two patients with orthostatic hypotension at baseline, three patients with left bundle branch block and two patients with right bundle branch block.

There were no significant baseline differences in blood pressure or ECG observations between patients with vs. without positive CSM. The response to CSM has been unchanged in each patient during the different clinical evaluations in the first 8 months.

No CSM-related cerebrovascular complication was observed.

**Syncope**

During the 20-month follow-up, four syncopal events occurred in three of the 30 patients, including two patients in the group with positive CSM at baseline. One patient developed syncope during the first 8-month period, during which the adverse cardiovascular effects of donepezil were being monitored. This patient had a positive CSM at baseline (patient number 4 in Table 1) and suffered a single episode of syncope in the third month of the protocol. Following the syncope episode and during neuro-cardiovascular investigations, including cardiac electrophysiological studies, repeat CSM was associated with two blocked P-waves without symptoms, as had been observed during baseline CSM. The final diagnosis was orthostatic hypotension, since her blood pressure fell from 154/72 to 118/70 mmHg, and
she became presyncopal, upon arising from the supine to the upright position. This patient suffered no recurrence of syncope after alleviation of her drug regimen for systemic hypertension, and despite continuation of cholinergic therapy. Syncope occurred in two other patients during the 12 additional months of follow-up. One patient, who had a positive baseline CSM (patient number 1 in Table 1), experienced two syncopal episodes with convulsions 4 months apart. Despite detailed neuro-cardiovascular investigations after both episodes, the cause of syncope remained undetermined. The third patient, whose baseline CSM was negative, also had unexplained syncope after thorough evaluation.

Discussion

Neurocardiogenic syncope, including vaso-vagal syncope, carotid sinus syncope and situational syncope, is the main cause of syncope.1–3,6,27 Orthostatic hypotension and arrhythmias are other common causes. In a general US population, the prevalence of syncope was 6.2 per 1000 person-years.27 Its cause remains undetermined in approximately one-third of patients.27–29 These observations seem similar in the general and elderly populations, though few studies of the mechanisms of syncope in the elderly have been published.28,30,31 In patients over 70 years of age, the annual incidence of syncope may be 6% with a 30% recurrence rate over a 10-year period, and a prevalence estimated at 23%.32 The most common causes of syncope in older adults are orthostatic hypotension, neurally mediated syncope including carotid sinus hypersensitivity and cardiac arrhythmias.9,30,31 The prevalence of carotid sinus hypersensitivity, rarely observed before age 40, increases with advancing years;7–9 cardio-inhibitory carotid sinus syndrome being a cause of symptoms in 20–60% of elderly patients with syncope.10–12,14

Carotid sinus massage is one of the diagnostic manoeuvres used in neuro-autonomic evaluations, although it was not included by Low.33 among the functional tests to estimate the degree of autonomic failure. Pressure at the site of bifurcation of the common carotid artery elicits a reflex parasympathetic response.34,35 Its consequence might be the development of bradycardia by its negative chronotropic and dromotropic effects on sinus and atrio-ventricular nodes. The effects of CSM are attributed to the stimulation of efferent parasympathetic nerve fibres supplying the cardiac conduction system. Therefore, slowing of cellular automaticity and conduction by parasympathetic stimulation may represent a physiological response. Indirect peripheral consequences may also be observed in the form of systemic hypotension, perhaps related to interference with sympathetic neural activity by parasympathetic stimulation. Mechanisms of hyper-responsiveness of the autonomic nervous system may also be operative, with the sudden activation of unmyelinated C fibres (or mechanoreceptors), which might send an excessive amount of neural traffic to the medulla, mimicking the conditions normally seen in hypertension, causing sympathetic withdrawal with consequent vasodilation and hypotension.36

The definition of a positive CSM used in this study was broader than that applied by other authors. We chose to broaden the definition because (i) we observed only two patients who met the criteria of a positive CSM according to usual definitions, and (ii) we believed that, as this prospective study was launched, that patients who had prominent changes in heart rate in response to CSM before the initiation of cholinergic therapy might develop more prominent adverse effects from cholinergic medication than
patients in whom CSM produced no changes in heart rate. This choice did not affect the results of our study, the objective of which was not to develop a more sensitive or specific definition of carotid sinus hypersensitivity. Therefore, this broad definition of positive CSM is only applicable to our study in accordance with our initial aim.

Head-up tilt testing is another means of evaluation of the autonomic nervous system, and diagnosis of neurally mediated syncope. It is, however, unhelpful in the elderly since vagal tone declines with advancing age, and because of difficulties in clearly identifying what constitutes a positive response, reducing the specificity of the test. We observed cardio-inhibitory or mixed, but no vasodepressive responses to CSM. This might have been due to our performance of CSM in the supine position, which probably underestimated the magnitude of the vasodepressor component of carotid sinus hypersensitivity in our patients. It has been recommended to repeat CSM in the upright position to identify a vaso-depressive response perhaps concealed by ventricular asystole during severe cardio-inhibition, which may prevent the inappropriate implantation of a pacing system. In our study, the repetition of CSM in the upright position had not been planned, since the original role of CSM was to predict vagally mediated bradycardia with donepezil by a simple clinical manoeuvre, and not to specifically study carotid sinus syndrome.

Other than the drug therapy used for this disorder, there is no clinical reason to suspect that the risk of carotid sinus hypersensitivity, and related syncope, differs in patients with AD from that observed in age-matched AD-free controls. According to the classical definition, a 12.5% prevalence of carotid sinus hypersensitivity associated with symptoms has been observed among asymptomatic persons 65 years of age or older, in contrast to two patients (6.7%) in our study. This discrepancy might be explained by our performance of CSM in the supine position. However, it is noteworthy that in our patients with AD, carotid sinus syndrome was infrequent, in contrast to patients suffering from dementia with Lewy bodies. This difference between these dementias can be related to their distinct pathophysiological characteristics.

Despite the presence of treatment with CI, no change in the response to CSM was observed, and a positive CSM at baseline did not predict the later occurrence of syncope. Patients treated with CI combined with a drug that slows cardiac conduction were no more susceptible to developing syncope. Vagally mediated gastro-intestinal adverse effects were observed in 30% of our patients. The absence of predictive value of CSM with respect to these peripheral vagally related manifestations demonstrates that vagal afference and efference have multiple origins and targets, which do not systematically respond to a single stimulus.

It is not always clear whether a response elicited by the stimulation of sympathetic or parasympathetic autonomic function is normal or due to abnormal autonomic nervous system activity. Carotid sinus hypersensitivity as a cause of spontaneous and unexplained syncope was indirectly incriminated from studies showing the absence of recurrences after pacemaker implantation. The low prevalence of severe carotid sinus hypersensitivity in our patients, who had no history of syncope, and who developed no bradycardia-related syncope during long-term follow-up, vs. the high prevalence of positive CSM reported among

<table>
<thead>
<tr>
<th>Patient gender/age (years)</th>
<th>Weight (kg)</th>
<th>CV history</th>
<th>AA drugs (mg/day)</th>
<th>Baseline</th>
<th>Carotid sinus massage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F/73</td>
<td>65</td>
<td>None</td>
<td>Flecainide 100</td>
<td>143/74</td>
<td>122/76</td>
</tr>
<tr>
<td>2 F/82</td>
<td>76</td>
<td>None</td>
<td>Atenolol 50</td>
<td>182/95</td>
<td>171/92</td>
</tr>
<tr>
<td>3 F/85</td>
<td>60</td>
<td>Hypertension</td>
<td>Acebutolol 200</td>
<td>185/91</td>
<td>171/92</td>
</tr>
<tr>
<td>4 F/82</td>
<td>68</td>
<td>Hypertension</td>
<td>Propafenone 600</td>
<td>175/83</td>
<td>164/77</td>
</tr>
<tr>
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<td>Propranolol 100</td>
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<td>153/77</td>
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<tr>
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<td>50</td>
<td>None</td>
<td>Acebutolol 200</td>
<td>160/74</td>
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<tr>
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<td>160/74</td>
<td>153/77</td>
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</tr>
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<tr>
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<td>65</td>
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<td>None</td>
<td>153/77</td>
<td>153/77</td>
</tr>
</tbody>
</table>

AA, antiarhythmic; AF, atrial fibrillation; bpm, beats per minute; CV, cardiovascular; F, female; HR, heart rate; ms, millisecond; S/D BP, systolic/diastolic blood pressure.
elderly patients presenting with syncope, supports the view that the elicitation of a positive CSM after syncope is not fortuitous, and points to the probable cause of previously unexplained syncope.

The two patients with prolonged asystole and one patient with two consecutive non-conducted P-waves during CSM at baseline received precise instructions to limit their risk of carotid sinus stimulation in daily life. While the clinical significance of these observations was uncertain, they were concerning, particularly at the time of initiation and rapid increase in the doses of donepezil. The implantation of a pacemaker was considered though not carried out. It might have influenced the outcome of these three patients but not of the others, who received no particular instructions in order to not modify their daily routine.

No pacemaker implantation was recommended for patients who developed spontaneous syncope during follow-up, including the two patients who had positive CSM at baseline. This decision was made since CSM, repeated in these two patients after the syncopal events, was again 'positive', though without prolonged heart block or symptoms, as had been observed at baseline. Normal electrophysiological studies help in recommending not to follow with permanent cardiac pacing. The implantation of a pacemaker was considered though not carried out. It might have influenced the outcome of these three patients but of the others, who received no particular instructions in order to not modify their daily routine.

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Study limitations

The study population was small. However, no similar report has been published describing observations made in a larger group of similarly elderly patients and in a prospective manner. As generally observed in studies in the elderly, a majority of the overall population, and all the patients of the positive CSM group, were women, which may limit our conclusions to the female gender.

Conclusion

A positive CSM was observed in 30%, and carotid sinus hypersensitivity in 6.7% of elderly patients with AD and no history of pre-syncope or syncope. This observation was not predictive of an increased risk of bradycardia-mediated syncope. Although syncope was observed in 10% of the patients during long-term follow-up, it was attributable to orthostatic hypotension or undetermined causes. Treatment with CI or drugs that slow cardiac conduction or the presence of a bundle branch block did not modify the response to CSM or increase the incidence of syncope in this population.

Conflict of interest: none declared.

References


