



Pacing in elderly recurrent fallers with carotid sinus hypersensitivity: a randomised, double-blind, placebo controlled crossover trial

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ABSTRACT

Objectives: While carotid sinus syndrome (CSS) is traditionally defined by the association of carotid sinus hypersensitivity (CSH) with syncope, uncertainty remains over the role, if any, of complex pacing in patients with CSH and unexplained or recurrent falls. We sought to clarify the role of dual chamber pacing in this patient group in the first placebo-controlled study in CSH.

Design: Randomised, double-blind, crossover, placebo-controlled trial.

Setting: Specialist falls and syncope facility.

Patients: Consecutive subjects aged over 55 years with CSH as the sole attributable cause of three or more unexplained falls in the 6 months preceding enrolment.

Intervention: Dual-chamber permanent pacing with rate-drop response programming. The pacemaker was switched on (DDD/RDR) or off (ODO (placebo)) for 6 months, then crossed over to the alternate mode for a further 6 months, in randomised, double-blind fashion.

Main outcome measure: The primary outcome measure was number of falls in paced and non-paced modes.

Results: Twenty-five of 34 subjects (mean 76.8 years (SD 9.0), 27 (79%) female) recruited completed the study. Pacing intervention had no effect on number of falls (4.04 (9.54) in DDD/RDR mode, 3.48 (7.22) in ODO; relative risk of falling in ODO mode 0.82, 95% CI 0.62 to 1.10).

Conclusion: Permanent pacing intervention had no effect on fall rates in older patients with CSH. Further work is urgently needed to clarify the role, if any, of complex pacing in this patient group.

Carotid sinus hypersensitivity (CSH) has been causally implicated in spontaneous syncope and presyncope and dizziness for more than 70 years,^{1 2} but it is only in the last decade or so that increasing interest has focused on the association between CSH and non-accidental or unexplained falls in the absence of overt loss of consciousness.^{3–9} Recent guidelines^{10–12} have favoured permanent pacing as the treatment of choice in the cardioinhibitory and mixed subtypes of CSH associated with syncope, but there is controversy over the role of pacing in patients with CSH and non-accidental falls.¹³ The largest randomised study to date investigating the role of pacing in this patient population showed a two-thirds reduction in the number of falls in the intervention group,⁸ but the study is hampered by the absence of blinding and a placebo arm, both important components in intervention studies in neurally mediated disorders.¹⁴ To address these questions, we investigated whether cardiac pacing

reduced events in patients with recurrent falls and cardioinhibitory carotid sinus hypersensitivity in an exploratory, randomised, double-blind, crossover, placebo-controlled trial.

METHODS

Subjects

Consecutive subjects aged 55 years and over presenting to the emergency department or the syncope service with three or more unexplained falls (per self report and witness account where available) and no overt syncope in the preceding 6 months were investigated according to national and international guidelines.^{9–12 15} Unexplained falls were defined as those for which no immediate cause was apparent, either intrinsic (eg, stroke, myocardial infarction [MI], gastro-intestinal haemorrhage or other medical diagnosis) or extrinsic (eg, simple trip over carpet, ill-fitting footwear) following detailed clinical evaluation per national and international guidance.^{9 15} Syncope work-up included morning active stand to evaluate orthostatic hypotension, surface electrocardiogram (ECG), head-up tilt table testing, ambulatory ECG and blood pressure monitoring, echocardiogram and carotid sinus massage (CSM).^{10–12} Those with an otherwise negative work-up and cardioinhibitory (CI) or mixed (Mx) subtypes (>3 s asystole induced by 5 s of bilateral sequential CSM performed supine and erect¹⁶ with (Mx) or without (CI) a 50 mm Hg fall in systolic blood pressure following 600 µg injection of intravenous atropine) of CSH as the sole attributable cause of their falls were invited to participate in the pacing intervention study.

Exclusions

Subjects were excluded if there were other possible causes of their falls or if they had moderate to severe cognitive impairment (Mini Mental State Examination¹⁷ ≤15/30), stroke or MI within 3 months (or other contraindication to CSM^{10 12}) or any history of syncope.

The study had approval from the local Research Ethics Committee.

Intervention

All subjects underwent dual-chamber permanent pacemaker implantation. In all subjects, the device implanted was the Kappa DR (Medtronic, Minneapolis, Minnesota) system programmed to the rate-drop response (RDR) algorithm, which allows backup pacing for patients with occasional drops in heart rate.¹⁸ Following pacemaker implantation, all

subjects' pacemakers were programmed to *on* (ie, in DDD/RDR mode) for a 1-month run-in period in order to ensure that they were unaware of pacing intervention. At 1 month, subjects were randomised (by table of random numbers) in double-blind fashion to either continue in DDD/RDR mode, or for the pacing to be turned *off* (ODO mode). Six months later, patients crossed over to the opposite mode for the remaining 6 months of the study.

Permanent crossover to the DDD/RDR mode occurred if a further indication for pacing therapy was diagnosed, if syncope supervened or at the behest of other physicians caring for the patient concerned.

Event monitoring

All subjects completed daily fall diaries returned at weekly intervals using prepaid postage to avoid confounding due to inaccurate recall of falls. Information from the falls diaries was held at a central database; failure of diary return initiated a telephone prompt to keep diary returns contemporaneous.

Outcome measures

The primary outcome measure was the number of falls. This was assessed in two ways: whether or not a participant falls at all during each study period and the number of falls in each study period. The secondary outcome measure was the time to first fall.

Sample size

Previous work (based on preliminary data⁵) suggested that we might expect pacing to result in a reduction in falling of around 27% and that this corresponded to an effect size of approximately 0.5. This was a significantly lower treatment effect than the 66% reduction in fall rates seen in the SAFE-PACE study,⁸ but these data were not available at the time of power calculation. Based on the 27% treatment effect, a sample size calculation for a paired comparison indicated that a total sample of 32 subjects would be required to detect an effect size of 0.5 with 80% power assuming a type 1 error rate of 5%. A target sample size of 34 was specified to allow for drop out during the study (an attrition rate of 5.9%).

Statistical analysis

McNemar test was used to compare the number of participants falling during the 6 months with their pacemaker turned off with the number of participants falling during the 6 months with their pacemaker turned on. The numbers of falls in the two periods were compared using negative binomial regression with variation between subjects and variation between periods included as fixed effects and the log of the number of days at risk included as an offset. The time to first fall was investigated using Kaplan–Meier plots and survival analysis using SPSS Version 10.

RESULTS

Baseline clinical characteristics

Thirty-four patients were recruited to the study. Baseline clinical characteristics of the study population, including age, sex, MMSE, falls history and consequences, medications and comorbidity, are shown in table 1. Haemodynamic consequences of baseline carotid sinus massage are shown in table 2.

Falls-outcome data

Twenty-five patients completed the study. Three subjects permanently crossed-over to DDD/RDR pacing from ODO

mode (one because of syncope, two because of physician preference), one subject refused further participation because of pacemaker erosion, four subjects died (three from ischaemic heart disease, one postemergency colectomy for ischaemic bowel), and one suffered a total anterior circulation stroke.

Ninety-one point four per cent of falls diaries were completed and returned for analysis. None of the subjects reported awareness of pacing during the 1-month prerandomisation period, during which they experienced a mean of 0.64 falls (SD 1.07). The number of falls for each participant is described in table 3. There were a mean of 3.48 (7.22) falls during the 6 months in ODO mode, compared with 4.04 (9.54) falls during the 6 months in DDD/RDR mode. On average, there were 0.56 fewer falls per participant during the period with the pacemaker turned on. Analysing the number of falls using negative binomial regression indicates that the relative risk of falling with the pacemaker turned on compared with the pacemaker turned off is 0.82 with a 95% CI of 0.62 to 1.10.

Of the 25 participants completing the study, seven did not fall in either period, and 12 fell in both periods. Of the remaining six participants, two fell only while their pacemaker was turned off, and four fell only while their pacemaker was turned on. This difference was not significant ($p = 0.69$, McNemar test).

Survival analysis (treating the pacemaker on/off groups as independent samples) showed that there were no significant differences in time to first fall between DDD/RDR and ODO modes (fig 1; $p = 0.57$).

Pacemaker interrogation following falls

On three occasions, subjects presented to the pacing department within 4 h of falling. Unfortunately, on these occasions, the pacemakers were in ODO mode, so bradyarrhythmias could not be detected. There was no evidence of malignant tachyarrhythmia in any of these cases, however. Two of the three patients who died suddenly at home (coroner's postmortem reported ischaemic heart disease as the cause of death in each case) were in ODO mode at the time of death. Although the pacemakers were recovered and interrogated, there were no diagnostically useful data retrieved.

Consequences of falls

There were relatively few injuries during the study period. During the DDD/RDR study period, one subject sustained a wrist fracture, another suffered a scalp laceration requiring sutures, and a third required medical attention for a sprained ankle. During the ODO study period, one subject suffered a back injury and severe bruising secondary to falls, while the patient who suffered the wrist fracture sought medical advice for falls on three different occasions.

DISCUSSION

Our study suggests that the benefits of permanent pacing in subjects with unexplained falls and CSH in this, the first, randomised, double-blind, placebo-controlled trial in its field, are at best modest. There was no evidence that pacing intervention reduced the percentage of patients who fell. The rationale for pacing in such individuals is either that they are experiencing transient "micro-syncope" with collapse and memory of a fall rather than loss of consciousness or that the sudden catastrophic cerebral hypoperfusion caused by cardiac asystole and hypotension secondary to CSH causes transient balance abnormalities resulting in falls. As both falls and syncope are multifactorial in aetiology in many older patients,

Table 1 Baseline clinical characteristics of subjects with carotid sinus hypersensitivity and unexplained falls

	Patients with unexplained falls (n = 34)
Age, years (SD)	76.8 (9) (range 56 to 89), median 77.5
Sex	
Female	27 (79%)
Male	7 (21%)
Mean Mini-Mental State Examination (SD) (median)	27 (2.5) (27)
Mean no falls in 6 months	7 (median 6) (range 3 to 40)
Mean symptom duration	13 months (median 9) (range 5 to 60)
Mean no episodes ever (SD)	13 (12.8) (median 8) (range 3 to 50)
Hospital admissions/A&E attendances*	16 (47%)
Fractures*	8 (24%)
Soft-tissue injuries*	14 (41%)
Requiring medical attention	9 (26%)
Facial bruising	5 (15%)
Medications	
Polypharmacy	7 (20%)
Cardiovascular	11 (32%)
Psychoactive	4 (12%)
None	6 (18%)
Ischaemic heart disease	8 (24%)
Hypertension	5 (15%)
Osteoarthritis	9 (26%)
Stroke	3 (9%)
Dementia	3 (9%)
Chronic obstructive pulmonary disease	8 (24%)
Type II diabetes	3 (9%)

*Secondary to falls/syncope; polypharmacy: four or more prescribed drugs.

we were careful to exclude other causes of these problems in a systematic and evidence-based manner. Our study population was thus a relatively “clean” one, although the high pre-enrolment fall burden was striking, suggesting the possibility of undetected falls risks.

The quality of the falls outcome data is excellent, with a 91.4% fall diary completion rate, but while the current study benefits from a more powerful study design (placebo-controlled with crossover) than that of Kenny *et al*⁸ (no placebo limb) or Crilley *et al*⁴ (retrospective, with poorly defined symptom complexes) studies, it suffers from the small number of patients completing the study. Though the baseline sample met the initial power calculation requirements, the 26% attrition rate (vs an expected 5%) left the study with fewer patients than anticipated. As a result, the study may be significantly

underpowered, although the lower interval for relative risk of falling (0.62; corresponding to the most optimistic estimate of the clinical effectiveness in the SAFE-PACE study) implies that the impact of pacing is not as large as the effects observed in non-blinded studies,⁸ lessening the impact of the lower than anticipated study completion rate.

Carotid sinus massage induced cardioinhibitory and mixed subtypes in almost equal proportions. There was a profound fall in mean systolic blood pressure during CSM (76.2 mm Hg; table 2) in the group overall, with a similar vasodepressor response evident in those undergoing massage post-atropine (table 2). Although a clinical commonplace, the significant increase in vasodepression in the head-up tilt position during CSM has not previously been documented under experimental conditions. While none of the patients in this study experienced neurological (or any other) complications due to CSM, the larger degree of vasodepression during CSM in the upright position may predispose towards watershed-type cerebrovascular events.¹⁹ Though a causal association between profound vasodepression and neurological complications during CSM has not been formally established, the current pragmatic approach of performing massage supine initially and to ensure a long period of supine recovery before ambulation post-CSM related vasodepression is reinforced by these findings.¹⁰ Similarly, the fact that 71% of initially positive CSM episodes were on the right side reinforces the suggestion that massage be performed sequentially right- then left-sided.¹⁰ The high proportion of subjects whose initial positive response to CSM was in the upright position (59%) is noteworthy and reinforces the importance of repeating negative supine CSM in the upright position.¹⁶

The high death rate in this study is worthy of mention. Three died suddenly at home, with coroner's post-mortem results showing only ischaemic heart disease. None of these subjects had suffered a fatal myocardial infarction, raising the spectre of

Table 2 Results of carotid sinus massage in subjects with carotid sinus hypersensitivity and unexplained falls

	Patients with unexplained falls (n = 34)
CSH subtype	CI 15 (44%) Mx 17 (50%) U 2 (6%)
Mean max asystole (s) (SD)	5.06 (1.5)
Mean max VD (mm Hg) (SD)	76.7 (35.2)
VD postatropine (n = 19)	
Mean VD supine (mm Hg) (SD)	73.4 (15.1)*
Mean VD upright (mm Hg) (SD)	87.2 (18.6)
Laterality of initial positive CSM	24 (71%) right
Initial CSM positive upright	20 (59%)
LOC during CSM	22 (64%)
Amnesia for LOC	21 (95% of LOC) 12 (57%) upright

*p = 0.000034.

CI, cardioinhibitory; CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; LOC, loss of consciousness; max, maximum; Mx, mixed; U, unclassifiable; VD, vasodepressor response.

Table 3 Number of days at risk and number of falls for each subject by period

No of falls					No of days	
Running in period	Pacemaker turned off*	Pacemaker turned on†	Total	Off-on	Pacemaker turned off*	Pacemaker turned on†
0	0	0	0	0	182	196
0	0	0	0	0	81	377
0	0	0	0	0	189	175
0	0	0	0	0	182	189
0	0	0	0	0	182	186
0	0	0	0	0	203	196
0	0	0	0	0	182	210
0	0	1	1	-1	182	185
0	0	1	1	-1	186	196
0	1	0	1	1	189	189
0	0	2	2	-2	144	230
0	1	1	2	0	182	186
0	2	0	2	2	188	169
0	1	1	2	0	190	168
0	0	2	2	-2	170	183
0	1	2	3	-1	203	182
0	2	1	3	1	182	185
0	2	3	5	-1	174	189
2	3	1	6	2	182	190
2	1	4	7	-3	182	182
3	9	3	15	6	200	199
2	6	10	18	-4	168	193
3	5	14	22	-9	161	176
2	24	7	33	17	182	167
2	43	34	79	9	168	182
Means:						
0.64	4.04	3.48	8.16	0.56‡	177.4	195.2

*Off, ODO mode.

†On, DDDR mode.

‡Relative risk of falling with pacemaker turned on compared with off: 0.82 (95% CI 0.62 to 1.10).

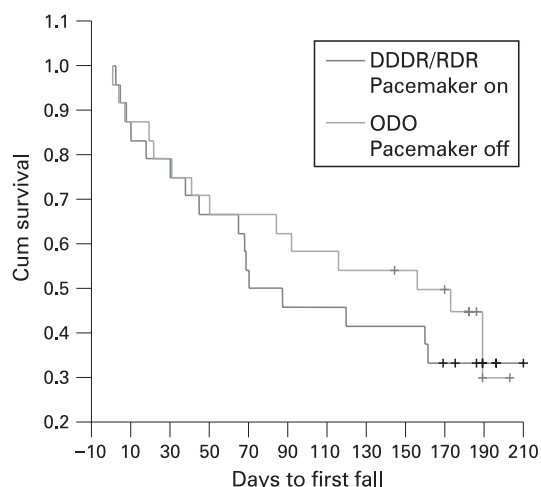
occult ventricular tachyarrhythmias as a potential cause of symptoms and sudden death. Potentially causative ventricular tachycardia has been documented during electrophysiology studies in subjects with carotid sinus syncope.²⁰ All three of the deceased had normal 24 h ambulatory ECG recordings but had features of ischaemic heart disease on surface ECG, but as with all the study patients, none had suffered syncope at any time and had a negative “syncope work-up” as detailed above, including normal ejection fractions on echocardiography. The

presence of any putative malignant tachyarrhythmias must thus remain speculative.

The distribution of falls during the paced and non-paced periods hints at a placebo effect. In favour of this hypothesis is the overall reduction in the number of falls in *both* 6-month periods compared with the pre-enrolment fall burden (mean seven falls) and the high number of subjects who experienced no falls at all during the course of the study (regardless of pacing mode status). It is possible that the short duration of follow-up in paced and non-paced modes may be a source of bias, though this is unlikely given the high mean and median number of falls in the 6 months prior to enrolment. The highly symptomatic nature of the patients enrolled may also imply “regression to the mean” during follow-up rather than either a placebo effect.

The high proportion of subjects with loss of consciousness during CSM (64%; table 2) is noteworthy. In the context of the investigation of unexplained syncope, recent guidelines suggest that CSM is diagnostic only in the presence of both haemodynamic changes *and* symptom reproduction,¹² the so-called “method of symptoms.”²¹ Our patients clearly could not reproduce a fall during the confines of laboratory CSM, and so do not fit conventional diagnostic criteria. Our group has recently shown that up to one-third of community dwelling elders fulfil criteria for CSH during CSM regardless of symptoms of falls, dizziness or syncope,²² so the attribution of CSH in a causal role in our patients’ falls must now be open to speculation.

In conclusion, we found no evidence that pacing helped improve the fall burden in patients with CSH who had

**Figure 1** Time to first fall: survival analysis.

undergone a comprehensive battery of investigations to exclude any other causes for their symptoms. The overall number of falls fell, but the number of falls was similar regardless of pacing or placebo intervention in this crossover study. Although enrolment initially fulfilled our sample estimate, our study population suffered a high attrition rate, leaving the study underpowered for the final analysis. This work is important in showing that a placebo-controlled pacing study is feasible and well tolerated in this population, and further work is needed to establish the continued relevance of permanent pacing in unexplained fallers with carotid sinus hypersensitivity.

Competing interests: None.

Ethics approval: Ethics approval was provided by the Newcastle Local Research Ethics Committee.

Patient consent: Obtained.

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