

# Benefits of fludrocortisone in the treatment of symptomatic vasodepressor carotid sinus syndrome

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## Abstract

**Objective**—To assess treatment with fludrocortisone in vasodepressor carotid sinus syndrome.

**Patients and methods**—Eleven patients, mean (SD) age 83 (5) years, with daily dizzy episodes and a median of five (range two to 20) syncopal episodes over a median of one year were studied. All had vasodepressor carotid sinus syndrome (> 50 mm Hg fall in systolic blood pressure during carotid sinus massage independent of bradycardia). Carotid sinus massage was carried out while the patient was supine and upright (tilt table) before and after 600 µg intravenous atropine. Phasic heart rate and blood pressure recordings were monitored throughout. The study was repeated after 100 µg of fludrocortisone daily by mouth for two weeks. Patients continued to take fludrocortisone for a six month follow up period.

**Results**—Baseline systolic blood pressure was (mean (SD)) 169 (31) mm Hg and the RR interval was 770 (150) ms. After carotid sinus massage, systolic blood pressure fell to 113 (27) mm Hg ( $p < 0.01$ ) and RR was 1060 (210) ms (NS). The vasodepressor response was 56 (12) mm Hg. Baseline systolic blood pressure after two weeks of fludrocortisone treatment was 171 (37) mm Hg (NS); but the fall in systolic blood pressure during carotid sinus massage was significantly reduced (32 (14) mm Hg;  $p < 0.01$ ). At six months follow up, two patients complained of intermittent dizziness and no patients had syncope.

**Conclusion**—Fludrocortisone effectively reduces the vasodepressor response and relieves the symptoms of vasodepressor carotid sinus syndrome.

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When carotid sinus massage is regularly performed in syncopal elderly patients, carotid sinus syndrome is as frequent an indication for cardiac pacing as sick sinus syndrome.<sup>1,2</sup> Under these circumstances the annual incidence of cardiac implant is 40/million for carotid sinus syndrome and 37/million for sick sinus syndrome and 20% of pacemaker implants for atrial bradyarrhythmias are for carotid sinus syndrome alone or in association with sick sinus syndrome.<sup>1</sup> Nevertheless,

symptoms will persist in 12% to 30% of patients despite appropriate pacing due to the inherent vasodepressor response to massage that is present to varying degrees in most patients.<sup>3,4</sup> Furthermore, a proportion of patients with the syndrome do not have cardioinhibition and have only a vasodepressor response. To date, no effective treatment is available for the vasodepressor response.<sup>5,6</sup>

Orthostatic hypotension is present in up to 20% of patients with vasodepressor carotid sinus syndrome.<sup>2,4,6</sup> Fludrocortisone is of benefit in orthostatic hypotension, acting by direct vasoconstriction of venous capacitance vessels, through sodium retention and increased vascular sensitivity to circulating catecholamines.<sup>7,8</sup>

Our study was to determine whether fludrocortisone is beneficial in the treatment of symptomatic vasodepressor carotid sinus syndrome.

## Patients and methods

The study group comprised 11 patients (mean (SD) 83 (5) years) with vasodepressor carotid sinus syndrome (either alone (eight) or in combination with significant cardioinhibition (three)) referred for investigation of unexplained syncope. Patients had experienced a median of five syncopal episodes (range two-20) over a median period of one year (range : immediately before admission to in excess of five years). Nine also complained of dizzy episodes (daily (four), twice weekly (four), and at monthly intervals (one)). Four patients had sustained a fracture during syncope. Precipitating factors for syncope were prolonged standing (three), head turning (four), looking up (three), postural changes (four) and eating (three). None was taking cardiovascular medications at the time of study; all were in sinus rhythm. Symptom free postural hypotension was present in five at one minute after head up tilt (supine systolic blood pressure 169 (23) mm Hg dropping to 136 (27) mm Hg when upright).

A > 50 mm Hg fall in systolic pressure during carotid sinus massage, independent of the cardioinhibitory response, with reproduction of symptoms, was diagnostic of vasodepressor carotid sinus syndrome.<sup>5,9,10</sup> Other causes of syncope were excluded after detailed history and examination, 48 hour ambulatory cardiac monitoring, 24 hour ambulatory blood pressure monitoring (TM 2020), 45 minute head up tilt to 70° (Akron foot plate support table),<sup>11</sup> and cross sectional echocardiography.

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Longitudinal massage was performed over the carotid sinus, at the bifurcation of the internal and external carotid artery for six seconds. Right sided massage was followed, after a one minute interval, (to allow resetting of the gain of the baroreflex), by massage of the left carotid sinus in both the supine and 70° head up positions on the tilt table. This sequence was repeated before and three minutes after bolus doses of 600 µg of atropine given through a 20 gauge cannula in the dorsal hand vein.

Blood pressure and heart rate were continuously monitored throughout the study. Because intra-arterial cannulation may alter autonomic tone and hence cardiovascular responses to carotid sinus massage,<sup>7</sup> non-invasive phasic blood pressure was recorded by continuous digital artery plethysmography (Finapres finger cuff).<sup>12</sup>

Massage was repeated to ensure reproducible responses in heart rate and blood pressure. Baseline measurements were taken from an average of 10 consecutive RR intervals and blood pressure recordings. Measurements of the maximum RR interval and the maximum fall in blood pressure were used in analysis.

Subjects were then given 100 µg of fludrocortisone daily. After two weeks, the same study protocol was repeated. Patients who had a significant cardioinhibitory response before atropine, were then referred for dual chamber cardiac pacing. Recurrence of symptoms was recorded regularly during a minimum follow up of six months. Wilcoxon paired tests were used for comparison of responses before and after treatment. Results are expressed as mean (SD).

## Results

The degree of vasodepressor response for both systolic and diastolic pressures was significantly reduced by fludrocortisone treatment for two weeks. The vasodepressor response was rapid: the maximum fall in systolic blood pressure occurred at 18 (3) s after carotid sinus massage and had returned to baseline by 45 (15) s. The vasodepressor response was present and reproducibly > 50 mm Hg in all patients when upright, and in 70% when supine. Baseline blood pressures were not increased by treatment. Baseline heart rates and the maximum slowing of heart

rate did not differ before and after treatment (table).

At six months, all patients continued to take 100 µg fludrocortisone a day. None reported side effects. All reported a considerable improvement in symptoms: nine were symptom free, none had experienced any further syncope, and two had intermittent dizzy episodes.

## Discussion

Carotid sinus syndrome is increasingly recognised as a cause of unexplained falls, syncope, and dizziness in the elderly.<sup>13</sup> The vasodepressor component of the syndrome is less often diagnosed as it requires simultaneous beat to beat monitoring of arterial blood pressure, which is both invasive and time consuming. Non-invasive arterial monitoring with continuous digital artery plethysmography has the advantages of convenience, speed, and accuracy, and does not alter underlying autonomic tone, unlike arterial cannulation.<sup>7,12</sup> In our study, the maximum fall in arterial pressure occurred rapidly and pressures had returned to baseline within one minute, thus emphasising the brevity of the hypotensive response and the need for phasic blood pressure monitoring to detect changes.

Mixed cardioinhibitory and vasodepressor carotid sinus syndrome is best treated by dual chamber cardiac pacing.<sup>3,4</sup> In most patients with mixed disease, symptoms are more persistent with single ventricular chamber pacing.<sup>3,4</sup> Atrial pacing does not protect against atrioventricular conduction block, which occurs in up to 70% of cardioinhibitory episodes.<sup>14</sup>

Carotid sinus massage is a crude technique for diagnosis of the syndrome. In particular, the degree of pressure applied cannot be quantified and cardioinhibitory responses are not always reproducible.<sup>15</sup> None the less, other methods of diagnosis, such as head up tilt, negative neck chamber suction, and baroreflex responses to vasoconstriction (phenylephrine pressor test), whereas they reflect enhanced vagal activity and sinus bradycardia, they lack adequate specificity.<sup>16</sup> To overcome bias, the same examiner performed massage on each occasion and was blind to heart rate and blood pressure responses. Furthermore, the mean of results for two consecutive procedures was used in analysis. Reproducibility of the response on two separate occasions was necessary before inclusion in the study. The encouraging preliminary results require further evaluation by double blind randomisation of treatment.

The pathophysiology of the vasodepressor response to massage is not as yet clearly defined. In head up tilt induced vasodepressor vasovagal syncope, sudden withdrawal of sympathetic activity has been shown and a similar response is proposed for vasodepressor carotid sinus syndrome.<sup>17</sup>

The rationale for treatment of vasodepressor symptoms with fludrocortisone is because of the overlap between the diagnoses

Heart rate and blood pressure data (mean (SD)) in 11 patients with vasodepressor carotid sinus syndrome after 600 µg of intravenous atropine, before (study 1) and after (study 2) treatment with 100 µg of fludrocortisone for two weeks

	Study 1	Study 2	p Value
Baseline systolic BP	169 (31)	171 (37)	NS
Lowest systolic BP after CSM	113 (27)	139 (41)	< 0.01
Systolic VD response	56 (12)	32 (14)	< 0.01
Baseline diastolic BP	87 (15)	85 (17)	NS
Lowest diastolic BP after CSM	64 (13)	71 (18)	NS
Diastolic VD response	23 (17)	15 (8)	< 0.05
Baseline RR interval	770 (150)	780 (160)	NS
Maximum RR interval after CSM	1060 (210)	960 (180)	NS

BP, blood pressure; CSM, carotid sinus massage; VD, vasodepressor response.

of vasodepressor carotid sinus syndrome and orthostatic hypotension. In one series, 30% of patients with vasodepressor carotid sinus syndrome also had orthostatic hypotension<sup>2</sup> and Brignole *et al* found poorer responses to single ventricular chamber pacing for relief of symptoms in patients with both conditions.<sup>1</sup>

Previous pharmacological studies have shown that in orthostatic hypotension there is both impairment of noradrenaline release from sympathetic nerve endings and denervation supersensitivity of vascular  $\alpha$  receptors.<sup>18</sup> As these receptors are the effectors of the sympathetic system, they are essential to the regulation of vascular tone and blood pressure. Fludrocortisone increases pressor sensitivity to circulating catecholamines and angiotensin, alters intravascular volumes, and may have central adrenergic effects.<sup>7,8</sup> Fludrocortisone may benefit both orthostatic hypotension and vasodepressor carotid sinus syndrome by one or all of these mechanisms.

The significant reduction in vasodepressor response cannot be attributed to less noticeable reductions in heart rate: the maximum RR interval did not shorten after treatment. Fludrocortisone treatment for six months was well tolerated with considerable improvement of symptoms. Diastolic blood pressure was not greatly altered by treatment although the vasodepressor diastolic response was reduced.

Fludrocortisone effectively reduces the vasodepressor response and relieves symptoms in vasodepressor carotid sinus syndrome.

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