Carotid sinus syndrome

Mark Mallet

This article reviews the recent literature about carotid sinus syndrome. It looks principally at the various ways in which it may present, the limited knowledge of its pathophysiology, and the role of carotid sinus massage in the investigation of carotid sinus syndrome.

Carotid sinus hypersensitivity (CSH) is increasingly recognized as having an important role in the aetiology of syncope and recurrent or otherwise unexplained falls. CSH is the term used to reflect an exaggerated baroreceptor-mediated reflex which results in bradycardia and/or hypotension in response to stimulation of the carotid sinus; when CSH is demonstrated in the context of symptoms of syncope or presyncope this comprises carotid sinus syndrome (CSS). There are three subtypes: cardioinhibitory, defined arbitrarily as asystole for more than 3 seconds; vasodepressor (defined as a fall in systolic blood pressure (BP) greater than 50 mmHg), and a mixed type combining features of both.

PREVALENCE

Prolongation of the RR interval in response to carotid sinus massage (CSM) varies continuously in the normal population, possibly lengthening slightly with age, and is abnormal (>3 seconds) in 0–4% of healthy elderly people (Brignole et al, 1985; McIntosh et al, 1994; Jeffreys et al, 1996). In patients with coronary artery disease and carotid atherosclerosis (Kallikazaros et al, 1997) this prevalence is increased significantly, and corresponds to the degree of coronary or carotid stenosis. CSH is also more common in patients with hypertension. It is essentially a disease of older people, being found increasingly commonly with advancing age, and is rare in people below the age of 50 years in the absence of significant coronary or cerebrovascular disease.

PRESENTATION

There is usually little or no prodrome, so symptoms occur suddenly and unpredictably, although they can be precipitated by head turning while wearing tight neckwear. CSS commonly presents with episodes of syncope or presyncope, but can also appear in other guises. For example, the incidence of CSH is increased in patients presenting with femoral fractures: in one study 36% of cases compared to 0–17% of controls had CSH, and this was more likely if there were previous unexplained falls or if the index fall was unexplained (Ward et al, 1999). Out of 100 nursing home patients 14 were found to have CSH, and those with CSH had a four-fold increase in fractures and a ten-fold increase in syncope over the next 33 months compared to those without CSH (Murphy et al, 1986).

A high incidence of CSH has also been found in older patients who presented with drop attacks, i.e. a 'sudden loss of postural tone without loss of consciousness'. CSH was found in 24 out of 35 (69%), and considered to be a definite attributable cause in 18 (51%) (Dey et al, 1997). The majority had cardioinhibitory CSH (CICSH) or mixed CSH, and most had amnesia for loss of consciousness demonstrated with CSM, raising the possibility that at least some drop attacks may in fact be syncopal events with retrograde amnesia. In another study 74 patients with apparent treatment-resistant epilepsy underwent cardiovascular investigations; an alternative diagnosis was found in 31 (42%), and 7 (9.5%) had CICSH (Zaidi et al, 2000). CSS has also rarely been associated with carotid body or other head and neck tumours.

CSH is an important cause of syncope and presyncope, being found in 55 of 80 patients (66%) (Morillo et al, 1999) and 917 of 1719 patients (53%) (Puggioni et al, 2002) with recurrent syncope. Other age-related conditions such as orthostatic hypotension, postprandial hypotension and vasovagal syncope also manifest as bradycardic or hypotensive episodes, and it is increasingly recognized that all these conditions which result in such 'neurovascular instability' can present in quite varied ways, with a large overlap between falls, syncope and dizziness. In series of elderly patients presenting with any of these symptoms, CSH was found in 48% (McIntosh et al, 1993), and in those presenting with falls or syncope in 15–21% (Bacon and Grunstein, 2000; Eltrafi et al, 2000). In one study symptoms were precipitated by head movement in about half the cases; half sustained injury, and a quarter a fracture (of whom 93% had no warning prodrome) (Morillo et al, 1999).

Dr Mark Mallet is Consultant Physician in the Medical Assessment Unit, Royal United Hospital, Bath BA1 3NG

CSH AND FALLS

CSH has been found in a high proportion (23–73%) of otherwise unexplained falls in older people, with the proportion rising in more advanced age (Davies and Kenny, 1996; Richardson et al, 1997; Davies et al, 2001). A witness account of the events is often unavailable; many patients with demonstrable CSH as the cause of their falls or dizziness deny syncope, and amnesia for loss of consciousness induced by CSM is only seen in 23–51% of those presenting only with falls or falls and dizziness (Shaw and Kenny, 1997). In some patients with underlying gait and balance instability, hypotension caused by CSH results in loss of balance; however, unrecognized syncope is more likely to be the cause of many recurrent or unexplained falls in the presence of demonstrable CSH.

Those with CSH who present with recurrent falls differ somewhat from those who present with syncope: more are female, there is less cardiovascular co-morbidity, and a higher proportion only have a positive response to CSM when upright (Parry et al, 1998). But could CSH just be an associated physical sign in recurrent falls, in a population of patients likely to have underlying atherosclerotic disease? Studies have been unblinded, the provocation test of CSM gives an unstandardized stimulus to the baroreceptor reflex pathway, and there is little convincing trial evidence of benefit of treatment (O'Mahony, 2001). Of greatest interest is whether CSM reproduces the pathophysiological process occurring during spontaneous episodes of falls, syncope or presyncope. Currently these are unknown; this reinforces the need to insist on reproducing the presenting symptom in order for a positive response to CSM to be labelled as the attributable cause.

PATHOPHYSIOLOGY

Slowing of the heart rate in response to carotid pressure was first described in 1799, and the first case of CSS was reported in 1930 (McIntosh and Kenny, 1994). The carotid sinus is located at the bifurcation of the internal and external carotid arteries. Sensory nerve endings in the elastic tissue of the sinus join the glossopharyngeal nerve; some fibres run with the vagus and hypoglossal nerves and the cervical sympathetic nerves. The afferent limb passes to the nucleus tractus solitarius in the medulla, and the efferent limb of the reflex includes sympathetic components to the heart and vasculature, and parasympathetic elements to the sinus and atrioventricular nodes. The vasodepressor reflex is principally mediated by sympathetic inhibition, and the cardioinhibitory component by an increase in vagal tone.

The cause of apparent hypersensitivity of the carotid sinus reflex has not been identified, and baroreflex sensitivity tends to be blunted in old age and those with hypertension. Efferent autonomic function seems to be preserved, and despite the higher prevalence of carotid atherosclerosis afferent pathways remain intact. Ischaemic damage in the central nucleus might result in hypersensitivity of the reflex (O'Mahony, 1995), and there may also be a component resulting from impaired cerebral autoregulation (Leftheriotis et al, 2000). Another suggestion is that chronic up-regulation of post-synaptic receptors results in exaggerated efferent responses on stimulation of the carotid sinus, causing carotid sinus 'irritability' rather than hypersensitivity (Cole et al, 2001). Another possibility is the involvement of neuromuscular structures around the carotid stretch receptors (Blanc et al, 1997).

Overlap with other causes of neurovascular instability is well recognized: orthostatic hypotension was found in 27% and vasovagal syncope (predominantly vasodepressor) in 20% of patients with CSS by McIntosh et al (1993), and one or other in 60% of those with vasodepressor CSH by Puggioni et al (2002). This implies that at least to some degree a common pathological process is involved; the physiological changes in CSH and vasovagal syncope in particular are very similar, both involving inappropriately enhanced autonomic reflex activity.

INVESTIGATION

CSH is diagnosed by CSM. After consent has been obtained, longitudinal massage is carried out over the point of maximum pulsation of the carotid artery for 5–10 seconds (Brignole et al, 2001). Continuous electrocardiographic and BP monitoring are essential in order to detect rapid changes in RR interval or BP. Massage is performed first over the right carotid sinus and then after 30–60 seconds rest on the left (since more positive results are gained on the right side); after performing CSM in the supine position it should be repeated upright (70° head-up tilt), since at least 30% are only abnormal in the upright position (McIntosh et al, 1993; Parry et al, 2000).

Atropine may be given to abolish the cardioinhibitory response and reveal the extent of any vasodepressor element. The vasodepressor reflex lasts longer than the cardioinhibitory reflex, and may contribute to a more prolonged hypotension (Gaggioli et al, 1995); it is best evaluated in the upright position. It is important to establish whether there is a vasodepressor component, since pacing is less effective in mixed CSH with a major vasodepressor component than in pure CICSH.

Current UK recommendations list the contraindications to CSM as the presence of a carotid bruit; a stroke, transient ischaemic attack (TIA) or myocardial infarction in the last 3 months; or a history of a sustained ventricular arrhythmia. Others would only exclude those with recent cerebral ischaemic attacks, and complication rates are no worse with this strategy, with three TIAs occurring in 1719 patients (0.17%) (Puggioni et al, 2002). Complication rates in three other large series varied from 0.07–0.24% episodes of CSM, with most of these being transient and fully reversible; permanent deficits occurred in five out of 24 805 (0.02%) episodes of massage (Munro et al, 1994; Davies and Kenny, 1998; Richardson et al, 2000).

The cardioinhibitory reflex has been shown to have good reproducibility with a significant correlation of maximum RR intervals (r = 0.79), and concordance with a normal or abnormal result in 93% (Brignole et al, 1985). A positive response to CSM also correlates to some extent with spontaneous episodes of syncope, since syncopal events are reduced by pacing (Brignole et al, 1992), and significant pauses were also detected by pacemakers in 53% of patients treated for syncope over a 2-year follow-up period (Menozzi et al, 1993).

MANAGEMENT

No treatment is necessary in asymptomatic subjects. Earlier intervention is being considered for those with symptoms to prevent falls and significant injuries, although long-term mortality in these individuals is unaffected. In the first instance, CSM should be repeated after stopping any identified culprit medication. If persistent, syncope resulting from CICSH can be successfully treated by dual chamber pacing in at least 80% of cases, although some patients will continue to experience dizziness or presyncope (Brignole et al, 1992). Dual chamber implants improve symptoms and prevent hypotension better than single chamber implants (McIntosh et al, 1997); a rate drop response algorithm might also improve efficacy. Questionnaire follow-up of 40 patients who underwent pacing for CICSH found a marked overall improvement with pacing, although there were persistent severe symptoms in 16% and persistent minor symptoms in 40% (Crilley et al, 1997).

Vasodepressor CSH is more difficult to treat effectively. Fludrocortisone reduces the BP responses to CSM, although its use is limited by long-term side effects in the elderly. The α-agonist midodrine is an alternative, and is generally well tolerated, but supine hypertension is sometimes a problem. There is some evidence that selective serotonin re-uptake inhibitors may be of benefit (Dan et al, 1997), possibly by downregulating the sudden loss of sympathetic tone. Surgical denervation of the carotid sinus is generally reserved for CSS which is resistant to other therapy, or in the context of coexisting neck pathology or carotid endarterectomy (Fachinetti et al, 1998).

Treatment of falls attributed to CSH is less well established than that of syncope. The SAFE PACE study (Syncope And Falls in the Elderly - Pacing And Carotid sinus Evaluation; Kenny et al, 2001) found a reduction in falls (mean 4.1 *vs* 9.3; odds ratio = 0.42, confidence interval = 0.23–0.75), as well as 40% fewer syncopal episodes and 70% fewer injurious events in the paced group compared to the controls. This was an unblinded, preliminary study, however, and the results of a multicentre randomized control trial (SAFE PACE 2) are awaited, which will assess the efficacy of dual chamber pacing in CSH and recurrent unexplained falls (Kenny, 1999).

CSH AND DEMENTIA

Neurovascular instability of one form or another (orthostatic hypotension, vasovagal syncope or CSH) is more common in patients with Lewy body dementia (DLB) and Alzheimer's disease. In one study 77% of DLB and 57% of Alzheimer's disease patients had at least one form of neurovascular instability (more than six times the frequency in a normal elderly population), with CSH occurring in 51% of DLB and 44% of Alzheimer's disease patients. CICSH was particularly common in DLB patients (41%) (Ballard et al, 1998).

A second study in DLB and Alzheimer's disease patients (Ballard et al, 2000) found that a drop of more than 30 mmHg in systolic BP in response to CSM or standing was significantly associated with the severity of deep white matter and basal ganglia hyperintensities on magnetic resonance imaging. Patients with CICSH having the largest drops in BP were most at risk. These results are intriguing, and further studies are underway to clarify the relationship between neurovascular instability and dementia. This is also relevant to current practice, since cholinesterase inhibitors might be expected to exaggerate vagally-mediated bradycardias, and are increasingly used in DLB as well as Alzheimer's disease.

CONCLUSION

CSH is a common cause of unexplained falls and syncope in the elderly. It is rare in the healthy population, although it is associated with atherosclerotic disease, and its mechanism is unknown. It is likely to be underdiagnosed, possibly because of failure to test appropriately. Some forms of CSH can be successfully treated by pacing, although

others are less amenable to current therapies. CSH seems to be more common in older patients with dementia, although the implications of this are not yet clear. A lot remains to be learned about the pathophysiology, significance and most effective methods of treatment of this condition. **HM**

Conflict of interest: none.

Bacon M, Grunstein JA (2000) A diagnostic service for eliciting carotid sinus hypersensitivity and vasovagal symptoms in a district general hospital. *Age Ageing* **29:** 501–4

Ballard C, Shaw F, McKeith I, Kenny R (1998) High prevalence of neurovascular instability in neurodegenerative dementias. *Neurology* **51:** 1760–2

Ballard C, O'Brien J, Barber B, Scheltens P, Shaw F, McKeith I, Kenny RA (2000) Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. *Ann N Y Acad Sci* **903:** 442–5

Blanc JJ, L'Heveder G, Mansourati J, Tea SH, Guillo P, Mabin D (1997) Assessment of a newly recognized association. Carotid sinus hypersensitivity and denervation of sternocleidomastoid muscles. *Circulation* **95**(11): 2548–51

Brignole M, Gigli G, Altomonte F et al (1985) Cardioinhibitory reflex provoked by stimulation of carotid sinus in normal subjects and those with cardiovascular disease [Italian]. *G Ital Cardiol* **15:** 514–9

Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G (1992) Long-term outcome of paced and nonpaced patients with severe carotid sinus syndrome. *Am J Cardiol* **69:** 1039–43

Brignole M, Alboni P, Benditt D et al (2001) Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* **22:** 1256–306

Cole CR, Zuckerman J, Levine BD (2001) Carotid sinus 'irritability' rather than hypersensitivity: a new name for an old syndrome? *Clin Auton Res* **11**(2):109–13

Crilley JG, Herd B, Khurana CS et al (1997) Permanent cardiac pacing in elderly patients with recurrent falls, dizziness and syncope, and a hypersensitive cardioinhibitory reflex. *Postgrad Med J* **73:** 415–8

Dan D, Grubb BP, Mouhaffel AH, Kosinski DJ (1997) Use of serotonin re-uptake inhibitors as primary therapy for carotid sinus hypersensitivity. *Pacing Clin Electrophysiol* **20:** 1633–5

Davies AJ, Kenny RA (1996) Falls presenting to the accident and emergency department: types of presentation and risk factor profile. *Age Ageing* **25:** 362–6

Davies AJ, Kenny RA (1998) Frequency of neurologic complications following carotid sinus massage. *Am J Cardiol* **81:** 1256–7

Davies AJ, Steen N, Kenny RA (2001) Carotid sinus hypersensitivity is common in older patients presenting to an accident and emergency department with unexplained falls. *Age Ageing* **30:** 289–93

Dey AB, Stout NR, Kenny RA (1997) Cardiovascular syncope is the most common cause of drop attacks in the elderly. *Pacing Clin Electrophysiol* **20:** 818–9

Eltrafi A, King D, Silas JH, Currie P, Lye M (2000) Role of carotid sinus syndrome and neurocardiogenic syncope in recurrent syncope and falls in patients referred to an outpatient clinic in a district general hospital. *Postgrad Med J* **76:** 405–8

Fachinetti P, Bellocchi S, Dorizzi A, Forgione FN (1998) Carotid Sinus Syndrome: a review of the literature and our experience using carotid sinus denervation. *J Neurosurg Sci* **42**(4): 189–93

Gaggioli G, Brignole M, Menozzi C et al (1995) Reappraisal of the vasodepressor reflex in carotid sinus syndrome. *Am J Cardiol* **75:** 518–21

Jeffreys M, Wood DA, Lampe F, Walker F, Dewhurst G (1996) The heart rate response to carotid artery massage in a sample of healthy elderly people. *Pacing Clin Electrophysiol* **19:** 1488–92

Kallikazaros I, Stratos C, Tsioufis C, Stefanadis C, Sideris A, Sideris S, Toutouzas P (1997) Carotid sinus hypersensitivity in patients undergoing coronary arteriography: relation with the severity of carotid atherosclerosis and the extent of coronary artery disease. *J Cardiovasc Electrophysiol* **8:** 1218–28

Kenny RA (1999) SAFE PACE 2: Syncope and Falls in the Elderly–Pacing and Carotid Sinus Evaluation: a randomized controlled trial of cardiac pacing in older patients with falls and carotid sinus hypersensitivity. *Europace* **1**(1): 69–72

Kenny RA, Richardson DA, Steen N, Bexton RS, Shaw FE, Bond J (2001) Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J Am Coll Cardiol* **38:** 1491–6

Leftheriotis G, Dupuis JM, Victor J (2000) Cerebral hemodynamics in carotid sinus syndrome and atrioventricular block. *Am J Cardiol* **86**(5): 504–8

McIntosh SJ, Kenny RA (1994) Carotid sinus syndrome in the elderly. *J R Soc Med* **87**(12): 798–800

McIntosh SJ, Lawson J, Kenny RA (1993) Clinical characteristics of vasodepressor, cardioinhibitory, and mixed carotid sinus syndrome in the elderly. *Am J Med* **95:** 203–8

McIntosh SJ, Lawson J, Kenny RA (1994) Heart rate and blood pressure responses to carotid sinus massage in healthy elderly subjects. *Age Ageing* **23**(1): 57–61

McIntosh SJ, Lawson J, Bexton RS, Gold RG, Tynan MM, Kenny RA (1997) A study comparing VVI and DDI pacing in elderly patients with carotid sinus syndrome. *Heart* **77**(6): 553–7

Menozzi C, Brignole M, Lolli G et al (1993) Follow-up of asystolic episodes in patients with cardioinhibitory, neurally mediated syncope and VVI pacemaker. *Am J Cardiol* **72:** 1152–5

Morillo CA, Camacho ME, Wood MA, Gilligan DM, Ellenbogen KA (1999) Diagnostic utility of mechanical, pharmacological and orthostatic stimulation of the carotid sinus in patients with unexplained syncope. *J Am Coll Cardiol* **34:** 1587–94

Munro NC, McIntosh S, Lawson J, Morley CA, Sutton R, Kenny RA (1994) Incidence of complications after carotid sinus massage in older patients with syncope. *J Am Geriatr Soc* **42**(12): 1248–51

Murphy AL, Rowbotham BJ, Boyle RS, Thew CM, Fardoulys JA, Wilson K (1986) Carotid sinus hypersensitivity in elderly nursing home patients. *Aust N Z J Med* **16:** 24–7

O'Mahony D (1995) Pathophysiology of carotid sinus hypersensitivity in elderly patients. *Lancet* **346:** 950–2

O'Mahony D (2001) Carotid sinus hypersensitivity in old age: clinical syndrome or physical sign? *Age Ageing* **30:** 273–4

Parry SW, O'Shea D, Kenny RA (1998) Demographic and clinical characteristics of patients with carotid sinus hypersensitivity who present with recurrent unexplained falls (abstract). *Heart* **79**(suppl 1): 16

Parry SW, Richardson DA, O'Shea D, Sen B, Kenny RA (2000) Diagnosis of carotid sinus hypersensitivity in older adults: carotid sinus massage in the upright position is essential. *Heart* **83**(1): 22–3

Puggioni E, Guiducci V, Brignole M et al (2002) Results and complications of the carotid sinus massage performed according to the 'method of symptoms'. *Am J Cardiol* **89:** 599–601

Richardson DA, Bexton RS, Shaw FE, Kenny RA (1997) Prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the accident and emergency department with 'unexplained' or 'recurrent' falls. *Pacing Clin Electrophysiol* **20:** 820–3

Richardson DA, Bexton R, Shaw FE, Steen N, Bond J, Kenny RA (2000) Complications of carotid sinus massage – a prospective series of older people. *Age Ageing* **29:** 413–7

Shaw FE, Kenny RA (1997) The overlap between syncope and falls in the elderly. *Postgrad Med J* **73:** 635–9

Ward CR, McIntosh S, Kenny RA (1999) Carotid sinus hypersensitivity - a modifiable risk factor for fractured neck of femur. *Age Ageing* **28:** 127–33

Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP (2000) Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* **36:** 181–4

KEY POINTS

- Carotid sinus hypersensitivity is a common cause of syncope in the elderly.
- It is frequently found in patients with recurrent or unexplained falls.
- The pathological mechanism of carotid sinus hypersensitivity is unknown.
- Many cases of cardioinhibitory or mixed carotid sinus hypersensitivity can be effectively treated with dual chamber pacing.
- Carotid sinus hypersensitivity and other forms of neurovascular instability are common in patients with dementia.