Postural syncope: mechanisms and management

Gautam Vaddadi, Elisabeth Lambert, Susan J Corcoran and Murray D Esler

The only difference between syncope and sudden death is that in one you wake up.[1]

Syncope is a transient and abrupt loss of consciousness and postural tone that is generally followed by rapid recovery without the need for a major intervention. It is due to a transient reduction in cerebral blood flow, is frequently related to posture, and is the most common cause of transient loss of consciousness. Syncope has a lifetime cumulative incidence of 35%[2] and accounts for 1%–2% of all emergency department visits.[3,4] Morbidity, even from "benign" causes of syncope, is profound: 70% of people experiencing recurrent syncope suffer impairment to activities of daily living, 6% suffer fractures, 64% restrict their driving and 39% change employment.[5-7] Recurrent syncope can have a major impact on quality of life, with devastating psychosocial consequences similar to those associated with other chronic diseases.[6,7]

The quote above illustrates a commonly held view that most causes of syncope are potentially lethal and that, once these are excluded, there is no further need for diagnostic evaluation. We intend to dispel this myth.

Syncope can be classified into three categories: cardiac syncope, non-cardiac syncope and syncope of undetermined cause (Box 1). Patients with cardiac syncope have the highest mortality rate and need prompt evaluation. However, the majority of patients fall into the non-cardiac syncope category — the most challenging form of syncope to investigate and manage. Most of these patients have a disorder of postural circulatory control (Box 2), the mechanism of which is poorly understood. The diagnosis and treatment of this patient group is the major focus of our clinical update.

Epidemiology of syncope

Postural syncope has a bimodal distribution in the general population. The first peak, at around 15 years, predominates in girls, with the vast majority of cases being due to vasovagal syncope.[3] In the second peak, at over 60 years, vasovagal syncope, orthostatic hypotension and situational syncope (eg, during micturition or after meals) are predominant, but clinical presentations are often diverse, posing a diagnostic challenge. Cardiac syncope remains a major culprit in this age group and must be excluded.

Does my patient have cardiac syncope?

The important question of whether a patient has cardiac syncope must always be answered and, in the majority of cases, this can be done with a thorough history and electrocardiography. In patients under 40 years of age with no known cardiac disease, no symptoms suggestive of cardiac disease, no family history of sudden death at a young age, no experience of syncope during exercise, and a completely normal electrocardiogram (ECG), the probability of cardiac syncope is extremely low.[8,9] Patients over 60 years of age tend to have more atypical presentations and are more likely to have occult heart disease.[10] Strong consideration should be given to more aggressive investigations in this age group. It is worth noting that about 50% of patients with syncope and heart disease have a non-cardiac cause of syncope.[9]

ABSTRACT

- Postural syncope is a transient loss of consciousness secondary to a reduction in cerebral blood flow and is typically precipitated by standing. It is the commonest cause of recurrent transient loss of consciousness.
- Recurrent unexplained postural syncope is most often due to one of the five disorders of circulatory control: vasovagal syncope, postural tachycardia syndrome, chronic autonomic failure, initial orthostatic hypotension, or persistently low supine systolic blood pressure.
- Failure to identify the underlying cause of postural syncope can result in ongoing morbidity, impaired quality of life and high health care costs.
- With a detailed history, examination, blood pressure assessment and electrocardiography, most disorders of circulatory control can be diagnosed.
- In difficult cases, analysis of sympathetic nervous system and circulatory responses during head-up tilting can aid diagnosis.
- Treatment is challenging and compounded by a lack of evidence. Most patients can be managed in an outpatient setting, and hospital admission or emergency department assessment is rarely warranted.

MJA 2007; 187: 299–304

Postural syncope: a practical differential

We recognise five clinical phenotypes of postural syncope:

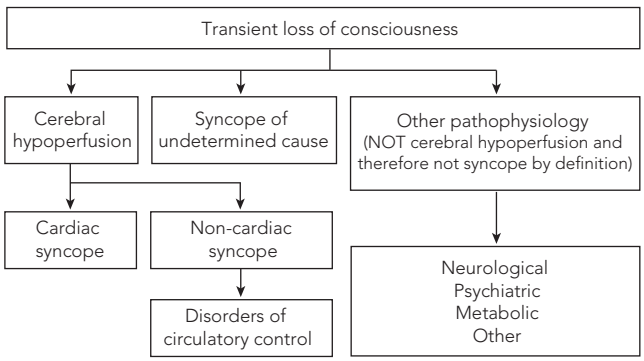
- Vasovagal syncope;
- Postural tachycardia syndrome (POTS);
- Autonomic failure;
- Persistently low supine systolic blood pressure; and
- Initial orthostatic hypotension.

Disorders of circulatory control are frequently disabling and difficult to treat. Recognising the various subgroups is helpful for matching treatment to the patient's specific disorder.

Vasovagal syncope

Vasovagal syncope is a common and clinically challenging disorder widely recognised in the lay community as a faint or "blackout". It is characterised physiologically by sudden hypotension and varying degrees of bradycardia (Box 3). The mechanism remains a matter of controversy. Excess venous pooling and abnormal vasodilation while standing, thus reducing venous return to the heart, is the most commonly accepted explanation. Vasovagal syncope is classically provoked by prolonged standing or sitting. However, other stimuli may be operative in "situational" syncope (eg, in response to venepuncture, pain or emotion). Most patients can be diagnosed by careful history taking,[12] examination and electrocardiography. Symptoms consistent with vasovagal syncope and most predictive of the diagnosis include visual blurring, sweating, nausea, warmth, light-headedness and fatigue.[10,13] Palpitations are also a common feature of the prodrome. A third of

1 Physiological classification of transient loss of consciousness



patients have no warning symptoms.[14] Young patients tend to present with typical features, while older patients more commonly have an atypical presentation. A brief convulsion is quite common, and mild seizure activity due to cerebral hypoperfusion may occur in up to two-thirds of patients.[15] It has been estimated that about 20% of patients undergoing long-term follow-up in hospital epilepsy clinics are misdiagnosed — their transient loss of consciousness being due to syncope rather than epileptic seizure.[15] Tilt-table testing may be needed to confirm a suspected diagnosis of vasovagal syncope. The key is in correlating symptoms on the tilt table with those in the real world.

Postural tachycardia syndrome

POTS is a perplexing condition that has only been recently identified in the medical literature.[16] The disorder, which most commonly affects young women, is characterised by fatigue, palpitations, exercise intolerance, light-headedness, visual blurring, chest pain, inability to concentrate and episodic syncope or presyncope (ie, the sensation that fainting may occur without actual syncope).[16] Anxiety and depression are frequent comorbidities. A hallmark of this condition is that, during syncope, blood pressure is maintained or only falls minimally, while heart rate increases dramatically (Box 3). An increase in heart rate of at least 30 beats/min after 10 minutes of standing, or a heart rate of > 120 beats/min with prolonged standing, is suggestive of the diagnosis. The onset of POTS is often abrupt and, in about 50% of cases, follows a minor infection. POTS appears to be a manifestation of sympathetic nervous system hyperactivity[17] during standing and is the subject of ongoing research by our group.

Chronic autonomic failure

Chronic autonomic failure is an uncommon but important group of conditions that cause orthostatic intolerance. Syndromes of chronic autonomic failure include pure autonomic failure (PAF) (degeneration of sympathetic nerves), multiple system atrophy (MSA) (degeneration of the central nervous system), diabetic autonomic neuropathy and Parkinsonism with autonomic failure. Autonomic failure clinically manifests as progressive fatigue and orthostatic intolerance. Other features include erectile dysfunction, urinary retention, loss of sweating, pain in the neck and shoulders, abdominal discomfort and diarrhoea. Supine hypertension is common, with a substantial postural drop in blood pressure upon standing and absent reflex tachycardia. The onset of PAF is typically in the fifth or sixth decade of life, and men are affected twice as often as women. In PAF there is degeneration of the sympathetic nerves, including those in the heart, producing near-total sympathetic denervation.[18]

MSA, on the other hand, is a central nervous system deterioration. Clinically, MSA has cerebellar signs, Parkinsonian signs or mixed signs. It is a progressive disorder that usually results in death 7–10 years after onset. This is in stark contrast to PAF, in which long-term survival is the norm. Differentiating MSA with Parkinsonian signs from Parkinson's disease can be difficult. However, Parkinson's disease tends to respond more favourably to levodopa treatment and shows patchy sympathetic denervation on myocardial scintigraphy using ^{123}I-metaiodo-benzylguanidine.[19]

Persistently low supine systolic blood pressure

Persistently low supine systolic blood pressure is not emphasised in the medical accounts of postural syncope but was recognised in a large syncope trial.[4] In general, the medical view is that low "normal" blood pressure is healthy, protecting against the development of cardiovascular disease. However, some patients with frequent presyncope or syncope have systolic blood pressures of 85–100 mmHg on a "good day". Systolic blood pressure can easily fall to 80 mmHg as a result of minimal dehydration or drinking a small amount of alcohol. In clinical practice we find this to be a common cause of syncope — patients frequently complain of ongoing fatigue and may also have a prominent tachycardia during orthostasis, which can make differentiation from POTS difficult. Our preliminary data suggest that these patients have low resting sympathetic activity as the basis of their low blood pressure and are prone to vasovagal events.

Initial orthostatic hypotension

Initial orthostatic hypotension is a common cause of presyncope and syncope immediately (5–10 s) after standing up. A clear

2 Aetiology of syncope and transient loss of consciousness

Syncope

Low cardiac output/pump failure:

- Arrhythmias
- Haemodynamic obstruction
- Severe heart failure

Disorders of circulatory control:

- Vasovagal syncope
- Postural tachycardia syndrome
- Autonomic failure
- Persistently low supine systolic blood pressure
- Initial orthostatic hypotension
- Other disorders (relating to drugs, hypovolaemia, anaemia)

Transient loss of consciousness

Neurological:

- Generalised seizure
- Stroke/transient ischaemic attacks

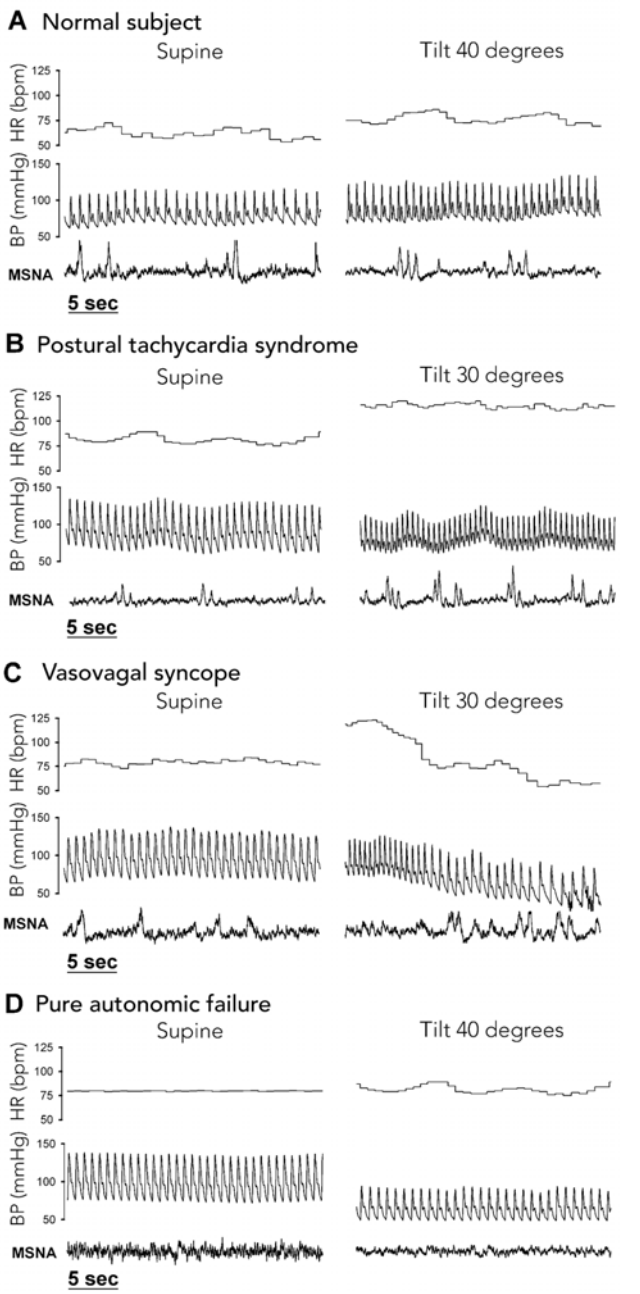
Psychiatric:

- Pseudoseizures
- Factitious conditions

Metabolic:

- Hypoglycaemia ◆

3 Diagnostic profiles in postural syncope during invasive head-up tilt testing*



BP = blood pressure. HR = heart rate. MSNA = muscle sympathetic nerve activity.

* Invasive tilt testing involves cardiac monitoring and placement of an arterial line for blood pressure monitoring. Patients with postural tachycardia syndrome (Figure B) show an excessive rise in heart rate with tilt and increased sympathetic nerve firing (MSNA). Figure C shows the classic features of vasovagal syncope — a rapid fall in blood pressure, and a fall in heart rate (a variable feature). We have preliminary data, as shown in this example, that sympathetic nerve firing persists during a faint. This contrasts with the view that cessation of sympathetic nerve activity underlies the development of hypotension and bradycardia in vasovagal syncope.[11] Figure D shows a classic case of pure autonomic failure, characterised by fixed heart rate and a progressive fall in blood pressure with tilt. There is virtually no detectable sympathetic nerve activity, which is consistent with post-ganglionic sympathetic degeneration. ◆

history of the immediacy of symptoms is the cornerstone of diagnosis. It occurs most often after prolonged recumbency or after squatting. Initial orthostatic hypotension is defined physiologically as an exaggerated transient fall in blood pressure of > 40 mmHg (systolic) and/or 20 mmHg (diastolic) within 15 seconds of standing up.[20] This contrasts with typical orthostatic hypotension that occurs within 3 minutes of standing and may be delayed for up to 10 minutes after standing. Continuous beat-to-beat blood pressure monitoring is required for a physiological diagnosis, but this diagnostic method has a high false-negative rate.[20] Initial orthostatic hypotension is common in young adults,[21] with an incidence of 3.6%.[2]

Diagnostic evaluation of syncope and transient loss of consciousness

Various guidelines have been published for evaluating syncope.[8,9,22,23] Our preferred diagnostic algorithm is shown in Box 4. The recent consensus statement of the American Heart Association and the American College of Cardiology Foundation[23] is primarily useful for providing a diagnostic path for excluding cardiac causes of syncope associated with sudden death. It does not address diagnosis and management of postural syncope and is neglectful of the clinical importance of disorders of circulatory control.[24]

History, physical exam and blood pressure

Taking a detailed history is the most powerful tool for diagnosing syncope. Measuring supine and standing blood pressures is crucial: typical orthostatic hypotension is characterised by a fall in blood pressure of > 20 mmHg (systolic) and/or 10 mmHg (diastolic) after 3 minutes of standing. It is also important to test blood pressure after prolonged standing (10 minutes), as delayed hypotension is common.[25] The absence of reflex tachycardia on standing suggests autonomic failure.

Blood investigations

Routine blood investigations should be done only if clinically indicated. In general, the yield in syncope patients is low.

Cardiovascular investigations

For cardiovascular investigations, a 12-lead ECG is essential (Box 5). It may identify arrhythmias or preconditions for arrhythmia (eg, a long QT interval) or indicate underlying ischaemic heart disease. An abnormal ECG has prognostic value. Yet despite its obvious clinical importance, only 59% of patients with syncope presenting to US emergency departments in 2004 were given an ECG at presentation.[26]

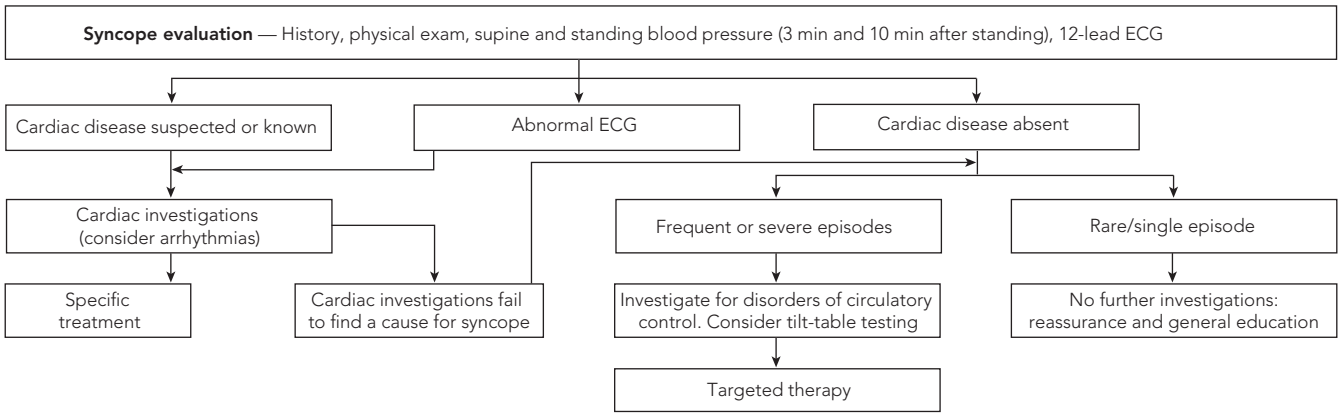
Twenty-four-hour blood pressure monitoring, coupled with diary recording by the patient, is extremely useful — for example, it may demonstrate persistently low blood pressure. A relatively fixed heart rate is an important clue to autonomic failure.

Cardiac rhythm monitoring is probably overused in patients with postural syncope, which is infrequently caused by cardiac arrhythmias.

Twenty-four-hour Holter monitoring has a sensitivity of only 10% in unexplained syncope, and should only be used in patients who experience daily events.

External loop recorders, which may be worn for 1 month, require patient activation when symptoms occur. They increase diagnostic yields to 25%,[27] but problems with dermal electrode

4 Evaluation of syncope*



ECG = electrocardiogram. * Adapted from European Society of Cardiology recommendations.[9] ◆

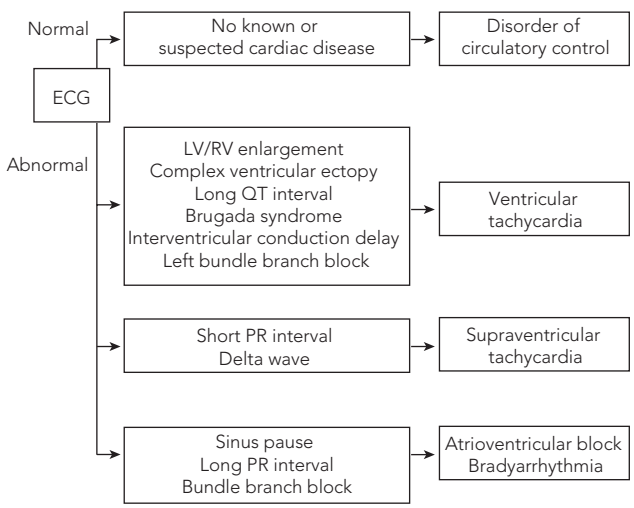
tolerance and forgetting to trigger recording at the onset of symptoms limit their effectiveness.[28]

Implantable loop recorders are inserted under the skin of the chest wall, requiring only local anaesthetic. A recent study of patients with at least three severe episodes of neurally mediated syncope (orthostatic hypotension excluded) demonstrated the value of early loop recorder implantation and subsequent guided therapy.[29]

Prolonged cardiac monitoring should only be employed when "symptom–rhythm" correlation is of clinical value (particularly when arrhythmia is thought to be a likely culprit).

Echocardiography, although rarely diagnostic, is important for the exclusion of structural heart disease if clinically indicated — for example, in cases of impaired left ventricular function, abnormal right ventricular function suggestive of arrhythmogenic right ventricular dysplasia, and hypertrophic cardiomyopathy, a common cause of sudden death in the young.

5 Role of the 12-lead electrocardiogram (ECG) in syncope



LV = left ventricle. RV = right ventricle. ◆

Electrophysiological testing in cases of unexplained syncope remains controversial and is limited to select patients, usually those with structural heart disease.[8]

Tilt-table testing is a widely used method for evaluating postural syncope. It is predominantly used to diagnose vasovagal syncope. It may also be used to train patients to recognise the vasovagal prodrome — some patients can then abort a vasovagal event using counter-manoeuvres such as leg-crossing.[30] The diagnosis should only be made if the event during tilt-table testing reproduces the patient's real-world event. The use of tilt-table testing remains controversial:[31] publications report a wide range of sensitivity and specificity, with lack of specificity being a particular problem. The use of provocation testing with isoprenaline is of questionable merit[32] — it is possible to induce vasovagal syncope in almost anyone with an adequately aggressive tilt test. In a patient with a normal ECG, structurally normal heart, no neurological features, normal supine blood pressure and a negative tilt test, vasovagal syncope is still the likely diagnosis.

Neurological investigations should only be performed when clinically indicated and do not form part of the routine investigation of syncope.

Research investigations: invasive tilt testing

At the Baker Heart Research Institute we perform invasive tilt testing. This involves cardiac monitoring and placement of an arterial line for blood pressure monitoring. We routinely determine whole-body spillover of noradrenaline to plasma, as a neurochemical measure of sympathetic nervous system activity.[33] Microneurography, measuring sympathetic nerve firing in fibres passing to skeletal muscle blood vessels, is performed using a fine tungsten electrode placed in the peroneal nerve.[34] The response to orthostasis measured using these two techniques provides important complementary diagnostic information for many causes of unexplained postural syncope (Box 3).

Treatment

Therapy for disorders of circulatory control (Box 6) is based on limited randomised trial data. Evidence for many aspects of treatment is restricted to small observational series and case reports. Our treatment recommendations are based on limited

6 Therapy for disorders of circulatory control

Therapeutic intervention	Comments
Fluids: water drinking	Proven to improve orthostatic tolerance
Elastic support stockings	Thigh-length stockings useful and safe, but often uncomfortable. Poor compliance, especially in hot weather
Salt	"Liberal" use with food suggested. Particularly useful in autonomic failure and low blood pressure
Leg-muscle tensing and physical counter-manoeuvres	Evidence for efficacy in vasovagal syncope
Fludrocortisone	Hypokalaemia and excess fluid retention can be a problem, but drug has proven efficacy in autonomic failure
Pressor agents: midodrine, dihydroergotamine	Evidence supports use in autonomic failure. Some evidence for use in selected patients with vasovagal syncope. May be helpful in other disorders of circulatory control
Erythropoietin	Evidence for use in autonomic failure
Other therapies (eg, SSRIs, SNRIs,* methylphenidate)	Little or no data. Empirical use only

SNRI = serotonin–norepinephrine reuptake inhibitor. SSRI = selective serotonin reuptake inhibitor. * Reboxetine, venlafaxine. ◆

available data, referenced where appropriate, but based also on our clinical experience.

1. Vasovagal syncope

Treatment centres on education, awareness of precipitants, and staying safe. Avoiding dehydration, carrying a water bottle (with the target of keeping urine clear), and increasing salt intake are beneficial. Lower-body muscle tensing[35] and physical manoeuvres such as leg-crossing[30] are effective and evidence-based.

Treatment with fludrocortisone, a highly selective mineralocorticoid, may reduce the frequency of attacks by expanding intravascular volume through salt and water retention. The drug is the subject of an ongoing clinical trial.[36] Pressor agents such as midodrine may be effective: limited randomised trial data support therapy with midodrine for selected patients (under the Therapeutic Goods Administration Special Access Scheme).[37] Beta-blockers have long been advocated to treat vasovagal syncope, but a recently published syncope prevention trial investigating metoprolol versus placebo in 206 patients showed no benefit.[38] Reboxetine, a noradrenaline transporter inhibitor used for depression, may be helpful and has been shown to prolong the time taken to faint during head-up tilt testing in healthy subjects.[39]

Cardiac pacing has been studied in several clinical trials, with mixed results. Overall, the evidence does not support pacemaker insertion as first-line therapy — for example, the second vasovagal pacemaker study, a randomised, double-blinded trial of 100 patients with severe vasovagal syncope, failed to show a reduction in vasovagal events.[40]

2. Postural tachycardia syndrome

Treatment of POTS is challenging. Education and psychosocial support are critical; adequate hydration[41] and increased salt intake may help. Mineralocorticoids, such as fludrocortisone in low doses,[42] or natural liquorice may reduce the frequency of events. Pressor agents have mixed success and there is great variability in patients' response to treatment.[41,43] Acetylcholinesterase inhibitors reduce tachycardia and appear to benefit some patients.[44] Beta-blockers may help reduce palpitations but rarely help syncope, which may get worse. Selective serotonin reuptake inhibitors may be beneficial.[5] Anecdotally, calcium channel blockers in low doses have proved useful, presumably by reducing cerebral vasospasm, which is thought to be the basis of postural syncope occurring in the absence of postural hypotension.

3. Chronic autonomic failure

Therapy for orthostatic intolerance includes fluids, salt intake, fludrocortisone and pressor agents. Direct-acting α-adrenergic agonists such as dihydroergotamine[45] or midodrine[46] are most useful in PAF, but are also of use in MSA. Erythropoietin improves orthostatic tolerance in patients with autonomic failure and may be considered when other agents are ineffective.[47] Supine hypertension is common and can be severe, often requiring bedtime dosing with short-acting antihypertensives such as hydralazine.[48]

4. Persistently low supine systolic blood pressure

Patients with persistently low supine systolic blood pressure are the subject of ongoing research. They respond well to education, increased fluid intake and liberal use of salt. Fludrocortisone or natural liquorice tablets are also effective. Pressor agents are occasionally needed.

5. Initial orthostatic hypotension

Treatment revolves around education and limiting precipitants. No therapy has been studied systematically, but it is sensible to recommend getting up slowly and sitting for a short time before standing, and it is logical to encourage fluid and salt intake. Immediate bending over to lower the head after standing, followed by a gradual return to normal posture, may reduce cerebral hypoperfusion. Wieling et al advocate the tensing of leg muscles immediately after standing to abort hypotensive events.[20]

Conclusion

Syncope is a common and challenging clinical problem and a frequent cause of disability. Patients with underlying heart disease are at particular risk of sudden death and require expeditious investigation. Cardiovascular causes of syncope are frequently misdiagnosed as epilepsy. Unexplained postural syncope is most commonly due to a disorder of circulatory control and is a frequent cause of visits to general practitioners, cardiologists and neurologists. These disorders, which result in a substantial psychosocial burden, must be appropriately investigated and managed. Diagnostic testing should be focused and limited. No universal approach can be applied, and unnecessary hospital admissions and emergency department presentations should be avoided. The vast majority of cases can be managed in an outpatient setting with collaborative expert input as needed.

Acknowledgements

We thank the National Health and Medical Research Council (NHMRC) and National Heart Foundation for continued funding of our research. Gautam Vaddadi is the recipient of a cofunded Postgraduate Research Scholarship, Elisabeth Lambert is the recipient of an NHMRC Career Development Award, and Murray Esler is a Senior Principal Research Fellow of the NHMRC.

Competing interests

None identified.

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(Received 9 Jan 2007, accepted 29 May 2007) ❑