To stand on one's own legs

Christopher J Mathias

ABSTRACT – A fundamental human expectation is to stand upright. This exposes the cardiovascular system to gravitational forces, with a fall in pressure above heart level exposing organs such as the brain to impaired perfusion if adequate adaptive mechanisms are not activated. The autonomic nervous system plays an important role in the initial response to standing upright, and can be affected by several disorders, some rare, some common. Autonomic failure can result in orthostatic hypotension with hypoperfusion of vital organs, causing a variety of symptoms including syncope. Thus, it is important to recognise orthostatic hypotension, determine its aetiology, evaluate and treat it. Intermittent autonomic dysfunction (such as neurally mediated syncope without chronic neurogenic failure) also results in falls and syncope; various forms include the 'common faint' (vasovagal syncope) and carotid sinus hypersensitivity (especially in the elderly). Orthostatic intolerance without orthostatic hypotension is increasingly recognised as due to an autonomic disturbance. New techniques are helping to unravel the functional anatomy of cerebral autonomic centres and their pathways in the causation of orthostatic intolerance.

Key words: autonomic failure, baroreceptors, carotid sinus hypersensitivity, CPD, hypotension, orthostatic post-prandial hypotension, sympathetic activity, syncope, tachycardia, vasovagal syncope

Introduction

To stand uppon our owne feete, to feele with our owne handes, and to see with our owne eyes[1]

One of the fundamental expectations we hold dear is to stand upright. However, the transformation from quadrupeds into bipeds, assuredly for beneficial purposes, exposed us to gravitational forces first observed by Sir Isaac Newton. These forces are of particular relevance to the functioning of the cardiovascular system in humans. Standing results in translocation of 500–700 ml of blood from central compartments to the lower limbs, causing marked pressure differentials, with a substantial rise in pressure below, and a fall in pressure above, heart level[2] (Fig 1). Without adequate adaptive mechanisms, gravitational stresses on standing upright can expose organs, especially those above the level of the heart, to impaired perfusion and malfunction.

Comparative biology

Biped humans are not alone in their susceptibility to gravitational stress. Studies in comparative biology exemplify diversity of adaptation, even in the same species, to cope with differences in morphology, activities and terrain. Sea (aquatic) snakes are relatively unaffected by gravity and can cope with vertical pressure gradients, despite a low level of blood pressure (15–39 mmHg), as the density of their blood is similar to that of salt water[3]. Furthermore, they can adjust their lung volume so as to be effectively weightless and thus similar to objects in outer space. They differ from the often larger land (terrestrial) snakes that have a higher level of blood pressure. Land snakes are able to utilise muscle activation (with body coiling and tail movements) to maintain cranial pressure, especially when raising the head to exhibit threatening behaviour. In contrast, tree (arboreal) snakes can withstand considerably greater gravitational forces. They have the highest level of blood pressure (50–90 mmHg), in part due to increased vascular muscle tone. Thus, they differ markedly from sea snakes that are vulnerable to blood vessel collapse when bereft of the support of surrounding water. Tree snakes are often slimmer, with a thinner tail to prevent pooling, and have the heart closer to the head, thus aiding cerebral perfusion.

In other animals, different mechanisms are operative to maintain vital organ perfusion, as in the giraffe whose head is 20 feet above heart level. These mechanisms include:

- an elevated systemic blood pressure (280/180 mmHg, almost twice that of humans) achieved by a large and muscular heart
- a series of one-way valves in the jugular vein to prevent backflow
- thick-walled arteries that in the lower limbs lie beneath an extremely tight skin that prevents pooling.

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Fetal giraffes are in a near gravitational free state in the uterus and have thin leg blood vessels that rapidly thicken soon after birth.

Baroreceptor reflexes

The ability of humans to overcome the initial effects of gravitational stress on the cardiovascular system largely depends on a highly developed autonomic nervous system that includes an exquisitely sensitive baroreceptor reflex to maintain suitable levels of blood pressure. Afferent pathways in the carotid sinus, heart and major cardiopulmonary vessels relay information to the brain through the vagus and glossopharyngeal nerves. There are numerous cerebral connections. The efferent pathways comprise the sympathetic outflow to blood vessels and heart, and the parasympathetic (vagus) nerves to the heart. These pathways exert beat-by-beat control of blood pressure, a vital component being vasoconstriction induced by increased sympathetic activity, as elegantly demonstrated in humans by sympathetic microneurography[4] (Fig 2).

The autonomic nervous system innervates every organ in the body and is involved in control of organ function and also of integrative systems that regulate body temperature and help maintain fluid and metabolic balance. Rapid and responsive autonomic integration is necessary to ensure adequate perfusion of organs and to adapt to specific needs when there are varying demands in vascular regions, such as in the splanchnic bed after food ingestion and in contracting muscles during exercise. The autonomic nervous system accomplishes this by a complex system of multiple synapses and numerous transmitters in the brain, spinal cord and periphery. This provides immense flexibility and the capability to respond rapidly. The downside, however, is that many sites may be affected by disease or dysfunction (Table 1)[5], with failure to adapt to gravitational stress causing orthostatic (postural) hypotension.

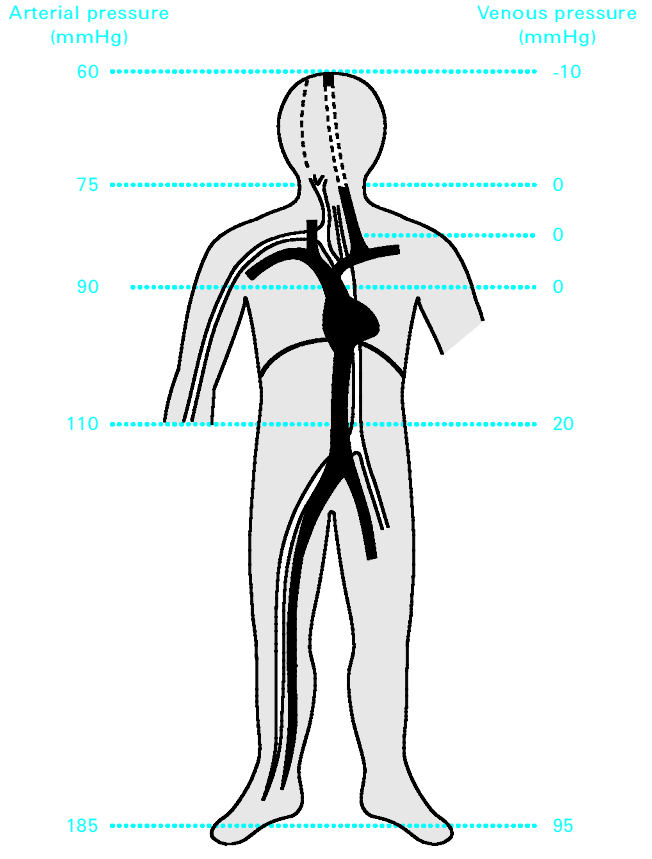

Fig 1. Effects of gravity on arterial and venous blood pressures in an erect, motionless man. In the lower part of the body arterial and venous pressures are increased; in the upper part they are decreased[2].

Orthostatic hypotension

Definition and evaluation

Orthostatic hypotension is arbitrarily defined as a fall in blood pressure of over 20 mmHg systolic or 10 mmHg diastolic on standing upright or following three minutes of head-up tilt to 60°(Fig 3)[6]. A variety of factors, neurogenic (Table 1) and non-neurogenic (Table 2), may cause or contribute to orthostatic hypotension. It is important that a detailed history and examination with relevant testing is performed to determine the precise cause. If due to neurogenic failure, components of the baroreceptor reflex that are impaired must be ascertained. Autonomic screening tests determine whether there is sympathetic vasoconstrictor and parasympathetic cardiac failure[7]. A variety of additional tests may be needed to ascertain the site of the lesion and the functional deficit.

Prevalence

The true incidence and prevalence of orthostatic hypotension are not known, for reasons that include the methods for detection and the groups studied. In clinical practice, blood pressure is rarely measured supine and standing, unless features favour orthostatic hypotension. A number of symptoms are caused by a postural fall in blood pressure[8] (Table 3). These can differ between individuals, with considerable variation even in the same subject. Many factors in daily life (Table 4) are now recognised to influence orthostatic hypotension (Fig 4 (a) and (b)). A prominent feature of orthostatic hypotension is syncope (loss of consciousness, fainting), but this may not occur despite a severe fall in pressure, especially in chronic disorders. The reasons include improved cerebrovascular autoregulation. The prevalence of orthostatic hypotension increases with age: using standard criteria, it was recorded in 24% of subjects over 65, with a fall of over 30 mmHg and over 40 mmHg systolic in 10% and 5%, respectively[12]. Duration of disease, drug therapy and coincidental disease also influence incidence: for example, in Parkinson's disease the wide range reported (from rare to 58%)[13,14] probably reflects the varying composition of the groups studied.

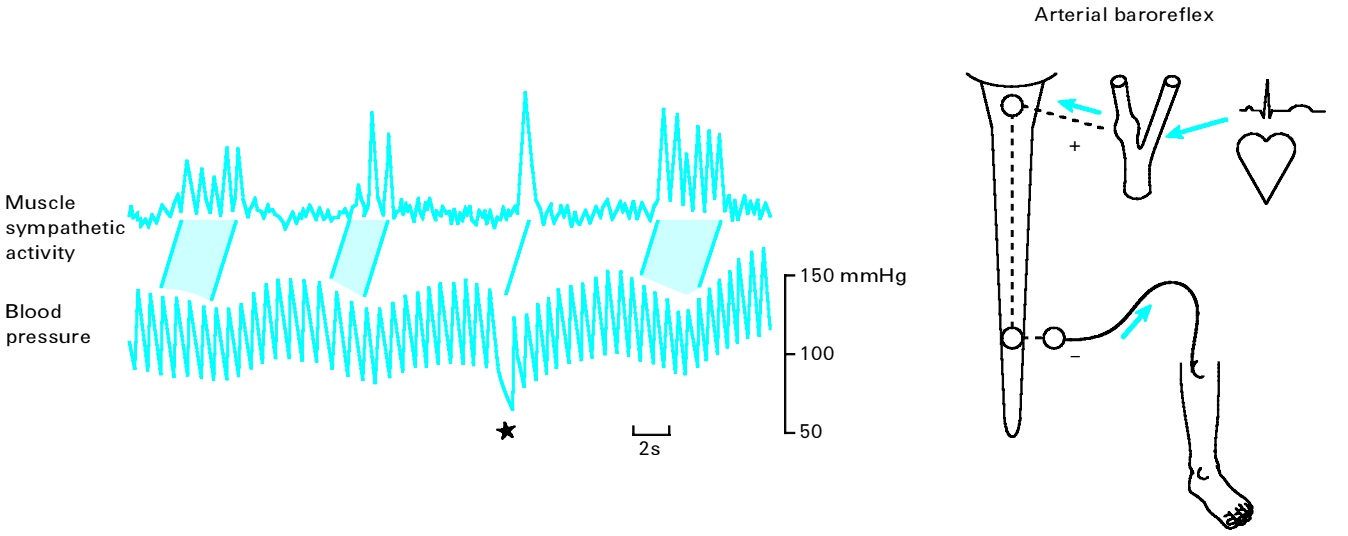

Fig 2. Relationship between spontaneous fluctuations of blood pressure and muscle nerve sympathetic activity (left) recorded in the right peroneal nerve. The arterial baroreceptor reflex is outlined on the **right** to indicate afferent activity from blood vessels and heart that influence sympathetic efferent activity. This accounts for the pulse synchrony of nerve activity and the inverse relationship to blood pressure fluctuations (* = diastolic blood pressure fall due to sudden AV block; stippling = corresponding sequences of bursts and heart beats) (from Ref 4).

Treatment

The modern treatment of orthostatic hypotension should be centred around evaluating the underlying pathophysiological mechanisms and, where possible, rectifying the primary cause. Treatment is more likely to be corrective in non-neurogenic forms. Neurogenic failure is usually irreversible and more difficult to treat, and often needs a combination of non-pharmacological and pharmacological measures[15] (Table 5). Factors in daily life that influence orthostatic hypotension need to be considered on an individual basis, and should involve educating the patient.

Drug treatment. Drugs usually are needed in moderate to severe orthostatic hypotension. These include:

- low-dose fludrocortisone (to increase salt and fluid retention)
- a sympathomimetic to replace the deficient neurotransmitter, noradrenaline.

Sympathomimetics are usually a poor substitute for replacing endogenous neurotransmitters. They cannot mimic the fine control exerted by sympathetic nerves, with rapid con-

Table 1. Examples of autonomic causes of orthostatic hypotension and orthostatic intolerance (adapted from Ref 5).

Primary:	
Acute/subacute dysautonomias	Pure pandysautonomia Pandysautonomia with neurological features
Chronic autonomic failure syndromes	Pure autonomic failure Multiple system atrophy (Shy-Drager syndrome) Autonomic failure with Parkinson's disease
Secondary:	
Congenital	Nerve growth factor deficiency
Hereditary	Autosomal dominant trait Familial amyloid neuropathy
Autosomal recessive trait	Familial dysautonomia (Riley-Day syndrome) Dopamine beta-hydroxylase deficiency
Metabolic diseases	Diabetes mellitus Chronic renal failure Chronic liver disease Alcohol-induced
Inflammatory	Guillain-Barré syndrome Transverse myelitis
Infections	Bacterial: tetanus Viral: HIV infection
Neoplasia	Brain tumours, especially of 3rd ventricle or posterior fossa Paraneoplastic, to include adenocarcinomas of lung and pancreas
Surgery	Vagotomy & drainage procedures ('dumping syndrome')
Trauma	Cervical & high thoracic spinal cord transection
Drugs	By their direct effects By causing a neuropathy
Neurally-mediated syncope	Situational syncope Vasovagal syncope Carotid sinus hypersensitivity
Postural tachycardia syndrome	

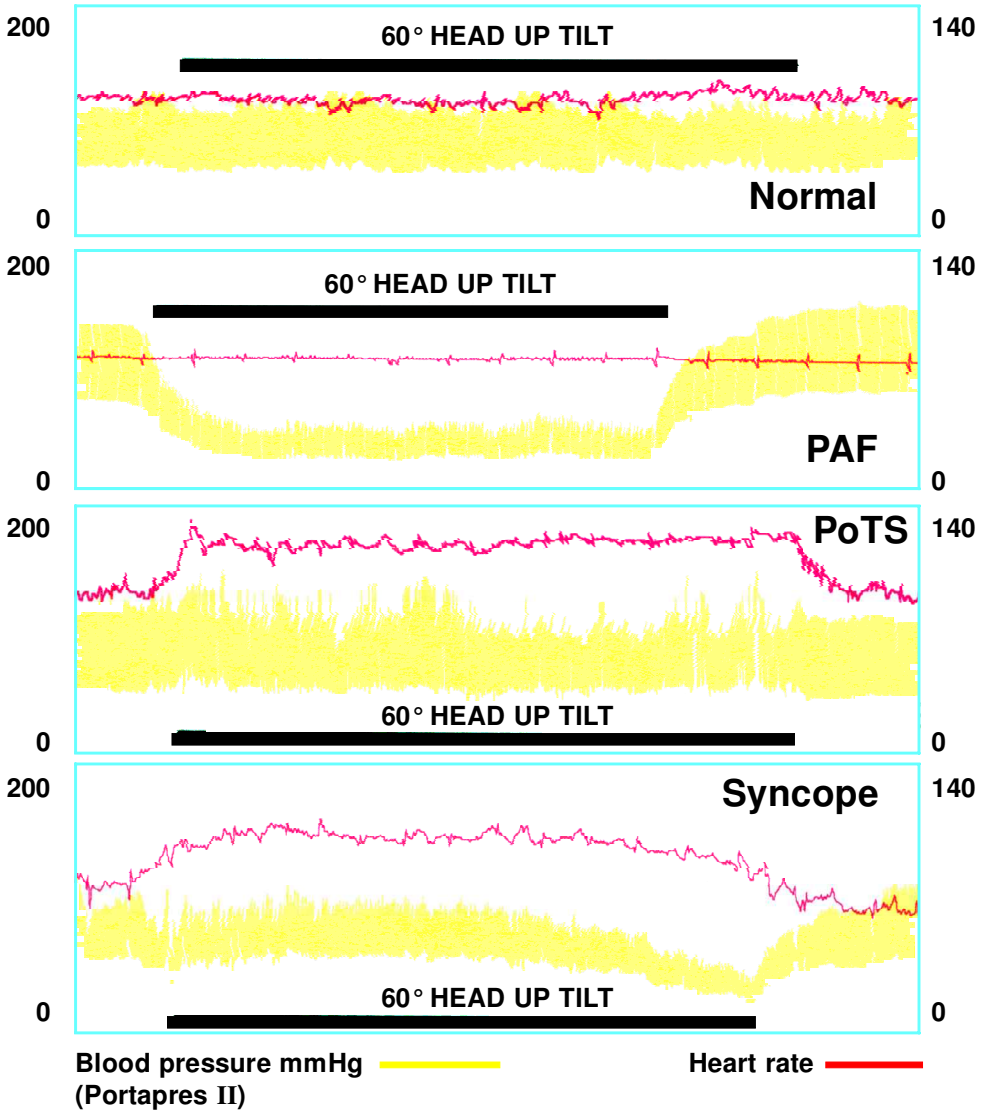

Fig 3. Blood pressure and heart rate measured (non-invasively) continuously before, during and after 60° head-up tilt (by the Portapres II) in a normal subject and in three subjects with different autonomic disorders: pure autonomic failure (PAF), postural tachycardia syndrome (PoTS) and vasovagal syncope (syncope) (bpm = beats per minute).

strictor responses in specific vascular regions and vasodilatation due to sympathetic withdrawal in other regions. An exception is the rare disorder dopamine beta-hydroxylase deficiency in which plasma levels of noradrenaline and adrenaline are undetectable, and levels of the precursor dopamine extremely high. The pro-drug, l-threo-dihydroxyphenylserine (l-DOPS), which has a similar catecholamine structure to noradrenaline except for a carboxyl group, is converted by the ubiquitous enzyme dopa-decarboxylase to noradrenaline, thus bypassing the enzymatic deficit[16–18]. This replacement is highly effective, and has beneficially transformed the lives of these patients.

As sympathomimetics are not so successful in most patients with neurogenic orthostatic hypotension, other approaches are used. Continuous, but variable rate, noradrenaline infusion has some benefit but also potential drawbacks[19]. Specific drug targeting may correct the underlying pathophysiological mechanisms that worsen orthostatic hypotension by reducing postprandial hypotension, volume loss associated with nocturnal polyuria, and anaemia[15].

In secondary autonomic failure, additional strategies need to take into account the effects of the primary disorder and its treatment. Thus, in high spinal cord injuries, paroxysmal hypertension may complicate autonomic dysreflexia; the latter can be induced by visceral, skeletal muscle or cutaneous stimulation which increases reflex spinal sympathetic activity not controlled by the brain[20]. Caution is needed to watch that the benefits provided by treating the primary disorder are not undone by excessive hypertension. In diabetes mellitus, orthostatic hypotension in association with renal failure is enhanced by anaemia and can be successfully treated by erythropoietin[21].

Other aspects of management. The management of orthostatic hypotension should involve the patients' relatives and carers. For rare disorders, briefing of associated medical and support staff is often beneficial. Ideally, treatment should be integrated with the help of autonomic liaison and nurse specialists. It is essential that patients (and, if needed, relatives) are given a realistic indication of the goals of treatments and the limitations of current

Table 2. Non-neurogenic factors that may cause orthostatic hypotension[7].

Low intravascular volume:	
Blood/plasma loss	Haemorrhage, burns, haemodialysis
Fluid/electrolyte	Inadequate intake: anorexia nervosa Fluid loss: vomiting, diarrhoea, losses from ileostomy Renal/endocrine: salt-losing neuropathy, adrenal insufficiency (Addison's disease), diabetes insipidus, diuretics
Vasodilatation	Drugs: glyceryl trinitrate Alcohol Heat, pyrexia Hyperbradykinism Systemic mastocytosis Extensive varicose veins
Cardiac impairment:	
Myocardial	Myocarditis
Impaired ventricular filling	Atrial myxoma, constrictive pericarditis
Impaired output	Aortic stenosis

Table 3. Some of the symptoms resulting from orthostatic hypotension and impaired perfusion of various organs (adapted from Ref 7).

Cerebral hypoperfusion	Dizziness Visual disturbances: Blurred (tunnel) Scotoma Greying out (blacking out) Colour defects Syncope Cognitive deficits
Muscle hypoperfusion	Paracervical and suboccipital ('coathanger') ache Lower back/buttock ache
Renal hypoperfusion	Oliguria
Non-specific	Weakness Lethargy Fatigue Falls

Table 4. Factors influencing orthostatic hypotension (adapted from Ref 7).

- Speed of positional change
- Time of day (worse in the morning)
- Prolonged recumbency
- Warm environment (hot weather, central heating, hot bath)
- Raising intrathoracic pressure (micturition, defecation, coughing)
- Food and alcohol ingestion
- Water ingestion*
- Physical exertion
- Physical manoeuvres and positions (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)**
- Drugs with vasoactive properties (including dopaminergic agents)

*This raises blood pressure in autonomic failure[9].
**These manoeuvres usually reduce the postural fall in blood pressure.

management. It should be emphasised that **the symptoms of orthostatic hypotension, not the level of blood pressure, are of crucial importance**, especially as the two may be dissociated.

A major aim of treatment is to improve the quality of life and help subjects lead a full and independent life. Preventing falls and trauma is of prime importance, especially in the elderly. Many benefit from treatment.

Syncope not due to chronic autonomic failure

The challenges described above in patients with orthostatic hypotension due to neurogenic failure relate mainly to those with 'fixed' lesions of the autonomic nervous system. Syncope caused by a transient autonomic abnormality[22], usually while upright, may occur in subjects who otherwise have preserved autonomic function. There are three types, all of which fall into the category of neurally-mediated syncope:

1 *Vasodepressor:* an intermittent, usually short-lived, fall in blood pressure resulting from a rapid withdrawal of sympathetic activity.
2 *Cardioinhibitory:* bradycardia resulting from increased cardiac parasympathetic activity.
3 *Mixed:* the above two forms in combination.

Hypotension impairs cerebral perfusion and may cause syncope without warning. In other patients, presyncopal features include palpitations, sweating and nausea, along with dizziness and visual disturbances. On fainting and falling flat, blood pressure returns to normal, often with rapid return of consciousness and lucidity of thought. However, there may be hypoxic seizures, myoclonic jerks and even urinary incontinence, but without the classical features of epilepsy[23]. Clinical examination often reveals no abnormality, orthostatic hypotension is not present and there is no evidence of autonomic failure on formal

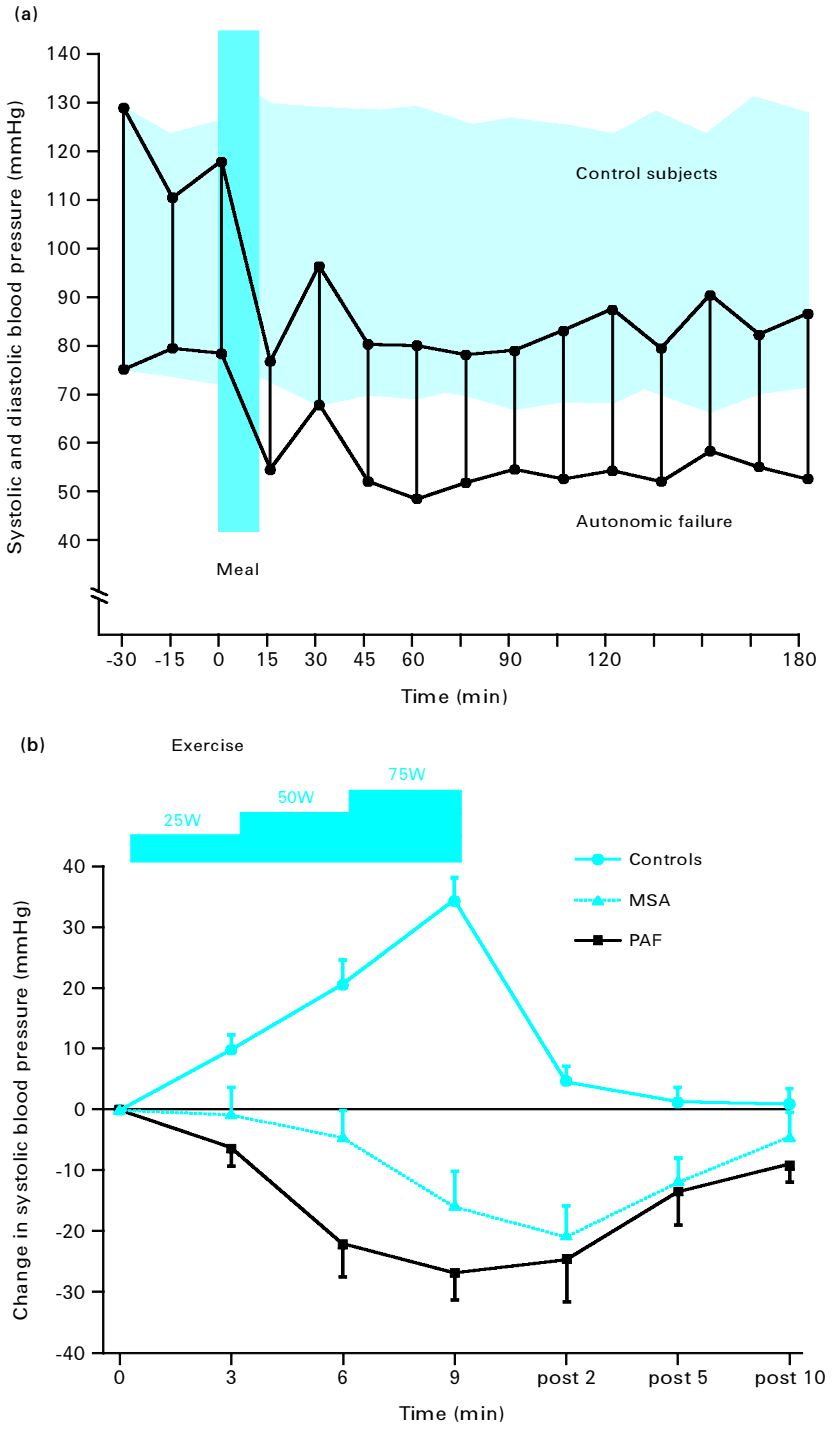

Fig 4. (a) Food intake and blood pressure: systolic and diastolic blood pressure before and after a standard meal while remaining horizontal in normal subjects (controls) (stippled area) and in a patient with autonomic failure. Blood pressure does not change in normal subjects after a meal. In the patient, it rapidly falls to around 80/50 mmHg and remains low over three hours (from Ref 10).
(b) Changes in systolic blood pressure during horizontal bicycle exercise at three incremental levels in normal subjects (controls) and in patients with multiple system atrophy (MSA) and pure autonomic failure (PAF). In both MSA and PAF, unlike controls, there is a fall in blood pressure (adapted from Ref 11).

testing[24]. Episodes may be provoked in the autonomic laboratory using a variety of stimuli that transiently induce abnormal sympathetic and/or parasympathetic activity — hence the term 'neurally-mediated syncope'. The provocative stimulus, often physiological or emotional, may be specific to the individual. This selectivity does not apply when pharmacological, supraphysiological, and even combinations of such stimuli[25,26], are used in laboratories to mimic an episode. The relevance of these investigations remains shrouded in doubt[27].

Neurally-mediated syncope

Neurally-mediated syncope broadly falls into three groups:

1 Situational syncope.
2 Carotid sinus hypersensitivity.
3 Vasovagal syncope.

Situational syncope. In 'situational syncope', physiological stimuli, such as caused by the 'mess trick', trumpet blowing (causing an exaggerated Valsalva manoeuvre) or even micturition (usually while upright and after heavy drinking of alcohol), induce an episode[28]. A pathological enhancement of responses, as in swallowing associated with glossopharyngeal neuralgia, neoplastic infiltration or drugs[29], may cause syncope.

Carotid sinus hypersensitivity. In the elderly, carotid sinus hypersensitivity is increasingly identified as a cause of falls[30]. These patients do not necessarily provide a classical history of activation of afferents in the neck, as with buttoning the collar, shaving or cervical movements.

The cardio-inhibitory and mixed forms often respond favourably to a demand cardiac pacemaker.

Vasovagal syncope. The most common cause of neurally-mediated syncope is vasovagal syncope (Fig 3). Subjects who present in their teenage years often have a family history of syncope[31]. The history may provide clues to precipitant factors that range from standing still at school assembly to venepuncture, the sight of needles and blood, and sometimes even discussion of these stimuli (hence the alternative term 'emotional syncope'). Some subjects have a low level of supine blood

pressure which, in the presence of fluid and salt depletion and heat exposure, may predispose to syncope. The term 'common faint' is indicative of its wide prevalence.

In subjects with vasovagal syncope and an identifiable trigger, there is interest in the relationship between the brain, emotion and cardiovascular autonomic regulation. The mapping of cerebral autonomic centres in humans has been enhanced by the ability to image the brain non-invasively using positron emission tomography and functional magnetic resonance image scanning (Fig 5)[32,33]. These techniques enable morphological and, importantly, functional activation of regions described previously in animals[34], including the anterior cingulate gyrus, insular cortex, amygdala and other brainstem cardiovascular centres, especially in the medulla. In normal humans, there are differential responses to pictures showing fear, disgust or pain with either right or left amygdala activation, depending on whether the aversive stimuli are conditioned or non-conditioned[35,36]. In patients with absent autonomic responses due to peripheral autonomic denervation, there is decreased conditioning-related activity in amygdala and insula[37]. It remains to be determined whether in vasovagal syncope preconditioning to certain stimuli in daily life may trigger aberrant function in cerebral centres and induce the intermittent autonomic abnormality.

The prognosis in vasovagal syncope is excellent, but the condition can be disruptive to the patient and family, especially when there are recurrent episodes, at times without warning or with convulsions. There may be diagnostic difficulties in separating neurally mediated syncope from epilepsy, concerns about driving and operating machinery, and loss of confidence especially in young subjects. Management should include reassurance, non-pharmacological measures to prevent a fall in blood pressure, and activation techniques to raise blood pressure in relevant situations. In some, the continuation of attacks necessitates measures ranging from antihypotensive and psychotherapeutic drugs to demand cardiac pacemakers and behavioural psychotherapy. Determination of the precise mechanisms will aid future therapeutic targeting and also individual tailoring of treatment in this common condition.

Table 5. Some of the approaches used in the management of orthostatic hypotension, especially in patients with chronic autonomic failure (adapted from Ref 15).

Non-pharmacological measures:	
To be avoided	Sudden head-up postural change (especially on waking) Prolonged recumbency Straining during micturition and defecation High environmental temperature (including hot baths) 'Severe' exertion Large meals (especially with refined carbohydrate) Alcohol Drugs with vasodepressor properties
To be introduced	Head-up tilt during sleep Small, frequent meals High salt intake Judicious exercise (including swimming) Body positions and manoeuvres
To be considered	Elastic stockings Abdominal binders Water ingestion
Pharmacological measures:	
Starter drug	Fludrocortisone
Sympathomimetics	Ephedrine or midodrine
Specific targeting	Octreotide, desmopressin or erythropoietin

Key Points

- **There are neurogenic (autonomic) and non-neurogenic causes of orthostatic hypotension**
- **The autonomic nervous system can be affected at sites in the brain, spinal cord or periphery**
- **Orthostatic hypotension impairs organ perfusion and can result in a variety of symptoms that include syncope**
- **Both non-pharmacological and pharmacological measures are needed to treat neurogenic orthostatic hypotension**
- **Orthostatic intolerance and syncope also may be due to intermittent autonomic dysfunction, as in vasovagal syncope (emotional or common fainting) and carotid sinus hypersensitivity**
- **In the postural tachycardia syndrome, orthostatic intolerance occurs without orthostatic hypotension**

Orthostatic intolerance without orthostatic hypotension

An inability to stand on one's legs may also occur independently of orthostatic hypotension, as increasingly recognised in a group of autonomic disorders collectively categorised under the term 'postural tachycardia syndrome' or 'neuropathic postural tachycardia syndrome'[38,39]. In these disorders, orthostatic hypotension does not occur with head-up tilt or standing, and the heart rate speeds up substantially (by over 30 beats per min) (Fig 3). It predominantly affects women below the age of 50, and their lives often are disrupted disproportionately. Symptoms include marked dizziness on postural change or with modest exertion, usually without syncope. There is usually no evidence of generalised autonomic failure. Associated disorders include the chronic fatigue syndrome, mitral valve prolapse and hyperventilation. It is unclear whether there is a relationship with previously described psychosomatic disorders, such as da Costa's syndrome, soldier's heart syndrome and neurocirculatory asthenia. In some, specific pathophysiological mechanisms have been recognised, including partial autonomic denervation predominantly affecting the lower limbs[39,40] and, in one family, a genetic abnormality linked to the noradrenaline transporter[41]. Psychogenic components remain to be evaluated, especially when hyperventilation contributes.

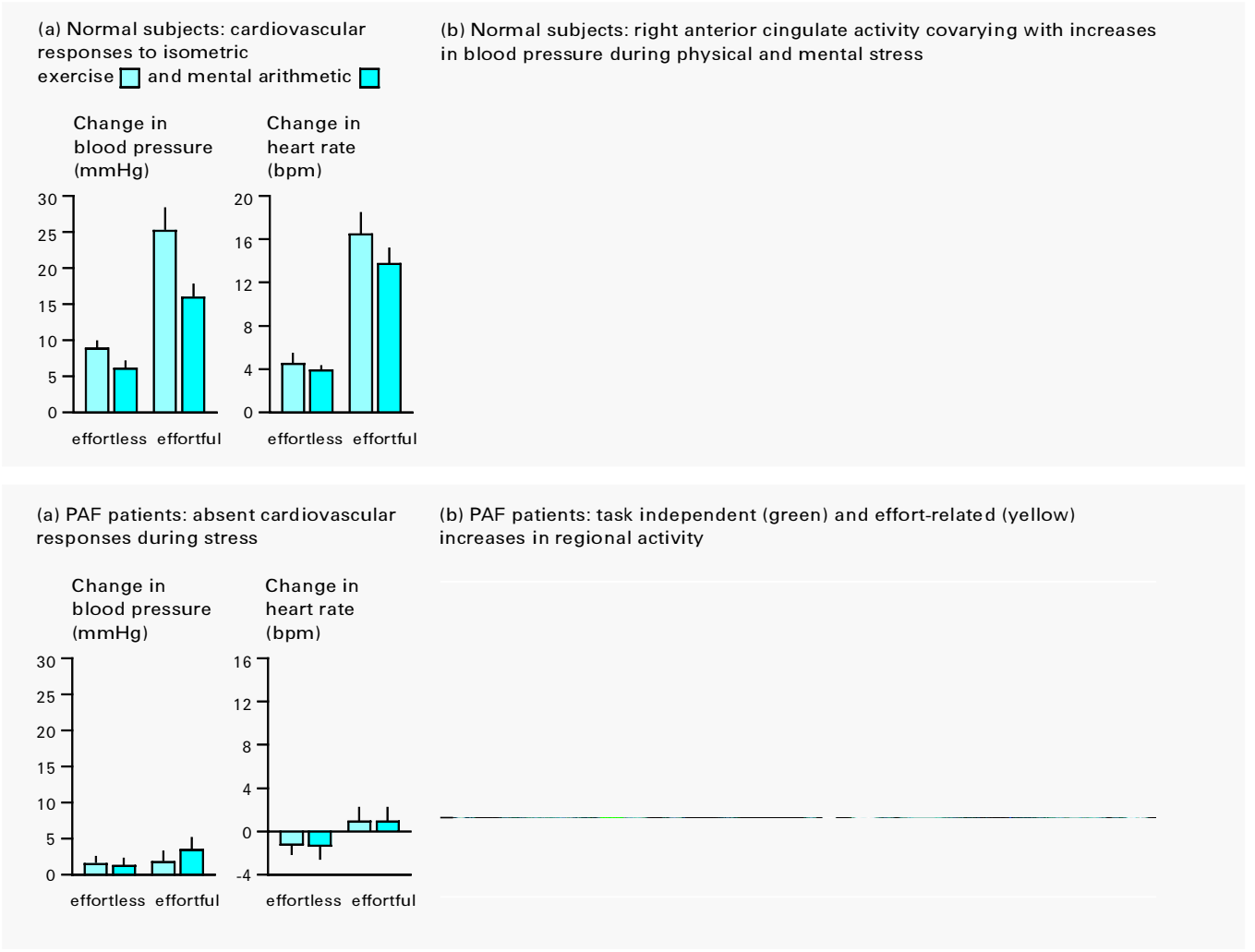

Fig 5. (a) Changes in cardiovascular autonomic measurements (blood pressure and heart rate) during control tasks and effortful isometric exercise and mental arithmetic in normal subjects (top panels) and in patients with pure autonomic failure (PAF) (lower panels). (b) Changes in regional cerebral (mainly right anterior cingulate) activity. Normal subjects show positive covariance with mean arterial pressure during exercise and mental arithmetic. In PAF there is an increase in activity also in the brain stem (pontine) areas, despite no change in blood pressure. Thus the central autonomic centres in PAF are preserved, and some may be abnormally active because of uncoupling of central efferent control and afferent feedback of autonomic responses (derived by H. Critchley from Refs 32 and 33).

Many different therapeutic approaches are applied because of the heterogeneous nature of the disorder[42]. Beta-blockers are sometimes helpful, although it is unclear whether the improvement results from drug treatment or spontaneous remission as part of the natural history.

Conclusions

In conclusion, a wide range of disorders can affect the autonomic nervous system, causing a fall in blood pressure when upright and an inability to stand. The disorders include primary and secondary autonomic failure, the effects of drugs and intermittent autonomic disorders that result in neurally-mediated syncope. Orthostatic intolerance also may occur without orthostatic hypotension, as in the postural tachycardia syndrome. Thus, the inability to stand on one's own legs, when associated with or caused by dysfunction of the autonomic nervous system, continues to pose a major challenge in recognition, investigation and treatment.

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