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Editorial

Treatment of postural hypotension

Postural (orthostatic) hypotension is defined as a fall in blood pressure of over 20 mm Hg systolic, (or 10 mm Hg diastolic), on standing or during head-up tilt to at least 60°.[1] In neurological practice, it may result from diseases or drugs that impair the activity of sympathetic vasoconstrictor nerves. Postural hypotension may be a presenting feature in certain autonomic disorders (such as pure autonomic failure), it may be a pointer towards an alternative diagnosis (as in multiple system atrophy presenting with parkinsonian features), and it may complicate drug therapy (as with levodopa). Postural hypotension is associated with increased morbidity and also mortality, especially in elderly people, in whom falls result in injuries. Advances have resulted in a better understanding of the pathophysiological processes, and in the treatment of postural hypotension.

Recognition and evaluation

Postural hypotension usually is considered when there are characteristic features resulting from cerebral ischaemia such as loss of consciousness (fainting, syncope). Other symptoms may occur (table 1).[2] Measuring blood pressure while lying and after 2 minutes of standing often confirms a postural fall. However, the lack of a fall, in the presence of suggestive symptoms, should warrant further investigation. There are various disorders, including the chronic fatigue syndrome and the postural tachycardia syndrome, in which postural intolerance may not be accompanied by hypotension. Additional factors may be needed to unmask postural hypotension (table 2), especially in mild to moderate autonomic failure.

Table 1 Some of the symptoms resulting from postural hypotension, and impaired perfusion of various organs

Cerebral hypoperfusion
Dizziness
Visual disturbances
Blurred
Tunnel
Scotoma
Greying out
Blacking out
Colour defects
Loss of consciousness
Impaired cognition*
Muscle hypoperfusion
Paracervical and suboccipital (coathanger) ache[1]
Lower back/buttock ache[1]
Cardiac hypoperfusion
Angina pectoris[2]
Renal hypoperfusion
Oliguria
Non-specific
Weakness, lethargy, fatigue
Falls*

* More common in elderly people. 1=these are relieved by supine rest and are presumed to be due to muscle hypoperfusion. 2=an example of a relatively rare symptom. Adapted from Mathias[2].

Further evaluation is best undertaken in an autonomic laboratory. Studies ideally should utilise a tilt table, as patients with neurological disabilities or a profound fall in blood pressure can rapidly and safely be returned to the horizontal position. Additional screening tests (the Valsalva manoeuvre, pressor responses, and heart rate changes to respiratory stimuli), provide information on sympathetic vasoconstrictor and cardiac parasympathetic function.[3] Technical advances enable accurate measurement of beat by beat blood pressure and heart rate (as with the Finapres), thus excluding the previous need for intra-arterial measurements. Non-neurogenic causes of postural hypotension which include intravascular volume depletion (blood or fluid loss and Addison's disease), vasodilatation (drugs such as levodopa or glyceryl trinitrate), and cardiac impairment,[3] should be considered.

The underlying diagnosis is of particular importance, and actively should be sought (table 3),[4] as treatment needs to be linked with that of the primary condition, especially in secondary autonomic failure. In neurally mediated syncope, the intermittent loss of consciousness, usually while upright, results from withdrawal of sympathetic vasoconstrictor (lowering blood pressure), and increased cardiac parasympathetic activity (causing bradycardia). Between attacks, patients often have normal autonomic function. To confirm the diagnosis, additional testing such as prolonged tilting, venepuncture (a common precipitant of vasovagal syncope), or carotid sinus massage are needed. These should be performed in laboratories with trained staff and facilities for resuscitation.

The history may provide information on factors that worsen postural hypotension and its symptoms (table 2). Objective testing may be needed, especially to major stimuli in daily life such as food ingestion[5] and exercise,[6] for which there are specially adapted protocols. The improved accuracy of ambulatory blood pressure and heart rate

Table 2 Factors that may influence postural hypotension

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, defaecation or coughing
Food and alcohol ingestion
Physical exertion
Manoeuvres and positions (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)*
Drugs with vasoactive properties (including dopaminergic agents)

* These manoeuvres usually reduce the postural fall in blood pressure, unlike the others.

Table 3 Outline classification and examples of disorders in which postural hypotension results from neurogenic failure.

Primary
Acute/subacute dysautonomias
Pure pandysautonomia
Pandysautonomia with neurological features
Chronic autonomic failure syndromes
Pure autonomic failure
Multiple system atrophy (Shy-Drager syndrome)
Parkinson's disease with autonomic failure
Secondary
Congenital
Nerve growth factor deficiency
Hereditary
Autosomal dominant trait
Familial amyloid neuropathy
Autosomal recessive trait
Familial dysautonomia: Riley-Day syndrome
Dopamineβhydroxylase deficiency
Metabolic
Diabetes mellitus
Chronic renal failure
Inflammatory
Guillain-Barré syndrome
Transverse myelitis
Infections
Bacterial: tetanus
Viral: human immunodeficiency virus infection
Neoplasia
Brain tumours: especially of posterior fossa
Paraneoplastic, to include adenocarcinomas of lung and pancreas
Surgery
Splanchnic sympathectomy
Trauma
Spinal cord transection
Drugs
Direct effect
Sympatholytic drugs: guanethidine
Neuropathy
Alcohol, vincristine, cisplatin
Neurally mediated syncope*
Vasovagal syncope
Carotid sinus hypersensitivity
Micturition syncope
Cough syncope
Swallow syncope
Associated with glossopharyngeal neuralgia

Adapted from Mathias[4]. *For mechanisms see text.

recorders, with suitable protocols, enable 24 hour evaluation.[7]

Aims of treatment

The key aims are to provide low risk therapy, ensure appropriate mobility and function, prevent falls and associated trauma, and maintain a suitable quality of life. Reducing the postural blood pressure fall should not be the singular aim, as often there is dissociation between symptoms and the level of blood pressure. The generalised use of self blood pressure monitoring should be discouraged because of the variability of blood pressure, its propensity to change rapidly, and difficulties with accurate recording especially when low. The physician must be aware of those in whom blood pressure measurements take over their lives! Measurements, however, are vital for evaluation, especially of therapy. In individual cases, such as with supine hypertension, a home blood pressure record is of value in decisions on therapy. Standing time, an advocated index of improvement, is often irrelevant in practice as it will be influenced by additional neurological disabilities (as in multiple system atrophy), or by the multitude of influencing factors in daily life.

The main therapeutic strategies include both non-pharmacological and pharmacological measures (table 4). The first, in particular, is dependent on the cooperation of the patient and carers. Patient education thus is of importance.

Non-pharmacological measures

Patients must be made aware of factors that can be avoided or circumvented. Some are obvious, such as sudden head-up postural change. Others are less so, such as warm weather and even a hot bath, through cutaneous vasodilatation. Some are more difficult to avoid, such as straining during micturition or defecation, which also may be affected in autonomic disorders. Straining raises intrathoracic pressure, as during the Valsalva manoeuvre. Many patients are worse in the morning, probably because of overnight recumbency induced diuresis and natriuresis. Exercise can lower blood pressure[8] (fig 1), through skeletal muscle vasodilatation not opposed by sympathetic vasoconstriction. Postprandial hypotension is more likely to occur after large meals containing carbohydrate. Some are intolerant of even small amounts of alcohol, which acts by similar mechanisms, through splanchnic vasodilatation. Drugs, even with relatively minor vasodilator properties, may lower blood pressure unduly.

Table 4 Summary outline of non-pharmacological and pharmacological measures in the management of postural hypotension due to neurogenic failure. Non-neurogenic factors, such as fluid loss due to vomiting or diarrhoea, may substantially worsen postural hypotension and if present need to be concurrently treated

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)
Physical activity*
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
Pharmacological measures
Starter drug: fludrocortisone
Sympathomimetic drugs: ephedrine, midodrine
Specific targeting: octreotide, desmopressin, erythropoietin

*Varies individually (see fig 1).

Measures that can be introduced include head-up tilt at night, by raising the bedhead by blocks or a polystyrene wedge beneath the mattress. Benefit may result from activation of the renin-angiotensin-aldosterone system, and other mechanisms that reduce recumbency induced diuresis. An improvement in cerebrovascular autoregulation may occur with time due to recurrent exposure to low blood pressure. Small, frequent meals ensure an adequate caloric intake, and reduce postprandial hypotension. A high salt intake is to be encouraged. Regular exercise is important, but it may induce hypotension and it often needs to be tailored individually. Exercising in a more horizontal position, such as by swimming or use of a rowing machine, seem beneficial. Various body positions and manoeuvres prevent, or reverse, postural hypotension.[9] The use of appropriate aids, such as lightweight portable chairs, is to be encouraged (fig 2).[10]

Physical measures such as elastic stockings and modified abdominal binders[11] may help, although often they are not acceptable. Antigravity suits have virtually no role. They often are difficult to fit as they have been designed mainly for the physically able; furthermore, when not in use the blood pressure fall may be more precipitous because compensatory mechanisms have not been recruited.

Cardiac pacemakers have no place in postural hypotension due to chronic neurogenic failure. The lack of sympathetic vasoconstriction causes peripheral pooling and reduces venous return, ventricular filling, and cardiac output. Raising the heart rate does not affect the underlying

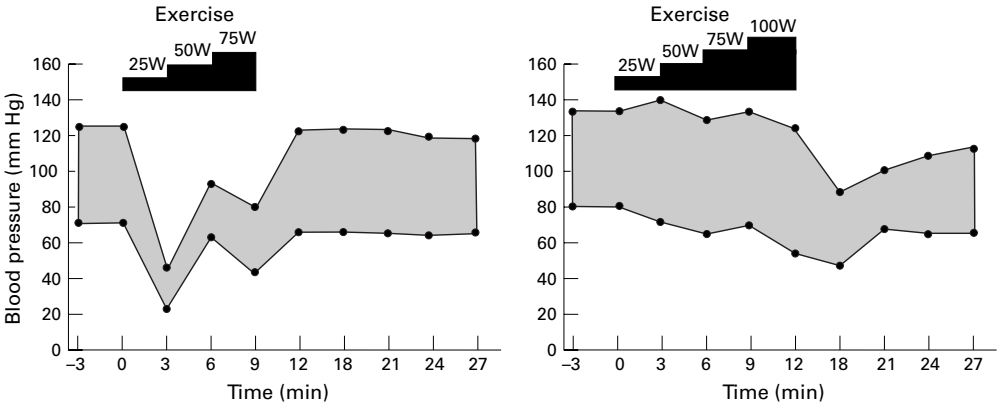

Figure 1 Systolic and diastolic blood pressure in two patients with primary autonomic failure before, during, and after bicycle exercise performed in the supine position at different workloads, ranging from 25 to 100 W. In the patient on the left there is a marked fall in blood pressure on initiating exercise; she had to crawl upstairs because of severe exercise induced hypotension. In the patient on the right, there are minor changes in blood pressure during exercise, but a marked decrease soon after stopping exercise. This patient was usually asymptomatic while walking, but developed postural symptoms when he stopped walking and stood still. Postexercise hypotension probably was due to vasodilatation in exercising skeletal muscle, not opposed by the calf muscle pump. (Reproduced with permission.[8])

defect and provides no benefit. In certain forms of neurally mediated syncope, a demand cardiac pacemaker may be of value.

Pharmacological measures

Drugs are needed when non-pharmacological approaches are unsuccessful. They may raise blood pressure in various ways (table 5). The recommended starter drug is the mineralocorticoid fludrocortisone, which probably acts by reducing salt and water loss, and possibly increases α-adrenoceptor sensitivity. A low dose of 50–200 μg is used at night, when there is the greatest natriuresis and diuresis. In these doses side effects are minimal. In higher doses, hypokalaemia and excessive fluid retention may occur. Its benefits may not be realised until it is stopped.

Drugs that mimic the deficient neurotransmitter noradrenaline should be considered next. Ephedrine has both direct and indirect actions, and is of value in central autonomic failure, such as that due to multiple system atrophy. The dose is 15–45 mg thrice daily. It is best taken on waking up, with further doses before lunch and dinner. Its is not recommended at night, when its pressor effects are not needed; furthermore, it may cause insomnia. Other side effects, with higher doses, include tremulousness, a reduction in appetite, and, in males, urinary retention due to its effects on the urethral sphincter. In patients refractory to ephedrine, as in peripheral lesions, a directly acting sympathomimetic drug should be introduced. An example is the prodrug midodrine, which is converted to desglymidodrine and stimulates α-1 adrenoreceptors.[12 13] It is used

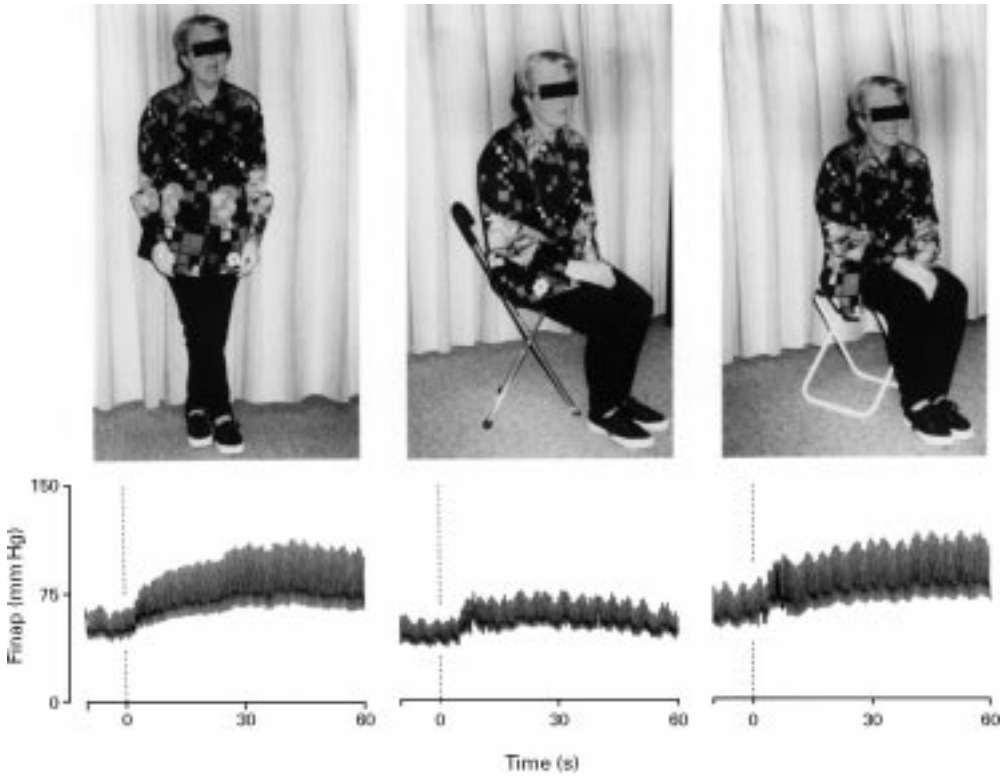

Figure 2 The effect on finger arterial blood pressure of (A) standing in the crossed leg position with leg muscle contraction, (B) sitting on a derby chair, and (C) fishing chair in a patient with autonomic failure. Orthostatic symptoms were present while standing and disappeared while crossing legs and sitting on the fishing chair. Sitting on a derby chair caused the least rise in blood pressure and did not relieve completely the patient's symptoms. (Reproduced with permission.[10])

Table 5 Outline of the major actions by which a variety of drugs may reduce postural hypotension

Reducing salt loss/plasma volume expansion:
Mineralocorticoids (fludrocortisone)
Reducing nocturnal polyuria:
Vasopressin-2-receptor agonists (desmopressin)
Vasoconstriction: sympathetic:
Directly on resistance vessels (midodrine, phenylephrine, noradrenaline, clonidine) and on capacitance vessels (dihydroergotamine)
Indirectly (ephedrine, tyramine with monoamine oxidase inhibitors, yohimbine)
Prodrug (L-threo-dihydroxyphenylserine)
Vasoconstriction: non-sympathetic
Vasopressin-1 agonists (terlipressin)
Preventing vasodilatation:
Prostaglandin synthetase inhibitors (indomethacin, flurbiprofen)
Dopamine receptor blockade (metoclopramide, domperidone)
β_2-Adrenoceptor blockade (propranolol)
Preventing postprandial hypotension:
Adenosine receptor blockade (caffeine)
Peptide release inhibitors (somatostatin analogue: octreotide)
Increasing cardiac output:
β Blockers with intrinsic sympathetic activity (pindolol, xamoterol)
Dopamine agonists (ibopamine)
Increasing red cell mass:
Recombinant erythropoietin

in doses of 2.5–10 mg thrice daily. Its side effects include cutis anserina (goose bumps), tingling of the skin, pruritis, especially of the scalp, and in the male urinary hesitancy and retention. Sympathomimetic drugs should be avoided, or used with caution, with coexisting ischaemic heart disease, cardiac dysrhythmias, and peripheral vascular disease.

If the combination of fludrocortisone and sympathomimetic drugs does not produce the desired effect, then selective targeting is needed, depending on the pathophysiological abnormalities. In postprandial hypotension the somatostatin analogue octreotide is often beneficial.[7 14] It inhibits release of gastrointestinal peptides, some of which have vasodilatory properties. A low dose (25–50 μg subcutaneously) half an hour before a meal often reduces postprandial, and to a lesser extent, postural and exercise induced hypotension. It does not enhance nocturnal hypertension.[7] Nausea and abdominal colic may occur. Larger doses of octreotide are used in endocrine disorders, when it may affect the gall bladder and cause cholelithiasis. In nocturnal polyuria the vasopressin analogue desmopressin, which acts on renal tubular vasopressin-2 receptors, is of value.[15] It is given at night as a nasal spray (10–40 μg) or orally (100–400 μg). It may reduce morning postural hypotension. Hyponatraemia and water intoxication may occur. In patients with anaemia the peptide erythropoietin may be beneficial.[16 17] A mild normocytic normochromic anaemia may occur in pure autonomic failure; more severe anaemia occurs in renal failure complicating diabetes mellitus and amyloidosis. Erythropoietin is used in a dose of 50 μg/kg body weight three times a week for 6–8 weeks, sometimes with oral iron. It raises the red cell mass and packed cell volume, and may increase the potential for maintaining adequate cerebral oxygenation when the blood pressure falls. Whether it is of value in patients with postural hypotension who are not anaemic remains to be determined.

A long list of drugs, in addition to those above, have been used in the treatment of postural hypotension (table 5). Indomethacin and flurbiprofen may reduce salt and water loss but have potential side effects, especially on the gastrointestinal tract. Various ergot derivatives have been used. Dihydroergotamine is available in an oral form but has low bioavailability, whereas ergotamine as a lingual spray has the potential side effects of such alkaloids. The combination of tyramine and monoamine oxidase inhibitors (including the newer agent, moclobemide[18]), may improve postural hypotension, but poor control and excessive hypertension is a problem. Drugs that stimulate cardiac function, such as pindolol and xamoterol, have deleterious effects; ibopamine has been used in only a few patients, with limited success. As with all therapeutic agents, appropriate trials need to be performed in adequate numbers of clearly defined patients, so that their value and side effects can be delineated clearly.

Therapy in specific disorders

The approaches described above are used in primary autonomic failure. In secondary autonomic dysfunction modifications may be needed to take account of differences in pathophysiological processes and the effects of the underlying disease and its treatment. In diabetes mellitus there may be a fine dividing line between the benefits gained by reducing postural hypotension and the enhancement of supine hypertension that may impair renal function. In amyloidosis, excessive proteinuria and hypoalbuminaemia with peripheral oedema complicate the low intravascular volume thus preventing use of fludrocortisone and causing refractoriness to sympathomimetic drugs. Patients with high spinal cord lesions are often worst affected in the early stages of injury or after prolonged recumbency. Repeated head-up tilt may be all that is needed, with occasional use of ephedrine. Some spinal patients utilise the ability to activate peripheral sympathetic pathways by compressing the abdominal wall to stimulate the urinary bladder; this induces autonomic dysreflexia and raises blood pressure.[19] In dopamine β-hydroxylase deficiency, with undetectable plasma noradrenaline and adrenaline concentrations, the ideal therapy is the prodrug L-threo-dihydroxyphenylserine, which is similar in structure to noradrenaline except that it has a carboxyl group; the enzyme dopadecarboxylase converts it into noradrenaline.[20] It has potential value in primary autonomic failure[21] and further studies are warranted.[22] In neurally mediated syncope with an emotional or "central" component, inhibitors of 5-hydroxytryptamine uptake may be of value.[23]

Some treatments may reverse or prevent progression of the underlying disorder and thus reduce postural hypotension. Intravenous gammaglobulin has successfully reversed acute dysautonomia in two patients.[24 25] It is not clear if transplantation of the pancreas in diabetes mellitus, and of the liver in familial amyloid polyneuropathy, will reduce postural hypotension.

Concluding remarks

The management of postural hypotension entails consideration of many factors. These include the variability of symptoms despite a similar fall in blood pressure, the responses to activities in daily life that can worsen postural hypotension substantially, the presence in some of supine hypertension, and the effects of the underlying disorder and its therapy. It is important that the patient is made aware that treatment, even with a combination of various measures and drugs, is unlikely to be a substitute for the rapid and complex responses of the autonomic nervous system that maintain blood pressure and ensure adequate perfusion of major organs, such as the brain. The management therefore, is dependent on an integrated approach, with education of the patient playing a pivotal part.

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