Postural tachycardia syndrome —current experience and concepts

Christopher J. Mathias, David A. Low, Valeria Iodice, Andrew P. Owens, Mojca Kirbis and Rodney Grahame

Abstract | Postural tachycardia syndrome (PoTS) is a poorly understood but important cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. PoTS is distinct from the syndromes of autonomic failure usually associated with orthostatic hypotension, such as pure autonomic failure and multiple system atrophy. Individuals affected by PoTS are mainly young (aged between 15 years and 40 years) and predominantly female. The symptoms—palpitations, dizziness and occasionally syncope—mainly occur when the patient is standing upright, and are often relieved by sitting or lying flat. Common stimuli in daily life, such as modest exertion, food ingestion and heat, are now recognized to be capable of exacerbating the symptoms. Onset of the syndrome can be linked to infection, trauma, surgery or stress. PoTS can be associated with various other disorders; in particular, joint hypermobility syndrome (also known as Ehlers–Danlos syndrome hypermobility type, formerly termed Ehlers–Danlos syndrome type III). This Review describes the characteristics and neuroepidemiology of PoTS, and outlines possible pathophysiological mechanisms of this syndrome, as well as current and investigational treatments.

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Introduction

Postural tachycardia syndrome (PoTS), as it is now commonly known, was recognized as a condition in 1982 by Rosen and Cryer[1] and subsequently in 1993 by Schondorf and Low,[2] although probable descriptions date back to the 19th century. PoTS predominantly affects young individuals, with relatively few patients over the age of 40 years.[3] This demographic is likely to be largely attributable to diagnosis at a relatively young age, but symptoms might also resolve as patients get older. The incidence is higher in women than men.[4] The prevalence of PoTS is unknown, although one study has estimated at least 170 cases per 100,000 individuals in the general population.[5] As the diagnosis is not readily made, current estimates are unreliable and the true prevalence is likely to be higher. The acronym POTS (postural orthostatic tachycardia syndrome) was previously used to denote this condition, but we use 'PoTS' in this Review, as the term 'orthostatic' is now considered to be redundant owing to both terms, orthostatic and postural, being used interchangeably.

The aim of this Review is to describe the characteristics of PoTS as well as its presentation and associations with various disorders; in particular, joint hypermobility syndrome (also known as Ehlers–Danlos syndrome hypermobility type, formerly Ehlers–Danlos syndrome type III [referred to throughout this article as EDS type III]). The possible pathophysiological mechanisms will be outlined, along with investigational and treatment strategies.

Competing interests
The authors declare no competing interests.

A historical overview

A description similar to what is now recognized as PoTS was published by Jacob Mendes Da Costa in 1871, during the American Civil War, in which he referred to the disorder as irritable heart syndrome.[6] This paper was followed with a more detailed description published by Sir Thomas Lewis, who coined the term 'soldier's heart', owing to the frequent occurrence of this condition among military personnel in the First World War.[7,8] Da Costa and Lewis attempted to separate valvular and cardiac disease from the conditions they had described, the unwritten implication being that this disorder might have a nonorganic component. This conclusion was also supported by Paul Wood, in his 1941 lectures,[9–11] by which time the disorder was known as Da Costa syndrome, as well as anxiety neurosis (effort intolerance).

The term postural tachycardia syndrome was first used in 1982 to describe a patient with disabling postural tachycardia who did not have orthostatic hypotension.[1] The syndrome was subsequently renamed the postural orthostatic tachycardia syndrome, or POTS, by Schondorf and Low in 1993.[2] Further descriptions of the syndrome provided a basis for distinguishing autonomic failure (in which orthostatic hypotension causes orthostatic intolerance) from probable PoTS, which was previously described variously as vasoregulatory asthenia, neurocirculatory asthenia,[12] hyperadrenergic orthostatic hypotension[13] or sympathotonic orthostatic hypotension.[14] The descriptions provided for each of these latter four groups suggest that patients diagnosed as having these conditions did not have autonomic failure (or orthostatic hypotension). The patients were often young, predominantly female, and had no

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Key points

- Postural tachycardia syndrome (PoTS) is a poorly understood but important cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction
- PoTS mainly affects young individuals (aged 15–40 years) who are predominantly female; onset might be linked to infection, trauma, surgery or stress
- Symptoms (palpitations, dizziness and, in some patients, syncope) usually occur when standing, and can be exacerbated by common stimuli in daily life, including modest exertion, food ingestion and heat
- Proposed pathophysiological mechanisms include alterations in neural control, humoral factors, vascular properties and intravascular volume, as well as physical deconditioning
- PoTS can be associated with various disorders; in particular, joint hypermobility syndrome, also known as Ehlers–Danlos syndrome (EDS) type III or EDS hypermobility type
- A multifactorial treatment strategy that includes pharmacological agents as well as nonpharmacological measures and interventions is often required

evidence of associated neurological or allied disease, although orthostatic hypotension was noted in some individuals.[13] However, the fall in blood pressure when upright may have been caused by autonomic (neurally) mediated syncope of the vasovagal variety. In our clinical experience, one-third of patients with PoTS have a syncopal episode during head-up tilt testing; during this test, measurements of blood pressure and heart rate are made with the patient supine and then, usually for 10 min, when tilted head-up to 60°. Many PoTS patients report such syncopal episodes, especially in the early stages of the condition.

Clinical presentation

PoTS is characterized as a marked rise in heart rate of 30 bpm or greater occurring within 10 min of head-up tilt or standing, or a heart rate while upright of >120 bpm, but without orthostatic hypotension, which remains the accepted, although arbitrary, definition (Figure 1).[2,15]

History

The patient's history is of importance. Many report a sudden onset of orthostatic intolerance, with either syncope or presyncope, usually specifically related to postural change or exertion.[16] Onset may occur after a febrile illness, a traumatic event or surgery. In addition, palpitations are often reported, again usually only when upright, and relief is often obtained by lying flat (Box 1). Symptoms might worsen while standing still and after even modest exertion.[16] In some patients, food ingestion (usually carbohydrates), alcohol, exercise and/or heat (that is, being in a hot environment or bath) can worsen the symptoms (Box 2).[17] Each of these stimuli is associated with vasodilatation and central hypovolemia, and these mechanisms might explain the tachycardia as a compensatory but excessive response (Figure 2). Not unexpectedly, especially in young patients who have not yet been diagnosed as having PoTS, anxiety and panic attacks might occur. Many patients learn to avoid fainting because of the related negative symptoms associated with presyncope, and syncope often tends to be become infrequent.

Other frequent clinical features in patients with PoTS include fatigue, sometimes associated with systemic or constitutional hypotension.[18] Many patients experience headaches, often similar to migraine in nature but with postural enhancement when standing upright.[19] A subset have symptoms indicative of visceral involvement, including gastroesophageal reflux and nausea, abdominal distension, lower gastrointestinal tract dysfunction with constipation and diarrhea (often diagnosed as irritable bowel syndrome),[20] urine retention, and urinary frequency.[3,21] Pelvic pain might also occur.[3] Patients with PoTS often exhibit features suggestive of peripheral blood pooling or inappropriate vasoconstriction and vasodilatation, such as blotchy or marbled skin, particularly over the feet, which may turn mauve or purple (Figure 3). These signs are dependent on posture, as they occur while upright and are reversed on lying flat.

Alternatively, patients might present with few abnormal signs other than the cardinal features of postural tachycardia while upright, without orthostatic hypotension (Figure 1). In the outpatient clinic, the presence of these features might not be readily ascertained, especially as in some individuals a rise in the heart rate of at least 30 bpm may only occur after standing for more than 10 min, or when upright after food or alcohol ingestion, after exercise and/or in hot weather. These scenarios are associated with vasodilatation in different vascular beds.

Associated conditions

The clinical history and examination should include identification of symptoms and signs related to the various disorders now known to be associated with PoTS, as recognition of these conditions can aid the investigation and appropriate management of the associated deficits. In our clinics, which are national referral centers for autonomic disorders, the condition most frequently associated with PoTS is joint hypermobility syndrome, which is believed to be indistinguishable from, if not identical to, EDS type III.[22,23] Initial examination may reveal features suggestive of EDS type III, such as joint hypermobility (double-jointedness, dislocations, clicking joints; Figure 3), a positive Gorlin sign (the ability to touch the nose with the tip of the tongue), lax skin and subcutaneous tissues, and paper-thin (papyraceous) scars.[24] Auscultation in patients with PoTS might suggest mitral valve prolapse, which can occur alone or in association with EDS type III.[24]

Diagnosis

The investigations for PoTS are considered under two categories: autonomic investigations (Box 3) and other tests. Determination of which additional tests are required depends on the nature of any associated disorders that are suspected.

Autonomic investigations

During head-up tilt (60° for 10 min) and standing, patients with PoTS do not experience a fall in blood pressure,

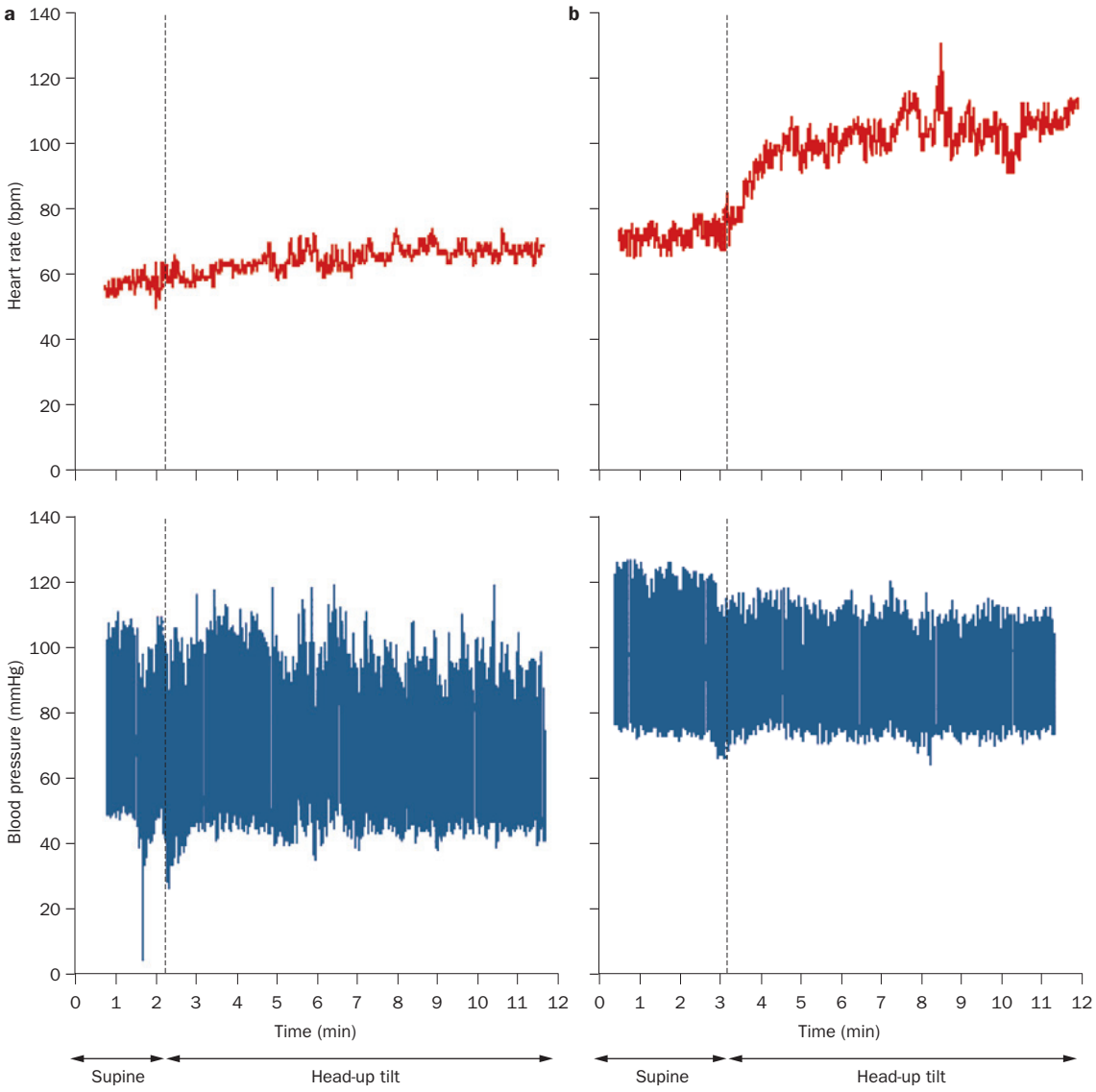

Figure 1 | Blood pressure and heart rate profiles obtained while supine and during head-up tilt. **a** | Profile of a healthy individual. **b** | Profile from a patient with PoTS. The vertical dashed line indicates the onset of postural change (head-up tilt). Excessive tachycardia is observed after the onset of head-up tilt in the patient with PoTS. Abbreviation: PoTS, postural tachycardia syndrome.

but there is a marked rise in heart rate, which is reversed on lying flat (Figure 1). Autonomic mediated syncope of the vasovagal type might occur in some individuals. Tachycardia often increases with time spent upright, presumably because of increased dependent limb pooling, microvascular filtration,[25] and concomitant reductions in stroke volume.[26,27]

Details of the different autonomic investigations employed have been reviewed elsewhere.[28] The focus of investigation should be on cardiovascular autonomic function, and in particular to exclude disorders that cause autonomic failure resulting from a fixed and irreversible lesion.[17] As the autonomic nervous system is essentially preserved in patients with PoTS, the results of autonomic function screening tests are invariably normal, which excludes underlying neurological or allied disorders. 24-h ambulatory monitoring of blood pressure and heart rate using the London Autonomic Units protocol,[28] with a diary that details the times of prescribed exercises and maneuvers for patients to complete in their day-to-day lives, provides valuable information (Figure 4). Testing of sympathetic vasoconstrictor function with pressor stimuli (such as isometric exercises, cutaneous cold and mental arithmetic), and tests of cardiac parasympathetic function with heart rate responses to deep breathing, Valsalva maneuvers and hyperventilation, are essential to exclude autonomic failure (Box 3). In addition, these investigations help to determine the response to activation stimuli that could be used to reduce the symptoms of PoTS.

The measurement of plasma norepinephrine and epinephrine levels, both in supine and upright (during head-up tilt or standing) positions, is of value. A rise in plasma norepinephrine levels while standing upright

Box 1 | Symptoms of PoTS

The symptoms listed below occur in the upright position and are often relieved by lying flat.

- Dizziness and light-headedness
- Palpitations
- Visual disturbances
- Clamminess
- Loss of consciousness
- Nausea
- Headache
- Pain (chest or upper abdomen)
- Shortness of breath
- Nonspecific symptoms, including fatigue, lethargy, and difficulty thinking or concentrating

Abbreviation: PoTS, postural tachycardia syndrome.

Box 2 | Factors that induce or worsen PoTS symptoms

- Time of day (may be worse in the morning, especially on initial rising after wakening)
- Speed of positional change
- Raised temperature (hot weather, hot bath)
- Dehydration
- Food ingestion
- Alcohol
- Physical exertion
- Menstrual period
- Deconditioning or prolonged recumbency
- Drugs that cause vasodilatation

Abbreviation: PoTS, postural tachycardia syndrome.

is typical in patients with PoTS; this response can be exaggerated in some individuals, who are described as having hyperadrenergic PoTS,[3,29] although in our experience this exaggerated response does not occur in the majority of patients with the syndrome. Basal plasma catecholamine levels are usually normal, unlike the subnormal levels seen in some patients with autonomic failure. Meta-iodobenzylguanidine myocardial scintigraphy has been used in patients with PoTS to estimate local myocardial sympathetic innervation and function,[30] although its diagnostic utility in PoTS remains to be determined.

A variety of tests to determine the cardiovascular autonomic responses to events in daily life may be required, depending on the patient's history and the need to provide individually tailored advice on management of their symptoms (Box 2). Tests include the responses to prolonged head-up tilting, food ingestion, exercise and heat stress. Each of these stimuli causes a redistribution of blood flow with fluid shifts caused by gravity in the lower limbs and vasodilatation in relevant vascular regions: namely, in the splanchnic circulation after food ingestion, in the muscle vascular beds after exercise, and in the cutaneous circulation on exposure to heat. These stimuli, as encountered in daily life, can unmask or worsen tachycardia and associated symptoms in patients with PoTS. These signs and symptoms might not be observed, or are less obvious, while the patient is upright before the stimulus (Figure 2).

In some patients, additional autonomic testing might be needed. A thermoregulatory sweat test may provide evidence of distal sudomotor dysfunction, suggestive of a small-fiber neuropathy.[31] Neurophysiological studies should also include the sympathetic skin response, and should exclude other causes of peripheral neuropathy.

Non-autonomic investigations

The choice of non-autonomic investigations will vary depending on which associated conditions are suspected, and on any complicating features that are present. These investigations might include echocardiography in patients with suspected mitral valve prolapse, neuroimaging of the brainstem to detect suspected Chiari malformation, thermal threshold studies in those with suspected small-fiber neuropathy, and psychological assessment. Depending on the patient's presenting features, urinary bladder, gut and pelvic investigations may also be needed.

Differential diagnosis

Tachycardia may be caused by a number of disorders, including cardiac and endocrine diseases among others,[32] as well as orthostatic intolerance.[33] Disorders with clinical features that overlap with PoTS need to be considered and, if necessary, excluded. An ECG must be obtained in all patients, and endocrine testing should be performed, where appropriate, to exclude common diseases such as hyperthyroidism, and uncommon conditions such as Addison disease and pheochromocytoma.[34,35] Autonomic screening tests, in conjunction with the other investigations selected according to the patient's clinical features, usually exclude those autonomic disorders that have features overlapping with PoTS.

Pathophysiological mechanisms

The wide range of associated disorders and conditions associated with PoTS probably accounts for the numerous pathophysiological mechanisms proposed to underlie this syndrome, which are likely to differ between individuals.

Neural mechanisms

The majority of patients with PoTS have preserved autonomic function, and in our experience most do not have non-autonomic neurological deficits. In some patients, however, PoTS is associated with regional autonomic denervation, usually in the lower limbs.[36,37] This feature might account for abnormal findings in response to the Valsalva maneuver, such as a reduced increase in blood pressure suggestive of attenuated sympathetic vasoconstrictor responsiveness.[38] Impaired norepinephrine release in response to physiological maneuvers and also to pharmacological stimuli, such as sodium nitroprusside and tyramine,[39] has been described in some patients, suggestive of predominantly lower limb autonomic denervation.

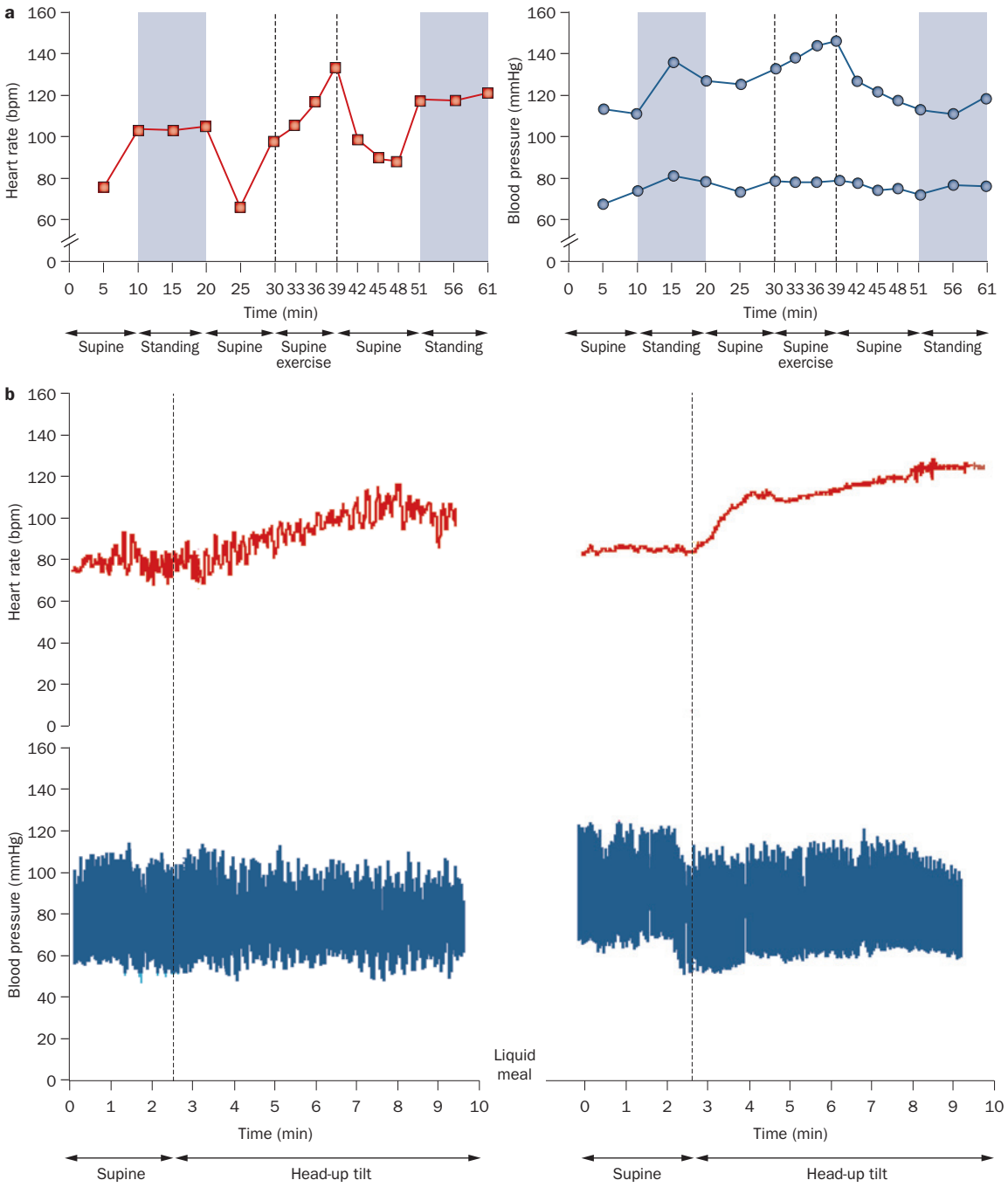

Figure 2 | Changes in blood pressure and heart rate associated with various stimuli in a patient with PoTS. **a** | Changes observed during standing, as well as before and after a graded supine cycling exercise. **b** | Changes observed while supine and during head-up tilt, before and after ingestion of a balanced liquid meal. The patient's blood pressure (top line, systolic blood pressure; bottom line, diastolic blood pressure) and heart rate responses to exercise are preserved, but while standing after exercise (even 10–15 min later) the heart rate remains elevated and above the rate measured before exercise. A greater rise in the heart rate is observed on head-up tilt after ingestion of the meal, compared with the rate during head-up tilt before the meal. Abbreviation: PoTS, postural tachycardia syndrome.

Sympathetic microneurography provides a quantitative index of reflex sympathoexcitation via baroreflex unloading. One study showed that compared with healthy controls, patients with PoTS exhibited a greater increase in sympathetic nerve activity (both burst frequency and burst incidence) during a hypotensive challenge with nitroprusside.[40] However, the change in mean burst area, a measure of the number of actively firing sympathetic neurons, was similar in both groups. To reconcile these findings, the researchers concluded that an increased sympathetic outflow response occurred in the patients with PoTS during a hypotensive challenge, but the lack of a concomitant increase in mean burst area was suggestive of sympathetic denervation.

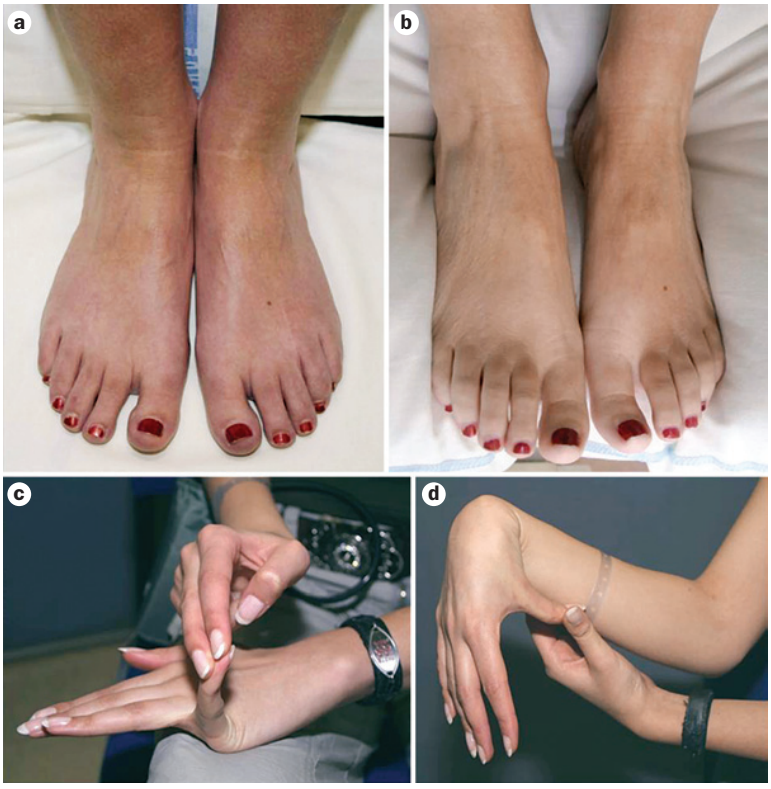

Figure 3 | Clinical signs of PoTS. **a** | Peripheral vascular pooling in the lower limbs during head-up tilt. **b** | An image of the same patient, showing that no pooling occurs while supine. **c**,**d** | Joint hypermobility in a patient with PoTS and EDS type III (also known as EDS hypermobility type). Abbreviations: EDS, Ehlers–Danlos syndrome; PoTS, postural tachycardia syndrome.

Box 3 | Investigations for PoTS

These investigations measure the cardiovascular autonomic responses to postural changes (head-up tilt and standing), and determine the responsiveness of the autonomic nervous system to stimuli in daily life.

Autonomic screening tests

- Head-up tilt (at an angle of 60° for 10 min)
- Standing
- Pressor stimuli (to determine sympathetic vasoconstrictor function): isometric exercise, cutaneous cold, Valsalva maneuver and mental arithmetic
- Heart rate responses (to determine cardiac parasympathetic responsiveness) to: deep breathing, the Valsalva maneuver, hyperventilation, standing and head-up tilt
- Plasma norepinephrine and epinephrine levels: supine, and during head-up tilt or standing
- 24-h ambulatory blood pressure and heart rate profile using the London Autonomic Units protocol

Additional tests

- Prolonged head-up tilt (at an angle of 60° for up to 60 min)
- Liquid meal challenge to determine preprandial and postprandial cardiovascular autonomic responses to the transition from supine to head-up tilt or standing
- Modified, graded exercise, to determine the cardiovascular autonomic responses while exercising in a supine position, and to compare these responses with before and after this exercise and while standing

Abbreviation: PoTS, postural tachycardia syndrome.

Abnormalities of sudomotor autonomic function could reflect an underlying neural deficit that also impairs cardiovascular autonomic function, as is the case in patients with features of small-fiber neuropathy. These patients have impaired postganglionic sudomotor function, particularly in the lower limbs, which indicates autonomic C-fiber involvement.[31,41] The titer of nicotinic acetylcholine receptor autoantibodies might correlate with the severity of autonomic dysfunction, which raises the possibility that an immune response directed at autonomic ganglia or more-distal neurological targets accounts for these abnormalities.[3,42]

Humoral factors

Elevated plasma norepinephrine levels with raised systolic blood pressure during head-up tilt, an exaggerated pressor response to the Valsalva maneuver, and an increase in muscle sympathetic nerve activity have been described in some patients with PoTS, which suggests that this syndrome could have a hyperadrenergic basis underpinned by either neural or humoral mechanisms.[3,43–46] The results of pharmacological challenge with the ganglionic blocker trimetaphan, as well as the α1-adrenergic receptor agonist phenylephrine and the β-adrenergic receptor agonist isoprenaline, both before and after ganglionic blockade, favor this possibility.[29] A centrally induced increase in sympathetic neural activity, possibly relating to the presence of an anxiety state, is another potential mechanism that could be considered in some patients.

Humoral factors that account for PoTS might include substances causing excessive vasodilatation, as occurs, for example, in patients with mast cell activation disorder.[46] These individuals often have additional features (such as episodic flushing, diarrhea, nausea and vomiting) accompanying the usual symptoms of PoTS. An association with Takotsubo cardiomyopathy has also been reported.[47] Elevated levels of angiotensin II might be present in some patients with PoTS who have low blood volumes, and this factor could contribute to the local blood flow dysregulation observed in the periphery of these individuals, resulting from vasoconstriction and reduced nitric oxide bioavailability.[48]

Decreased intravascular volume

Even in individuals without PoTS, tachycardia can be caused by hypovolemia due to loss of blood (from visceral hemorrhage), losses of fluid and electrolytes (in renal failure), and as a result of endocrine disorders (diabetes insipidus or Addison disease). In some patients with PoTS, even when these conditions have been excluded, hypovolemia is thought to contribute to tachycardia.[49,50] Many patients' symptoms are worse in the morning on first standing after awakening, which could be related to reduced intravascular volume because of increased overnight urine secretion while supine.[51] Changes in

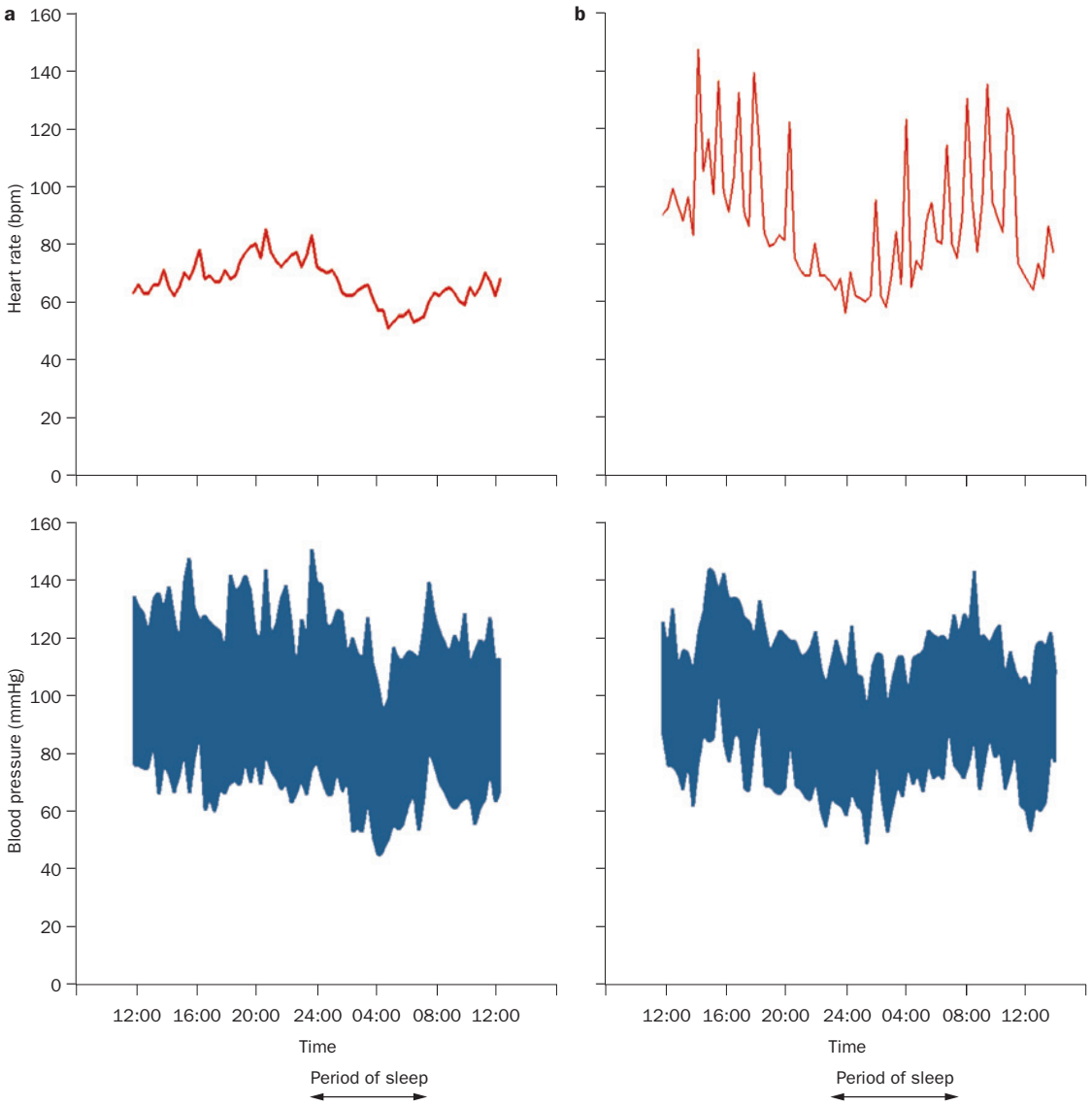

Figure 4 | Blood pressure and heart rate profiles during 24-h ambulatory monitoring using the London Autonomic Units protocol. **a** | Profile from a healthy individual. **b** | Profile from a patient with PoTS. The elevations in heart rate observed in the patient with PoTS were mainly related to periods of being upright. Abbreviation: PoTS, postural tachycardia syndrome.

the levels of—or responsiveness to—hormones (such as the renin–angiotensin–aldosterone system), or in the renal control of fluid secretion, have been suggested to contribute to changes in intravascular volume.[52] Partial renal denervation, which impairs sodium and water retention (and possibly also regulation of red cell mass, via erythropoietin), has also been considered to promote hypovolemia.[52,53] Some patients with PoTS who are refractory to standard therapy seem to respond favorably to intravenous infusions of saline,[54] and others seem to respond well to erythropoietin treatment, which provides further support for the notion that renal denervation affects both red cell mass and intravascular volume.[55]

Other vascular mechanisms

Many patients with PoTS seem to have excessive peripheral blood pooling in the lower limbs while standing upright, which is reversed on return to the horizontal position. Although this feature is often interpreted as evidence of accentuated venous pooling,[13] excessive venous capacitance and compliance, and an increased collection of blood within the venous vasculature during orthostasis, this may not always be observed in PoTS.[37,56] Various classifications of PoTS have been suggested, based on lower limb and splanchnic blood flow.[57] In some patients, increased blood flow in the lower limbs and pelvis might result from inadequate peripheral (arterial) vasoconstriction, which produces a passive redistribution of blood within the peripheral venous capacitance beds[37] and/or increased microvascular filtration when standing upright.[25] In those with normal or reduced limb blood flow, the vascular deficit while upright is thought to result primarily from blood pooling in the splanchnic vascular bed, which causes increased vasoconstriction in other vascular beds to counteract such vasodilatation.[58] Other factors, such as

nitric oxide deficiency, a reduction in the calf muscle pump, or increased angiotensin II and local vascular smooth muscle abnormalities, might be the cause of low peripheral blood flow in some patients with PoTS.[59,60] Whether reductions in connective tissue proteins (such as collagen, fibrillin and tenascin) have a role in peripheral pooling in patients with both PoTS and EDS type III also needs to be considered.

Abnormal responses in the cerebral circulation while standing upright could cause a reduction in cerebral perfusion that would result in symptoms of PoTS. Evidence for this mechanism is inconclusive, with reductions in cerebral blood flow reported in some studies,[61–64] but not in others,[65] during head-up tilt. Cerebral perfusion is dependent on a range of factors, including systemic blood pressure, sympathetic and parasympathetic neural control, and local vascular regulators (metabolic factors such as CO_2 levels, and myogenic factors).[66,67] Arterial CO_2 levels are affected by hyperventilation, which might occur in some patients with PoTS.[62,63] Studies using the α1-adrenergic receptor agonist phenylephrine and the α-adrenergic receptor antagonist phentolamine suggest that increased sympathetic neural activity relating to the cerebral circulation could account for some of the symptoms of PoTS.[61] Transcranial Doppler ultrasound and beat-to-beat middle cerebral artery blood velocity, together with indirect techniques using fast-acting and slow-acting regulatory component analysis, provide further information on local vascular regulation in key vascular regions; for example, on cerebral autoregulation.[64,68]

Physical deconditioning

Many patients with PoTS fatigue readily, and a number of factors might underlie this feature. Exercise intolerance, in addition to orthostatic intolerance, might in part be due to being physically unfit,[27] whereas in some patients a low systemic blood pressure could contribute. PoTS has some similarities to chronic fatigue syndrome.[18] In studies using a protocol that separates cardiovascular autonomic responses to exercise from those induced by gravitation, patients with PoTS often exhibit greater and more-persistent tachycardia when upright after exercise, especially when compared with healthy individuals.[69] By contrast, tachycardia during exercise has been associated with reduced stroke volume rather than altered autonomic control.[70,71] In many patients, physical deconditioning, which is characterized by hypovolemia and cardiac atrophy, might be a secondary factor rather than the primary cause of PoTS.[27] This suggestion is consistent with the description, in many patients, of a sudden onset of PoTS symptoms temporally linked with infections, surgery, a general anesthetic, or stress of various sorts, whereas physical deconditioning occurs some time afterwards.[26] This observation further emphasizes the need for patients with PoTS to avoid physical inactivity, which will exacerbate many of their symptoms. Improving exercise tolerance, using a variety of techniques including endurance exercise training, ameliorates various features of PoTS.[27,72,73]

Genetic mutations

A specific neurohumoral abnormality has been reported in a single family with a genetic mutation in the *SLC6A2* gene, which encodes the sodium-dependent norepinephrine transporter. This mutation results in increased accumulation of norepinephrine in the synaptic cleft, and thus exacerbated heart rate responses.[74,75] This genetic mutation was reported in identical twins; although both possessed the same genotype, only one expressed the PoTS phenotype. No further families with such mutations have been reported to date.

In addition to the above genetic mutation, PoTS in some patients is associated with polymorphisms in the gene encoding endothelial nitric oxide synthase. These alterations might contribute to the vascular changes observed in patients with PoTS, especially those with low peripheral blood flow,[76] although excessive angiotensin II and oxidative stress seem to be the key causes of reduced bioavailable nitric oxide in this syndrome.[48,77] For the patients with PoTS in whom anxiety (and possibly hyperventilation) might contribute to the symptoms, an underlying genetic predisposition might be present.

In some patients with PoTS who also have EDS type III, a strong familial association is observed, sometimes involving three or more generations. The molecular genetic defects underlying EDS type III involve connective tissue that is probably common to joints and the vasculature, and might predispose carriers of these mutations to PoTS as well as to autonomic syncope.[78,79]

Panic disorder and anxiety syndromes

PoTS and panic disorder share many physical symptoms (such as palpitations, tachycardia, hyperventilation, hyperhidrosis and chest pain), as well as psychological features (including tremulousness, health anxiety and impaired concentration) that might have contributory or coincidental roles in PoTS.[80] Anxiety or panic disorder might be either causative or independent of a somatic disorder.[81,82] In patients who experience the onset of PoTS around late adolescence (when substantial supplementary psychosocial adjustment often occurs, independent of PoTS symptomatology), a combination of physical and psychological factors might act in an additive or synergistic manner. Unlike the cardiac symptoms of panic disorder, tachycardia in PoTS is provoked by a physiological challenge—primarily orthostatic stress, but in some individuals also after exercise and meals, usually while upright. Furthermore, patients with PoTS who hyperventilate have hyperpnea (increased depth of breathing), whereas those with panic disorder have tachypnea (increased rate of breathing).[83]

Hyperactive traits, often seen in individuals with anxiety disorders and PoTS, are absent during the presymptomatic phase of childhood in patients who go on to develop PoTS,[84] suggesting that hyperactivity is unlikely to be a primary causative factor of PoTS. However, interoceptive feedback might contribute to the symptoms and trigger secondary anxiety complexes in some patients with PoTS, particularly as abnormally

high somatic vigilance is a common trait in patients with this syndrome.[82,84,85] Isoprenaline and other peripherally acting drugs that increase sympathetic activity provoke anxiety even in individuals without anxiety disorders,[86–89] and can induce acute panic attacks in those with established anxiety or panic states.[90–92] The sympathetic responses to provocative physical stimuli in patients with PoTS are comparable to the peripheral actions of sympathomimetic drugs, and might be a further contributory factor in some patients.

Patients with EDS type III demonstrate a high prevalence (60–68%) of anxiety and, in particular, panic disorders.[93–95] These conditions are especially prevalent among young female patients. The interactions between PoTS, EDS type III and anxiety states merit further investigation.

Mechanisms linked with tachycardia

PoTS is defined as an excessive heart rate elevation while standing upright, without orthostatic hypotension, and various mechanisms could contribute to tachycardia in this condition.

A compensatory rise in heart rate might occur as a reflex in response to vasodilatation and fluid shifts in major vascular regions and in the periphery (that is, in the lower limbs when standing upright, and also in the splanchnic, skeletal muscle or cutaneous vascular beds). This reflex would explain the tachycardia that occurs in the upright position, and the sometimes progressive increase in heart rate in some patients with PoTS when standing still, after food ingestion, following exercise, and in hot weather when greater vasodilatation is to be expected. This mechanism would also explain why many patients with PoTS find that their symptoms worsen after they are started on β-blocker monotherapy, especially when such therapy involves nonselective β-blockers that tend to lower blood pressure. The tachycardia is also likely to be enhanced by drugs with vasodilatatory and volume-depleting effects. Inappropriate vasodilatation might reflect an underlying disorder, such as reduced connective tissue in patients with EDS type III, or it may be the result of rare conditions associated with humorally induced vasodilatation, such as mast cell activation disorders.

Increased activation of cardiac β-adrenergic receptors might also cause the rise in heart rate. The activation might be humorally mediated; that is, resulting from a rise in circulating epinephrine or norepinephrine (the latter occurs in the rare norepinephrine transporter deficiency syndrome). Receptor activation can also be centrally mediated, resulting from increased sympathetic nerve activation, as occurs in anxiety states. Whether intrinsic alterations in sinus node channel properties also contribute to tachycardia in some patients with PoTS remains unclear.[96]

A reduction in cardiac parasympathetic (vagal) responsiveness and activity can contribute to a rise in heart rate. This mechanism has been suggested in patients with diabetes mellitus, in whom cardiac autonomic neuropathy usually precedes sympathetic nerve damage.[97]

Box 4 | Key nonpharmacological measures in PoTS

The primary nonpharmacological measures used in the management of PoTS.

To be avoided

- Sudden head-up postural change (especially on waking)
- Prolonged recumbency
- High environmental temperatures (including hot baths)
- Large meals (especially of refined carbohydrate)
- Alcohol
- Undue exertion
- Drugs with vasodepressor and/or vasodilatator properties (such as diuretics, nitrates and nifedipine)

To be introduced

- High salt intake (in patients who do not have hypertension)
- Water repletion (especially in the morning on wakening)
- Small, frequent meals
- Judicious regular exercise (including swimming)
- Head-up tilt at night
- Physical countermaneuvers to include activation exercises

To be considered

- Elastic stockings
- Abdominal binders

Abbreviation: PoTS, postural tachycardia syndrome.

Treatment

The treatment of patients with PoTS needs to be multipronged, with a focus on addressing cardiovascular autonomic dysfunction and the ensuing symptoms. Other factors, including underlying and associated disorders, are also essential to consider. A number of patients might have been subjected to a delay in diagnosis, or an erroneous diagnosis with a psychiatric label. Consideration of psychological aspects is, therefore, needed as an additional component in the management of some patients. With appropriate management, the prognosis of PoTS is favorable, with many patients improving within 5 years of diagnosis, and 60% returning to their level of function before symptom onset.[16]

Managing cardiovascular autonomic dysfunction

The key goals in the management of cardiovascular autonomic dysfunction in patients with PoTS are to reduce the symptoms associated with postural change and exercise in particular, and to reduce postural tachycardia, which serves as the most readily measured biomarker of the syndrome. Raising the resting blood pressure (if it is low) and reducing peripheral pooling often benefits patients. Nonpharmacological measures are an initial step that must be implemented even if drugs are used (Box 4).

Nonpharmacological measures

Nonpharmacological treatments for PoTS are similar to those used in the treatment of other causes of orthostatic intolerance, including orthostatic hypotension (Box 4).

Table 1 | Pharmacological treatments for PoTS

Therapeutic strategy	Drug class or mechanism of action	Agent
Reducing salt loss and/or plasma volume expansion	Mineralocorticoid	Fludrocortisone
Vasoconstriction	Sympathetic action on resistance vessels	Midodrine
Ganglionic nicotinic receptor stimulation	Anticholinesterase inhibitors	Pyridostigmine
Preventing vasodilatation and tachycardia	β_2-adrenoreceptor blockers, ideally cardioselective	Bisoprolol
Preventing postprandial tachycardia	Peptide release inhibitors Somatostatin analogs	Octreotide
Directly reducing tachycardia	Selective sinus node blockade	Ivabradine
Lowering blood pressure if elevated and reducing tachycardia	Central sympatholytic	Clonidine

Abbreviation: PoTS, postural tachycardia syndrome.

These measures are applicable to the majority of patients with PoTS who have a low supine blood pressure. However, some measures, such as the addition of salt in the diet, will not be applicable to patients with elevated blood pressure.

In patients with a low supine blood pressure, hypovolemia might account for worsening of symptoms at particular times; for example, on changing posture after first waking in the morning. Fluid repletion, particularly on wakening, is needed in the majority of patients. Avoidance of excessive consumption of caffeine-containing beverages, which can increase diuresis and promote hypovolemia, is also important. Many patients might be on low-salt diets as part of lifestyle changes to prevent hypertension, which needs to be reversed (in patients who do not have hypertension) by salt repletion and, if necessary, salt tablets.[98] These measures seem to be especially effective when combined with gradual physical training.[27]

Activation exercises, such as sustained hand grip, increase sympathetic activity and raise the blood pressure for a short period. These exercises are of value while changing position from supine to sitting or upright, after exercise, and postprandially. Preventative and physical measures to reduce pooling, including activation of the calf muscle pump, are often of value;[99] suitable compression stockings or tights may provide further benefit.[100]

In some patients, specific advice is needed in particular situations. Food, and even small amounts of alcohol, may worsen their symptoms; this effect is reduced by eating small meals at frequent intervals. Varying the composition of food (refined carbohydrates are more likely than other food constituents to cause splanchnic vasodilatation), and use of activation exercises and other strategies to prevent pooling, especially when standing after eating, can be beneficial.

Exercise, even if modest, often worsens tachycardia.[69] Patients should be aware that this effect will be enhanced if they exercise after eating, or in hot weather. Those who are deconditioned need specialist advice on using graded exercise, especially to strengthen the lower limb musculature. The adverse effects of deconditioning have particular importance in patients with PoTS and EDS type III, who experience joint instability and muscle disuse due to their fear that movement will cause pain (kinesiophobia).[101] Exercise performed while semirecumbent, such as swimming or rowing, has advantages for patients with PoTS owing to a reduction in the extent of orthostatic stress in the semirecumbent compared with the upright position.

Pharmacological measures

Drugs are needed when nonpharmacological measures alone are not effective. Treatment needs to be individualized depending on the clinical features and circumstances of each patient, the information gained from the autonomic investigations, and the resting supine blood pressure. Any underlying disorders or associated conditions must also be taken into account (Table 1).

A low supine blood pressure level, alone and without symptoms of orthostatic intolerance, does not warrant treatment, but does need to be addressed in patients with PoTS. A useful first-line drug is fludrocortisone,[45] ideally in doses that do not exceed 300 μg daily to avoid adverse effects, such as a low plasma potassium level. Fludrocortisone should not be used in patients with a tendency to retain fluid. Vasoconstrictor agents, such as midodrine, are the usual second-line treatments,[54] but vasoconstrictors that increase the heart rate, such as ephedrine, must be avoided. Midodrine causes vasoconstriction, prevents pooling, and can raise the blood pressure, which reduces the compensatory tachycardia. Adverse effects of this drug, such as itching of the scalp and goose bumps, are often transient. Midodrine can cause urinary retention in men who have prostatic hypertrophy—an unlikely occurrence in younger male patients with PoTS.[102] Midodrine treatment should be initiated at a dose of 2.5 mg, three times daily before meals, and increased if needed after a few weeks, according to the patient's blood pressure and heart rate, which should be measured in both lying and standing positions. The recommended maximum dose is 30 mg daily. If symptoms remain and the patient's heart rate remains elevated while standing upright, cardioselective β-blockers, such as bisoprolol, can be added.[103] β-blockers are contraindicated in patients with asthma, and might lower the blood pressure.[104] The selective sinoatrial node blocker ivabradine is of benefit in patients who have substantial tachycardia.[105] Alternative agents include pyridostigmine, an acetylcholinesterase inhibitor that increases ganglionic activity;[106] however, gastrointestinal adverse effects associated with this agent can be troublesome in some patients.

In patients with PoTS who have a normal or elevated supine blood pressure, pressor agents, such as fludrocortisone and midodrine, should not be used. The ideal approach is to use a drug that lowers the heart rate and possibly also reduces the blood pressure if it is elevated. β-blockers, including the cardioselective agent bisoprolol, or nonselective drugs, such as propranolol,

should be considered. Clonidine, a centrally active sympatholytic agent, reduces tachycardia and can lower blood pressure.[107] Ivabradine can also be effective in these patients.[105]

In patients with PoTS who experience marked postprandial features, especially those in whom other treatments have been ineffective, subcutaneous octreotide can be beneficial in small doses of 25–50 μg, administered twice or three times daily before food ingestion.[108] A rapid-acting formulation should be used, ideally starting with a single trial dose, and titrated upwards as required. Adverse effects include gastrointestinal disturbances and, in a minority of individuals, hypoglycemic features. These disadvantages need to be considered carefully before using intramuscular preparations with a long duration of action (30 days).[109]

Some patients' symptoms are considerably worse in the morning, possibly owing to increased fluid loss overnight while supine. When fluid replacement alone, especially on wakening, does not help, nocturnal desmopressin (at the doses prescribed for patients with autonomic failure) might have a therapeutic role.[110] Intravenous infusion of saline has been reported to be beneficial in these patients.[54]

Drug interventions for underlying conditions can also improve the symptoms of PoTS. Treatment of migraine headaches with nonselective β-blockers, such as propranolol, can have dual benefits. Orthostatic intolerance can worsen during the menstrual period, and introduction of a contraceptive agent, or a change of drug if such therapy is already present, may need consideration with a specialist. Erythropoietin has also been helpful, especially in patients with PoTS who are anemic.[55]

Managing associated features and disorders

A multidisciplinary approach to treatment of the nonautonomic features of PoTS should ideally involve a range of specialists. Examples of such features and associated disorders include physical deconditioning, fatigue, painful syndromes such as fibromyalgia (a common feature in EDS type III), and a low threshold to pain. Drugs used to treat these conditions could worsen orthostatic intolerance and may interact with the agents used to treat PoTS. In patients with EDS type III, prevention of muscle and joint damage is important. A subgroup of patients with EDS type III have visceral dysfunction affecting the upper or lower gastrointestinal tract (reflux esophagitis, gastroparesis, intestinal dysmotility, reduced colonic motility and impaired bowel movements—often labeled irritable bowel syndrome) and urinary bladder (frequency, retention and recurrent infections). Specialist investigation and intervention for these conditions is often needed.[18,20–22,51,84,95]

Conclusions

PoTS is a heterogeneous condition, and the presence of tachycardia and orthostatic intolerance is often a pointer towards an underlying or associated disorder, which also needs to be addressed. Patients with PoTS seem to belong to one of two main groups: those with and those without EDS type III. The majority of patients with PoTS have no additional neurological or allied features, but in some cases partial distal neuropathy, small-fiber neuropathy, or features suggesting increased sympathetic activity might be present. In patients with both PoTS and EDS type III, a cluster of features additional to cardiovascular autonomic dysfunction and orthostatic intolerance might need active management, including joint and muscle damage, fatigue, physical deconditioning, neurological features (Chiari malformation) and, in some individuals, involvement of the gastrointestinal tract and urinary bladder. The psychological implications of the condition, especially in young people with PoTS, can be considerable.

In summary, PoTS in many patients is essentially a multisystem disorder, in which orthostatic intolerance and syncope are often the key features at presentation, with postural tachycardia as the biomarker that alerts the clinician to investigate whether underlying and associated conditions are present. In addition to specialized treatment of the autonomic features of PoTS, a holistic view is essential for the appropriate and effective management of patients with this condition.

Review criteria

English-language articles (full-text papers and abstracts) were selected for this Review using the PubMed database. The search terms used were "PoTS", "postural tachycardia syndrome", "orthostatic intolerance" and "joint hypermobility syndrome", with no limit on the years of publication searched. Reference lists of identified papers were also searched for further relevant publications.

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Author contributions

All six authors contributed to writing the article. C. J. Mathias, D. A. Low, V. Iodice, A. P. Owens and M. Kirbis researched data for the article. C. J. Mathias, D. A. Low, V. Iodice and R. Grahame made substantial contributions to discussions of the content, and C. J. Mathias, D. A. Low, A. P. Owens and R. Grahame undertook review and/or editing of the manuscript before submission.