

## Review Article

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# Postural Orthostatic Tachycardia Syndrome (POTS)

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Postural orthostatic tachycardia syndrome (POTS) is defined as the development of orthostatic symptoms associated with a rapid (within 10 minutes) increase in heart rate by more than 30 beats per minute or to a heart rate that exceeds 120 beats per minute without orthostatic hypotension. The symptoms of orthostatic intolerance are due to brain hypoperfusion and sympathetic overaction. Patients are usually female and aged 15 to 50 years. POTS represents a category of disease rather than a single distinct illness. Patients with POTS can experience difficulty with daily routines including housework, shopping, eating, and attending work or school. Reports of patients with “POTS-like symptoms” have been made for over 100 years.

The pathophysiologic mechanisms of POTS include peripheral denervation,  $\beta$ -receptor supersensitivity, hypovolemia and impaired cerebral autoregulation. Prolonged deconditioning may also interact with these mechanisms to exacerbate symptoms. Although 3 types of POTS (low-flow, normal-flow, and high-flow POTS) have been distinguished based on differences in peripheral blood flow and peripheral arterial resistance, thoracic hypovolemia is the common final pathophysiologic mechanism.

Therapies are directed at relieving the central hypovolemia or at compensating for the circulatory dysfunctions. Treatments include use of water, saline infusion,  $\alpha$ -agonists,  $\beta$ -antagonists, and other agents that may correct the central hypovolemia. These have resulted in varying degrees of success, and they are often used in combination.

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**Key words:** Postural orthostatic Tachycardia syndrome, Orthostatic intolerance, Orthostatic hypotension, Chronic fatigue syndrome

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## Introduction

Postural orthostatic tachycardia syndrome (POTS) is a syndrome of orthostatic intolerance (OI) characterized by excessive tachycardia and cerebral hypoperfusion in the upright position.<sup>1–3)</sup> POTS is

defined as a sustained heart rate increase of  $\geq 30$  bpm or up to  $\geq 120$  bpm within the first 10 min of orthostasis associated with symptoms of OI but without significant orthostatic hypotension (OH). Its symptoms include palpitation, dizziness, light-headedness, and syncope.<sup>1–3)</sup> Patients with POTS are predominately female and relatively young,<sup>4,5)</sup>

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but can range in age from 15 to 50 years. There are no detailed epidemiological studies, but millions of people might be affected by POTS in the USA.<sup>6)</sup> Possible pathophysiological mechanisms of POTS include peripheral denervation, venous pooling, hypersensitivity of  $\beta$ -adrenergic receptor,<sup>7)</sup> hypovolemia,<sup>8)</sup> and brain stem dysregulation.<sup>9)</sup> A wide range of pharmacological treatments for POTS has been attempted: for example, fludrocortisone has been used to increase intravascular volume,  $\alpha$ -agonists such as midodrine have been used to induce peripheral vasoconstriction, and  $\beta$ -blockers or ivabradine (a selective inhibitor of  $I_f$  current) have been used to suppress heart rate.<sup>10)</sup> This article reviews pathophysiology, diagnosis, and management of POTS.

**History and background**

By the mid-19th century, physicians had noticed patients who were afflicted with a condition characterized by extreme fatigue and significantly reduced exercise tolerance that seemed to occur suddenly without obvious causes. During the American Civil War, terms like “irritable heart syndrome” and “soldier’s heart” were used by DaCosta,<sup>11)</sup> who first drew attention to patients’ complaints of tachycardia and palpitation. By the time of the World War I, a series of reports had come out on similar conditions that were called by a variety of names including “vasoregulatory asthenia” and “neurocirculatory asthenia.” These reports postulated that affected patients had some sorts of functional cardiac abnormality due to poor neural regulation of peripheral blood flow.<sup>12)</sup> Around the time of the World War II, MacLean et al.<sup>13)</sup> described a group of patients who exhibited orthostatic tachycardia associated with only a modest fall in blood pressure or who suffered from exercise intolerance, palpitation, lightheadedness, and generalized weakness. They postulated that the mechanism responsible for these complaints might be a reduction in venous return to the heart due to an impairment at the capillary venous level.

In the 1960s, Frolich et al.<sup>14)</sup> published a report on two patients who had developed pronounced postural tachycardia with palpitation, anxiety, dizziness, and near syncope. Both patients exhibited an exaggerated response to intravenous isoproterenol and  $\beta$ -blockade reduced symptoms. In 1982, Rosen and Cryer<sup>15)</sup> used the term “postural tachycardia syndrome” in reference to a patient who displayed a rise in heart rate >44 bpm upon standing (without hypotension) and also complained of postural palpitations, fatigue,

**Table 1** Syndromes characterized by orthostatic intolerance (Adopted from Ref. 28)

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- Idiopathic orthostatic intolerance
- Postural tachycardia syndrome (POTS)
- Orthostatic tachycardia syndrome
- Sympathotonic orthostatic hypotension
- Hyperadrenergic orthostatic hypotension
- Hyperdynamic  $\beta$ -adrenergic state
- Idiopathic hypovolemia
- Mitral valve prolapse syndrome
- Solider’s heart
- Vasoregulatory asthenia
- Irritable heart
- Orthostatic anemia

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and exercise intolerance. Fouad et al.<sup>8)</sup> labeled this disorder “idiopathic hypovolemia,” based on the role of hypovolemia in postural tachycardia. In a more contemporary study by Streeten, patients having “postural tachycardia” were shown to have marked venous pooling of sodium pertechnetate Tc99 when standing as well as an exaggerated response to infusion of isoproterenol.<sup>16,17)</sup> Hoeldtke et al. subsequently described a cohort of patients, all of whom exhibited symptoms of postural tachycardia along with exercise intolerance, anxiety, and cognitive impairment.<sup>18,19)</sup>

In 1993, Schondorf and Low<sup>20)</sup> performed an extensive analysis of 16 patients with profound exercise intolerance, severe fatigue, lightheadedness, and bowel hypomotility. During head-up tilt table testing, these patients exhibited markedly abnormal cardiovascular responses with a dramatic rise in heart rates to as much as 120–170 bpm, often within the first 2–5 minutes of upright tilt. In 1995, they operationally defined the term “postural tachycardia syndrome” as an increase in heart rate by more than 30 bpm or to more than 120 bpm within 10 minutes of changing from a supine to an upright position without associated hypotension.<sup>20)</sup> Grubb et al.<sup>21)</sup> subsequently reported on a total of 28 patients with these symptoms. During head-up tilt table testing, each patient demonstrated a minimum increase in heart rate  $\geq 30$  bpm during the first 10 minutes of upright posture. The peak heart rate exceeded 120 bpm within the first 10 minutes of upright tilt in almost all cases.

As is often the case in disorders that remain unclarified, many names have been used to describe this syndrome (Table 1). Many investigators have used the term “postural orthostatic tachycardia syndrome (POTS)” to describe this constellation of

signs and symptoms, and have felt that it represents a mild (yet significant) disturbance in autonomic nervous system function (i.e., dysautonomia).<sup>3,20)</sup>

### Epidemiology

The prevalence of POTS is unknown. In clinical practice, it is probably about 5–10 times as common as OH. One estimate of the prevalence was at least 170/100,000<sup>22)</sup> based on the investigators' documentation that 40% of patients with chronic fatigue syndrome have POTS. Robertson et al.<sup>23)</sup> have reported that approximately 500,000 Americans may suffer from some forms of POTS or OI. If this prevalence is employed, there could be over 200,000 Japanese suffering from POTS. Approximately 75% to 80% of POTS patients are female and between 15 and 50 years old,<sup>24)</sup> therefore, the typical POTS patient is somewhere between menarche and menopause. POTS is relatively uncommon in preadolescent children and may have a different pathophysiology in the very young. The reasons for its female predominance are unclear, although women are known to be more vulnerable to orthostatic stress.<sup>25)</sup> Associations with the menstrual cycle or with altered estrogen or progesterone levels are yet to be established, though some female patients report an increase of symptoms in the premenstrual phase.<sup>26)</sup> The illness may follow a remitting and relapsing clinical course, often enduring for years, but seems in many instances to be self-limited. Pregnancy may resolve abnormalities.<sup>6)</sup> As currently construed, POTS was first reported in adults,<sup>3,20,23,27,28)</sup> but pediatric cases have shown that POTS is a common form of OI during upright tilt in adolescents with chronic fatigue syndrome (CFS).<sup>29,30)</sup> In adults with CFS, approximately 25% of patients exhibit typical signs of POTS.<sup>31)</sup>

### Diagnosis

POTS is presently defined as the development of OI symptoms accompanied by a heart rate increase of at least 30 bpm or to a rate >120 beats/min occurring within the first 10 minutes of standing or head-up tilt and in the absence of other chronic debilitating disorders, prolonged bed rest, or medications that impair autonomic reflexes (Tables 2 and 3).<sup>3,28,32)</sup> Low et al.<sup>33)</sup> stated, with regard to the typical age range of POTS patients (15–50 years), that an increase of 30 beats/min exceeds the 99th percentile for control subjects from 10 to 13 years of age.

Most investigators focused on postural tachycardia as an excessive increase in heart rate, representing the earliest, most consistent, and most easily measurable finding of OI. It is important to realize, however, that most patients with OI do not have OH (a decrease in blood pressure of >20/10 mmHg). Rather, most of these patients exhibit only a modest or no decrease in blood pressure, or even an increase in blood pressure when they assume an upright posture.<sup>28)</sup> Nevertheless, focusing only on heart rate has the drawback of overlooking nonorthostatic autonomic symptoms such as paroxysmal disturbances in sweating, blood pressure regulation, thermoregulation, and bowel function.<sup>34)</sup>

### Clinical features

The orthostatic symptoms in patients with POTS consist of symptoms of reduced cerebral perfusion coupled with those of sympathetic activation. The most common symptoms are lightheadedness, palpitation, symptoms of presyncope, tremulousness, and weakness or heaviness (especially of the legs). These

**Table 2** Criteria for POTS (Adopted from Ref. 3)

- 
- Heart rate increment  $\geq 30$  bpm within 5 min of standing or tilt-up
  - Heart rate  $\geq 120$  bpm within 5 min of standing or tilt-up
  - Orthostatic symptoms consistently develop
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bpm: beats-per-minute

**Table 3** Criteria of idiopathic orthostatic intolerance (OI) (Adopted from Ref. 28)

- 
- Long-standing ( $\geq 6$  months) and disabling orthostatic symptoms.
  - Orthostatic tachycardia ( $\geq 30$  bpm increase of heart rate on standing).
  - Absence of an underlying cause (debilitating disease, substantial weight loss, prolonged bed rest, peripheral neuropathy, medications that impair autonomic reflexes).
  - Upright plasma norepinephrine  $\geq 600$  pg/ml
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**Table 4** Orthostatic and nonorthostatic symptoms in patients with postural orthostatic tachycardia syndrome (Adopted from Ref. 4)

Symptoms	No. (%) of patients (N = 152)
<b>Orthostatic</b>	
Light-headedness or dizziness	118 (77.6)
Presyncope	92 (60.5)
Weakness	76 (50.0)
Palpitations	114 (75.0)
Tremulousness	57 (37.5)
Shortness of breath	42 (27.6)
Chest pain	37 (24.3)
Loss of sweating	8 (5.3)
Hyperhidrosis	14 (9.2)
Exacerbation by heat	81 (53.3)
Exacerbation by exercise	81 (53.3)
Exacerbation by meals	36 (23.7)
Exacerbation associated with menses	22 (14.5)
<b>Nonorthostatic</b>	
Bloating	36 (23.7)
Nausea	59 (38.8)
Vomiting	13 (8.6)
Abdominal pain	23 (15.1)
Constipation	23 (15.1)
Diarrhea	27 (17.8)
Bladder dysfunction	14 (9.2)
Pupillary dysfunction	5 (3.3)
<b>Generalized associated</b>	
Fatigue	73 (48.0)
Sleep disturbance	48 (31.6)
Migraine headache	42 (27.6)
Myofascial pain	24 (15.8)
Neuropathic pain	3 (2.0)

symptoms are commonly exacerbated by heat and exercise (**Table 4**).<sup>4)</sup> Other common symptoms are shortness of breath and chest pain. Unlike patients with OH, patients with POTS experience significant symptoms of sympathetic activation.<sup>35)</sup> Patients often complain of headaches beginning in the occipital region and radiating to the shoulders. There may be an overrepresentation of migraine, sleep disorders, and fatigue, and fibromyalgia is sometimes associated.<sup>3)</sup> There is a clear overrepresentation of women.<sup>4)</sup>

Previous studies have indicated that central hypovolemia while upright is a consistent feature in patients with POTS (**Figure 1**).<sup>36,37)</sup> Therefore, any conditions associated with central hypovolemia that

may cause tachycardia (dehydration, anemia, or hyperthyroidism) may also mimic POTS.<sup>37)</sup>

In addition to the tachycardia and OI, a striking physical feature of POTS is the peripheral acrocyanosis that occurs in 40–50% of patients with POTS.<sup>5)</sup> These patients experience a dark red-blue discoloration of their legs, which are also cold to the touch. This can extend from the feet to above the level of the knees. Although this appearance is often called venous pooling, the evidence does not support excessive pooling, the evidence does not support accumulation of venous blood within the vasculature. Instead, the available data indicate decreased overall blood flow in the affected extremities, which results in a relative coolness of the limbs and a type of “stagnant hypoxia.”<sup>38,39)</sup> This may be mediated by a deficit of locally produced nitric oxide and is not likely the result of increased pooling in venous capacitance vessels.<sup>4)</sup>

Early studies suggested that approximately half of patients were presumed to have viral illness,<sup>3,20)</sup> although recent experience suggests that this is less common. Other precipitating events include pregnancy, immunization, sepsis, surgery, and trauma.<sup>33)</sup> A feature of POTS induced by a precipitating event is the cyclic nature of symptoms. Some females will have marked deterioration of their symptoms at certain stages of their menstrual cycles, associated with significant weight and fluid changes. Typically, these patients have large fluctuations in their weights, sometimes up to 5 pounds.<sup>40)</sup>

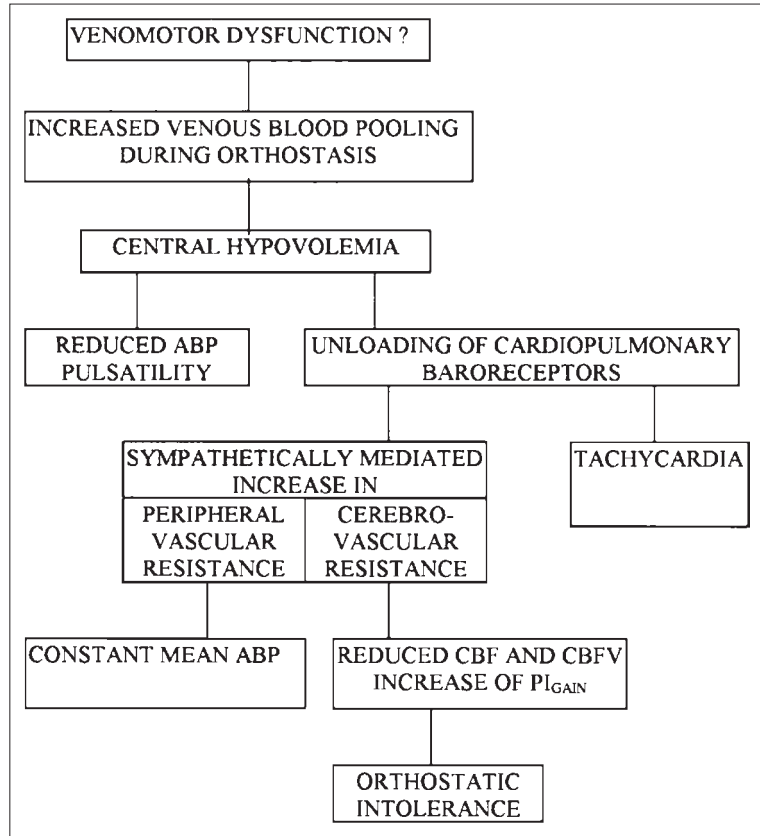
Fatigue is commonly present.<sup>4)</sup> Patients complain of poor exercise tolerance with physiological symptoms including reduced stroke volume and reflex tachycardia; these symptoms are typical of subjects who are deconditioned, such as persons who have undergone prolonged bed rest.<sup>40)</sup> Along with poor exercise tolerance, an excessively long recovery cycle following exercise is often described. Additionally, patients typically note that they have low energy levels, even at rest. A sense of fatigue will sometimes occur in cycles, lasting for days or even weeks and then receding.<sup>40)</sup>

### Pathophysiology

POTS is a clinical manifestation of multiple underlying mechanisms. It can be divided into a number of overlapping pathophysiological models as follows (**Table 5**).

#### Neuropathic POTS

About half of patients with POTS have a restricted autonomic neuropathy with a length-dependent dis-



**Figure 1** Proposed model of the pathophysiological and physiological mechanisms leading to postural tachycardia and orthostatic intolerance. (Adopted from Ref. 36)

tribution of neuropathy (Figure 2).<sup>4,20,41</sup> The term length-dependent neuropathy refers to neuropathy in which the ends of longer fibers are affected before those of shorter ones. The evidence in support of this is as follows. 1) Distal anhidrosis of the legs is commonly found in thermoregulatory sweat testing and quantitative sudomotor axon reflex testing (up to 50% of POTS patients).<sup>4,20,41</sup> 2) Ganglionic acetylcholine receptor antibody is positive in 10–15% of cases.<sup>4,42</sup> 3) There is a blunted increase in post-ganglionic sympathetic nerve discharge (muscle sympathetic nerve activity).<sup>27</sup> This peripheral abnormality might reflect partial dysautonomia. Astronauts returning from prolonged exposure to microgravity often display a form of OI with features similar to POTS.<sup>43</sup> This is believed to be due to abnormal muscle sympathetic nerve activity.<sup>44</sup> 4) Leg arteriolar vasoconstriction is impaired. Therefore, increased arterial inflow can enhance venous filling and cause venous pooling, despite the fact that venous capacitance is normal.<sup>39</sup> 5) The increase in norepinephrine spillover in the legs during orthostasis is smaller in POTS patients than in normal controls.<sup>45</sup> 6) Excessive leg vein constriction is observed in response to phenylephrine and NA

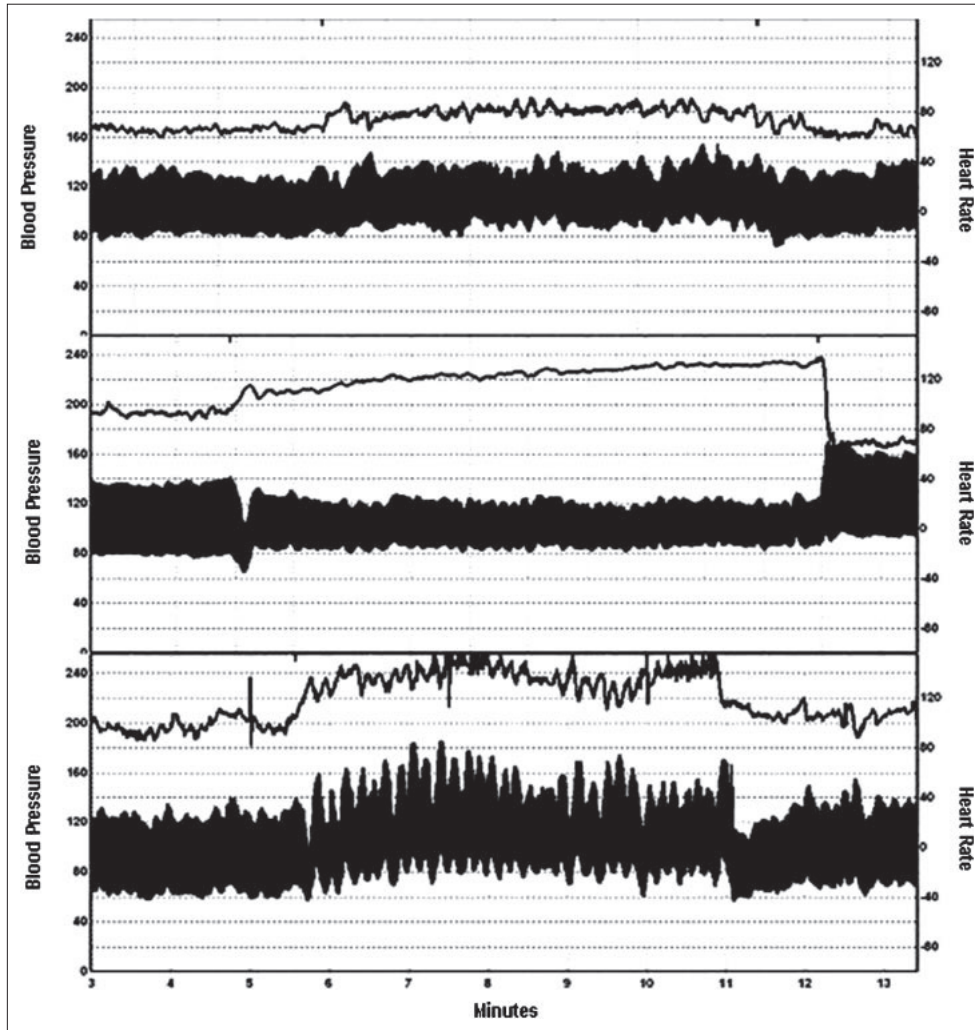
**Table 5** Proposed pathophysiological mechanisms of POTS

- Neuropathic
- Hyperadrenergic
- Genetic (Norepinephrine transfer protein deficiency)
- Hypovolemic
- Impaired cerebral autoregulation
- Histamine-related
- Deconditioning
- Regional blood volume and vascular properties (Low flow, normal flow and high flow POTS)
- Muscle pump defects

infusion, consistent with denervation hypersensitivity.<sup>17</sup>

**Hyperadrenergic POTS**

One subset of POTS is characterized by an excessive increase in plasma norepinephrine and an increase in BP on standing (Figure 2).<sup>46,47</sup> These patients seem to manifest a form of  $\beta$ -adrenergic receptor hypersensitivity, a disorder referred to as hyperadrenergic POTS.<sup>28</sup> They tend to have prom-



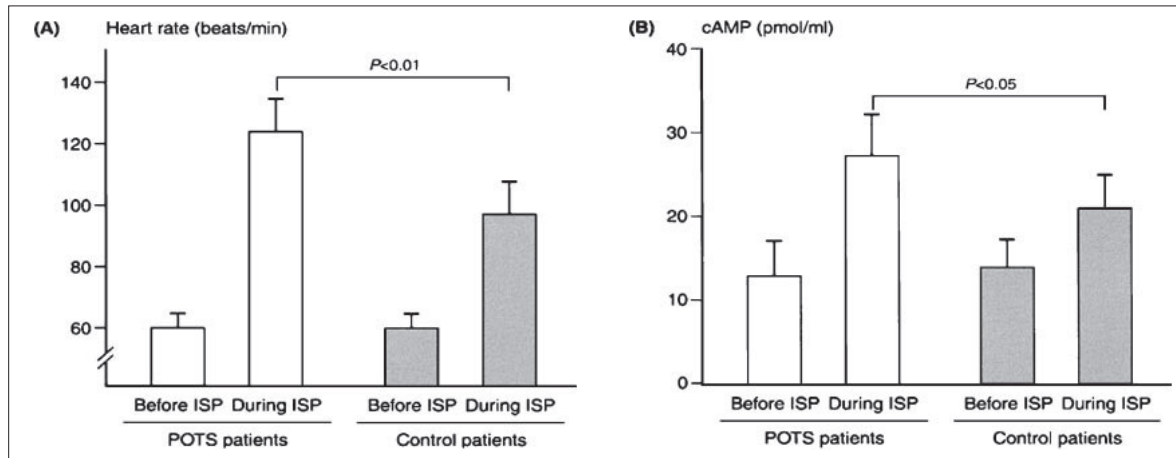
**Figure 2** Examples of blood pressure (BP) and heart rate recordings from a normal subject (**top panel**), a patient with neuropathic POTS (**middle panel**), and a patient with hyperadrenergic POTS (**bottom panel**). Note the modest reduction in BP in neuropathic POTS. Hyperadrenergic POTS is associated with prominent BP oscillations, an orthostatic increment in systolic BP, and a prominent norepinephrine response to head-up tilt. (Adopted from Ref. 41)

inent symptoms of sympathetic activation,<sup>47)</sup> such as palpitation, anxiety, tachycardia, and tremulousness. Over half of these patients will suffer from true migraine headaches that include a definite prodrome and unilateral (often frontal) onset with photophobia and nausea.<sup>27)</sup> Many of these patients will display orthostatic hypertension during standing or tilt and an exaggerated response to low-dose isoproterenol infusions while supine (**Figure 3**).<sup>7,48)</sup> It is unclear whether this hypersensitivity is primary in the nature of the condition or a manifestation of denervation sensitivity.<sup>49)</sup> These patients exhibit a larger decrease in BP following ganglionic blockade with trimethaphan, and higher upright plasma norepinephrine levels, compared to nonhyperadrenergic POTS pa-

tients,<sup>47)</sup> presumably indicating a major role of orthostatic sympathetic activation. Elevation of plasma norepinephrine ( $\geq 600$  pg/mL) was documented in 29.0% of patients tested in a recent study.<sup>4)</sup>

#### Genetic

Recently, norepinephrine transporter (NET) protein deficiency has been shown to produce a complex form of POTS in a single family. A single point mutation in the NET protein<sup>50)</sup> exerts both central and peripheral effects on vascular regulation.<sup>51)</sup> Despite its rarity, the illness has furnished an ideal monogenetic model for autonomic illness, and appropriate animal knockout models have been



**Figure 3** Heart rate (A) and plasma cyclic AMP (cAMP) (B) responses to low-dose isoproterenol (ISP) infusion in the supine position.

(A) Before isoproterenol infusion, there is no significant difference in heart rate between postural orthostatic tachycardia syndrome (POTS) patients and control subjects. After isoproterenol infusion, the heart rate of POTS patients increases significantly compared with that of control subjects ( $p < 0.01$ ). (B) Before isoproterenol infusion, there is no significant difference of the plasma cAMP concentration between POTS patients and control subjects. After isoproterenol infusion, the plasma cAMP concentration increases significantly in POTS patients compared with that in control subjects ( $p < 0.05$ ). (Adopted from Ref. 7)

constructed and investigated.<sup>52</sup>) NET-deficient mice have near-normal resting arterial pressure and heart rate, likely resulting from increased sympathoinhibition. When engaged in wakeful activities, however, these mice exhibited excessive tachycardia and elevated blood pressure.<sup>53</sup>)

#### Hypovolemic

Absolute hypovolemia and low red blood cell volume can occur in POTS patients and aggravate symptoms of OI.<sup>4,54</sup>) Relative hypovolemia can occur due to venous pooling and capillary leakage.<sup>55</sup>) Associated with this propensity to hypovolemia in POTS is an abnormal physiological response to volume depletion. For example, POTS patients lack the normal association between hypovolemia and elevated standing norepinephrine levels.<sup>4</sup>) The renin-angiotensin-aldosterone system plays a major role in the neurohumoral maintenance of plasma volume. In normal subjects, hypovolemia stimulates renin, leading to a subsequent increase in angiotensin II and aldosterone levels. These promote vasoconstriction, and renal sodium and water retention. Low renin and aldosterone levels were found in hypovolemic patients with OI and POTS, although the opposite had been expected.<sup>54,56</sup>) These conditions might contribute to impaired sodium retention and hypovolemia. The sympathetic nervous system is a determinant of renal renin release; therefore, partial renal sympathetic denervation could explain low renin levels.

#### Impaired cerebral autoregulation

POTS patients are found to have an excessive decrease in cerebral blood flow velocity during head-up tilt. It is controversial as to whether this decrease is due to an excessive sympathetic outflow to the cerebral vasculature or to hyperventilation.<sup>9,57</sup>) It is likely that these two factors interact, and that POTS is caused by their combination.

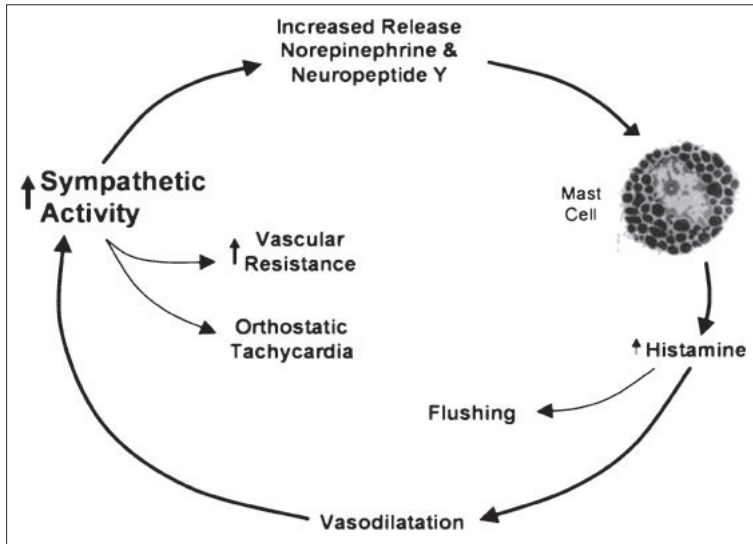
#### Histamine-related

Some patients with POTS have episodic flushing and increased urinary levels of methylhistamine, a primary urinary metabolite of histamine. These patients are thought to have a coexisting mast cell activation disorder that is associated with shortness of breath, headache, lightheadedness, diarrhea, nausea, and vomiting.<sup>58</sup>) Patients can experience a hyperadrenergic response resulting in orthostatic tachycardia and hypertension. At the present time, it is unclear whether mast cell activation-associated release of vasoactive mediators is the primary event or if sympathetic activation results in mast cell activation (Figure 4).<sup>58,59</sup>) In these patients, although  $\beta$ -adrenergic antagonists may exacerbate symptoms, treatment with antihistamines (H1 and H2 antagonists) in combination with nonsteroidal anti-inflammatory drugs may be beneficial.

#### Deconditioning

POTS patients have poor exercise tolerance, and deconditioning is often present, especially in patients





**Figure 4** Proposed pathophysiological mechanisms underlying the association between mast cell activation (MCA) and hyperadrenergic orthostatic intolerance. (Adopted from Ref. 58)

with prominent fatigue and fibromyalgia-type symptoms.<sup>40)</sup> Masuki et al.<sup>41)</sup> have suggested that, although anxiety is commonly present in POTS, the HR response to orthostatic stress in POTS patients is not caused by anxiety, but is rather a physiological response that maintains arterial pressure during venous pooling. These authors studied 13 patients with mild POTS and 10 matched controls. In POTS patients, exercise was associated with a greater HR elevation, especially while upright, which was secondary to reduced stroke volume and associated with poor exercise tolerance.<sup>60)</sup>

Both lower body negative pressure and exercise findings seem remarkably similar to models of pure deconditioning and bed rest. These findings in combination with the “somatic hypervigilance” noted above raise the possibility that, in at least some POTS patients, some event or illness initially evoked orthostatic symptoms which were then “over-interpreted,” leading to reduced physical activity and deconditioning. In this context, the residual symptoms of POTS may have a strong deconditioning component in at least some patients.<sup>40)</sup>

#### Regional blood volume and vascular properties

The distribution and disposition of gravitationally displaced blood is controlled by many factors, chief among them being regional blood flow and vascular compliance, and peripheral arterial and peripheral venous resistance. The relative functionality of these factors can provide a useful and physiologically important means to further categorize patients with POTS. Stewart et al.<sup>61-63)</sup> described 3 groups of

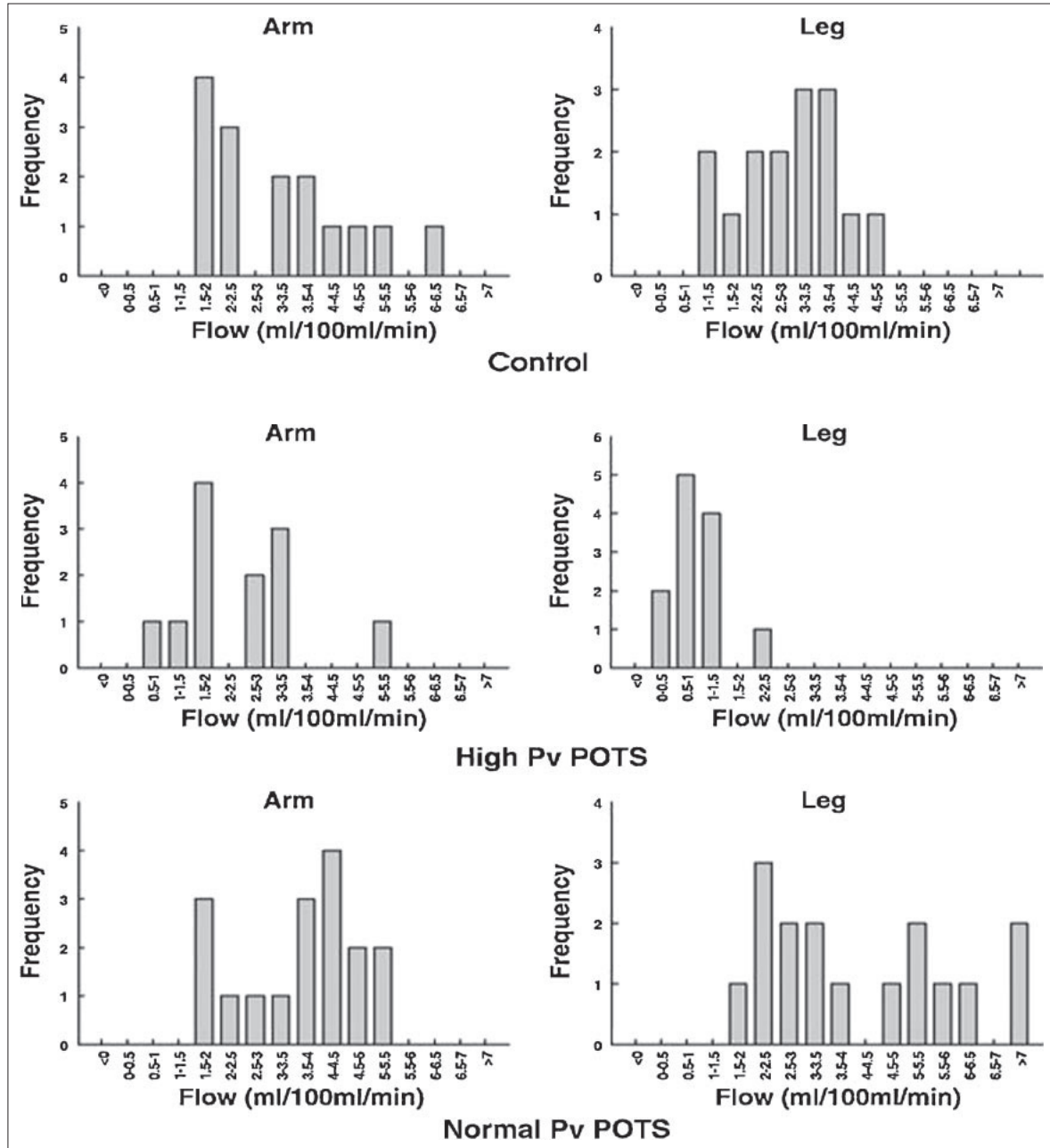
patients with POTS (Figures 5 and 6) based on differences in peripheral blood flow and peripheral arterial resistance:

1. A low-blood-flow, high-arterial-resistance, high-peripheral-venous-resistance group (“low-flow” POTS), characterized by pallor and generally decreased blood flow most notable in the dependent parts of the body. This low-flow condition is related to defects in local blood flow regulation and mild absolute hypovolemia.
2. A normal-blood-flow, normal-arterial-resistance, normal-peripheral-venous-resistance group (“normal-flow” POTS), characterized by a normal supine phenotype with normal peripheral resistance in the supine position but enhanced peripheral resistance in the upright position. This group exhibits specific venous pooling within the splanchnic vascular bed, making this a redistributive form of hypovolemia.
3. A high-blood-flow, low-arterial-resistance, normal- to decreased-peripheral-venous-resistance group (“high-flow” POTS), related to a long tract neuropathy and characterized by high cardiac output caused by inadequate peripheral vasoconstriction in the supine and upright positions. Patients typically are acyanotic and warm to the touch, with extensive filtration resulting in dependent edema.

#### Low-flow POTS

Low-flow POTS patients are intensely peripherally vasoconstricted while supine and have decreased



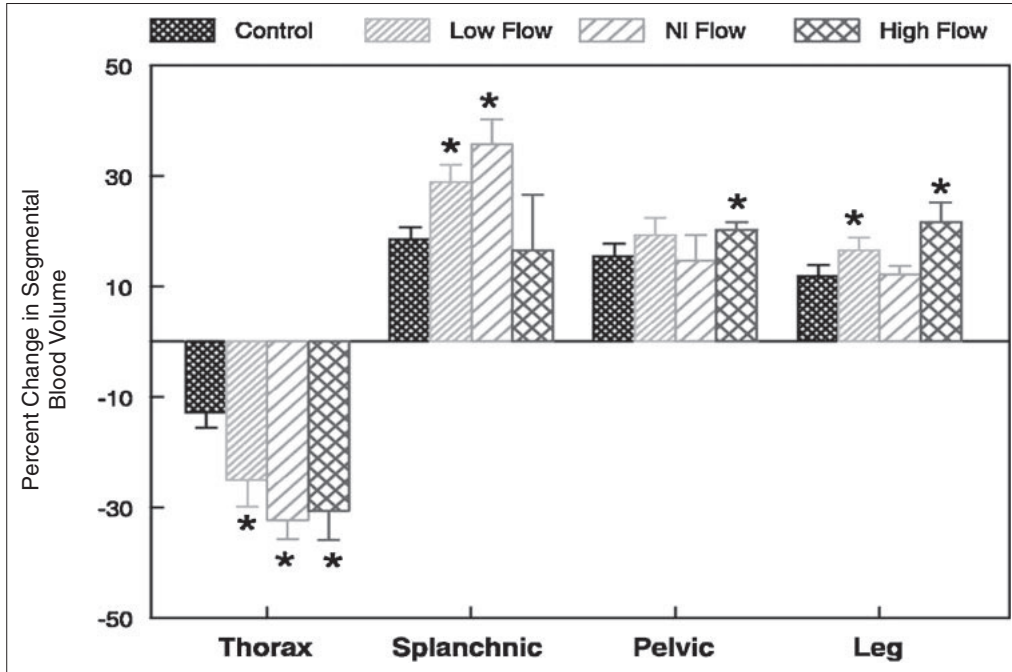


**Figure 5** Frequency distribution of peripheral blood flow in patients with postural tachycardia syndrome (POTS) with high venous pressure (Pv; **middle**) and normal Pv (**bottom**) compared with control subjects (**top**).

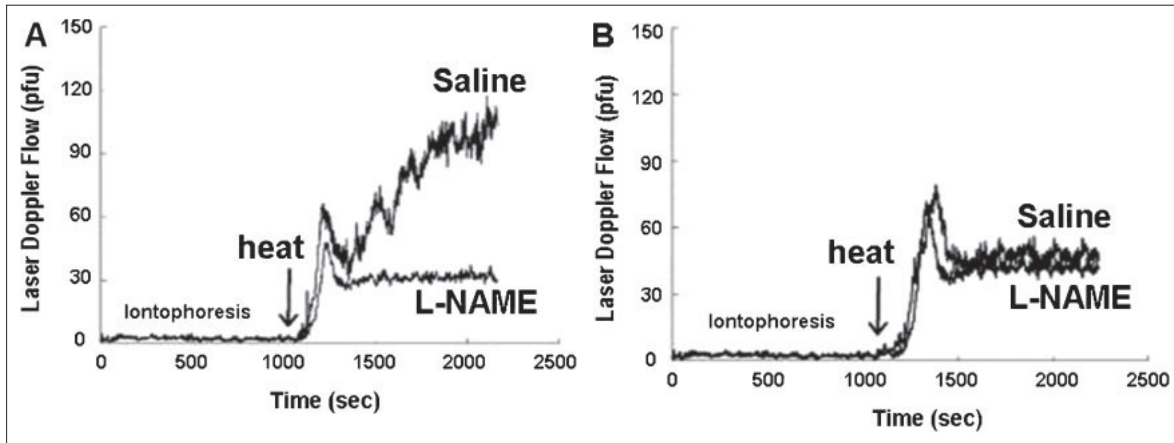
There is significantly decreased blood flow in POTS patients with high Pv (**middle right**) compared with control by  $\times 2$  and significantly increased leg blood flow in normal-Pv POTS patients (**bottom left** and **bottom right**) compared with control subjects. However, bottom data are bimodal, containing patients with normal blood flow and patients with increased blood flow. There appear to be (at least) 2 populations of POTS patients with normal Pv distinguished by blood flow and peripheral arterial resistance. (Adopted from Ref. 61)

blood volume, increased total peripheral resistance, and low resting cardiac output. They have a characteristic phenotype of pallor, extensive supine and upright acrocyanosis, cool skin and extremities, and defective skeletal muscle pump.<sup>61,65</sup> They are usually tachycardic while supine, more so during

orthostasis. Hyperemic blood flow, a measure of endothelial cell function, is abnormal compared with either control patients or patients with other subtypes of POTS, indicating abnormal local blood flow regulation in these patients. Medow et al.<sup>66</sup> have recently shown that abnormalities in the regulation



**Figure 6** Changes in thoracic, splanchnic, pelvic, and leg percent volume changes during upright tilt averaged over subject groups. Splanchnic changes dominate normal (NI)-flow POTS. Low-flow POTS patients have widespread blood collection. High-flow POTS patients have blood pooling in the dependent body parts. (Adopted from Ref. 61)



**Figure 7** **Left:** Saline or, *N* $\omega$ -nitro-L-arginine methyl ester hydrochloride (L-NAME; NO synthase inhibitor) administered to a representative reference subject by iontophoresis followed by local heating to 43°C. An initial peak occurs and is followed by a higher plateau after saline administration. Iontophoretic administration of L-NAME slightly blunts the initial peak and markedly decreases the plateau phase. **Right:** Local heating followed by saline or L-NAME in a representative low-flow POTS patient. The initial peak is present, but there is marked attenuation of the NO-dependent plateau, even after saline administration, which resembles blunting by the NO inhibitor L-NAME. Iontophoretic administration of L-NAME minimally blunts the initial peak but has no additional effect on the plateau phase because of preexistent impairment of NO release. (Adopted from Ref. 66)

of cutaneous blood flow are related to impairment of NO release in patients with low-flow POTS (Figure 7). Another report has shown that the frequencies of two polymorphisms that encode for endothelial NO synthase (eNOS) are significantly

lower in patients with POTS than in controls.<sup>67)</sup> This genotype may influence the development of POTS and the severity of POTS symptoms. It has been reported thoracic hypovolemia may be a result of increased angiotensin II, decreased renin, and rela-

tive hypovolemia in patients with low-flow POTS.<sup>62)</sup> Although increased blood volume may effectively alleviate signs and symptoms, no improvement after infusion of  $\beta$ -blocker was demonstrated in patients with low-flow POTS.

#### Normal-flow POTS

Some patients with POTS exhibit neither increased nor decreased recumbent blood flow compared with control subjects. These patients with so-called “normal-flow POTS” make up an increasing subset of identified patients. When supine, they appear perfectly well; when upright, however, they develop excessive tachycardia, greatly enhanced peripheral vasoconstriction, and often acrocyanosis. There are no findings suggesting a local peripheral defect. Instead, their excessive vasoconstriction appears to be related to thoracic hypovolemia and reciprocal splanchnic pooling.<sup>63)</sup>

#### High-flow POTS

Stewart et al.<sup>6,61)</sup> have indicated that patients designated as having “high-flow POTS” are peripherally vasodilated and mildly tachycardic when supine and have relatively increased blood volume, reduced total peripheral resistance, and high resting cardiac output compared with healthy control subjects. Support for a “long tract neuropathy” with a neuropathic adrenergic vasoconstrictive defect comes from Jacob et al.<sup>68)</sup> These patients exhibit defective peripheral vasoconstriction during orthostasis that leads to excess blood delivery to the lower limbs, enhanced microvascular filtration, and edema formation. Acrocyanosis does not generally occur in patients with this type of POTS. Persistent upright vasodilation responds to vasoconstrictor therapy with midodrine or similar agents. Patients are extremely likely to develop illness after a viral infection.<sup>37)</sup> A peripheral autoimmune neuropathy may be involved; if so, it is self-limiting, although its clinical course could extend for several months to 1 year or more.<sup>6)</sup>

#### Muscle pump defects

Physical forces comprise a primary defense against the pooling of blood in the dependent lower extremities in humans. This occurs through activity of the “skeletal muscle pump” in which contractions of leg and gluteal muscles increase interstitial pressure and propel sequestered venous blood back to the heart.<sup>69)</sup> Effectiveness of this pumping action is facilitated by the presence of one-way venous valves. Patients whose venous valves are incompetent or congenitally absent have severe OI.<sup>70)</sup>

**Table 6** Summary of treatment options for POTS

Non-pharmacological
<ul style="list-style-type: none"> <li>• Water and salt supplementation</li> <li>• Exercise</li> <li>• Elastic support hosiery</li> <li>• Catheter ablation (sinus node modification)*</li> </ul>
Pharmacological
<ul style="list-style-type: none"> <li>• Fludrocortisone</li> <li>• Desmopressin (DDAVP)</li> <li>• <math>\alpha</math>1-adrenoreceptor agonist (midodrine, phenylephrine)</li> <li>• <math>\beta</math>-blockers (propranolol, esmolol)</li> <li>• Central sympatholytic agents (clonidine, methyl dopa, phenobarbital)</li> <li>• Pyridostigmine</li> <li>• Ivabradine</li> <li>• Octreotide</li> <li>• Erythropoietin</li> <li>• Selective serotonin reuptake inhibitors (SSRIs)</li> <li>• Selective norepinephrine reuptake inhibitors (SNRIs)</li> <li>• Methylphenidate</li> </ul>

\*The efficacy of sinus node modification for POTS remains controversial.

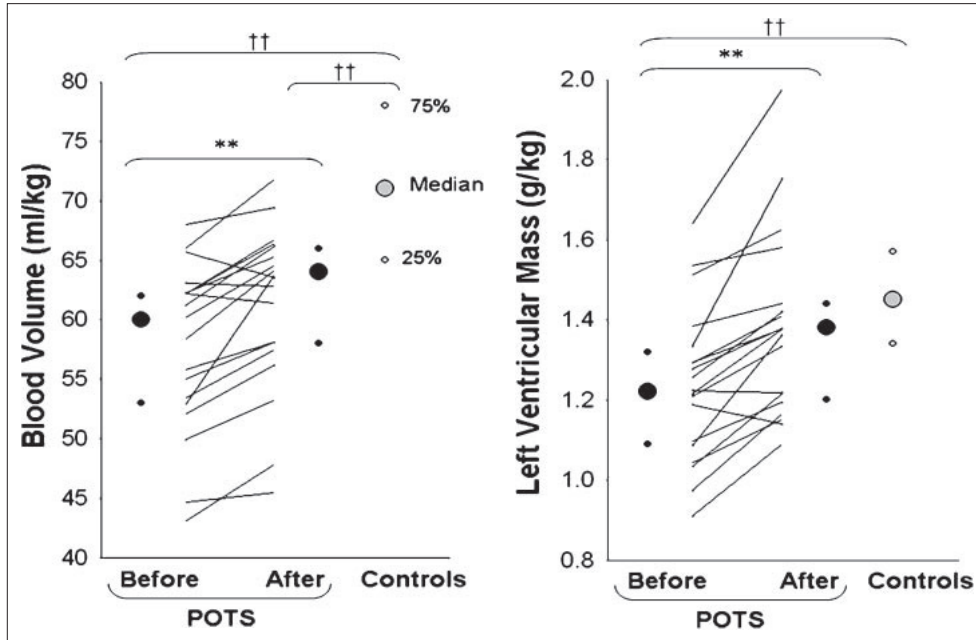
Skeletal muscle may also be involved in neurogenic compensation through chemoreceptors and local control mechanisms.<sup>71)</sup> Recent data indicate that, although most patients with POTS have a normal muscle pump, the muscle pump is defective in patients with low-flow POTS who also have decreased resting peripheral blood flow unrelated to exercise capability but exacerbated by bed rest.<sup>65)</sup> Ambulation is therefore essential for reduction of POTS symptoms.

#### Treatment

##### Non-pharmacological

Treatment of POTS (Table 6) is difficult because no single therapy has been shown to be effective, and large-scale blinded studies have not been performed yet.

Initially, any potentially reversible causes must be identified; these may require their own special treatment. Once a diagnosis has been established, patients and their families must be educated as to the nature of the disorder and necessity of avoiding any aggravating factors like dehydration, extreme heat, and consumption of alcohol. Increase in their fluid and sodium intake, and sleep with the heads of their beds slightly elevated to help condition their bodies to orthostatic stress are helpful to reduce symptom. To reverse the effects of hypovolemia, blood volume



**Figure 8** Blood volume and left ventricular mass in POTS patients before and after 3 months of exercise training and in controls. Values are expressed as individuals and median (25th, 75th percentiles). \*\*p < 0.01 compared with before training in the postural orthostatic tachycardia syndrome (POTS). ††p < 0.01 compared with controls. (Adopted from Ref. 73)

expansion can be achieved rapidly by infusion of saline. Infusion of 1 L saline over 1 hour significantly reduces tachycardia in subjects with POTS.<sup>68)</sup> The beneficial effects of saline infusion are sometimes delayed by a day or more. Although volume expansion is effective and provides relatively rapid relief from symptoms, it is seldom a practical option for regular, prolonged use, as the vascular access required for this procedure is associated with risk of infection. Major treatment modalities are listed in **Table 6**.

Aerobic exercise and resistance training are also beneficial.<sup>72)</sup> Patients with POTS should therefore be encouraged to slowly work up to doing aerobic exercise for 20 min 3 times per week.<sup>34)</sup> An exercise program incorporating regular aerobic exercise and lower limb resistance training may aid blood volume expansion and reverse deconditioning. In a randomized controlled trial, endurance exercise training (a 3-month jogging program, starting at 30 min of jogging per day, 3 days per week, and increasing the duration by 10 min each month up to 50 min per day, 3 days per week) improved OI symptoms in POTS patients.<sup>72)</sup> More recently, Fu et al.<sup>73)</sup> have reported that short-term exercise training increased cardiac size and mass and expanded blood and plasma volume, and thus improved or even cured POTS (**Figure 8**). This suggests that POTS per se is in fact

a consequence of deconditioning, and carefully prescribed exercise training can be used as an effective nondrug therapy for POTS patients. Patients with signs of deconditioning may benefit from initial exercise training in a swimming pool. This confers the benefits of both buoyant support and hydrostatic pressure-enhanced venous return. Exercise has the added benefit of increasing blood volume, thereby diminishing hypovolemia-related symptoms. Elastic support garments such as pantyhose and Lycra bicycle shorts and leggings can also minimize venous pooling and enhance venous return. These are most useful if they can provide 30 to 40 mm Hg counterpressure.<sup>37)</sup>

#### Pharmacological

##### *Fludrocortisone and desmopressin (DDAVP)*

For long-term treatment of patients with hypovolemia, a mineral corticoid agent, fludrocortisone, is often used. It not only expands plasma volume but also appears to sensitize peripheral  $\alpha$ -adrenergic receptors to the patient's own catecholamines.<sup>74)</sup> Fludrocortisone, bisoprolol or both improved the symptoms and lessened the hemodynamic abnormalities in patients with POTS.<sup>75)</sup> Side effects include hypokalemia and hypomagnesemia. Another volume expanding agent that may be helpful is

desmopressin (an oral vasopressin analog), especially in patients who complain of nocturnal polyuria. However, desmopressin may sometimes cause headaches and hyponatremia.<sup>34)</sup>

#### *$\alpha$ -1 adrenoceptor agonist*

Midodrine causes peripheral arterial and venous constriction, and improved symptoms and suppressed the heart rate response to tilting in patients with POTS.<sup>76)</sup> In another similar study, midodrine (10 mg) suppressed the standing heart rate but did not alter the standing time of nine POTS subjects.<sup>77)</sup> Midodrine (5–10 mg) reduced resting and upright heart rate significantly.<sup>68)</sup> It should be noted that all of these studies were concerned with acute rather than long-term POTS treatment. Intravenous phenylephrine improved OI and suppressed heart rate increase when the subject was tilted to an angle of 35 degrees in patients with POTS.<sup>78)</sup> Using strain gauge plethysmography, the same study showed that phenylephrine causes significant peripheral vasoconstriction and venoconstriction. Side effects include supine hypertension and piloerection.

#### *$\beta$ -blockers*

In patients with POTS, propranolol (single dose) reduced the resting heart rate, and the immediate and 5 min heart rate responses to tilt, though symptoms did not improve.<sup>76)</sup> Long-term propranolol (10 mg daily) can be used successfully in the treatment of POTS and to alleviate associated symptoms.<sup>79)</sup> Esmolol, a  $\beta$ -1 adrenergic antagonist (rapid onset and a very short duration of action), did not improve OI or hemodynamics in patients with POTS.<sup>78)</sup> Dose-limiting side effects include fatigue and postural hypotension that could contribute to dizziness.

#### *Central sympatholytic agents*

Agents with central sympatholytic activity can be helpful in the treatment of selected patients, but they should be used carefully as some patients can be quite sensitive to their effects. Clonidine, an  $\alpha$ -2 agonist with a central sympatholytic effect, has been one of the most effective agents against POTS.<sup>80)</sup> Clonidine can stabilize heart rate and blood pressure in patients with a high degree of postganglionic sympathetic involvement and hypersensitive post-junctional  $\alpha$ -2 receptors (which are abundant in the venous system). Some groups have reported similar success with methyl dopa, while other groups have suggested that phenobarbital may also be useful.<sup>28,33)</sup> These agents may cause drowsiness, dry mouth, or dizziness. Due to their effects on blood pressure, central sympatholytic agents should be reserved for

patients exhibiting hemodynamic and symptomatic changes consistent with hyperadrenergic POTS. Although they are often recommended as treatment possibilities in expert reviews,<sup>28,33)</sup> only very limited evidence supports such use; instead, their use should be limited to patients with refractory symptoms on a trial basis.

#### *Pyridostigmine*

The acetylcholinesterase inhibitor pyridostigmine is used successfully to treat POTS.<sup>81)</sup> It achieves this effect by increasing the availability of acetylcholine at both ganglionic nicotinic acetylcholine receptors and postganglionic muscarinic acetylcholine receptors. This results in increased parasympathetic tone, increased cardiovagal tone, and decreased heart rate.<sup>81)</sup> Procholinergic side effects include diarrhea and excess salivation.

#### *Ivabradine*

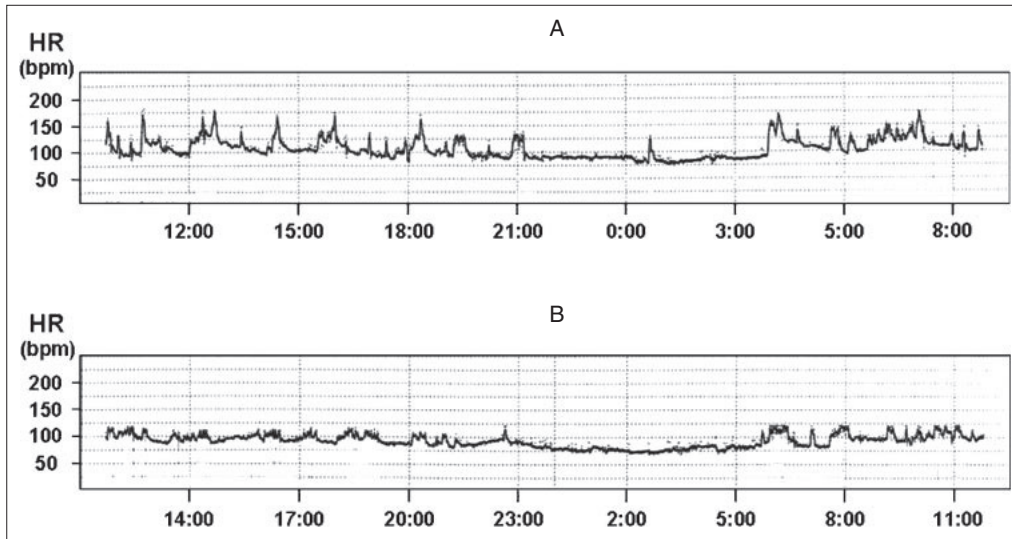
Ivabradine is a selective inhibitor of cardiac pacemaker  $I_f$  current that contributes to sinus node automaticity. This selectivity confers an ability to reduce heart rate without affecting inotropic or dromotropic activity. Some investigators have suggested that ivabradine could be used in the treatment of POTS.<sup>82)</sup> We have also reported a POTS patient in whom ivabradine significantly reduced heart rate upon standing and dramatically improved orthostatic symptoms.<sup>83)</sup>

#### *Octreotide*

Octreotide, a somatostatin analog, produces systemic vasoconstriction as well as selective splanchnic vasoconstriction, and is used for the treatment of POTS, postprandial hypotension, and hypotension associated with diabetic neuropathies.<sup>19)</sup> Its use is, unfortunately, limited by side effects that include abdominal pain and diarrhea, and inconvenience of subcutaneous administration. It is used successfully in combination with midodrine hydrochloride, which seems to potentiate its effects.<sup>84)</sup>

#### *Erythropoietin*

Erythropoietin is a growth factor that stimulates production of red blood cells in the bone marrow, thereby increasing red blood cell mass and central blood volume. Erythropoietin increases sensitivity to angiotensin II with vasoconstrictive effects.<sup>85,86)</sup> A single observational study yielded little objective evidence for efficacy of erythropoietin against POTS.<sup>87)</sup> Erythropoietin is occasionally suggested for patients with refractory symptoms, where conservative or evidence-based approaches have failed.



**Figure 9** Heart rate trend from Holter monitoring in a 42-year-old woman with POTS. Tachycardia responses to standing were frequently demonstrated before the atrioventricular node ablation (**panel A**). Following the procedure, these responses were effectively suppressed and heart rate seldom reached the upper tracking rate of 120 bpm of the pacemaker (**panel B**). HR = heart rate. (Adopted from Ref. 83)

*Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs)*

Efficacy of SSRIs in preventing neurocardiogenic syncope and OH has been demonstrated in a double-blind, randomized, placebo controlled trial and in various observational studies.<sup>88,89</sup> Serotonin plays an important role in central control of both heart rate and blood pressure.<sup>90</sup> Despite the fact that SSRIs have been documented as a useful treatment option for POTS, this is anecdotal and there is no experimental evidence of their efficacy in this context.

There are similar anecdotal descriptions, but no evidence, of the efficacy of venlafaxine, an SNRI. Venlafaxine has cardiovascular side effects including tachycardia, palpitation, OH, and an increase in mean arterial pressure.<sup>91</sup> In healthy subjects, SNRIs (reboxetine and sibutramine) reduce tilt-induced syncope or pre-syncope and increase supine blood pressure, but are associated with a significant increase in heart rate pre- and post-tilting.<sup>92,93</sup>

*Methylphenidate*

Methylphenidate causes vasoconstriction by increasing presynaptic catecholamine release, decreasing reuptake, and inhibiting monoamine oxidase. Methylphenidate is useful for treatment of vasovagal syncope<sup>94</sup> and suggested to reduce postural symptoms in POTS; however, there is no evidence for this.

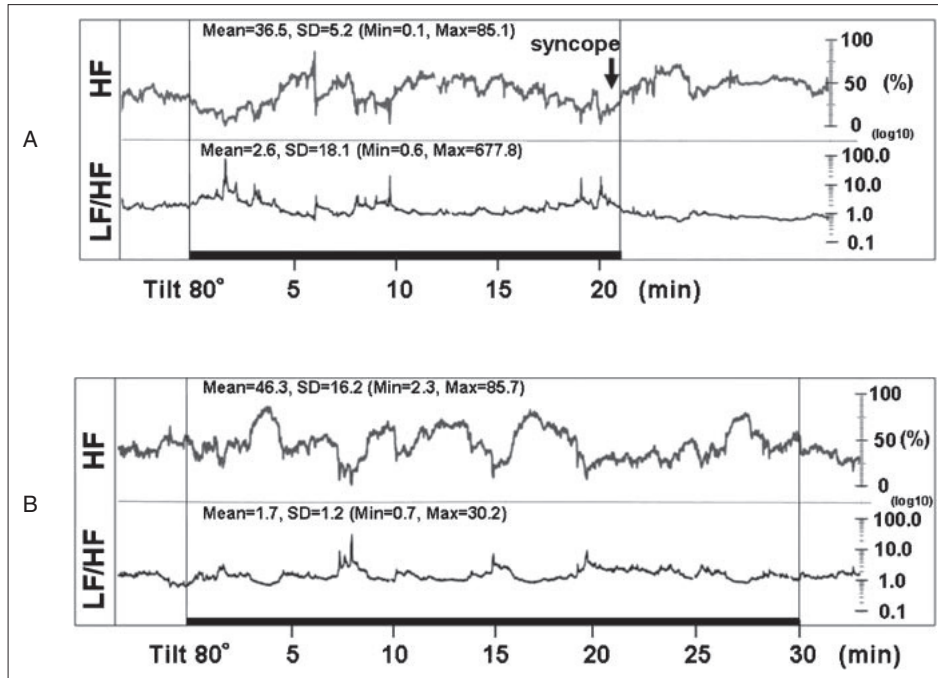
**Catheter ablation**

The efficacy of sinus node modification in patients

with POTS remains controversial. Shen et al.<sup>95</sup> have reported that sinus rate was effectively slowed by sinus node modification, but clinical symptoms did not significantly improve. Moreover, in some patients, sinus node modification worsened the symptoms of cerebrovascular hypoperfusion because of uncompensated central hypovolemia. In contrast, Brady et al.<sup>96</sup> reported that sinus node modification improved orthostatic symptoms in POTS patients with a pathophysiology resembling inappropriate sinus tachycardia. Because of the heterogeneous etiologies of POTS patients, the effects of sinus node modification could differ greatly from patient to patient.

Only limited data have been published regarding the efficacy of atrioventricular node ablation and pacemaker implantation therapy in patients with POTS. Shen et al.<sup>95</sup> reported four patients with POTS in whom atrioventricular node ablation and pacemaker implantation were performed, yet in whom most of the extracardiac symptoms remained unrelieved. In contrast, we have recently reported a patient with drug-refractory POTS in whom atrioventricular node ablation and pacemaker implantation dramatically improved symptoms and eliminated syncope.<sup>83</sup> In our patient, sinus rate upon standing was suppressed by the procedure, and heart rate variability analyses revealed a decrease in the ratio of low-frequency to high-frequency components along with an increase in the high-frequency component during a head-up tilt test, indicating





**Figure 10** Analysis of heart rate variability during head-up tilt tests before (A) and after (B) the atrioventricular node ablation and pacemaker implantation in the same patients with **Figure 9**. The analysis using only sinus rhythm demonstrated suppression of spiky increases in the low frequency component/high frequency component ratio (LF/HF) and increases in the high frequency component (HF) in the upright position following the procedure. (Adopted from Ref. 83)

postprocedural suppression of the patient's excessive sympathetic drive upon standing (**Figures 9** and **10**). On the other hand, Kanjwal et al.<sup>97)</sup> have recently reported a series of 6 patients who developed new-onset POTS following successful slow pathway ablation for atrioventricular nodal reentrant tachycardia. Damage to the vagal fibers supplying the sinus and atrioventricular nodal area was suggested as a possible mechanism for the onset of POTS. Because cardiac adrenergic and cholinergic nerves are closely juxtaposed,<sup>98)</sup> cholinergic and adrenergic withdrawal could occur after ablation of the atrioventricular nodal area, possibly depending on differences in ablation procedures, e.g., sites and amounts of application of radiofrequency energy.

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