



# Updates in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is the most common form of orthostatic intolerance in young people. However, it is still considered an underrecognized disorder and so deserves more attention from clinicians. This review covers the diagnostic challenges, correlations between the symptoms, evidence of autoimmune involvement in the pathogenesis, and treatment strategies in POTS.

**Key words:** Postural orthostatic tachycardia syndrome; Diagnosis; Symptoms; Autoimmunity; Treatment

## INTRODUCTION

Postural tachycardia syndrome (POTS) is a common cause of orthostatic intolerance that is characterized by an excessive increase in heart rate (HR) upon standing.<sup>1,2</sup> POTS not only causes the well-recognized symptoms of dizziness and palpitation, but also various other symptoms including headache, fatigue, profuse perspiration, blurred vision, difficulty concentrating, and gastrointestinal discomfort.<sup>3,4</sup> The clinical significance of POTS has recently increased with findings of associations with depression,<sup>5,6</sup> sleep disturbance,<sup>7</sup> chronic fatigue syndrome,<sup>8-10</sup> and diminished quality of life (QOL).<sup>7,11</sup> Despite the increased prevalence of POTS reported over the past 2 decades due to the increased awareness of this syndrome,<sup>1</sup> it is still considered an underdiagnosed disease and deserves more attention from clinicians.<sup>4,12</sup>

## DIAGNOSTIC CHALLENGES: MULTIPLE PHENOTYPES AND DIURNAL VARIABILITY

POTS can be diagnosed in patients with orthostatic intolerance symptoms when the fol-

lowing criteria are fulfilled: HR increment of  $\geq 30$  beats/min (or  $\geq 40$  beats/min in individuals aged 12-19 years) within 10 minutes of standing or head-up tilting, and in the absence of orthostatic hypotension (a decrease in systolic blood pressure [BP] of  $\geq 20$  mmHg and/or decrease in diastolic BP of  $\geq 10$  mmHg) and other causes of tachycardia.<sup>13,14</sup> However, there are challenges associated with diagnosing POTS. For example, patients often present with various symptoms other than the typical ones of dizziness and palpitations, which may obscure an accurate diagnosis.<sup>1</sup> Many POTS patients complain of headache, depression, fatigue, difficulty concentrating, and gastrointestinal disturbances such as abdominal pain and irregular bowel movements.<sup>12,15</sup> Therefore, an accurate POTS diagnosis requires a detailed knowledge of the history of the patient's symptoms.

Many patients also complain of worsening of symptoms in the morning with subsequent improvement throughout the course of the day, which may be explained by the diurnal variability of hemodynamic parameters.<sup>16</sup> It has been demonstrated that orthostatic HR increments are greater in the morning than in the afternoon, and so some patients may fulfill the criteria for POTS in the morning but not later in the day.<sup>17</sup> This discrepancy is probably due to the physiological changes that occur during sleep associated with being supine for a prolonged period without any fluid intake.<sup>1</sup> Therefore, when there is clinical suspicion of POTS, repeated orthostatic vital-sign tests should be conducted, including one in the early morning.

## ORTHOSTATIC INTOLERANCE SYMPTOMS IN POTS

Orthostatic intolerance is the main characteristic of POTS,<sup>15</sup> and can manifest as a variety of symptoms such as headache, dizziness, nausea, lightheadedness, blurred vision, palpitations, tremors, and difficulty concentrating.<sup>4,15</sup> It has been reported that the degree of orthostatic HR increment is not directly correlated with clinical symptoms, probably due to the diurnal variability of orthostatic tachycardia.<sup>3</sup> However, the severity of orthostatic intolerance symptoms is significantly correlated with depression and QOL. In particular, chest discomfort and difficulty concentrating are strongly associated with depression, and nausea and difficulty

concentrating are associated with diminished QOL.<sup>3</sup>

## EVIDENCE FOR AUTOIMMUNITY

The exact pathogenesis underlying POTS remains unknown. Several clinical characteristics support the possibility that POTS is an autoimmune disorder, such as female predominance, preceding viral illness, prior vaccination history, and coexistence of other autoimmune disorders, characteristics that are frequently reported in other autoimmune diseases.<sup>18</sup>

There have been many reports describing patients who developed POTS after receiving a polyvalent human papilloma virus (HPV) vaccine.<sup>19-24</sup> However, the American Autoimmune Society recently issued a statement concluding that the available evidence was insufficient to confirm a causal relationship between receipt of an HPV vaccination and development of POTS.<sup>25</sup>

The presence of various types of autoantibody in patients with POTS and their effects on cholinergic and adrenergic receptors has been found in numerous studies.<sup>26,27</sup> While the presence of antibodies to ganglionic acetylcholine receptors (AChRs) has both low sensitivity and specificity for a POTS diagnosis, antibodies to adrenergic receptors are likely to be involved in the pathogenesis and can be used as a potential diagnostic biomarker.<sup>28</sup> One group found that most patients with POTS harbored antibodies that activate the  $\beta 1$  adrenergic receptor, while a smaller proportion of patients had antibodies that activate the  $\beta 2$  adrenergic receptor and also act as partial agonists/antagonists to  $\alpha 1$  receptors.<sup>18,27</sup> Moreover, patients with POTS have a higher positive rate of antinuclear antibodies than general population,<sup>29</sup> as well as a higher incidence of systemic autoimmune disease, including Hashimoto's thyroiditis, Sjögren's syndrome, lupus, and rheumatoid arthritis.<sup>28</sup> Therefore, it has been suggested that POTS should be considered a novel member of the family of autoimmune disorders.<sup>25</sup>

An association with human leukocyte antigen allele status was recently reported in Korean patients with severe POTS, defined as an orthostatic HR increment of  $\geq 50$  beats/min or experiencing syncope/near-syncope during orthostatic vital-signs measurement.<sup>30</sup> Seven of 17 patients (41%) harbored *DQB1\*06:09* and six (35%) had the *A\*33:03-B\*58:01-*

C\*03:02-DRB1\*13:02-DQB1\*06:09 haplotype, a significantly higher proportion than was found among healthy Koreans (Table 1).<sup>30</sup>

Based on these findings, at least a proportion of POTS cases should be considered autoimmune in nature. The development of the first animal model of POTS, achieved by immunization of rabbits with adrenergic receptor peptides,<sup>31</sup> promises to be useful for future mechanistic studies. These animals exhibit POTS-like phenotypes *in vivo*, such as orthostatic tachycardia.<sup>32</sup>

## TREATMENT

### Nonpharmacological management

Many nonpharmacological therapies are available for the treatment of POTS,<sup>33</sup> among which lifestyle modification and exercise are the two mainstays. Drinking 500 mL of

water quickly before getting out of bed in the morning or before prolonged standing is recommended, while standing up abruptly from a sitting or recumbent position should be avoided. A leg-crossing maneuver is a practical measure that can be used when patients encounter situations that require a prolonged upright posture. It is also important to avoid situations that can exacerbate symptoms, including heat exposure, consuming a large meal, and drinking alcohol.<sup>1</sup>

Exercise is an essential part of POTS treatment,<sup>34</sup> with isometric exercises and squatting being particularly beneficial.<sup>35</sup> Isometric exercises involve contracting muscles without moving the body, such as the leg-pillow squeeze or arm-pillow squeeze, acting to compress the muscles and push the blood back toward the heart. These are simple exercises that can be done at any time while sitting in a chair or lying in a bed. Reclined aerobic exercise, such as swimming or recumbent bicycling, is also highly beneficial.<sup>36</sup>

The major challenge of nonpharmacological treatment is the achievement of regular and consistent patient compliance for at least 3 months.<sup>1,37</sup> Some patients will complain that they feel more fatigued during the first week of exercise, which may lead to them stopping the exercise program.

**Table 1.** Evidence for an autoimmune component in POTS

Evidence supporting autoimmunity in POTS
Female predominance
History of preceding viral infection
HLA associations: <i>DQB1*0609</i> ( <i>A*3303-B*5801-C*0302-DRB1*1302-DQB1*0609</i> haplotype)
Autoantibodies: antiadrenergic receptor Abs, anti-AChR Abs (increased prevalence of antiphospholipid Abs, antinuclear Abs)
Response to immunotherapy: demonstrated in small case-series studies (warrants further investigation)

POTS, postural tachycardia syndrome; HLA, human leukocyte antigen; Abs, antibodies; AChR, acetylcholine receptor.

### Pharmacological treatments

Given the low compliance with exercise interventions, pharmacological treatment should be initiated early in POTS patients. The symptoms of POTS are known to worsen in a vicious cycle. They may develop in susceptible individuals after certain triggering events such as infection, concussion, and enforced bedrest. Orthostatic intolerance in these patients consequently leads to diminished activity, cardiovascular deconditioning, and worsening of symptoms.<sup>1</sup> It is

**Table 2.** Pharmacological treatments for POTS

Drug	Dosing information	Side effects
Propranolol	10-20 mg up to four times daily	Hypotension, bradycardia, bronchospasm
Bisoprolol	2.5-5 mg daily	Headache, bradycardia, nausea
Pyridostigmine	30-60 mg up to three times daily	Diarrhea, vomiting, abdominal cramps
Midodrine	2.5-15 mg three times daily	Headache, supine hypertension
Fludrocortisone	0.1-0.2 mg daily	Hypokalemia, edema, headache
Desmopressin	0.1-0.2 mg as needed	Hyponatremia, edema
Droxidopa	100-600 mg three times daily	Headache, nausea, hypertension, tachycardia

POTS, postural tachycardia syndrome.

important to break this vicious cycle as soon as possible after the diagnosis, using both nonpharmacological and pharmacological approaches.

The United States Food and Drug Administration has not yet approved any medications for POTS, but there are several agents that could be beneficial. Numerous studies have shown that beta-blockers such as propranolol<sup>38</sup> and bisoprolol,<sup>39</sup> the AChR inhibitor pyridostigmine,<sup>40</sup> the anti-hypotensive midodrine,<sup>41</sup> and the steroid fludrocortisone<sup>39</sup> and others are effective treatments for POTS (Table 2).<sup>42</sup> Several randomized trials have demonstrated the efficacy of propranolol, pyridostigmine, and midodrine for improving orthostatic tachycardia; however, most of the drug trials for these agents were designed to evaluate only the acute response (i.e., 2-4 hours after administration).<sup>38,40,41</sup> Few studies have investigated the sustained effects of daily medical treatments.<sup>43,44</sup>

My group recently demonstrated that four different treatment protocols consisting of propranolol or bisoprolol with or without pyridostigmine for 3 months were effective for improving orthostatic intolerance symptoms in patients with POTS.<sup>43</sup> A remarkable finding of this work is that 3 months of this medical treatment was also effective for improving symptoms of depression and diminished QOL, even without concomitant administration of antidepressants.

Given the potential involvement of autoimmune mechanisms in POTS, it is possible that immunotherapy can help improve the symptoms, or at least in a specific subgroup of patients. The efficacy of immunotherapies, including steroid pulse and intravenous immunoglobulin treatment, has yet to be established and warrants further investigation.

In summary, pharmacological treatment is an important part of the management of POTS, and is especially useful for the early improvement of symptoms when applied in combination with nonpharmacological management. After 3 months of combined treatment, medications can be reduced or maintained depending on the patient's persisting symptoms.

## CONCLUSION

POTS is a heterogeneous clinical syndrome that causes chronic orthostatic intolerance and is accompanied by other

medical conditions. It is important to understand that diurnal variability of hemodynamic parameters exists and that the symptoms of orthostatic intolerance are associated with depression and diminished QOL. The pathophysiology of POTS is not fully understood, but an autoimmune component has recently been proposed. An integrative approach combining nonpharmacological and pharmacological treatments is important for the management of this condition.

## Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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