Exercise Training Versus Propranolol in the Treatment of the Postural Orthostatic Tachycardia Syndrome

Qi Fu, Tiffany B. VanGundy, Shigeki Shibata, Richard J. Auchus, Gordon H. Williams, Benjamin D. Levine

See Editorial Commentary, pp XX–XX

Abstract—We have found recently that exercise training is effective in the treatment of the postural orthostatic tachycardia syndrome (POTS). Whether this nondrug treatment is superior to “standard” drug therapies, such as β-blockade, is unknown. We tested the hypothesis that exercise training but not β-blockade treatment improves symptoms, hemodynamics, and renal-adrenal responses in POTS patients. Nineteen patients (18 women and 1 man) completed a double-blind drug trial (propranolol or placebo) for 4 weeks, followed by 3 months of exercise training. Fifteen age-matched healthy individuals (14 women and 1 man) served as controls. A 2-hour standing test was performed before and after drug treatment and training. Hemodynamics, catecholamines, plasma renin activity, and aldosterone were measured supine and during 2-hour standing. We found that both propranolol and training significantly lowered standing heart rate. Standing cardiac output was lowered after propranolol treatment (P=0.01) but was minimally changed after training. The aldosterone:renin ratio during 2-hour standing remained unchanged after propranolol treatment (4.1±1.7 [SD] before versus 3.9±2.0 after; P=0.46) but modestly increased after training (5.2±2.9 versus 6.5±3.0; P=0.05). Plasma catecholamines were not affected by propranolol or training. Patient quality of life, assessed using the 36-item Short-Form Health Survey, was improved after training (physical functioning score 33±10 before versus 50±9 after; social functioning score 37±9 versus 48±6; both P<0.01) but not after propranolol treatment (34±10 versus 36±11, P=0.63; 39±7 versus 39±5, P=0.73). These results suggest that, for patients with POTS, exercise training is superior to propranolol at restoring upright hemodynamics, normalizing renal-adrenal responsiveness, and improving quality of life. (Hypertension. 2011;58:00-00.) ● Online Data Supplement

Key Words: long-term orthostasis • renin-angiotensin-aldosterone system • hemodynamics • β-blockade • quality of life

We have demonstrated recently that carefully prescribed short-term exercise training improves or even cures the postural orthostatic tachycardia syndrome (POTS), also called the “Grinch Syndrome,” because as a group, POTS patients have a heart that is “2 sizes too small.” Whether this nondrug treatment is superior to “standard” drug therapies, such as β-blockade, is unknown. Although β-blockers are used in POTS patients to empirically reduce tachycardia, the chronic effects of these medications are unclear.

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the neurohumoral regulation of hemodynamics during prolonged orthostasis in humans. Recent studies have shown that POTS patients have a blunted aldosterone response to an increase in renin, namely, a reduced aldosterone:renin ratio during standing. Raj et al termed this dysregulation in POTS the “renin-aldosterone paradox.” The underlying pathophysiology is unknown but may be related to sympathoexcitation and/or tachycardia. A similar reduced aldosterone:renin ratio has also been found in healthy individuals after a period of bed rest (ie, simulated microgravity exposure) in which “cardiovascular deconditioning” (ie, cardiac atrophy and hypovolemia) occurs. Numerous studies have demonstrated that real or simulated microgravity exposure elicits a “POTS-like” syndrome even in healthy fit people. Based on these findings, we speculated that the “deconditioning” phenotype rather than a secondary effect attributable to tachycardia contributes, at least in part, to the blunted adrenal response in POTS. If this model is true, we would expect to see an improvement in renal-adrenal function after “reconditioning” but not after lowering heart rate with β-blockade treatment.
The primary objective of this study was to test the hypothesis that, in POTS patients, increases in physical fitness with exercise training can improve upright hemodynamics and increase the aldosterone:renin ratio during orthostasis, whereas lowering upright heart rate by \( \beta \)-blockers alone does not. We further hypothesized that exercise training but not \( \beta \)-blockade treatment improves patient overall well being. To accomplish these objectives, we compared the effects of exercise training and a nonselective \( \beta \)-blocker, propranolol, on renal-renal and hemodynamic responses during prolonged (ie, 2 hours) standing in patients with POTS. Patient quality of life was assessed using the 36-item Short-Form Health Survey\(^{12} \) before and after propranolol treatment, as well as exercise training.

### Methods

#### Participants

Nineteen POTS patients (18 women and 1 man) completed a 4-week double-blind drug trial (propranolol or placebo), followed by 3 months of exercise training. All of the patients met the inclusion without exclusion criteria for POTS\(^{13} \) and had a heart rate rise \( \geq 30 \) bpm or a rate that exceeded 120 bpm that occurred after 10 minutes of standing without any evidence of orthostatic hypotension.\(^{1} \) All were nonsmokers. None was an endurance-trained athlete.\(^{14} \) All were screened with a careful medical history, physical examination, 12-lead ECG, and a 10-minute stand test. Patients had stopped taking medications that could affect the autonomic nervous system \( \geq 2 \) weeks before screening and \( \geq 4 \) weeks before testing. Fifteen age-matched healthy individuals (14 women and 1 man) served as controls. All were informed of the purpose and procedures used in the study and gave their written informed consent to a protocol approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

### Measurements

#### Heart Rate and Blood Pressure

Heart rate was monitored from the ECG (Hewlett-Packard), and beat-to-beat arterial pressure was derived by finger photoplethysmography (Portapres). Arm cuff blood pressure was measured by electroxysphymomanometry (SunTech), with a microphone placed.

## Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Controls (n=15)</th>
<th>Exercise Training (n=19)</th>
<th>Propranolol (n=9)</th>
<th>Placebo (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Age, y</td>
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<td>27±9</td>
<td>28±9</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>BMI, kg/m²</td>
<td>23±2</td>
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</tr>
<tr>
<td>Peak oxygen uptake, mL/kg per min</td>
<td>...</td>
<td>26±4</td>
<td>29±5*</td>
<td>...</td>
</tr>
<tr>
<td>Plasma volume, mL/kg</td>
<td>48±7</td>
<td>38±4†</td>
<td>40±4*†</td>
<td>38±6†</td>
</tr>
<tr>
<td>Blood volume, mL/kg</td>
<td>72±12</td>
<td>58±7†</td>
<td>61±7†</td>
<td>59±8†</td>
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<tr>
<td>Total hemoglobin mass, g/kg</td>
<td>9.09±2.77</td>
<td>7.49±0.89†</td>
<td>7.90±1.08*†</td>
<td>7.59±0.88†</td>
</tr>
<tr>
<td>Red blood cell volume, mL/kg</td>
<td>23.9±5.7</td>
<td>19.8±2.7†</td>
<td>20.8±3.0*†</td>
<td>20.7±3.2†</td>
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<tr>
<td>Hematocrit, %</td>
<td>37.8±3.4</td>
<td>39.2±2.8</td>
<td>38.7±3.1</td>
<td>39.9±3.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI indicates body mass index.

\( *P<0.05 \) compared with pretraining within the group.

\( †P<0.05 \) compared with healthy controls.

## Table 2. Blood and Urine Electrodes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Controls (n=15)</th>
<th>Exercise Training (n=19)</th>
<th>Propranolol (n=9)</th>
<th>Placebo (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Blood pH</td>
<td>7.40±0.04</td>
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<td>7.39±0.03</td>
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<td>Na⁺, mmol/L</td>
<td>138±1</td>
<td>137±3</td>
<td>138±2</td>
<td>137±2</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>4.2±0.4</td>
<td>4.3±0.4</td>
<td>4.3±0.3</td>
<td>4.4±0.4</td>
</tr>
<tr>
<td>Ca²⁺, mmol/L</td>
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<td>1.1±0.1</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
</tr>
<tr>
<td>24-h urine output mL</td>
<td>2142±805</td>
<td>2224±1037</td>
<td>2041±873</td>
<td>2088±1218</td>
</tr>
<tr>
<td>Osmolality, mosmol/kg</td>
<td>401±152</td>
<td>417±207</td>
<td>437±153</td>
<td>495±293</td>
</tr>
<tr>
<td>pH</td>
<td>6.48±0.26</td>
<td>6.53±0.24</td>
<td>6.53±0.24</td>
<td>6.52±0.31</td>
</tr>
<tr>
<td>Na⁺, mmol/24 h</td>
<td>149±57</td>
<td>158±60</td>
<td>157±61</td>
<td>151±76</td>
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<tr>
<td>K⁺, mmol/24 h</td>
<td>54±20</td>
<td>59±25</td>
<td>54±26</td>
<td>53±30</td>
</tr>
<tr>
<td>Ca²⁺, mmol/24 h</td>
<td>1.6±0.8</td>
<td>1.5±1.0</td>
<td>1.6±1.3</td>
<td>1.1±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Cardiac Output
Cardiac output was measured with the acetylene rebreathing technique, from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (Marquette), after adequate mixing in the lung has been confirmed by a stable helium concentration. Stroke volume was calculated from cardiac output and the heart rate measured during rebreathing. Total peripheral resistance was calculated as the quotient of mean arterial pressure and cardiac output, multiplied by 80 (expressed as dyn s cm⁻⁵). Mean arterial pressure was calculated as [(systolic pressure - diastolic pressure)/3]+diastolic pressure.

Protocol
All of the subjects were on an isocaloric diet consisting of 200 mEq of sodium, 100 mEq of potassium, and 1000 mg of calcium 3 days before testing. Fluid intake was ad libitum and assessed by 24-hour urine output the day before testing to verify dietary compliance. Female subjects were tested during the midluteal phase (19 to 22 days after the onset of menstruation) of their menstrual cycles to avoid the effects of sex hormone fluctuations on renal-adrenal and hemodynamic responses. Subjects were required not to exercise 2 to 4 times per week for 30 to 45 minutes per session by using a recumbent bike, rowing, or swimming. The use of only semirecumbent exercise at the beginning of the program was a critical strategy, allowing patients to exercise while avoiding the upright posture that elicits their symptoms. As the patients became relatively fit, the duration of the base training sessions was prolonged, and, subsequently, sessions of increased intensity (ie, maximal steady state)

over the brachial artery to detect Korotkoff sounds. Respiratory excursions were detected by a nasal cannula.

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Exercise Training Propranolol Placebo

Table 1 depicts subject characteristics. POTS patients had smaller plasma/blood volume, total hemoglobin mass, and red blood cell volume compared with healthy controls (all $P<0.05$). However, blood electrolytes, as well as 24-hour urine output, osmolality, and urine electrolytes were not different between patients and controls (Table 2).

Exercise Training

Three months of exercise training increased plasma/blood volume, total hemoglobin mass, and red blood cell volume in POTS patients (all $P<0.05$; Table 1). Blood electrolytes, as well as 24-hour urine output, osmolality, and urine electrolytes, remained unchanged after training (Table 2).

Systolic pressure was lower, whereas diastolic pressure tended to be lower during 2-hour standing after training (Figure 1). Standing heart rate was lower (Figure 2). Standing stroke volume remained stable, and standing cardiac output tended to be lower during 2-hour standing after training (Figure 2). Training did not affect plasma catecholamine increases modestly (21%) but had no impact on aldosterone increases during 2-hour standing (Figure 4). Thus, the aldosterone:renin ratio increased modestly after training (4.6±3.7 before versus 5.9±3.7 after in the supine position, 5.2±2.9 versus 6.5±3.0 after 2 hours of standing; ANOVA $P=0.05$ for training). Training did not affect plasma catecholamine increases during 2-hour standing (Figure 5). Three patients had presyncope before training, but only 1 patient had presyncope after training. Patient quality of life was improved substantially after training in this subset (Figure 6), as has been reported previously.1
Propranolol Treatment
Four weeks of propranolol treatment did not alter plasma/blood volume, total hemoglobin mass, or red blood cell volume in POTS patients (Table 1). Blood and urine electrolytes remained unchanged after treatment (Table 2). However, 24-hour urine output tended to be smaller \( (P = 0.08) \), which may be attributable to a decrease in cardiac output and renal blood flow induced by \( \beta \)-adrenergic blockade. Urine osmolality was similar after treatment compared with before treatment (Table 2).

Systolic pressure trended lower, whereas diastolic pressure was significantly lower during 2-hour standing after propranolol treatment (Figure 1). Standing heart rate was significantly lower, but standing stroke volume was not augmented by the lower heart rate after treatment (Figures 2 and 3). Standing cardiac output was, therefore, markedly lower (Figure 3). Standing total peripheral resistance did not change after propranolol treatment (Figure 2).

Propranolol attenuated both plasma renin activity and aldosterone increases during 2-hour standing (Figure 4), and, therefore, the aldosterone:renin ratio remained unchanged after treatment \( (3.6 \pm 1.4 \text{ before versus } 4.7 \pm 1.6 \text{ after in the supine position; } 4.1 \pm 1.7 \text{ versus } 3.9 \pm 2.0 \text{ after 2 hours of standing; } ANOVA \ P = 0.46 \text{ for treatment}) \). Propranolol did not affect plasma catecholamine increases during 2-hour standing (Figure 5). Two patients had presyncope before treatment, whereas 3 had presyncope after treatment. Patient quality of life remained unchanged after propranolol treatment (Figure 6). Placebo had no impact on plasma/blood volume, total hemoglobin mass, red blood cell volume, hemodynamic and renal-adrenal responses, orthostatic tolerance, and quality of life in POTS patients (Tables 1 and 2 and Figures 1 to 6).

Discussion
Our major findings are as follows: (1) in POTS patients, both propranolol treatment and exercise training lowered standing heart rate; (2) propranolol attenuated plasma renin activity and aldosterone increases during 2-hour standing, and, therefore, it did not change the aldosterone:renin ratio; (3) conversely, exercise training attenuated plasma renin activity increases with preserved increases in aldosterone during prolonged standing, so that the aldosterone:renin ratio increased; and (4) patient quality of life was improved with training but not with propranolol treatment, despite the markedly lower heart rate.

Thus, increases in physical fitness with exercise training improved the function of the RAAS and patient overall well being, whereas lowering heart rate by propranolol did not change the aldosterone-to-renin response or symptoms in POTS patients. It is suggested that the “deconditioning” phenotype rather than a secondary effect because of sympahtoexcitation/tachycardia contributes, at least in part, to the blunted adrenal responsiveness in POTS, and exercise training appears to be a more effective therapy than simply lowering the heart rate with \( \beta \)-blockade.
**Exercise Training**

In POTS patients, short-term exercise training lowered standing heart rate, which was attributable to a training-induced increase in baroreflex sensitivity. Blood pressure decreased to a lesser extent compared with propranolol treatment, stroke volume was preserved, cardiac output remained unchanged during prolonged standing after training. These results suggest that exercise training is superior to propranolol at restoring upright hemodynamics. More importantly, patient quality of life was significantly improved after training, which was distinctly different from propranolol treatment. In addition to POTS, exercise training has also been found to be effective for chronic fatigue syndrome and fibromyalgia.

Exercise training modestly attenuated plasma renin activity increases during prolonged standing in POTS patients, it did not change serum aldosterone during standing. Thus, the aldosterone:renin ratio increased, indicating that the adrenal responsiveness was improved with training. This result cannot be explained by plasma volume expansion. One previous study showed that the reduced aldosterone:renin ratio after simulated microgravity exposure was independent of plasma volume, because fluid loading after bedrest did not normalize this ratio. There are 3 well-defined control mechanisms for aldosterone secretion, the RAAS, potassium, and adrenocorticotropic hormone (ACTH). In POTS patients, training-induced suppression of renin release would have caused a decrease in aldosterone secretion. Therefore, the RAAS did not seem to contribute to the increased aldosterone:renin ratio after training. Potassium was also not responsible for the increased aldosterone:renin ratio, because plasma potassium concentration and 24-hour urine potassium excretion did not differ after training compared with before training. It has been found that exercise training increases plasma ACTH levels in humans, ACTH, a pituitary peptide, has some stimulating effects on aldosterone probably by stimulating the formation of deoxycorticosterone, a precursor of aldosterone. It is, therefore, possible that training augmented the effect of

![Figure 4. Plasma renin activity (PRA) and aldosterone (ALDO) increases during 2-hour standing in healthy controls (○) and in postural orthostatic tachycardia syndrome (POTS) patients before (□) and after (●) drug treatment or exercise training. S indicates supine. Values are expressed as mean±SE. *P<0.05 compared with before treatment within the group. †P<0.05 compared with healthy controls.](http://hyper.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.111.173091?journalID=HYT&doi=10.1161/HYPERTENSIONAHA.111.173091)
ACTH on aldosterone production during standing; however, the relationship of ACTH pulsations to adrenal responsiveness is complex and beyond the scope of this study. Because dopamine suppresses aldosterone secretion, and atrial natriuretic factor is an antagonist of aldosterone secretion, training-induced changes in dopamine and/or atrial natriuretic factor levels also have contributed to the increased aldosterone:renin ratio in POTS patients. Unfortunately, we did not measure ACTH, dopamine, and atrial natriuretic factor. Future studies are needed in this regard.

**Figure 5.** Plasma norepinephrine and epinephrine concentration (NE and Epi) responses during 2-hour standing in healthy controls (▲) and in postural orthostatic tachycardia syndrome (POTS) patients before (●) and after (▲) drug treatment or exercise training. S indicates supine. Values are expressed as mean±SE.

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**Figure 6.** Effects of exercise training, propranolol, and placebo treatment on patient quality of life assessed by the 36-item Short-Form Health Survey. Values are expressed as individuals and mean±SE.
Although 3 months of training increased aldosterone:renin ratio in POTS patients, this ratio was still far below the levels of healthy sedentary individuals (ie, 6.5±3.0 after training in POTS patients versus 14.0±7.2 in healthy controls after 2 hours of standing\textsuperscript{3}; \(P<0.001\)). It is possible that 3 months of training may not be long enough to restore the adrenal function to the normal level in these patients. Whether a longer duration of training can normalize the function of the RAAS in POTS patients needs to be determined in future studies.

Effects of Propranolol in POTS
Studies regarding the effectiveness of \(\beta\)-blockers in POTS have been limited, and the results are inconsistent (see the online Data Supplement and Table S1 at http://hyper.ahajournals.org for details). Raj et al\textsuperscript{[4]} reported recently that acute administration of low-dose (20 mg) oral propranolol significantly attenuated tachycardia and improved symptoms in POTS, whereas a high dose (80 mg) of propranolol did not further improve, and may worsen, symptoms. We used long-acting propranolol (80 mg daily), which is similar to the low dose on a chronic basis. Upright heart rate was normalized to the level of healthy controls after 4 weeks of treatment, but patient quality of life remained unchanged, suggesting that chronic propranolol treatment cannot improve patient overall well being. It is likely that the markedly reduced cardiac output and blood pressure after propranolol treatment during upright posture could worsen fatigue and/or dizziness, especially if the heart rate rise in the untreated state is “appropriate.” Our results indicate that propranolol is no better than placebo on average, although we must acknowledge that some patients did improve symptoms, perhaps because of a decrease in palpitations.

Propranolol is a nonselective \(\beta\)-adrenergic blocker; as a consequence, it blocks \(\beta\)-receptors located on the juxtaglomerular cells of the kidney, resulting in a decrease in renin secretion.\textsuperscript{[5]} In addition, there is evidence that \(\beta\)-blockers may also inhibit intrarenal conversion of prorenin to renin.\textsuperscript{[6]}

Whether propranolol can block renal baroreceptor-mediated renin release in humans is unknown. One previous investigation in hypertensive patients showed parallel suppression of angiotensin II and plasma renin activity during \(\beta\)-blocker therapy.\textsuperscript{[7]} Angiotensin II is a major physiological stimulus for aldosterone production; a decrease in angiotensin II may cause a suppression of aldosterone release from the adrenal cortex.\textsuperscript{[8]} However, this assumption is not supported by the studies of Stewart et al\textsuperscript{[9]} and Mustafa et al.\textsuperscript{[10]} showing that some POTS patients have inappropriately high plasma angiotensin II but low aldosterone levels. It has been suggested that suppression of aldosterone can cause the retention of potassium by the kidney. Because small changes in plasma potassium content can suppress renin release, it is likely that propranolol-induced hyperkalemia might also contribute to the inhibition of renin release by this drug.\textsuperscript{[11]}

It was shown previously that, in cirrhotic patients, propranolol treatment did not alter the ratio between the 2 main RAAS mediators, namely, the angiotensin-1-7:angiotensin II ratio,\textsuperscript{[12]} which has been used to evaluate the final functional effect of the RAAS. Consistent with this finding, we observed in POTS patients for whom the aldosterone:renin ratio remained unchanged after propranolol treatment. These results support the notion that nonselective \(\beta\)-adrenergic blockers suppress the RAAS but do not affect the final functional effect of this system in humans.

Perspectives
Patients with POTS have a blunted aldosterone:renin response during orthostasis. Results from our study suggest that the blunted adrenal function in these patients appears to be a consequence or signature of “cardiovascular deconditioning” rather than a secondary effect attributed to sympathoexcitation or tachycardia. Given the fact that exercise training but not propranolol treatment improved adrenal function, POTS symptoms, and, most importantly, patient quality of life, it is reasonable to conclude that this nondrug therapy is superior to \(\beta\)-blockers. Because there are no effective pharmacological therapies for POTS patients so far, and many patients have disabling adverse effects with standard drug treatments, exercise training would appear to be the best initial therapy for this condition. It is important to emphasize that even the most symptomatic patients completed our training program, and that training was facilitated by avoiding upright exercise in the early stage. This training program has been found to be effective for POTS patients in a research setting in this and our recent studies.\textsuperscript{[1]}

Whether it is also effective in a community environment (ie, outside the constraints of a controlled clinical trial) needs to be determined.

Acknowledgments
The time and effort put forth by the patients is greatly appreciated. We thank Robin P. Shook, Kazunobu Okazaki, Jeffrey L. Hastings, M. Dean Palmer, Daniel L. Cresent, Colin L. Conner, Diane Bedenkop, and Peggy Fowler for their valuable laboratory assistance.

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Disclosures
None.

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Exercise Training versus Propranolol in the Treatment of the Postural Orthostatic Tachycardia Syndrome

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Running title: Drug vs. Nondrug Therapy in POTS

DISCUSSION

Studies regarding the effectiveness of β-blockers in POTS have been limited and the results are inconsistent. Table S1 summaries the current literature on β-blockers in POTS patients. Data on chronic β-blockade treatment in POTS are lacking. Future research is needed in this regard.

REFERENCES

Table S1. The Effectiveness of β-Blockers in POTS

<table>
<thead>
<tr>
<th>Types</th>
<th>Authors, Year, Reference</th>
<th>Agents</th>
<th>Patient Characteristics</th>
<th>Study Design</th>
<th>Measured Variables</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β-blockers</td>
<td>Sumiyoshi et al, 1999¹</td>
<td>Propranolol (oral, 10 mg daily)</td>
<td>1 male POTS patient (age 16 y)</td>
<td>Case report, treatment duration not reported</td>
<td>Heart rate variability, clinical symptoms</td>
<td>Effective, symptoms abolished, orthostatic tolerance improved</td>
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<tr>
<td></td>
<td>Abe et al, 2000²</td>
<td>Propranolol (oral, 30 mg)</td>
<td>POTS patients (8 women, 2 men, age 15-28 y)</td>
<td>Acute case-control study</td>
<td>Heart rate, clinical symptoms</td>
<td>Symptoms abolished in ~70% of patients</td>
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<td>Gordon et al, 2000³</td>
<td>Propranolol (oral, 40 mg)</td>
<td>POTS patients (20 women, 1 man, age 14-39 y)</td>
<td>Acute, randomized crossover design</td>
<td>Heart rate, blood pressure, symptom scores</td>
<td>Tachycardia improved, symptom tended to be improved</td>
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<td></td>
<td>Freitas et al, 2000⁴</td>
<td>Bisoprolol</td>
<td>POTS patients (n = 11, all women)</td>
<td>Acute case-control study</td>
<td>Heart rate, blood pressure, baroreflex, orthostatic tolerance</td>
<td>Improved greatly</td>
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<td></td>
<td>Raj et al, 2009⁵</td>
<td>Propranolol (oral, low-dose 20 mg or high-dose 80 mg)</td>
<td>POTS patients (~90% women, mean age 34 y)</td>
<td>Acute, randomized crossover design</td>
<td>Heart rate, blood pressure, symptoms</td>
<td>Effective, low-dose was better than high-dose</td>
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<td>Selective β₁-blockers</td>
<td>Stewart et al, 2002⁶</td>
<td>Esmolol (rapid infusion 300 μg/kg for 3 min, then at 200 μg/kg/min to attain a ~20% decrease in heart rate)</td>
<td>POTS patients (11 girls, 3 boys, age 13-19 y)</td>
<td>Acute case-control study</td>
<td>Heart rate, blood pressure variability, peripheral blood flow, orthostatic tolerance</td>
<td>Did not improve orthostatic tolerance or hemodynamics</td>
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<td></td>
<td>Seeck et al, 2002⁷</td>
<td>Bisoprolol (oral, 5 mg/day for 10 wks)</td>
<td>1 female POTS patient with partial epilepsy (age 20 y)</td>
<td>Case report</td>
<td>Heart rate, blood pressure</td>
<td>Effective, tachycardia and associated anxiety disappeared</td>
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<td></td>
<td>Chen et al, 2007⁸</td>
<td>Metoprolol (oral)</td>
<td>POTS patients (n = 27, 50% women, age 5-19 y)</td>
<td>Randomized design</td>
<td>Clinical symptoms</td>
<td>Improved in ~69% of patients</td>
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<td>Lai et al, 2009⁹</td>
<td>Metoprolol or atenolol (treated for &gt;6 mo in 64% of patients)</td>
<td>POTS patients (11 women, 3 men, age 11-17 y)</td>
<td>Retrospective study, single center, chart review, survey</td>
<td>Heart rate, clinical symptoms</td>
<td>Symptom improved in 57% of patients</td>
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</tbody>
</table>