Endothelial NO Synthase Polymorphisms and Postural Tachycardia Syndrome

Emily M. Garland, Robert Winker, Scott M. Williams, Lan Jiang, Krista Stanton, Daniel W. Byrne, Italo Biaggioni, Ingolf Cascorbi, John A. Phillips III, Paul A. Harris, Hugo Rüdiger, David Robertson

Abstract—Postural tachycardia syndrome (POTS) is a heterogeneous disorder characterized by an excessive rise in heart rate and symptoms consistent with cerebral hypoperfusion in the upright position. NO produced by endothelial NO synthase is a significant factor in the regulation of blood flow. Genetic polymorphisms in the promoter region (T-786C) and exon 7 (E298D) of the NO synthase isoform 3 gene affect enzyme activity and have been associated with a number of cardiovascular diseases. Because some findings in POTS suggest aberrant NO-mediated functions, we postulated that the variant genotypes of these polymorphisms may increase the risk of developing POTS and correlate with more severe symptoms. We genotyped 136 patients with POTS (mean age 32.2 ± 9.9 years; 46 men and 90 women) from Nashville, Tenn, and Vienna, Austria, and compared them with 191 healthy volunteers (mean age 29.1 ± 8.0 years; 127 men and 64 women). Participants also underwent orthostatic testing with blood pressure, heart rate, and plasma norepinephrine measurements while supine and upright. The frequencies of the -786CC and 298DD genotypes were significantly lower in patients with POTS than in control subjects (odds ratio [OR], 0.28; 95% confidence interval [CI], 0.14 to 0.57; P = 0.001 for -786CC; and OR, 0.44; 95% CI, 0.21 to 0.91; P = 0.033 for 298DD). According to 2-locus genotype analyses, patients with -786CC and 298EE or 298ED experienced the largest changes in heart rate and plasma norepinephrine with standing. These results indicate that NO may influence the development of POTS and the severity of POTS symptoms. (Hypertension. 2005;46:1103-1110.)

Key Words: tachycardia ■ genetics ■ nitric oxide ■ hemodynamics ■ heart rate ■ norepinephrine

Postural tachycardia syndrome (POTS), a condition of orthostatic intolerance that affects ~500 000 Americans, is characterized by an excessive rise in heart rate (HR) on standing, without a significant fall in blood pressure (BP), and often by elevated plasma norepinephrine (NE) levels. Many patients with POTS are so debilitated by their orthostatic symptoms that they are unable to work. A number of different pathophysiologies underlie symptoms in subgroups of patients, but the basis of POTS remains obscure in most afflicted individuals. Genes encoding the NE transporter (SLC6A2), the β1- and β2-adrenergic receptors, and endothelin-1 (R. Winker, unpublished data, 2005) are associated with the development of POTS. However, variations in these genes only explain a minor proportion of cases, and a number of other genes are likely to contribute to this multifactorial syndrome.

NO interacts in complex ways with the regulation of the cardiovascular system by the autonomic nervous system, making it an excellent candidate for a role in disorders, such as POTS, in which the cardiovascular response to standing is impaired. Circulating NO is synthesized mainly by the constitutively expressed endothelial NO synthase (eNOS). Cardiac effects of NO produced by eNOS within cardiomyocytes include attenuation of the inotropic and chronotropic effects of catecholamines. NO also modulates release of catecholamines. In the vascular system, endothelial NO mediates vasodilatation, regulates regional and cerebral blood flow, and inhibits leukocyte and platelet adhesion to the endothelium. Therefore, several features of POTS, including increased HR, elevated plasma levels of NE, decreased cerebral blood flow, deficient peripheral vasoconstriction with standing, and enhanced peripheral venous pooling, would be consistent with a reduction in peripheral levels of NO.

In the gene encoding eNOS, NOS isoform 3 (NOS3), a substitution of Asp for Glu (E298D) in exon 7 and a T to C transition at -786 in the promoter region (T-786C) are reported to affect eNOS activity. In an in vitro system, using placental cells, the 298D variant results in increased mRNA levels but in decreased eNOS protein formation. The C

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allele of the T-786C polymorphism reduces eNOS activity as a result of suppressed NOS3 transcription.25

Previous studies have shown inconsistent associations between these polymorphisms and cardiovascular disease, including hypertension,26,27 coronary artery disease,28,29 coronary artery spasm,30 and myocardial infarction.31–35 We hypothesize that the T-786C and E298D NOS3 polymorphisms, because of their potential to lower peripheral NO levels, are associated with the presence of POTS. We further propose that in those with the POTS phenotype, the magnitude of the HR and plasma NE orthostatic changes are intensified in patients homozygous for the -786C and 298D alleles of NOS3. To test these hypotheses, we compared the distribution of the polymorphic alleles in patients and healthy subjects and then studied the relationship between NOS3 genotypes and the response to standing in POTS patients.

Methods

Study Population

The study was approved by the ethics committees of the participating institutions, and subjects gave written informed consent. A total of 136 patients with POTS, who were referred to either the Autonomic Dysfunction Center at Vanderbilt University, Nashville, Tenn (89 females and 12 males) or to the Division of Occupational Medicine at the Medical University Vienna, Austria (1 female and 34 males), participated in the study. We therefore had the opportunity to compare 2 different patient populations and also to increase the number of patients for comparison with healthy volunteers. Patients were enrolled based on: (1) an increase of ≥30 bpm in HR, (2) plasma NE concentrations ≥600 pg/mL after 30 minutes upright (or at the maximum time standing could be tolerated), and (3) presence of orthostatic symptoms, including dizziness, lightheadedness, and blurred vision. Patients were compared with 191 healthy volunteers (63 women and 45 men from Nashville and 1 woman and 82 men from Vienna). All participants were white and from 17 to 64 years of age. Exclusion criteria were: (1) history of metabolic or neurological diseases that might affect the autonomic nervous system, (2) supine BP ≥90/50 or ≥140/90 mm Hg, (3) orthostatic hypotension (fall in BP >20/10 mm Hg with standing), or (4) use of medications that might affect BP.

Genotyping

Genomic DNA was prepared from blood using Puregene DNA Purification Kit (Gentra Systems) or a genomic DNA isolation kit (Qiagen). DNA samples were genotyped for the T-786C and E298D polymorphisms of NOS3 by the 5'-H11032 manufacturer instructions. Details are included in the online supplement, available at http://www.hypertensionaha.org.

Orthostatic Tolerance Testing

All subjects in Vienna underwent a tilt table test. Arterial BP was measured continuously with a Task Force Monitor56 as described previously.57 Subjects rested in a supine position for 30 minutes before being tilted to 60°C upright for 30 minutes. BP and HR measurements obtained while supine and after 3 and 5 minutes upright were used for this study.

In Nashville, posture studies were performed on 95 patients and 36 control subjects after an overnight fast and ≥30 minutes of supine rest. BP and HR were recorded while supine and after 3 minutes and 5 minutes of standing by the bedside, using single measurements from an automated device (Dinamap).58

In both centers, plasma catecholamine levels were determined at rest and after 30 minutes upright (or when symptoms necessitated resuming the supine position) by high-performance liquid chromatography, as described previously.59

Statistical Analysis

Power calculations were based on detecting a 1 SD difference between genotypes in the orthostatic change in HR. With 80% power and an α-level of 0.05, we calculated that we would be able to detect a 5.3-bpm difference between groups based on 10 subjects in the -786C homozygote or 298D homozygote group and 30 subjects in the -786T homozygote or 298E homozygote group (PS power and sample size software, version 2.1.30).40

Genotype frequencies were compared between patients and controls by χ2 analysis. Association between genotypes and POTS was analyzed by logistic regression and expressed as odds ratio (OR) with 95% confidence interval (CI). The effects of the -786C and the 298D alleles were evaluated by assuming dominant and recessive models of inheritance. Interactions with age, gender, study site, and body mass index (BMI) were determined by entering these as covariates in the logistic regression analyses, and adjusted ORs were ascertained for the -786CC and 298DD genotypes. The 2-locus genotype distributions were compared between patients and controls using the program R X C and were based on the Metropolitan method.41 Linkage disequilibrium (D’) was calculated, using the expectation maximization algorithm, as implemented in the software package Powermarker, version 3.23.

Student’s t test and Mann–Whitney U test were used to test for significant differences between POTS patients and control subjects for the following variables: age, BMI, BP, HR, and plasma NE. Gender ratio was analyzed by χ2 analysis. Data from the 2 sites were compared separately and in combination.

Supine BP, HR, and NE were compared between genotypes by ANOVA, with post hoc analysis by the Scheffe test and the Kruskal–Wallis test. Repeated-measures ANOVA was performed to assess differences between genotypes regarding orthostatic changes. Analyses compared heterozygotes separately from the major and minor allele homozygotes (3-way analysis) and combined with the major allele homozygotes (2-way analysis).

Statistical analysis was performed using the statistical software SPSS for Windows, version 13.0 (SPSS Inc.) except where noted. Reported P values are 2-tailed, and P<0.05 was considered significant. The results are expressed as mean±SD unless otherwise indicated.

Results

Demographic Characteristics

Descriptive characteristics of the subjects are presented in Table 1. The patient population was slightly older, leaner, and had a significantly greater proportion of female subjects compared with the control population. Comparisons of the study populations by study site revealed that case-control differences in BMI were significant only for Nashville.

Although 98% of the Vienna participants were male, most of the Nashville subjects were female (27% male). This gender difference was driven by differences in ascertainment between Nashville and Vienna. In the latter, the subjects were Austrian military volunteers.

Patients with POTS had higher supine HR than controls and higher supine NE levels. Consistent with the inclusion criteria, patients had significantly greater orthostatic changes in HR and plasma NE (Table 1; P<0.001 for both HR and NE). Upright systolic BP was lower in the patients compared with controls. BP and HR data at 5 minutes were similar to 3-minute data.

As might be expected from the diverse populations and procedures for orthostatic testing, differences existed between participants in Nashville and Vienna (Table 1). Supine systolic BP and diastolic BP were lower for patient and control groups in Nashville (P≤0.001 for comparisons be-
TABLE 1. Characteristics of the Subjects According to Diagnosis and Study Site

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Participants</th>
<th>Vanderbilt</th>
<th>Vienna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.1±8.0</td>
<td>29.5±9.8</td>
<td>29.1±8.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6±4.3</td>
<td>23.3±4.2</td>
<td>24.6±4.3</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67±9</td>
<td>73±10</td>
<td>68±9</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>118±11</td>
<td>113±14</td>
<td>124±12</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>71±9</td>
<td>69±10</td>
<td>72±7</td>
</tr>
<tr>
<td>Plasma NE (nmol/L)</td>
<td>1.0±0.56</td>
<td>1.56±0.75</td>
<td>1.16±0.99</td>
</tr>
</tbody>
</table>
| Continuous variables are presented as means±SD. n=No. of people genotyped; hemodynamic data were available from 119 control subjects and 130 patients; *to convert nmol/L to pg/mL, divide by 0.0059.

TABLE 2. eNOS T-786C Polymorphism Genotype Frequencies in Control Subjects and Patients With POTS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Control</th>
<th>POTS</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>56 (29.5%)</td>
<td>52 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>89 (46.8%)</td>
<td>73 (53.7%)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>45 (23.7%)</td>
<td>11 (8.1%)</td>
<td>0.28 (0.14 to 0.57)</td>
</tr>
</tbody>
</table>

n (percent within diagnosis); technical problems precluded genotyping in 1 individual in the control group.

*Odds for CC compared with TT+TC.

TABLE 3. eNOS E298D Polymorphism Genotype Frequencies in Control Subjects and Patients With POTS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Control</th>
<th>POTS</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE</td>
<td>90 (47.6%)</td>
<td>61 (45.5%)</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>67 (35.4%)</td>
<td>62 (46.3%)</td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>32 (16.9%)</td>
<td>11 (8.2%)</td>
<td>0.44 (0.21 to 0.91)</td>
</tr>
</tbody>
</table>

n (percent within diagnosis); technical problems precluded genotyping in 2 individuals in the control group and 2 individuals in the patient group

*Odds for DD compared with EE+ ED.

Distribution of Polymorphisms

By χ² analysis, distributions of the T-786C and E298D genotypes in the Nashville control and POTS populations did not differ significantly from those in the Vienna groups (for between Nashville and Vienna). Also, compared with controls in Vienna, the controls in Nashville had lower supine HR (difference between sample means 4.6; 95% CI, 1.0 to 8.2; P=0.009) and higher upright NE (difference between sample means 0.92; 95% CI, 0.55 to 1.29; P=0.001), whereas the patients had higher supine HR (difference between sample means 5.7; 95% CI, 1.9 to 9.6; P<0.001) and lower supine NE (difference between sample means 0.59; 95% CI, 0.32 to 0.87; P<0.001).

The 2 sites also differed in some case-control comparisons. For example, supine NE (P<0.001) and the orthostatic change in systolic BP (P=0.022) differed between patients and controls only in Vienna, whereas supine HR differed significantly between patients and controls only in Nashville (P<0.001). The latter finding can likely be attributed to the higher percentage of females in the Nashville and combined patient populations compared with the control populations because supine HR is higher in women than in men.42

Garland et al NOS and Postural Tachycardia Syndrome 1105

T-786C: OR, 0.27; 95% CI, 0.12 to 0.63 in Nashville and OR, 0.32; 95% CI, 0.09 to 1.15 in Vienna; for E298D: OR, 0.52; 95% CI, 0.22 to 1.23 in Nashville and OR, 0.28; 95% CI, 0.06 to 1.27 in Vienna), nor did the distributions for males differ from those for females (for T-786C: OR, 0.35; 95% CI, 0.14 to 0.87 in females and OR, 0.21; 95% CI, 0.07 to 0.70 in males; for E298D: OR, 0.45; 95% CI, 0.16 to 1.24 in females and OR, 0.46; 95% CI, 0.15 to 1.40 in males). Therefore, genotypic data were pooled for Nashville and Vienna and for males and females. At an α-level of 0.05, this gave us 80% power to detect an OR of 0.42 for T-786C and of 0.35 for E298D.

Tables 2 and 3 summarize the genotypic data for the T-786C and E298D polymorphisms of NOS3. Genotype frequencies were in Hardy–Weinberg equilibrium in patients and controls for T-786C, and in patients for E298D. For both polymorphisms, the association between the minor allele and POTS was consistent with a recessive model of decreased risk. Genotype frequencies for T-786C differed significantly between patients and controls (P=0.001), with a smaller proportion of CC homozygotes in patients with POTS (9.1%) compared with controls (23.7%; OR, 0.28; 95% CI, 0.14 to 0.57; P<0.001; TT+TC combined used as reference). Fre-
plasma NE changes were also highest in the CC homozygotes (to 6.27±3.77 compared with 4.38±1.90 nmol/L for TC and 4.41±1.91 nmol/L for TT; \( P = 0.046 \)). A 2-way comparison of the CC homozygotes with T allele carriers (ie, TC+TT) also indicated a significant interaction between genotype and the orthostatic increases in HR and plasma NE (\( P < 0.001 \) and 0.014, respectively; Table 4). The T-786C genotypes did not associate with the changes over time in upright systolic or diastolic BPs.

Significant orthostatic effects noted for the E298D polymorphism (Table 5) included change in systolic BP (\( P = 0.045 \)) and increase in plasma NE (\( P = 0.029 \)) when E allele carriers were compared with DD. The difference in the diastolic BP response neared significance (\( P = 0.057 \)).

In a 2-locus analysis of the data, plasma NE in -786CC/298EE+ED (n=7) increased from 2.11±0.93 to 6.82±4.16 nmol/L with upright posture, an effect that was significantly greater than for -786TT+TC/298DD (n=8; \( P = 0.014 \)) and for -786TT+TC/298EE+ED (n=112; \( P = 0.045 \); Figure 2). The orthostatic change in HR, similarly, was significantly greater in individuals with the -786CC/298EE+ED genotype (Figure 3).

Neither the T-786C nor E298D genotypes were associated with the orthostatic changes in systolic BP, diastolic BP, HR, or NE in the control population (data not shown).

**Discussion**

Our study shows that genotype frequencies for the T-786C and E298D polymorphisms of NOS3 differed significantly between patients with POTS and healthy control subjects, as did 2-locus genotype frequencies. In addition, these genotypes associated significantly with the orthostatic rise in HR and plasma NE in patients. Whereas both variant genotypes were less common in POTS, orthostatic responses related to HR and plasma NE were larger in 786CC patients and smaller in 298DD patients. These findings could become clinically important if these effects on the pathophysiology of POTS are confirmed, and they could provide new avenues for treatment.

The T-786C and 298D polymorphisms, or a variant in linkage disequilibrium, weakly protected against the development of POTS, with ORs of 0.28 and 0.44, respectively. The allelic frequencies in our control group were in agreement with other studies, and the linkage disequilibrium between the T-786C and E298D polymorphisms also confirmed previous reports. The single locus findings were confirmed by the results of our 2-locus genotype analysis, with a lower risk for POTS in individuals homozygous for -786C and 298D, based on OR and 95% CI. Although haplotype analysis also indicated a significant difference between the POTS and control groups, we chose to focus on the results of genotype analyses, which are more biologically meaningful.

These results suggest that higher levels of eNOS are associated with the development of POTS, consistent with studies of microgravity-induced orthostatic intolerance. In studies using the hindlimb unweighted rat model, the experimental animals demonstrated an upregulation of NOS. Additional research is needed to determine whether NOS is...
similarly upregulated in POTS patients and whether upregulation is limited in the -786CC and 298DD genotypes.

In contrast to the protective effect against POTS of -786CC in our case-control study, under orthostatic stress, the HR and plasma NE changes of patients homozygous for -786C exceeded those of other genotypes. Perhaps the -786CC genotype is protective against a liability for POTS only below a certain level. When other factors strongly predispose to POTS, this protection is “overwhelmed,” so that patients with an exceptionally large liability have more severe orthostatic consequences.^

Differences in hemodynamic and catecholamine responses to upright posture were not found between the NOS3 genotypes in the control population of this study, suggesting that some impairment in POTS must precede the enhanced orthostatic response. Other investigators have speculated that the polymorphic genotypes affect vascular function only in situations of endothelial dysfunction.^

**TABLE 4. Hemodynamic Variables of Patients With POTS Stratified by T-786C Genotype**

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>T-786C Genotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n=47)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>69±10</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>107±15</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>117±13</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>117±16</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>70±12</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>76±13</td>
</tr>
<tr>
<td>Plasma NE (nmol/L)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>1.63±0.78</td>
</tr>
<tr>
<td>Thirty minutes upright</td>
<td>4.41±1.91</td>
</tr>
</tbody>
</table>

P1 indicates P value for comparison between 3 genotypes, CC, TC and TT; P2, P value for comparison between CC and (TC+TT); supine P value is for comparison between groups by ANOVA, upright P values are for group x time interaction by repeated measures ANOVA.

*Data are included only for those patients on whom heart and BP readings were available at both time points.

**TABLE 5. Hemodynamic Variables of Patients With POTS Stratified by E298D Genotype**

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>E298D Genotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EE (n=55)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>69±11</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>107±18</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>116±12</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>119±15</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>69±11</td>
</tr>
<tr>
<td>Three minutes upright</td>
<td>76±11</td>
</tr>
<tr>
<td>Plasma NE (nmol/L)</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>1.71±0.80</td>
</tr>
<tr>
<td>Thirty minutes upright</td>
<td>4.76±2.24</td>
</tr>
</tbody>
</table>

P1 indicates P value for comparison between 3 genotypes: EE, ED, and DD; P2, P value for comparison between DD and (EE+ED); supine P value is for comparison between groups by ANOVA; upright P values are for group x time interaction by repeated-measures ANOVA.

*Data are included only for those patients for whom heart and BP readings were available at both time points.
release and enhanced central and peripheral blood flow might be blunted, as we initially proposed.

The orthostatic tachycardia and hyperadrenergic state in POTS are also consistent with less NO activity in the central nervous system. eNOS and neuronal NOS are expressed in the central nervous system, where NO acts in the rostral ventrolateral medulla and the nucleus tractus solitarii to decrease BP, HR, and urinary NE excretion. These brain regions are involved in the baroreflex response to orthostatic stress, and impaired baroreflex function has been proposed to underlie the increased central sympathetic outflow and the postural tachycardia of POTS.

It was somewhat surprising that the 298DD genotype, which also was present at a lower frequency in POTS and is in linkage disequilibrium with the T-786C eNOS polymorphism, was associated with a smaller rise in plasma NE with upright posture. However, the majority of 298DD individuals were -786T allele carriers, so the hemodynamic effects of 298DD might track with those of -786TT and -786TC.

Our findings might also suggest that the T-786C and E298D NOS3 polymorphisms either do not influence NO function or have differential effects on eNOS activity and endothelial NO levels. This is consistent with variable findings by others on associations between NOS3 polymorphisms, NO levels, and NO-mediated endothelial responses. NO function needs to be more directly assessed in POTS patients.

Other polymorphisms of NOS3 have been identified in the promoter region and introns, but the evidence for functional effects is more substantial for T-786C. Nevertheless, additional single-gene analyses, as well as multiple-gene analyses, of NOS3, other NOS genes, and other candidate genes selected on the basis of physiology, are needed to clarify the genetic basis of POTS. Another point to consider is whether different subgroups of POTS patients might have an increased prevalence of a particular NOS3 genotype or demonstrate orthostatic responses that are influenced by NO status. For this reason, more patients homozygous for 786C and 298D need to be characterized compared with patients with the other NOS3 genotypes.

In addition to problems inherent in relatively small case-control studies, the present study is complicated by the fact that study subjects were recruited from 2 different areas, although both groups were exclusively whites. This enabled us to obtain a sufficiently large POTS sample. By using stringent inclusion criteria, we avoided potential confounding effects, and our findings were similar across sites.

In conclusion, because POTS is a heterogeneous disorder, only limited levels of correlation are expected in analyses that focus on one particular genetic mechanism. Although our data show a protective effect of NOS3 polymorphisms on the risk of developing POTS, our finding that genotypes associate with the hemodynamic response to upright posture suggests that NOS3 polymorphisms contribute to the severity of the orthostatic phenotype in individuals who develop POTS.

**Perspectives**

In summary, NOS3 alleles that encode the predominant isoform of NOS in the vasculature represent genetic factors associated with POTS in patients from Nashville and Vienna. Identification of the genetic variants involved in the different pathophysiologies of POTS may improve our understanding of the mechanisms underlying POTS and help us to identify subgroups in which specific treatments will be more effective. Future studies will need to focus on subgroups of patients with POTS, other NOS isoforms, and interactions between multiple genotypes.

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References


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