

# Angiotensin II Type 1 Receptor Autoantibodies in Postural Tachycardia Syndrome

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**Background**—Both the adrenergic and renin-angiotensin systems contribute to orthostatic circulatory homeostasis, which is impaired in postural orthostatic tachycardia syndrome (POTS). Activating autoantibodies to the  $\alpha$ 1-adrenergic and  $\beta$ 1/2-adrenergic receptors have previously been found in sera from patients with POTS. We hypothesized that patients with POTS might also harbor activating autoantibodies to the angiotensin II type 1 receptor (AT1R) independently of antiadrenergic autoimmunity. This study examines a possible pathophysiological role for AT1R autoantibodies in POTS.

**Methods and Results**—Serum immunoglobulin G from 17 patients with POTS, 6 patients with recurrent vasovagal syncope, and 10 normal controls was analyzed for the ability to activate AT1R and alter AT1R ligand responsiveness in transfected cells in vitro. Of 17 subjects with POTS, 12 demonstrated significant AT1R antibody activity in immunoglobulin G purified from their serum. No significant AT1R antibody activity was found in the subjects with vasovagal syncope or healthy subjects. AT1R activation by POTS immunoglobulin G was specifically blocked by the AT1R blocker losartan. Moreover, POTS immunoglobulin G significantly shifted the angiotensin II dosage response curve to the right, consistent with an inhibitory effect. All subjects with POTS were positive for one or both autoantibodies to the AT1R and  $\alpha$ 1-adrenergic receptor.

**Conclusions**—Most patients with POTS harbor AT1R antibody activity. This supports the concept that AT1R autoantibodies and antiadrenergic autoantibodies, acting separately or together, may exert a significant impact on the cardiovascular pathophysiological characteristics in POTS. (*J Am Heart Assoc.* 2018;7:e008351. DOI: 10.1161/JAHA.117.008351.)

**Key Words:** angiotensin II type 1 receptor • autoimmunity • autonomic nervous system • postural orthostatic tachycardia syndrome • vasoconstriction

Postural orthostatic tachycardia syndrome (POTS) is a multisymptomatic disorder characterized by an abnormally increased heart rate during standing.<sup>1,2</sup> It is frequently

accompanied by other vascular and nonvascular symptoms. The syndrome affects predominantly young women (70–80%), but its cause has not been established.<sup>3–5</sup> In 2014, our laboratory demonstrated that a marked relationship of activating autoantibodies (AAbs) to the  $\alpha$ 1-adrenergic ( $\alpha$ 1AR) and  $\beta$ 1/2-adrenergic ( $\beta$ 1/2AR) receptors existed in 14 of 14 such patients.<sup>6</sup> A second confirmatory report demonstrated a similar AAb pattern in most of 17 additional patients with POTS; data were collected independently in Sweden and assayed in blinded manner in the same laboratory as before but using modified assay techniques for the  $\alpha$ 1AR-AAb.<sup>7</sup> We previously demonstrated that  $\alpha$ 1AR-AAbs possess the orthosteric ability to directly activate the target receptor; however, they also produce an allosteric inhibition of  $\alpha$ 1AR, resulting in a net inhibitory effect on receptor responsiveness to its orthosteric ligand phenylephrine in rat resistance cremaster arteries.<sup>6</sup> In contrast, there was an AAb-mediated allosteric facilitation of  $\beta$ 1/2AR responsiveness to the  $\beta$ AR agonist isoproterenol in transfected cells. We believe the opposing effects of these AAbs on their specific receptors may account in part for many of the

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## Clinical Perspective

### What Is New?

- Activating autoantibodies to the posture-related angiotensin II type 1 receptor were present in a cohort with postural orthostatic tachycardia syndrome.
- Angiotensin II type 1 receptor–activating autoantibodies had a negative allosteric effect on angiotensin II action.

### What Are the Clinical Implications?

- These data support previous reports for an impaired responsiveness to angiotensin II in postural orthostatic tachycardia syndrome and a rationale for the beneficial impact of salt loading on blood pressure and pulse responsiveness in postural orthostatic tachycardia syndrome.
- Pharmacological or physiological suppression of relevant autoantibodies may have a therapeutic benefit in postural orthostatic tachycardia syndrome.

cardiovascular manifestations in POTS. In the second report, we observed 4 of 17 subjects with POTS had  $\beta$ 1/2AR-AABs, but their  $\alpha$ 1AR-AABs were not measurable.<sup>7</sup>

The renin-angiotensin-aldosterone system is involved in the homeostatic control of blood pressure (BP) in the upright position,<sup>8</sup> and the angiotensin II (Ang II) type 1 receptor (AT1R) belongs to the same family of G-protein–coupled receptors as the adrenergic receptors. We therefore hypothesized that the presence of AABs to the AT1R could potentially contribute to the cardiovascular instability observed in POTS. For the purpose of this study, we have included patients with POTS and 2 different control groups, one being autonomic controls with classic recurrent vasovagal syncope (VVS) who previously had failed to demonstrate any known relationship to  $\alpha$ 1AR-AABs or  $\beta$ 1/2AR-AABs, and the other being healthy subjects without a history of syncope and with normal postural hemodynamics.

## Methods

The Health Insurance Portability and Accountability Act–sensitive data, including sera and proprietary protected method, cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure. All other data are available in the article.

## Study Patients

Sera from 6 subjects with POTS in our original article<sup>6</sup> from Vanderbilt University (Nashville, TN) were screened for the presence of AT1R-AABs. These studies had been approved by the Vanderbilt University Institutional Review Board. These positive data encouraged us to study in more detail 17 patients

with POTS, 6 patients with VVS, and 10 normal controls who were obtained through the SYSTEMA (Syncope Study of Unselected Population in Malmö) in Sweden. These subjects have been studied for their  $\alpha$ 1AR-AAB and  $\beta$ 1/2AR-AAB activity, as previously reported.<sup>7</sup> Briefly, patients with POTS reported typical symptom onset at least 1 year before the index examination. The average period from onset to examination was  $6\pm 6$  years; none of patients with POTS had the symptoms from birth (ie, in each case, it was an acquired syndrome). The average age at the onset was  $18\pm 6$  years; and at the index examination,  $24\pm 6$  years. Both the Institutional Review Board at the Oklahoma University Health Sciences Center (Oklahoma City, OK) and the Regional Ethical Review Board in Lund, Sweden, approved the study protocol. Each subject gave his or her signed informed consent.

## Sample Preparation

Blood samples for the present study were obtained after overnight fasting and were from the same group, as previously described.<sup>7</sup> Serum was separated by centrifugation and stored at  $-80^{\circ}\text{C}$  before shipping of duplicate aliquots in dry ice to the laboratory in Oklahoma City. The frozen integrity of each aliquot was confirmed on arrival, and samples were immediately placed in a  $-80^{\circ}\text{C}$  freezer before thawing of one aliquot for the first assay. The identity of each aliquot was blinded to the laboratory personnel until after the assays were completed. Serum immunoglobulin G (IgG) was purified using the NAB Protein A/G Spin Kit (Pierce Biotechnology).

## Cell-Based AT1R Assay

AT1R autoantibody activity was measured in AT1R-transfected Chinese hamster ovary cells using the PathHunter eXpress  $\beta$ -arrestin G-protein–coupled receptor assay kit (DiscoverX, Fremont, CA), as previously described.<sup>9</sup> Briefly, 10 000 AT1R Chinese hamster ovary cells were dispensed into each well of a 96-well culture plate and incubated for 48 hours. Assay buffer containing serum IgG (0.125–1 mg/mL) in the presence and absence of the selective AT1R blocker losartan (10  $\mu\text{mol/L}$ ) was then added and incubated for 90 minutes. Negative (buffer) and positive Ang II controls were included in each assay. All samples were tested in triplicate. After sample treatment, PathHunter detection reagents were added and the luminescence signal was quantified to determine  $\beta$ -arrestin recruitment. The  $\beta$ -arrestin values were expressed as percentage of buffer baseline to normalize the data.

Dosage response curves of Ang II ( $10^{-9}$ – $10^{-6}$  mol/L) in the absence or presence of serum IgG (0.5 mg/mL) from 4 AT1R-AAB–positive subjects with POTS were constructed to examine the allosteric effect of IgG on the Ang II–induced response.

## Complementary Analyses

In a subset of patients with POTS (13/17) and vasovagal controls, we measured plasma sodium, potassium, and creatinine, according to routine laboratory methods at the Swedish center, and renin concentration using an immunoradiometric assay (Renin III Generation; Cisbio Bioassays International, Codolet, France). These assays were performed in the Lund University (Malmö, Sweden) laboratory.

## Statistical Analyses

Data were expressed as mean±SD. Group comparisons were performed using Student *t* test for comparison of 2 groups or 1-way ANOVA, followed by post hoc Tukey's test, for multiple group comparisons. The positivity of bioactive autoantibodies was defined as values above the mean+2 SDs from the normal subject control group. The number of samples for the dosage responses was limited partly because of limited available sera and the consistent data, despite the number limitation. The data in all cases were symmetrical and without outliers. Statistical significance was set at  $P<0.05$ .

## Results

### Clinical Characteristics

The demographic and clinical characteristics for each group have been previously published.<sup>7</sup> The mean age for the Swedish patients with POTS was not significantly different from those with VVS and normal control subjects. One Hashimoto thyroiditis case was reported in each group (ie, POTS positive and negative;  $P=0.5$ ).

### Clinical Laboratory Values

There was no significant difference between patients with POTS and vasovagal controls in regard to sodium ( $140.2\pm 1.6$  versus  $139.4\pm 2.1$  mmol/L;  $P=0.31$ ), potassium ( $3.8\pm 0.2$  versus  $3.7\pm 0.2$  mmol/L;  $P=0.58$ ), creatinine ( $76.4\pm 10.9$  versus  $69.9\pm 18.2$   $\mu$ mol/L;  $P=0.24$ ), and renin ( $24.4\pm 17.0$  versus  $15.7\pm 8.6$  mU/L;  $P=0.24$ ) plasma levels. There was no significant difference in renin plasma levels between AT1R-AAb-positive ( $n=9$ ) and AT1R-AAb-negative ( $n=4$ ) patients ( $18.3\pm 7.7$  versus  $34.5\pm 27.2$  mU/L;  $P=0.42$ ).

### Autoantibody Activity

In the pilot study, remaining sera from 6 subjects with POTS previously submitted from Vanderbilt University<sup>6</sup> were tested for  $\alpha$ 1AR and AT1R autoantibody-mediated contractile activity using an isolated rat cremaster arteriole assay. After the  $\alpha$ 1AR blocker prazosin was added, residual contractility in 4

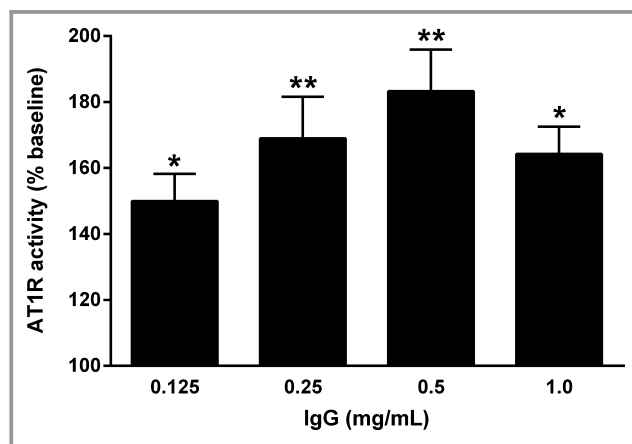
subjects was suppressed by addition of the AT1R blocker losartan. These data were compatible with the copresence of circulating  $\alpha$ 1AR-AAb and AT1R-AAb in these patients (data not shown).

Serum IgG from the subjects with POTS and control subjects, submitted from Lund University, was examined for AT1R-AAb activity in AT1R-transfected Chinese hamster ovary cells. IgG from 3 of the patients with POTS was tested at 4 different concentrations to determine an optimal concentration for study. There was a significant dose effect of IgG on AT1R activation, and the maximal effect appeared to occur at  $\approx 0.5$  mg/mL of IgG (Figure 1).

IgG from all 17 patients with POTS was then tested at a concentration of 0.5 mg/mL and demonstrated a variable, but significant, capacity to activate AT1R. Twelve of these patients (70%) showed elevated AT1R-AAb activity (Table and Figure 2A). No AT1R-AAb activity was found in patients with VVS or healthy subjects. The mean AT1R-AAb activity value was significantly higher in the POTS group ( $113.9\pm 9.8\%$ ) than for either subjects with VVS ( $100.3\pm 3.9\%$ ,  $P=0.001$ ) or healthy subjects ( $103.6\pm 3.2\%$ ,  $P=0.0007$ ) (Figure 2B). There was no significant difference between the latter 2 groups.

In the previous study, 4 of the 17 subjects with POTS did not demonstrate  $\alpha$ 1AR-AAb activity.<sup>7</sup> Each of these 4 subjects demonstrated significant AT1R-AAb-mediated orthosteric activation of AT1R (Table).

The effect of the selective AT1R blocker losartan on AT1R-AAb-induced AT1R activation in vitro was tested in 13 patients with POTS (Figure 3A). Losartan markedly suppressed AT1R-AAb activity in IgG from the POTS group ( $124.0\pm 8.2\%$  to  $111.4\pm 3.3\%$ ,  $P<0.001$ ) (Figure 3B). No



**Figure 1.** Dose effect of serum immunoglobulin G (IgG) from 3 subjects with postural orthostatic tachycardia syndrome (POTS) on angiotensin II type 1 receptor (AT1R) activation in AT1R-transfected Chinese hamster ovary cells. Values are expressed as percentage of buffer baseline. There was a significant dosage-dependent increase in AT1R activation with a maximal effect at 0.5 mg/mL.  $n=3$ . \* $P<0.05$ , \*\* $P<0.01$  vs baseline.

**Table.** Sex/Age, Plasma Renin Concentrations, and Autoantibody Test Positivity (Direct Activating and/or Ligand-Modulating Activity) Among Patients With POTS

| Patient No. | Sex/Age, y | Renin, mU/L | $\alpha$ 1AR Ab* | AT1R Ab | $\beta$ 1AR Ab* | $\beta$ 2AR Ab* |
|-------------|------------|-------------|------------------|---------|-----------------|-----------------|
| 1           | F/23       | 22          | x                | x       |                 | x               |
| 2           | F/29       | 30          |                  | x       | x               |                 |
| 3           | F/19       | 12          | x                | x       | x               | x               |
| 4           | M/34       | 14          | x                | x       | x               | x               |
| 5           | F/21       | 24          | x                | x       | x               |                 |
| 6           | F/18       | 24          |                  | x       | x               | x               |
| 7           | F/17       | 6           | x                | x       | x               |                 |
| 8           | F/36       | 12          | x                | x       | x               |                 |
| 9           | F/32       | 22          |                  | x       | x               | x               |
| 10          | M/16       | ...         |                  | x       | x               | x               |
| 11          | F/25       | ...         | x                | x       | x               | x               |
| 12          | F/33       | ...         | x                | x       | x               | x               |
| 13          | F/22       | 9           | x                |         |                 | x               |
| 14          | F/21       | 65          | x                |         |                 | x               |
| 15          | F/20       | 10          | x                |         |                 |                 |
| 16          | F/35       | 54          | x                |         | x               | x               |
| 17          | F/20       | ...         | x                |         | x               | x               |
| Total       | ...        | ...         | 13/17            | 12/17   | 13/17           | 12/17           |

$\alpha$ 1AR indicates  $\alpha$ 1-adrenergic receptor;  $\beta$ 1AR,  $\beta$ 1-adrenergic receptor;  $\beta$ 2AR,  $\beta$ 2-adrenergic receptor; Ab, antibody; AT1R, angiotensin II type 1 receptor; F, female; M, male; and POTS, postural orthostatic tachycardia syndrome.

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significant effect of losartan was observed in IgG from the normal subject control group.

### AT1R-AAb Activity and Hemodynamics

There was a nonsignificant trend toward a lower supine BP in AT1R-AAb–positive patients with POTS compared with those with AT1R-AAb–negative POTS (118/69 mm Hg versus 130/76 mm Hg;  $P=0.11$ ). There was no difference in supine heart rates (73 versus 73 beats per minute;  $P=0.94$ ). During head-up tilt testing, minimal BP was significantly lower in AT1R-AAb–positive patients with POTS compared with AT1R-AAb–negative patients with POTS (107/73 versus 120/83 mm Hg;  $P=0.043$  for diastolic BP). There was no significant difference in maximal heart rate (110 versus 115 beats per minute;  $P=0.44$ ).

### Effect of AT1R-AAb on Ang II Dose Response

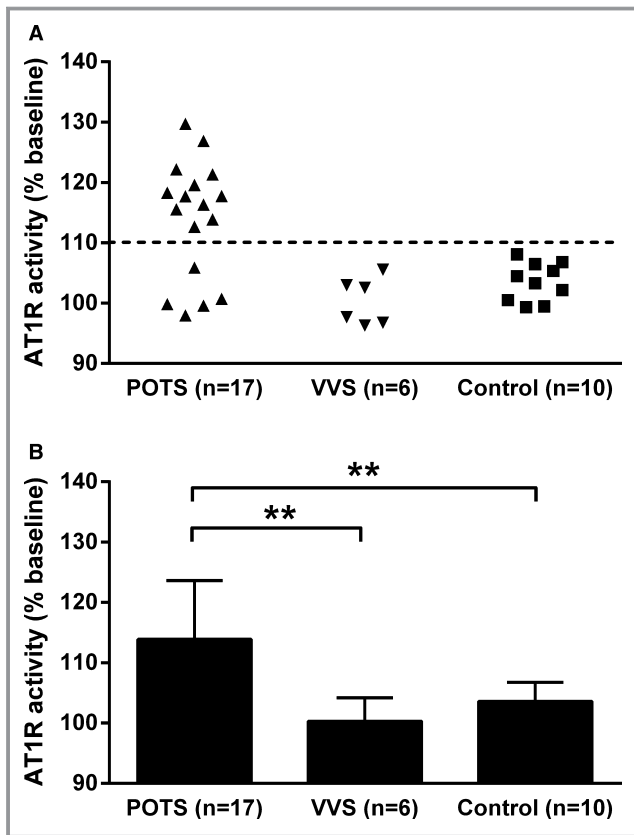
Dosage response curves for Ang II ( $10^{-9}$ – $10^{-6}$  mol/L) with and without POTS IgG (0.5 mg/mL) were constructed and compared. IgG samples from 4 patients with POTS who were positive for AT1R-AAb were used for curve comparisons. In the presence of POTS IgG, the Ang II response curve was

significantly shifted to the right, demonstrating a decreased AT1R response (Figure 4). Control IgG showed minimal modulating effects.

### Discussion

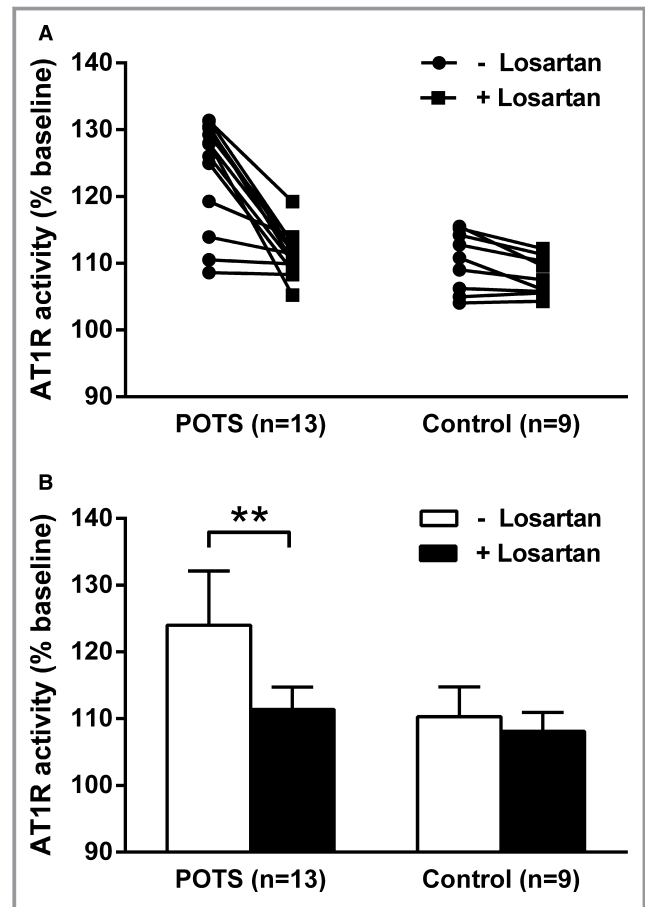
We have demonstrated that most of 17 patients with POTS have circulating autoantibodies to the AT1R. These autoantibodies may exert a direct agonist effect in the absence of their normal ligands. They also demonstrated the ability to alter the orthosteric ligand response. Autoantibodies to the AT1R were not detected in the current subjects with recurrent VVS and normal controls.

We previously reported serum IgG from patients with POTS contains circulating autoantibodies, some with a direct stimulatory effect on adrenergic receptors. Most also exerted a positive allosteric effect on  $\beta$ 1AR and a negative allosteric effect on  $\alpha$ 1AR activity. We hypothesized these and possibly other autoantibodies directed toward other receptors within the G-protein–coupled receptor family may exert variable biological effects and explain, in part, the different constellations of symptoms presenting in patients with POTS. Although there was a significant positive correlation between  $\beta$ 1AR-AAb activity and the cardiac response in POTS, the



**Figure 2.** Effects of serum immunoglobulin G (IgG) from subjects with postural orthostatic tachycardia syndrome (POTS), subjects with vasovagal syncope (VVS), and healthy control subjects on activation of angiotensin II type 1 receptor (AT1R) in AT1R-transfected Chinese hamster ovary cells. A, Most subjects with POTS demonstrated elevated AT1R antibodies, whereas none of these antibodies were found in the VVS and normal control groups. B, The mean activity values of AT1R antibodies were significantly higher in the POTS group than for both subjects with VVS and normal controls. No significant difference between the VVS and normal controls was observed. IgG was tested at a concentration of 0.5 mg/mL. The dashed line is the threshold derived from the mean activity values+2 SDs of the healthy controls. Values are expressed as percentage of buffer baseline. \*\**P*<0.01.

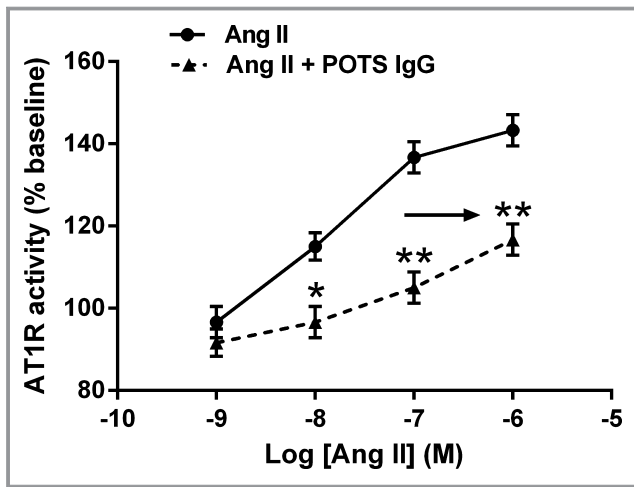
expected correlation of the  $\alpha$ 1AR-AAb activity and heart rates was present but at a lower level of significance than for the  $\beta$ 1AR-AAb activity.<sup>7</sup> The absence of any apparent  $\alpha$ 1AR-AAb activity, by either direct assay or allosteric modulation of ligand activity, in 4 of the 17 subjects with POTS clearly contributed to this apparent decrease in significance. Our present study, using IgG from these 4  $\alpha$ 1AR-AAb-negative subjects with POTS, demonstrated significant direct in vitro activation of AT1R. We also demonstrated significant AT1R-AAb activity, along with  $\alpha$ 1AR-AAb activity, in another 8 of the original 17 subjects. IgG from 4 of the patients with POTS who were positive for AT1R-AAb showed a significant shift of their dosage response curve to the right compared with that from



**Figure 3.** Effects of angiotensin II type 1 receptor (AT1R) blockade on immunoglobulin G-induced AT1R activation in AT1R-transfected Chinese hamster ovary cells. A and B, The addition of the selective AT1R blocker losartan (10  $\mu$ mol/L) suppressed the AT1R activity values observed in the subjects with postural orthostatic tachycardia syndrome (POTS) to control levels. Losartan produced no significant change in the AT1R activity in the control subjects. Values are expressed as percentage of buffer baseline. \*\**P*<0.01.

Ang II alone and confirmed our original report of an inhibitory allosteric impact of AT1R-AAb on the natural receptor ligand Ang II.<sup>10</sup> The AT1R-AAbs, therefore, appear to act as a partial agonist in vitro.

Because the renin-angiotensin-aldosterone system is involved in the subacute and prolonged responses to upright posture, we believe that AT1R-AAbs may confound normal orthostatic circulatory homeostasis. AT1R-AAb produced in a rabbit model attenuated the Ang II-induced vasoconstriction<sup>10</sup> and may lead to an impaired vascular response, similar to that induced by  $\alpha$ 1AR-AAb.<sup>6,7</sup> In the present study, the minimal BP during passive orthostatic challenge was significantly lower in AT1R-AAb-positive patients with POTS compared with AT1R-AAb-negative patients with POTS. These data would support a negative impact on upright BP of this partial agonist. There was no difference in maximal heart rates between the groups,



**Figure 4.** Effects of serum immunoglobulin G (IgG) from patients with postural orthostatic tachycardia syndrome (POTS) on angiotensin II (Ang II) responses in Ang II type 1 receptor (AT1R)-transfected Chinese hamster ovary cells. IgG from 4 patients with POTS with positive AT1R antibodies shifted the Ang II dosage response curve to the right, indicating an inhibitory allosteric effect. Control IgG failed to alter these curves.  $n=4$ . \* $P<0.05$ , \*\* $P<0.01$  vs Ang II alone.

suggesting the compensatory  $\beta$ AR adrenergic response in the 2 groups was comparable. Renin concentration assays were performed but failed to provide any significant correlations. Unfortunately, sodium intake and/or excretion was not measured in this study and can vary widely in subjects with POTS. These differences may have variably affected the renin values and their interpretation. Serum aldosterone values were not obtained.

There are clinical circumstances to demonstrate the relative importance of the renin-angiotensin-aldosterone system in maintenance of normal postural homeostasis.<sup>11,12</sup> This relationship has been examined previously before our discovery of AT1R-AAbs. Two groups have documented elevated Ang II levels in POTS<sup>13,14</sup>; of these groups, one also demonstrated relatively low serum aldosterone levels.<sup>13</sup> This group posited possible receptor problems to explain the inadequate transduction from Ang II to aldosterone. An interfering inhibitory AAb could be the missing link. Another report on AT1R-AAb in subjects with primary aldosteronism demonstrated different effects of these AAbs on the vascular and adrenal AT1R, depending on sodium intake.<sup>9</sup> The Vanderbilt group has also reported an impaired vascular pressor response to Ang II in patients with POTS.<sup>15</sup>

Sodium loading is frequently used to ameliorate some of the cardiovascular symptoms associated with POTS. Such salt loading would normally suppress endogenous Ang II concentrations and concurrently increase the sensitivity of vascular AT1R to their circulating autoantibodies. This would allow circulating AT1R-AAbs to maintain (or elevate) vascular tone

and moderate the impairment of cardiovascular responsiveness to upright posture mediated by  $\alpha$ 1AR-AAbs. The variability in presentation of these 2 separate autoantibodies in complementary receptor-driven systems that modulate cardiovascular homeostasis could partially account for the different cardiovascular responses in POTS.

The primary objective of this study was to determine if cardiovascular autoantibodies other than the  $\alpha$ 1AR-AAb or  $\beta$ 1/2AR-AAb were present, with the capacity to modify their functionality for postural homeostasis. We have provided direct evidence for the copresence of AT1R-AAbs in POTS. It would be of interest to determine in an animal model if these autoantibodies can individually or in combination reproduce the characteristic cardiovascular effects observed in POTS. We have previously documented an impact of M2/3 muscarinic receptor autoantibodies on the cardiovascular system in diverse conditions, such as idiopathic postural hypotension<sup>16,17</sup>; for  $\beta$ 1AR and M2 receptor autoantibodies in atrial fibrillation associated with Graves disease<sup>18</sup>; and now autoantibodies directed toward at least 3 cardiovascular receptor targets in POTS, including the  $\alpha$ 1AR,  $\beta$ 1/2AR, and AT1R. Recent presentations by Dubey et al have provided preliminary evidence for autoantibodies to the M1/2 muscarinic receptors in POTS sera.<sup>19</sup> These autoantibodies likely will affect cardiovascular function at their putative sites of action. Other groups have recently provided data confirming this hypothesis.<sup>20–22</sup>

POTS has challenged afflicted patients, their families, and caregivers. The variable presentation and associated autonomic disorders have led to various symptom-based therapies, some of which have partially ameliorated the patients' condition. However, a pathophysiologically based effective treatment against POTS is still not available. Thus, it is important to define the cause of POTS and develop a rationale for specific interventions. A high percentage of subjects with POTS examined by our group presented with an apparent autoimmune diathesis, which supports the concept that autoantibodies play an important role in POTS pathophysiological characteristics.

Although the identified AT1R-AAbs have demonstrated in vitro activity, it will be important to establish their relevance in vivo in animal models and eventually in human subjects who harbor these suspect antibodies. Ultimately, successful removal or inactivation of the antibodies and concurrent improvement of their signs and symptoms will be needed to conclusively document their role in POTS. The marked presence of either or both AT1R-AAbs and  $\alpha$ 1AR-AAbs in concordance with  $\beta$ 1/2AR-AAbs provides a rational framework to support an autoimmune pathophysiological condition in POTS. This concept, if validated, will provide the basis for development of novel therapeutic approaches against POTS based on immunotherapy.

These data support an autoimmune relationship to the cardiovascular components of POTS. This relationship may also relate to other manifestations of this otherwise perplexing disease. Because POTS has several presentations that are similar to those observed in chronic fatigue syndrome, in several other autonomic dyscrasias, and even with some people with otherwise unexplained protean diseases, it is important that the clinician who cares for these patients be aware of possible relationships that may exist and provide important clues in our future understanding of their pathophysiological characteristics.

These data are of interest because they demonstrate that activating autoantibodies may present with differing and opposing effects on a given receptor complex. They, therefore, provide an enigma requiring the observer to determine which or whether both effects are operative. The absence of applicable animal models is also a roadblock to such studies. It appears likely that final resolution of the autoantibodies' relative importance to the pathophysiological characteristics will depend on our ability to remove the antibodies from limited animal models and, eventually, patients with POTS and to determine whether they will permit a return to normal homeostasis.

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## Disclosures

None.

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