

Hop to It: The First Animal Model of Autoimmune Postural Orthostatic Tachycardia Syndrome

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Postural orthostatic tachycardia syndrome (POTS) is a chronic form of orthostatic intolerance that elicits daily symptoms, such as lightheadedness, fatigue, weakness, and nausea, which can substantially impact quality of life.¹ POTS is defined by the presence of these symptoms and orthostatic tachycardia (an increase in heart rate from supine of at least 30 beats per minute in adults or 40 beats per minute in adolescents within 10 minutes of standing or head-up tilt).² The cause of POTS is currently unknown and likely heterogeneous. POTS predominately affects premenopausal women, and the onset is often triggered by an event such as a viral illness or injury.¹

There is an emerging body of evidence that suggests an autoimmune basis for POTS.³ Several studies have investigated the presence of autoantibodies in POTS and their effects on cholinergic and adrenergic receptors.³ Low levels of antibodies to ganglionic cholinergic receptors were found in a minority of people with POTS (5%–29%). However, low levels of these antibodies were found in healthy volunteers and in people with unrelated autoimmune disorders at similar rates. Although the presence of cholinergic receptor antibodies in POTS has both low sensitivity and specificity, functional antibodies to adrenergic receptors may be a potential biomarker for diagnosing POTS.³ One group has consistently found autoantibodies that bind and activate adrenergic receptors in all patients with POTS tested from 2 different countries.^{4,5} These studies found antibodies that activate the β 1 adrenergic receptor in most participants

with POTS (n=28/32), and a smaller subset of participants with POTS was positive for antibodies that activate β 2 adrenergic receptors and act as partial agonists/antagonists to α 1 receptors.^{4,5} However, these are small studies, and it is unknown whether most or all patients with POTS have functional autoantibodies to the α 1 and β adrenergic receptors and how many healthy individuals have similar autoantibodies. Further research on the prevalence of these adrenergic autoantibodies in POTS by other groups and in larger samples is needed to confirm these findings.

Autoantibodies to adrenergic receptors may contribute to the pathophysiological features of POTS because adrenergic receptors are key regulators of blood pressure and heart rate.⁶ In addition, patients with POTS have impaired α 1 adrenergic receptor-induced vasoconstriction and enhanced β 1 adrenergic receptor-induced tachycardia.^{6,7} How the levels of adrenergic antibodies in POTS are related to symptom severity or outcomes has not been investigated. A previous study by Li et al⁴ found that autoantibodies in POTS serum induce functional allosteric adrenergic effects in vitro in isolated rat arteries.⁴ In this study, antibodies to the α 1 adrenergic receptor acted as antagonists in phenylephrine-induced vasoconstriction assays and autoantibodies to the β 1 or β 2 adrenergic receptors increased the responses to the nonselective β agonist, isoproterenol.⁴

In this issue of the *Journal of the American Heart Association (JAHA)*, “Adrenergic Autoantibody-Induced Postural Tachycardia Syndrome in Rabbits” by Li et al⁸ builds on the group’s previous work on the role of adrenergic autoantibodies in POTS. In this new study, the authors developed adrenergic receptor peptide-immunized rabbits to examine the role of adrenergic autoantibodies in vivo. The authors investigated the functional role of these adrenergic autoantibodies, which are functionally similar to those isolated from POTS patients’ serum, and whether the antibodies could be cleared in vivo using decoy peptide inhibitors. The main findings of this study are that the adrenergic autoantibodies induced a POTS-like phenotype in rabbits, including exacerbated orthostatic tachycardia and adrenergic receptor dysfunction that was suppressed by selectively clearing the antibodies in vivo.

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This study offers 2 important advances to POTS research. First, the development of an animal model of POTS, based on an autoimmune cause, is crucial for future POTS research. One challenge with performing mechanistic studies in POTS is that the patients are heterogeneous in cause and pathophysiological features.⁶ The lack of biomarkers and standardized phenotypic studies makes it difficult to recruit and properly characterize specific populations with POTS. As POTS has no distinct cause, animal models that mimic the pathophysiological changes are needed for future mechanistic studies. Other rodent models, such as hind limb suspension to simulate deconditioning, have been proposed for use in POTS. Although many patients with POTS have symptoms of physical deconditioning, such as exercise intolerance and decreased cardiac mass,⁶ deconditioning does not specifically induce POTS in most humans or animals. Thus, the finding that immunization of rabbits with adrenergic receptor peptides can induce POTS-like physiological features *in vivo* is a significant advance for the field. The findings by Li et al⁸ offer a novel animal model of POTS that is homogeneous and reversible. However, it is unclear how similar this model is to the patient population with POTS. As mentioned above, the exact prevalence and clinical relevance of these antibodies are still unclear. Another potential issue is how specific these autoantibodies are to POTS as antiadrenergic receptor antibodies have been found in several cardiovascular diseases as well as chronic fatigue syndrome, dementia, and ocular disease.^{3,9–12} Although the autoantibodies are clearly functional in the rabbit model, it is unclear whether the presence of adrenergic autoantibodies in participants with POTS is a bystander effect of the primary disease process or whether they are centrally pathogenic. There is a precedence for bystander antibodies in other diseases, such as rheumatoid arthritis, in which autoantibodies are present well before pathologic changes occur and even persist in remission.¹³ Finally, it is controversial whether a quadrupedal animal model can accurately model an orthostatic syndrome like POTS. Although the rabbits injected with adrenergic autoantibodies had exaggerated orthostatic tachycardia during head-up tilt compared with controls, being upright is not natural for rodents and does not mimic orthostatic stress in humans.

The second important contribution of this work, is that it establishes targeted immune therapy as a potential therapeutic for POTS. Unfortunately, a large percentage of patients with POTS is significantly disabled, despite current management. Estimates suggest that up to 25% are disabled from working or attending school, and morbidity is on par with end-stage heart failure and chronic obstructive pulmonary disease.^{14,15} Thus, as a community, there is a strong need to both better understand mechanisms and consider novel treatments, despite risks, in subsets of patients. The article by Li et al⁸ provides evidence that immune therapy can prevent

POTS-like physiological features, at least in rabbits. The study demonstrated suppression of orthostatic tachycardia in the rabbit model of POTS by blocking the adrenergic autoantibodies from binding to their targets *in vivo* with the use of stable soluble peptide mimics. The use of immunotherapy in POTS is currently controversial, although case reports and case series have shown that immune therapy improves POTS symptoms in patients with comorbid autoimmune diseases and refractory disease.^{3,15,16} There is also an ongoing randomized controlled clinical trial to evaluate the efficacy of intravenous immunoglobulin in POTS (ClinicalTrials.gov Identifier: NCT03919773), which is a first step to understanding the role of autoimmunity in POTS. As with any immune therapy, the risks and potential benefits need to be assessed. In the United States, immune therapy to target autoantibodies largely relies on therapeutic plasma exchange, intravenous immunoglobulin, and/or B-cell depleting strategies. However, none of these treatments is ideal for treating autoimmune diseases, including autoimmune POTS. Therapeutic plasma exchange involves exchanging large volumes of plasma with albumin, which, after several treatments, removes autoantibodies, although it does not target levels of autoantibody production. Risks of plasma exchange include hypotension, coagulopathies, central access complications, and potential reactions to reagents. Intravenous immunoglobulin likely targets autoimmunity through multiple mechanisms, including anti-idiotypic binding, Fc γ signaling, and dilutional catabolism of autoantibodies and endogenous immunoglobulin Gs.¹⁷ However, immunoglobulin G antibodies are distributed throughout the body, and removal from plasma may only partially remove total body levels. Intravenous immunoglobulin has adverse effects, including inflammatory reactions, hemolytic anemia, and aseptic meningitis, which anecdotally patients with POTS may be more susceptible to. B-cell–depleting therapies, including rituximab, target CD20⁺ B cells to remove B-cell populations that are precursors to antibody-producing plasma cells. As a single agent, rituximab has a strong safety profile, although infections and severe reactions (especially in response to the first infusion) do occur.¹⁸ One issue with B-cell–depleting therapy is that long-lived antibody-producing plasma cells, which do not express CD20, may be unaffected by B-cell–depleting therapy. In other countries, immunoadsorption has been used to selectively remove specific adrenergic receptor autoantibodies with some efficacy in diseases, including cardiovascular disorders, chronic fatigue syndrome, dementia, and glaucoma.^{9,11,12,19} Antigen-specific immunoadsorption is similar to therapeutic plasma exchange, but the patients' serum passes through a column that contains solid-phase ligands that bind only autoantibodies and the rest of the plasma is returned to the patient. Thus, immunoadsorption may be a potentially promising therapeutic approach to selectively target

autoantibodies in autoimmune forms of POTS and is a similar strategy used in the report by Li et al.⁸

Overall, Li et al⁸ have advanced the field of POTS research by developing an in vivo animal model of autoimmune POTS. POTS is a syndrome that could greatly benefit from an animal model to use for mechanistic and therapeutic research. Questions remain on how well this rabbit model of POTS represents the heterogeneous patient population and whether it will contribute to further advancements toward novel therapeutics for POTS.

Disclosures

None.

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