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EDITORIAL COMMENT

Novel Mechanisms of Postural Hyperventilation in Postural Orthostatic Tachycardia Syndrome

Toward Discovery of Terra Incognita

Stefanos Zafeiropoulos, MD, PhD,[a] Stavros Stavrakis, MD, PhD[b]

Postural orthostatic tachycardia syndrome (POTS) poses numerous diagnostic and therapeutic challenges for both patients and health care providers. As the prevalence of POTS continues to rise, there is an urgent need for a deeper understanding of its underlying pathophysiology to improve diagnosis, management, and quality of life for affected individuals. Many pathophysiological mechanisms have been proposed, including, but not limited to, inadequate volume regulation (hypovolemic POTS), peripheral noradrenergic denervation (neuropathic POTS), increased sympathetic activity and circulating catecholamines (hyperadrenergic POTS), mast cell activation, and the presence of activating autoantibodies.[1] Nonetheless, it is likely that a significant overlap exists between these mechanisms. Another potential causal driver for POTS is postural hyperventilation, which causes hypocapnia and decreased cerebral blood flow, but the exact mechanisms contributing to its pathophysiology remain poorly understood. The prevailing mechanism includes peripheral chemoreceptor overactivity, which in response to relative hypovolemia with standing, leads to increased ventilation and sympathetic activation. An alternative hypothesis is that brain hypoperfusion at the onset of orthostasis underlies increases in ventilation and sympathetic activity.[2,3]

In this issue of *JACC: Basic to Translational Science*, Baker et al[4] conducted an innovative study to investigate the roles of peripheral chemoreceptor activity and changes in cardiovascular and cerebrovascular hemodynamics as drivers of postural hyperventilation and sympathetic hyperactivation in patients with POTS. By collecting human data and performing a set of translational experiments, the authors unveiled crucial underlying mechanisms of postural ventilation and sympathetic activation in POTS. The authors ought to be congratulated for this elegant, translational study, which sheds light on the intricate mechanisms driving postural hyperventilation in POTS and represents a paradigm shift in our understanding of POTS pathophysiology.

First, the study conducted by Baker et al[4] challenges the prevailing pathophysiological notion regarding peripheral chemoreceptor hyperactivity in POTS. By using inspired hyperoxia to inhibit the peripheral chemoreceptors, they found no difference in the respiratory and sympathetic responses between patients with POTS and healthy subjects. This finding suggests that peripheral chemoreceptor signaling is not affected in POTS, and it is thus unlikely to be a driving mechanism of postural ventilation. On the contrary, the study highlights the postural reductions in stroke volume and brain perfusion, which play a central role in shaping respiratory and sympathetic responses in POTS. This elegant study introduces a new paradigm in the mechanisms driving postural hyperventilation in POTS. However, some aspects of these novel and subversive findings warrant further study to fully elucidate their implications.

The reduced stroke volume observed in patients with POTS is partially attributed to the reduced

From the [a]Department of Cardiology, University Hospital of Zürich, Zürich, Switzerland; and the [b]Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA.
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cardiac preload. However, the role of venous or splanchnic pooling, alterations of peripheral venous hemodynamics, impaired blood volume regulation (relative central hypovolemia), absolute hypovolemia, peripheral small fiber neuropathy, and cardiovascular deconditioning as potential mechanisms of reduced stroke volume, brain hypoperfusion, and, in turn, postural ventilation have to be explored.[1]

Given the heterogeneous nature of the pathophysiological mechanisms underlying POTS, it is plausible that different POTS subtypes exist, albeit with varying degrees of overlap. Each subtype has distinct underlying mechanisms that may precipitate orthostatic intolerance and deconditioning, which is the final common pathway.[5] A detailed characterization of the POTS patient population and a focus on long-term outcomes therefore hold great clinical significance. The role of machine learning in identifying distinct phenotypes that share common clinical and biochemical characteristics should also be explored. Collectively, such an approach could pave the way for novel and personalized therapeutic approaches, including immunotherapy and peripheral neuromodulation.[6,7]

In addition, the sex-specific disparities in hemodynamics and hormonal levels that could explain the pronounced prevalence of POTS in women remain partially unknown.[8] Women with POTS have also reported fluctuations in the severity of symptoms throughout their menstrual cycle.[9] One notable limitation of the present study[4] is that the clinical study comprised female patients, whereas the preclinical experiments were performed on male rats, making exploration of sex as a biological variable problematic. Therefore, examining the role of sex differences and hormonal influences on cerebral perfusion and postural hyperventilation in carefully designed preclinical studies, as well as in adequately powered clinical studies including both sexes, is urgently needed to better understand the sex differences in this condition.

In conclusion, the study by Baker et al[4] provides valuable insights into the pathophysiology of POTS by showing a possible causal relationship between brain hypoperfusion during orthostatic stress and postural hyperventilation and sympathetic overactivation in POTS. This research also identifies important therapeutic targets, including brain perfusion and pulsatility and impaired systemic hemodynamics. Thus, moving from terra incognita toward a better understanding of the pathophysiological mechanisms that drive POTS symptoms would enable the development of novel, personalized therapeutic strategies for the management of patients with this vexing disease.

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ADDRESS FOR CORRESPONDENCE: Dr Stavros Stavrakis, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, 800 Stanton L. Young Boulevard, Suite 5400, Oklahoma City, Oklahoma 73104, USA. E-mail: Stavros-stavrakis@ouhsc.edu.

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