



Review

Moving from the present to the future of Postural Tachycardia Syndrome – What we need

Satish R. Raj^{a,b,*}, David Robertson^b

^a Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, AB, Canada

^b Autonomic Dysfunction Center, Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA

ABSTRACT

Our understanding about Postural Tachycardia Syndrome (POTS) has advanced significantly over the last 25 years. Despite the significant advances that have been made in defining the syndrome and finding some treatments for our patients, there is much work to be done to significantly improve our understanding of the disorder and improve therapeutics. In this article, 5 NEEDS are identified that will be required over the next several years if we want future care to move beyond where we are in the present. These include: (1) a NEED for better administrative data to track POTS diagnoses and the impact of the illness; (2) a NEED to improve physician awareness about POTS, which is a prerequisite for improved access to care; (3) a NEED to better understand the multiple pathophysiologies underlying POTS and the roles of the different medical comorbidities; (4) a NEED for data on effective treatments for POTS; and (5) a NEED for more research funding to study POTS.

1. Introduction

It has now been a quarter century since Schondorf and Low (1993) defined Postural Tachycardia Syndrome (POTS) in close to its current form (outlined in another article in this Special POTS Issue of Autonomic Neurosciences) (Arnold et al., 2018). In that time, there have been many advances in our understanding of some pathophysiological mechanisms that underlie POTS (Jacob et al., 2000; Shannon et al., 2000; Raj et al., 2005a; Medow et al., 2005; Shibao et al., 2005), and several small studies have advanced our understanding about how to treat patients with POTS (Raj et al., 2009; Fu et al., 2010; Raj et al., 2005b; Coffin et al., 2012; Ross et al., 2014). Several patient advocacy groups have been effective at providing education for patients with POTS, bringing POTS patients and clinical researchers together, and bringing communities of patients together by leveraging social media. Professional societies have written consensus statements about the definitions (Freeman et al., 2011) and treatment (Sheldon et al., 2015) of POTS.

While there has been progress, there is still much that needs to be done. POTS is a disorder that is characterized by significant patient suffering and functional disability (Bagai et al., 2011; Benrud-Larson et al., 2002). However, we still do not have a good handle on exactly how many patients suffer from POTS. There is still poor physician recognition of POTS, and POTS patients suffer from lengthy delays in

getting an appropriate diagnosis (Raj et al., 2016). There is a lack of multicenter, placebo-controlled, randomized clinical trials (considered “high quality evidence”) to guide treatment of patients with POTS. It is not known whether patients with POTS should be treated in a monolithic manner or if certain subgroup features should guide initial treatment.

2. Five big needs for the Future of POTS

If we want to be able to look back 25 years from now, and marvel at the marked improvements in the care of POTS patients, then there are several key early steps that are needed. Five of these critical needs are outlined below (Table 1).

2.1. Need to better understand the pathophysiologies underlying POTS

POTS is an end-phenotype and not a disease in itself. In this way, the diagnosis of POTS is like a diagnosis of fever. While there are criteria for each of fever and POTS, and each can benefit from direct treatment (such as acetaminophen for fever), there are multiple underlying disorders or mechanisms that can lead to POTS (Jacob et al., 2000; Shannon et al., 2000; Raj et al., 2005a; Medow et al., 2005; Shibao et al., 2005) and fever. The broad, multisystem symptoms that are seen in POTS can make it difficult to get a handle on the specific underlying

* Corresponding author at: Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, GAC70 HRIC Bldg, 3280 Hospital Dr. NW, Calgary, AB T2N 4Z6, Canada.

E-mail address: satish.raj@ucalgary.ca (S.R. Raj).

<https://doi.org/10.1016/j.autneu.2018.06.007>

Received 11 March 2018; Received in revised form 25 April 2018; Accepted 29 June 2018
1566-0702/ © 2018 Elsevier B.V. All rights reserved.

Table 1

Five Big NEEDS for the future of POTS.

1. NEED to better understand the pathophysiologies underlying POTS.
2. NEED better data on the number of POTS patients and the impact of POTS
3. NEED to improve physician awareness about POTS to improve accurate diagnosis and access to care.
4. NEED data on effective treatments for POTS.
5. NEED more research funding.

issues. The issue is complicated even further because there are many comorbid diagnoses that can co-exist within an individual patient with POTS (e.g. Ehlers Danlos Syndrome, Mast Cell Activation Disorder, autoimmune disorders, and small fiber neuropathy). There is currently a poor understanding of how these disorders relate to each other, and how each contribute to the symptoms of an individual patient.

Ideally, we need to reach a stage where we can have meaningful, and agreed upon, criteria for diagnosing POTS “endophenotypes”. These subtypes of POTS would ideally be mutually exclusive of each other, have clearly discernable natural histories, and have targeted treatment algorithms. An example of this can be seen in the management of heart failure, where treatment strategies vary between patients with preserved LVEF and those with reduced LVEF.

2.2. Need better data on the number of POTS patients and the impact of POTS

“If you can't measure it, you can't improve it”

–VF Ridgeway (Caulkin, 2008)

It is estimated that there are between 300,000 and 3,000,000 patients with POTS in the United States alone. These estimates come from the “best guess” of various specialists and patient-advocacy groups. In contrast, we know how many patients there are with myocardial infarction, multiple sclerosis, and even other autonomic disorders such as orthostatic hypotension. The reason for this discrepancy is that those other disorders have administrative codes in the International Classification of Diseases (ICD) Ninth revision (ICD-9) and Tenth revision (ICD-10). Efforts are currently underway to get POTS included as a diagnosis in ICD-11, which is currently under development. Once we can track the diagnosis of POTS, it will be easier to quantify financial impacts of POTS. These include direct costs to the patients and their families (Bourne et al., 2017), costs to the healthcare system and costs to society. This knowledge is a critical step in being able to manage the impacts of POTS.

2.3. Need to improve physician awareness about POTS to improve accurate diagnosis and access to care

Physicians cannot diagnose disorders that they do not know. There is a significant lack of awareness about POTS across medical specialties. This can lead to significant delays, which can last for several years, from the onset of symptoms to acquiring a diagnosis of POTS (Raj et al., 2016). The flipped side of this coin is that with a little bit of awareness, but incomplete understanding, patients are sometimes now labeled with POTS without meeting the diagnostic criteria for POTS (Arnold et al., 2018).

POTS is not taught in most medical schools or in many residency programs. Awareness is slowly increasing, but more efforts are needed. This will likely involve trying to engage even more in the traditional methods of physician education, including presenting at Grand Rounds and Continuing Medical Education sessions, and writing articles in medical journals (such as the current Special Issue on POTS in *Autonomic Neurosciences*). However, these methods alone are often ineffective in closing the evidence-practice gap in other disorders, even for proven therapies such as the use of angiotensin-converting enzyme inhibitors for patients with reduced cardiac left ventricular ejection

fraction (LVEF) (Zwarenstein et al., 2007).

We need to find novel methods to educate physicians about POTS. Social media has evolved tremendously in the last decade, and some physicians have started to leverage these tools for their continuing medical education. As these tools further evolve, there may be great opportunities to exploit them to educate physicians more broadly about POTS.

An alternative approach that has been successful is a “grassroots approach” where patients with POTS help to educate their physicians and learn about POTS together. The nature of clinical medicine is such that physicians often learn best from individual patients. There are multiple anecdotes about physicians who have a patient diagnosed with POTS, and then “find” several other patients with POTS in their practice. Perhaps this “bottom-up” approach to physician education will be suitable to scale up physician knowledge about POTS.

2.4. Need data on effective treatments for POTS

There have been some placebo-controlled randomized trials in patients with POTS (Raj et al., 2009; Raj et al., 2005b; Coffin et al., 2012; Ross et al., 2014) that has informed the treatment of patients with POTS. However, most of the studies that guide treatment are small (involving ≤ 30 patients) (Fu et al., 2010; Raj et al., 2005b; Coffin et al., 2012; Ross et al., 2014) and single-center studies (Raj et al., 2009; Fu et al., 2010; Raj et al., 2005b; Coffin et al., 2012; Ross et al., 2014). The studies are often of a very short duration (Raj et al., 2009; Raj et al., 2005b; Coffin et al., 2012; Ross et al., 2014). While these data are important, most patients seek durable and long-lasting effective therapies.

As this field matures, we need to develop clinical trial networks to conduct larger, multicenter, placebo-controlled, randomized clinical trials of sufficient duration to define effective therapies for POTS as a whole, or for endophenotypes of POTS. These will take a high level of organization on the part of physicians and scientists to develop networks to conduct these trials, commitment from patients to participate in placebo-controlled trials, and funding to implement these trials (and randomized clinical trials are not cheap).

2.5. Need more research funding

As outlined above, there is much work that is required to move the POTS field forward. Work is required to understand the different pathophysiologies underlying POTS, the role of different co-morbidities, and how to treat issues relating to debilitating symptoms in POTS such as cognitive impairment and fatigue. Well-designed randomized clinical trials are needed to define effective therapies for patients with POTS.

All of these priorities will require research funding. At present, POTS is in an unenviable position of being too common to be considered a “rare disease” (which has some dedicated research funding), but it is often considered too rare and poorly understood for many other funding opportunities. Special programs to encourage and fund high quality research into POTS are likely going to be required.

3. The future

“If she's amazing, she won't be easy. If she's easy, she won't be amazing. If she's worth it, you won't give up. If you give up, you're not worthy.”

–Bob Marley (2011)

While Bob Marley was not discussing POTS, his words still do apply. If we want the “POTS Future” to be better than the “POTS Present”, then it is going to take commitment from all of the involved stakeholders – patients, clinicians, researchers, administrators and funders. It is the POTS Future that we need.

Acknowledgements

None.

Funding sources

SRR receives research support from the Canadian Institutes of Health Research (CIHR; Ottawa, ON, Canada) grant MOP142426 and the Cardiac Arrhythmia Network of Canada (CANet; London, ON, Canada) grants SRG-15-P01-001 and SRG-17-P27-001, and the Vanderbilt Institute for Clinical and Translational Research funded by a Clinical and Translational Science Award from the National Center for Advancing Translational Science from the National Institutes of Health (UL1 TR000445).

Disclosures

SRR is a consultant for Lundbeck NA Ltd., GE Healthcare, Abbott Laboratories, Boston Scientific Corporation and Allergan.

References

- Arnold, A.C., Ng, J., Raj, S.R., 2018 February 28. Postural tachycardia syndrome - diagnosis, physiology, and prognosis. *Auton. Neurosci.* <http://dx.doi.org/10.1016/j.autneu.2018.02.005>. (pii: S1566-0702(17)30354-5) (Epub ahead of print).
- Bagai, K., Song, Y., Ling, J.F., et al., 2011 April 15. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J. Clin. Sleep Med.* 7 (2), 204–210.
- Benrud-Larson, L.M., Dewar, M.S., Sandroni, P., Rummans, T.A., Haythornthwaite, J.A., Low, P.A., 2002 June. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin. Proc.* 77 (6), 531–537.
- Bourne, K., Ng, J., Stiles, L., et al., 2017. Employment and economic impacts of postural tachycardia syndrome: insights from a cross-sectional community-based survey. *Clin. Auton. Res.* 27, 332 (Ref Type: Abstract).
- Caulkin, S., 2008. The rule is simple: be careful what you measure. In: *The Guardian* 8 A.D. (Feb 9).
- Coffin, S.T., Black, B.K., Biaggioni, I., et al., 2012 September. Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome. *Heart Rhythm.* 9 (9), 1484–1490.
- Freeman, R., Wieling, W., Axelrod, F.B., et al., 2011 April 26. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton. Neurosci.* 161 (1–2), 46–48.
- Fu, Q., Vangundy, T.B., Galbreath, M.M., et al., 2010 June 22. Cardiac origins of the postural orthostatic tachycardia syndrome. *J. Am. Coll. Cardiol.* 55 (25), 2858–2868.
- Jacob, G., Costa, F., Shannon, J.R., et al., 2000 October 5. The neuropathic postural tachycardia syndrome. *N. Engl. J. Med.* 343 (14), 1008–1014.
- Marley, B., 2011. *Bob Marley: Guitar Chord Songbook*. Hal Leonard.
- Medow, M.S., Minson, C.T., Stewart, J.M., 2005 October 25. Decreased microvascular nitric oxide-dependent vasodilation in postural tachycardia syndrome. *Circulation* 112 (17), 2611–2618.
- Raj, S.R., Biaggioni, I., Yamhure, P.C., et al., 2005 April 5a. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation* 111 (13), 1574–1582.
- Raj, S.R., Black, B.K., Biaggioni, I., Harris, P.A., Robertson, D., 2005 May 31b. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation* 111 (21), 2734–2740.
- Raj, S.R., Black, B.K., Biaggioni, I., et al., 2009 September 1. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation* 120 (9), 725–734.
- Raj, S.R., Stiles, L., Shaw, B., et al., 2016. The diagnostic experience in postural tachycardia syndrome: insights from a cross-sectional community-based survey. *Clin. Auton. Res.* 26, 356 (Ref Type: Abstract).
- Ross, A.J., Ocon, A.J., Medow, M.S., Stewart, J.M., 2014 February. A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural tachycardia syndrome. *Clin. Sci. (Lond.)* 126 (4), 289–296.
- Schondorf, R., Low, P.A., 1993 January. Idiopathic postural orthostatic tachycardia syndrome: An attenuated form of acute pandysautonomia? *Neurology* 43 (1), 132–137.
- Shannon, J.R., Flattem, N.L., Jordan, J., et al., 2000 February 24. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N. Engl. J. Med.* 342 (8), 541–549.
- Sheldon, R.S., Grubb, B.P., Olshansky, B., et al., 2015 June. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm.* 12 (6), e41–e63.
- Shibao, C., Arzubiaga, C., Roberts, L.J., et al., 2005 March. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 45 (3), 385–390.
- Zwarenstein, M., Hux, J.E., Kelsall, D., et al., 2007 November 26. The Ontario printed educational message (OPEM) trial to narrow the evidence-practice gap with respect to prescribing practices of general and family physicians: a cluster randomized controlled trial, targeting the care of individuals with diabetes and hypertension in Ontario, Canada. *Implement. Sci.* 2, 37.