Clin Auton Res (2008) 18:300–307
DOI 10.1007/s10286-008-0487-7

REVIEW ARTICLE

Michael J. Joyner
Shizue Masuki

POTS versus deconditioning: the same or different?

Received: 21 May 2008
Accepted: 1 July 2008
Published online: 12 August 2008

M.J. Joyner, MD (✉)
Dept. of Anesthesiology
Mayo Clinic
200 First Street SW
Rochester (MN) 55905, USA
Tel.: +1-507/255-4288
Fax: +1-507/255-7300
E-Mail: joyner.michael@mayo.edu

S. Masuki, PhD
Dept. of Sports Medical Sciences
Shinshu University Graduate School of Medicine
Matsumoto, Japan

Abstract The 2007 Streeten Lecture focused on the idea that physical deconditioning plays a key role in the symptomology and pathophysiology of POTS. Parallels were drawn between the physiological responses to orthostatic stress seen in POTS patients and the physiological responses seen in "normal" humans after prolonged periods of bedrest, deconditioning, or space flight. Additionally, the idea that endurance exercise training might ameliorate some of these symptoms was also advanced. Finally, potential parallels between POTS, chronic fatigue syndrome, and fibromyalgia were also drawn and the potential role of exercise training as a "therapeutic intervention" in all three conditions was raised. The conceptual model for the lecture was that after some "initiating event" chronic deconditioning plays a significant role in the pathophysiology of these conditions, and these physiological changes in conjunction with "somatic hypervigilence" explain many of the complaints that this diverse group of patients have. Additionally, the idea that systematic endurance exercise training might be helpful was advanced, and data supportive of this idea was reviewed. The main conclusion is that the medical community must retain their empathy for patients with unusual conditions but at the same time send a firm but empowering message about physical activity. As always, we must also ask what do the ideas about physical activity and inactivity and the conditions mentioned above not explain?

Key words orthostatic stress · exercise · somatic hypervigilance

Introduction

This paper represents an "editorial" review based on the 2007 Streeten Lecture given at the Combined AAS and EFAS meetings in Vienna, Austria, in the fall of 2007. The overall goal of the lecture was to compare and contrast the postural orthostatic tachycardia syndrome (POTS) with physical deconditioning. Additionally, questions were raised about how physical conditioning might serve as a treatment for POTS, and how it might also serve as a treatment for syndromes such as fibromyalgia and chronic fatigue syndrome, which appear to have some overlap with POTS. A fundamental perspective is that deconditioning may be a final common pathway that makes these conditions, whatever their cause, worse.

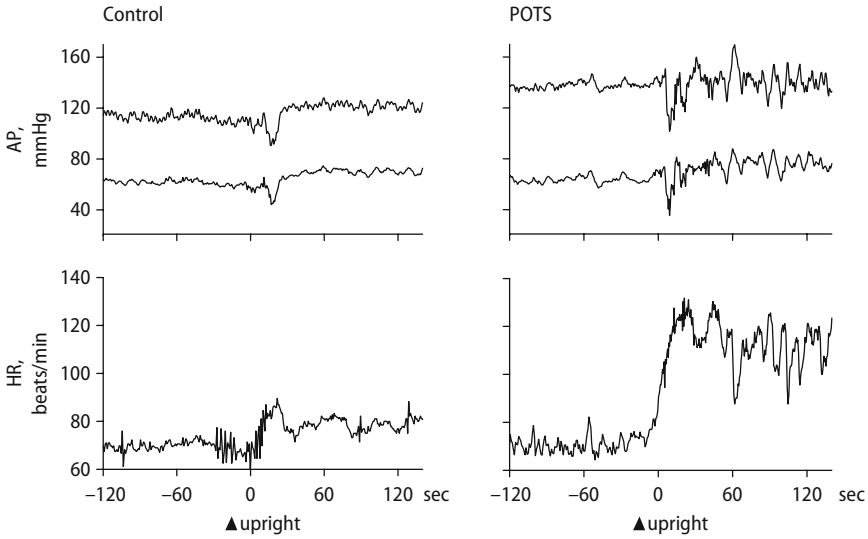

Fig. 1 Individual records of the arterial pressure (AP) and heart rate (HR) responses to the upright posture. The record includes 120 seconds of supine rest followed by 120 seconds of upright posture. In addition to having a more marked rise in heart rate during the upright posture, the POTS patient also showed much more variability in their heart rate and arterial pressure responses

David Streeten

As noted above, this paper is based on the Streeten Lecture. In this context, it is always important to remember exactly who Dr. Streeten was. First, he was a native of Bloemfontein, South Africa, and he received his primary medical degree in 1946 from the University of Witwatersrand in Johannesburg. He subsequently received a Doctorate of Pharmacology from Oxford in 1951 and he went on to a distinguished career in clinical investigation. He served as president of the society in 1996, and he was clearly a senior and respected investigator as the American Autonomic Society emerged in the 1990's. Most importantly, Dr. Streeten was a classic "triple threat" academic clinician-investigator who was interested in the detailed and mechanistic phenotyping of patients. His main interests were hypertension and its reciprocal condition, orthostatic intolerance, and his papers were known for their high level of scholarship. As we think back about Dr. Streeten and what he represents, one can only hope that in the era of "outcomes" research and "omics" individuals interested in careful phenotyping of unusual patients will continue to find a place in biomedical research [20, 21].

What is POTS?

POTS emerged as a recognized syndrome in the 1990's and is marked by baseline sinus rhythm with no evidence of cardiac disease but with a sustained increase in heart rate of more than 30 BPM with 10 minutes of upright tilting [12]. However, there is no sustained or marked orthostatic hypotension but patients frequently complain of lightheadedness, weakness, palpitations, blurred vision, breathing difficulties, nausea, and headaches, and these symptoms resolve with re-assumption of the supine position. Finally, there is no other obvious cause or explanation for the marked tachycardia with tilting. Figure 1 is an individual record of a normal patient and a patient with POTS showing the marked rise in heart rate during standing in POTS. It is also of note that both blood pressure and heart rate are far less stable in the POTS patient than in the control patient.

Is POTS psychogenic?

Anyone who has interacted with POTS patients and other types of orthostatic syndromes occasionally ask themselves to what extent are these conditions psychogenic? There are likely complex sociologic reasons about how patients interact with physicians and other caregivers that lead to this question and at some level it may reflect frustration on the part of clinicians because they can't find anything "obviously" wrong with the patients and conclude, therefore, the problems are likely psychogenic. Additionally, it is well known that patients with POTS do have a condition called "somatic hypervigilence" meaning that they tend to report relatively mild or routine sensory information as more intense or distressing than "normal" [1, 2].

In an effort to address this idea in a more definitive way, we studied 14 patients with an established diagnosis of POTS [13]. These patients were subjected to venous pooling via lower body negative pressure (LBNP) and they were also subjected to two forms of sham LBNP [8, 13]. We initially hypothesized that at least some of the patients with POTS would have a marked tachycardic response to the sham LBNP, thus

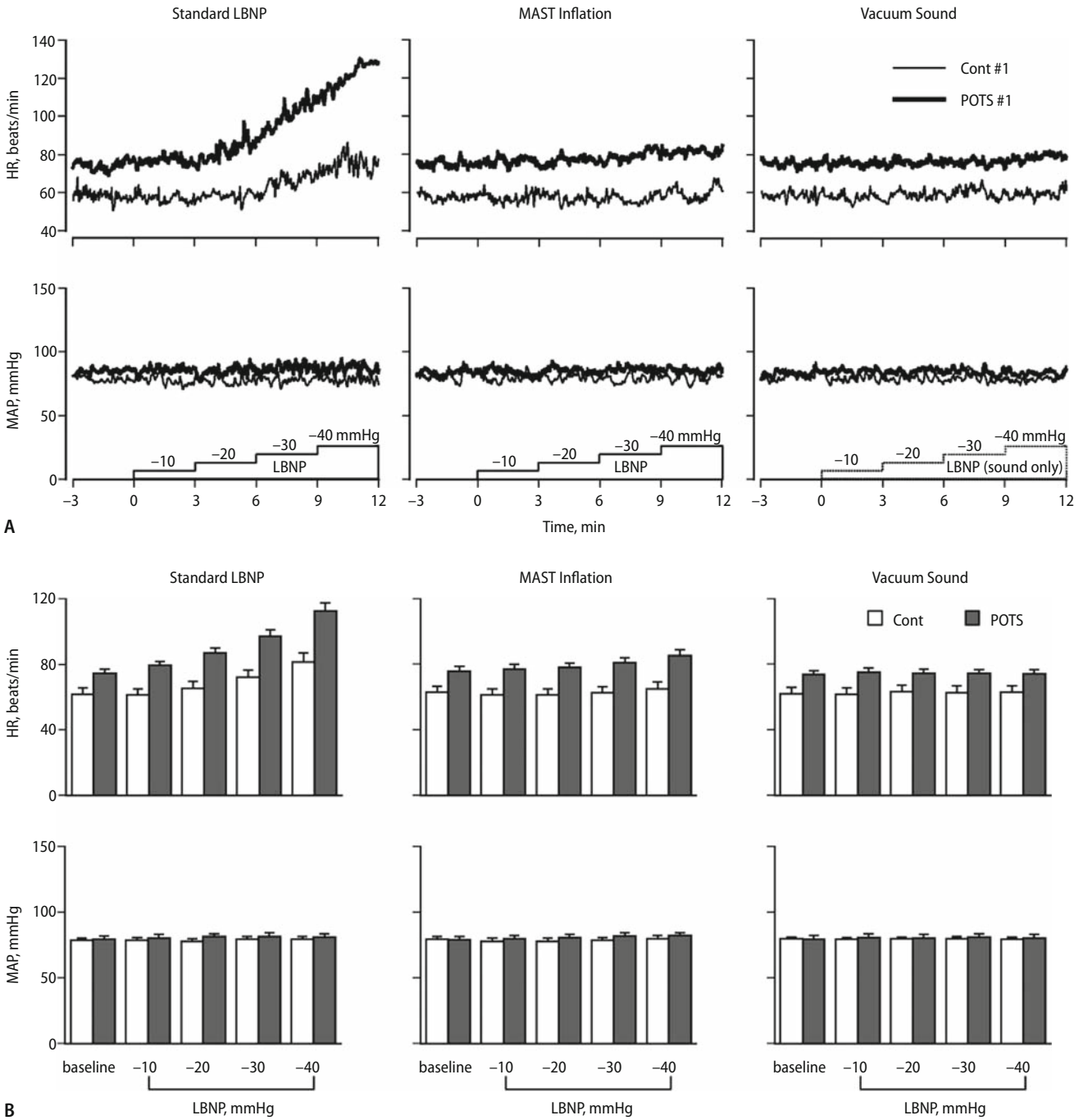

Fig. 2 The upper panels (**a**) show heart rate (HR) and mean arterial pressure (MAP) responses to standard lower body negative pressure (left upper panels), HR and mean arterial pressure MAP responses to sham-LBNP with MAST trouser inflation to prevent venous pooling (middle upper panels), and HR and MAP responses to the vacuum sound only (right upper panels). These are representative tracings from an individual control subject and a POTS patient. The bottom *bar graphs* (**b**) demonstrate the group responses. A key point from this slide is that the excessive heart rate response in POTS only occurred during real venous pooling. Figure from reference [13]

confirming a psychogenic contribution to POTS. However, while we found the expected marked rise in heart rate during venous pooling with LBNP, during sham LBNP there was no increase in heart rate (Figure 2). Additionally, these patients did not have excessive heart rate responses to mental stress. However, psychological testing confirmed that these patients did in fact have somatic hypervigilence

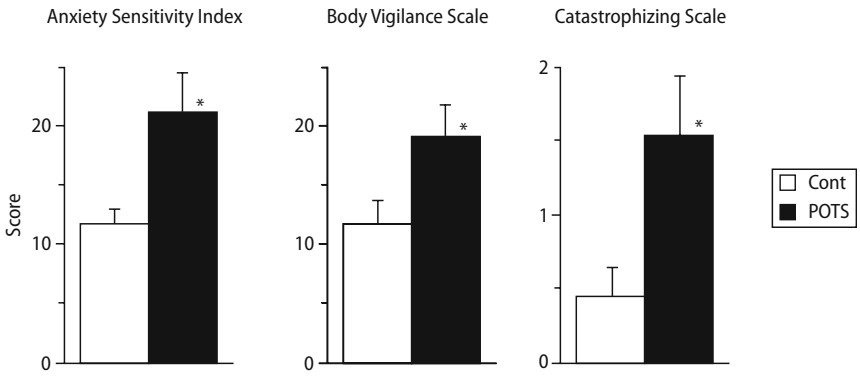

Fig. 3 Differences between control subjects and POTS patients on psychological markers associated with their tendency to report physiological responses as more intensely experienced than control subjects. Figure from reference [13]

(Figure 3). This means that while patients with POTS perceive and report sensory information in a more dramatic way than control subjects, the tachycardic response that they experience during venous pooling is truly a compensatory physiological response.

Is the rise in heart rate with POTS really "excessive?"

If one accepts the proposition that the rise in heart rate with POTS is "physiological" the question is why is it so marked? Does this represent some sort of altered or excessive regulatory response, or does it reflect a normal regulatory response? In this context, it seemed like there were several possible explanations and experiments that might help distinguish between these possibilities.

First, is there any evidence that baroreflex control of heart rate is altered in POTS so that small reductions in blood pressure evoke larger than normal increases in heart rate? Second, a host of bed rest deconditioning studies suggest that after periods of bed rest deconditioning there is a reduction in heart volume (cardiac atrophy), a reduction in blood volume, and marked tachycardic responses to standing or upright tilting which can also include unusually high levels of blood pressure variability [4, 9–11, 18] (Figure 4). To address these issues we performed both baroreflex testing and supine vs. upright exercise studies in the same POTS patients who were subjected to the sham vs. real LBNP [13–15].

Interestingly, during supine exercise at 25, 50, and 75 watts, cardiac output was similar and heart rate was higher in the POTS patients, suggesting that even when cardiac filling was optimized by the supine position, stroke volume was reduced in POTS (Figure 5). The differences in stroke volume were much greater during upright exercise, but again cardiac output was similar between the control subjects and POTS patients. Pulse pressure tended to be lower in the POTS patients and there was much greater beat-to-beat variability in arterial pressure [14, 15].

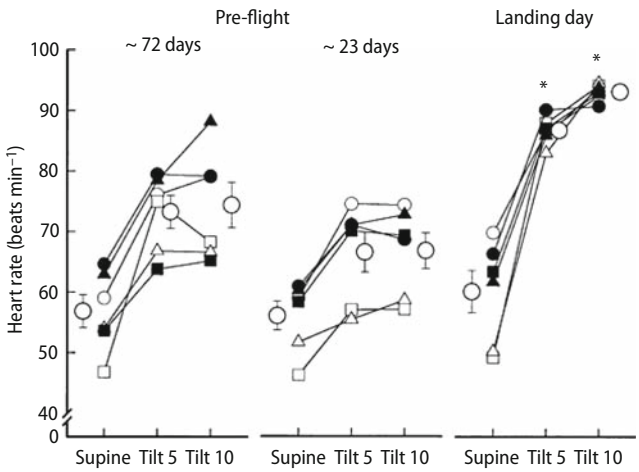

Fig. 4 Heart rate responses to upright tilting 72 and 23 days before space flight and on the landing day. The responses to upright tilt appear "POTS-like" after space flight. Since space flight is associated with cardiac atrophy and a reduction in blood volume which can also be seen in POTS, this and related data raises questions about the role of deconditioning in the pathophysiology of POTS. Figure from reference [10]

When phenylephrine boluses were given during exercise to raise blood pressure and test baroreflex control of heart rate, the reflex bradycardic responses to a rise in pressure were different at given workloads between the control subjects and the POTS patients suggesting that baroreflex control of heart rate was blunted in POTS [14]. However, when the responses were corrected for heart rate things were surprisingly "normal." In fact, as we thought more about the exercise responses in POTS patients they appeared strikingly similar to those seen in either highly deconditioned humans or subjects who have undergone prolonged periods of bed rest [4, 9–11, 18].

At about the same time, investigators in both Dallas and Austria, with collaborators from Vanderbilt, were coming to similar conclusions [6, 7, 9, 24]. Since deconditioning is marked by cardiac atrophy and reduced blood volume, and POTS is also marked

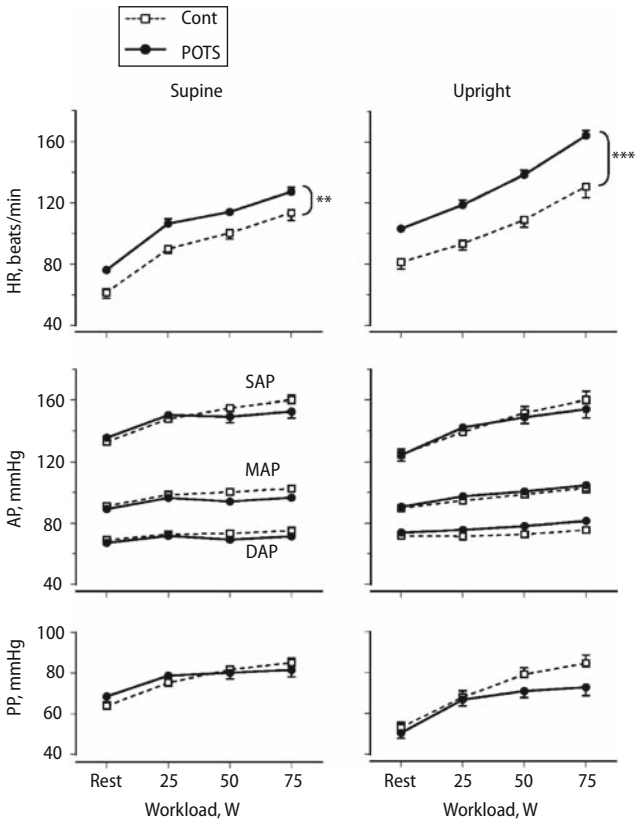

Fig. 5 Heart rate, arterial pressure, and pulse pressure responses to graded exercise in the supine and upright position in POTS patients. The cardiac output responses were similar in both groups during exercise, indicating that stroke volume was lower in the POTS patients. Increased heart rate responses on a lower stroke volume are also suggestive of deconditioning. Figure from reference [15]

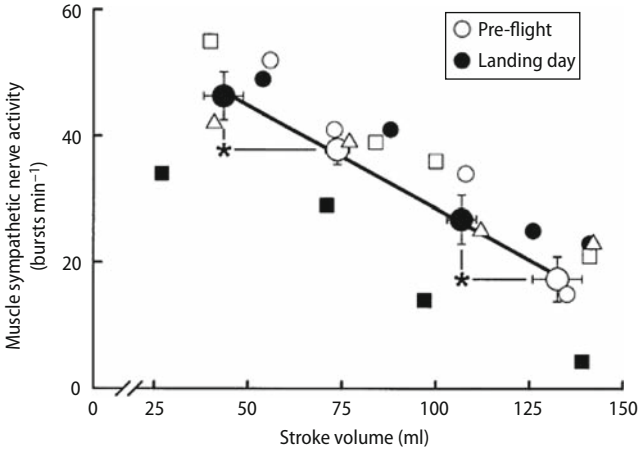

Fig. 6 Relationship between stroke volume and muscle sympathetic nerve activity before and after space flight. This figure makes the point that the relationship between stroke volume and MNSA is constant before and after space flight but that the changes in cardiac size and blood volume shift the responses to the left on the curve. This data suggests that the responses seen in POTS might be due to the fact that the patients are simply on different parts of the stimulus response curves that relate afferent signals from barosensitive areas in the cardiovascular system to heart rate, and MSNA responses. Figure from reference [10]

by cardiac atrophy and reduce blood volume, the idea is that perhaps deconditioning plays a role in the clinical manifestations of POTS.

Is peripheral vasoconstrictor tone "abnormal" in POTS?

Another idea that has received some attention as a potential explanation for POTS is that there is somehow either inadequate activation of peripheral sympathetic vasoconstrictor nerves during the upright posture, or that activation of these nerves does not evoke a "normal" vasoconstrictor response [3, 5, 17]. While there have been limited studies that recorded muscle sympathetic nerve activity in patients with POTS, in general, baseline MSNA does not appear to be markedly increased [3, 6, 17]. However, during either upright tilt or infusions of nitroprusside, it appears as if there is an augmented MSNA response in patients with POTS. Curiously, augmented MSNA responses to tilting are also seen after the deconditioning associated with space flight or bed rest. Again, the MSNA responses in POTS look very similar to those seen in normal subjects after periods of deconditioning.

The next question is whether or not a given rise in MSNA causes the expected vasoconstriction in POTS or is there somehow inadequate vasoconstriction for a given rise in MSNA? The most comprehensive data set on this topic comes from Fu et al. in Dallas who showed that MSNA responses for a given change in heart volume were normal in POTS, and that the vasoconstriction evoked by these changes in MSNA were also normal [6, 7]. So again, there is nothing grossly physiologically abnormal about POTS; it is just as if these individuals are on different parts of stimulus response curves that relate afferent signals from barosensitive areas in the cardiovascular system to efferent heart rate and MSNA responses (Figure 6).

Interim summary

So far the case has been made that the physiological responses seen in POTS reflect primarily a deconditioned cardiovascular system and in fact "normal" relationships between afferent signals in the cardiovascular system and efferent responses that should be considered reasonable for individuals with small hearts and small plasma volumes (e.g., deconditioned). If that is the case, the obvious question is,

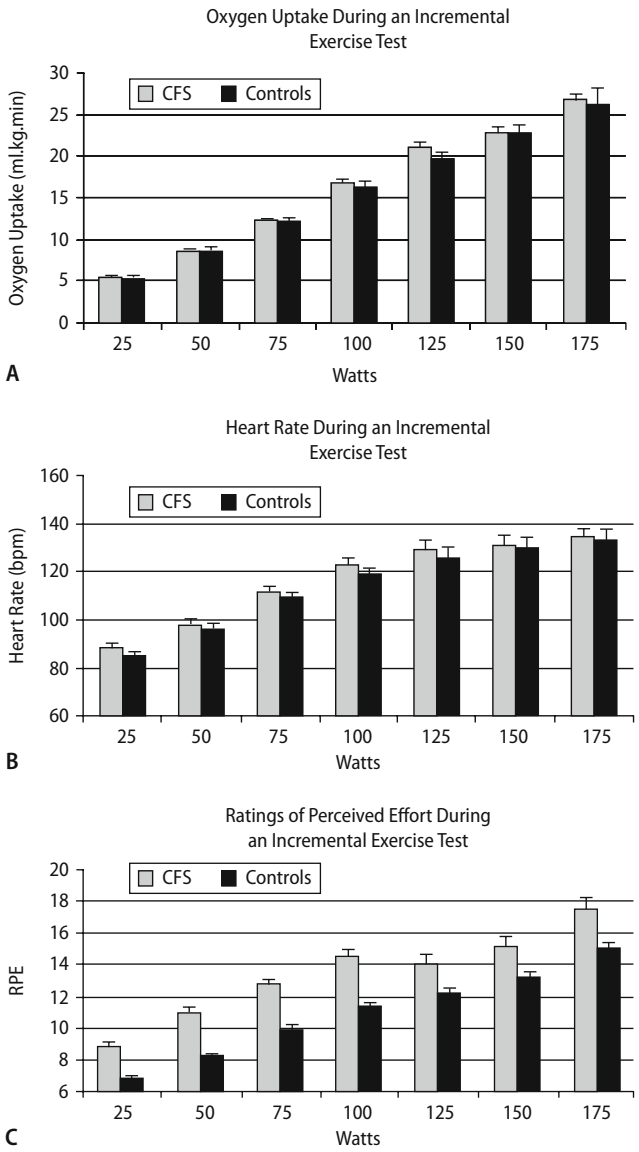

Fig. 7 Oxygen uptake (**a**), heart rate (**b**), and readings of perceived exertion (**c**) in patients with chronic fatigue syndrome. This figure demonstrates that there is a mismatch between the perception of effort and the physiological responses to graded exercise in these patients that is conceptually similar to the somatic hypervigilence concept advanced in POTS. Figure from reference [23]

how do patients with POTS and perhaps other forms of orthostatic intolerance respond to physical conditioning? In this context, Fu et al. in Dallas have started prolonged graded exercise training in POTS patients and preliminary data demonstrates a dramatic resolution in symptoms that accompanied increases in cardiac volume. Likewise, Winker et al. studied Austrian army recruits and subjected individuals with histories of orthostatic intolerance to a 3 month period of endurance exercise training [24]. This training dramatically reduced the symptoms in these individuals and also improved their physiological responses to orthostatic stress. Together this data suggests that exercise training can work in these conditions.

POTS, chronic fatigue syndrome, fibromyalgia: the same or different?

Clinicians who treat patients with POTS frequently comment that there is some "overlap" between POTS and conditions like chronic fatigue syndrome and fibromyalgia. Additionally, those who take care of patients with chronic fatigue syndrome and fibromyalgia sometimes comment on their impression that orthostatic intolerance is more common in these patients. These observations, and a variety of reports suggesting that all of these conditions are associated with marked deconditioning, raise a number of interesting questions. The most obvious question is, will programs of therapeutic exercise "rehabilitation" be effective in all three conditions. As mentioned above, there is at least some evidence that suggests exercise training will be effective in POTS and other forms of orthostatic intolerance. In this context, the physiological responses to exercise appear remarkably normal in many patients with chronic fatigue syndrome, but there is a mismatch between the perception of effort and objective measures of the physiological stress [16, 22]. These results seem analogous to the somatic hypervigilence seen in patients with POTS. In other words, normal physiological responses are perceived very differently in these patients (Figure 7). Additionally, in at least one randomized clinical trial of exercise training for chronic fatigue syndrome graded exercise training resulted in improvements in the relationships between physiologic markers of stress and perceptions of stress [23].

Exercise training has also been shown in a number of trials to improve symptoms and functionality in fibromyalgia [19]. All of these observations suggest that graded exercise training might be affected in conditions that defy a clear pathophysiological explanation but are marked by "mismatches" between a given level of physiological stress and the perceptual experience of certain individuals.

How might all of this fit together?

Clearly, patients with POTS, chronic fatigue syndrome, and fibromyalgia all have symptoms that are "very real" to them. Many can also describe a relatively normal life that was "interrupted" by a flu-like syndrome or some other precipitating event followed by the observation that since then they have essen-

tially "never been the same." A question raised by the data reviewed above is whether or not there is typically a triggering event followed by a prolonged period of inactivity. Deconditioning could then operate in concert with somatic hypervigilence to lead to a disturbing mismatch between physiological responses and perception in some individuals. This could then lead to a vicious cycle of less activity and more deconditioning which makes a difficult situation worse. This scenario could also be made worse by the "medicalization" of these patients who then go from doctor to doctor convinced that there is something wrong with them but unable to find a satisfactory explanation for it.

Summary and what to do next

The ideas presented above suggest that:

- After some initiating event, deconditioning plays a major role in sustaining POTS. This is made worse by somatic hypervigilance.
- There is nothing physiologically abnormal about POTS; but these individuals appear to be on different parts of stimulus response curves that relate afferent signals from barosensitive areas in the cardiovascular system to efferent heart rate and MSNA responses.
- Increasing evidence suggests that exercise training is a viable therapeutic option in POTS.

Based on the above ideas, it seems that exercise-based rehab would appear to be a wise prescription for many patients with POTS and other forms of orthostatic intolerance. This might best be done in a setting that de-medicalizes the training and purposely avoids the hospital or clinic setting. So-called "phase III cardiac rehabilitation," which is frequently conducted in community-based exercise facilities, can be very effective and send patients a powerful message that they are in fact able to be active just like everyone else. In addition to exercise training and the de-medicalization of these conditions, perhaps more attention should be paid to perceptual re-training and psychological coping strategies that might be of high value to these patients. Finally, it is important that the medical community retain their empathy for patients with unusual conditions, but at the same time perhaps we should send a firm but empowering message about physical activity to them. Last but not least, we must always ask ourselves, 'what do the ideas presented above fail to explain?'

Acknowledgments The author's work on this topic was supported by NS 32352. The author would also like to thank his many collaborators over the years, and especially Dr. Phillip A. Low, who first suggested that he conduct physiological studies on patients with orthostatic intolerance.

References

1. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA (2002) Quality of life in patients with postural tachycardia syndrome. Mayo Clin Proc 77:531–537.
2. Benrud-Larson LM, Sandroni P, Haythornthwaite JA, Rummans TA, Low PA (2003) Correlates of functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. Health Psychol 22:643–648.
3. Bonyhay I, Freeman R (2004) Sympathetic nerve activity in response to hypotensive stress in the postural tachycardia syndrome. Circulation 110:3193–3198.
4. Dorfman TA, Levine BD, Tillery T, Peshock RM, Hastings JL, Schneider SM, Macias BR, Biolo G, Hargens AR (2007) Cardiac atrophy in women following bed rest. J Appl Physiol 103:8–16.
5. Fu Q, Shook RP, Okazaki K, Hastings JL, Shibata S, Conner CL, Palmer MD, Levine BD (2006) Vasomotor sympathetic neural control is maintained during sustained upright posture in humans. J Physiol 577:679–687.
6. Fu Q, Shook RP, Shibata S, Hastings JL, Okazaki K, Conner CL, Palmer MD, Levine BD (2007) Vasomotor sympathetic and hemodynamic responses during upright tilt in postural orthostatic tachycardia syndrome. FASEB J 21:A879.
7. Fu Q, Shook RP, Shibata S, Okazaki K, Hastings JL, Dorfman T, Conner CL, Palmer MD, Jacob G, Levine BD (2006) Cardiac size: a potential mechanism for gender differences in orthostatic intolerance and POTS? Clin Auton Res 16:321.
8. Halliwill JR, Lawler LA, Eickhoff TJ, Joyner MJ, Mulvagh SL (1998) Reflex responses to regional venous pooling during lower body negative pressure in humans. J Appl Physiol 84:454–458.
9. Levine BD (2006) The Grinch syndrome: a new name for orthostatic hypotension and syncope. In: 2006 ACSM annual meeting named lectures [DVD]. American College of Sports Medicine, Monterey, healthy learning.
10. Levine BD, Pawelczyk JA, Ertl AC, Cox JF, Zuckerman JH, Diedrich A, Biaggioni I, Ray CA, Smith ML, Iwase S, Saito M, Sugyama Y, Mano T, Zhang R, Iwasaki K, Lane LD, Buckey JC Jr, Cooke WH, Baisch FJ, Eckberg DL, Blomqvist CG (2002) Human muscle sympathetic neural and haemodynamic responses to tilt following spaceflight. J Physiol 538:331–340.
11. Levine BD, Zuckerman JH, Pawelczyk JA (1997) Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. Circulation 96:517–525.
12. Low PA, Opfer-Gehrking TL, Textor SC, Benarroch EE, Shen WK, Schondorf R, Suarez GA, Rummans TA (1995) Postural tachycardia syndrome (POTS). Neurology 45:S19–S25.
13. Masuki S, Eisenach JH, Johnson C, Dietz NM, Benrud-Larson L, Schrage WG, Curry TB, Sandroni P, Low PA, Joyner MJ (2006) Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. J Appl Physiol 102:896–903.

14. Masuki S, Eisenach JH, Schrage WG, Dietz NM, Johnson CP, Wilkins BW, Dierkhising RA, Sandroni P, Low PA, Joyner MJ (2007) Arterial baroreflex control of heart rate during exercise in postural tachycardia syndrome. J Appl Physiol 103:1136–1142.
15. Masuki S, Eisenach JH, Schrage WG, Johnson CP, Dietz NM, Wilkins BW, Sandroni P, Low PA, Joyner MJ (2007) Reduced stroke volume during exercise in postural tachycardia syndrome. J Appl Physiol 103:1128–1135.
16. McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH (2004) Muscle metabolism with blood flow restriction in chronic fatigue syndrome. J Appl Physiol 96:871–878.
17. Muenter Swift N, Charkoudian N, Dotson RM, Suarez GA, Low PA (2005) Baroreflex control of muscle sympathetic nerve activity in postural orthostatic tachycardia syndrome. Am J Physiol Heart Circ Physiol 289:H1226–H1233.
18. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, Peshock RM, Weatherall PT, Levine BD (2001) Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 91:645–653.
19. Richards SC, Scott DL (2002) Prescribed exercise in people with fibromyalgia: parallel group randomized controlled trial. Br Med J 325:185.
20. Streeten DH, Anderson GH Jr, Richardson R, Thomas FD (1988) Abnormal orthostatic changes in blood pressure and heart rate in subjects with intact sympathetic nervous function: evidence for excessive venous pooling. J Lab Clin Med 111:326–335.
21. Streeten DH, Scullard TF (1996) Excessive gravitational blood pooling caused by impaired venous tone is the predominant non-cardiac mechanism of orthostatic intolerance. Clin Sci (Lond) 90:277–285.
22. Wallman KE, Morton AR, Goodman C, Grove R (2004) Physiological responses during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports Exerc 36:1682–1688.
23. Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM (2004) Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med J Aust 180:444–448.
24. Winker R, Barth A, Bidmon D, Ponocny, Weber M, Mayr O, Robertson D, Diedrich A, Maier R, Pilger A, Haber P, Rudiger HW (2005) Endurance exercise training in orthostatic intolerance: a randomized, controlled trial. Hypertension 45:391–398.