Deconditioning in patients with orthostatic intolerance

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ABSTRACT

Objective: To study the frequency and degree of deconditioning, clinical features, and relationship between deconditioning and autonomic parameters in patients with orthostatic intolerance.

Methods: We retrospectively studied all patients seen for orthostatic intolerance at Mayo Clinic between January 2006 and June 2011, who underwent both standardized autonomic and exercise testing.

Results: A total of 184 patients (84 with postural orthostatic tachycardia syndrome [POTS] and 100 without orthostatic tachycardia) fulfilled the inclusion criteria. Of these, 89% were women, and median age was 27.5 years (interquartile range [IQR] 22–37 years). Symptom duration was 4 years (IQR 2–7.8). Of the patients, 90% had deconditioning (reduced maximum oxygen uptake [VO_{2max}%] <85%) during exercise. This finding was unrelated to age, gender, or duration of illness. The prevalence of deconditioning was similar between those with POTS (95%) and those with orthostatic intolerance (91%). VO_{2max}% had a weak correlation with a few autonomic and laboratory parameters but adequate predictors of VO_{2max}% could not be identified.

Conclusion: Reduced VO_{2max}% consistent with deconditioning is present in almost all patients with orthostatic intolerance and may play a central role in pathophysiology. This finding provides a strong rationale for retraining in the treatment of orthostatic intolerance. None of the autonomic indices are reliable predictors of deconditioning. *Neurology*® 2012;79:1435–1439

GLOSSARY

BP = blood pressure; **DBP** = diastolic blood pressure; **HR** = heart rate; **HUT** = head-up tilt; **II_E** = early phase II; **II_L** = late phase II; **MET** = metabolic equivalent; **OI** = orthostatic intolerance; **POTS** = postural orthostatic tachycardia syndrome; **PP** = pulse pressure; **RER** = respiratory exchange ratio; **SBP** = systolic blood pressure; **TST** = thermoregulatory sweat test; **VM** = Valsalva maneuver; **VO_{2max}** = maximum oxygen uptake; **VR** = Valsalva ratio.

The postural tachycardia syndrome (POTS) is a disorder of orthostatic intolerance mostly affecting young and middle-aged women. The pathophysiology of POTS and the role of deconditioning in this syndrome are poorly understood.[1]

Recent evidence suggests that POTS is strongly associated with cardiovascular deconditioning. Cardiovascular changes attributable to deconditioning are similar to those seen after prolonged bedrest and space flight. We have emphasized a reduction in stroke volume,[2] whereas others have emphasized cardiac atrophy.[3] To a variable degree, orthostatic tachycardia has been shown to be reversible with a structured exercise program.[3–6] Some researchers advocate that POTS is a disorder of deconditioning alone and can be cured by reconditioning. However, a recent study reported that even though orthostatic tachycardia improves with regular exercise, patients' symptoms remain,[5] suggesting that deconditioning may be a secondary mechanism in patients with POTS. A comprehensive study formally assessing exercise capacity (the gold standard to assess for deconditioning) in a large and well-characterized group of patients with

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Supplemental Data

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From the Department of Neurology, Mayo Clinic, Rochester, MN.

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POTS and orthostatic intolerance (OI) without fulfilling the heart rate criteria for POTS (OI) is lacking.

Clinical observations in reviewing autonomic testing in those patients suggests that certain autonomic parameters might be related to the degree of deconditioning and identifying them would help in predicting deconditioning without the need for dedicated exercise testing. We hypothesize that a large proportion of patients with POTS and OI have various degrees of deconditioning. We furthermore hypothesize that selected autonomic and laboratory parameters can predict the presence and the degree of deconditioning.

METHODS

We retrospectively reviewed the medical records of all patients who underwent autonomic and exercise testing for orthostatic symptoms at Mayo Clinic, Rochester, Minnesota, between January 2006 and June 2011. Minors (<18 years), patients with medical conditions or taking medications known to cause orthostatic tachycardia, and those with incomplete medical records were excluded from the study.

Standard protocol approvals, registrations, and patient consents. Our study was approved by the Institutional Review Board of Mayo Clinic, Rochester, Minnesota. All patients authorized the use of their medical records for research purposes.

Definition of different variables. POTS was defined as a symptomatic increase in HR on 70° passive tilt for 10 minutes done after 10 minutes of supine resting (head-up tilt [HUT]) ≥30 bpm. OI was defined as the development of previously defined symptoms of cerebral hypoperfusion or sympathetic activation with standing, but with a HR increment <30 bpm.[1] Patients with VO_{2max} <85% on exercise testing were considered deconditioned, whereas those with VO_{2max} ≥85% were considered normal. Mild deconditioning was defined as VO_{2max} between 85% and 65%, and severe deconditioning was defined as VO_{2max} <65%.

Exercise test parameters. VO_{2max} was defined as the maximum capacity of an individual's body to transport and use oxygen during incremental exercise, which reflects the physical fitness of the individual. VO_{2max}% was calculated as measured VO_{2max} (ml/kg/minute) divided by predicted VO_{2max} (60 − age × 0.5 for men and 40 − age × 0.4 for females) multiplied by 100. HR recovery time was calculated as peak HR − HR at 1 minute after the cessation of exercise during the recovery period.[7]

Valsalva test parameters. We assessed the changes (Δ) in systolic (SBP) and diastolic blood pressure (DBP) during early phase II (II_E), late phase II (II_L), and phase IV of the Valsalva maneuver (VM) compared with averaged baseline blood pressure (BP). The magnitude of BP during II_E and II_L was measured at the end of each phase, and magnitude of BP overshoot in phase IV was defined as the maximum BP within 2 minutes of the end of the expiratory effort.

HUT parameters. Resting HR and BP were defined as average HR and BP during the 5 minutes of resting in the supine position. ΔHR, ΔSBP, ΔDBP, and Δ pulse pressure (PP) were defined, respectively, as the difference between average HR, SBP, DBP, and PP during the second half of HUT and were averaged baseline values.

Exercise test. A symptom-limited graded treadmill exercise test was performed using the following protocol. Initial workload was 2 mph at 0% grade (equivalent to 2.5 metabolic equivalents [METs]), which was increased by 2 METs every 2 minutes. This was followed by an active recovery period of 3 minutes at a speed of 1.7 mph with 0% grade and then 3 or more additional minutes of seated recovery. Almost all subjects exercised to maximum or near-maximum level using the metabolic cart (Medical Graphics CPX; Medical Graphics Corporation, St. Paul, MN); all expired gases were monitored from rest throughout exercise and 1 minute of active recovery. The EKG was recorded during exercise and recovery. BP measurements were performed at 1.5 minutes of every stage, at peak exercise, and at 30 s and 2.5 minutes of seated recovery by left arm sphygmomanometer. Effort was rated based on the peak respiratory exchange ratio (RER) as follows: RER >1.15 indicated maximal effort; RER 1.05–1.15 indicated valid albeit submaximal effort, and RER <1.05 suggested inadequate effort.

Autonomic tests. All the autonomic function tests (quantitative sudomotor axon reflex test, HR response to deep breathing, VM, Valsalva ratio [VR], and thermoregulatory sweat test [TST]) were performed and assessed as defined previously.[8,9]

Data collection. Different exercise and autonomic parameters were collected from our cardiophysiology and autonomic database, respectively. Demographic data, clinical symptoms, and other clinical data were collected from electronic medical records.

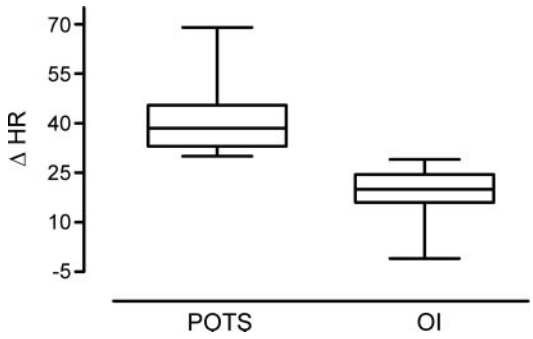
Statistical considerations. Data are reported as median and range for continuous measures, and discrete variables are shown as counts and percentages. Correlation between autonomic parameters and exercise parameters were tested by Pearson correlation. A multivariable stepwise logistic regression model was used to assess the predictors of deconditioning. Comparisons between 2 groups of categorical variables were analyzed with χ^2 or Fisher exact tests and for continuous variables with a 2-sample t test or Wilcoxon rank-sum test, as appropriate. All statistical analysis was performed using JMP 9 (SAS Institute, Cary, NC). All calculated p values were 2-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

We identified 184 patients who fulfilled our inclusion and exclusion criteria. Of these, 84 patients fulfilled the HR criteria for POTS, and 100 did not (OI). Figure 1 shows the orthostatic change in HR in both patient groups. The OI group was slightly older than the POTS group (POTS vs OI: 25 years, interquartile range [(IQR] 20–32 years) vs 32 years, IQR 24–40 years, $p < 0.0001$). Patients were mostly women (89%) (table 1).

Onset of symptoms were acute (1 month) in 7 (4%), subacute (1–3 months) in 4 (2%), gradual (>3 months) in 155 (84%), and not specified in 18 (10%) patients. Of the patients, 181 (98%) had reduced work capability since the onset of the symptoms; 60 (33%) patients identified a preceding event as possible trigger for their symptoms, with viral illness being the most common.

Figure 1 Orthostatic change in heart rate



HR = heart rate; OI = orthostatic intolerance; POTS = postural orthostatic tachycardia syndrome.

Clinical presentation included orthostatic, nonorthostatic (i.e., nausea, vomiting, diarrhea, constipation, bladder, and pupillary dysfunction), and generalized (fatigue and sleep disturbances) symptoms (table 1). Ganglionic antibodies were tested in 120 (65%) patients, and results were normal in all subjects (range 0.00–0.04 nmol/L, normal ≤0.05 nmol/L). A gastric transit study was performed in 18 patients (10%): 2 (11%) had delayed transit, 1 (6%) had rapid transit, and the rest had normal transit.

Responses to different medications (table 2) were poor in both groups. Most patients (130 [71%]) had a static course, 38 patients (21%) had mild improvement, and only 1 patient had moderate to good improvement in symptoms. The remaining 15 patients (8%) had a progressive course with continuous worsening.

A total of 171 (93%) patients had evidence of cardiovascular deconditioning. The prevalence of deconditioning was similar between patients with POTS (95%) and those with OI (91%, $p = 0.39$) (figure 2). The severity of deconditioning was also similar between patients with POTS (mild 50%, severe 50%) and those with OI (mild 42%, severe 58%; ($p = 0.28$). Deconditioning was not correlated to age ($r = 12$, $p = 0.13$) or duration of illness ($r = 0.003$, $p = 0.97$). Furthermore, deconditioning was similar in both genders ($p = 0.15$). Effort was maximal in 70% and submaximal in 21%, and performance was considered inadequate in 9% of the subjects based on RER.

The correlation between VO_{2max}% and different autonomic parameters is shown in appendix e-1 on the *Neurology*® Web site at www.neurology.org. Among patients with POTS, TST anhydrosis %, ΔII_E SBP, ΔII_L SBP, and 24-hour urine volume were significantly correlated with VO_{2max}%; however, the strength of correlation was generally weak ($r \leq 0.34$). Among patients with OI, ΔII_L SBP, ΔII_L DBP, VR, and supine plasma norepinephrine had significant but weak correlation with VO_{2max}% ($r \leq 0.32$). There was no significant correlation between ΔHR and VO_{2max}%. Appendix e-2 describes the correlation between HR recovery at 1 minute and different autonomic parameters. For all patients, TST

Table 1 Baseline demographic and clinical presentation of patients with orthostatic intolerance[a]

	Value
Total no. of patients	184
Age at onset of symptoms, y, median (IQR)	27.5 (22–37)
Female gender	164 (89)
Duration of illness, y, median (IQR)	4 (2–7.8)
Lightheadedness	175 (95)
Weakness	83 (45)
Presyncope/syncope	126 (69)
Head pressure/headache	114 (62)
Palpitation	151 (82)
Tremulousness	28 (15)
Dyspnea	62 (34)
Chest pain	59 (32)
Decreased sweating	5 (3)
Increased sweating	30 (16)
Heat intolerance	42 (22)
Exercise intolerance	181 (98)
Post prandial intolerance	9 (5)
Bloating	40 (22)
Nausea	109 (59)
Vomiting	42 (23)
Abdominal pain	44 (24)
Constipation	65 (35)
Diarrhea	59 (32)
Visual abnormality (blurring, diplopia, and others)	36 (20)
Bladder symptoms	32 (17)
Sleep disturbances	101 (55)
Fatigue	131 (71)
Migraine	82 (45)
Myofascial pain	30 (16)
Neuropathic pain	7 (4)
Orthostatic intolerance related to menstruation	7 (4)
Cognitive decline/mental clouding	40 (22)
Past history of orthostatic intolerance	10 (5)
Family history of orthostatic intolerance	5 (3)
Mitral valve regurgitation	17 (9)
Mitral valve prolapse	3 (2)
Panic attack	11 (6)

Abbreviation: IQR = interquartile range.
[a] Data are n (%) unless otherwise indicated.

Table 2 Medications used for orthostatic intolerance

Medication	Total patients treated, n (%)
Midodrine	82/184 (45)
Fludrocortisone	85/184 (46)
β-Blockers	117/184 (64)
Pyridostigmine	27/184 (15)
Serotonin reuptake inhibitor	75/184 (41)

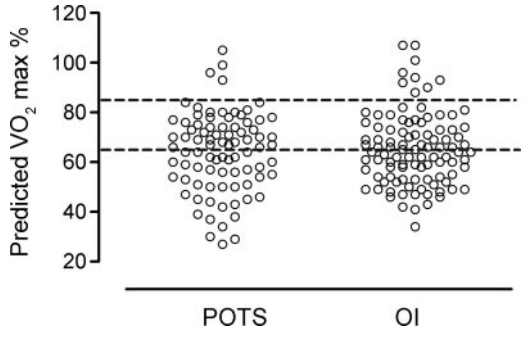
anhydrosis % was significantly and negatively correlated with VO_{2max}% ($r = -0.30$, $p = 0.002$).

Overall, none of the autonomic and laboratory parameters were significant predictors of deconditioning.

DISCUSSION The key finding of our study is that the prevalence of deconditioning was very high in patients with disorders of reduced orthostatic tolerance with or without orthostatic tachycardia (>90% in both groups). The second findings is that, overall, neither laboratory nor autonomic parameters can predict the degree of deconditioning.

The prevalence of deconditioning in our cohort was almost universal (93%) and much higher than reported previously among adolescents (68% had deconditioning based on peak VO_2 <80%).[10] The finding of deconditioning as a common feature in these patients is intriguing and supports the argument that deconditioning plays a role in the pathophysiology of OI. However, OI is a chronic condition associated with a severe limitation of activities of daily living.[11] Whether deconditioning is a primary or secondary phenomenon remains therefore unclear, although a major pathophysiologic role of this finding has to be postulated in most of the patients with this condition. Our findings support the approach of initiation of a vigorous reconditioning program in all patients with this condition, although further studies are necessary to document long-term outcome.

Figure 2 Prevalence of deconditioning



Normal, predicted maximum oxygen uptake (VO_{2max} >85%); mild deconditioning, predicted VO_{2max} between 85% and 65%; severe deconditioning: predicted VO_{2max} <65%. OI = orthostatic intolerance; POTS = postural orthostatic tachycardia syndrome.

Previous studies reported normalization of plasma volume and cardiovascular alterations after a structured exercise program, associated with improvement of orthostatic tachycardia and symptoms.[12,13] Some reported normalization of HR changes, plasma volume, catecholamines, and orthostatic intolerance with exercise.[13] Few reported that deconditioning is the sole underlying mechanism for orthostatic symptoms and found improved (although not resolved) symptoms, cardiac mass, blood volume, and HR increment with exercise training.[3] In contrast, others reported improvement in autonomic function tests without improvement in symptoms.[5]

A number of pharmacologic measures have been shown to be effective in the treatment of POTS in short-term studies. Apart from sodium and fluid intake,[14] drugs such as β-blockers, fludrocortisone, midodrine, serotonin reuptake inhibitors, and pyridostigmine can be effective, but these have not been shown to be effective in the long term and in our experience frequently lose efficacy over time. Heightened somatic vigilance has been identified as a common feature in many patients with OI,[11] which may explain the poor long-term symptomatic response to pharmacologic treatment and lack of more substantial symptomatic improvement with exercise alone. Cognitive retraining may be necessary in addition to a structured exercise training program for lasting and more substantial improvement. Similar to other conditions suggestive of a dysfunctional psycho-autonomic-somatic relationship such as irritable bowel syndrome, disorders of reduced orthostatic tolerance maybe more treatable than curable and may require a multidisciplinary strategy for a satisfactory functional outcome.

Limitations of our study are its retrospective nature, potential referral bias, and inadequate effort with exercise testing in some patients. However, >80% of patients with OI seen in 2 major clinics (one in neurology and one in cardiology) are routinely referred to the exercise facility. Hence, patients studied in the exercise facility are representative of patients with OI seen at Mayo Clinic, Rochester, Minnesota.

We found very few autonomic and laboratory parameters to have significant but weak correlation with VO_{2max}% and HR recovery at 1 minute. Therefore, deconditioning cannot be predicted by laboratory and autonomic parameters, so that exercise evaluation is necessary to define the presence and severity of deconditioning, which, however, has been

demonstrated to be almost invariably present in these patients.

AUTHOR CONTRIBUTIONS

Ajay Parsaik: study concept or design, analysis or interpretation of data, drafting/revising the manuscript for content, including medical writing for content. Thomas G. Allison: study coordination, revising the manuscript. Wolfgang Singer: study concept or design, drafting/revising the manuscript for content. David M. Sletten: study coordination, analysis or interpretation of data. Michael J. Joyner: study concept, revising the manuscript. Eduardo E. Benarroch: study concept, revising the manuscript. Phillip A. Low: study concept or design, drafting/revising the manuscript for content. Paola Sandroni: study concept or design, drafting/revising the manuscript for content.

DISCLOSURE

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