Chronic orthostatic intolerance (COI, also known as postural orthostatic tachycardia syndrome) is a disorder that most frequently affects young women (female-to-male ratio, 4:1). Presenting symptoms include lightheadedness, palpitations, fatigue, blurred vision, dizziness, exercise intolerance, chest discomfort, cognitive impairment, and occasionally syncope. These symptoms usually occur after upright posture is assumed and are associated with rapid development of tachycardia. Heart rate increases by >30 bpm or exceeds 120 bpm. There is usually only a modest, if any, fall in blood pressure. Indeed, symptoms frequently occur in the absence of any blood pressure reduction and even in the setting of an increase in blood pressure on standing. The cause of COI is unknown. The onset of the disorder is often predated by a recent viral infection. Associated conditions include mitral valve prolapse, irritable bowel syndrome, and chronic fatigue. Proposed pathophysiological characteristics include abnormalities in sudomotor function and excessive gravitational pooling caused by impaired venous tone. It is generally accepted that autonomic dysfunction is a hallmark of this disorder.

Autonomic dysfunction is often perceived as a black box of nebulous disorders, often not easily differentiated from variants of normality. There is a substantial incidence of false-negative and false-positive diagnoses. These difficulties are compounded by the heterogeneity of disease states in patients with orthostatic symptoms, spontaneous fluctuations in disease severity, and nonuniformity in nomenclature of disease classification. Inconsistencies in nosology complicate the study and delineation of pathophysiological mechanisms. These considerations are particularly applicable to studies of orthostatic intolerance.

Our insights into disorders of orthostatic homeostasis have been enhanced by the advent of tilt table testing. This allows simulation of standing, in carefully monitored and controlled conditions. The dynamic interplay between postural changes, hemodynamic responses, and symptoms can therefore be followed closely. In addition to tilt testing, direct intraneural measurement of efferent sympathetic nerve traffic to muscle blood vessels allows for continuous monitoring of sympathetic activity to the skeletal muscle vasculature, a major contributor to acute regulation of blood pressure. These microneurographic recordings of sympathetic traffic in effect provide a “window” on the sympathetic nervous system. Furlan and colleagues have combined tilt testing, microneurographic recordings, and spectral analysis of cardiovascular variability to provide a moment-by-moment characterization of hemodynamics, sympathetic traffic, and symptoms, recently in patients with neurally mediated syncope (NMS), and now in patients with COI. We will review their findings, first, with regard to the pathophysiology of COI, and second, with regard to a postulated common autonomic substrate linking COI, NMS, and chronic fatigue.

Furlan et al show that patients with COI have faster heart rates and increased sympathetic traffic to muscle blood vessels (muscle sympathetic nerve activity, MSNA), during supine rest. On upright tilt, blood pressure does not change. The changes in central venous pressure with upright tilt are similar to the changes in control subjects, but there is an exaggerated tachycardic response and a blunted increase in MSNA in COI patients compared with normal subjects. The potentiated chronotropic response is accompanied by an attenuated sympathetic (presumed vasoconstrictor) response, thus ruling out hypovolemia alone as an explanation. Increases in norepinephrine and the ratio of low-frequency to high-frequency components of RR are preserved in COI, suggesting that any blunting of autonomic function is selective for sympathetic efferent traffic to muscle blood vessels, perhaps for the lower extremities only. Measurements of upper limb MSNA and/or forearm blood flows would address directly the question of selective dysautonomia. These responses occur in the absence of either significant blood pressure changes or impaired baroreflex gain; the baroreflex is therefore unlikely to be implicated directly in this aberrant response to simulated standing. A key question, however, is whether there is impairment of the cardio pulmonary reflex, the primary mediator of the orthostatic cardiovascular responses. Furthermore, is cardiac output increased, as would be expected given the faster heart rate?

Autonomic dysfunction in these patients appears to comprise a hyperadrenergic state during supine rest and a blunted sympathetic vasoconstrictor response to standing, accompanied by an augmented (perhaps compensatory) cardiac sympathetic response. The mechanisms underlying this disor-
dant autonomic profile are unclear. Although little is known of its pathogenesis and natural history, COI may constitute part of a spectrum of disorders of orthostatic cardiovascular homeostasis, including NMS and perhaps the chronic fatigue syndrome (CFS). All 3 of these disorders are more prevalent in women.

How do orthostatic changes in COI compare to those seen in patients with NMS? In patients with NMS, upright tilt results in an initial increase in heart rate and a blunted increase in MSNA, a response similar to that seen in patients with COI. In contrast to COI, however, blood pressure, heart rate, and MSNA subsequently decrease dramatically in NMS.7,8 COI and NMS elicit similar symptoms, even though the blood pressure response in each of these conditions may be strikingly different. It may be that standing elicits different degrees of reflex neural inhibition in COI compared with NMS. The chronotropic and inotropic response to standing may be implicated in part in triggering cardiac mechanoreceptors. In COI, the potentiated tachycardia acting (perhaps) via ventricular receptors10 may induce a partial and selective reflex inhibition of MSNA. Blood pressure is maintained by the faster heart rate. In NMS, postural change may elicit a more potent neural inhibitory reflex that results in initial inhibition and eventual disappearance of MSNA, with hypotension and bradycardia. Perhaps with an increased stimulus intensity (such as with isoproterenol and/or volume depletion), COI patients might manifest hypotension and bradycardia similar to that seen in NMS. This construct does not address why heart rate is faster at rest and on standing in COI. Intravascular volume depletion is possible but has not been demonstrated consistently.14 Perhaps equally important is why symptoms of COI occur in the absence of any blood pressure reduction.

Studies of COI patients show convincingly that symptoms of lightheadedness, etc, occur on standing, even when blood pressure actually increases substantially.2,3 Some patients with COI develop symptoms despite a hypertensive response to standing, when diastolic blood pressure may increase by up to 50 mm Hg.1 This fascinating association suggests that the symptoms of COI may somehow be elicited by central responses to the inappropriate tachycardia, even in the absence of any actual reduction in perfusion pressure. The effects of rapid cardiac pacing in supine COI patients are unknown. Alternatively, symptoms in these patients may be triggered by cerebral vasoconstriction in response to upright tilt, as has been reported for patients with neurally mediated hypotensive syncope.11–14 The observation by Furlan et al15 of an increased respiratory frequency on tilt in COI but not in control subjects is suggestive of the possibility of hyperventilation-induced hypocapnia and consequent cerebral vasoconstriction in COI. The presence of corroborating hemodynamic responses but very similar to that seen in NMS.15,16 By contrast, 2 other studies of CFS patients and control subjects describe a hemodynamic profile in CFS very similar to that reported for COI.17,18

Freeman and Komaroff17 have reported that CFS patients had faster supine heart rates than control subjects. Blood pressures did not fall on standing, but CFS patients had a potentiated orthostatic tachycardia compared with control subjects. The onset of symptoms was predated by a viral infection in ≈50% these CFS patients. More recent data on office and ambulatory blood pressure and heart rate provide additional support for the concept of similar hemodynamic profiles in CFS and COI patients.18 In a well-controlled study of 38 CFS patients and 38 age-, sex-, and body mass index–matched control subjects, Duprez et al18 reported that office, daytime, and nighttime blood pressures were similar in CFS patients and in normal control subjects. By contrast, office, daytime, and nighttime heart rates were significantly (~10 bpm) faster in CFS patients. CFS patients were not on any medications, thus excluding an important potential confounding factor. This study provides several important insights into the relative tachycardia in CFS; first, that it is present outside the hospital environment; second, that it occurs independently of any hypotension; and third, that the faster heart rate may be present even during sleep. Thus, some patients with CFS may exhibit characteristics spanning those seen in both COI and NMS.15–18 In all 3 of these disorders, the potential role of physical deconditioning,17 both as a response to these ailments and as an exacerbating factor, needs to be recognized. Decreased physical activity in these patients as a consequence of their symptoms may serve to further accentuate the hemodynamic abnormalities.

Hence, the data from Furlan et al15 not only contribute importantly to our understanding of the hemodynamic-autonomic interactions in COI patients but also provoke speculation regarding a possible common autonomic substrate linking patients with COI, NMS, and CFS. Although there is considerable overlap in the symptoms of all 3 disorders, patients with COI are often symptomatic in the absence of significant blood pressure changes; patients with NMS present with frank syncope; and patients with CFS suffer chronic tiredness. Thus, the diagnostic categorization for a given patient is often determined by the initial presentation. There is no obvious explanation for the supine and orthostatic hemodynamic profiles in each of these conditions. The responses to tilt (or standing) on any particular occasion most likely represent a complex interplay between autonomic reflexes and a host of potential biochemical mediators, including catecholamines, nitric oxide, serotonin, and opiates,19 and are not consistently reproducible even within the same subjects.
The neurocirculatory profile in COI patients has implications beyond the theoretical considerations described above, in particular with regard to therapy. These patients have increased MSNA at rest but a relative decrease in vasoconstrictor MSNA on standing. A therapeutic strategy directed at either volume expansion with saline or augmenting peripheral vasoconstriction with the α-agonist midodrine is far more effective than one directed at blunting the hyperadrenergic state (using clonidine).4 This differential therapeutic response begs the question of why intravascular volume and vasoconstriction effectively relieve symptoms that occur in the absence of any hypotension. Thus, mechanisms mediating this disorder may extend beyond those acknowledged above.

Disorders of cardiovascular autonomic function are in some ways analogous to hypertension in terms of evolution of our understanding of a disease entity. First, it is conceivable that the natural history comprises transitions from one hemodynamic profile to another. Second, there is emerging evidence of a wider than anticipated prevalence of autonomic dysfunction, which is likely to increase further in an aging population. Third, heterogeneity of hemodynamic profiles of orthostatic intolerance and the presence of coexisting diseases require an individualized therapeutic approach. With improvements in diagnostic skills and technologies, standardization of diagnostic criteria and nomenclature, and heightened physician sensitivity to these disorders, it is likely that there will be increasing recognition both of the prevalence of cardiovascular autonomic dysfunction and of the contribution of autonomic dysfunction to other seemingly unrelated diseases.

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