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Chronic fatigue is a prominent symptom in a variety of overlapping syndromes of circulatory dysfunction, the most notable examples of which are neurally mediated hypotension (NMH) and postural tachycardia syndrome (POTS).

An early suggestion that such abnormalities were treatable causes of symptoms in what we now call chronic fatigue syndrome (CFS) was made in 1940 by Alexander MacLean and Edgar Allen. They described a group of patients who experienced excessive acceleration of the heart and hypotension after moving from the recumbent to the erect posture, usually associated with symptoms of orthostatic exhaustion, blurring of vision, weakness on exercise, and syncopal episodes.

McLean and Allen attributed the tachycardia to a reduced venous return to the heart, in part because symptoms and hemodynamic changes could be provoked within 10 seconds by Flack's test, which involved forced expiration into a tube to maintain a mercury column at 40 mm, thereby reducing blood flow into the thorax. They concluded that this orthostatic tachycardia syndrome seemed similar to "effort syndrome, irritable heart, or neurocirculatory asthenia" the synonyms of the day for what we now call CFS.

McLean and Allen reported that patients improved by increasing their intake of fluids and sodium, and by sleeping with the head of the bed elevated. The head-up bed may have helped to conserve intravascular volume by reducing blood flow to the kidney at night. It is a medical curiosity that these detailed observations were largely ignored for several decades.

In this issue of *The Journal of Pediatrics*, 3 articles address related aspects of orthostatic control of blood pressure and heart rate, two of which take advantage of newer methodologic tools to better understand microvascular flow and cerebral oxygenation. In 23 healthy adolescents, Stewart noted that 44% had reductions in blood pressure of >20 mm Hg systolic in the first minute of upright tilt to 70 degrees, associated with transient symptoms of lightheadedness. At a formal level, these patients met the adult criteria for orthostatic hypotension, but in contrast to the usual course in adults, the hemodynamic changes resolved during one minute and did not require treatment. The reduction in blood pressure correlated with increased calf blood flow measured by strain gauge plethysmography.

These valuable observations provide a physiologic explanation for common and self-limited episodes of lightheadedness in adolescents, and they support a conservative approach to treatment, provided resolution of symptoms is rapid. Stewart suggests a need for better pediatric norms for the response to orthostatic stress, and as we generate these, we will be wise to make them age-specific. There is now good evidence that pubertal children have a greater susceptibility to orthostatic stress than prepubertal children. Although the mechanisms for this change in susceptibility during adolescence are as yet unclear, the observation is in agreement with epidemiologic and clinical impressions that orthostatic intolerance syndromes and CFS are much less prevalent in prepubertal children.

The paper by Tanaka *et al* brings further insight to the pathophysiologic features of symptoms

during upright posture in patients with CFS. In orthostatic intolerance syndromes, it has been widely assumed that lightheadedness and other symptoms are caused by a reduction in cerebral blood flow. Our own studies using transcranial Doppler ultrasonography do not identify a distinctive pattern of cerebral blood flow velocity during upright tilt in adolescents and adults with CFS and orthostatic intolerance compared with controls. The much earlier onset of symptoms during head-up tilt in patients with CFS suggests that other factors not measured by transcranial Doppler may play an important role.

Near infrared spectroscopy (NIRS) offers a different insight into cerebral changes during upright posture. This noninvasive technique measures changes in the absorption of near infra-red light by oxygenated or deoxygenated hemoglobin and can be used to assess changes in cerebral tissue oxygenation rather than the changes in blood flow velocity that are available through transcranial Doppler studies. NIRS has been used to study cerebral oxygenation in a variety of settings, including upright tilt in patients with syncope, during lower body negative pressure (a simulated orthostatic stress), and in neonates.

Tanaka *et al* used NIRS to compare cerebral oxygenation between 20 healthy controls and 28 patients with either CFS or idiopathic chronic fatigue. Sixteen patients with chronic fatigue had hemodynamic evidence of orthostatic intolerance during a brief 7-minute period of active standing, compared with 2 of 20 controls of a similar age. After an initial drop in cerebral oxyhemoglobin at the onset of standing in most controls, 18 of 20 experienced a rapid recovery. In contrast, only 7 of 28 patients with chronic fatigue had a rapid recovery, and reductions below the basal level were more common in patients with CFS than in controls. Of interest, 6 of 12 patients with chronic fatigue and abnormal cerebral oxygenation had no evidence of orthostatic intolerance during the 7 minutes of standing, although it is impossible to know whether these patients would have gone on to develop hypotension after a longer period of orthostatic stress.

The results of this study are intriguing but will need to be corroborated by others. Further

support for the relevance of reduced cerebral oxygenation to the development of CFS symptoms will depend on showing whether cerebral oxygenation normalizes in patients whose CFS symptoms improve either spontaneously or with treatment of the orthostatic intolerance. It will be important in future studies to ensure that the orthostatic stress is sufficiently long to identify clinically important NMH, which in most cases would be missed by a 7-minute test. Another noninvasive technique that would add to such studies would be the incorporation of end-tidal carbon dioxide measures, to assess the effect of changes in carbon dioxide tensions on cerebral blood flow and oxygenation.

In the third article, Stewart provides a concise summary of the growing literature on the pathophysiology and current treatment of common syndromes of orthostatic intolerance. Treatment of these disorders begins, as it did in 1940, with education, reassurance, dietary measures, postural maneuvers to prevent blood from pooling in the limbs, the use of compression garments, and avoidance of situations that provoke symptoms.

An underappreciated aspect of management is the need for effective control of other comorbid conditions that may independently contribute to orthostatic intolerance, including allergies, asthma, dysmenorrhea, migraine headaches, movement dysfunctions (especially those associated with joint hypermobility), and anxiety and depression. Failure to bring these problems under adequate control in the setting of clinical trials will lead to underestimates of the effect size of any intervention.

Of the medications that have been proposed, stimulant medications may have received less attention than they may deserve in the treatment of pediatric orthostatic intolerance, despite being used as therapy for hypotension long before their discovery for the treatment of attention deficit disorder and hyperactivity.

As Stewart notes, clinicians have few randomized controlled trials available to guide their decisions about treating orthostatic intolerance, and even fewer when it comes to medications targeted to adolescents. Further progress is likely to come as we gain an improved understanding of the pathophysiologic heterogeneity of these syndromes, but in the interim, a much greater effort needs to be devoted to treatment trials.

One methodologic challenge posed by the heterogeneity of these disorders is that randomized trials of single agents will need large sample sizes, thereby making them rather unwieldy to conduct and expensive for funding agencies. A more economic design for the determination of efficacy of medications may be to study treated patients at a stable point in their illness. Persons who have improved by using a medication assumed, but not proven, to be efficacious could be randomized to either active medication or placebo. This randomized withdrawal design would have the advantage of being relatively brief in duration, less costly, and low in new adverse events. If cerebral oxygenation is consistently abnormal in patients with orthostatic intolerance and CFS, its measurement may prove useful as a more objective marker of the response to treatment than self-report of symptoms."

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