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Chronic fatigue syndrome: comments on deconditioning, blood volume and resulting cardiac function

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Abstract

Cardiovascular and autonomic dysfunction have been suggested to underlie the symptoms accompanying CFS (chronic fatigue syndrome). In the present issue of *Clinical Science*, Hurwitz and co-workers have investigated whether deficits were present in cardiac output and blood volume in a cohort of patients with CFS and if these were linked to illness severity and sedentary lifestyle. The results clearly demonstrate reduced cardiac stroke volume and cardiac output in more severely afflicted patients with CFS, which is primarily attributable to a measurable reduction in blood volume. Similar findings are observed in microgravity and bed rest deconditioning, in forms of orthostatic intolerance and, to a lesser extent, in sedentary people. The circulatory consequences of reduced cardiac output may help to account for many of the findings of the syndrome.

Keywords

anaemia; cardiac output; chronic fatigue syndrome; deconditioning; echocardiography; hypovolaemia

The interesting paper in the present issue of *Clinical Science* by Hurwitz et al. [1] entitled ‘Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function’ is important because it aligns current thinking regarding CFS (chronic fatigue syndrome) with ongoing work concerning circulatory regulation, particularly as it relates to decreased overall blood volume and issues of orthostatic intolerance. In addition, despite significant cardiac findings, the paper [1] effectively puts to rest arguments in favour of a causative role for heart disease in CFS.

This requires explanation. There is no controverting these results, which demonstrate decreased blood volume in a subset of CFS patients effectively reducing venous return to the heart, namely diastolic cardiac volume and cardiac output [1]. The results do not imply heart disease, but rather point to circulatory impairment. Classically, cardiac stroke volume is determined by preload and afterload, by contractility and by geometry; where preload corresponds to stretch or ventricular wall stress imposed by venous return before active

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contraction occurs, afterload corresponds to active intramural wall stress of contraction, contractility is the intrinsic cardiac muscle's ability to contract and geometry includes chamber sizes, wall thicknesses and their shapes [2]. Reduced venous return and diastolic heart volume (preload) thus results in a decrease in stroke volume and cardiac output. Using a corrected velocity of circumferential shortening (Vcf_c), the authors [1] also conclude that cardiac contractility is modestly reduced in the most severely ill CFS patients. Vcf_c combined with measures of end-systolic force (the force–velocity relationship) [3,4] is one of two classic load-independent means to assess cardiac contractility. However, Vcf_c alone, even when corrected for heart rate, is preload-dependent, increasing when cardiac preload is increased (increased cardiac filling) and decreasing when cardiac preload is decreased (decreased cardiac filling), as occurs in CFS patients and some sedentary control subjects. Vcf_c is therefore a load-sensitive measure and may overestimate or underestimate global systolic contractility under different loading conditions.

Thus significant cardiac output findings derive from the effects of reduced venous return and cardiac unloading. Interestingly, although diastolic cardiac size is reduced in CFS, cardiac mass is not decreased. This defines the designation of 'the under filled heart' [5], which may be observed in hypovolaemia of whatever cause.

A major attribution is made to deconditioning. Use of the term deconditioning needs cautious interpretation because deconditioning may not be a single entity: there is cardiac deconditioning, taking its most extreme form during heart failure, and gravitational deconditioning, exemplified by prolonged microgravity exposure and easily duplicated by chronic bed rest or prolonged head-down tilting [6,7]. On the one hand, cardiac deconditioning is best demonstrated during exercise stress, whereas gravitational deconditioning is best demonstrated during orthostatic stress, as experienced by every astronaut, every long-bed-rested subject and many CFS patients, especially those with the severest symptoms. All forms of gravitational deconditioning produce a reduction in blood volume, and may result in a loss of bone and muscle mass as in chronic bed rest and microgravity. Decreased blood volume has not been entirely explained, although redistribution of extracellular fluids has a role. Changes in patterns of peripheral vasoconstriction occur [7]. Hypovolaemia leads to larger decreases in both venous return and stroke volume, particularly during orthostatic stress, thus compromising blood pressure control. There are also changes in autonomic regulation during all forms of microgravity deconditioning which, when combined with hypovolaemia, place the patients at risk of orthostatic intolerance [8]. The chronic reduction in blood volume under conditions of microgravity may account for the actual reduction in cardiac mass as well as the decrease in end-diastolic chamber volume [9], and this has been demonstrated further to occur preferentially in women [10]. Blood volume can also be affected by inactivity, and it is clear that athletes develop both an increase in blood volume as well as a form of benign cardiac hypertrophy known as 'athletes' heart' [11], which regresses along with expanded blood volume with progressive detraining.

Blood volume reduction is part of the underlying pathophysiology of chronic orthostatic intolerance also known as POTS (postural tachycardia syndrome) in which symptoms of orthostatic intolerance, such as impaired consciousness, dizziness, headache, fatigue and

cognitive loss, are associated with an excessive increase in heart rate when upright and may be related to abnormalities in the renin–angiotensin–aldosterone system [12,13]. Symptoms of POTS and other forms of orthostatic intolerance overlap with CFS, and may represent an underlying pathophysiology for CFS in younger patients and are associated with CFS in older patients [14,15]. Although orthostatic testing was not performed, a relatively large fraction (55%) of those with posturally related symptoms relieved by recumbence were documented in the study by Hurwitz et al. [1], suggesting a large overlap between the CFS patients and patients with chronic forms of orthostatic intolerance.

The reduction in cardiac output reported by Hurwitz et al. [1] can be explained entirely in terms of reduced venous return to the heart, reduced cardiac preload and, therefore, reduced stroke volume. In this context, a reduction in diastolic dimension makes perfect sense. The authors [1] observed unchanged cardiac mass and, to an approximation, cardiac mass ~wall thickness × chamber surface area, where chamber area ~chamber length × chamber diameter. Given constant mass but reduced stroke volume, the patient with severe CFS and a reduction in diastolic size should have an increase in diastolic wall thickness: ventricles are ‘less thinned’ in diastole due to reduced ventricular filling. Thus changes in wall thickness and chamber dimensions go hand-in-glove, and all of the differences among the analysed groups can be attributed to reduced venous return, presumably due to reduced blood volume. Correlative analysis would be welcome.

In summary Hurwitz and co-workers [1] have importantly and clearly demonstrated a reduction in blood volume, both in plasma and in red cell mass, that produces a decrease in cardiac filling via reduced venous return even when measured in the supine position. This reduction in cardiac input accounts entirely for decreases in cardiac output in severely afflicted patients and should not be regarded as evidence for heart disease itself. I applaud the authors for their meticulous data collection and analysis.

Abbreviations

CFS	chronic fatigue syndrome
POTS	postural tachycardia syndrome

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