Concept Paper

Orthostatic Dysfunction and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Close Reciprocal Relationship Beyond Cardiac Preload Failure and Hypoperfusion

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Orthostatic Dysfunction and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Close Reciprocal Relationship Beyond Cardiac Preload Failure and Hypoperfusion

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Abstract

Orthostatic dysfunction, including postural orthostatic tachycardia syndrome (POTS) is highly prevalent in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Although cardiac preload failure and hypoperfusion provide plausible explanations for orthostatic symptoms, they may not fully account for the prolonged symptom exacerbation related to orthostatic stress. A hypothesis is proposed in which orthostatic dysfunction and ME/CFS may interact through mechanisms extending beyond disturbed hemodynamics. Orthostatic stress may markedly increase skeletal muscle sodium influx through sympathetic activation and α1-adrenergic stimulation of the sodium–proton exchanger NHE1, whereas the concomitant increase in sodium efflux mediated by Na^+/K^+-ATPase may be substantially attenuated by impaired β2-adrenergic receptor signaling resulting from receptor desensitization and autoantibodies, small fiber neuropathy, and reactive oxygen species. This imbalance between sodium influx and efflux could promote intracellular sodium accumulation, potassium depletion, and membrane depolarization, ultimately favoring reverse mode operation of the sodium–calcium exchanger and consequent intracellular calcium overload. Orthostatic stress may therefore lower the threshold for post-exertional malaise (PEM) and, with prolonged exposure or in severe ME/CFS, potentially trigger PEM even in the absence of physical exertion. This hypothesis provides a potential mechanistic link between orthostatic dysfunction and the presumed core pathophysiology of ME/CFS, extending beyond hemodynamic factors to implicate disturbances in skeletal muscle ion homeostasis.

Keywords: myalgic encephalomyelitis/chronic fatigue syndrome; orthostatic dysfunction; orthostatic intolerance; postural tachycardia syndrome; orthostatic stress; hypovolemia; post-exertional malaise; sodium-proton-exchanger; Na^+/K^+-ATPase; sodium-calcium-exchanger

1. Introduction

Hypovolemia and orthostatic intolerance are well-established clinical features of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and are thought to play a direct role in its underlying pathophysiology (van Campen, Rowe, and Visser 2018), (Okamoto et al. 2012), (Hurwitz et al. 2010), (Streeten and BellMD 1998), (Farquhar et al. 2002). The most widely recognized manifestation of orthostatic dysfunction is postural orthostatic tachycardia syndrome (POTS), followed by orthostatic hypotension. A third, less well-characterized form occurs in the absence of marked tachycardia or hypotension and is instead associated with reduced cerebral blood flow, potentially resulting from excessive cerebral vasoconstriction (van Campen et al. 2020), (van Campen et al. 2023). Across these forms of orthostatic dysfunction, impaired cerebral perfusion and the resulting orthostatic stress and sympathetic activation appear to contribute substantially to symptom development. These hemodynamic disturbances may, in turn, trigger compensatory responses,

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including tachycardia and increased vasoconstriction, which can further exacerbate abnormalities in cardiovascular and cerebral blood flow regulation.

Reduced intravascular volume decreases cardiac preload and impairs ventricular filling, both of which are important determinants of cardiac output and adequate tissue perfusion (Joseph et al. 2021), (van Campen, Rowe, and Visser 2024). This can impair the ability to maintain cardiovascular stability during orthostatic stress and restrict the capacity to increase cardiac output during physical exertion. In combination with other hemodynamic and microvascular abnormalities, these changes may reduce exercise capacity and contribute to tissue hypoperfusion. Such impaired perfusion may play an important role in exercise intolerance and post-exertional malaise (PEM).

However, hypovolemia alone does not fully explain reductions in cardiac preload, orthostatic dysfunction, or the limited increase in cardiac output during exercise. Cardiac preload and ventricular filling are influenced not only by blood volume but also by the contractile properties of the capacitance vessels. Venous pooling can occur when these capacitance vessels become excessively distensible, as may be seen in connective tissue disorders, or when vasodilation is triggered by vasoactive mediators such as histamine or by impaired contractile signaling (Roma et al. 2018), (Rowe et al. 1999), (Wirth and Löhn 2023). Therefore, even relatively modest abnormalities in either mechanism may, when combined, produce substantial impairment of cardiac filling and contribute to significant orthostatic dysfunction.

A key question is whether preload failure and the resulting tissue hypoperfusion alone can account for the close relationship between orthostatic dysfunction and ME/CFS. Orthostatic stress alone can trigger PEM in patients with ME/CFS (van Campen et al. 2021), but not in otherwise healthy individuals with orthostatic intolerance. Moreover, in severely affected patients, even activities requiring minimal physical exertion but an upright posture, such as brushing one's teeth or taking a shower, can trigger PEM. This observation suggests that orthostatic dysregulation may play a substantial role in the development of PEM. At the same time, it raises the question of whether reduced cardiac preload and the resulting impairment of tissue perfusion are sufficient to explain the close relationship between orthostatic dysfunction and ME/CFS. Decreased stroke volume and cardiac output, together with exaggerated vasoconstriction, would be expected to produce acute symptoms by reducing cerebral and skeletal muscle blood flow, thereby impairing organ function and limiting physical and cognitive performance. This could manifest as light-headedness, pallor, fatigue, weakness, dizziness, cognitive impairment, and, in severe cases, syncope. However, these acute hemodynamic disturbances associated with orthostatic dysregulation alone do not readily explain the prolonged symptomatology or the characteristic, ME/CFS-specific phenomenon of PEM. Indeed, the observation that orthostatic stress can substitute for physical exercise in triggering PEM suggests that the consequences of orthostatic stress extend beyond transient reductions in blood flow and organ perfusion. The strength and specificity of this association therefore suggest that additional pathophysiological mechanisms may be involved, mechanisms that are more directly linked to the core pathophysiology of ME/CFS.

In the following, I examine the hypothesis that the consequences of orthostatic intolerance extend beyond tissue hypoperfusion to include dysregulation of ion transport in skeletal muscle. I propose that, because dysregulated ion transport in skeletal muscle represents a core pathophysiological component of ME/CFS within my conceptual framework, it may also provide a potential explanation for the close and potentially ME/CFS specific association between orthostatic intolerance and ME/CFS (Wirth and Scheibenbogen 2021), (Wirth and Löhn 2024).

2. Potential Disturbances of Ion Transport in Skeletal Muscle by Orthostatic Stress

2.1. Is Sodium Influx Increased in Skeletal Muscle by Orthostatic Stress in ME/CFS?

Hypovolemia and dysfunction of capacitance vessels cause orthostatic stress. The resulting sympathetic activation may stimulate the sodium-proton-exchanger isoform 1 (NHE1, SLC9A1) via

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α1-adrenergic receptors raising sodium influx in skeletal muscle. Crucially, skeletal muscle myocytes, and not just the surrounding vasculature, receive sympathetic innervation in addition to somatic motor innervation (Martin, Tolley, and Saffitz 1990), (Liu et al. 2009), (Rudolf, Kettelhut, and Navegantes 2024). Stimulation of NHE1 and the resulting sodium influx via α1-adrenergic signaling is well established in the heart (Karmazyn, Sawyer, and Fliegel 2005), (Yokoyama, Yasutake, and Avkiran 1998), whereas direct experimental evidence in skeletal muscle is lacking. Nevertheless, skeletal muscle expresses all the components required for this pathway, including α1-adrenergic receptors (Martin et al. 1990), the downstream signaling mechanisms that activate NHE1, and NHE1 itself although it seems that the ß2-adrenergic receptor (ß2AdR) is the predominant functionally relevant adrenergic receptor in skeletal muscle under physiological conditions.

NHE1 activity and the resulting sodium influx may be amplified by other, ME/CFS specific alterations. MRI based measurements of skeletal muscle pH in ME/CFS patients have demonstrated three changes (Jones et al. 2012), (He et al. 2013): 1) a more alkaline resting intracellular pH. 2) a greater decline in pH during exercise. 3) an impaired post exercise pH recovery compared with healthy controls (Jones et al. 2010). Protons cannot freely diffuse through the cell membrane; they are transported. NHE1 is the principal proton extruder in skeletal muscle, as it is in the heart (Orlowski and Grinstein 1997), (Juel 2008). NHE1 extrudes one proton for the cellular import of one sodium ion which delivers energy for the transport. Therefore, it is compelling to try to relate the observed changes in pH at rest and during exercise and proton handling in skeletal muscle in ME/CFS to possible changes in NHE1 activity: at rest, NHE1 may be already activated, thereby accounting for the elevated resting pH. A higher intracellular pH due to higher NHE1 activity before exercise would entail a higher intracellular sodium so that a patient would start exercising already with an elevated intracellular sodium. Exercise further raises intracellular sodium. Indeed, in patients with ME/CFS some muscles of the lower leg showed a higher sodium level already before starting exercise and also the expected further rise with exercise (Petter et al. 2022). How this is related to the lowering of the PEM threshold will be explained in length below.

The reasons for the stronger decline of skeletal muscle pH during exercise in patients and its delayed recovery following exercise will be discussed in the following sections, in conjunction with other arguments.

Sodium influx at the onset of exercise in the upright position may be much higher than in healthy individuals because orthostatic stress resulting from hypovolemia and impaired capacitance-vessel function elicits sympathetic activation that may be considerably greater than that occurring under normal physiological conditions. If NHE1 is upregulated in skeletal muscle by an underlying mechanism, as suggested by the higher resting intracellular alkaline pH, sympathetic stimulation of sodium influx would be expected to be further amplified. Thus, sympathetically stimulated NHE1 activity in skeletal muscle may be markedly increased under the pathophysiological conditions associated with ME/CFS. Importantly, orthostatic stress is invariably accompanied by continuous activity of the postural muscles, which remain tonically contracted to maintain upright posture even in the absence of deliberate physical activity or locomotion. Thus, the combination of higher resting sodium and strong rise in sodium influx in the beginning of exercise in the upright position may lead to an early critical rise in intracellular sodium in skeletal muscle.

2.2. Anaerobic Metabolism Raises Sodium Influx in Skeletal Muscle via NHE1 Activity

Hypovolemia, orthostatic stress, and exercise become closely interconnected from the very onset of physical activity by multiple mechanisms. Hypoperfusion may result from a combined effect of cardiac preload failure decreasing cardiac output and sympathetically induced vasoconstriction favored by endothelial and microvascular dysfunction. The resulting anaerobic metabolism causes enhanced proton production and subsequent NHE1 mediated sodium influx. Once ME/CFS has developed and mitochondrial dysfunction is established, impaired oxidative metabolism and loss of oxidative type 1 fibers (Charlton et al. 2026) further increases anaerobic metabolism, leading to greater proton production and additional activation of NHE1 for proton extrusion. During exercise,

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excessive proton production due to anaerobic metabolism may exceed the extrusion capacity of NHE1, resulting in greater intracellular acidification and explaining the lower pH found in the MRI study mentioned above despite its presumed higher activity at rest (Jones et al. 2012), (He et al. 2013).

2.3. Sodium Efflux from Skeletal Muscle Is Decreased in ME/CFS Due to Deficient Hormonal Stimulation of Na^+/K^+-ATPase and Inhibition by Reactive Oxygen Species

While a higher sympathetic tone due to orthostatic stress may stimulate sodium influx via NHE1 through α1-adrenergic signaling it does not proportionally stimulate sodium efflux via β2-adrenergic receptor (β2AdR)-mediated stimulation of the Na^+/K^+-ATPase. During exercise Na^+/K^+-ATPase is physiologically stimulated by ß2AdR and calcitonin-gene related peptide (CGRP) (Clausen 2003). ß2AdR are highly sensitive to desensitization by agonistic stimulation in contrast to α1-adrenergic receptors (Cotecchia, Stanasila, and Diviani 2012). β2AdR desensitization occurs due to chronic or repeated stress, with orthostatic stress potentially representing a major contributor. Autoantibodies directed against β2AdR found in ME/CFS (Scheibenbogen et al. 2018) may further impair β2AdR mediated stimulation of the Na^+/K^+-ATPase. Sodium efflux may even be impaired and reduced relative to the healthy state, thereby disturbing the normal balance between sodium influx and efflux.

Several additional severe factors may further and limit Na^+/K^+-ATPase activity: Calcitonin gene-related peptide (CGRP), physiologically released from small sensory nerve fibers, constitutes an early hormonal stimulus for Na^+/K^+-ATPase activation during exercise (Sejersted and Sjøgaard 2000), (Clausen 2003). Similar to β2AdR signaling, CGRP activates the Na^+/K^+-ATPase via the protein kinase A (PKA) pathway. Due to small fiber neuropathy CGRP should be deficient so that both main hormonal stimuli fail to adequately stimulate Na^+/K^+-ATPase for sodium efflux and potassium influx (Abrams et al. 2022), (Joseph et al. 2021), (Oaklander and Nolano 2019). Even before overt degeneration of the small sensory nerve fibers occurs the release of CGRP and other vasodilatory neuropeptides from these nerve endings may be disturbed: dysfunction of the ion channel TRPM3 has been shown in leukocytes (Eaton-Fitch et al. 2022). TRPM3 ion channels are also expressed in sensory nerve endings and involved in the secretion of neuropeptides from small nerve fibers (Held et al. 2015). Hence, TRPM3 dysfunction, if also present in sensory nerve endings, may diminish CGRP release from sensory nerve endings and by that reduce stimulation of Na^+/K^+-ATPase even before overt small nerve fiber degeneration occurs (Löhn and Wirth 2024).

Furthermore, reactive oxygen species (ROS) are generated to even inhibit the Na^+/K^+-ATPase. Together, these alterations further promote intracellular sodium accumulation while causing potassium loss (Jammes et al. 2020).

In line with a diminished activity of the Na^+/K^+-ATPase intracellular sodium in skeletal muscle was found increased in ME/CFS patients (Petter et al. 2022) and whole body potassium was found decreased in severe chronic fatigue (Burnet et al. 1996). 75 to 80% of whole body potassium is located in skeletal muscle (Palmer and Clegg 2019). It should be noted that, at the time of the potassium study, the current ME/CFS diagnostic criteria had not yet been applied. Instead, patients had been classified as suffering from severe fatigue.

The impaired proton extrusion observed during the recovery phase after exercise in the MRI based pH measurement studies in skeletal muscle in ME/CFS mentioned above is consistent with a reduction in the driving force for NHE1 reducing its activity which is dependent on the sodium gradient (Jones et al. 2012), (He et al. 2013). One plausible explanation is intracellular sodium accumulation during exercise, which diminishes the transmembrane sodium gradient required for continued proton extrusion. Reduced Na^+/K^+-ATPase function would further compromise the sodium gradient, thereby limiting NHE1 mediated proton extrusion. This mechanism may already become operative during exercise, contributing to the lower intramuscular pH observed during exercise, together with an increased proton load resulting from anaerobic metabolism. The delayed pH recovery after exercise is certainly another, indirect argument for intracellular sodium loading in skeletal muscle during exercise that has indeed been shown in direct MRI based sodium measurements in skeletal muscle (Petter et al. 2022). As mentioned, in line with the assumption of a

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decreased activity of the Na^+/K^+-ATPase as a contributor to a rise in sodium, total body potassium has been found decreased in patients with severe chronic fatigue.

Altogether, in ME/CFS, orthostatic stress may acutely increase sodium influx through α1-adrenergic stimulation of NHE1, particularly under conditions favoring anaerobic metabolism, while chronically impairing sodium efflux through β2AdR desensitization which diminishes Na^+/K^+-ATPase activity. The combination of these three factors may promote intracellular sodium accumulation at the onset of exercise in the upright position.

3. How Orthostatic Dysfunction and Hypovolemia Lower the PEM Threshold and Trigger It

In my concept of ME/CFS pathophysiology, the clinical PEM threshold is based on a biological threshold. The key mechanism is the intracellular sodium concentration, the sodium threshold at which the sodium–calcium exchanger (NCX) switches to reverse mode. Once intracellular sodium has risen to cross this reverse mode threshold, the NCX imports calcium into the cell rather than exporting it, resulting in calcium overload and subsequent cellular damage (McAllister et al. 2009), (Karmazyn et al. 2005) (Wirth and Scheibenbogen 2021). The mechanisms of sodium loading have been explained in length above. Skeletal muscle damage has indeed been demonstrated after a cycling effort in ME/CFS patients (Appelman et al. 2024). A more positive action potential resulting from depolarization due to intracellular potassium loss further favors the reverse mode of the NCX (Blaustein and Lederer 1999). Depolarization of the sarcolemma may be present before exercise or develop with exercise as a consequence of intracellular potassium loss in skeletal muscle due to insufficient Na^+/K^+-ATPase activity. Depolarizations cause hyperexcitability (but a loss of force). Via a stress induced rise in muscle tone, this promotes fasciculations, which are inappropriate excitations with futile contractions that cause further sodium influx and potassium efflux even at rest. Acting in concert, the disturbances described above can rapidly increase intracellular sodium beyond the NCX reverse mode threshold causing calcium overload and skeletal muscle damage. Apart from increasing intracellular sodium, overexertion also triggers the various mechanisms of hypovolemia as outlined in a previous paper worsening orthostatic stress with the consequences just outlined (Wirth 2026a).

These considerations regarding disturbed ion transport help explain why the PEM threshold can become markedly reduced and how orthostatic dysregulation contributes to this process. Once the PEM threshold has been substantially lowered, even orthostatic stress or minimal physical exertion can readily trigger PEM, potentially explaining why activities such as brushing one's teeth or taking a shower are sufficient to provoke PEM in patients with severe ME/CFS. Orthostatic dysfunction interacts strongly with physical exertion in promoting the underlying ionic disturbances. In severe cases or long exposure to the upright position, it may even substitute for physical exercise as the primary trigger of PEM. These considerations also explain how orthostatic exertion alone can trigger PEM (van Campen et al. 2021), not only by aggravating hypovolemia and impaired tissue perfusion but also by disturbing ionic homeostasis favoring sodium- and calcium overload in skeletal muscles.

These considerations raise the question of the potential role of the α1-adrenergic agonist midodrine in the treatment of orthostatic dysfunction. Although α1-adrenergic stimulation may be beneficial by enhancing vascular tone and thereby reducing orthostatic stress, direct α1-adrenergic signaling in skeletal muscle induced by midodrine could promote sodium influx through activation of NHE1, potentially exerting an unfavorable effect.

These insights also help explain why orthostatic dysfunction and POTS are frequently and closely associated with ME/CFS. They also provide a mechanistic link for why these conditions represent strong risk factors for the development of ME/CFS and may further worsen as the disease progresses.

Finally, apart from hypovolemia, another mechanism contributing to orthostatic dysfunction that is closely associated with ME/CFS deserves consideration. As discussed in detail in a previous publication, the structural integrity and mechanical properties of the connective tissue of the

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capacitance vessels may further deteriorate by ME/CFS specific pathomechanisms, thereby exacerbating venous pooling and further impairing orthostatic regulation (Wirth 2026b).

4. Does Mental Stress Induce Physiological Responses Similar to Those Observed During Orthostatic Stress?

These considerations regarding the role of orthostatic stress can also be extended to mental stress. As discussed above, NHE1 may be upregulated in ME/CFS, resulting in elevated intracellular sodium concentrations already under resting conditions. Mental exertion and stress may, in analogy to orthostatic stress, then further stimulate sodium influx through α1-adrenergic NHE1 activation in skeletal muscle. Mental stress also raises skeletal muscle tone. The interaction between mental stress induced increases in skeletal muscle tone and skeletal muscle depolarization, which is caused by loss of intracellular potassium, has been discussed previously (Wirth and Steinacker 2025). This interaction causes muscle weakness and fasciculations. Fasciculations as inappropriate excitations increase sodium influx and potassium efflux. This process exacerbates intracellular sodium accumulation while accelerating intracellular potassium depletion. Consequently, mental stress may not only activate NHE1 but also induce fasciculations. Both mechanisms may act synergistically to substitute for physical exercise as a trigger of PEM.

Interestingly, in the above mentioned studies of skeletal muscle pH, a higher resting skeletal muscle pH was associated with lower cerebral blood flow, a finding that the authors attributed to autonomic dysregulation (He et al. 2013). This relationship suggests a mechanistic link between skeletal muscle symptoms and neurological symptoms. Notably, cerebral blood flow is reduced through the same mechanisms implicated in disturbed skeletal muscle sodium ion homeostasis and pH regulation: during orthostatic stress, hypovolemia and cerebral α1-adrenergic vasoconstriction driven by elevated sympathetic activity can reduce cerebral perfusion triggering neurological symptoms. Consequently, orthostatic dysfunction and POTS provide a compelling mechanistic link between the neurological and skeletal muscle manifestations of ME/CFS. This association extends beyond impaired perfusion, as dysregulation of ion transport in skeletal muscle may contribute to disease pathophysiology induced by orthostatic stress. These mechanisms are closely interconnected, with hypoperfusion and ionic disturbances likely reinforcing one another through the mechanisms described above.

The hypotheses presented here are conceptual and require validation through appropriate clinical investigations. A key experimental approach would be to assess changes in pH or intracellular sodium concentration in skeletal muscle following α1-adrenergic stimulation and orthostatic stress at rest, as has been already demonstrated in the heart. An important question is why the heart would not be similarly affected by sodium loading in ME/CFS as a consequence of sympathetically mediated α1-adrenergic stimulation during mental or orthostatic stress. One possible explanation is that the heart has a greater capacity to prevent an increase in intracellular Na^+, owing to its higher capacity of the Na^+/K^+-ATPase compared with skeletal muscle (Sejersted and Sjøgaard 2000).

5. Conclusions

Orthostatic dysfunction, including POTS, and ME/CFS are closely associated, likely not only through impaired cardiac preload and vasoconstriction in response to orthostatic stress, but also through the presumed underlying pathophysiology of ME/CFS itself. This may involve dysregulated ion transport in skeletal muscle, resulting in intracellular sodium and calcium accumulation and potassium loss. Orthostatic stress may further exacerbate this ionic imbalance, while the resulting consequences may contribute to worsening hypovolemia and, consequently, further impairment of orthostatic function.

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