Review

In Search of Lost Volume: The Potential Causes of Hypovolemia in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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In Search of Lost Volume: The Potential Causes of Hypovolemia in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

Hypovolemia and orthostatic intolerance are hallmark features of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) but remain incompletely understood. This review summarizes the physiological control of intravascular volume and discusses how these mechanisms may be disturbed in ME/CFS. Reduced intravascular volume limits cardiac filling and perfusion. Both main volume-regulating systems—vasopressin and the renin–angiotensin–aldosterone system (RAAS)—appear impaired. Low vasopressin despite hypovolemia may result from disturbed serotonergic-, noradrenergic- and angiotensin II–mediated stimulation of vasopressin. RAAS activation is blunted despite volume depletion. Excessive release of vasoactive mediators from metabolically impaired skeletal muscle may cause renal sodium and water loss, but suppress compensatory renin secretion, and increase microvascular permeability, along with elevated levels of cytokines, reactive oxygen species (ROS), and potentially hypoxia-inducible factors (HIFs). Dysfunction of ß$_2$-adrenergic receptors weakens their physiological role in inhibiting microvascular leakage and impairs sodium absorption via the main transporter, sodium-proton-exchanger subtype 3 (NHE3). Exercise-induced fluid shift into the intracellular skeletal muscle compartment appears exaggerated due to intracellular accumulation of osmolytes due to the poor energetic situation resulting from the combined effect of poor perfusion and mitochondrial dysfunction. Collectively, hypovolemia arises from interacting volume regulatory disturbances, is amplified by exertion and contributes to post-exertional malaise.

Keywords: myalgic encephalomyelitis/chronic fatigue syndrome; hypovolemia; orthostatic intolerance; renin–angiotensin–aldosterone system dysfunction; vasopressin; renin paradox; exercise-induced fluid shifts; β_2-adrenergic receptor dysfunction; mitochondrial dysfunction; post-exertional malaise

Introduction

Hypovolemia and orthostatic intolerance are clinical features of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and likely contribute directly to 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). A reduction in intravascular volume leads to diminished cardiac preload and impaired ventricular filling, a key determinant of cardiac output and tissue perfusion (Joseph et al. 2021). This compromises orthostatic regulation and limits the heart's ability to augment cardiac output during physical activity. As a result—together with additional hemodynamic and microvascular disturbances—exercise capacity is diminished and tissue hypoperfusion may develop. This impaired perfusion likely contributes to exercise intolerance and post-exertional malaise (PEM), the hallmark symptom of ME/CFS. In addition, sustained orthostatic stress may disturb neurotransmitter balance through chronic sympathetic activation and cause downregulation of β_2-adrenergic receptors (β_2AdR) (Wirth and Scheibenbogen 2026). Hypovolemia may therefore contribute both to disease onset and persistence by establishing a self-perpetuating vicious cycle.

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Importantly, hypovolemia is not the sole cause of reduced cardiac preload, orthostatic dysfunction, or exercise-limited cardiac output. Cardiac preload and right ventricular filling are determined not only by circulating blood volume but also by vascular filling and the contractile function of capacitance vessels. Impaired constriction of capacitance vessels—primarily veins and large arteries—can prevent adequate mobilization of blood toward the central circulation and thereby reduce preload, even in the absence of marked hypovolemia. Hypovolemia and capacitance vessel dysfunction may therefore coexist and act synergistically to produce cardiac preload failure. Consequently, neither disturbance needs to be pronounced in isolation to collectively result in severe impairment of cardiac filling and orthostatic tolerance.

This paper aims to identify potential mechanisms that may contribute to hypovolemia in ME/CFS. A more comprehensive understanding of these disturbances may facilitate the development of targeted therapeutic strategies. The hypotheses proposed herein are conceptual in nature and require validation through appropriate experimental and clinical investigations.

I first outline the major physiological systems regulating water and sodium homeostasis and then discuss how these systems may be disturbed in ME/CFS, with a particular focus on pathophysiological mediators already described in this condition. Finally, I integrate these individual disturbances into a coherent framework and discuss their possible sequence, interactions, and interdependencies.

Main Regulatory Systems of Body Fluid Volume and Possible Disturbances in ME/CFS

Vasopressin

The frequent patient-reported symptoms of polyuria and polydipsia prompted an investigation of vasopressin levels, as well as plasma and urine osmolality, in ME/CFS (Huhmar et al. 2024). In this study, vasopressin concentrations were found to be low in patients with ME/CFS following a 10-hour water deprivation and overnight fasting. Plasma osmolality was unchanged in the majority of patients, whereas urinary osmolality was reduced, indicating impaired urinary concentration. This pattern is reminiscent of diabetes insipidus, a condition characterized by insufficient vasopressin secretion leading to excessive renal water loss.

In diabetes insipidus, reduced vasopressin secretion typically results from damage to the hypothalamus or posterior pituitary caused by idiopathic or autoimmune mechanisms, head trauma or surgery, tumors, infections, inflammatory or infiltrative diseases, vascular injury, or rare genetic defects (Refardt, Winzeler, and Christ-Crain 2020), (Mutter et al. 2021). None of these etiologies is apparent in ME/CFS. If vasopressin deficiency were the sole or primary mechanism underlying hypovolemia in ME/CFS, treatment with the vasopressin analogue desmopressin—effective in diabetes insipidus—would be expected to correct the condition. This is evidently not the case, suggesting a more complex pathophysiology.

Physiologically, vasopressin promotes water retention via activation of V2 receptors, leading to the insertion of aquaporin-2 channels into the membranes of renal collecting duct cells, thereby facilitating water reabsorption. Vasopressin is synthesized by magnocellular neurons located in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. It is transported along axons bound to neurophysin and released into the circulation from the posterior pituitary (neurohypophysis) (Sparapani et al. 2021), (Holmes, Landry, and Granton 2003). The most potent stimuli for vasopressin synthesis and secretion are plasma hypertonicity, severe hypotension, and hypovolemia.

Importantly, the neurotransmitters serotonin and noradrenaline play modulatory roles in vasopressin secretion (serotonin: (Gibbs and Vale 1983), (Ivanova, Kochkaeva, and Melidi 2007), (Jørgensen et al. 2002), (Jørgensen et al. 2003); noradrenaline: (Yamashita, Inenaga, and Kannan 1987), (Willoughby et al. 2008), (Shioda et al. 1997), (Randle et al. 1986), (Brooks, Share, and Crofton 1986). Both neurotransmitter systems have been reported to be disturbed by ME/CFS. In addition, angiotensin II is a well-established stimulus for vasopressin release.

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Given that the classical pathogenic mechanisms of diabetes insipidus appear unlikely in ME/CFS, the question arises as to how vasopressin secretion may be impaired in this condition. In the following sections, I therefore outline potential disturbances in serotonergic, noradrenergic, and angiotensin II–mediated stimulation of vasopressin that could contribute to dysregulation of water homeostasis in ME/CFS.

Serotonin: Serotonin stimulates vasopressin release via activation of 5-HT_1A and 5-HT_2 receptors. In ME/CFS, central serotonergic signaling may be reduced as a consequence of diminished availability of its precursor, tryptophan. Altered serotonin metabolism is therefore likely to be of pathophysiological relevance in ME/CFS.

Reduced tryptophan availability may result from gut dysbiosis (Iqbal et al. 2025), (Simadibrata et al. 2023), (Zhang et al. 2023), (Oh et al. 2025) as well as from increased diversion of tryptophan into the kynurenine pathway, potentially driven by elevated activity of indoleamine 2,3-dioxygenase (IDO) enzymes (Guo et al. 2023), (Rus 2025). IDO1, in particular, is induced by interferons during viral infections and may therefore contribute to sustained tryptophan depletion in post-infectious conditions. Consistent with this hypothesis, several studies report reduced circulating tryptophan levels in patients with post-COVID syndrome (PCS) (Cysique et al. 2022), (Cron 2023), (Chilosi et al. 2022).

Measurements of peripheral serotonin or its metabolite 5-methoxytryptamine have yielded decreased or unchanged levels in ME/CFS and related conditions (Wong et al. 2023), (Raij and Raij 2024), (Nagy-Szakal et al. 2018), (Mathé et al. 2025). However, peripheral serotonin does not cross the blood–brain barrier and therefore does not directly reflect central serotonergic neurotransmission. In contrast, brain serotonin synthesis depends on the availability of circulating tryptophan. Consequently, reduced blood tryptophan levels may represent a more relevant proxy for impaired central serotonin signaling and, by extension, diminished serotonergic stimulation of vasopressin release in ME/CFS.

Angotensin II: Angiotensin II is a potent stimulus for the release of vasopressin. However, in ME/CFS the activity of the renin–angiotensin–aldosterone system (RAAS) is low or fails to increase appropriately despite hypovolemia; consequently, this stimulus may be insufficient (De Lorenzo, Hargreaves, and Kakkar 1997), (Boneva et al. 2007), (Miwa 2017). Disturbances of the RAAS in ME/CFS and its potential causes are discussed in the following sections.

Noradrenaline: Noradrenaline, acting via the α1-adrenergic receptor, stimulates vasopressin release in magnocellular neurons and is thought to mediate the well-established water-retaining response to decreases in arterial pressure (Yamashita et al. 1987), (Willoughby et al. 2008), (Shioda et al. 1997), (Randle et al. 1986), (Brooks et al. 1986). In ME/CFS, sympathetic tone and noradrenergic brain nuclei appear to be chronically overstimulated, a state that could promote desensitization of adrenergic receptors. Although the α1-adrenergic receptor shows the lowest propensity for desensitization among adrenergic receptor subtypes, the chronic nature of ME/CFS may nevertheless allow such desensitization to develop over time (Cotecchia, Stanasila, and Diviani 2012). A well-known clinical example of α1-adrenergic receptor desensitization is the tachyphylaxis observed with nasal decongestants containing α1-adrenergic agonists after 3–5 days of continuous use. In addition, autoantibodies directed against alpha1-adrenergic receptor autoantibodies have also been observed in some patients with ME/CFS (Freitag et al. 2021). An alternative or complementary explanation for a potentially reduced noradrenergic stimulation of vasopressin release is that the central noradrenergic system is chronically overactivated and consequently could become functionally exhausted, limiting its ability to mount an adequate response when required, such as during exercise, orthostatic regulation, and possibly also for volume regulation, as discussed previously (Wirth and Scheibenbogen 2026). Impaired noradrenergic activation may then even coincide with desensitization of α1-adrenergic receptors.

Dysfunction of two neurotransmitter systems—noradrenaline and serotonin—as well as abnormalities of the RAAS, all of which have been reported in ME/CFS, may impair vasopressin

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secretion. Additionally, other as-yet-unknown factors may play a role and create a vulnerability to hypovolemia.

The renin-angiotensin-aldosterone system (RAAS)

An unexpected finding in ME/CFS is that plasma renin activity is often low or inappropriately normal, despite the presence of hypovolemia that would normally elicit a robust renin response (De Lorenzo et al. 1997), (Boneva et al. 2007), (Miwa 2017). This failure of renin to increase appropriately in the context of reduced intravascular volume has been termed the *renin paradox* (Raj et al. 2005). Renin is a key regulator of physiological volume homeostasis, initiating activation of the RAAS. Renin activity leads to the generation of angiotensin II, which exerts multiple effects, including stimulation of vasopressin release, and the secretion of aldosterone, which promotes renal sodium retention. Aldosterone increases sodium reabsorption by upregulating epithelial sodium channels (ENaC) on the luminal membrane and Na^+/K^+-ATPase on the basolateral membrane of cells in the renal collecting duct. In addition, aldosterone enhances sodium absorption in the gastrointestinal tract, primarily in the colon, although this contribution is modest compared with its potent renal effects.

Together, these observations suggest that both principal systems governing water and sodium homeostasis—vasopressin and the RAAS—are both functionally impaired in ME/CFS, underscoring the severity of volume control dysregulation. A potential explanation for the renin paradox is discussed in the following sections.

Pathological stimulation of loss of plasma fluid into the interstitial space and of renal excretion of water and salt by vasoactive mediators

The vasoactive mediators bradykinin, prostacyclin, prostaglandin E_2, adenosine, and likely histamine are physiologically released from skeletal muscle during normal exercise and, to an even greater extent, during ischemia, where they serve as compensatory mediators to increase local perfusion (Staszewska-Barczak, Ferreira, and Vane 1976), (Hashimoto et al. 1977), (Linz, Wiemer, and Schölkens 1996), (Koch et al. 2003), (Pan et al. 2000), (Stebbins et al. 1990), (Tegeder et al. 2002). In ME/CFS, impaired muscle energetics and a chronically unfavorable metabolic state are likely to exaggerate the production of these vasoactive mediators as a compensatory attempt to augment local blood flow and improve energy supply.

Excessive production may result in spillover of these mediators into the systemic circulation. Under physiological conditions, owing to their short half-lives, their effects are largely confined to the local tissue, where they are released. However, in ME/CFS, excessive release could allow them to exert systemic actions. Beyond vasodilation, these mediators possess algesic and hyperalgesic properties and increase microvascular permeability, the latter promoting plasma extravasation and local edema (Mullins 1986), (Szabó and Magyar 1982).

Dysfunction of β_2AdR may further favor plasma exudation and vascular fluid loss. This is because β_2AdR signaling physiologically counteracts increases in microvascular permeability by reducing endothelial gap formation, an important physiological mechanism during exercise to preserve intravascular volume and maintain cardiac preload (Svensjö, Persson, and Rutili 1977), (Mullins, Malias, and Hudgens 1989), (Rhaleb, Yang, and Carretero 2011), (Hébert et al. 2005), (Wang et al. 2000). The benefit of adrenaline in the treatment of anaphylaxis is partly based on the stimulation of ß2AdR and subsequent reduction of microvascular leakage. The fact that adrenaline physiologically released during exertion reduces microvascular leakage suggests that this effect serves a physiological purpose. It implies that exercise is associated with a tendency toward increased microvascular leakage that requires counterregulation. In ME/CFS, ß2AdR dysfunction impairs this counterregulatory mechanism, so that microvascular leakage can be increased during exercise contributing to hypovolemia.

In the kidney vasoactive mediators released from skeletal muscle raise renal blood flow to stimulate glomerular filtration. Additionally, bradykinin and PGE2 inhibit sodium reabsorption in the distal renal tubuli. Both effects lead to renal loss of sodium and water (Katori and Majima 1997), (Rhaleb et al. 2011).

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Other mediators/mechanisms that could increase microvascular permeability in ME/CFS are cytokines, hypoxia-inducible factor-1α (HIF-1α) and reactive oxygen species (ROS).

Cytokines: Multiple independent studies have found elevations of pro- and some anti-inflammatory cytokines in ME/CFS patients (Maksoud et al. 2023). Pro-inflammatory cytokines (e.g., TNF-α and IL-1β) increase microvascular permeability (Kerkar et al. 2006) by activating endothelial signaling pathways that reorganize the actin cytoskeleton, disrupt tight and adherens junctions (such as VE-cadherin), and promote leukocyte transmigration, resulting in intercellular gap formation and leakage of fluid and proteins into tissue (Sprague and Khalil 2009), (Marcos-Ramiro, Garcia-Weber, and Millan 2014).

HIF-1α**:** It can increase microvascular through downstream effectors like VEGF or gap junction disruption (Song et al. 2017), (Yan, Zhang, and Shi 2012), (Qi et al. 2011), (Meng et al. 2019). HIF-1α levels are physiologically raised by hypoxia and pseudohypoxia (Salminen, Kaarniranta, and Kauppinen 2016). The latter includes activation by reactive oxygen species (ROS). There is enough evidence for cellular hypoxia or ROS generation by mitochondrial dysfunction in ME/CFS so that it is reasonable to assume that HIF-1α levels are raised. HIF levels are difficult to measure, however.

ROS: Apart from raising HIF-1α, ROS increase microvascular permeability by disrupting endothelial junctions, promoting cytoskeletal contraction, and inducing inflammatory mediators (Monaghan-Benson and Burridge 2009), (Karki and Birukov 2019), (Boueiz and Hassoun 2009). Particularly interesting is that mitochondrial ROS can also cause mast cell degranulation establishing a relationship between ROS and histamine (Piotin et al. 2024). Mast cells are present in skeletal muscle (Van der Stede et al. 2025). Thereby, ROS-induced histamine release in skeletal muscle might contribute to microvascular leakage.

Speculatively, cytokines, HIF-1α, and ROS increase microvascular leakage, perhaps only moderately, creating a chronic baseline disturbance that raises the responsiveness to vasoactive mediators such as bradykinin, histamine and prostaglandin E2 that cause microvascular leakage. These mediators are primarily released during exercise due to the poor metabolic situation as a compensatory mechanism to enhance blood flow and to improve the energetic situation.

Taken together, excessive production of vasoactive mediators, resulting from impaired skeletal muscle energetics, can contribute to hypovolemia after spilling into the systemic circulation through two mechanisms: (1) promoting renal loss of sodium and water, and (2) inducing excessive plasma exudation. These vasoactive mediators can act synergistically with cytokines, ROS, and HIF-1α to increase microvascular permeability, so that even minor perturbations in each factor may collectively produce a substantial effect. Concurrently, β2AdR dysfunction may compromise its physiological role in limiting microvascular leakage, thus permitting excessive plasma exudation and vascular fluid loss

Inhibition of renin secretion and a blunted RAAS response to hypovolemia

Renin secretion is physiologically stimulated by three mechanisms: by decreased renal perfusion pressure, reduced sodium chloride delivery to the macula densa, and increased sympathetic activity mediated via β_1-adrenergic receptors (Kurtz 2011). In the kidney, vasoactive mediators such as bradykinin, histamine and prostaglandins released from metabolically depleted skeletal muscle increase renal blood flow and glomerular filtration. In addition, bradykinin and prostaglandin E_2 inhibit sodium reabsorption in the distal renal tubules, increasing sodium delivery to the macula densa. Both effects suppress renin release (Katori and Majima 1997), (Rhaleb et al. 2011). Thus, increased renal perfusion and inhibition of distal tubular sodium reabsorption directly promote renal sodium and water loss and blunt the compensatory rise in renin (Wirth and Scheibenbogen 2020). Renin levels remain paradoxically low or inappropriately normal despite hypovolemia, thereby preventing effective refilling of the vascular compartment (De Lorenzo et al. 1997), (Boneva et al. 2007), (Miwa 2017).

In summary, the two principal mechanisms of volume regulation are compromised in ME/CFS: vasopressin-mediated water retention and RAAS-mediated sodium and water conservation.

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Concurrently, plasma volume is further depleted by enhanced microvascular permeability driven by vasoactive mediators and insufficiently counteracted due to β_2AdR dysfunction.

Return of extravasated fluid to the venous circulation

The return of extravasated fluid to the venous system is a key determinant of intravascular volume regulation. Given the likelihood of increased plasma exudation, an undisturbed return of this fluid is particularly important. The critical question is whether this process is impaired. Lymphatic fluid is actively transported by rhythmic contractions of smooth muscle within the lymphatic vessel wall, supported by skeletal muscle movement (Thorup et al. 2023). While passive mechanisms such as skeletal muscle contractions and negative intrathoracic pressure during inspiration contribute to lymph flow, propulsion is largely driven by lymphatic pumping. This process depends on upstream valves and coordinated contractile cycles consisting of a contraction phase followed by a relaxation phase, as in the heart, which allows refilling of the lymphatic pump.

Potential disturbances of lymphatic pump function: Lymphatic pump activity is regulated by several mediators, including histamine, nitric oxide (NO), and the sympathetic nervous system. Histamine exerts concentration-dependent effects: at low concentrations it enhances lymphatic contractility, whereas at higher concentrations it induces relaxation and inhibits contractions (Nizamutdinova et al. 2014). Nitric oxide (NO) is a key modulator of lymphatic pumping, promoting vessel relaxation—particularly following contraction—thereby facilitating lymphatic filling and optimizing pump efficiency (Lee et al., 2022). At physiological levels, histamine and NO appear to improve lymphatic flow. In pathological states, however, these regulatory mechanisms may be disturbed. Histamine levels are elevated in patients with mast cell hyperactivity, while NO availability may be reduced due to endothelial dysfunction or scavenging by reactive oxygen species. Both alterations would be expected to impair lymphatic pumping, reduce lymphatic vessel filling, and ultimately diminish venous return of lymphatic fluid.

Sympathetic activity, mediated via α_1-adrenergic receptors, physiologically stimulates rhythmic lymphatic contractions and enhances lymph flow (McGeown, McHale, and Thornbury 1987), (Mahe et al. 1989). This stimulatory influence may be attenuated by two opposing mechanisms. First, reduced lymphatic contractility may result from autoantibodies targeting α_1-adrenergic receptors or from insufficient sympathetic activation, particularly during exercise. Second, excessive sympathetic stimulation may also impair active lymphatic transport by inducing hypercontractility, increasing vascular resistance and compromising the relaxation phase required for effective lymphatic vessel refilling (Mahe et al. 1989), (Howarth et al. 1999).

Volume shift from the vascular space into skeletal muscle during exercise

During intense exercise in healthy individuals, skeletal muscles transiently swell and take up fluid from the circulation, thereby reducing circulating blood volume (Sleboda, Wold, and Roberts 2019), (Freitas et al. 2017), (Ploutz-Snyder, Convertino, and Dudley 1995), (Mandić et al. 2021). This fluid shift involves both the intracellular compartment of skeletal muscle and the interstitial compartments of the body, as outlined above. In healthy volunteers, fluid uptake into skeletal muscle correlates with intracellular glucose-6-phosphate concentrations, which act as an important osmolyte during exercise (Mandić et al., 2021).

In ME/CFS, the shift of sodium from the intravascular space into skeletal muscle cells during muscular activity is significantly greater than in healthy controls (Petter et al., 2022) and thought to result from increased activity of the sodium–proton exchanger NHE1, driven by anaerobic metabolism and intracellular acidosis, combined with insufficient sodium extrusion due to impaired Na^+/K^+-ATPase function (Wirth and Scheibenbogen 2021), (Löhn and Wirth 2024). During exercise, stimulation of the Na^+/K^+-ATPase relies primarily on β_2AdR signaling and calcitonin gene–related peptide (CGRP). Both pathways may be compromised in ME/CFS, potentially due to autonomic dysfunction and autoantibodies to ß2AR and small fiber neuropathy. Furthermore, Na^+/K^+-ATPase activity is inhibited by reactive oxygen species and reduced ATP availability, which are expected consequences of mitochondrial dysfunction.

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As a result, osmolytes such as glucose-6-phosphate, lactate and sodium may accumulate to a greater extent in the skeletal muscle of patients with ME/CFS than in healthy individuals, leading to a more pronounced and sustained shift of fluid into the intracellular muscular and interstitial compartments and thereby contributing to hypovolemia. In healthy subjects, these exercise-induced fluid shifts are transient and rapidly reversible (Mandić et al., 2021). In contrast, in ME/CFS the impaired energetic state may render these shifts more severe, longer lasting, and more widespread, potentially involving auxiliary and postural muscles that become prematurely fatigued.

The resulting loss of intravascular volume into the intracellular and interstitial spaces may further impair post-exertional perfusion and exacerbate the metabolic deficit, thereby promoting additional release of vasoactive mediators and establishing a self-reinforcing vicious cycle.

Intestinal sodium absorption and renal tubular reabsorption

The main sodium transporters in the intestine and kidney are the epithelial sodium channel (ENaC; SCNN1), the sodium–proton exchanger subtype 3 (NHE3), the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2), and the Na^+/K^+-ATPase with its basolateral cellular location. Dysfunction of the Na^+/K^+-ATPase plays a key role in the pathophysiology of sodium and secondary calcium overload in skeletal muscle. Impaired Na^+/K^+-ATPase activity is primarily attributable to insufficient stimulation by β_2AdR and calcitonin gene–related peptide (CGRP)—the only hormonal activators of the pump during muscle contraction—as well as inhibition by reactive oxygen species (ROS) and reduced ATP availability. In contrast, regulation of the Na^+/K^+-ATPase in the kidney and intestine with its basolateral location in the cell differs fundamentally as in these organs, insulin and aldosterone are the principal stimulators.

NHE3 is the most important transporter mediating intestinal sodium absorption and proximal tubular sodium reabsorption from the glomerular filtrate, respectively (Donowitz et al. 2009), (Fenton et al. 2017). In the kidney. Angiotensin II enhances proximal tubular sodium reabsorption by stimulating NHE3. However, in ME/CFS the RAAS is not sufficiently activated despite hypovolemia, resulting in insufficient stimulation of sodium absorption via both ENaC and NHE3.

Although β_2AdRs do not stimulate the Na^+/K^+-ATPase in the kidney or intestine, they can augment sodium absorption in these tissues by activating NHE3 by an indirect mechanism (Hall et al. 1998). Under basal conditions, NHE3 activity is inhibited through binding to the Na^+/H^+ exchanger regulatory factor (NHERF). Upon agonist activation, β_2AdRs bind directly to NHERF via a PDZ-domain interaction at the receptor's C-terminus, thereby preventing NHERF-mediated binding and inhibition of NHE3 through a mechanism that is independent of G proteins and cAMP. This interaction enables β_2AdR-dependent stimulation of NHE3-mediated sodium absorption.

The physiological relevance of this mechanism is underscored by observations in individuals carrying the Arg16Gly polymorphism of the β_2AdR, in whom significant differences in sodium and volume excretion are observed following sodium and volume loading (Snyder, 2006). In ME/CFS, β_2AdR dysfunction—potentially due to receptor desensitization, internalization, or binding of autoantibodies—may impair the interaction between β_2AdRs and NHERF. As a result, unbound NHERF could more effectively inhibit NHE3, leading to reduced sodium absorption.

Given that NHE3 is also the dominant sodium uptake mechanism in the intestine, impaired β_2AdR–NHE3 signaling may contribute both to reduced intestinal sodium absorption and to renal sodium wasting.

Experimental pharmacological studies of NHE3 inhibitors have shown that sodium loss from proximal tubular NHE3 inhibition can be compensated by increased sodium reabsorption in the distal nephron (unpublished data). In ME/CFS, however, reduced proximal tubular sodium reabsorption due to impaired NHE3 activation (from β_2AdR dysfunction and low angiotensin II) coincides with inhibition of distal tubular sodium reabsorption by bradykinin and prostaglandin E_2. These mechanisms may act highly synergistically to promote substantial renal sodium and water loss. Together, these mechanisms provide a plausible pathway by which sodium imbalance and hypovolemia may arise and persist in ME/CFS.

Disturbances in Volume Regulation and Aggravation by Exercise

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A key insight of this analysis is that the principal systems regulating intravascular volume are largely disturbed by mediators and pathomechanisms already implicated in other aspects of ME/CFS. This is especially evident for the dysfunction of β2AdR. Their broader relevance to ME/CFS, as well as their specific contribution to hypovolemia, will be summarized at the end of this section.

Hypovolemia can be easily worsened by dehydration or insufficient fluid intake. While many patients can avoid these volume stressors under resting conditions, the defining feature of ME/CFS—exercise intolerance—raises a critical question: are volume disturbances amplified during physical exertion? I therefore examined whether exercise-related pathophysiological mechanisms might worsen underlying volume dysregulation. In the following section, I outline how the single disturbances outlined above may be linked in a pathophysiological and temporal sequence.

Exercise induces a physiological shift of fluid into tissues, predominantly into skeletal muscle. This shift involves movement of fluid from the intravascular space into the intracellular compartment of muscle fibers due to the accumulation of sodium and other osmotically active metabolites such as lactate and glucose-6-phosphate. Because of the impaired metabolic state in ME/CFS, this exercise-induced fluid shift is likely to be substantially more pronounced than in healthy individuals, in whom this phenomenon is already well established. Simultaneously, interstitial fluid accumulation is promoted by the release of vasoactive mediators, cytokines and ROS that enhance microvascular permeability. These vasoactive mediators are produced excessively in response to the impaired skeletal muscle energetic state, presumably as a compensatory attempt to improve perfusion. Once produced in excess, they may spill over into the systemic circulation. Under physiological conditions, microvascular leakage is inhibited by β_2AdR stimulation. However, β_2AdR dysfunction in ME/CFS may limit this protective mechanism, allowing vasoactive mediators to induce excessive microvascular leakage and interstitial fluid accumulation. Following spillover into the systemic circulation, these vasoactive mediators—such as bradykinin, prostacyclin, prostaglandin E_2, adenosine, and histamine—increase renal perfusion and inhibit distal tubular sodium reabsorption (particularly bradykinin and prostaglandin E_2). This can promote substantial renal sodium and water loss.

Compensatory mechanisms that physiologically counteract such losses of sodium and water fail in ME/CFS. Vasopressin release is inadequate. Simultaneously, RAAS activation is insufficient. Renin secretion does not rise appropriately because of increased renal blood flow and higher sodium concentration in the distal tubules. Additionally, the third physiological mechanism of renin release—β-adrenergic stimulation mediated by β_1-adrenergic receptors—may also be impaired during exercise (Wirth and Scheibenbogen 2026). Failure of these compensatory volume-regulating mechanisms delays recovery of skeletal muscle metabolism due to inadequate perfusion.

The persistently impaired energetic state of skeletal muscle leads to continued release of vasoactive mediators which raise microvascular permeability and cause renal loss of sodium. Cytokines and ROS produced as a consequence of mitochondrial dysfunction raises the responsiveness to vasoactive mediators to increase microvascular permeability. Concurrently, osmotically active metabolites are not cleared efficiently in skeletal muscle because of poor perfusion and mitochondrial dysfunction, resulting in sustained intracellular fluid retention within muscle cells. The combined effects of these exercise-induced disturbances result in a self-sustaining impairment of skeletal muscle perfusion and metabolic function delaying recovery.

As a background disturbance, intestinal sodium absorption and particularly renal proximal tubular sodium reabsorption are likely impaired due to β_2AdR dysfunction, given the role of this receptor in activating the sodium transporter NHE3. Inhibition of proximal tubular sodium reabsorption coincides with inhibition of distal tubular sodium reabsorption by bradykinin and prostaglandin E_2.

The Role of β_2AdR Dysfunction in Disturbed Volume Regulation in ME/CFS

This analysis extends the spectrum of β_2AdR-related dysfunction in ME/CFS to include impaired volume regulation and hypovolemia, integrating these disturbances into the broader

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pathophysiological framework of the disease. β_2AdR dysfunction may contribute to hypovolemia through three distinct mechanisms:

1. Impaired activation of NHE3, reducing intestinal and renal sodium absorption.
2. Reduced inhibition of microvascular leakage by β_2AdR activation due to dysfunction of this receptor on endothelial cells, facilitating extravasation of intravascular fluid into the interstitial space.
3. Indirect worsening of skeletal muscle energetics through impaired activation of the Na^+/K^+-ATPase and inadequate prevention of intracellular sodium and calcium overload, promoting intracellular osmolyte accumulation and fluid shift into the intracellular space of skeletal muscles.

Broader Role of β_2AdR in ME/CFS Pathophysiology

β_2AdR stimulation increases blood flow to skeletal muscle, heart, and brain; induces bronchodilation; and exerts chronotropic, inotropic, lusitropic, and dromotropic effects on the heart (Wirth and Scheibenbogen 2020). In skeletal muscle, β_2AdR activation is critical for stimulating Na^+/K^+-ATPase activity during exercise. Failure of this mechanism may lead to intracellular sodium accumulation, calcium overload via reversal of the sodium–calcium exchanger, and subsequent cellular damage (Wirth and Scheibenbogen 2021). In ME/CFS, β_2AdR function may be compromised by three mechanisms:

1) Chronic elevation of sympathetic tone may promote β_2AdR desensitization as this is well known to occur in heart failure and experimental medicine.

2) β_2AdR-autoantibodies may further impair receptor signaling.

3) Chronic overstimulation may lead to functional "exhaustion" of the adrenergic system, thereby limiting its capacity to adequately activate β_2AdR during exercise. Because these receptors are already impaired by the two mechanisms described above, a substantially higher degree of adrenergic stimulation would be necessary to generate an adequate physiological response during physical exertion.

Conclusion

Hypovolemia in ME/CFS appears to result from the synergistic interaction of multiple abnormalities in volume regulation, such that even mild impairments in individual regulatory mechanisms can collectively produce substantial volume depletion. In addition to hypovolemia Impaired contraction of the capacitance vessels may also be present and may act in concert with reduced blood volume, thereby contributing to orthostatic dysfunction and impaired skeletal muscle perfusion during exercise.

The mediators and mechanisms involved in dysregulated sodium and water handling overlap with pathways previously implicated in other proposed pathomechanisms and symptoms of ME/CFS which is particularly evident in the case of ß2AdR signaling. Importantly, these abnormalities appear to be both causally and temporally linked to exercise and the subsequent development of PEM.

Hypovolemia is likely exacerbated during PEM and, hence, may represent a key contributor to its pathophysiology. It may drive underlying mechanisms, contribute to symptoms, and potentially extend PEM episodes. To my knowledge, cardiac preload and plasma volume have not yet been measured after exercise or during the PEM phase. Thus, the severity of hypovolemia and its contribution to PEM may currently be underestimated. By worsening tissue perfusion, hypovolemia may both aggravate and prolong PEM. The hypotheses presented here are conceptual and require confirmation through appropriate clinical investigations.

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