Research reveals it involves:

Simplified sequence:

1. **Autoantibodies** impair vascular control (β_2 & M3/M4).
2. **Vasoconstriction** and microcirculatory shunting reduce blood and oxygen flow.
3. **Hypoxia** forces anaerobic metabolism → lactate, acidosis, ROS.
4. **Hypovolaemia** → poor cerebral/muscular perfusion.
5. **Calcium overload** damages mitochondria and muscle fibres.
6. **Bradykinin** increases vascular leak and disrupts **RAAS** → salt loss, hypovolaemia. Crosses the BBB, amplifying pain and neuroinflammation
7. **Neuroinflammation** from microglial activation worsens autonomic and vascular control.
8. **Feedback loop** locks the system into energy failure → PEM.

Together, these malfunctions could create the chaotic autonomic storm typical of ME - unstable heart rate, erratic blood pressure, poor circulation, and profound fatigue. This has resulted in some cases of sudden death.

The Role of Bradykinin in ME

Based on the Scheibenbogen and Wirth model, in which vascular dysfunction and endothelial leak are central to ME, bradykinin dysregulation may act as one of the key amplifiers of this vicious cycle. When the endothelium (the lining of blood vessels) becomes damaged or leaky, bradykinin can escape regulation - intensifying inflammation, pain, and vascular instability.

Reducing its excessive effects - through kallikrein inhibition, endothelial stabilisation, or microglial suppression - could theoretically help reduce brain fog, pain, orthostatic intolerance, and post-exertional worsening in ME.

Bradykinin and the Blood–Brain Barrier (BBB)

Bradykinin normally acts within the peripheral circulation, but during cytokine surges, oxidative or nitrosative stress, or endothelial injury, the blood–brain barrier (BBB) can become more permeable. observed in ME patients. Once breached, bradykinin can directly activate B2 receptors (B2R) on endothelial cells and neurons within the central nervous system.

This initiates neuroinflammatory and vasogenic effects that align closely with the post-exertional symptom exacerbation.

Major Effects of Bradykinin Within the CNS

1. **Neuroinflammation**

Bradykinin activates microglia and astrocytes, triggering the release of inflammatory mediators such as IL-1β, TNF-α, and nitric oxide. These mediators produce headache, malaise, cognitive dysfunction, and the 'sickness behaviour' typical of ME during post-exertional crashes.

2. **Vasogenic oedema and impaired cerebral perfusion**

Bradykinin increases capillary permeability, leading to fluid leakage and local swelling. This disrupts cerebral autoregulation and worsens hypoperfusion already observed in ME brain imaging. Clinically, this may manifest as pressure headaches, dizziness, blurred vision, or orthostatic intolerance.

3. **Altered neurotransmission**

Bradykinin modulates glutamate and GABA systems, increasing neuronal excitability. Overactivation of NMDA receptors and excessive calcium influx can cause cognitive overstimulation, sensory hypersensitivity, and the "wired but tired" state frequently reported by patients.

4. **Pain amplification**

Bradykinin sensitises both peripheral and central pain pathways, contributing to widespread pain, allodynia, and hyperalgesia - symptoms often overlapping with fibromyalgia.

5. **Autonomic disruption**

In the brainstem and hypothalamus, bradykinin can interfere with baroreceptor and cardiovascular control centres, potentially worsening postural tachycardia, blood pressure instability, and temperature dysregulation.

Bradykinin dysregulation can act as a critical downstream amplifier. Once it penetrates the central nervous system, it transforms a primarily vascular disorder into a neurovascular and neuroinflammatory condition, bridging immune, vascular, and neurological domains.

Recognition of the pathophysiology of ME by medical professionals is critical for the survival of the severe patient.

Ref: https://www.nice.org.uk/guidance/ng206

All relevant published papers are available online.

Myalgic Encephalomyelitis (M.E.).

Pathophysiology

Jenny Wilson
(Associate Member, Doctors With ME)

ME/CFS is-

'…low output heart failure secondary to mitochondrial failure… Both macrocirculatory and microcirculatory factors have been shown to impair organ perfusion in ME/CFS. The end result of the above-described cascade may be a crisis in the cells of the skeletal muscles, heart, brain, kidney, endocrine, and other systems.'

Journal of the American College of Cardiology, 2021

Myalgic Encephalomyelitis (ME/CFS) is a documented serious multisystem neuroimmune-endocrine-cardiovascular disease with autoimmune features. The Quality-of-Life scores are lower than those of all the major chronic diseases with which it has been compared (Hvidberg, 2015). It is also a potentially fatal disease, especially if medically mismanaged. Its defining symptom is Post-Exertional Malaise (PEM), a delayed exacerbation of the disease's major symptoms following minimal physical or cognitive activity. Failure to recognise its biomedical pathology constitutes a foreseeable risk of patient harm, and even death, and a potential regulatory breach with legal consequences.

Research and Autopsy Evidence

By the late 20th century, biomedical researchers had established that ME was a systemic physiological illness characterised by profound disturbances in cardiovascular, autonomic, and metabolic function. Studies revealed chronic, measurable instability: a lowered anaerobic threshold, neuroinflammation, immune dysregulation, hypovolaemia, muscle abnormalities, impaired cardiac filling, autonomic dysregulation, endothelial dysfunction, gastrointestinal dysfunction, and reduced oxygen utilisation during exertion. Each successive study reinforced the concept of ME as a disease of pathological energy limitation, rooted in circulatory and mitochondrial dysfunction.

Since 1956, autopsy evidence has revealed serious, measurable pathology. All point to a consistent pathophysiological pattern: widespread microvascular inflammation, autonomic and diencephalic involvement, and multi-organ stress culminating in metabolic and circulatory collapse. These autopsies confirm that ME is a systemic biomedical disease with discernible tissue pathology. Dorsal root ganglionitis the length of the spinal cord has been repeatedly reported, accounting for the extreme sensitivities to light, sound and touch. A recent conference report on seven autopsies described how all the Corticotropin-releasing hormone (CRH) receptors on the hypothalamus and pituitary of all seven who had died with/of ME were missing, perhaps illustrating the findings of de Bellis et al.'s paper, 2021, that reported autoantibodies targeting the HPA axis in ME. In 2025, Polo et al published their findings that ME patients had low vasopressin, thereby causing a diabetes insipidus-like condition resulting in polyuria and hypovolaemia, thereby providing further support to the 20th-century observations that ME patients are hypovolaemic.

Hypovolaemia, often severe, is common in ME

Nearly four decades after Dr David Bell and Dr David Streeten documented profound hypovolaemia in patients with ME, contemporary research continues to demonstrate severe circulatory impairment, especially in the most affected individuals. Vink et al reported in their 2025 paper that in severe ME, cerebral hypoperfusion can be less than 50% of normal. This can account for the swallowing problems experienced by patients. Bell also proposed that chronic hypovolaemia increases blood viscosity, which may explain the elevated risk of thrombotic and cardiac events, including strokes, seen in ME patients.

ANS dysfunction of hypovolaemia causes intestinal failure

Given the autonomic features of ME, assessment of blood volume and orthostatic cerebral blood flow is particularly important in patients with chewing or swallowing difficulties. Dysphagia may arise in part from reduced blood flow to brainstem regions that control the upper gastrointestinal tract. In severe cases, chronic hypoperfusion of the gut can lead to life-threatening malnutrition if interventions like tube feeding or total parenteral nutrition (TPN) are delayed or withheld. Routine assessment of blood volume and cerebral perfusion could, therefore, be life-saving for patients with severe autonomic dysfunction. While nuclear medicine facilities are not readily available to all, doctors should not make the error of using blood markers to assess dehydration or the degree of hypovolaemia in these patients, as probably

happened in the well-known case of Maeve Boothby O'Neil. Hypovolaemia is a universal feature in this disease, especially in severe patients. Their inability to sit up and difficulties swallowing are strong indicators of hypovolaemia, requiring the daily administration of 2-3 litres of IV saline.

Poor perfusion helps explain many hallmark symptoms of ME, including extreme fatigue, post-exertional malaise, POTS, NMH, cognitive impairment, dizziness, and dysphagia.

Professors Scheibenbogen and Wirth ME Research

Recent work by Professors Scheibenbogen, Wirth et al, has elucidated autoantibody-mediated dysautonomia, bradykinin-mediated RAAS suppression, endothelial leakage, and chronic hypovolaemia, providing a coherent mechanistic framework that mirrors earlier 20th-century clinical insights.

In a subset of patients, Scheibenbogen found β_2-adrenergic receptor (β_2-AR) dysfunction, driven by autoantibodies that disrupt vascular and autonomic regulation. These antibodies - along with those targeting muscarinic M3/M4 receptors - destabilise the fine control of blood vessel tone, leading to:

- *Arteriovenous shunting* (blood bypassing capillaries),
- *Microvascular constriction and endothelial leak*,
- *Hypovolaemia and low cardiac preload*,
- *Sympathetic overactivation and parasympathetic underactivity*.

These processes are thought to impair oxygen delivery, resulting in local tissue hypoxia, and energy failure – consistent with the hallmark symptoms of ME: post-exertional malaise, orthostatic intolerance, cognitive dysfunction, and widespread pain.

Scheibenbogen and Wirth"s clinical findings include:

- *Low atrial, ventricular, and vascular filling pressures* (as noted earlier by P.Cheney),
- *Suppressed RAAS activity, contributing to hypovolaemia*
- *Increased bradykinin and capillary leak, leading to further salt and fluid loss.*

Together, these mechanisms depict ME as an **autoimmune, vascular, and metabolic disease** described as an *Acquired Ischaemic*

Mitochondrial Myopathy (AIMM) characterised by endothelium damage, neuroinflammation, and bioenergetic collapse.

Professor Klaus Wirth's Mechanistic Contribution

Professor **Klaus Wirth** joined forces with **Scheibenbogen** after she discovered β_2-adrenergic autoantibodies in an ME subset. Together, they developed a mechanistic explanation showing how these immune attacks on blood vessel control lead directly to muscle cell damage.

Wirth's key insights:

- Reduced vasodilation in skeletal muscle leads to poor blood flow and oxygen shortage during exertion.
- This lack of oxygen, combined with disrupted receptor signalling, impairs the sodium-potassium pump (Na^+/K^+-ATPase) – this could allow sodium to build up inside cells.
- The imbalance potentially reverses the sodium - calcium exchanger (NCX), forcing toxic calcium into the cell instead of out.
- Calcium overload is toxic and damages mitochondria, disrupts ATP energy production, and triggers inflammation.
- Repeated stress causes microinjury and incomplete muscle repair - a pattern confirmed in biopsies and by metabolic tests showing spikes in creatine and other muscle breakdown products after exertion.

Wirth's proposed ionic cascade shows how immune-driven vascular dysfunction could lead to cellular energy failure - the biological underpinning of post-exertional malaise.

Proposed Hypothetical Mechanistic Chain:

Autoantibodies → receptor dysfunction (β_2-AdR, muscarinic receptors) → autonomic and endothelial dysregulation → low blood volume and microvascular constriction → impaired oxygen delivery → mitochondrial failure and ionic collapse in muscle (Na^+ accumulation, Ca^{2+} overload) → structural microinjury → post-exertional malaise and multi-system symptoms.

PEM Explained

PEM, the defining diagnostic marker for ME, is a *metabolic, vascular, and neuroimmune collapse* triggered by exertion