

## **What is PEM in Myalgic Encephalomyelitis?**

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*NOTE: For the avoidance of doubt and to prevent any confusion, this article refers to Myalgic Encephalomyelitis (ME) and not to Chronic Fatigue Syndrome (CFS), as some mental health professionals deem "CFS" to be synonymous with ME but simultaneously to be synonymous with "chronic fatigue".*

Post-exertional malaise, known as PEM, is a cardinal feature of ME, but what exactly is PEM?

PEM is not fatigue. It is the consequence of impaired nitric oxide signalling, endothelial dysfunction and failure of blood flow regulation.

The result is inadequate oxygen delivery, metabolic collapse, and a reactive immune sequence that peaks 24-48 hours after exertion.

### Why ME patients "crash" after even trivial exertion

Soluble guanylate cyclase (sGC) is the receptor for nitric oxide (NO) in vascular smooth muscle. The NO-sGC pathway is essential for regulating blood flow, maintaining vascular homeostasis, supporting neuronal signalling, and controlling inflammation.

In healthy people, exertion increases tissue demand; endothelial cells release NO which activates sGC and blood vessels dilate to deliver oxygen as needed.

In ME, this pathway is malfunctioning. Research shows clear evidence of endothelial dysfunction -- see the published work of Dr Vance Spence, Senior Research Fellow, Section of Vascular Medicine, Department of Medicine, Ninewells Hospital and Medical School, Dundee, who looked at arterial stiffness and inflammation in people with ME and found abnormally high levels of free radical by-products and C-reactive protein in patients but not in controls. C-reactive protein levels were significantly correlated with increased arterial stiffness. The logical consequences of increased arterial stiffness are exercise intolerance and diastolic (cardiac) dysfunction.

Transcutaneous aortovelography/arteriographs via Doppler screening confirm very much reduced oxygenation levels, perfusion and pulsilities, with an abnormal pattern in the function of blood vessels. There is a lack of endothelial-derived NO availability, with reduced nitric oxide diffusion from endothelial cells to smooth muscle cells in blood vessels, resulting in impaired blood vessel relaxation and reduced oxygen delivery at both systemic and microcirculatory levels. As a result, there is insufficient blood flow to provide tissue demands resulting from even modest exertion.

This mismatch has two phases:

**During exertion**, tissues switch prematurely to anaerobic metabolism. Lactate and oxidative stress build up, while blood vessels fail to dilate.

**After exertion**, the immune system reacts to this metabolic distress. Oxidative and nitrosative stress further blunt sGC activity. Inflammatory mediators peak 12-24 hours later, worsening vascular stiffness and micro-clotting.

The outcome is PEM. It is not simple fatigue, but a delayed systemic "crash", with ME patients facing the combined effects of inadequate perfusion, metabolic injury, and immune activation.

A "crash" is not a "false belief" in exhaustion: it is a pathological failure of blood flow and energy delivery, leaving ME patients struggling to function after activities that would be trivial for a healthy person.