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Invited Review Article

Attenuating post-exertional malaise in Myalgic encephalomyelitis/chronic fatigue syndrome and long-COVID: Is blood lactate monitoring the answer?

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Lactic acid is a by-product of anaerobic metabolism that is quantified by assessing concentrations of lactate within the blood. Blood lactate has long been used in sports medicine as a surrogate marker of anaerobic thresholds and is commonplace in elite sports. Equally, there is potential to monitor anaerobic thresholds in chronic disease states where impaired oxygen delivery to cells and mitochondrial dysfunction are features of the disease process.[1] Factors associated with increased concentrations of blood lactate have been explained elsewhere[2] but include oxygen delivery, mitochondrial capacity, and the ability to clear and utilize lactate by other cells throughout the body. Lactate ($C_3H_6O_3$) originates from accumulating pyruvate ($C_3H_4O_3$), an important substrate in metabolic pathways during both anaerobic (metabolic activity that occurs in the absence of oxygen) and aerobic (in the presence of oxygen) exercise.[3] The development and validation of portable blood lactate monitors[4] that use small amounts of blood (>0.7 microliters), have made monitoring blood lactate an accessible and popular tool for athletes and coaches to monitor the responses to exercise and/or training.

Lactate monitoring has the potential to extend beyond applied sports settings and could be used to monitor the physiologic and pathophysiological responses to external and internal stimuli in chronic disease areas such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Post-COVID syndrome or Long COVID. It is applicable due to the recurrent, episodic and often disabling post-exertional symptom exacerbation (PESE) otherwise referred to as post-exertional malaise (PEM) which is a

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characteristic symptom of ME/CFS and Long COVID that can last for days (mostly) and/or weeks (rarely).[5] Whilst a dearth of understanding remains in the pathophysiologic mechanisms in these conditions[6] PEM/PESE is associated with an abnormal response and worsening of symptoms that includes loss of physical and mental stamina, rapid muscular, and cognitive fatigability following physical, cognitive, emotional, and orthostatic exertion.[7] PEM/PESE is associated with a slow return to baseline which can last for several days or even weeks and has a significant impact on functional status and quality of life. Detail pertaining to the mechanisms is outside the scope here, but relates to the transport, delivery, and utilisation of oxygen within skeletal muscles, thus affecting aerobic and anaerobic contributions to the provision of energy at a cellular level. It is postulated that anaerobic thresholds are reduced in athletic populations with Long COVID which the authors attribute to virally mediated mitochondrial dysfunction that extends beyond expected post-viral infection deconditioning and could be caused by impaired tissue oxygenation and substrate oxidation.[8] In context, structural and mechanistic impairments result in reduced total aerobic contribution and increase the reliance on anaerobic provisions which is time limited. It is plausible that patients with ME/CFS and Long COVID could be working anaerobically at markedly lower intensities compared to healthy controls (Fig. 1). Whilst lactate is not responsible for reduced muscular function[9] and can be elevated in numerous clinical situations,[10,11] in the context of mild exertion in patients with ME/CSF and Long COVID accumulating lactate levels are a biomarker of abnormally increased anaerobic activity which is used to supplement metabolic activity/energy production. Therefore, monitoring blood lactate levels could be used effectively to monitor metabolic disturbance and regulate pacing strategies in patients with chronic diseases that are compounded by PESE and PEM. Furthermore, this approach can also determine and monitor the metabolic responses at a mitochondrial level in response to potential therapies for Long COVID and ME/CSF which target improved a) oxygen delivery to cells and b) improving intrinsic mitochondrial function.[12]

A secondary impact of PEM/PESE is to withdraw from social and economic activities that form an important part of each person's identity.[13,14] In the absence of detailed mechanistic understanding and effective therapeutic approaches, there is a need to develop effective management strategies that allow patients to plan, monitor and adjust their activities of daily life. In time, blood lactate monitoring could be used alongside pharmacological treatments for Long COVID & ME/CSF to safely and effectively increase functional capacity through the design and implementation of informed and objective interdisciplinary rehabilitation programs.[15,16] However, we are aware that more detailed rehabilitation recommendations are needed which should be informed by a greater understanding of the complex, multi-system nature of ME/CFS and Long COVID.

Lactate monitoring presents an opportunity to support those living with ME/CFS and Long COVID, by allowing patients and practitioners to determine the intensity and anaerobic contribution to everyday tasks which could aid the development of pacing strategies that prevent PEM/PESE. Approaches that are widely used in the exercise sciences,[17,18] should be considered and tested for use in chronic disease settings whilst research into therapeutics for Long COVID and ME/CSF is ongoing.

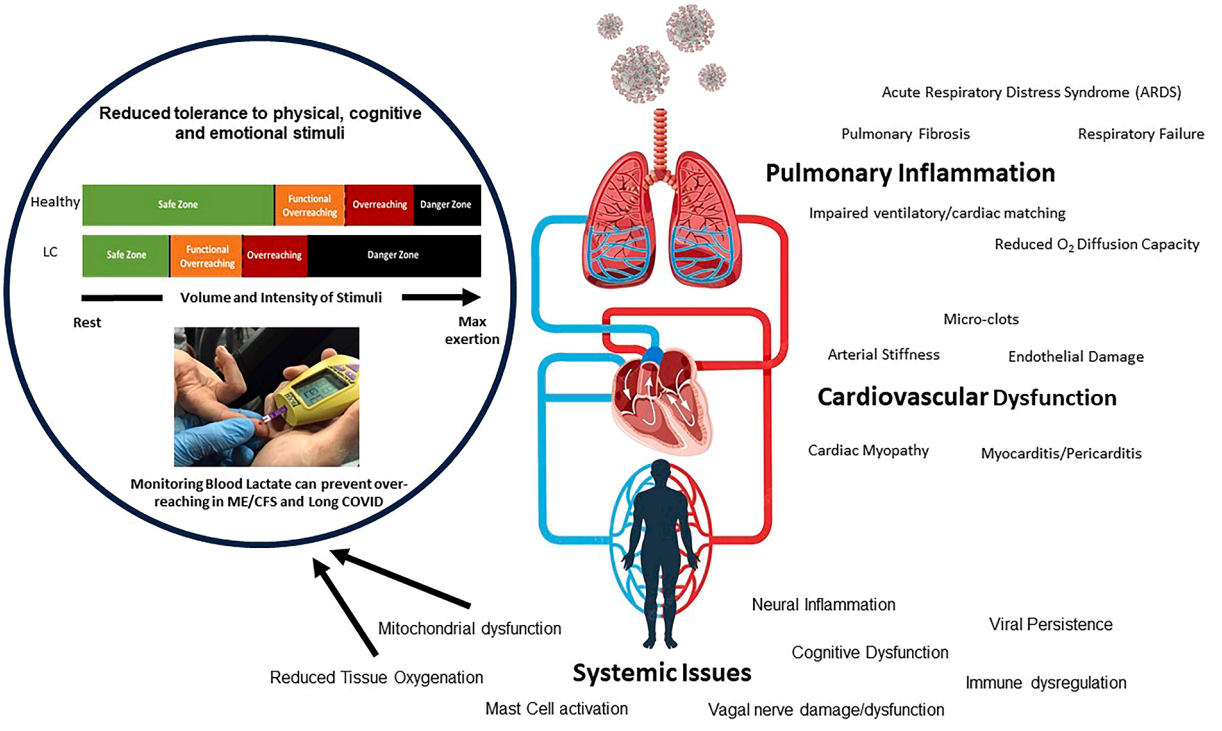

Fig. 1. A visualisation of proposed mechanisms of impaired metabolic function and the impact upon aerobic and anaerobic metabolic activity.

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Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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