

**Title:** Profiling plasma metabolites during fatiguing exercise: Searching for metabolic markers of fatigue

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**Purpose:** The primary mechanisms leading to muscular fatigue have long been debated. The purpose of this study was to examine the plasma-metabolite profile at the point of fatigue, with the aim of identifying novel metabolites involved in the onset of fatigue during exercise.

**Methods:** Twenty-one young ( $25.8 \pm 4.9$  yr), non-obese male ( $n=12$ ) and female ( $n=9$ ) participants completed a Time to Fatigue (TTF) trial at a constant work-rate corresponding to 110% of work-rate at Ventilatory Threshold 1 (VT1). Blood was sampled via finger prick pre-exercise, at 15 min intervals during exercise, at fatigue, and 10min post-exercise. Blood was aliquoted into two containers, one for analysis of blood-pH, lactate, glucose, calcium, sodium and potassium, while the remainder was centrifuged and the plasma assessed using metabolomics.

**Results:** 76 unique metabolites were identified in the metabolomic analysis. Principal component analysis identified lactate, fatty acids (oleic acid, octadecenoic acid, octadecadienoic acid and hexadecanoic acid), glycerol, alanine and urea as having the greatest effect on the development of fatigue. Follow-up statistical analysis revealed that these metabolites demonstrated a significant change in concentration between the pre-fatigue and the fatigue sample. Six metabolites were identified as having the greatest effect between male and females (lactic acid, urea, glycerol, glucopyranose, valine and glucose), however none of these reached significance.

**Conclusions:** Plasma fatty acid concentrations were identified as contributing the greatest to the fatigue profile, indicating that the role triglyceride mobilisation to the development of fatigue warrants further study. No significant differences in the plasma metabolite profile during fatiguing exercises between males and females or individuals with differing  $VO_2$  peak values were identified, however the duration of exercise caused significant alterations in the plasma metabolite profile.