Physical inactivity does not explain reduced exercise capacity in long COVID and ME

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Study Aims

1. Compare whole body exercise capacity in long COVID and ME to healthy people undergoing 60-days of strict bed rest
2. Differentiate skeletal muscle adaptations in long COVID and ME from those seen after bed rest

Background + Methods

- Myalgic encephalomyelitis (ME) and long COVID (LC) are diseases typically characterized by decreased exercise tolerance and post-exertional malaise (PEM), which is the worsening of symptoms following exertion.
- We recently observed skeletal muscle abnormalities in LC that can explain muscle fatigue and PEM.
- Many ME and LC patients live sedentary lives to avoid PEM and PEM relapses.
- Physical inactivity impairs skeletal muscle form and function, but how physical inactivity contributes to skeletal muscle alterations and exercise capacity in ME and LC has not been studied.

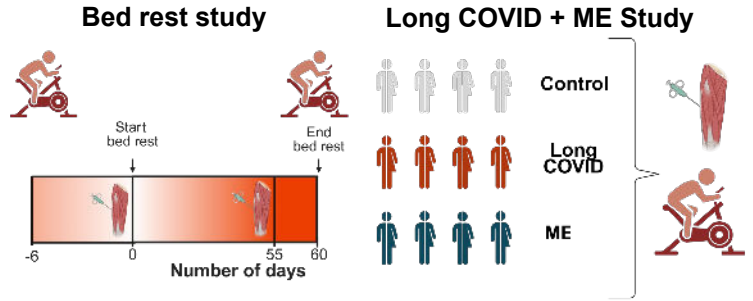


Fig 1: Participants from the AGBRESA bed rest study underwent 60 days of strict bed rest. LC and ME patients were recruited through outpatient clinics at the Amsterdam UMC. All participants had biopsies taken from the vastus lateralis, which were used to assess mitochondrial function, muscle capillarization and fibre cross-sectional area. All participants performed cardiopulmonary testing to assess whole body exercise capacity.

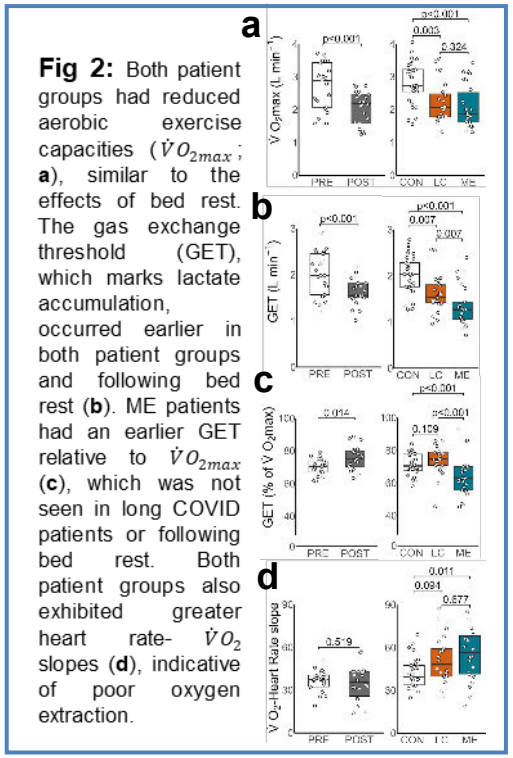


Fig 2: Both patient groups had reduced aerobic exercise capacities ($\dot{V}O_{2max}$; **a**), similar to the effects of bed rest. The gas exchange threshold (GET), which marks lactate accumulation, occurred earlier in both patient groups and following bed rest (**b**). ME patients had an earlier GET relative to $\dot{V}O_{2max}$ (**c**), which was not seen in long COVID patients or following bed rest. Both patient groups also exhibited greater heart rate- $\dot{V}O_2$ slopes (**d**), indicative of poor oxygen extraction.

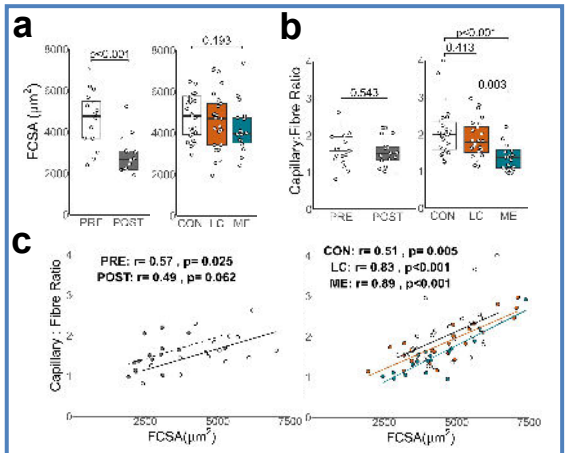
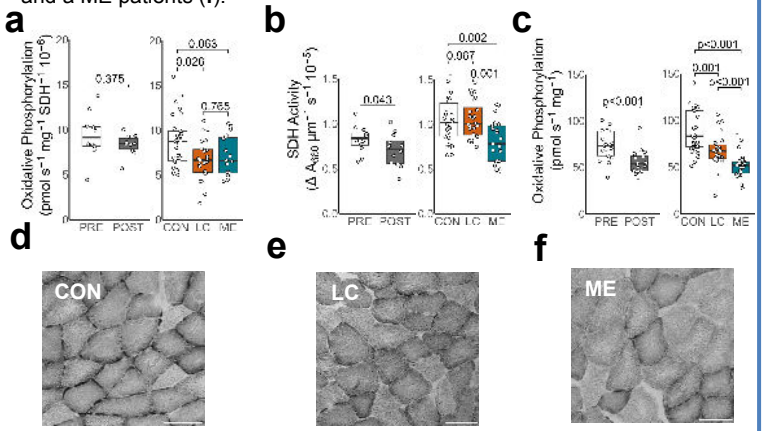


Fig 3: Strict bed rest resulted in severe reductions in muscle fibre cross sectional area (FCSA), while long COVID and ME patients had similar muscle FCSA compared to healthy controls (**a**). Bed rest did not alter capillarization, however ME patients had significantly less capillaries per fibre than healthy controls (**b**). Both patient groups had reduced capillarization for a given FCSA (**c**).

Fig 4: Mitochondrial respiration was reduced following bed rest, and both patient groups exhibited lower mitochondrial respiration compared to healthy controls (**a**). Succinate dehydrogenase (SDH) activity, an estimate for mitochondrial content, decreased following bed rest, while only ME patients had lower SDH activity than healthy controls (**b**). After normalizing mitochondrial respiration to SDH activity, both patient groups had reduced mitochondrial function, which was not seen following bed rest (**c**). Typical examples of SDH activity of a healthy control (**d**), a long COVID patient (**e**), and a ME patients (**f**).



Conclusions

- **Bed rest, long COVID and ME all result in a severe reduction in exercise capacity.**
- **ME patients have an earlier onset of lactate accumulation relative to their maximal aerobic capacity.**
- **Long COVID and ME patients have indications of poor oxygen extraction.**
- **Capillary supply for a given FCSA is lower in both patient groups, which may impair nutrient supply and waste removal from muscle.**
- **Bed rest results in reduced mitochondrial density, whereas intrinsic mitochondrial function is impaired in long COVID and ME patients.**
- **Physical inactivity cannot fully explain alterations in exercise capacity and skeletal muscle structure and function in patients with long COVID or ME.**