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# Innovative assessment of the metaboreflex using a dose-response curve with control of intramuscular metabolic perturbation in humans

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## Résumé

### Introduction

The metaboreflex plays a critical role in the cardiovascular adjustments occurring during exercise. While the post-exercise circulatory occlusion technique (PECO) is well-established, studies using this non-invasive methodology do not control for the level of intramuscular metabolites and usually investigate only one level of activation of the metaboreflex. The lack of control of the intramuscular metabolites is a key limitation in studies comparing groups, as exercising at a similar relative intensity does not guarantee identical concentrations of metabolites between individuals (and therefore similar levels of metaboreflex activation) (Hureau et al., 2021). Consequently, a specific test using a dose-response curve is necessary to better characterize an exaggerated or buffered metaboreflex in response to both maximal and submaximal stimuli. Considering the invasive nature of muscle biopsies, we propose to evaluate the intramuscular metabolite concentrations through the quantification of peripheral fatigue, which indirectly reflects the level of intramuscular metabolic perturbation (Hureau et al., 2022). This innovative approach to assess the metaboreflex will permit to evaluate the dose-response of the metaboreflex while controlling for intramuscular metabolic perturbation.

### Method

Twenty-six subjects (13 females) visited the laboratory 3 times to complete a familiarization and 2 experimental visits, to validate a dose-response test to assess the relationship between peripheral fatigue and metaboreflex activation, and assess its reproducibility. During each experimental visit, participants executed four exercise bouts interspersed with 2-min of PECO. Each fatigue task involved a sustained isometric contraction of the quadriceps at 20% of the maximal voluntary contraction during 1 min (bout 1), 2 min (bouts 2 and 3) and up to task failure (bout 4). To ensure a progressive accumulation of intramuscular metabolites throughout the test, intramuscular metabolites were trapped using PECO. Peripheral fatigue was assessed throughout the test via the pre-to-post exercise and post-PECO changes

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\*Intervenant

in quadriceps twitch force (Qtw). Mean arterial pressure (MAP) was continuously recorded non-invasively. The dose-response relationship between peripheral fatigue and MAP (i.e. the metaboreflex activation) was determined by plotting post-PECO peripheral fatigue against the % change in MAP during the last 30s of PECO. Reproducibility between the visits was assessed using the intraclass correlation coefficient (ICC) and Bland-Altman plots.

## Results

As expected by design, during both visits, Qtw was similar between post-fatigue task and post-PECO ( $P > 0.99$ ), indicating that PECO has successfully maintained exercise-induced intramuscular metabolic perturbation between each fatigue task. Peripheral fatigue and MAP increased progressively across the four bouts ( $P < 0.001$ ) confirming that our test induced four distinct levels of intramuscular metabolic perturbation and graded metaboreflex activation. Metaboreflex activation increased in a linear fashion with the level of intramuscular metabolic perturbation as evidenced by the significant correlation observed between Qtw and MAP ( $r^2=0.95$ ;  $P=0.02$ ). Qtw, MAP and their correlation were not statistically different between visit 1 and visit 2 (Qtw V1 vs V2:  $P=0.21$ ; MAP V1 vs V2:  $P=0.93$ ; MAP-Qtw correlation at V2:  $r^2=0.95$ ;  $P=0.02$ ; Fisher's r-to-Z test:  $Z=1.83$ ) and were associated with good to excellent reliability (ICC=0.91 for Qtw, ICC=0.77 for MAP). The bias for the Qtw was  $-0.2 \pm 0.8$  (upper limit,  $16.6 \pm 1.5$ ; lower limit,  $-17.1 \pm 3.0$ ). For the MAP, the bias was  $-0.3 \pm 1.4$  (upper limit,  $30.0 \pm 6.3$ , lower limit,  $-30.6 \pm 4.0$ ).

## Discussion and conclusion

Our test demonstrates that the metaboreflex is activated in a dose-dependent manner. This is supported by the strong linear relationship between the four distinct levels of intramuscular metabolic perturbation and the associated MAP responses during the PECO intervention. This relationship confirms the validity of this new approach, and the reliability indices show that the test provides consistent results across the visits. These findings provide evidence that evaluation of the metaboreflex needs to be reconsidered, in particular when between group comparisons are made.

## References

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