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# Skeletal muscle mitochondrial function cannot be properly inferred from PCr resynthesis without taking pH changes into account

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**MAGNETIC  
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3 **Skeletal muscle mitochondrial function cannot be**  
4 **properly inferred from PCr resynthesis without taking**  
5 **pH changes into account**

6 To the Editor:  
7

8 We have read with much interest the paper recently  
9 published by Khushu et al. regarding the impaired muscle  
10 metabolism in hypothyroid patients [1]. Although the results  
11 of this investigation are of potential interest, we are actually  
12 concerned about the utilization of the phosphocreatine  
13 recovery rate constant (kPCr) as a simple index of  
14 mitochondrial function and the corresponding conclusions  
15 regarding the impact of hypothyroidism on muscle metabo-  
16 lism during exercise. The real issue is actually to clearly  
17 determine whether one can infer about mitochondrial  
18 function on the basis of PCr rate constants measurements.

19 During recovery from exercise, PCr is resynthesized  
20 purely as a consequence of oxidative adenosine triphosphate  
21 (ATP) synthesis [2], and measurements of the kPCr have  
22 been used in order to characterize mitochondrial function in a  
23 variety of conditions [3]. However, several studies have  
24 clearly demonstrated that cytosolic pH has a strong influence  
25 [3]. It is actually well acknowledged that kPCr is inversely  
26 related to the extent of intracellular acidosis and PCr  
27 consumed [3]. In other words, a significant intracellular  
28 acidosis and a large PCr consumption in exercising muscle  
29 would be associated with a slower PCr resynthesis [3]. In the  
30 Khushu et al. study, cytosolic pH was found to be  
31 significantly lower after a 6-min constant-load plantar  
32 flexion exercise in hypothyroid patients compared to  
33 controls ( $6.95 \pm 0.02$  vs.  $7.02 \pm 0.06$ , respectively). Therefore,  
34 the conclusions of an altered mitochondrial function in  
35 hypothyroid patients [1] on the single basis of kPCr  
36 measurements have to be interpreted cautiously. Of note,  
37 several kinetic parameters are commonly used to describe  
38 PCr changes during exercise-to-recovery transition, includ-  
39 ing kPCr, the initial rate of PCr recovery (ViPCr) and the  
40 maximum aerobic capacity ( $Q_{max}$ ) [4]. These three  
41 parameters characterizing PCr resynthesis are correlated to  
42 oxidative capacity. However, in contrast to kPCr, ViPCr and  
43  $Q_{max}$  are insensitive to exercise intensity and end-of-  
44 exercise metabolic conditions [3]. On that basis, ViPCr and  
45  $Q_{max}$  should be considered as additional indices to compare  
46 the postexercise PCr recovery rate and mitochondrial

oxidative capacity across different populations when end- 47  
of-exercise pH and PCr concentration values are different or 48  
not taken into account. These additional parameters were 49  
considered in some previously published studies which 50  
investigated in vivo mitochondrial function from childhood 51  
to young and/or late adulthood [5,6]. In contrast, these 52  
parameters were not taken into account in other studies 53  
which investigated age-related changes in mitochondrial 54  
oxidative capacity from childhood to adulthood [7] and 55  
examined the association between mitochondrial alterations 56  
and insulin sensitivity in overweight and normal-weight 57  
children [8]. In the Khushu et al. study, the  $Q_{max}$  calculation 58  
was oversimplified as the product of kPCr and the resting 59  
[PCr], as previously described [9]. This oversimplification is 60  
actually derived from the calculation of the ViPCr from an 61  
exponential fitting. In that case, ViPCr is represented by the 62  
product of kPCr and the amount of PCr consumed at the end 63  
of exercise. On that basis, a few authors have calculated 64  
 $Q_{max}$  similarly to ViPCr, with the amount of PCr consumed 65  
being replaced by the resting [PCr]. Although mathemati- 66  
cally plausible, this calculation is not supported by any 67  
control model, and the corresponding  $Q_{max}$  is devoid of any 68  
enzymatic meaning, as it is the case for the calculation of 69  
 $Q_{max}$  using ADP within a Michaelis–Menten framework. 70  
This method is then largely questionable because it ignores 71  
the commonly accepted theory considering adenosine 72  
diphosphate as a key regulator of oxidative ATP synthesis 73  
[10]. In addition, with such an approximate calculation, 74  
 $Q_{max}$  becomes strongly dependent on kPCr and/or [PCr] 75  
measured at rest. In their study, Khushu et al. [1] reported no 76  
significant difference in the resting [PCr] values between 77  
hypothyroid patients and controls ( $43.6 \pm 0.8$  vs.  $42.0 \pm$  78  
 $1.0$  mmol kg<sup>-1</sup>, respectively). Given that the resting [PCr] 79  
values were similar, the corresponding calculated  $Q_{max}$  80  
values were lower in hypothyroid patients than in controls on 81  
the single basis of lower kPCr measurements in hypothyroid 82  
patients. Consequently, this result should be interpreted 83  
with caution. 84

85 Overall, it is of utmost importance to keep in mind that  
86 one cannot simply infer on mitochondrial function on the  
87 basis of measurements of the rate constant of PCr resyn-  
88 thesis given that end-of-exercise conditions have been  
89 shown to exert a strong influence. Future studies should  
90 then pay attention to these methodological inaccuracies  
91 which might hedge data interpretation and confound the  
92 corresponding conclusions.

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