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This information is current as of August 13, 2007 .

The following is the abstract of the article discussed in the subsequent letter:

**Stellingwerff T, LeBlanc PJ, Hollidge MG, Heigenhauser GJF, Spriet LL.** Hyperoxia decreases muscle glycogenolysis, lactate production, and lactate efflux during steady-state exercise. *Am J Physiol Endocrinol Metab* 290: E1180–E1190, 2006. First published January 10, 2006; doi:10.1152/ajpendo.00060.2007.— The aim of this study was to determine whether the decreased muscle and blood lactate during exercise with hyperoxia (60% inspired O<sub>2</sub>) vs. room air is due to decreased muscle glycogenolysis, leading to decreased pyruvate and lactate production and efflux. We measured pyruvate oxidation via PDH, muscle pyruvate and lactate accumulation, and lactate and pyruvate efflux to estimate total pyruvate and lactate production during exercise. We hypothesized that 60% O<sub>2</sub> would decrease muscle glycogenolysis, resulting in decreased pyruvate and lactate contents, leading to decreased muscle pyruvate and lactate release with no change in PDH activity. Seven active male subjects cycled for 40 min at 70%  $\dot{V}O_{2\text{ peak}}$  on two occasions when breathing 21 or 60% O<sub>2</sub>. Arterial and femoral venous blood samples and blood flow measurements were obtained throughout exercise, and muscle biopsies were taken at rest and after 10, 20, and 40 min of exercise. Hyperoxia had no effect on leg O<sub>2</sub> delivery, O<sub>2</sub> uptake, or RQ during exercise. Muscle glycogenolysis was reduced by 16% with hyperoxia (267 ± 19 vs. 317 ± 21 mmol/kg dry wt), translating into a significant, 15% reduction in total pyruvate production over the 40-min exercise period. Decreased pyruvate production during hyperoxia had no effect on PDH activity (pyruvate oxidation) but significantly decreased lactate accumulation (60%: 22.6 ± 6.4 vs. 21%: 31.3 ± 8.7 mmol/kg dry wt), lactate efflux, and total lactate production over 40 min of cycling. Decreased glycogenolysis in hyperoxia was related to an ~44% lower epinephrine concentration and an attenuated accumulation of potent phosphorylase activators ADP<sub>f</sub> and AMP<sub>f</sub> during exercise. Greater phosphorylation potential during hyperoxia was related to a significantly diminished rate of PCr utilization. The tighter metabolic match between pyruvate production and oxidation resulted in a decrease in total lactate production and efflux over 40 min of exercise during hyperoxia.

*Reply to letter “Pyruvate metabolism in working human skeletal muscle” by Henderson et al.*

*To the Editor:* We would like to respond to the letter to the editor written by Henderson et al. in this Journal's January issue (6). Our laboratory would have appreciated the chance to have immediately rebutted the original letter to the editor, but we were not made aware of it until its final publication. The aim of our study was to examine the effects of hyperoxia on decreasing muscle and blood lactate concentrations, and thus required lactate release measurements (10). In previous studies from our laboratory, we measured lactate release to account for the removal of three carbon units derived from glycolysis during exercise. This was based on existing literature, which showed that the majority of 3-carbon-unit release from exercising muscle was lactate, with concurrent pyruvate release being minor in comparison (1, 2, 7, 9). However, after reading the 2004 Henderson et al. paper (5) with much interest, which reported that working muscles released the same amount of lactate and pyruvate, we decided that both metabolites must be measured in order to get an accurate estimate of total carbohydrate-derived 3-carbon-unit release across the exercising muscle. However, contrary to Henderson et al. (5), we found nearly a fivefold greater net lactate release during exercise compared with pyruvate release. Unlike the recent letter to the

editor from Henderson et al., which surprisingly seems to focus only on pyruvate exchange across working muscles, we would like to further discuss the release of *both* pyruvate and lactate. This discussion is in line with the original Henderson paper, which states seven times “that working muscle releases similar amounts of lactate and pyruvate.”

In agreement with the Brooks laboratory, there is a paucity of data that examine the net exchange of pyruvate across working skeletal muscle in humans. Thus, very few data sets examine both pyruvate and lactate exchange simultaneously during exercise. To our knowledge, there are only four previous studies that have examined both pyruvate and lactate release in vivo in humans, and all four of those studies have reported greater net lactate release than pyruvate release during at least the first 90 min of exercise (1, 2, 7, 9). In fact, Henderson et al. even alluded to this in their original paper when they stated, “Others have shown significant muscle pyruvate release during exercise in dogs and humans (1, 9), although at most time points the net lactate release was greater than net pyruvate release.” Therefore, we stand by our original conclusions that the Henderson paper seems to be “at odds with the majority of published results” when pertaining to their conclusion that working muscle releases the same amounts of lactate and pyruvate.

When one methodically studies the paper from Henderson et al. (5), and their related paper that was published five years earlier (3), it becomes apparent that there are several ambiguous statements regarding the time course of their pyruvate and lactate release data, and there appear to be several methodological errors. First, since there are fluid shifts occurring between muscle and the vascular space during exercise, plasma protein, hemoglobin, and hematocrit are often used to provide a measure of relative changes in intravascular volume when applying the Fick equation. Unfortunately, there is no mention of whether this was done in the Henderson study (5). However, their companion paper (3) does mention that they used a hematocrit correction instead of using a plasma protein-based correction for changes in venous plasma volume. In fact, a hematocrit correction can cause such a disparity in the data that some refuse to accept that the hematocrit correction has any validity whatsoever as a measure of change in plasma volume (4). Second, when their two papers are closely examined (3, 5), it becomes apparent that pyruvate was measured in whole blood whereas lactate was measured in the plasma. To our knowledge, there are no data examining compartmental distribution of pyruvate. However, it is well established that the gradient for lactate between the plasma and the erythrocyte is ~2:1 (8). Since Henderson et al. (5) did not measure pyruvate and lactate in the same blood compartment, their comparisons of measured pyruvate and lactate concentrations in venous and arterial samples, leading to their calculated release data, become flawed. Although we did not explicitly state this in our paper (10), both pyruvate and lactate were measured in the same whole blood compartment and via the same methodology. Finally, in the Henderson paper, the assertion of equal pyruvate and lactate release is observed only during the last 15 min of the 60-min exercise bout. When the lactate and pyruvate release is back-calculated at each measured time point over the first 45 min of exercise from their two papers (3, 5), their data seem to be in closer agreement with the existing literature. During the first 45 min of exercise they show a 2.1- to 2.9-fold greater release of lactate than pyruvate. However, they did not report this in their paper.

In conclusion, after further examining the Henderson et al. study (5), we stand by our original conclusions, that “the findings of Henderson et al. (5) seem to be at odds with the majority of published results” and appear to be flawed by several analytical errors. Obviously, with the paucity of existing data, and the current conflicting results and interpretation, we hope that this discussion will encourage more scientific attention and properly conducted and controlled studies examining the metabolic production and release of both pyruvate and lactate from skeletal muscle.

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