Commentaries on Viewpoint: Evidence that reduced skeletal muscle recruitment explains the lactate paradox during exercise at high altitude

TO THE EDITOR: Noakes (5) and other authors have proposed that central motor command (CMC) and, consequently, exercise performance in hypoxia is determined by the following.

1) By simple negative feedback (1, 2) or complex feedback/feedback (4) subconscious homeostatic control systems that, based on different information from central and peripheral chemoreceptors, limit skeletal muscle recruitment to avoid dangerous brain deoxygenation (4), respiratory failure (2), or excessive locomotor muscle fatigue and pain (1), or

2) by the direct negative effects of severe brain hypoxia on maximal voluntary CMC and/or motivation to exercise (1, 6).

However, these authors have overlooked a third possibility, which, in our opinion, is simpler and biologically more plausible. Indeed, it is well established that the sensation of respiratory effort increases when ventilation is reflexly stimulated by hypoxia. According to our psychobiological model of exercise performance based on Brehm’s motivational intensity theory (3), this perceptual effect of hypoxia can increase overall perceived exertion and cause subjects to disengage from a task (which, in physiological terms, means a sudden reduction in CMC and exhaustion) earlier than in normoxic conditions even assuming no effect of hypoxia on motivation to exercise. During time trials, subjects are able to compensate for the increased sensation of respiratory effort by voluntarily reduce power output. This behavioral strategy maintains overall perception exertion within normal limits to ensure successful completion of the time trial despite hypoxia. Future studies need to control for rival hypotheses and establish experimentally which of the above three models is the most valid explanation for reduced CMC and exercise performance in hypoxia.

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REDUCED SKELETAL MUSCLE RECRUITMENT DOES NOT EXPLAIN THE LACTATE PARADOX—PART I

TO THE EDITOR: Although Dr. Noakes (4) affirms that the results of previous—not his own—studies (1, 2) support his visions, his argumentation appears to be dissociated from those data. He obviously ignores clear findings and claims, entirely un-
founded, that “the studies of Amann et al. (1, 2) provide the final evidence necessary to solve the ‘lactate paradox’.” However, we argue that the data from these authors actually refute his claim. First, although 5-km cycling time-trial exercise (workload voluntarily adjustable) in acute moderate hypoxia was characterized by a lower level of skeletal muscle recruitment (and power output) compared to that measured in normoxia, end-exercise capillary blood lactate (\([L_a - B]\)) values were almost identical in both conditions (1). Second, at exhaustion following high-intensity constant workload cycling exercise in acute moderate hypoxia vs. normoxia, the levels of end-exercise skeletal muscle recruitment and \([L_a - B]\) were identical, despite the shorter exercise time in simulated altitude (2). Third, the debilitating effects of acute severe hypoxia on the CNS led to the voluntarily termination of constant-workload exercise within only 2 min (2). This short-duration exercise was accompanied by a substantial level of end-exercise peripheral fatigue. Although skeletal muscle recruitment was lower at exhaustion in acute severe hypoxia vs. normoxia, the comparison of end-exercise \([L_a - B]\) values is irrelevant since exhaustion in acute severe hypoxia was reached after only 2 min—a duration too short to reach a lactate equilibrium in capillary blood (5). Finally, the idea that the three “paradoxes” may be explained with one theory seems at odds with findings of normal lactate concentrations but reduced heart rates (3). Combined, these data clearly contradict Noakes’ claims.

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REDUCED SKELETAL MUSCLE RECRUITMENT DOES NOT EXPLAIN THE LACTATE PARADOX—PART II

TO THE EDITOR: The “lactate paradox” is defined as “reduced blood lactate concentrations during submaximal and maximal exercise following acclimatization to high altitude.” Dr. Noakes claims that the data of Amann (1, 2) “solve the lactate paradox” (5). This postulate, however, is unsubstantiated since it ignores the real data (see Part I by M. Amann, above) and wrongly refers to data only from maximal exercise. Instead, the “paradox” seems to be due to changes in relative exercise intensity since the “paradox” is absent when comparing same relative workloads at sea level vs. acute hypoxia (4). Also, since increases in \(C_aO_2\) do not (3), but increases in \(\Delta aO_2\) and \(P_aO_2\) do (1, 2) lead to further muscle recruitment and increased exercise performance in severe hypoxia, \(P_aO_2\) can be viewed as the dominant determinant of central fatigue at extreme altitudes (1, 2). With chronic exposure to altitude, \(C_aO_2\), and \(P_aO_2\) increase (3) and this adaptation might lead to additional muscle recruitment in the face of even lower end-exercise lactate values compared with acute severe hypoxia. In conclusion, reduced maximal blood lactate concentrations at extreme altitudes might not reflect the reduced potential for glycolytic energy production, but rather—as assuming Noakes is in part right—that the maximal attainable lactate concentration is reduced because exercise is terminated due to different fatigue patterns at these extreme altitudes (1, 2). If, at the same time assuming that our research group is right by claiming that lactate is reduced during submaximal exercise because of changes in exercise intensity (i.e. no “lactate paradox”), then the issue seems solved.

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ORIGIN OF THE LACTATE PARADOX: MUSCLES OR BRAIN?

TO THE EDITOR: Noakes proposes, without giving evidence, that the so-called lactate paradox (LP) seen in chronic hypoxia is due to reduced muscle recruitment imposed by a central nervous system governor that, sensing its imminent demise, shuts down \(O_2\) transport and muscle contraction to protect itself from dangerous hypoxia (3). He focuses on lactate at maximal exercise, but the LP is manifest just as clearly over the entire exercise range from rest to exhaustion by the initially elevated lactate-\(VO_2\) relationship in acute hypoxia (near) falling back to its normoxic sea level trajectory after acclimatization—despite persistent hypoxemia (4). He does not address this. Note that because in acute hypoxia, maximal lactate is as high as at sea level (2, 4), the LP depends completely on this return of the lactate-\(VO_2\) relationship to its sea level configuration after acclimatization.

We do agree that, upon acclimatization, maximal lactate falls progressively with increasing altitude because maximal power output falls progressively with increasing altitude. However, we disagree on the physiological mechanism of the reduced maximal power output. There is much evidence...
from studies in intact humans (5), as well as in isolated perfused contracting muscles where the brain has no influence (1), that reduced maximal power output reflects limits to muscle O₂ availability caused by finite O₂ transport system conductance.

Additionally, Noakes’ viewpoint implies that cerebral O₂ availability is a function of exercise intensity—that some level of exercise is reached at which the brain ceases to receive enough O₂, directing the legs to quit. Is there evidence for that?

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TO THE EDITOR: It appears that the cerebral metabolism and motor function of the human brain become deteriorated if the average cerebral mitochondrial oxygen tension is reduced by more than ~7 mmHg (5). This may occur during acute exposure to strenuous exercise at high altitude and central fatigue seems be a main factor influencing performance and muscle recruitment during such exercise conditions (1, 5). However, this does not provide the complete explanation for the lactate paradox. Thus peak lactate levels following maximal exercise with an incremental protocol seem to be unaffected during acute exposure to severe hypoxia (3), whereas maximal constant load cycling resulting in exhaustion after 5–6 min is reported to be associated with lower blood lactate levels at the point of exhaustion (2). Therefore, blood lactate levels following maximal exercise may depend on the applied exercise protocol and it should be considered that blood lactate only provides indirect information about the metabolic state of the skeletal muscles and it is not a particular good indicator of the functional state of the skeletal muscle. It is correct that hypoxia may impair muscle recruitment and that the physiological determinants of exercise performance may switch from a predominantly peripheral origin to a hypoxia-sensitive central component of fatigue. However, the physiological explanation for the lactate paradox may be a little more complex than the one provided by Noakes (4).

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REDUCED SKELETAL MUSCLE RECRUITMENT DOES NOT EXPLAIN THE LACTATE PARADOX

TO THE EDITOR: In his paper Dr. Noakes (1) forwards the interesting hypothesis that the “lactate paradox” observed during altitude acclimatization may be due to a reduced maximal “muscle recruitment,” possibly aimed at “protecting” cerebral oxygenation. Two pieces of evidence, gathered by our group during the Pyramid (5,050 m above sea level) expeditions in the 1990s, would be against such an hypothesis. In those experiments (2) we observed a clear lactate paradox: with incremental exhausting cycloergometric exercises, peak blood lactate concentration ([La]b peak) fell from 11.5 ± 2.2 (mM, x ± SD) before the expedition to 8.0 ± 3.3 and 6.3 ± 0.9, respectively, after 1 and 5 wk at altitude. The lower [La]b peak was associated with lower peak workload and peak heart rate (35% and 25 beats/min lower, respectively, vs. pre-expedition), apparently in agreement with Dr. Noakes’ hypothesis. Interestingly enough, however, when the same study (2) experiments were repeated weekly during the first month after return to sea level. In the presence of peak workload values only ~7% lower than pre-expedition, [La]b peak was significantly lower than pre-expedition for 2 wk (8.0 ± 1.9 and 9.4 ± 1.7 mM, respectively). Thus the lactate paradox developed during 5 wk of acclimatization to 5,050 m, persisted for a few weeks after the subjects returned to sea level, and was not directly related to the reduced peak workload.

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ORIGIN OF THE LACTATE PARADOX: MUSCLES OR BRAIN?

PART II

TO THE EDITOR: The Viewpoint by Timothy Noakes (2) on the lactate paradox at altitude is mainly based on the central governor
model that postulates that the extent of muscle recruitment by the central nervous system is determined by the need of the brain to protect itself and the body by ensuring the maintenance of integrity, during and after exercise. In the context of the neuromuscular system in vivo there are so far any known evidence that reduced skeletal muscle recruitment explains the lactate paradox during exercise in hypoxia. It looks like an oversimplification to consider such a link. While our research group is in favor of a progressive central contribution to muscle fatigue prior to the moment of task failure at sea level (3, 4), the full explanation for the so-called lactate paradox at altitude is likely more complex. Decreased cerebral oxygenation might reflect reduced central motor command at volitional fatigue in response to global (3, 5) and local (4) exercise with reduced skeletal muscle recruitment in hypoxia in cycling (1) but not during a local fatiguing exercise (4). Importantly we need to consider and better emphasize mechanisms underlying the lactate paradox. Working muscle beds can simultaneously produce and consume lactate, diverse tissues can produce lactate for consumption by working muscle, and the sympathetic nervous system greatly influences carbohydrate metabolism at altitude. No longer can we regard lactate as a simple by-product of glycolytic energy production measured in the blood compartment.

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CEREBRAL CONTROL OF SKELETAL MUSCLE RECRUITMENT DURING EXERCISE AT ALTITUDE

TO THE EDITOR: Regulation of blood flow to the activated brain is different from the regulation of flow to working skeletal muscles. When the brain is activated by exercise, the increment in cerebral blood flow enhances cerebral oxygenation, whereas muscle oxygenation progressively decreases with work rate (3). A lower O2 availability does not influence cerebral uptake of lactate or glucose during exercise (5), whereas brain function deteriorates when its average oxygenation becomes reduced >10% (1, 3). A reduced skeletal muscle recruitment during high altitude exercise by less cerebral oxygenation is proposed as an explanation for the reduction in blood lactate levels during maximal exercise at altitude (2). We consider that acclimatization to high-altitude exposure gradually returns the initially reduced peak blood lactate accumulation during exhaustive exercise to values equal to those seen at sea level and equally during acute hypoxia at sea level (4). Thus, allowing lowlanders to accustom to altitude uncovers the transient nature of the “lactate paradox” (4). Where the brain decides when to slow down work rate, Noake’s choice for a reduced skeletal muscle recruitment by inadequate cerebral oxygenation seems attractive (2). However, considering that, e.g., increased skeletal muscle capillary density and a gradual increase in arterial O2 delivery capacity by elevation of hemoglobin are as well among the numerous undefined players in the cardiovascular adaptation to high altitude, this hypothesis may set a preliminary limit to their identification.

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TO THE EDITOR: Dr. Noakes (4) presents a view previously put but seemingly ignored “that heavy exercise at high altitude involving large muscle groups may be limited by a reduced central drive” (3). Although the existence of the lactate paradox is a common feature of many exercise physiology texts and has been recently debated (5), the evidence for the occurrence of this physiological phenomenon is indeed overwhelming. The issue, however, is not whether the lactate paradox occurs but rather what its likely cause might be. To answer this question, Dr. Noakes (4) attempts to pull together two other paradoxes that could provide the insights needed to explicate this physiological phenomenon. One, the overwhelming fatigue that develops at high altitude with low blood and muscle lactate concentrations and, two the observation that maximum cardiac output falls with increasing altitude. For the reduced maximum cardiac output when tissue oxygenation is lowest cannot occur to protect the muscle from desaturation as presumably this does not occur given the very low concentrations of blood and muscle lactate. This understanding is entirely consistent with findings that show that electromyographic activity is reduced as hypoxia increases (1) but more salient is that muscle twitch force is attenuated across the range of normoxia to severe hypoxia so that the major determinants of central motor output are most likely related to a hypoxia-sensitive central component of fatigue (1). If this were the case then the only logical explanation would be to reduce the
amount of skeletal muscle recruitment to protect the brain from the consequences of hypoxia (2).

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IT TAKES A BRAIN

TO THE EDITOR: In his commentary once again Noakes (3) emphasizes that the study of neuromuscular recruitment requires a brain. Beyond recognizing the obvious, the main criticism is that Reeves et al. (5) should have been referenced along with Kayser et al. (4) as being supportive of his position that central limitations can affect muscle power output at high altitude. Proceeding from the specific to the general, two sequels unfold. The first is that if one holds to a Pasteur effect and believes that lactate accumulation is the result of oxygen-limited metabolism, then the reduction in circulating lactate seen during maximal exertion at high altitude seems paradoxical (1). Instead, if one recognizes that muscle power output is reduced at altitude, then the reduction muscle recruitment results in decreased glycolytic flux and lactate production (5). The original finding of a Lactate Paradox (1) is highly reproducible if studies are adequately controlled (e.g., 4). However, it is to be recognized that in the absence of controls for dietary carbohydrate and energy, body mass, the extent of pre-study acclimatization, lack of statistical power analysis, and the like, not all can reproduce the Lactate Paradox (e.g., 2). By his reference to a “Lactate Paradox” Noakes calls our attention to the more encompassing concept of a Central Governor in regulating, and at times limiting various forms of athletic performances ranging from running at sea level to climbing the highest mountains. To some, exhortation to basic designs physiology may seem simplistic, but it is irrefutable that the motor cortex and higher centers control numerous organ systems. It is perhaps regrettable also that the brain’s role in exercise physiology has been overlooked. Admittedly, it is extremely difficult to assess central function during human exercise, but the presence of a Lactate Paradox during maximal exertion at altitude is one of the strongest demonstrations of a central limitation to exercise performance.

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TO THE EDITOR: T. Noakes’ Viewpoint on “lactate paradox” at high altitude is not based on direct evidence of central limitation of exercise “performance” in hypoxia, but indirect measurements such as integrated EMG as indicators of muscle fatigue or recruitment (5). He argues that maximal exercise may be limited by a reduced central drive, the teleological argument of which being the protection of noble organs such as brain or heart. All experiments using O2 inhalation fail to give any decisive argument on the site of exercise limitation since they restore oxygen availability in all organs (brain, heart, muscles) (1). Brain as the location of a hypoxia sensor that would limit motor drive is doubtful since a decrease in maximal aerobic performance has been demonstrated at altitudes as low as 800 m (especially in trained athletes), where brain hypoxia is improbable. Chronic hypoxia is associated with a decrease in O2 availability in the muscle capillary through hypoxia and exercise-induced decrease in arterial O2 saturation (SaO2). This occurs despite the increase in hemoglobin, offset by a decrease in maximal heart rate, fully explained by biochemical processes involving signal transduction in cardiac receptor pathways: downregulation of β-adrenergic and upregulation of muscarinic receptors, confirmed by extensive experimental evidence (2). This autoregulation process clearly aims at protecting the myocardium against a too high energy demand in conditions of reduced O2 availability. In endurance athletes, the importance of O2 diffusion limitation in altitude-induced reduction in performance is exacerbated. Physical laws of convection and diffusion are sufficient to account for this “double limitation”: exaggerated exercise-induced decrease in SaO2 limits O2 diffusion at the periphery, and extremely low O2 pressure in venous blood returning to the lungs limits O2 transfer at the pulmonary level, leading to a vicious circle dramatically limiting O2 availability (4). However, limited O2 diffusion from the capillary to the mitochondria should give rise to biochemical and/or EMG signs of muscle fatigue (3). Local biochemical feedback systems remain to be explored that could account for a hypoxia-induced inhibition of contractile machinery without production of anaerobic metabolites such as lactate (6).

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