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The "Anaerobic Threshold" Concept Is Not Valid in Physiology and Medicine

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Lactate turnover.

Lactate is at the fulcrum of metabolism; hence, factors that affect lactate production exert extreme leverage on metabolic rate and energy substrate partitioning (1).Lactate is the main fuel energy source, the main gluconeogenic precursor, and a molecule that signals physiological adaptation to metabolic stress (2), and it directly as well as indirectly controls the use of other fuel energy sources such as free fatty acids (1). Lactate is produced and disposed of continuously under fully aerobic conditions from the moment of conception through the termination of life (3). The rate of glycolysis leading to lactate production is influenced by a variety of normal conditions that require ATP to support cell work in its various forms (4). Examples of aerobic glycolysis *in vivo* include sperm motility (5), the beating heart (6), cerebral executive function (7), and of course working muscle (8). Significant advances in the field of lactate metabolism have been possible through the use of technologies such as isotope tracer methodology as applied to studies on mammalian animal models (9) and humans (10) and magnetic resonance spectroscopy (MRS) as applied to mammalian muscle (11). Isotope tracer and MRS technologies not only reveal that lactate production occurs under fully aerobic conditions but also that the dynamic range of lactate metabolism far exceeds that of glucose and lipids. Greater lactate production than glucose disposal is attributable to the role of glycogen in providing substrate for glycolytic flux (1). Restated, low and stable tissue lactate levels belie high rates of lactate turnover (production and removal). Restated still another way, we cannot know lactate turnover, or for that matter turnover of any metabolite, from concentration measures alone.

Lactate and tissue oxygenation.

For decades, investigators have posited and produced data suggesting that lactate is produced under fully aerobic conditions. Of note are reports of Jöbsis and Stainsby (12) using fluorescence spectroscopy to measure intracellular NAD^+/NADH in working canine muscles and Connett and colleagues (13) using myoglobin cryomicroscopy to determine intracellular oxygenation, also in working canine muscles. More recently, Richardson and colleagues(14)used a combination of arterial–venous difference, blood flow measurements, and myoglobin MRS to determine myoglobin O_2 saturation in working human skeletal

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muscle. The results clearly showed net muscle lactate release (and, therefore, production) in working muscle in which the intracellular PO_2 was well above the critical mitochondrial O_2 tension (i.e., O_2 tension below which the mitochondrial reticulum cannot achieve V_{max}). Most recently, researchers in the Jue lab used ^{13}C NMR hyperpolarization technique to observe lactate kinetics in rat skeletal under fully aerobic conditions (11).

- To the point of discussion then, because lactate is always continuously produced under fully aerobic conditions, there is no “anaerobic threshold” (AT). Lactatemia during exercise and other conditions is a biomarker for the presence of appropriate physiological strain responses.

Tradition.

Historically, lactate accumulation has been taken as a biomarker for the strain of oxygen inadequacy, but the seminal studies involved noncirculated and nonoxygenated amphibian tissues (15). Regrettably, the correlation between lactate accumulation and loss of muscle contraction in response to stimulation was incompletely reasoned. Rather than assuming that lactate was a fatigue agent, 1920s understanding gave no consideration to the alternative hypothesis that lactate production was a means to produce ATP to power and sustain muscle contraction. Hence, rather than the nearly century-old misconception of it as an indicator of O_2 lack (4), and hence, a stress biomarker, lactate is in fact a biomarker of metabolic strain in response to stress (1).

Elevated blood [lactate], what does it mean?

There are many conditions in exercise physiology, sports, and other specialties in medicine in which elevated blood [lactate] (lactatemia) is observed. Such conditions include physical exercise (16), trauma (17), sepsis (18), heart failure (19), hepatitis and pancreatitis (20), and dengue (21). It is important to note that in only one condition, physical exercise, are there definitive data on meaning of lactate accumulation in exercise; specifically, blood [lactate] rises when lactate Ra > Rd because clearance cannot keep pace with Ra (16,22). However, in other conditions, particularly severe clinical conditions, Marik and Bellomo (18) have emphasized that there are no data to support the traditional idea that lactatemia is due to O_2 insufficiency. Rather, although there are hundreds, if not thousands, of clinical reports on lactatemia in the conditions cited above, the citations given here were specifically chosen because the authors encourage lactate therapy to manage those conditions.

Lactate as a biomarker of physiological and metabolic strain.

To sum up, and perhaps to achieve a note of concordance with the position of Dr. Rossiter, when blood [lactate] is rising or when blood [lactate] is higher than predicted based on previous experience, we know that an individual is not in a metabolic steady state; for exercise performance, we know that rising lactate predicts a curtailed or diminished performance. Rising or extremely high blood [lactate] means that Ra > Rd due to the inadequacy of clearance mechanisms. Conversely, lower than predicted blood lactate levels in individuals engaged in hard exercise means enhanced lactate clearance capacity as the result of endurance training (16), genetics, or both genetic and training-induced adaptations

(23). Recognizing these facts, some investigators have developed the concept of a maximal lactate steady state (MLSS) that is determined by repeated, constant-rate exercise tasks, which may (24) or may not be correlated with heart rate response (25). To this writer, the MLSS seems like a reasonable approach to knowing when lactate Ra and Rd are in balance when tracer technology is not available. The important caveat to interpreting MLSS data is that rising or inexplicitly high lactate levels are due to limited disposal, probably due to limited mitochondrial respiratory capacity, and not oxygen lack as occurs in anaerobiosis.

Concluding statement.

Although the AT (lactate threshold) concept was an important and laudable application of early 20th century biology to physiological assessment, and remains as a tool in the arsenal of physiological assessment under certain circumstances, the concept of an AT is woefully inadequate in terms of contemporary biology (1). Lactate is produced continuously, under fully aerobic conditions, and it is an important fuel energy source (8), the major gluconeogenic precursor (26), and an important signaling molecule that works by changing cellular redox (27), allosteric binding to receptors (28), and gene expression by lactylation of histones (29). Rising or high lactate levels provide little or no information on adequacy of tissue oxygenation, but rather the balance between lactate production and disposal. We know that during physical exercise, lactate disposal is accomplished mainly by oxidation (75%–80%) in working muscle (8), the beating heart and elsewhere (6), and the remainder by gluconeogenesis (26). Historically, rising or high blood lactate levels under conditions of physiological or metabolic stress have been misinterpreted (4). Lactate production is an important strain response the purpose of which is to mitigate stress. Understood in this light, blood lactate level can be an important biomarker of physiological stress/strain relationships, and ironically, as now appreciated by investigators conducting a variety of clinical experiments and clinical trials, lactate supplementation can be an important adjunct to therapy in several physiological or life-threatening conditions (1).

RESPONSE TO ROSSITER

Given historical and contemporary findings related to basic physiology and assessing exercise performance and clinical outcomes related to lactate metabolism and the ventilatory responses to physical exercise, MSSE editors Poole and Gladden asked that Dr. Rossiter and I present perspectives on the “anaerobic threshold” (AT) and its validity in science and medicine. I believe that we the protagonists agreed to participate in a discussion of a historically important physiological concept (30) to advance understanding of contemporary physiology and consider the effects that better understanding might have on clinical practice. From that viewpoint, I congratulate Dr. Rossiter on his perspective (31) for its historical rendition of events leading to the articulation of the AT concept and its subsequent application to human physiological assessment. Simply, Dr. Rossiter’s position paper is about as good as it gets. As such, I encourage all to read and appreciate his perspective. That said, what is the crux of our discussion?

Fully acknowledging the contributions of early AT advocates (30,32–34), central standpoints in my perspective (35) are that the ideas underpinning the AT concept, although popular,

were based on unproven assumptions and are otherwise time limited. Respectfully, key elements in Dr. Rossiter's perspective are shown in the figure he has reproduced from Wasserman and McIlroy (30). The assumptions, unproven or untrue, are listed here: first, that lactate is produced because of oxygen lack, but tissue lactate production occurs under fully aerobic conditions (8,14,36); second, that glycolysis produces lactic acid, but glycolysis is not the sole source of hydrogen ion production in skeletal muscle (1,4,37); third, that glycolysis leading to lactate, hydrogen ion, and CO_2 production occurs in absence of the influences of other metabolites and redox balance systems, but although a case can be made for lactate as a "fulcrum of metabolism" (38), numerous metabolic and redox control systems are involved in the metabolic responses to stress, such as physical exercise; and fourth, the key concept, the Rosetta Stone of AT theory, predates discoveries such as the presence of cellular lactate transporters (39), the presence of mitochondrial lactate (40) and pyruvate transporters (41), the presence of mitochondrial lactate dehydrogenase (42), the role of lactate as a signaling molecule by affecting cellular redox balance (38), allosteric binding to receptors (28), gene expression by lactylation of histones (29), and the role of lactate in illnesses and injuries such as sepsis (1,43) and traumatic brain injury (44). Rephrased, the two position papers contrast mid-20th and early 21st century perspectives.

Perhaps in accepting our charge to write perspectives on the validity of the AT, Dr. Rossiter should have argued for substitution of the word "utility" for "validity" in our titles? Then there might have been more common ground as in our laboratory we routinely include ventilatory threshold (VT) and blood lactate threshold (LT) determinations in screening subjects and for assigning relative work intensities in studies of exercise metabolism, e.g., Messonnier et al. (16). We do that knowing full well that the VT and LT measure different but important things related to physiology and metabolism (45). Recognizing that lactate, particularly rising blood lactate concentration, is a biomarker for an imbalance between lactate production and removal provides practitioners in diverse fields with important information on the physiological status of athletes and the ill and injured. Applications for this information include hydration physiology (46), pulmonary medicine and cardiology (47), sports medicine (23,24), critical care medicine (48), and oncology (49). Thus, regardless of the AT as a measure of hypoxemia or tissue oxygen lack, measuring the blood lactate responses to stress can be an important tool in the armamentarium of clinicians and other practitioners.

Concluding statement.

Positing the AT concept was neither the beginning nor the end of a path of discovery; however, perhaps the AT concept was a necessary although insufficient milestone.

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