Comments on Point:Counterpoint"Lactic acid is/is not the only physicochemical contributor to the acidosis of exercise"

GOOD BYE "LACTIC ACID"; HELLO LACTATE AND ACID

TO THE EDITOR: I benefited from reading this Point:Counterpoint discussion (2, 3) and some of the papers cited therein and was shocked to learn that the construct of "lactic acidosis" has been questioned before (4).

However, it is clear (from Ref. 1) that the reduction of pyruvate to lactate consumes two protons, and as Robergs et al. (4) have said, the production of lactate retards the development of acidosis and is definitely not the cause of it.

My renewed understanding is that the proximate cause of metabolic acidosis in cells is a decline in ratio of [ATP] to [ADP] in the face of normal levels of ATP. Under anerobic conditions accompanied by a declining energy charge, the production of lactate is a homeostatic mechanism serving to regenerate NAD so that glycolysis can continue to energize the cell. I am uncomfortable continuing to use the term "lactic acidosis" just because the development of acidosis from ATP hydrolysis and the rise in cellular lactate is temporally aligned.

As Robergs et al. (4) have noted, it is also clear why muscle pH does not drop during anerobic exercise in patients with McArdle's disease (5); because less ATP is produced, the amount of acid generated is also less.

One would also expect that the arguments raised by Robergs (4) apply equally to entities such as "ketoacidosis"—the formation of ketoacid anions is a response to falling energy charge and is not certainly the actual cause of acidosis.

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SCIENCE VS. PERSONAL BIAS IN ACID-BASE PHYSIOLOGY

TO THE EDITOR: The facts concerning lactate vs. lactic acid are irrefutable. *1*) The proton coefficient of the lactate dehydrogenase reaction reveals proton consumption at 1.001 to 1.004 mol H^+/mol lactate from pH 7.0 to 6.0 (3, 6). *2*) Lactate production is a component of metabolic proton buffering (5) and should not be used to estimate the proton load (1). *3*) There is a far greater proton load of muscle catabolism than lactate production (3, 5, 6). *4*) The Stewart approach, while based on physico-chemical principles, is not synonymous with physicochemical theory. The Stewart approach has numerous assumptions that add error to the prediction of blood pH and an understanding of acid-base chemistry (2,4). *5*) The prediction of blood $[H^+]$ from the Stewart approach during intense exercise-induced metabolic acidosis has unacceptable error, especially for pH <6.65 (2). When using rigorously proven applications of analytical chemistry to muscle metabolism and adhering to the realities of the organic chemistry of chemical reactions, there is no lactic acidosis. Estimation of pH from changes in equilibrium constants and strong ions also proves to be unacceptably inaccurate, with dubious cause-effect interpretations and no clear application to intramuscular energy catabolism (2). Science is meant to be based on empiricism. If the fields of acid-base chemistry and physiology are indeed sciences, then there needs to be greater respect of the scientific method, requiring meticulous adherence to empiricism. There remains a need for a valid explanation and model of exercise-induced metabolic acidosis, proton buffering, and related electrolyte shifts at levels of the cell, blood, and systemic circulation.

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NO SINGLE MECHANISM

TO THE EDITOR: In Peter Stewart's (6) original synthesis of the physicochemical analysis of acid- base status, it is stated, "no single mechanism in these complex systems can ever by itself provide quantitative, nor even correct qualitative, understanding of hydrogen ion behavior." If one considers lactic acid, or more accurately lactate, as the only contributor to the acidosis of exercise (1), the series of events that determines acid-base status is lost. Only by considering the contributions of active and inactive tissues, plasma, red blood cells, arterial and venous compartments, and the biological membranes that separate all of them, can one get a complete picture of the series of events that determine acid-base status (3). By applying the physicochemical approach, it has been determined that at some time points lactate is not the only, or even the most important, independent factor influencing acid-base status (2). The strong correlation between calculated $[H^+]$ and measured pH lends

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support to the physicochemical approach (2) for determination of the mechanisms determining acid-base status during various types of exercise (2) and other physiological manipulations (4, 5). Although for the sake of clarity, complex physiology is often reduced to simple, linear changes, in reality acid-base change can only be understood by considering the multiple factors and spatial relationships that determine its outcome.

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CAUSE AND EFFECT?

TO THE EDITOR: The central issue in acid-base balance remains the question of cause and effect. What are the independent and dependent variables in acid-base balance; i.e., what causes a particular [H^+] (3)? By focusing only on lactate in arterial blood, Böning and Maassen (1) provide an incomplete picture. The Stewart model, advocated by Lindinger and Heigenhauser (4), points to three independent variables: PCO2, [Atot], and [SID]. This model is mathematically valid (2) and emphasizes the importance of considering all independent variables. Robergs et al. (5) asserts that production/addition and consumption/removal of H^+ ions are the independent causes of [H^+]. Which view is correct? Wooten (6) contends that all current models of acid-base are essentially bookkeeping methods and that claims for independent variables are more philosophical than physiological in nature. Nevertheless, at the moment, I give the edge to the Stewart approach because it is more comprehensive and there is some evidence that changes in [SID] cause shifts in the position of water equilibrium to cause changes in [H^+]. As one example, ionic charge may disrupt hydrogen bonds and affect the properties of water; see Corey (2). Additional studies of this type are needed as well as investigations at the molecular level where "proton and bicarbonate transporters" are being examined in detail. While the emphasis has been on the protons and bicarbonate, closer examination reveals that strong ions are involved either as symported or antiported species. Hopefully, further study will reveal which ions are actually causative, and whether H^+ and HCO3 actually move across membranes.

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ANOTHER "GREAT TRANS-ATLANTIC ACID-BASE DEBATE" (1)?

TO THE EDITOR: The two papers (3, 4) provide different views of the acidosis in exercise, related in part to different methods, but also to conceptual differences. In the first debate (Boston-Copenhagen) in 1963, Boston's Schwartz and Relman, argued cogently against the Copenhagen approach of Astrup. They concluded "with this knowledge (of integrative physiology) determinations of *standard bicarbonate* and *base excess* are superfluous; without such knowledge they are often misleading"(5).

As in many similar debates, the differences between the two approaches seem more apparent than real. For example, Böning and Maassen's (2) own data show that increases in plasma [Cl^-] contribute to the acidosis, and they are left to conclude "more La^- than H^+ leaves the fibers but this effect is probably caused by temporary changes in extracellular buffer concentration or by delayed equilibration of HCO_3^- and Cl^- across the capillary wall."

Böning and Maassen believe that *standard base excess* may be considered as a 1:2 mixture of blood and "interstitial fluid." This notion has its origin in Siggaard-Andersen's studies of hypercapnia, in which a fall in BE was similar to in vitro titration with an Hb level of 5 g/dl; the effect ("error") was interpreted as due to leakage of ions into interstitial fluid (6).

Peter Stewart pointed out that movement of H^+ (or HCO_3^-) ions per se between two compartments can have no effect on [H^+] or [HCO_3^-] in either compartment; changes in these two variables only occur with changes in [SID], weak acids ("buffers") and/or P_{CO_2} (3).

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RESPONSE TO POINT:COUNTERPOINT ON "LACTIC ACID"

TO THE EDITOR: The counterpoint argument raised by Lindinger and Heigenhauser (3) in response to Boning and Maassen (2) overlooks key data documented in the literature over the past 40 years showing that exercise causes a metabolic acidosis only when lactate concentration increases in arterial blood above the lactate threshold (1, 4, 6). Arterial bicarbonate decrease and lactate increase are identical and opposite, i.e., 1 mmol decrease in arterial bicarbonate for 1 mmol of lactate increase (1, 6), after lactate increases by approximately 0.5 mmol (4). There is no metabolic acidosis (nonrespiratory pH decrease) during exercise until lactate increases above the lactate threshold (~55% of $\dot{V}o_{2max}$) (4). During above lactate threshold exercise, there is no bicarbonate consumed other than that required to buffer lactic acid at the pH of arterial blood (1, 4, 6). What is the mechanism of buffering the first 0.5 mmol of lactic acid increase that does not appear to be buffered by bicarbonate? In reality, this early increase in lactate is also buffered by bicarbonate formed, consequent to the splitting of phosphocreatine, and release of K^+ from muscle (5). Thus HCO_3^- buffers the first lactic acid formed, as well as the larger H^+ load formed with lactate of heavy exercise. If the new HCO_3^- formed from phosphocreatine splitting is added to the resting HCO_3^- value, the total HCO_3^- decrease mirrors the total lactate increase in a 1:1 fashion (4). In summary, there is no metabolic acid formed during exercise that requires buffering at arterial blood pH values, other than lactate.

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COMBINED GLYCOLYTIC PRODUCTION OF LACTATE$^-$ AND ATP^{4-} DERIVED PROTONS (= DISSOCIATED LACTIC ACID) IS THE ONLY CAUSE OF METABOLIC ACIDOSIS OF EXERCISE—A NOTE ON THE OH$^-$ ABSORBING FUNCTION OF LACTATE^{1-} PRODUCTION

TO THE EDITOR: The only nonvolatile acid occurring in exercise is dissociated lactic acid, since, as observed in isolated stimulated muscle in vitro (1) and in contrast to (4), equal[a] amounts of lactate^{1-} and H^+ are produced.

Acidosis of exercise is related to the metabolism of glycolytic ATP^{4-}(5). In contrast to Robergs et al. (5), we believe that the production of lactate^{1-} is highly pertinent for exercise acidosis: from a stoichiometric point of view, ATP^{4-} production is associated with OH$^-$ production, ATP^{4-} breakdown with OH$^-$ consumption: $ADP^{3-} + HPO_4^{2-} \leftrightarrow ATP^{4-} + OH^{1-}$.

In *mitochondrial synthesis* of ATP^{4-} as well as in ATP^{4-} *formation from phosphocreatine*, the OH$^-$ of ATP^{4-} synthesis is liberated into the water and balances the OH$^-$ uptake of ATP^{4-} breaking down; no changes in OH$^-$ and H^+ concentrations occur. In *glycolytic synthesis of ATP^{4-}*, the OH$^-$ produced is incorporated into the carbohydrate, forming lactate^{1-} (CH3-CHOH-COO^{1-}), which is neutral in terms of acid-base relations. Because of this *OH$^-$-absorbing function of lactate^{1-} production*, glycolytic ATP^{4-}, when breaking down, causes unbalanced consumption of OH$^-$ from the water; H^+ concentration rises.

Lactate^{1-} leaves the muscle exclusively by the proton-lactate^{1-} cotransport (3); H^+ leaves the muscle in addition by CO_2, leading to a fall in intracellular HCO_3^- concentration followed by Cl^-/HCO_3^- exchange and by H^+/Na^+ exchange. Cl^-/HCO_3^- exchange and H^+/Na^+ exchange redistribute acid-base without net acid-base production. Immediately after accumulation of dissociated lactic acid in the muscle, more H^+ than lactate$^-$ leaves the muscle (1). Thereafter, lactate flux catches up so that, after minutes, base deficit and lactate^{1-} become equal in the extracellular fluid (2).

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DESCRIPTIVE VS. MECHANISM-BASED APPROACHES TO UNDERSTANDING EXERCISE ACIDOSIS

TO THE EDITOR: Presented are two disparate methodological and conceptual viewpoints on the assessment and causal interpretation of exercise-induced acidosis (1, 3). Boning and Maassen (1) propose that the only contributor to whole body, nonrespiratory acidosis is lactate. Their argument is based on the traditional proton production/consumption equilibrium model determining [H^+] (6) and rationalized from blood/ECF ion-BE relationships. Boning and Maassen discount the Stewart [SID] model's assertion of [H^+] regulation (electroneutrality, water dissociation equilibria), but oddly chose to ignore PCO2 and the influence of nonvolatile buffers

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(proteins and phosphates), which cannot be excluded from any acid-base cause-effect argument. If lactate were the only organic strong ion produced during exercise, it would be acceptable to conclude that it was the only mechanism for systemic (non-respiratory) acidification owing to whole body water distribution and electroneutral ion shifts. Unfortunately, such an assertion is too simplistic. Exercise induces the formation of new buffer (e.g., free creatine and hexose phosphates) and acids (e.g., fatty acids) that contribute to $[H^+]$ independently of lactate. Furthermore, explanations based on observational relationships in the blood/ECF do not apply to other physicochemical systems (e.g., contracting and noncontracting ICF) where ion flux, membrane characteristics, and the features of the H^+-buffering systems are quite different (2, 4). Complexity and resource intensiveness are drawbacks, but the Stewart approach provides a comprehensive mechanisms-based method for modeling physiological processes determining compartmental acid-base status. It is evident from experiments and models utilizing this approach that it is more than just lactate causing changes in $[H^+]$ (2, 4, 5).

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RESPONSE TO POINT:COUNTERPOINT ON "LACTIC ACID"

TO THE EDITOR: The present discussion highlights a basic question in muscle physiology—the cause of exercise-induced acidosis. In their rebuttal, Lindinger and Heigenhauser (3) question the cause-effect relationship between lactate accumulation and acidosis. Instead they argue that "primarily the increase in metabolic CO_2 production is responsible for the intracellular acidosis." However, this seems unlikely since the bicarbonate-CO_2 is part of the buffering system and rather than being a source of H^+ it counteracts acidosis. The large decrease in muscle total CO_2 (−50%) after exhaustive cycling (5) is consistent with this view.

Muscle pH drops from 7.0 to 6.5 (or even more) after heavy exercise and due to the high muscle buffer capacity, it corresponds to a large release of H^+ (~30 mM). Glycolysis is coupled to ATP turnover and it has been argued that ATP hydrolysis is the main source of H^+ production (4). Although theoretically correct, this view remains highly confusing. The rate of ATP resynthesis is identical to the rate of ATP hydrolysis and the production of H^+ by ATP hydrolysis is balanced by an equal rate of H^+ consumption. Under most conditions there is a negligible change in muscle ATP content and therefore no effect of ATP hydrolysis on acid-base balance.

By considering the net changes in muscle metabolites after heavy exercise it has been calculated that 90% or more of the released H^+ is due to lactate accumulation (2). This gives some support for the view advocated by Böning and Maassen (1).

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STILL NO CONVINCING EVIDENCE TO CALL OUT THE POST LACTIC ACIDOSIS ERA

TO THE EDITOR: The coincidence that the total amount of fixed base required to titrate a blood sample to pH 7.4 equates with the increase in lactate ($[La^-]$), is no convincing case for the term lactic acidosis (3). However, an increase of glycolytic rate and $[La^-]$ at short lasting, exhaustive exercise is undisputed (1, 3). At physiological pH, bicarbonate ($[HCO_3^-]$) is the largest dependent strong ion difference (SID) variable giving SID = $[HCO_3^-]$ under electrical neutrality conditions (6). The Henderson-Hasselbalch Equation defines the extracellular acid base status as $pH_{extra} = pK_{extra} + \log10([HCO_3^-]/([P_{CO_2}$ 0.03 mmol/(l mmHg)]). Consequently, the reaction [HLa] + [NaHCO3] ↔ [NaLa] + H_2O + CO_2 reflects the $[La^-]$ related decrease in pH in the extracellular space. Factors of intracellular pH control increasing [SID], such as free creatine, phosphate, and proteins and to a minor extent $[HCO_3^-]$ sum up to an intracellular buffer capacity of ~55 mval/l (5). At high glycolytic rates, the increase in $[La^-]$ decreases intracellular [SID] decreasing intracellular pH. Intracellular pH control is also highly sensitive to changes in P_{CO_2} (4). Describing these effects analog to the Henderson-Hasselbalch Equation gives $pH_{intra} = pK_{intra} + \log10$ ([intra cellular buffer capacity] − [La-intra])/[(P_{CO_2} 0.03 mmol/(l/mmHg)]). This quantitative, although simplifying concept clearly identifies glycolysis and $[La^-]$ as the dominant cause of exercise induced acidosis. It is compatible and timely with respect to current experimental evidence and quantitative modeling. It even fits to old and still puzzling suggestions that H^+ does not cross the cell membrane (2).

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