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

**POINT: LACTIC ACID IS THE ONLY PHYSICOCHEMICAL CONTRIBUTOR TO THE ACIDOSIS OF EXERCISE**

TO THE EDITOR: During intense exercise, pH markedly decreases in working muscle fibers, interstitial fluid, and blood. Here we consider not the effects of the rising $\text{PCO}_2$ in muscles and venous blood but the nonrespiratory acidosis caused, according to traditional views, by lactic acid (HLa). Contributions by other organic acids, e.g., pyruvic acid (27), can be neglected. HLa dissociates nearly completely (pK 3.8), thus the total amount of added lactic acid is almost equal to that of lactate ($\text{La}^-$; the sum of HLa and La$^-$ is here called La). If, however, a salt of HLa with a nonmetabolizable cation (e.g., Na$^+$ La$^-$) is introduced into the body, a nonrespiratory alkalinosis develops (18) because La$^-$ is consumed and substituted by HCO$_3^-$.

During hard exercise, anaerobic glycolysis is the source of energy for the synthesis of several hundred millimoles of ATP accompanied by La$^-$ production and H$^+$ liberation. The amount of the latter is not directly measurable because it is mainly bound to buffers. Traditionally HLa is considered to be the end product of glycolysis: glucose $\rightarrow$ 2 HLa $\rightarrow$ 2 La$^-$ + 2 H$^+$. This concept has been challenged by three hypotheses.

1) La$^-$ and H$^+$ are produced by independent pathways without quantitative relation.

2) Acidosis is mainly caused by changes in the strong ion difference (SID) in which La$^-$ is only one component.

3) More H$^+$ than La$^-$ leave the working muscle and enter the extracellular space indicating the production of other acids.

Regarding hypothesis 1, Robergs et al. (20) state that glycolysis produces La$^-$ and not HLa. Indeed H$^+$ is only liberated when consuming the synthesized ATP (ATP$_3^-$ + H$_2$O $\rightarrow$ ADP$_3^-$ + HPO$_4^{2-}$ + H$^+$). The underlying physiological cause for acidosis is, however, that synthesis of ATP during glycolysis does not include the consumption of H$^+$ (1,3-biphosphoglycerate$^4^-$ + ADP$^3^-$ $\rightarrow$ 3-phosphoglycerate$^3^-$ + ATP$_3^-$).

Strangely Robergs et al. are convinced that production of La$^-$ and H$^+$ by different reactions is principally no synthesis of lactic acid. This principle would create a new law in chemistry. Both ions appear coincident in the cell and their effects are equal to those of adding HLa from outside. A similar case is the secretion of gastric juice: Cl$^-$ and H$^+$ are secreted or produced by completely different reactions, but does anybody doubt that hydrochloric acid is present in the stomach?

Furthermore there cannot be much quantitative difference between the outputs of La$^-$ and H$^+$ ions since the produced ATP is immediately consumed for contraction. Robergs et al. however, try to proof their hypothesis by demonstrating that the amounts of new La$^-$ and H$^+$ are different depending on the source of glucose. Splitting of glucose entering the fiber from blood ends in the formation of 2 La$^-$: Beginning with glycogen the process even consumes one H$^+$ per molecule glucose. Robergs et al. conclude that there must be an alkalinizing effect of this pathway. But they do not consider that three instead of only two ATP per glucosyl unit are synthesized when starting with glycogen. The consumption of one additional ATP liberates one H$^+$ ending again in two La$^-$ and two H$^+$ (4). Later these authors (21, 22) suggested quantitative differences by partly splitting ADP to AMP and IMP despite resynthesis to ATP. But considering that several hundred millimoles La are produced during short intense exercise, whereas “muscle AMP and IMP increase to a sum total of ~2 mmol/kg wet wt” (22), the loss of such a small amount of ATP cannot cause important differences between the amounts of La$^-$ and H$^+$.

An additional argument of Robergs et al. against lactic acid is that binding of H$^+$ by intracellular buffers shall be much larger then the amount of La$^-$ present in the muscle fiber. But we (4) as well as Kemp (10) detected that their buffer values are too high, they do not correspond to the values in the cited sources. More contributions to this discussion have been published elsewhere (11, 13).

Regarding hypothesis 2, Lindinger et al. (13) are convinced that SID (essentially [Na$^+$ + K$^+$ – Cl$^-$ – La$^-$]), in which [La$^-$] is only a part, determines [H$^+$] in body fluids to a large extent. This concept is disputed in the physiological community (24). Lindinger et al. state explicitly that changes in SID cause changes in [H$^+$]. But SID is a pure difference derived from a balance equation (electroneutrality equation). This is no chemical reaction equation determining the dissociation of an acid.

However, there is no dispute that changes in SID are summary measures for the amount of added or subtracted strong acids and bases. During exercise acidosis, SID in the muscle is reduced additionally to the effect of increasing [La$^-$] by a decrease of [K$^+$] (12). This is, however, accompanied by a rise of [K$^+$] in the extracellular fluid partly because of transport across membranes. Also Na$^+$ and Cl$^-$ migrate between compartments; a water shift into the muscle dilutes all dissolved substances while concentrating them in the extracellular space. These changes cannot cause acidosis in muscle, extracellular fluid and blood at the same time because they cancel out. Only [La$^-$] rises in all compartments.

The SID concept is also not convincing because of methodical drawbacks [cumulative measurement errors, unknown ions (26)]. In blood changes of base excess (BE) are equivalent to changes of SID and much easier to determine. The concentrations of Na$^+$, K$^+$, and Cl$^-$ in the erythrocytes are not consistent in papers of the Lindinger group (e. g., Refs. 18 and 19) and differ (especially Na$^+$ by a factor of 2–3) from values published over decades (5–8, 14, 15, 25). Since red blood cell concentrations are calculated from measurements in plasma (not deviating from usual values) and hemolyzed whole blood using the correct formula, there must exist methodical problems with determinations in hemolysates.

Regarding hypothesis 3, it is long known that the decrease of actual BE (ABE, BE of whole blood) is larger after exercise than the increase of [La$^-$]blood. Corresponding differences were also observed when comparing arteriovenous differences (1, 9, 16). It has been concluded from these observations that more H$^+$ (up to 75%) than La$^-$ leave the muscle and enter the
extracellular space. However, ABE is biased under in vivo conditions (e., Refs. 2, 23) because blood can interchange substances with the interstitial fluid. During acidosis HCO₃⁻ originating from the erythrocytes leaves the blood while Cl⁻ is taken up. This explains nearly completely the difference between ABE and [La] in the same study. Bicarbonate is no substitute for those La⁻ ions that cannot enter the red blood cells because of the Donnan effect and therefore remain in the extracellular fluid.

Medbo et al. (17) applied standard BE (SBE, common BE of blood and interstitial fluid) to avoid the effects of ion shifts, but unfortunately compared it with [La] and obtained a similar bias. When SBE is compared with estimated [La] in the same study, (18) Cl⁻ is also taken up. This explains nearly completely the difference between ABE and [La] changes after exercise (3). Cl⁻ is a substitute for those La⁻ ions that cannot enter the red blood cells because of the Donnan effect and therefore remain in the extracellular fluid.

Thus there remain no arguments for other acids or other mechanisms of acidification. Lactic acid is the essential cause for nonrespiratory acidosis of exercise.

REFERENCES


COUNTERPOINT: LACTIC ACID IS NOT THE ONLY PHYSICOCHEMICAL CONTRIBUTOR TO THE ACIDOSIS OF EXERCISE

TO THE EDITOR: The acidification of blood during muscular exercise cannot be understood from an analysis of blood from a single site, nor from examination of only arterial (or arterialized) blood. Acidification of blood during muscular contraction occurs as a result of rapid and marked increases in skeletal muscle mitochondrial CO₂ production and decrease of cellular HCO₃⁻ (and other CO₂ stores; 2) resulting from intra- and extra-cellular acidification. Peak efflux of CO₂ occurs during the first 30 s of high (5, 8)- and moderate (7, 9, 13)-intensity exercise. With both high (5, 8)- and moderate-intensity (7, 9) exercise, blood is also acidified due to decreases in plasma strong ion difference, or [SID], and increases in plasma [protein]. The contributions of each of these independent variables of acid-base control to the changes in plasma [H⁺] and [HCO₃⁻] have been quantified in arterial, femoral, and antecubital venous bloods during leg bicycling exercise and recovery. In femoral venous plasma the increase in PCO₂ remains the primary contributor to the plasma acidosis during exercise and the initial recovery period. In mixed venous blood, increased PCO₂ is also the primary contributor to the plasma acidosis.