The lactate/lactic acid debate – an outsider’s perspective
By Dr. Keith David Kantor

Abstract
Exercise induced acidosis in muscle tissue is a long studied subject with several differing theories as to the cause. Even so, these theories share certain fundamentals. In this survey, the historical theory and the current relevant research as to the cause of acidosis will be discussed. Where agreement exists it will be illuminated and where disagreement exists it will be dissected to determine the most accurate picture of what is happening in the biological processes that lead to exercise induced acidosis.

NOTE: The following discussion will make no distinction between intracellular, intercellular, extracellular, plasma, blood, or any other fluid. This discussion will be limited to cellular conditions in broad terms and not a detailed analysis of physiology. Further, conditions of temperature, etc. will not be addressed but assumed to be within normal parameters. For clarities sake the hydrogen cation will be referred to as hydrogen or its equivalent symbol H⁺ throughout this article.

1.0 Muscle Acidosis
1.1 A Historical Survey
Early researchers into lactic acid’s role in muscle physiology were W. M. Fletcher and F. G. Hopkins (1907). Their work was built upon by A. V. Hill and Otto Meyerhof who shared the Nobel Prize for Physiology or Medicine in 1922 for their work in the area. For the next decade or so these two led many of the discoveries that furthered the understanding of muscle physiology and the role of lactic acid/lactate. It should be noted that lactic acid actually exists as two ions – the lactate ion and hydrogen ion (H⁺). As such, although it is called lactic acid, this is just a construct because they dissociate in an aqueous solution and are normally found as separate ions. Further clouding the picture, careless imprecision has led to the terms lactic acid and lactate being used interchangeably. In simple terms, a theory developed that the lactic acid that is produced during anaerobic glycolysis is the cause of fatigue in the muscles during high intensity exercise. This led to the term lactic acidosis. This theory is still the standard taught in most textbooks. (1,2,3,4,5,6)

L. B. Gladden calls the time from the 1930s through the 1970s the “dead-end waste product era” for the role most physiologists saw for lactate during this period. He continues to explain that in the 1970s physiologists began to question this assumption. (2) In 1985, George Brooks introduced the lactate shuttle hypothesis that began to look at lactate in a new light. (7)
revolution had begun and traditional views were being questioned. In 2004, two important articles came out that challenged the traditional view of muscle physiology during exercise. In the first article, Gladden explored the new discoveries of the role of lactate since the 1970s (2) and in the second R. A. Robergs et al. laid out the case for a new view of exercise induced acidosis (6). Although the traditional view was still stuck in the “dead-end waste product era”, these two authors challenged this mindset.

Gladden laid out the case for the true role of lactate “in numerous metabolic processes and pathways.” (2) Far beyond being merely a waste product of muscle contraction and energy creation during anaerobic glycolysis, lactate is produced during both anaerobic and aerobic glycolysis and is vital in many different biological processes in muscle tissue and the body as a whole. In his article, Gladden focused on the many varied roles of lactate and lactate shuttles but failed to understand its role in exercise induced acidosis. He explored the topic but came to no conclusions. (2)

This is where Robergs et al. advanced a new perspective on the cause of exercise induced acidosis. Robergs argued that instead of causing acidosis, lactate was actually part of the cell’s buffering system in handling acidosis. Its presence actually allowed the cell to operate longer before succumbing to acidosis and it was only after all of the buffering systems in the cell were overwhelmed, including lactate, that exercise induced acidosis occurred. This directly challenged the assertion that lactate ions and hydrogen ions maintain a 1 to 1 ratio. If these ions do not exist in a 1 to 1 ratio then the term lactic acidosis is incorrect. Robergs concluded that since lactate and H⁺ act independently from one another, the terms lactic acid and lactic acidosis are incorrect. This was a revolutionary approach. (6,8)

During the early 1980s Peter Stewart attempted to quantify acid-base physiology in a new way. In his 1981 book “How to Understand Acid-Base”, Stewart tried to redefine the hydrogen proton (H⁺) basis of both the Arrhenius theory and the Brønsted–Lowry theory because he asserted that H⁺ was a dependent variable. He put forth his theory that the only independent variables were strong ion difference (SID), total weak acid concentration (A_{tot}), and the partial pressure of CO₂ (P_{CO₂}). He used these to devise a quartic equation that replaced H⁺. (9,10,11)

These then are the three schools of thought as to what causes exercise induced acidosis. The traditional maintains it is lactic acid, lactate and H⁺ in equal amounts, resulting in lactic acidosis. Followers of Stewart explain it in terms of SID and see lactate as causing acidosis but do not recognize the role of H⁺. Robergs asserts that lactate and H⁺ should be considered separately and that lactate is not a good indicator of H⁺ levels since H⁺ can rise well above the levels of lactate. Both Stewart and Robergs argue that metabolic acidosis is a more accurate term to describe exercise induced acidosis.

1.2 Controversy and Analysis

Robergs contentions unleashed great controversy in the physiology community leading to much back and forth since its publication. Beyond this, three separate years led to published
discussions between the factions in 2005, 2008, and 2011. All of the back and forth has been chronicled in various publications and Point/Counterpoint articles, most notably in the *Journal of Applied Physiology* and the *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*. (12,13,14,15,16,17,18,19,20,21,22,23)

The basic argument can be simplified as follows. All sides agree that the energy needed during high intensity exercise comes from anaerobic glycolysis once the aerobic glycolysis has been exhausted. Traditionalists hold that this production produces lactate and H⁺ in a 1 to 1 ratio (lactic acid) resulting in lactic acidosis. Robergs maintains that this ratio can increase to as much as 3 to 1 with more H⁺ being produced than lactate resulting in metabolic acidosis. The difference in H⁺ production is attributed to non-mitochondrial ATP energy generation. Stewart holds that lactate is being produced but that H⁺ cannot explain the metabolic acidosis because many other processes are happening in the cell at the same time and the sum of all of this activity must be taken into account to ascertain the true cause of the metabolic acidosis.

The chart below outlines the differences and agreements between the three schools of thought about exercise induced acidosis. The chart attempts to cover most areas of contention between the schools of thought.

<table>
<thead>
<tr>
<th>Contention</th>
<th>School of Thought</th>
</tr>
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<tbody>
<tr>
<td>Lactate is the proximate cause of acidosis</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>Lactic acid is the proximate cause of acidosis</td>
<td>Traditionalists: agree</td>
</tr>
<tr>
<td>H⁺ is the proximate cause of acidosis</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>Lactic acidosis is most accurate</td>
<td>Traditionalists: agree</td>
</tr>
<tr>
<td>Metabolic acidosis is most accurate</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>Lactate is a positive force when considering acidosis</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>H⁺ rates can be determined</td>
<td>Traditionalists: agree</td>
</tr>
<tr>
<td>H⁺ rates and Lactate rates are equal</td>
<td>Traditionalists: agree</td>
</tr>
<tr>
<td>H⁺ is irrelevant to determining acidosis</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>pH is a valid measure of acidosis</td>
<td>Traditionalists: agree</td>
</tr>
<tr>
<td>SID is critical in determining acidosis</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>H⁺ is a dependent variable</td>
<td>Traditionalists: disagree</td>
</tr>
<tr>
<td>Acidosis is a state of imbalance towards the positive spectrum</td>
<td>Traditionalists: disagree</td>
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### 2.0 Final Assessment

Maintaining the traditional view that lactic acid is the cause of acidosis during high intensity exercise fails to account for the advancements in understanding that have come about in recent years. The role of lactate and the role of hydrogen cannot be adequately explained by this view. The following will outline where the weaknesses lie and what advancements in understanding have arisen.
2.1 Lactate

The first problem is recent research points to the far more diverse role lactate plays in many different metabolic processes than as just a place to park energy until the body’s oxygen supply can catch back up. (2,7,24) For example, a 2002 study done by Miller et al. on the role of lactate in whole body context using exogenous lactate infusion during rest and exercise concluded: “Finally, lactate infusion into exercising men was not associated with an increase in the sensation of fatigue. Results are consistent with the concept that lactate is a useful carbohydrate source that can spare blood glucose and liver glycogen in times of increased energy demand.” (25) This study demonstrates that instead of causing fatigue, lactate actually was “a useful carbohydrate source” or in other words a useful energy source. If this is true in a whole body context why would it not also be true in a cellular muscle context? It does not make sense that lactate in the muscle would lead to acidosis and fatigue but in the whole body it would prove beneficial. But one might counter that in the cell there would be H⁺ present during the creation of lactate that was not present in the study because it was lactate infused without the presence of H⁺. This then actually proves the point that it is the presence of H⁺ that matters and not the presence of lactate in causing acidosis and fatigue. So the name lactic acidosis is completely misleading since lactate has nothing to do with it but H⁺ is the problem.

To further illuminate the role of lactate it is beneficial to look at three studies that focused on lactate and the brain. First, a 2008 study called “Cerebral blood flow and metabolism during exercise: implications for fatigue” found that brain metabolism during exercise remained stable. It concluded that this was due to lactate uptake by the brain. From the study: “Also the earlier consideration that brain metabolism relies only on oxygenation of glucose has changed dramatically by the finding that during intense exercise, the brain may take up as much lactate as glucose, and, together, the carbohydrate uptake by the brain is much larger than can be accounted for by the uptake of O₂.” (26) Second, another study the same year stated: “In summary, cerebral lactate uptake becomes significant when arterial lactate is elevated and the brain is activated, as during intense exercise. The brain should be added to the list of organs that contribute to the elimination of plasma lactate, thus taking advantage of accidental availability of additional chemical energy and thereby sparing glucose.” (27) Third, a study from 2012 found that “High lactate levels that arise during strenuous exercise or hypoxic episodes may be ‘biologically intended’ to be glucose-sparing, similar to ketone bodies during starvation.” (28) All of these studies show that far from causing acidosis or fatigue, lactate actually helped the brain function during strenuous exercise. If lactate is helpful and beneficial to the brain during strenuous exercise, why would it be any different for the muscle? As before, the name lactic acidosis is misleading at best because lactate has no role in it.

These are varied studies covering whole body metabolism and brain metabolism during high intensity exercise but each one comes to the same conclusion - far from being harmful, lactate is actually beneficial. Clearly lactate is far more than a metabolic dead end where the muscle parks energy until it can be converted back to a useable form once oxygen becomes available again. Not only does the lactate from the muscle go to the liver once it leaves the muscle, it also goes to
the brain where it is used to help the brain during the stress of high intensity exercise. (26,27,28) As it circulates throughout the body, it can be a source of energy for the whole body and not just shuttled back to the liver. (25)

### 2.2 Hydrogen

The roles of the hydrogen proton and the hydroxide ion in an aqueous solution are the foundation upon which acid-base theory was built. These two ions act differently and share properties that no other ion in an aqueous solution does. This fact alone sets them apart. It is these properties as they relate to the hydrogen proton that will now be the focus.

Hydrogen has very unique properties both in an aqueous solution and in its role in the metabolism of the body. Its role in metabolism is well documented even if there is debate about exactly how it all plays out. Its role in an aqueous solution however is still an area of great interest and research. A look at the most current understanding will shed insight.

In a June 2016 article in *Chemical Reviews* titled “Protons and Hydroxide Ions in Aqueous Systems”, Agmon et al. stated: “Biological applications reviewed include proton transport along the hydration layer of various membranes and through channel proteins, problems that are at the core of cellular bioenergetics.” (29) Observations made in the article include:

1) **Hydrogen bonding in water is inextricably linked with proton (H\(^+\)) and hydroxide ion (OH\(^-\)) dynamics and structure.** From the article: “Despite extensive efforts, achieving detailed, molecular-scale insight has been challenging, partly because the structure and dynamics of protons and hydroxide ions is inextricably linked with the hydrogen bond (HB) dynamics of water, and thus, insight into the former requires a detailed understanding of the latter.”

2) **The properties governing H\(^+\) and OH\(^-\) differ dramatically from other ion species.** From the article: “We begin by briefly describing the founding experiments of the field. These observations strongly suggested that H\(^+\) and OH\(^-\) are unlike other ions in water: e.g., their solvation and transport properties differ dramatically.”

3) **The properties of hydrogen bonding observed in bulk water carry over to biological systems.** From the article: “In spite of this wide range of different systems, the basic observation of abnormally fast proton transport through the HB network appears to carry over from bulk water to biological systems.”

4) **Nuclear Quantum Effects (NQE) influence hydrogen bonding.** From the article: “These studies showed, for example, that NQE strengthen strong HBs and weaken the weak HBs, and that in both bulk liquid water and confined water NQE cause proton ‘cluster’ in acidified bulk water.”

5) **The properties of H\(^+\) and OH\(^-\) are inherently both electronic and nuclear.** From the article: “Modeling the proton and hydroxide ions remains challenging also because their physical and chemical properties are inherently quantum mechanical, involving both the
electronic and nuclear degrees of freedom. In particular, the importance of quantum fluctuations of the nuclei will be an important issue to consider in future studies.”

So how does any of this apply to exercise induced acidosis and the role of hydrogen/lactate in that? Simply put, hydrogen by its very nature has properties that do not apply to lactate and as such must be looked at in a different light. The observed properties of hydrogen in bulk water can be translated into biological metabolic processes. Electroneutrality alone does not govern the behavior of hydrogen in the cell but nuclear physics should also be considered. The fast proton transport that governs $H^+$ must be considered as its mobility is greater than that of other ions in the cell, including lactate. The fact that hydrogen bonding is so intertwined in any understanding of water and by extension the cell shows that hydrogen plays a role far greater than lactate can or does.

Next, one must consider the fact that $H^+$ and lactate act independently of each other in the cell because lactic acid has a dissociation rate of over 99% at physiological pH. (2,24) So whether $H^+$ and lactate entered the cell as lactic acid or they came into the cell by separate methods, they reside in the cell as loosely linked ions at best. Add to this the fact that the dissociated hydrogen proton does not actually exist by itself but attaches itself to a water molecule to form hydronium ($H^+ + H_2O = H_3O^+$) and the link between lactate and $H^+$ becomes even more tenuous. Finally, consider the fact that hydronium is the strongest acid in an aqueous solution and it becomes clear that $H^+$ as hydronium is responsible for exercise induced acidosis. This makes the term lactic acidosis even more misleading.

3.0 Conclusion

Lactate is a much more important and dynamic ion than is presented in the traditional view but it is not responsible for exercise induced acidosis. Further, the accumulation of hydrogen alone is responsible for exercise induced acidosis whether it comes into the cell as part of lactic acid or through other means. For these reasons alone the term lactic acidosis must be rejected.

Beyond this, any view that seeks to represent an accurate picture of the metabolism involved in exercise induced acidosis should account for several conditions. It should:

1) Recognize that lactate and $H^+$ act independently from one another and any linkage is tenuous at best.
2) Include an accurate portrayal of lactate and the role it plays not only in the muscle cell but throughout the body.
3) Illustrate the dynamic role hydrogen plays as the source of acidosis and the unique properties it possesses that no other ion in an aqueous solution possesses but hydroxide.
4) Recognize others factors may contribute to overall fatigue and performance degradation but that hydrogen is the main cause of acidosis.

The traditional view cannot meet these criteria. Its limits have been known for decades and have spurred the investigations that have now born fruit. The traditional approach is static and rigid.
with its adherence to the lactic acid construct and the 1 to 1 ratio. Its view of lactate is lacking and misses the bigger picture.

In the 1980s Stewart attempted to address some of the failings of the traditional view with mixed results. His insight into the nature of hydronium and the formula he created for it deserves special attention. Here is the formula: \( \text{H:}(\text{H}_2\text{O})_n^+ \). (30) Basically this means a hydrogen proton will attach to any number of water molecules because of the clumping nature of water and the increased stability derived from the attachment of multiple molecules. This formula captures the essence of well-known cations like the Eigen cation and Zundel cation, both of which are important in biological processes. The problem with Stewart is that he failed to see the importance of hydrogen and instead tried to replace it with his new equations. This is a fundamental failure. Since the beginning with Arrhenius and Brønsted-Lowry, hydrogen’s role in acidity has been recognized. An attempt to change this is problematic at best. Consider also the unique and irreplaceable role hydrogen plays in the body’s metabolism and in aqueous solutions generally, and it becomes clear that this approach must be rejected.

Although the Stewart approach’s popularity is on the rise amongst some clinicians, chiefly in the fields of anesthesia and intensive care, it remains problematic. Two recent articles reviewing Stewart lay out the case succinctly. Dr. Rastegar states: “Clinically, the traditional approach is intuitive in nature and is supported by a large body of robust empirical observations. The traditional approach should be abandoned only if proponents of Stewart’s approach could provide clear empirical observations supporting its superiority as a clinical tool in diagnosing and treating patients with acid-base disorders.” (31) Kurtz et al. conclude: “Importantly, the lack of a mechanistic basis to justify the use of the Stewart formulation is critical. In this regard, the hypothesis that in a given compartment, SID (a mathematical construct and not a physicochemical property) mechanistically influences \([\text{H}^+]\) to maintain electroneutrality has no experimental basis.” (32) Both of these articles were written in the field of nephrology but their conclusions can be applied generally. Although Stewart’s approach may offer some insight, there is not yet enough proof of its superiority to the traditional approach it tries to replace.

This leaves us with Robergs approach. Of the three possibilities this approach meets the criteria set forth better than either the traditional approach or the Stewart approach. Robergs is dynamic and pliable with room for exponential expression. Its adherence to a ratio as great as 3 to 1 fits more with what takes place during exercise induced acidosis. Robergs sees lactate as a buffer to acidosis and not a cause of it. This is far more in line with research looking at lactate’s role in other areas including whole body and brain metabolism during high intensity exercise.

Although Robergs directly challenges the traditional view of lactic acid, even he admitted in an exchange with his editor for his 2001 article that the net result in the cell of both his view and that of the traditional is the same until acidosis occurs. Robergs’ cell ends up with two lactate ions and two hydrogen protons, exactly what happens when lactic acid dissociates as in the traditional view. His editor thought if that was the case then there should be no real objection to the term lactic acidosis. (8) In reality there is a big difference according to Robergs. The
traditional view is stuck in a purely linear mathematical construction of a 1 to 1 ratio with no room for exponential growth. Robergs view, however, allows for a more geometric approach in that the $H^+$/lactate ratio has the potential of being as much as 3 to 1. (22)

The end result of all of this is that the traditional view maintains that the $H^+$ in the cell as a result of exercise induced acidosis is a direct result of lactic acid dissociation and therefore the ratio of $H^+$ to lactate must be a 1 to 1 ratio. Robergs counters that the $H^+$ found in the cell is a direct result of ATP hydrolysis and not lactic acid dissociation. The presence of lactate helps buffer the cell against this $H^+$ production. Because the $H^+$ does not come from lactic acid dissociation, the $H^+$ can and will be in a ratio greater than 1 to 1 with lactate when exercise induced acidosis occurs.

When you consider the fact that the understanding of the role of lactate has broadened tremendously under researchers like Brooks and Gladden, it is hard to envision the traditional orthodoxy of lactate being a dead end metabolite in the cell surviving. When you add to this the dynamic and unique properties that govern the hydrogen proton and hydroxide ion that affect no other ions, it becomes apparent that far more is at play that can be explained by the simple idea that the dissociation of lactic acid into lactate and $H^+$ in the cell explains the presence of hydrogen in the cell during exercise induced acidosis. To maintain this dogma one would have to say no other possibility exists and the reality is far more complex than that.
REFERENCES


30. Stewart, pg. 22.
