Point:Counterpoint: Lactic acid accumulation is an advantage/disadvantage during muscle activity

PURPOSE AND SCOPE OF THE POINT:COUNTERPOINT DEBATES

This series of debates was initiated for the *Journal of Applied Physiology* because we believe an important means of searching for truth is through debate where contradictory viewpoints are put forward. This dialectic process whereby a thesis is advanced, then opposed by an antithesis, with a synthesis subsequently arrived at, is a powerful and often entertaining method for gaining knowledge and for understanding the source of a controversy.

Before reading these Point:Counterpoint manuscripts or preparing a brief commentary on their content (see below for instructions), the reader should understand that authors on each side of the debate are expected to advance a polarized viewpoint and to select the most convincing data to support their position. This approach differs markedly from the review article where the reader expects the author to present balanced coverage of the topic. Each of the authors has been strictly limited in the lengths of both the manuscript (1,200 words) and the rebuttal (400). The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.

POINT: LACTIC ACID ACCUMULATION IS AN ADVANTAGE DURING MUSCLE ACTIVITY

Lactic acid accumulation inside muscle fibers is not responsible for decreased muscle performance (“muscle fatigue”). Muscle fatigue occurs because of disturbance to any of the steps in excitation-contraction (EC) coupling. There are several broad types of muscle fatigue, and the contribution of each to the overall decline in performance depends on the muscle fiber type and the intensity and duration of the activity (1, 27). One type is caused by the buildup of K⁺ in the transverse-tubular (T-) system and in the immediate vicinity of the muscle fibers. This K⁺ buildup depolarizes the fiber, slowing or preventing Na⁺ channels from recovering from inactivation, with consequent reduced amplitude or failure of action potentials and reduction in force production. This type of fatigue is potentially of major importance because [K⁺] has been shown to reach very high levels (>10 mM) outside muscle fibers during vigorous activity (23). The other major type of fatigue, often termed “metabolic fatigue,” arises because of direct or indirect effects of the accumulation of metabolites (Pᵢ, ADP, Mg²⁺, reactive oxygen species) and decrease in substrates (ATP, creatine phosphate, glycogen) within muscle fibers. Force production can decrease because of reduction in Ca²⁺ release from the sarcoplasmic reticulum (SR), decline in maximum Ca²⁺-activated force, or decrease in Ca²⁺ sensitivity of the contractile apparatus (1). In the fastest type of twitch fibers, cellular ATP can drop to critically low levels (<1 mM) (11), reducing Ca²⁺ release (8). Metabolic fatigue can also occur due to effects of Pᵢ (7, 29), Mg²⁺ (27), and direct and indirect effects of glycogen depletion (6, 28).

Lactate ions in the cytoplasm, even at high concentration, do not impair EC coupling (20). High intracellular [H⁺] also has few, if any, deleterious effects on EC coupling because normal voltage-sensor controlled Ca²⁺ release is little, if at all, inhibited by very low pH (2, 13, 19) and at 30°C, maximum force production by the contractile apparatus is only reduced to a small extent (17). Furthermore, in single intact muscle fibers, decreasing pH from 7.1 to <6.7 does not cause or accelerate the onset of fatigue, but instead seemingly slows its onset (5). An increase in intracellular acidity in fact can help increase cytoplasmic [Ca²⁺] and consequent activation of the contractile apparatus, because the SR Ca²⁺ pump binds and resquesters less Ca²⁺ at acid pH (2, 13, 30), which can leave more of the released Ca²⁺ available to bind to troponin C (21), more than compensating for the small decrease in the Ca²⁺ sensitivity of the contractile apparatus occurring at acid pH. Also, elevated muscle acidity does not reduce muscle glycogenolysis/glycolysis (3) or otherwise inhibit energy metabolism in functioning fibers (5).

Importantly, decreasing intracellular pH to ~6.7 actually counters the inhibitory effect of raised extracellular [K⁺] (15, 22). This is because intracellular acidity blocks the Cl⁻ channels in the surface and T-system membranes and hence reduces the normal high leakiness to Cl⁻, thereby making it possible for action potentials to still propagate into the T-system despite the raised [K⁺] having caused substantial inactivation of the Na⁺ channels (18, 19). Extracellular [K⁺] does rise to critical levels during normal exercise (23), so it seems very likely that the decrease in intracellular pH has substantial beneficial effects in exercising humans by delaying the onset of fatigue due to action potential failure. This is further supported by findings in humans deficient in myophosphorylase activity (McArdle’s disease) who are unable to break down glycogen or accumulate lactic acid. These subjects display faster onset of fatigue, which is associated with failure of muscle excitation (14). These findings are fully consistent with muscle acidity normally playing a crucial role in helping keep action potentials propagating despite the large rise in extracellular [K⁺] occurring with strenuous activity.

The argument put forward by Kristensen and colleagues (12) that this effect does not occur in active muscle, is not valid because it is based on observations made with isolated whole soleus muscles that were stimulated at such a high rate that >60% of the preparation would have rapidly become completely anoxic (4). Stimulating a highly aerobic muscle under anaerobic conditions inevitably would have generated a large amount of reactive oxygen species and disrupted mitochondrial function, which is known to cause muscle depolarization and reduced force (16). Furthermore, there is no reason to expect that adding more H⁺ to that already being generated by the muscle activity should in any way be advantageous. It is a bit like opening up the carburetor on a car to let in too much air or throwing gasoline over the engine and then concluding that air and gasoline are deleterious to engine performance.

Experiments in which manipulation of body pH affects muscle performance should not be taken as evidence of a deleterious effect of intracellular muscle acidity. Altering body pH can have effects on blood oxygen saturation and unloading,
and on central drive and other factors. Experiments with perfused hindlimb preparations, where such variables were under some control, showed that a decrease in blood pH adversely affected muscle performance but that this was due to an effect of extramuscular pH, not the pH inside the muscle fibers (26). The accompanying perfusion pressure data indicate that the effect was quite possibly due entirely to the acidity disrupting the normal control of local blood flow in the vascular beds. Similarly, alkalosis in humans can delay the onset of fatigue (24), but alkalosis actually causes a decrease in extracellular [K⁺], which alone may account for the beneficial effects, particularly given that when this effect of alkalosis is avoided, no improvement in muscle performance is seen (25).

Further support for the proposition that lactate acid accumulation is advantageous during muscle activity is provided by the properties of the two major monocarboxylate transporters (MCTs), which play a major role in the regulation of intracellular pH and lactate concentration during intense muscle activity. The MCT4 isoform that is predominantly and abundantly expressed in fast-twitch glycolytic fibers, the major producer of lactic acid, has a relatively high dissociation constant (low affinity) Kᵣ of 20–35 mM, whereas the MCT1 isoform, which is predominantly expressed in slow-twitch oxidative fibers, has a Kᵣ of 3–5 mM (9, 10). The high Kᵣ of MCT4 for lactate explains why lactic acid is allowed to accumulate in the fast-twitch glycolytic muscle during exercise, causing acidification of the myoplasm. This must be beneficial for the muscle because otherwise the muscle would have expressed the low Kᵣ of MCT1 isoform. The lower Kᵣ value for lactate of MCT1 isoform in the slow-twitch, oxidative muscle fibers provides a higher affinity uptake mechanism for lactate and protons to be used in these fibers as a respiratory fuel.

Finally, we note that a rise in blood lactate (the “lactate threshold”) can indeed be used as an indicator of exhaustion. However, although lactate may well increase when muscle performance declines, lactate is not the cause of the decline. Lactate rises in the blood when the muscle cells are using ATP faster than they resynthesize it aerobically in the mitochondria. But it is the other changes occurring in the muscle, not the lactic acid accumulation, which cause the fatigue. Acidity associated with lactic acid accumulation actually helps delay the onset of muscle fatigue that would otherwise ensue from the other effects of vigorous activity.

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sium in muscle interstitium and earlier development of fatigue due to potassium release likely leads to a greater accumulation of potassium because ATP-sensitive potassium channels (18). The increased potassium release contributes indirectly, probably through the greater potassium concentration, to a decrease in muscle pH when the leg exercise was performed with prior arm exercise. In addition, potassium release was greater in the normal condition (Fig. 1; Ref. 2). The reduced muscle pH was different at exhaustion, it is not likely that the lowered pH per se is the crucial factor, but it may still contribute indirectly, probably through the greater potassium release (19) perhaps mediated by a larger opening of the ATP-sensitive potassium channels (18). The increased potassium release likely leads to a greater accumulation of potassium in muscle interstitium and earlier development of fatigue (10). The effect of changing only pH has also been investigated in humans. In a number of studies, blood pH has been elevated by infusion of sodium citrate or bicarbonate. It is a general finding that the alkalosis obtained by these procedures improves performance (see Refs. 16, 19). This effect may be mediated by an improved H⁺ and lactate release, increased extracellular buffering, lowered increase in blood potassium (16), and a reduced interstitial potassium accumulation during alkalosis (19). Taken together, the findings in human studies clearly suggest that lactic acid accumulation, and the associated lowering of pH in humans, is disadvantageous.

A high number of studies have examined the effect of lactic acid in animal models. One way to investigate the effects of lactic acid is to incubate a muscle in lactic acid before and during stimuli. Studies using lactic acid incubation and repetitive exhaustive stimulation have reported a faster fatigue development (3, 5, 9). For example, in rat skeletal muscle incubated with 20 mM lactate, force development was reduced during repetitive stimulation when compared with a control situation (7). However, it should be mentioned that some of the experiments using exhaustive repetitive stimulation have been carried out at temperatures in the range 25–30°C, and it has been reported that part of the negative effect disappears when experiments were conducted at body temperature (12). It has also been observed that the lactate ion per se reduces muscle force independent of any pH changes. In isolated dog muscle, lactate ion perfusion reduced twitch force by 15% (6) and lactate incubation reduced force in isolated mouse muscle (17), whereas lactate did not change force in skinned muscle fibers (15). These differences suggest that the effect of lactate is associated with the function of the muscle membrane. It must be noted that, although the investigations with intact fibers used lactate incubation without plasma pH changes, the lactate/H⁺ cotransporter will bring H⁺ into the cells, and thus changes in intracellular pH may occur. Therefore, it is possible that the effect of lactate is due to pH-induced changes in, for example, the potassium balance.

The cellular mechanisms of the negative effects of lactic acid accumulation and lowering of muscle pH may be multifactorial. In addition to the effect of lactate on the membrane, the most important effect may be the influence on the handling of intracellular Ca²⁺ during muscle activation. It has been reported that lactate and H⁺ induce an impairment of sarcoplasmic reticulum Ca²⁺ release channels (8), H⁺ depresses Ca²⁺ activation of thin filaments (9), and H⁺ induces a reduction of the Ca²⁺ reloading into sarcoplasmic reticulum (4; also see Refs. 3, 5).

So why this debate, when the evidence for lactic acid and pH having a negative effect on muscle performance is so strong? It was recently demonstrated that lactic acid incubation restores the force in rat muscle incubated in high K⁺ concentrations (11). The underlying mechanism has been investigated with skinned single fibers (13, 14). The positive effect appears to be that intracellular acidosis decreases chloride permeability in the T tubules, which allows action potentials to be propagated despite the K⁺-induced depolarization (13, 14) Thus it might be that lowered pH has a positive effect on specific ion transport systems in the contracting muscles. We do not question the outcome of these experiments, which we in part have reproduced (7). However, there are a number of experimental conditions that make it difficult to extrapolate these findings to humans. In an editorial of the journal Science, lactic acid was recently described as “the latest performance-enhancing drug” (1). The conclusion was based on studies of isolated rat skeletal and skinned skeletal muscle fibers (11, 13, 14), and the authors described as “the latest performance-enhancing drug” (1). The conclusion was based on studies of isolated rat skeletal and skinned skeletal muscle fibers (11, 13, 14), and the authors concluded that intracellular acidosis decreases chloride permeability in the T tubules, which allows action potentials to be propagated despite the K⁺-induced depolarization (13, 14) Thus it might be that lowered pH has a positive effect on specific ion transport systems in the contracting muscles. We do not question the outcome of these experiments, which we in part have reproduced (7). However, there are a number of experimental conditions that make it difficult to extrapolate these findings to
the in vivo condition, in particular, during exercise in humans. First, in the experiments by Nielsen et al. (11), a resting muscle was studied (stimulation took place every 10 min) and exhaustive repetitive stimulation was not used. Second, in vivo, the Na\(^+\)-K\(^+\) pump is activated both by hormones and the increase in intracellular Na\(^+\) associated with muscle activity and pH regulation. An active Na\(^+\)-K\(^+\) pump partly restores the membrane potential, thereby maintaining membrane excitability. In the experimental model used by Nielsen et al. (11), the Na\(^+\)-K\(^+\) pump was not activated. Thus the potassium-induced depolarization exceeded the depolarization during normal activity in intact muscle that has an active Na\(^+\)-K\(^+\) pump. Therefore, it is likely that the lactic acid may have overcome the negative effect of a large nonphysiological depolarization. Third, in the experimental model used by Nielsen et al. (11), lactic acid incubation lowered intracellular pH less than extracellular pH, which created a reduced transmembrane pH gradient. In contrast, the pH gradient is actually elevated in contracting skeletal muscles during exercise.

In conclusion, there is ample evidence in both humans and animals that accumulation of lactic acid during exercise contributes to the development of fatigue during intense exercise. It is also clear that lactic acid accumulation and the associated lowering of intracellular pH are not the crucial factors and the main effect may be that the lowered pH leads to a greater release of potassium from the contracting muscles.

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REBUTTAL FROM DRS. LAMB AND STEPHENSON

The Counterpoint by Bangsbo and Juel does not provide evidence that lactic acid accumulation in muscle is disadvantageous. Instead the authors agree with us in saying that “lactic acid accumulation and the associated lowering of intracellular pH are not the crucial factors” in the development of fatigue. They argue that raised extracellular [K\(^+\)] is the main cause of fatigue and agree that intracellular acidosis does have a positive effect by decreasing chloride permeability. Given this, we must say we are puzzled that they further argue that the results of Nielsen et al. (5) supporting these conclusions are somehow incorrect and based on “nonphysiological depolarization.” It cannot be claimed that humans are entirely different from other mammals in this regard while agreeing that raised extracellular [K\(^+\)] has the same deleterious effects on membrane potential and action potential propagation. There is also no question that human muscle, like that of other mammals, has a high resting chloride conductance that acts to depress membrane excitability; this is very well known, especially as the absence of this chloride conductance is the cause of myotonia.

The data of Bangsbo et al. (1) do not demonstrate a deleterious effect of lactate accumulation. As that paper itself concluded, the more rapid fatigue could well have been caused by central fatigue or other factors, as the authors did not demonstrate that the muscle itself was fatigued. The greater intracellular acidity in the prior exercise case in fact was likely keeping the muscle excitable. Furthermore, such experiments do not address the main issue of whether lactic acid produced in a muscle is advantageous or disadvantageous.

When arguing that intracellular acidification is deleterious, Bangsbo and Juel do not refer to the large body of data published over the last 15 years showing that acidification does not inhibit physiological Ca\(^{2+}\) release (4, 6, 9). Furthermore, they do not appreciate that inhibition of Ca\(^{2+}\) uptake at acid pH

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actually favors increased force production. They do evidently agree with our findings (7) that intracellular lactate per se does not reduce the force response. The cited experiments where lactate was applied outside muscles (2, 8) do not show that lactate is deleterious, because there was an appreciable to very large increase in extracelllular osmolality, which would have drawn water out of the muscles and had direct inhibitory effects by increasing intracellular ionic strength (3).

In conclusion, the case for beneficial effects of lactic acid accumulation is clear.

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REBUTTAL FROM DRS. BANGSBO AND JUEL

We have read the contribution by Lamb and Stephenson with great interest. It was, however, a challenge to find data supporting their hypothesis. Most of the arguments seem to be based on speculation. They refer to a few human studies, and we agree that “extracellular K\(^+\) does rise to critical levels during normal exercise.” However, the argument that “it seems very likely that the decrease in intracellular pH has substantial beneficial effects in exercising humans by delaying the onset of fatigue” does not have experimental support. In contrast, a number of studies have shown that lowered pH leads to a greater potassium release and potassium accumulation in muscle interstitium, as we have described in our contribution. Furthermore, that the McArdle patients display faster onset of fatigue due to lack of lactate accumulation is hard to follow. Fatigue in these patients is more likely related to a high K\(^+\) efflux and the reduced number of Na\(^+\)-K\(^+\) pumps compared with control subjects (3).

The arguments for a positive role of lactic acid are based on studies of isolated noncontracting muscle and skinned muscle fibers. In our review we argued that these results represented artificial nonexercise-related conditions and it is not possible to extrapolate to the in vivo condition.

The argument that the results we obtained with isolated rat muscle incubated in Na-lactate are not valid because of progressive developing anoxic conditions (2) can be rejected, because the force reduction was obtained already in the first bout of activity (4).

It is argued by Lamb and Stephenson that the high K\(_{\text{in}}\) for the lactate/H\(^+\) cotransporter MCT4 in fast-twitch muscle is to allow for lactic acid accumulation, and this notion is used to support the theory that high lactate concentrations delays fatigue. They wrote “This must be beneficial . . .,” which is not a very strong argument. It could as well be that the high lactate is protecting the muscle cell from reaching a situation of very low ATP levels. The capacity for lactate/H\(^+\) transport in human muscle is increased by training and there is a positive correlation between transport capacity (i.e., efflux) and performance (5); these findings further suggest that lactic acid accumulation is a disadvantage.

In the 1990s, we argued that high lactate and low muscle pH is not the primary cause of fatigue in humans (1), but it seems to contribute during intense exercise. As it currently stands, evidence is still lacking that this is not the case.

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