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Lactic acid buffering, nonmetabolic CO_2 and exercise hyperventilation: A critical reappraisal

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Abstract

It has been suggested that hyperventilation and the disproportionate increase in $\dot{V}_{CO_2}$ versus $\dot{V}_{O_2}$ above the ventilatory threshold (V_{TH}) in ramp exercise are due to the production of nonmetabolic CO_2 in muscle because of lactic acid buffering by plasma bicarbonate entering the cell in exchange with lactate [Wasserman, K., 1982. Dyspnea on exertion. Is it the heart or the lungs? JAMA 248, 2039–2043]. According to this model, plasma standard bicarbonate concentration decreases in a ∼1:1 ratio with the increase in plasma lactate concentration, 1 mmol of CO_2 is generated above that produced by aerobic metabolism for each mmol of lactic acid buffered, and nonmetabolic CO_2 produced in the muscle is partly responsible for hyperventilation because of the resulting increase in the CO_2 flow to the lungs. The present report shows that this model is not consistent with experimental data: (1) bicarbonate is not the main buffer in the muscle; (2) the decrease in standard bicarbonate concentration is not the mirror image of the increase in lactate concentration; (3) buffering by bicarbonate does not increase CO_2 production in muscle (no nonmetabolic CO_2 is produced in tissues); (4) the CO_2 flow to the lungs, which should not be confused with $\dot{V}_{CO_2}$ at the mouth, does not increase at a faster rate above than below V_{TH}. The disproportionate increase in $\dot{V}_{CO_2}$ at the mouth above V_{TH} is due to hyperventilation (not the reverse) and to the low plasma pH which both reduce the pool of bicarbonate readily available in the body.

Keywords: Acid–base balance; Buffers; Lactate; Bicarbonate; Ventilatory threshold; Exercise test

Contents

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1. Introduction

This report re-examines a comprehensive model of acid–base balance and hyperventilation in response to exercise (Wasserman, 1982), which has been widely accepted and which is a central tenet in the interpretation of clinical exercise testing of patients with cardiopulmonary diseases (Wasserman, 1986b, 1988, 1997, 2002b; Casaburi et al., 1987, 1989, 1991; Wasserman and Sietsema, 1988; Patessio et al., 1992; Patessio and Donner, 1994; Johnson et al., 2003; Wasserman et al., 2005). This model is as follows (Fig. 1). Bicarbonate is the main buffer in the muscle, and the disproportionate increase in $\dot{V}_{CO_2}$ at the mouth above the ventilatory threshold (V_{TH}) reflects the production of extra CO_2 due to lactic acid buffering by plasma bicarbonate entering the cell in exchange with lactate. Plasma standard bicarbonate concentration decreases in an almost 1:1 ratio with the increase in plasma lactate concentration. For each mmol of lactic acid buffered in the muscle, 1 mmol (22.3 mL) of extra CO_2 is generated above that produced by aerobic metabolism. According to the model, this extra CO_2 also called "buffer" CO_2 (Wasserman, 1994; Zhang et al., 1994) or "nonmetabolic" CO_2 (Anderson and Rhodes, 1991; Patessio et al., 1992; Roecker et al., 2000) is in turn considered to be partly responsible for hyperventilation above V_{TH} because the resulting increase in CO_2 flow to the lungs is thought to stimulate pulmonary ventilation ($\dot{V}_E$) (Wasserman et al., 1977a,b, 1980, 1986b).

The main experimental arguments offered in support of this model are the reportedly close inverse relationship between changes in plasma lactate and bicarbonate concentrations, and the close relationship between $\dot{V}_{CO_2}$ at the mouth and $\dot{V}_E$ in a wide variety of situations. These arguments are presented in the original paper in which the model has been suggested

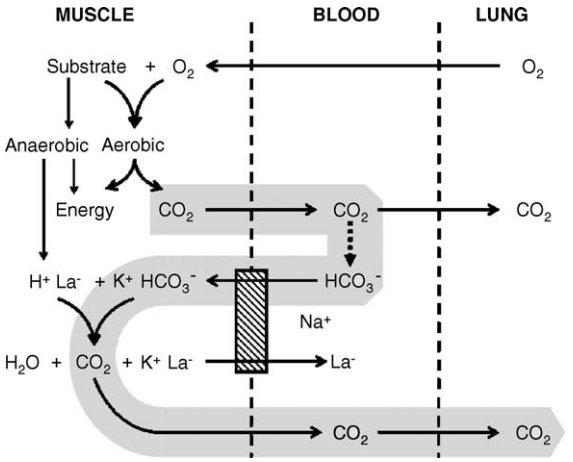

Fig. 1. The model for lactic acid buffering by bicarbonate, and the control of hyperventilation above V_{TH}: redrawn from Wasserman et al. (2005) (Fig. 2.2). According to this model (solid arrows), lactic acid is buffered in the muscle by plasma bicarbonate entering the cell in exchange with lactate through an antiport carrier mechanism (hatched box); plasma standard bicarbonate decreases in an almost 1:1 ratio with the increase in plasma lactate concentration, while lactic acid buffering by bicarbonate produces CO_2 in excess over that produced by aerobic metabolism (1 mmol or ~22.3 mL of CO_2 for each mmol of lactic acid buffered); the extra nonmetabolic CO_2 produced in the muscle increases the CO_2 flow to the lung, and this is one factor responsible for hyperventilation above V_{TH}. The dotted arrow between CO_2 produced by aerobic metabolism and bicarbonate, and the large shaded arrow in inverted S, which have both been added by us, show that the CO_2 released in the lung actually derives from the CO_2 produced by aerobic metabolism: no extra nonmetabolic CO_2 is produced in the process of lactic acid buffering by bicarbonate (see Section 4).

(Wasserman, 1982) as well as in several subsequent reviews (Wasserman, 1984a,b, 1986a,b, 1987, 1988, 2002a; Wasserman et al., 1986a,b, 1990, 1994; Wasserman and Casaburi, 1991; Whipp and Ward, 1991), and in a book (Wasserman et al., 2005). However, as explained in the present report and in contrast to the

assertions of the model, experimental data show that: (1) bicarbonate is not the main buffer in the muscle; (2) the decrease in plasma standard bicarbonate concentration during exercise is not the mirror image of the increase in plasma lactate concentration; (3) H^+ buffering by bicarbonate does not increase CO_2 production in the muscle over what is produced by aerobic metabolism (in other words, no nonmetabolic CO_2 is produced in the muscle); (4) the CO_2 flow to the lungs (which is confused with $\dot{V}_{CO}$ at the mouth in the model) does not increase with workload at a faster rate above than below V_{TH}; (5) the increase in $\dot{V}_E$ above V_{TH} is not due to the increase in $\dot{V}_{CO}$ at the mouth; (6) on the contrary, and as suggested before 1982 (Hill et al., 1924; Naimark et al., 1964; Wasserman and McIlroy, 1964), the disproportionate increase in $\dot{V}_{CO}$ at the mouth above V_{TH} is due both to the increase in $\dot{V}_E$ and the ensuing reduction in Pa_{CO_2}, and to the reduction in arterial pH.

2. Bicarbonate is not the main buffer of H^+ in the muscle cell

The model in Fig. 1 is based on the hypothesis that "bicarbonate is the primary buffer for the new H^+" released in the muscle cell (Wasserman et al., 2005; p. 28). It is recognized that protein and phosphate buffer systems are available and that creatine formed from the splitting of creatine phosphate might buffer the initial increase in lactic acid (Beaver et al., 1986a). However, based on changes in plasma bicarbonate and plasma lactate concentration, it was concluded that these intracellular buffers and other extra cellular buffers were only responsible for ~8% of the buffering, and thus that bicarbonate buffers ~92% of the H^+ released in the muscle during exercise (Beaver et al., 1986a).

These figures are in complete discordance with what is known about acid–base balance in the muscle (Sahlin et al., 1978; Hultman and Sahlin, 1980; Parkhouse and McKenzie, 1984; Johnson et al., 1996; Walter et al., 1999; Kemp et al., 2001; Heisler, 2004). There are in fact several buffers in the muscle, and bicarbonate, which is one of them only buffers at most ~25% of the muscle H^+ load during dynamic exercise (Hultman and Sahlin, 1980) (Fig. 2).

The total buffer capacity of the muscle (β_m, in Δmmol $H^+ L^{-1} \Delta pH^{-1}$, or slykes) estimated by titration of muscle homogenates or in response to

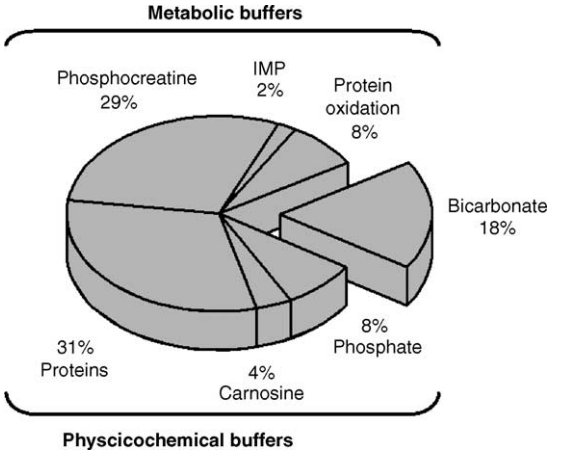

Fig. 2. Contributions of the various buffers and buffer mechanisms to the removal of the muscle H^+ load during dynamic exercise: drawn from data compiled by Hultman and Sahlin (1980). The contribution of bicarbonate was only estimated to be 6% in response to isometric exercise (a situation, where muscle blood flow and CO_2 removal from the muscle is impaired) indicating that bicarbonate mainly acts in the muscle as a diffusible buffer.

exercise from changes in muscle pH and changes in the H^+ load of the muscle (Sahlin, 1978; Mannion et al., 1993) is ~63 slykes (Table S1 and Fig. S1 in Supplementary data). From a functional point of view when muscle lactate concentration increases from an average value of 1.5 mmol/L at rest (see Table S1) to maximal values close to 45 mmol/L for very intense exercise (Sahlin et al., 1976; Spriet et al., 1987; Kowalchuk et al., 1988), muscle pH decreases from ~7.09 (see Table S1) to an average minimal value of ~6.4, i.e., $7.09 - [(45 - 1.5)/63]$.

Total β_m is the sum of the respective capacities of the various buffers or buffering mechanisms in the muscle (Parkhouse and McKenzie, 1984; Heisler, 2004). These include fixed physicochemical buffers, the consumption of H^+ by metabolic buffers, the reduction in muscle bicarbonate concentration (Parkhouse and McKenzie, 1984), and diffusion of H^+ outside the cell through the Na^+/H^+ exchanger system (Juel, 2000). The contribution of bicarbonate to the acid–base balance in the muscle during exercise is mainly due to the marked reduction in muscle bicarbonate concentration when muscle pH falls (Sahlin et al., 1978; Kowalchuk et al., 1988). Since bicarbonate actually leaves the cell under the form of CO_2, 1 mmol of H^+/L is removed for each 1-mmol/L reduction in

muscle bicarbonate (Sahlin, 1978). The amount of H^+ buffered thus depends on the initial and final muscle bicarbonate concentrations, which in turn depend on the initial and final muscle pH and P_{CO_2} according to Henderson–Hasselbalch's equation:

$$\mathrm{pH} = 6.1 + \log \frac{[\text{bicarbonate}]}{[0.03 \times P_{CO_2}]} \quad (1)$$

$$\text{hence } [\text{bicarbonate}]\,(\text{mmol/L}) = [0.03 \times P_{CO_2}] \times 10^{\mathrm{pH}-6.1} \quad (2)$$

Muscle P_{CO_2} is close to the muscle venous effluent P_{CO_2} (Pv_{CO_2}) (Sahlin et al., 1978). At rest, bicarbonate concentration in the muscle is much lower than that in plasma (Khuri et al., 1976; Sahlin et al., 1978; Heisler, 2004) because muscle pH is much lower than arterial pH, e.g., only ~13 mmol/L for muscle P_{CO_2} and pH equal to ~45 mmHg (Sahlin et al., 1978) and 7.09, respectively. In response to high intensity exercise the increase in muscle P_{CO_2} (Pv_{CO_2} ~ 80–100 mmHg) (Sahlin et al., 1978; Kowalchuk et al., 1988; McKenna et al., 1997a) is more than compensated for by the reduction in muscle pH (~6.4), and muscle bicarbonate concentration decreases to very low values (~5–6 mmol/L) (Sahlin et al., 1978). Thus, when the muscle H^+ load increases by ~44 mmol/L and muscle pH falls from ~7.09 to ~6.4, the amount of H^+, which is removed by bicarbonate acting as a diffusible buffer is ~7–8 mmol/L or ~16–18% of the H^+ load.

Bicarbonate also acts as a fixed physicochemical buffer but it is a weak fixed physicochemical buffer in the muscle, first because its concentration is low at rest and decreases in response to exercise (as seen above), and secondly because its pK is much lower than muscle pH at rest or exercise. The buffer capacity of bicarbonate acting as a fixed physicochemical buffer (β_{CO_2}) is given by the first derivative versus pH of the Henderson–Hasselbalch's equation applied to carbonic acid (Kemp et al., 2001):

$$\beta_{CO_2} = \frac{2.3[\mathrm{C}]}{(1 + 10^{\mathrm{pH}-\mathrm{p}K}) \times (1 + 10^{\mathrm{p}K-\mathrm{pH}})} \quad (3)$$

In this equation, pH is muscle pH and [C] (mmol/L) is the total concentration of the buffer:

$$[\mathrm{C}] = [\text{carbonic acid}] + [\text{bicarbonate}] = (0.03 \times P_{CO_2}) + (0.03 \times P_{CO_2} \times 10^{\mathrm{pH}-\mathrm{p}K}) \quad (4)$$

where P_{CO_2} is muscle P_{CO_2}. The low value of pK (6.1) results in high values for the denominator in Eq. (3), while [C] is low both at rest (P_{CO_2} ~ 45 mmHg, pH ~ 7.09, hence [C] ~ 14 mmol/L) and exercise (P_{CO_2} ~ 80–100 mHg, pH ~ 6.4, hence [C] ~ 7–9 mmol/L). The end result is the very low value for β_{CO_2} both at rest and exercise: ~3 and ~4.5 slykes, respectively, corresponding to only 5–7% of total β_m (~63 slykes).

These estimations of the contribution of bicarbonate to the removal of the muscle H^+ load (~16–18% as a diffusible buffer; ~5–7% as a fixed physicochemical buffer), are well in line with those made by Hultman and Sahlin (1980) (Fig. 2), and show that bicarbonate is not the main buffer in the muscle and does not buffer ~92% of the H^+ released in the muscle during dynamic exercise. As summarized in Fig. 2 the main physicochemical buffers in the muscle are the histidine residues in proteins and carnosine, and phosphate, while the main metabolic buffers are the breakdown of phosphocreatine, and ammonia formation (in the deamination of AMP in IMP, and in protein oxidation) (Hultman and Sahlin, 1980). These respective contributions of the various buffers and buffer mechanisms to the control of muscle acid–base balance during exercise illustrated in Fig. 2 should be taken as estimates. However, these figures, and in particular, the comparatively low contribution of the bicarbonate buffer have been confirmed by studies conducted on isolated muscle (Heisler, 2004) or in man using magnetic resonance spectroscopy (Walter et al., 1999; Kemp et al., 2001) or the physicochemical approach of Stewart (Kowalchuk et al., 1988). Thus, as far as the model in Fig. 1 is concerned, the hypothesis that bicarbonate is the main buffer in the muscle cell is not supported by any experimental evidence.

3. Standard bicarbonate is not the mirror image of lactate concentration

One of the experimental arguments in support of the model in Fig. 1 is the assertion that above V_{TH}, the reduction in standard plasma bicarbonate concentration is almost equal to the increase in plasma lactate concentration as soon as lactate concentration increases by ~0.5 to ~1 mmol/L (Wasserman, 1987, 1988; Wasserman et al., 1990; Wasserman and Casaburi, 1991). This is offered as evidence that lactate leaving the

muscle and plasma bicarbonate entering the muscle are exchanged in a 1:1 ratio through an antiport in the fiber membrane (Wasserman et al., 2005; p. 28), and that plasma bicarbonate entering the muscle cell buffers lactic acid. There is, however, no molecular basis and no evidence for a bicarbonate–lactate antiport carrier mechanism in the sarcolemma. Lactate is actually transported across the sarcolemma by two types of monocarboxylate transporters (MCT1 and MCT4) which act as symports and carry lactate along with H^+ (Juel and Halestrap, 1999; Bonen, 2001; Juel, 2001). In addition, the model in Fig. 1 does not account for the large release of H^+ observed from the exercising muscle and for the resulting reduction in plasma pH (Osnes and Hermansen, 1972; Sejersted et al., 1984; Bangsbo et al., 1992, 1997; Juel et al., 2004) since according to the mechanisms described, the buffering entirely occurs in the muscle with no H^+ being released in the blood.

3.1. Relationship between standard bicarbonate and lactate

The most serious problem with the hypothesis that changes in plasma bicarbonate are mirror image of those in plasma lactate concentration is that, although the general trend is for plasma lactate concentration to increase and for plasma standard bicarbonate concentration to decrease in response to exercise (Bouhuys et al., 1966; Wasserman et al., 1967; Osnes and Hermansen, 1972; Stringer et al., 1992), these variables actually do not always change in a 1:1 ratio. A remarkable correspondence between changes in lactate and standard bicarbonate concentrations was reported in each of the 10 subjects studied by Beaver et al. (1986a) but this phenomenon appears to be the exception rather than the rule. In the original study by Wasserman et al. (1967) and in the subsequent study by Stringer et al. (1992), a wide dispersion of the data points (∼3 mmol/L) was observed around the regression line of changes in standard bicarbonate concentration versus changes in plasma lactate concentration, particularly for increases in lactate concentration <6 mmol/L, where most of the observations were made. In addition, in both studies, for the largest changes in lactate concentration (∼10–16 mmol/L) the average changes in standard bicarbonate concentrationwere ∼1–1.5 mmol/L lower. The 106 data points from 38 studies plotted in Fig. 3 confirm that in response to exercise, standard bicarbonate concentration does not decrease with the increase in lactate concentration in a 1:1 ratio. In addition, as already observed (Bouhuys et al., 1966; Wasserman et al., 1967; Stringer et al., 1992), the regression line does not coincide with the identity line; when lactate concentration increases, the reduction in standard bicarbonate concentration becomes progressively smaller than the increase in lactate concentration.

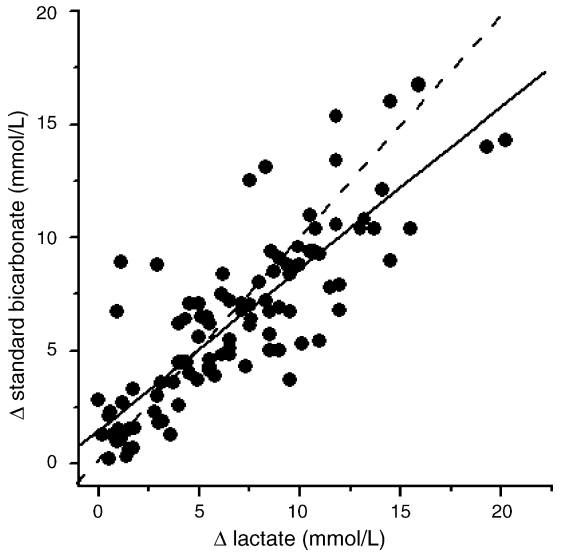

Fig. 3. Relationship between the reduction in plasma standard bicarbonate concentration (Δ standard bicarbonate) and the increase in plasma lactate concentration (Δ lactate) observed in 38 studies (106 data points: see details in Table S2 in Supplementary data; the dotted line is the identity line).

The progressive widening of the average lactate versus standard bicarbonate concentration difference with increasing lactate concentrations has to be expected since the maximum possible reduction in standard bicarbonate (∼24 mmol/L, i.e., the resting plasma bicarbonate concentration) is lower than the maximal possible increase in lactate concentration (∼30 mmol/L) (Osnes and Hermansen, 1972). The observation that changes in standard bicarbonate are not tightly related to those in lactate concentration should also be expected on the basis of the relationships between lactate concentration, pH, Pa_{CO_2} and standard bicarbonate concentration as detailed in the following section.

3.2. Relationships between lactate, pH, Pa_{CO_2} and standard bicarbonate

For a given hemoglobin concentration there exists only one value of standard bicarbonate for a given set of pH and Pa_{CO_2} without any possible variation (Siggaard Andersen, 1963; Sato et al., 1983). In contrast, the relationships between pH and Pa_{CO_2} on one hand and plasma lactate on the other hand, reflect biological phenomena which are subjected to variations including those due to pathological conditions. As for the relationship between lactate and pH, in response to exercise the release of H^+ from the muscle cell is higher and not closely related to that of lactate (Osnes and Hermansen, 1972; Sejersted et al., 1984; Bangsbo et al., 1992; Juel et al., 2004). In addition, changes in pH are not tightly related to those in the H^+ load of the blood. This is due to the fact that the capacity of fixed physicochemical buffers in the blood varies (e.g., with protein and hemoglobin concentrations, and with hemoglobin saturation) and that the ventilatory compensation of metabolic acidosis also varies. For example, pH is better maintained in a subject with a high than a low ventilatory response ("responder" versus "nonresponder") (Wasserman and Casaburi, 1991), and a lower pH is observed in asthmatic patients with carotid body resection and a blunted ventilatory response to exercise than in control healthy subjects (Wasserman et al., 1975). Consequently, although pH decreases when lactate concentration increases, a wide dispersion of the data points is observed when pH (or $[H^+]$) values are plotted against lactate concentration (Osnes and Hermansen, 1972; Sejersted et al., 1984; Medbo and Sejersted, 1985; Casaburi et al., 1991; Ratel et al., 2002).

As for the relationship between lactate and Pa_{CO_2}, the general trend in healthy subjects is for Pa_{CO_2} to decrease when lactate increases (Sejersted et al., 1984; Medbo and Sejersted, 1985; Casaburi et al., 1991; Hirakoba and Yunoki, 2002). However, changes in Pa_{CO_2} are not linked to changes in lactate concentration but are entirely dependent on the ventilatory response to exercise. This explains that changes in Pa_{CO_2} and in lactate concentration in response to exercise are not closely related (Sejersted et al., 1984; Medbo and Sejersted, 1985; Casaburi et al., 1991) and can actually be totally dissociated. For example in patients with obstructive lung disease both Pa_{CO_2} and lactate concentration increase in response to exercise (Casaburi et al., 1991). In contrast, in patients with McArdle disease, Pa_{CO_2} decreases because of hyperventilation although lactate concentration does not change (Hagberg et al., 1990). In healthy subjects a ~25% voluntary reduction in $\dot{V}_E$ (Sharp et al., 1991) or breath holding (Matheson and McKenzie, 1988) do not modify lactate concentration but increase Pa_{CO_2}. Finally, when compared to a subject with a large ventilatory response to exercise, or "responder", Pa_{CO_2} is higher in a "nonresponder" although plasma lactate concentration is similar (Wasserman and Casaburi, 1991).

The end result of the fixed relationship between standard bicarbonate, pH and Pa_{CO_2} on one hand, and of the loose relationships between lactate concentration, pH and Pa_{CO_2} on the other hand, is that changes in standard bicarbonate concentration in response to ramp exercise are only weakly related to those in lactate concentration (Fig. 3). As a consequence, the assertion that changes in these two variables "*are virtually mirror images of each other*" (Wasserman et al., 1994) is a factual error and thus cannot be offered in support to the model depicted in Fig. 1 or to the hypothesis that plasma bicarbonate entering the muscle is the main buffer of lactic acid.

4. Lactic acid buffering by bicarbonate does not generate CO_2 in tissues

One of the main assertions of the model in Fig. 1 is that lactic acid buffering by bicarbonate generates CO_2 in the muscle in addition to the CO_2 produced by aerobic metabolism, with "approximately 22.3 mL of CO_2 [. . .] produced over that from aerobic metabolism for each mmol of lactic acid buffered by HCO_3^-" (Wasserman et al., 2005; p. 28). This is offered as an argument to explain the "*obligatory*" increase in $\dot{V}_{CO_2}$ in tissues and at the mouth accompanying lactic acid production and buffering (e.g., Ozcelik et al., 1999). One problem with this phenomenon is the hypothesis that carbonic acid produced in the buffering of lactic acid by bicarbonate is converted into water and CO_2, and that the CO_2 diffuses into the blood to be carried under this form to the lung. This is very unlikely to occur because bicarbonate is not a volatile buffer in the muscle, where there is no gas phase for CO_2 to escape (Heisler, 2004). Since only small amounts of CO_2 can be dissolved in the cytosol or in the plasma, carbonic acid will be dissociated into H^+ and bicarbonate, and

any CO_2 escaping from the muscle into the blood will be quickly converted into bicarbonate.

A most serious problem with the mechanism depicted in Fig. 1 lies in the idea that lactic acid buffering by bicarbonate *produces* extra nonmetabolic CO_2 in the muscle. This is a misconception due to an incorrect mass balance of CO_2 in the reactions depicted in Fig. 1, which in turn stems from the fact that the source of plasma bicarbonate which is thought to enter the muscle, is not explicitly recognized. Plasma bicarbonate actually derives from "metabolic" CO_2 produced by aerobic metabolism, which diffuses into the blood, where it is converted into carbonic acid and bicarbonate (dotted arrow added by us in Fig. 1). Accordingly, lactic acid buffering by bicarbonate in the muscle, as hypothesized in the model in Fig. 1, should be explicitly written as follows:

$$\text{substrates} + O_2 \rightarrow H_2O + CO_2(\text{metabolic}) \quad (5)$$

$$(\text{metabolic})\, CO_2 + H_2O \rightarrow H^+ + \text{plasma}\, HCO_3^- \quad (6)$$

$$\text{plasma}\, HCO_3^- \rightarrow \text{intracellular}\, HCO_3^- \ (\text{i.e., } K^+ HCO_3^-) \quad (7)$$

$$H + \text{lactate}^- + K^+HCO_3^- \rightarrow K^+\, \text{lactate}^- + H_2O + CO_2\ (\text{nonmetabolic}) \quad (8)$$

This set of balanced reactions shows that the same amount of CO_2 is present in the right hand-side of Eq. (8) than in the right hand-side of Eq. (5) (see also Fig. 1). Consequently, the assertion that in the process of lactic acid buffering by bicarbonate 22.3 mL (or any other amount; Whipp and Ward, 1991) of CO_2 are *produced* in the muscle for each mmol of lactic acid buffered and, thus, the mere concept of extra nonmetabolic CO_2 which is central in the model in Fig. 1, are violations of the law of mass conservation and are untenable.

5. The CO_2 flow to the lungs levels off above V_{TH}

Consistent with the hypothesis of nonmetabolic CO_2 production in the muscle due to lactic acid buffering by bicarbonate, the model in Fig. 1 predicts that above V_{TH} the CO_2 flow to the lung increases. The CO_2 flow to the lung, or $\dot{Q}\bar{v}_{CO_2}$, in L of CO_2/min, is equal to $\dot{Q}_c \times C\bar{v}_{CO_2} \times 10^{-3}$, where $\dot{Q}_c$ and $C\bar{v}_{CO_2}$ are, respectively, the cardiac output in L/min, and the CO_2 content in mixed venous blood in mL/L. The increase in $\dot{Q}\bar{v}_{CO_2}$ above V_{TH} is considered to be one factor responsible for hyperventilation (Wasserman et al., 1977a,b, 1980, 1986b) although the hypothesis of a control of $\dot{V}_E$ by $\dot{Q}\bar{v}_{CO_2}$ through putative CO_2 receptors in the pulmonary artery, the lungs or the right heart has not been convincingly verified (Powers and Beadle, 1985; Forster, 2000). In addition, no experimental data have been offered in support of the assertion that $\dot{Q}\bar{v}_{CO_2}$ increases with workload and $\dot{V}_{O_2}$ at a faster rate above than below V_{TH}. On the contrary recent observations by Sun et al. (2001) actually show that the increase in $\dot{Q}\bar{v}_{CO_2}$ is much faster below than above V_{TH}, and that $\dot{Q}\bar{v}_{CO_2}$ tends to level off above V_{TH}. Data from Sun et al. (2001) (Table 1 and Fig. 4) show that $\dot{Q}_c$ increased almost linearly with $\dot{V}_{O_2}$ up to $\dot{V}_{O_2}$ max. As for $C\bar{v}_{CO_2}$ it also increased with $\dot{V}_{O_2}$ but peaked at ~60% $\dot{V}_{O_2}$max ($\dot{V}_{O_2}$ = 2.32 L/min) i.e., slightly above the "lactic acid threshold" which was detected using the "V-slope" method (Beaver et al., 1986b) and is actually the V_{TH}. A sharp decline in $C\bar{v}_{CO_2}$ was observed thereafter in spite of the sustained increase in $P\bar{v}_{CO_2}$. The increase in CO_2, which was linear up to V_{TH}, was thus much slower thereafter. In fact, $\dot{Q}\bar{v}_{CO_2}$ began to level off at ~70% O_2 max and was stable between ~85% $\dot{V}_{O_2}$ max and $\dot{V}_{O_2}$ max.

As discussed by Sun et al. (2001), the reduction in $C\bar{v}_{CO_2}$ above V_{TH}, which is the main factor for the eventual leveling off of $\dot{Q}\bar{v}_{CO_2}$, is due to the fall in pH $\bar{v}$. This reduces the amount of CO_2 present in the mixed venous blood because the concentration of bicarbonate in the blood (which is the main form of CO_2 transport) decreases with pH (Eq. (2)). Thus, in contrast to the assertion of the model in Fig. 1, the increase in the CO_2 flow to the lungs with workload or $\dot{V}_{O_2}$ is not faster above than below V_{TH}. This phenomenon should thus not be called upon to explain hyperventilation above V_{TH}. In addition there is no relevance to further discuss and investigate the possible mechanisms by which an increased CO_2 flow to the lungs beyond V_{TH} could stimulate $\dot{V}_E$.

6. Excess CO_2 released at the mouth and nonmetabolic CO_2

According to the model in Fig. 1 the excess CO_2 released at the mouth is the extra nonmetabolic CO_2 produced in the muscle due to lactic acid buffering

Table 1
Changes in the CO_2 flux to the lungs ($\dot{Q}\bar{v}_{CO_2} = \dot{Q}_c \times C\bar{v}_{CO_2} \times 10^{-3}$) in response to maximal ramp exercise

Exercise level	$\dot{V}_{O_2}$ (L/min[a])	$\dot{V}_{CO_2}$ (L/min[b])	$\dot{Q}_c$ (L/min[c])	$P\bar{v}_{CO_2}$ (mmHg)	$C\bar{v}_{CO_2}$ (mL CO_2/L[d])	$\dot{Q}\bar{v}_{CO_2}$ (L CO_2/min)
Rest	.38	0.28	6.66	46.8	510.5	3.40
Unloaded	.72	0.43	9.38	48.9	523.5	4.92
Ex-1	1.08	0.75	11.90	50.7	538.3	6.41
Ex-2	1.38	0.86	13.27	51.3	546.1	7.24
Ex-3	1.62	1.04	15.40	54.2	551.0	8.48
LAT	2.02	1.59	17.45	58.6	570.3	9.95
Ex-5	2.32	1.96	18.24	61.9	578.4	10.55
Ex-6	2.74	2.33	20.48	63.5	577.5	11.83
Ex-7	3.08	2.89	21.36	67.1	572.1	12.22
Ex-8	3.38	3.39	22.31	70.7	563.1	12.56
Max	3.91	4.61	23.26	78.1	534.9	12.44

Data are from Tables 1, 2 and 6 in the study by Sun et al. (2001) or computed from the data in these tables (see footnotes).
[a] From $\dot{V}_{O_2}$max (3.91 L/min) and the ratio $\dot{V}_{O_2}/(\dot{V}_{O_2}$ at the lactate threshold or LAT).
[b] From $(\bar{v} - a)_{CO_2}$ and $\dot{Q}_c$ determined by Fick's equation applied to CO_2.
[c] Average between $\dot{Q}_c$ determined by Fick's equation applied to CO_2 and O_2.
[d] From the value in mmol/L.

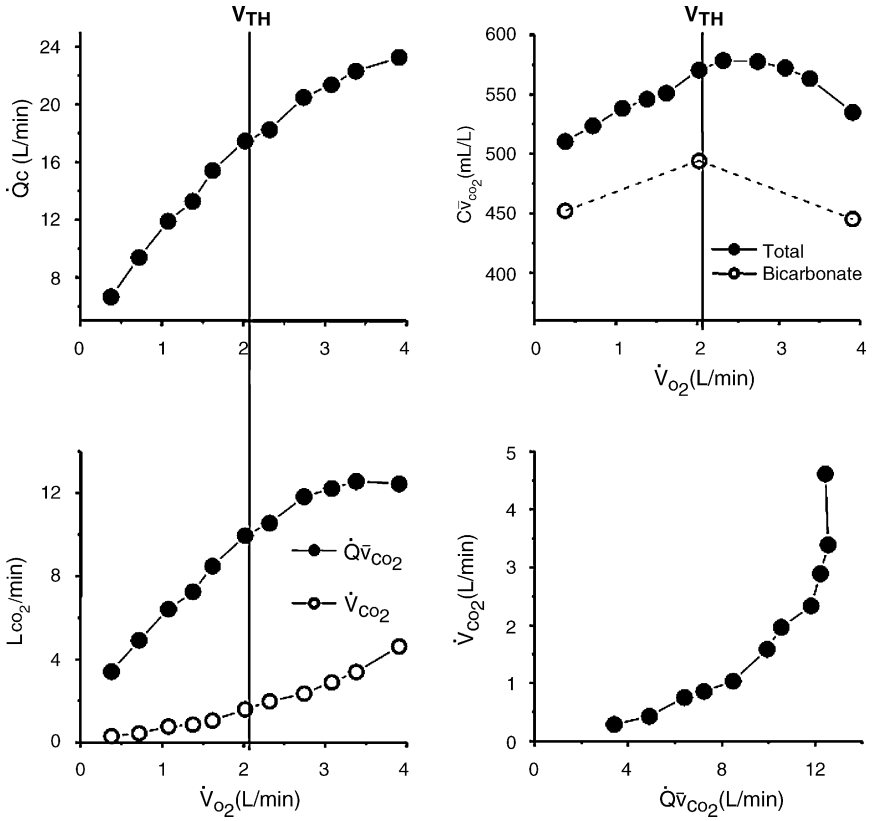

Fig. 4. Changes in the CO_2 flow to the lungs ($\dot{Q}\bar{v}_{CO_2}$) and its determinants in response to ramp exercise. In order to show the independence of $\dot{V}_{CO_2}$ from $\dot{Q}\bar{v}_{CO_2}$, these variables are plotted against $\dot{V}_{CO_2}$ (left bottom panel) and against each other (right bottom panel). Drawn from the data in Table 1 (Sun et al., 2001).

by bicarbonate and is equal, mole for mole, to the amount of lactic acid produced and buffered by bicarbonate. Based on this hypothesis several studies have attempted to estimate lactic acid production from the excess CO_2 released at the mouth (e.g., Ardevol et al., 1997; Roecker et al., 2000). These attempts were bound to fail because no nonmetabolic CO_2 is actually *produced* in the muscle, and because the excess CO_2 released at the mouth, which actually derives from the body CO_2 stores, is indirectly and weakly related to the amount of lactic acid produced or accumulated. This is well exemplified in response to high intensity short duration exercise in which changes in muscle and plasma lactate concentrations, and the oxygen deficit indicate that the amount of lactate accumulated is ∼0.7 mole (Medbo and Sejersted, 1985; Lacour et al., 1990). According to the model in Fig. 1, a similar amount of nonmetabolic CO_2 should be produced in the muscle, increasing $\dot{V}_{CO_2}$ at the mouth and/or the body CO_2/bicarbonate stores by ∼15 L (22.3 L CO_2/mole of lactic acid). Experimental data, however, show that this is not the case. For example, in the study by McKenna et al. (1997b), in response to a 30 s exercise leading to exhaustion, with plasma lactate concentration increasing to 16.2 mmol/L, the volume of CO_2 released at the mouth during the exercise and the subsequent 5-min recovery period only exceeded $\dot{V}_{O_2}$ by ∼6–7 L. In addition, the ∼45–55% reduction in the CO_2 content of the arterial and venous blood showed that the body CO_2 stores did not increase but actually decreased. Thus, in a situation, where the model in Fig. 1 predicts the appearance of a large amount of nonmetabolic CO_2, this phenomenon fails to materialize.

Prior to the introduction of the model (Wasserman, 1982) the excess CO_2 released at the mouth during ramp exercise above V_{TH}, was thought to derive from the pool of bicarbonate readily available in the blood and in well perfused tissues including the working muscles during exercise, with ∼0.4 L of CO_2 released for each 1-mmol/L reduction in plasma bicarbonate concentration (Wasserman and Whipp, 1975). Data from the two companion papers by McKenna et al. (1997a,b) provide an experimental support for this original explanation and these figures. Indeed, plasma bicarbonate concentration decreased by ∼15 mmol/L both in the arterial and peripheral venous blood (McKenna et al., 1997a), corresponding to ∼6 L of CO_2 released from the body CO_2 stores (15 mmol/L × 0.4 L for each mmol/L). This compares very well with the volume actually measured at the mouth (∼6–7 L) (McKenna et al., 1997b) and further confirms that the excess $\dot{V}_{CO_2}$ released at the mouth above V_{TH} is not the putative nonmetabolic CO_2 produced in tissues, but simply derives from the pool of CO_2 readily available under the form of bicarbonate in the body.

7. $\dot{V}_{CO_2}$ is not the CO_2 flow to the lungs

One of the experimental arguments in support of the hypothesis that the increase in $\dot{V}_E$ is due to an increase in the CO_2 flow to the lungs, is the observation that during exercise, changes in $\dot{V}_E$ are tightly coupled to changes in $\dot{V}_{CO_2}$ at the mouth in a wide variety of situations (Casaburi et al., 1977, 1987; Diamond et al., 1977; Wasserman et al., 1977a,b, 1986b; Ward et al., 1983; Wasserman and Whipp, 1983; Whipp et al., 1984; Anderson and Rhodes, 1989; Whipp and Ward, 1991; Schneider and Berwick, 1998; Sun et al., 2002). These observations are offered as evidence for "*the primary role of CO_2 flow to the lung in exercise hyperpnea*" (Wasserman et al., 1977a). However, this conclusion is based on the confusion between $\dot{Q}\bar{v}_{CO_2}$ and $\dot{V}_{CO_2}$ at the mouth. Indeed, these observations do not describe a close relationship between $\dot{Q}\bar{v}_{CO_2}$ and $\dot{V}_E$, but between $\dot{V}_{CO_2}$ at the mouth and $\dot{V}_E$. Obviously, $\dot{V}_{CO_2}$ at the mouth is not equal to $\dot{Q}\bar{v}_{CO_2}$ and changes in $\dot{V}_{CO_2}$ at the mouth in response to exercise do not reflect those in $\dot{Q}\bar{v}_{CO_2}$, as shown, for example by data from Sun et al. (2001) discussed above (Table 1 and Fig. 4, right bottom panel). It is thus not warranted to infer a close relationship between $\dot{Q}\bar{v}_{CO_2}$ and $\dot{V}_E$ based on the close association observed between $\dot{V}_{CO_2}$ at the mouth and $\dot{V}_E$.

The confusion between the relationships between $\dot{V}_E$ on one hand, and $\dot{Q}\bar{v}_{CO_2}$ and $\dot{V}_{CO_2}$ at the mouth on the other hand, may stem from the fact that when presenting the model in Fig. 1 or its applications, the relationship between $\dot{V}_{CO_2}$ at the mouth and $\dot{V}_E$ is frequently explained on the basis of the following rearrangement of the equation of alveolar gas (Casaburi et al., 1987, 1991; Patessio et al., 1992; Wasserman et al., 1997, 2005):

$$\dot{V}_E\,(L_{BTPS}/\min) = \frac{K \times \dot{V}_{CO_2}(L_{STPD}/\min)}{Pa_{CO_2} \times (1 - V_D/V_T)} \qquad (9)$$

In this equation (V_D/V_T) is the ratio between dead space and tidal volume, and the conversion factor, K, is equal to 863 at 760 mmHg ([760–47]/0.826). This equation is offered as evidence that $\dot{V}_E$ mechanistically increases when $\dot{V}_{CO_2}$ increases, and thus that "the ventilatory requirement is explicitly dictated by the CO_2 output"(Casaburi et al., 1987). However, the equation of alveolar gas does not indicate that $\dot{V}_E$ is mechanistically determined by $\dot{V}_{CO_2}$ but, on the contrary, that, at steady state, $\dot{V}_{CO_2}$ at the mouth is mechanistically determined by the CO_2 fraction in the alveolar gas (FA_{CO_2}), and the alveolar ventilation ($\dot{V}_A$):

$$\dot{V}_{CO_2} = FA_{CO_2} \times \dot{V}_A$$

This equation can be developed as follows:

$$\dot{V}_{CO_2}(L_{STPD}/\min) = (1/K) \times \dot{V}_E(L_{BTPS}/\min) \times Pa_{CO_2} \times [1 - (V_D/V_T)] \quad (10)$$

and shows that, for a given V_D/V_T, $\dot{V}_{CO_2}$ is determined by $\dot{V}_E$ and Pa_{CO_2}. Although mathematically correct, the rearrangement of Eq. (10) into Eq. (9) does not modify the physiological relationship by which $\dot{V}_{CO_2}$ mechanistically depends on $\dot{V}_E$, and thus cannot be used in support of the contention that $\dot{V}_E$ is determined by $\dot{V}_{CO_2}$.

8. $\dot{V}_{CO_2}$ during ramp exercise: role of hyperventilation and low pH

A counter argument for the assertion that $\dot{V}_{CO_2}$ at the mouth determines $\dot{V}_E$, is the observation that actually $\dot{V}_{CO_2}$ at the mouth follows changes in $\dot{V}_E$, as shown in studies, where $\dot{V}_E$ was voluntarily increased at rest (Brandi and Clode, 1969; Ward et al., 1983) or exercise (Fig. 5) (Jones and Jurkowski, 1979; Haffor et al., 1987; Ozcelik et al., 1999). The reduction of PA_{CO_2} due to hyperventilation favors CO_2 *release* at the mouth without any changes in CO_2 *production* in tissues. This phenomenon is only transient: the reduction in body CO_2 stores results in a reduction in $P\bar{v}_{CO_2}$ (Jones and Jurkowski, 1979; Haffor et al., 1987) and in the flow of CO_2 from the blood to the alveolar gas; $\dot{V}_{CO_2}$ at the mouth diminishes and a new steady-state of gas exchange is established at a higher $\dot{V}_E$ and lower PA_{CO_2} (Brandi and Clode, 1969; Jones and Jurkowski, 1979; Ward et al., 1983; Haffor et al., 1987; Ozcelik et al., 1999) (Eq. (10)). However, in the transition period between the initial and final steady-states, $\dot{V}_{CO_2}$ increases because $\dot{V}_E$ increases, not the reverse. The same phenomenon occurs during ramp exercise above V_{TH} when hyperventilation results in a continuous decrease in PA_{CO_2} and thus in a sustained increase in $\dot{V}_{CO_2}$ at the mouth. Data from Clark et al. (1996) observed in response to a Bruce protocol, show that when $\dot{V}_E$ was voluntarily multiplied by ~1.75 (versus the value observed in the control experiment), $\dot{V}_{CO_2}$ was ~25% higher than in the control experiment, confirming that "$\dot{V}_{CO_2}$ follows $\dot{V}_E$ rather than vice versa".

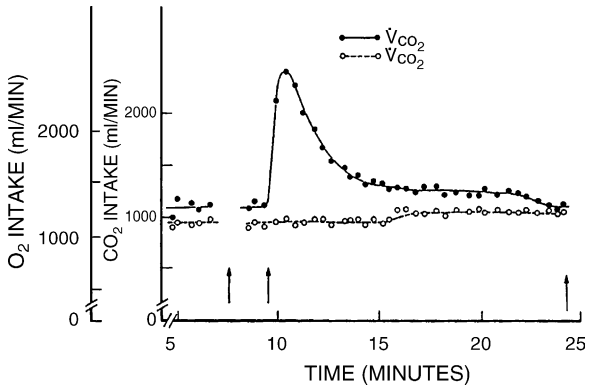

Fig. 5. Transient increase in $\dot{V}_{CO_2}$ at the mouth in response to hyperventilation during moderate exercise. Hyperventilation was initiated at 8 min (second arrow) in order to reduce end tidal P_{CO_2} from ~40 to ~25 mmHg (reproduced from Jones and Jurkowski (1979); used with permission from the American Physiological Society).

The reduction in plasma pH also transiently increases $\dot{V}_{CO_2}$ at the mouth. This is due to the fact that the amount of CO_2 under the form of bicarbonate in the blood decreases with pH (Eq. (2)), and that the CO_2 driven out of the blood is released at the mouth. In addition to the reduction in PA_{CO_2} due to hyperventilation, the reduction in plasma pH during ramp exercise above V_{TH} explains why $\dot{V}_{CO_2}$ at the mouth increases above $\dot{V}_{CO_2}$ in tissues. The role of the reduction in pH in the disproportionate increase in $\dot{V}_{CO_2}$ with workload is well exemplified in a study conducted in patients with McArdle disease (Hagberg et al., 1990). In these patients, a marked hyperventilation was observed at maximal exercise ($\dot{V}_E/\dot{V}_{O_2}$ = 37.9 versus 35.1 in controls; Pa_{CO_2} = 33 mmHg versus 38 mmHg in controls; resting values = 40 mmHg in both groups). In control

subjects, the reduction in Pa_{CO_2} associated with the fall in pH (from 7.41 at rest to 7.33) resulted in a large reduction in plasma bicarbonate concentration (from 24.5 to 19.5 mmol/L), and a substantial increase in $\dot{V}_{CO_2}$ was observed ($\dot{V}_{CO_2}/\dot{V}_{O_2}$ = 1.28 at maximal exercise). In contrast, pH increased from 7.37 to 7.48 in patients because of hyperventilation in absence of metabolic acidosis, and plasma bicarbonate concentration thus increased (from 22.3 to 23.7 mmol/L), in spite of the reduction in Pa_{CO_2}. As a result, $\dot{V}_{CO_2}/\dot{V}_{O_2}$ only increased to 1.02 at maximal exercise.

In response to sustained voluntary hyperventilation during exercise at constant moderate workload, $\dot{V}_{CO_2}$ quickly peaks and then progressively returns towards its initial value (Jones and Jurkowski, 1979; Haffor et al., 1987) (Fig. 5). However, the re-establishment of this new steady-state for gas exchange requires several minutes and thus cannot be achieved during ramp exercise. However, given enough time during exercise above V_{TH}, $\dot{V}_{CO_2}$ at the mouth also stops to closely follow $\dot{V}_E$. This phenomenon is observed during constant workload exercise above V_{TH}, during which $\dot{V}_E$ continuously increases with time while $\dot{V}_{CO_2}$ does not (Overend et al., 1992; Womack et al., 1995; Nielsen et al., 2002; Riley and Cooper, 2002; Perrey et al., 2003), and can even decrease late in the exercise period following a transient increase (Overend et al., 1992). This phenomenon, which is also observed at high workloads during ramp exercise when $\dot{V}_{CO_2}$ progressively fails to closely follow the increase in $\dot{V}_E$, and the ventilatory equivalent of CO_2 increases, is considered to be the onset of the respiratory compensation (Wasserman et al., 1986b), also called the "second V_{TH}" (McLellan, 1985; Smith et al., 1996; Weston and Gabbett, 2001). The dissociation between $\dot{V}_{CO_2}$ and $\dot{V}_E$ observed both during prolonged constant workload and at high workloads during ramp exercise reflects the depletion of the body CO_2 stores, and the inability to further release CO_2 from bicarbonate in spite of the low PA_{CO_2} and pH.

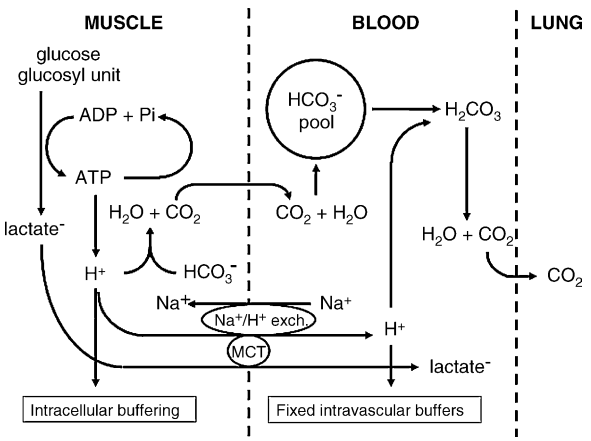

Fig. 6. Acid–base balance in the muscle and plasma CO_2 release from the bicarbonate pool above V_{TH} in response to ramp exercise (see Section 9).

9. Conclusion

In conclusion, the model in Fig. 1 for describing H^+ buffering in the muscle, acid–base balance and hyperventilation in ramp exercise does not appear to be valid. At the present time there is no comprehensive explanation for the control of ventilation in response to exercise below or above V_{TH} (Whipp, 1983; Whipp et al., 1984; Powers and Beadle, 1985; Wasserman et al., 1986b; Paterson, 1992; Mateika and Duffin, 1995; Forster, 2000). However, as shown in Fig. 6, the mechanisms by which hyperventilation and the reduction in plasma pH result in an increased $\dot{V}_{CO_2}$ at the mouth above V_{TH} in response to ramp exercise are well understood.

The simplified sequence of events is a follows. Hydrolysis of ATP generated by glycolysis, rather than glycolysis per se, releases H^+ in the muscle (Robergs et al., 2004). A portion of the muscle H^+ load is removed by metabolic and fixed physicochemical buffers, and by the reduction in muscle bicarbonate concentration, while another portion leaves the cell in exchange with Na^+ or along with lactate through MCTs. Plasma lactate and H^+ concentration thus increase. Although fixed physicochemical buffers in the blood (Cerretelli and Samaja, 2003) remove a portion of the H^+ load, plasma pH decreases, reducing the concentration of bicarbonate in the blood, and the CO_2 released appears in the expired gas. This is a first reason for the disproportionate increase in $\dot{V}_{CO_2}$ which could occur although PA_{CO_2} and Pa_{CO_2} do not decrease ("isocapnic buffering") as observed during ramp exercise with short (i.e., <2 min) stage duration (Wasserman et al., 1986b). Concurrently, hyperventilation develops thus reducing PA_{CO_2} and further

favoring the diffusion into the alveolar gas of CO_2 released from plasma bicarbonate. These phenomena are the two mechanisms by which, above V_{TH} in response to ramp exercise, $\dot{V}_{CO_2}$ released at the mouth exceeds $\dot{V}_{CO_2}$ produced in tissues and eventually $\dot{V}_{O_2}$.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.resp.2005.04.005.

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