Is lactic acidosis a cause of exercise induced hyperventilation at the respiratory compensation point?

T Meyer, O Faude, J Scharhag, A Urhausen, W Kindermann

Objectives: The respiratory compensation point (RCP) marks the onset of hyperventilation ("respiratory compensation") during incremental exercise. Its physiological meaning has not yet been definitely determined, but the most common explanation is a failure of the body’s buffering mechanisms which leads to metabolic (lactic) acidosis. It was intended to test this experimentally.

Methods: During a first ramp-like exercise test on a cycle ergometer, RCP (range: 2.51–3.73 l min\(^{-1}\) oxygen uptake) was determined from gas exchange measurements in five healthy subjects (age 26–42; body mass index (BMI) 20.7–23.9 kg m\(^{-2}\); \(\text{V}O_2\max\) 51.3–62.1 ml min\(^{-1}\) kg\(^{-1}\)). On the basis of simultaneous determinations of blood pH and base excess, the necessary amount of bicarbonate to completely buffer the metabolic acidosis was calculated. This quantity was administered intravenously in small doses during a second, otherwise identical, exercise test.

Results: In each subject sufficient compensation for the acidosis, that is, a pH value constantly above 7.37, was attained during the second test. A delay but no disappearance of the hyperventilation was present in all participants when compared with the first test. RCP occurred on average at a significantly (p = 0.043) higher oxygen uptake (+0.15 l min\(^{-1}\)) compared with the first test.

Conclusions: For the first time it was directly demonstrated that exercise induced lactic acidosis is causally involved in the hyperventilation which starts at RCP. However, it does not represent the only additional stimulus of ventilation during intense exercise. Muscle afferents and other sensory inputs from exercising muscles are alternative triggering mechanisms.

Subjects and general design
Within a period of 1 week, five healthy subjects (26–42 years; body mass index (BMI) 20.7–23.9 kg m\(^{-2}\); \(\text{V}O_2\max\) 51.3–62.1 ml min\(^{-1}\) kg\(^{-1}\)) carried out two identical incremental exercise tests separated by at least 1 day on a cycle ergometer. The first exercise served as a baseline test to determine the course and degree of the pH decline and the normal ventilatory stress reaction. In the second test, sodium bicarbonate was injected intravenously to offset blood acidification. Subjects were advised not to change their training routine between the tests and to abstain from strenuous exercise on the days preceding the tests. One of the subjects (no 5) was a well trained long distance runner, while the others were involved in different kinds of other sport without particular emphasis on endurance training.

Exercise testing
All subjects performed the ramp tests on an Excalibur Supersport cycle ergometer (Lode, Groningen, The Netherlands). Ramp increment was chosen so as to result in a test duration of approximately 10–12 min,\(^{12}\) that is, between 25 and 35 W min\(^{-1}\). The first test was carried out until volitional exhaustion occurred, and the second test was terminated after the same duration as the first one. Cycling cadence was recorded every minute during exercise and (intraindividually) was very similar between the two tests.

Gas exchange measurements (MetaMax I, Cortex, Leipzig, Germany) were carried out continuously during both tests. No averaging procedure was applied to smoothen the curves; recorded data were means over intervals of 10 s. Measurements of minute ventilation (VE), oxygen uptake (\(\text{V}O_2\)), and carbon dioxide output (\(\text{V}CO_2\)) were analysed. The
RCP was determined from the VE-VCO₂ plot by two experienced investigators who were blind to the subject under investigation. They determined RCP independently by visually estimating the point of departure from linearity.

To determine the onset of pH decline (defined as >0.02 compared to the resting pH without increasing again), arterialized blood was sampled during exercise from the hyperaemised earlobe at intervals of 2 min starting after the warm up, that is, at minutes 3, 5, 7, 9, etc, as well as 3 min after cessation of exercise (postexercise data not shown). Determinations were carried out using an ion selective electrode (Blutgassystem 288, CIBA Corning, Fernwald, Germany). Heart rate (from the written ECG) and lactate concentrations (enzymatic UV method from whole blood, Greiner, Flacht, Germany) were registered on a minute basis.

**Intervention**

During the second test, sodium bicarbonate (8.4%) was injected through an antecubital venous catheter to buffer the resulting acidosis at the end of exercise. The total dose was determined using the formula:

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[HCO₃⁻] = 24 \text{ mmol}·l^{-1}·(\text{min HCO}_3\text{ standard} \times 0.2 \text{ l}·\text{kg}^{-1}·\text{body weight})^{14}
\]

where \([HCO₃⁻]\) is the total amount of sodium bicarbonate to be injected, \text{min HCO}_3\text{ standard} is standard bicarbonate 3 min after cessation of the first ramp test, and 0.2 l·kg⁻¹ is the estimated extracellular volume (volume of distribution).

From the pH course in the first test, an appropriate temporal distribution of injection volumes was determined without an interindividually fixed pattern. A pretrial in one of the subjects aided the development of proper injection schedules. In addition to online ECG control, immediate serum potassium measurements (results available approximately 1 min after blood sampling) were carried out simultaneously with pH determinations to ensure the subjects’ medical safety. Sodium determinations were done in parallel, and the highest recorded values in the five subjects were 146.7, 150.0, 151.5, 150.9, and 152.8 mmol·l⁻¹.
respectively (ruleing out relevant disturbances in osmolarity due to the injections).

**Statistics**

Raw data (ranges) are demonstrated throughout without averaging procedures because of the low number of subjects. We defined the pH dependent change in minute ventilation in relation to carbon dioxide output as the main outcome variable, that is, the difference between the VE-VCO₂ plots of both tests. The only statistical testing procedure for differences between the first and the second trial was a Wilcoxon test conducted between the RCPs (corresponding VO₂).

**RESULTS**

All tests were medically uneventful, and no hypokalaemia or ECG abnormalities were recorded. Curves for VO₂, heart rate, and lactate were almost identical between trials and demonstrated clearly that there was no interference from training or habituation effects. In each subject sufficient compensation of the acidosis, that is, a constant pH value above 7.37, was achieved during exercise (fig 1).

A delay in but no disappearance of the hyperventilation was present in all participants when injected with bicarbonate. Plots of pH vs exercise time and VE vs VCO₂ are presented for all five subjects (fig 1). In the bicarbonate trial, RCP occurred at a significantly higher oxygen uptake (by 0.15 l·min⁻¹; p = 0.043).

**DISCUSSION**

Several studies have demonstrated the presence of a second rise in ventilation during incremental exercise; RCP, which is clearly distinguishable from the ventilatory threshold and must, hence, be based on different physiological mechanisms. There are indications from other studies that RCP occurs in response to an initial decrease in blood pH which represents the beginning of failure of the body’s buffering capacity. However, experimental proof was lacking. The present investigation indicates that blood pH is a relevant stimulus for the hyperventilation starting at RCP. However, other mechanisms must also be partly responsible for the hyperventilation.

To our knowledge, this investigation represents the first attempt to elucidate the physiological basis of RCP by directly, that is, intravenously, manipulating blood pH in human beings. Due to the invasiveness of the procedures, only a small number of subjects were recruited. However, their response to the bicarbonate intervention was uniform. Therefore, under the constraints of the design it could be demonstrated that a decline in blood pH due to insufficient buffering of exercise induced lactic acidosis represents an important stimulus for hyperventilation during intense exercise. Apart from the bicarbonate injection, all other circumstances were held constant between the two incremental tests which implies that the observed changes between the tests have to be attributed to the different pH course. This is even more likely because of the short biological half life of sodium bicarbonate itself which rules out enduring bicarbonate effects on various receptors.

It became evident that even under conditions of maintained resting pH during incremental exercise all subjects showed a delay (instead of an absent) hyperventilatory response compared to the pretest. As pH was held constant, there must be additional factors that stimulate ventilation under high intensity exercise. Candidates for this function are local muscle mechanoreceptors or metaboreceptors, pain perception, neuronal impulses of other origin, and serum potassium. However, acidosis due to failure of lactate buffering seems to be a major determinant for exercise hyperventilation. This is in accordance with results from Schneider and Berwick who observed an increased ventilatory response (despite a lowered Pco₂) in relation to VO₂ during an incremental exercise test which preceded by 60 s of maximal cycling. This short bout of intense exercise presumably led to decreased pH values throughout the subsequent incremental test when compared to a reference test which was conducted without prior exhaustive exercise. However, a close coupling between VE and VCO₂ was maintained during submaximal stages but the VO₂/VCO₂ ratio switched to a higher level.

In conclusion, for the first time it was directly demonstrated that exercise induced metabolic acidosis is causally involved in the onset of hyperventilation at RCP. However, it is probably not the only additional stimulus of ventilation during intense exercise. Muscle afferents and other sensory inputs from exercising muscles are alternative triggering mechanisms.

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