Journal of Physiology (1990), **429**, *pp.* 339–348
With 4 figures
Printed in Great Britain

CHANGES IN ARTERIAL K^+ AND VENTILATION DURING EXERCISE IN NORMAL SUBJECTS AND SUBJECTS WITH McARDLE'S SYNDROME

BY D. J. PATERSON, J. S. FRIEDLAND*, D. A. BASCOM, I. D. CLEMENT, D. A. CUNNINGHAM†, R. PAINTER AND P. A. ROBBINS

*From the University Laboratory of Physiology, Parks Road, Oxford OX1 3PT and *Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU*

(*Received 22 February 1990*)

SUMMARY

1. We have examined the relationship between ventilation ($\dot{V}_E$), lactate (La) and arterial plasma K^+ concentrations ($[K^+]_a$) during incremental exercise in six normal subjects and in four subjects with McArdle's syndrome (myophosphorylase deficiency) who do not become acidotic during exercise.

2. In normal subjects, $[K^+]_a$ rose to *ca* 7 mM at the point of exhaustion. The time courses of the increases in $\dot{V}_E$, La and $[K^+]_a$ were all similar during the exercise period. La reached its peak concentration during the recovery from exercise when both $\dot{V}_E$ and $[K^+]_a$ were returning to resting levels.

3. McArdle's subjects, like normal subjects, had a non-linear ventilatory response during incremental exercise. Their $[K^+]_a$ was closely related to $\dot{V}_E$ throughout exercise and recovery.

4. The arterial pH of McArdle's subjects, rather than remaining constant, actually rose from the onset of exercise.

5. For a given level of exercise, the levels of $\dot{V}_E$ and $[K^+]_a$ were greater in the McArdle's subjects than in normal subjects.

6. These findings are consistent with the idea that hyperkalaemia may contribute significantly to the drive to breathe, especially during heavy exercise.

INTRODUCTION

It is generally accepted that the control of breathing during exercise is regulated by a combination of both neural and humoral drives (Dejours, 1962; Asmussen, 1967; Cunningham, 1987) but controversy exists as to the exact nature of the controlling signals. Stimulation of the arterial chemoreceptors is thought to be the major factor underlying the non-linear increase in ventilation during incremental exercise at higher work rates (Wasserman, Whipp & Casaburi, 1986), since patients without carotid bodies do not show this ventilatory response (Wasserman, Whipp, Koyal & Cleary, 1975). Acidosis has traditionally been regarded as the stimulus to the arterial chemoreceptors which mediates this non-linearity. However, studies on

† Present address: Department of Physiology, University of Western Ontario, London, Canada N6A 5C1.

MS 8296

subjects with McArdle's syndrome (myophosphorylase deficiency) cast considerable doubt on this idea. These subjects, who cannot catabolize glycogen and make acid during exercise (McArdle, 1951) also show a non-linear ventilatory response during incremental exercise (Hagberg, Coyle, Carroll, Miller, Martin & Brooke, 1982; Hagberg, King, Rogers, Montain, Jilka, Kohrt & Heller, 1989). Therefore it seems likely that an additional stimulus may be sensed by the carotid bodies and causes a non-linear ventilatory response during exercise in these subjects and presumably also in normal subjects.

Recent work suggests that excitation of arterial chemoreceptors by potassium could be an important factor in the control of exercise hyperpnoea (Band, Linton, Kent & Kurer, 1985; Burger, Estavillo, Kumar, Nye & Paterson, 1988; Paterson, Robbins & Conway, 1989). Thus it is tempting to suppose that hyperkalaemia might be involved in generating the non-linear part of the ventilatory response to heavy exercise. This paper examines the relationship between potassium, acid (lactate) and ventilation during incremental exercise in normal subjects and in subjects with McArdle's syndrome.

Some of the findings presented here have been communicated in abstract form (Bascom, Clement, Cunningham, Friedland, Paterson & Robbins, 1989).

METHODS

Subjects

Four male subjects with histochemically proven myophosphorylase deficiency (McArdle's syndrome) volunteered to participate in the study. None had any history of respiratory or cardiovascular disease. Six healthy male volunteers were also studied. For a description of the subjects' age and weight see Table 1. Subjects gave informed consent after a detailed explanation both verbally and in writing of the aims of the study. Their physician was also asked to sanction the study. The study was approved by the Central Oxford Research Ethics Committee.

TABLE 1. Age and weight of McArdle's subjects and normal subjects

McArdle's subjects			Normal subjects		
No.	Age (years)	Weight (kg).	No.	Age (years)	Weight (kg)
762	26	64·5	724	19	78·2
764	40	75·4	766	19	75·4
783	40	80·2	785	19	73·4
788	32	65·4	786	19	76·0
			787	20	74·2
			791	19	62·4

Protocol

Subjects were asked to avoid strenuous exercise for 24 h and to refrain from smoking for 3 h before the experiment. A 21 G catheter was inserted into the brachial artery of the non-dominant arm under local anaesthesia to allow withdrawal of blood samples. Subjects breathed air through a mouthpiece and ventilation ($\dot{V}_E$) was determined breath-by-breath as previously described (Paterson *et al.* 1989). A three-lead ECG was recorded from the chest and heart rate was measured every 30 s. Exercise was performed on an electromagnetically braked cycle ergometer (Mijnhardt KEM-3). Subjects with McArdle's syndrome may experience muscle pain and cramps during heavy exercise. To minimize any possibility of this, these subjects undertook a warm-up period of

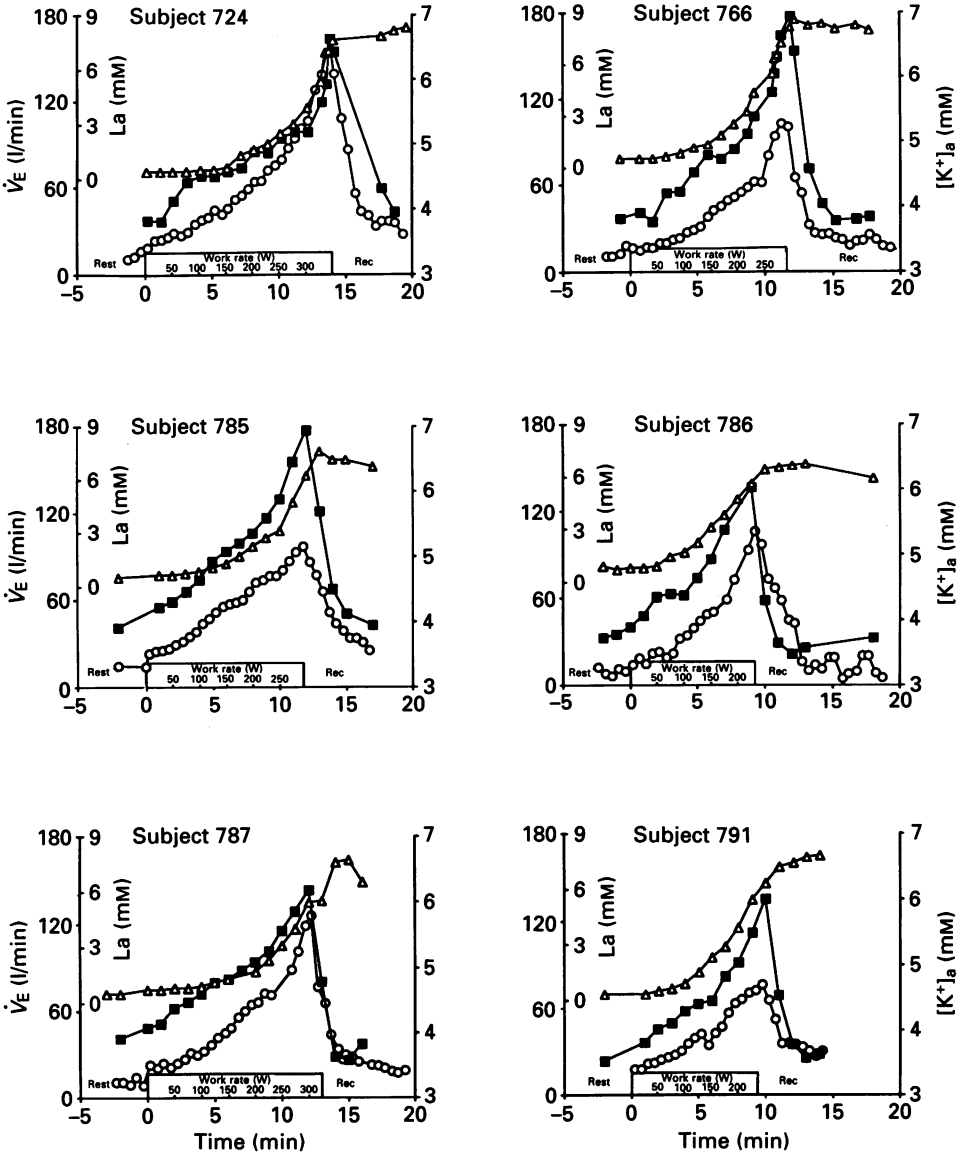

Fig. 1. Normal subjects. Changes in $[K^+]_a$ (■), $\dot{V}_E$ (○) and La (△) during an incremental work test to exhaustion. Note that $[K^+]_a$, $\dot{V}_E$ and La followed a similar time course during exercise; however, La continued to rise during recovery (Rec) when both $[K^+]_a$ and $\dot{V}_E$ were returning to resting levels.

unloaded exercise on the cycle ergometer for a period of 10 min before the exercise test. They were instructed to stop exercise immediately if they suffered marked muscle pain or felt that further exertion could result in excessive muscle fatigue and cramp. Normal subjects also had a similar warm-up period of unloaded cycle ergometry.

During the exercise test the work rate was increased each minute by increments of 25 W for the normal subjects and 5 W for the McArdle's subjects until both groups reached the point of volitional exhaustion. This point was attained when a perceived exertion rating (PER) of 19 was

reached (Borg, 1970) or when a pedal frequency of 60 r.p.m. could no longer be maintained. Blood was sampled from the catheter into heparinized syringes at the end of each minute of exercise and during the 10 min recovery period. Each blood sample (3 ml) was analysed immediately for arterial pH (Instrumentation Laboratory 1306) and lactate (Yellow Springs 23L). The plasma was then separated and analysed for potassium by flame photometry (Instrumentation Laboratory 943).

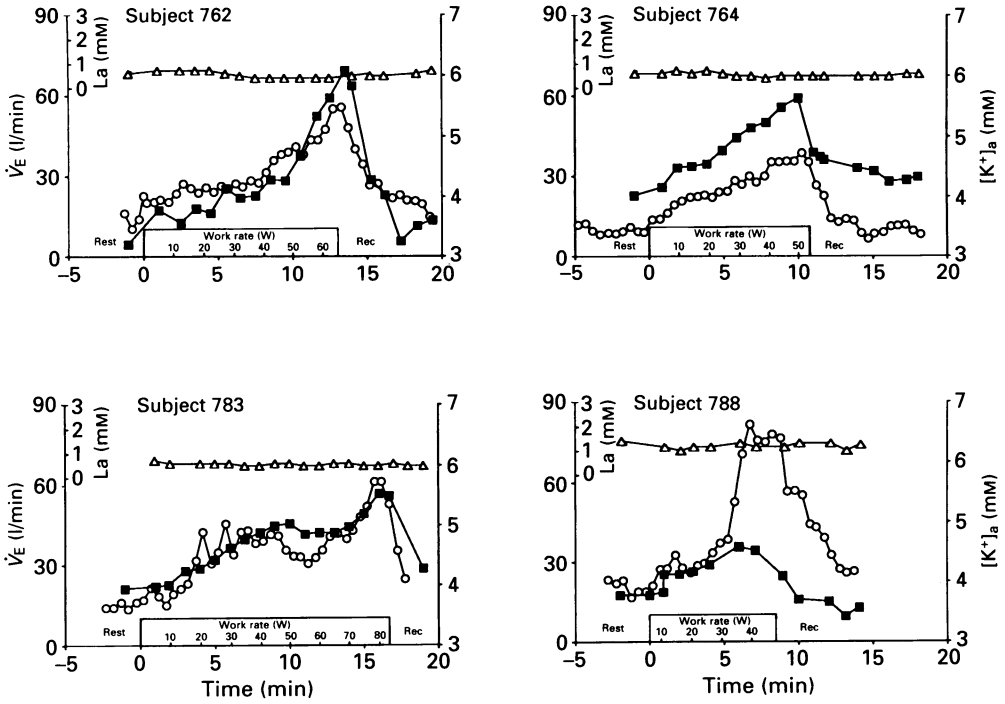

Fig. 2. Subjects with McArdle's syndrome. Changes in $[K^+]_a$ (■), $\dot{V}_E$ (○) and La (△) during an incremental work test to exhaustion. Note that there was no change in La during exercise and recovery (Rec). $[K^+]_a$ and $\dot{V}_E$ followed a similar time course during exercise and recovery, although in subject 788 $\dot{V}_E$ deviated from the close temporal relationship with $[K^+]_a$ during the last phase of the exercise test. This exercise test was stopped as it was realized that the subject had clearly become apprehensive during the latter stages.

RESULTS

Figure 1 shows the responses of the six normal subjects to incremental exercise and during the recovery period. The subjects became hyperkalaemic during exercise and reached arterial plasma potassium concentrations ($[K^+]_a$) approaching 7 mM at the end of exercise. The time courses of the increases in $\dot{V}_E$, La and $[K^+]_a$ were all similar during the exercise period. A smooth curve drawn through the points would be concave upwards for all three variables. During the recovery period $[K^+]_a$ and $\dot{V}_E$ both fell rapidly whereas lactate remained elevated and reached its peak concentration 2–4 min after exercise was stopped.

Figure 2 shows the response of the McArdle's subjects during incremental exercise. The maximum work rate attained by these subjects was *ca* 25% the maximum work rate in normal subjects. McArdle's subjects also became hyperkalaemic during

exercise. In three subjects there was a non-linear ventilatory response during incremental exercise similar in form to the response in all six normal subjects. The $[K^+]_a$ in McArdle's subjects followed a similar time course to $\dot{V}_E$ during exercise and in recovery. However, as expected and in contrast to normal subjects there was no

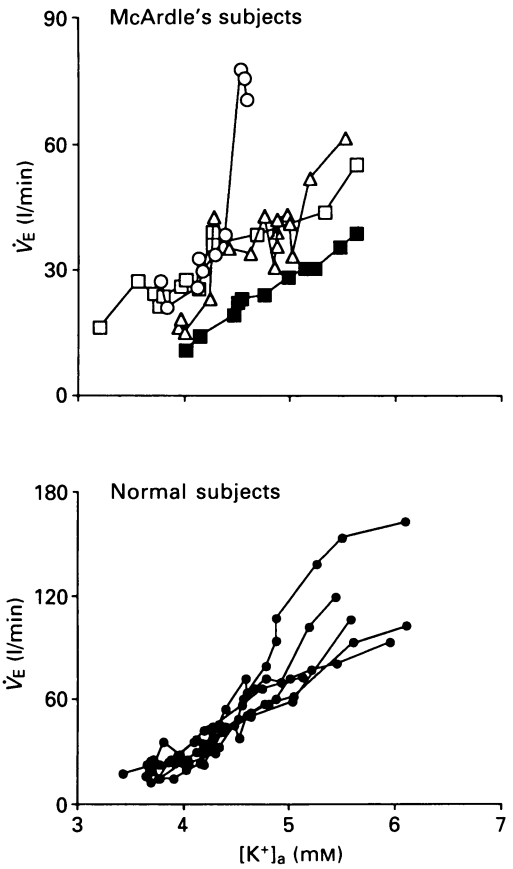

Fig. 3. Relationship between $\dot{V}_E$ and $[K^+]_a$ during an incremental work test for both normals and McArdle's subjects. These two variables appear to be linearly related. Each McArdle's subject is identified by a different symbol (762, □; 764, ■; 783, △; 788, ○).

change in blood lactate concentration. In both groups $\dot{V}_E$ and $[K^+]_a$ appeared to be linearly related (Fig. 3).

Figure 4 shows that arterial pH (pH_a) in normal subjects fell progressively during exercise, although most of the decline occurred during work rates above *ca* 60% maximum work rate. McArdle's subjects developed a progressive alkalosis from the onset of exercise. McArdle's subjects ventilated more and had a greater hyperkalaemic response for a given work rate than normal subjects. Their $[K^+]_a$ was 1–2 mM above resting levels for a work rate of *ca* 50 W, whereas $[K^+]_a$ had increased by only 0·5 mM during a work rate of 50 W in normal subjects. The heart rate in

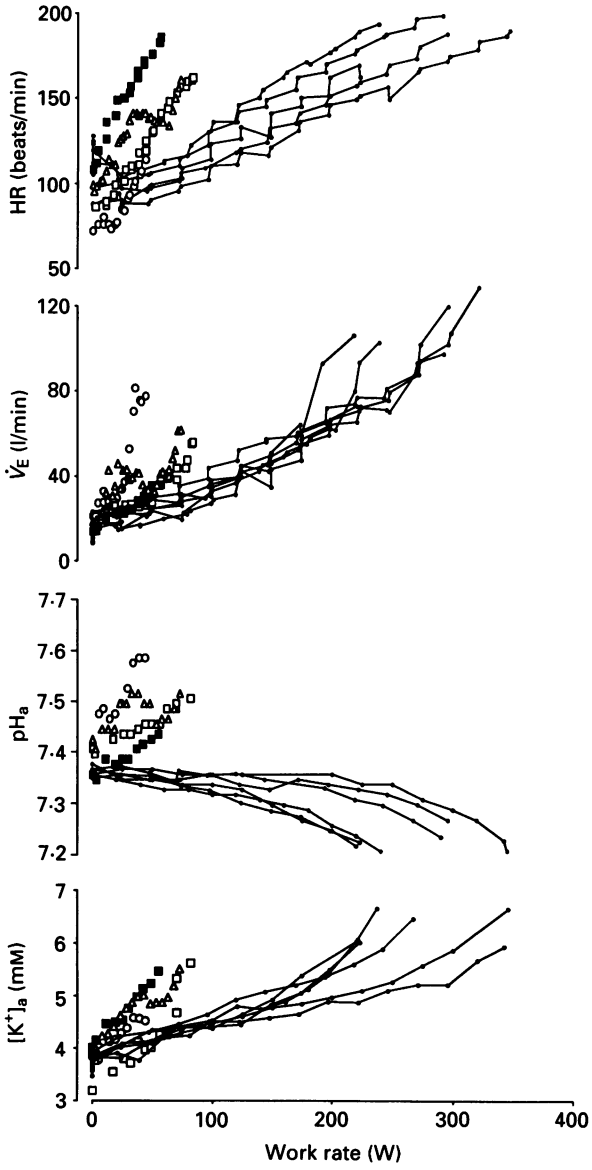

Fig. 4. Comparisons of the HR, $\dot{V}_E$, pH_a and $[K^+]_a$ responses of normal subjects (lines) with the responses of McArdle's subjects (symbols) during the incremental work test. Note that McArdle's subjects reach the point of exhaustion at lower work rates, but have a higher ventilatory, hyperkalaemic and heart rate response at this point compared with normal subjects. From the onset of exercise McArdle's subjects showed a progressive alkalosis in the blood.

McArdle's subjects at exhaustion was markedly higher than the heart rate in normal subjects at the same work rate.

DISCUSSION

Ventilation response

We confirm the observation by Hagberg *et al.* (1982, 1989) that McArdle's subjects, like normal subjects, appear to have a non-linear ventilatory response during incremental exercise. Our subjects ventilated more for a given work rate than normal subjects, which is similar to the finding of Haller & Lewis (1986) and the original description of a patient with myophosphorylase deficiency (McArdle, 1951). It is of interest that Haller & Lewis (1986) reported that an infusion of glucose reduced the ventilatory response to exercise of McArdle's subjects to levels seen in exercising controls. This response might be partly explained by a reduced exercise hyperkalaemia, since an infusion of glucose causes hypokalaemia by stimulating the activity of Na^+, K^+-ATPase (Clausen, 1986).

Potassium response

Both McArdle's and normal subjects reached their peak $[K^+]_a$ at the point of exhaustion, although McArdle's subjects had a greater hyperkalaemic response for a given work rate. McArdle (1951) described an increase in potassium in blood draining forearm muscle following ischaemic exercise, which he did not find in his normal subjects. A similar result has been reported by Salmon & Turner (1965) and by Kono, Mineo, Sumi, Shimizu, Kang, Nonaka & Tarui (1984). There are several possible explanations for the greater hyperkalaemic response to exercise in McArdle's subjects. It is conceivable that there may be a slowed reuptake of K^+ by Na^+, K^+-ATPase following muscle cell repolarization. However, a more likely explanation is that K^+ release from exercising muscle is increased. This increased K^+ efflux may occur through delayed rectifier K^+ channels as a result of the generation of a greater number of action potentials for a given work rate in the McArdle's subject, or by activation of ATP-sensitive K channels.

ATP-sensitive K channels (K_{ATP} channels) are found in the membranes of mammalian skeletal muscle cells (Woll, Lonnendonker & Neumcke, 1989). These channels are inhibited by an increase in intracellular ATP (see Ashcroft & Ashcroft, 1990) and may be involved in the loss of K^+ from metabolically exhausted skeletal muscle (Castle & Haylett, 1987). The intracellular coupling factor linking cellular metabolism to K_{ATP} channel inhibition in skeletal muscle is controversial; both a rise in intracellular ATP and a decrease in pH have been implicated (Ashcroft & Ashcroft, 1990). A reduction in intracellular pH (pH_i) in the presence of ATP results in enhanced K_{ATP} channel activity (Davies, 1990). This suggests that changes in pH_i may be important in coupling cellular metabolism to K_{ATP} channel activity in normal muscle. However, in McArdle's subjects this is unlikely to be the main coupling factor since these subjects become alkalotic during exercise. ^{31}P NMR studies suggest that total muscle cell ATP levels are not significantly lowered during exercise in normal subjects (Lewis, Haller, Cook & Nunnally, 1985). However, McArdle's subjects have a reduced muscle phosphorylation potential

([ATP]/[ADP][P_i]) (Lewis & Haller, 1986) so it is not inconceivable that their intracellular ATP may link channel inhibition to cellular metabolism.

Heart rate response

Subjects with McArdle's syndrome have heart rates which are markedly higher than those of normals for the same work rate. Braakhekke, De Bruin, Stegeman, Wevers, Binkhorst & Joosten (1986) suggested that the greater heart rate was bought about by an increased 'motor drive' for a given work rate, which reflects the extra effort required by McArdle's subjects to sustain a given level of work. Lewis, Haller, Cook & Blomqvist (1984) have suggested that the cardiovascular response in McArdle's subjects could also originate from a metabolic stimulus (possibly potassium) which activates a muscle afferent drive (through C fibres) to stimulate the cardiorespiratory centres (McCloskey & Mitchell, 1972). They found that increasing glucose (which causes relative hypokalaemia) lowered the heart rate response during exercise.

The control of exercise hyperpnoea

The main body of evidence supporting a role for hyperkalaemia as a respiratory stimulus during exercise comes from the following observations. (1) In the anaesthetized cat arterial chemoreceptors can be stimulated by physiological levels of K^+ (Linton & Band, 1985; Paterson & Nye, 1988). (2) This stimulation results in an increase in $\dot{V}_E$ which can be abolished by peripheral chemoreceptor denervation (Band *et al.* 1985). (3) Hypoxia augments chemoreceptor excitation by hyperkalaemia, but high oxygen reduces or abolishes its effects (Burger *et al.* 1988). (4) In normal man a close temporal relationship between $\dot{V}_E$ and $[K^+]_a$ has been reported during exercise (submaximal and maximal) and recovery (Paterson *et al.* 1989).

The gain of the arterial chemoreceptor reflex in man is enhanced both during submaximal exercise (Perret, 1960; Dejours, 1962; Cunningham, Lloyd & Spurr, 1966) and in heavy exercise (Asmussen & Nielsen, 1946; Bannister & Cunningham, 1954; Wasserman, 1976). The mechanism responsible for this increase in gain is uncertain. Previously we have argued that hyperkalaemia may increase the gain of the peripheral chemoreceptor reflex during exercise (Paterson *et al.* 1989). Subjects without carotid bodies are able to increase their $\dot{V}_E$ in response to exercise but their ventilatory transients are slowed and they do not show a relative hyperventilation during heavy exercise (Wasserman *et al.* 1975). This implies that carotid bodies are important mediators of the non-linear ventilatory response to heavy exercise.

It has been claimed that the exercise hyperpneoa in McArdle's subjects is a result of activation of pain afferents – C fibres (Whipp, 1983). We could find no evidence that our McArdle's subjects experienced discomfort or muscle pain over and above that of the normal subjects. However, we cannot rule out the idea that during maximal exercise some contribution to exercise hyperpnoea might result from stimulation of the C fibres by hyperkalaemia (Friedland & Paterson, 1988).

In conclusion, (1) acid is not the only stimulus which is closely correlated with $\dot{V}_E$ during incremental exercise in normals, (2) acid plays no role in the regulation of ventilation during exercise in subjects with McArdle's syndrome, and (3) the close temporal relationship between $[K^+]_a$ and $\dot{V}_E$ during exercise in both normal and

McArdle's subjects supports the idea that potassium may stimulate ventilation, especially during heavy exercise.

This study was supported by the MRC. D.J.P. is supported by the MRC and a Junior Research Fellowship at Christ Church, Oxford. We would like to thank the following consultant neurologists who gave permission for their patients to participate in this study: Drs J. A. Morgan-Hughes, P. Hudgson, W. J. K. Cumming and J. Ballantyne. We also thank Dr K. L. Dorrington for performing some of the arterial catheterizations and D. F. O'Connor and D. McKeown for technical support. This paper has benefited greatly from discussion with Drs P. C. G. Nye, D. H. Bergel, C. Peers and F. M. Ashcroft.

REFERENCES

ASHCROFT, S. J. H. & ASHCROFT, F. M. (1990). Properties and functions of ATP sensitive K channels. *Cellular Signalling* (in the Press).

ASMUSSEN, E. (1967). Exercise and the regulation of ventilation. *Circulation Research* **20 & 21**, suppl. 1, 132–145.

ASMUSSEN, E. & NIELSEN, M. (1946). Studies on the regulation of respiration in heavy work. *Acta physiologica scandinavica* **16**, 270–285.

BAND, D. M., LINTON, R. A. F., KENT, R. & KURER, F. L. (1985). The effect of peripheral chemodenervation on the ventilatory response to potassium. *Respiration Physiology* **60**, 217–225.

BANNISTER, R. & CUNNINGHAM, D. J. C. (1954). The effects on the respiration and performance during exercise of adding oxygen to the inspired air. *Journal of Physiology* **125**, 118–137.

BASCOM, D. A., CLEMENT, I. D., CUNNINGHAM, D. A., FRIEDLAND, J. S., PATERSON, D. J. & ROBBINS, P. A. (1989). Changes in arterial plasma potassium and ventilation in subjects with McArdle's syndrome. *Journal of Physiology* **417**, 141*P*.

BORG, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitative Medicine* **2**, 92–98.

BRAAKHEKKE, J. P., DE BRUIN, M. I., STEGEMAN, D. F., WEVERS, R. A., BINKHORST, R. A. & JOOSTEN, E. M. G. (1986). The second wind phenomenon in McArdle's disease. *Brain* **109**, 1087–1101.

BURGER, R. E., ESTAVILLO, J. A., KUMAR, P., NYE, P. C. G. & PATERSON, D. J. (1988). Effects of potassium, oxygen and carbon dioxide on steady-state discharge of cat carotid body chemoreceptors. *Journal of Physiology* **401**, 519–531.

CASTLE, N. A. & HAYLETT, D. G. (1987). Effect of channel blockers on potassium efflux from metabolically exhausted frog skeletal muscle. *Journal of Physiology* **383**, 31–45.

CLAUSEN, T. (1986). Regulation of active Na^+–K^+ transport in skeletal muscle. *Physiological Reviews* **66**, 542–580.

CUNNINGHAM, D. J. C. (1987). Studies on arterial chemoreceptors in man. *Journal of Physiology* **384**, 1–26.

CUNNINGHAM, D. J. C., LLOYD, B. B. & SPURR, D. (1966). Doubts about the 'anaerobic work substance' as a stimulus to breathing in exercise. *Journal of Physiology* **186**, 110–111*P*.

DAVIES, N. W. (1990). Modulation of ATP sensitive K channels in skeletal muscle by protons. *Nature* **343**, 375–377.

DEJOURS, P. (1962). Chemoreflexes in breathing. *Physiological Reviews* **42**, 335–358.

FRIEDLAND, J. S. & PATERSON, D. J. (1988). Potassium and fatigue. *Lancet* **ii**, 961–962.

HAGBERG, J. M., COYLE, E. F., CARROLL, J. E., MILLER, J. M., MARTIN, W. H. & BROOKE, M. H. (1982). Exercise hyperventilation in patients with McArdle's disease. *Journal of Applied Physiology* **52**, 991–994.

HAGBERG, J. M., KING, I. D., ROGERS, M. A., MONTAIN, S. J., JILKA, S. M., KOHRT, W. M. & HELLER, S. L. (1989). Exercise hyperventilation and recovery $\dot{V}_{O_2}$ responses of McArdle's disease patients. *Federation Proceedings* **3**, A849.

HALLER, R. G. & LEWIS, S. F. (1986). Abnormal ventilation during exercise in McArdle's syndrome: Modulation by substrate availability. *Neurology* **36**, 716–719.

KONO, N., MINEO, I., SUMI, S., SHIMIZU, T., KANG, J., NONAKA, K. & TARUI, S. (1984). Metabolic basis of improved exercise: Muscle phosphorylase deficiency after glucagon administration. *Neurology* **34**, 1471–1476.

LEWIS, S. F. & HALLER, R. G. (1986). The pathophysiology of McArdle's disease: clues to regulation in exercise and fatigue. *Journal of Applied Physiology* **61**, 391–401.

LEWIS, S. F., HALLER, R. G., COOK, J. D. & BLOMQVIST, C. G. (1984). Metabolic control of cardiac output response to exercise in McArdle's disease. *Journal of Applied Physiology* **57**, 1749–1753.

LEWIS, S. F., HALLER, R. G., COOK, J. D. & NUNNALLY, R. L. (1985). Muscle fatigue in McArdle's disease studied by ^{31}P-NMR: effect of glucose infusion. *Journal of Applied Physiology* **59**, 1991–1994.

LINTON, R. A. F. & BAND, D. M. (1985). The effect of potassium on carotid chemoreceptor activity and ventilation in the cat. *Respiration Physiology* **59**, 65–70.

MCARDLE, B. (1951). Myopathy due to a defect in muscle glycogen breakdown. *Clinical Science* **10**, 13–33.

MCCLOSKEY, D. I. & MITCHELL, J. H. (1972). Reflex cardiovascular and respiratory responses originating in exercising muscle. *Journal of Physiology* **224**, 173–186.

PATERSON, D. J. & NYE, P. C. G. (1988). The effect of beta adrenergic blockade on the carotid body response to hyperkalaemia in the cat. *Respiration Physiology* **74**, 229–238.

PATERSON, D. J., ROBBINS, P. A. & CONWAY, J. (1989). Changes in arterial plasma potassium and ventilation during exercise in man. *Respiration Physiology* **78**, 323–330.

PERRET, C. (1960). Hyperoxie et regulation de la ventilation durant l'exercise musculaire. *Helvetica physiologica et pharmacologica acta* **18**, 72–97.

SALMON, S. E. & TURNER, C. E. (1965). McArdle's disease presenting as convulsion and rhabdomyolysis. *American Journal of Medicine* **39**, 142–146.

WASSERMAN, K. (1976). Testing regulation of ventilation with exercise. *Chest* **70**, suppl., 173–178.

WASSERMAN, K., WHIPP, B. J. & CASABURI, R. (1986). Respiratory control during exercise. In *Handbook of Physiology*, section 3, *The Respiratory System*, vol. 2, ed. FISHMAN, A. P., CHERNIACK, N. S. & WIDDICOMBE, J. G., pp. 595–619. American Physiological Society, Bethesda, MD, USA.

WASSERMAN, K., WHIPP, B. J., KOYAL, S. N. & CLEARY, M. G. (1975). Effect of carotid body resection on ventilatory and acid–base control during exercise. *Journal of Applied Physiology* **39**, 354–358.

WHIPP, B. J. (1983). Exercise hyperventilation in patients with McArdle's disease. *Journal of Applied Physiology* **55**, 1638–1639.

WOLL, K. H., LONNENDONKER, U. & NEUMCKE, B. (1989). ATP sensitive K^+ channels in adult mouse skeletal muscle. *Pflügers Archiv* **414**, 622–628.