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IS THE VOLUNTARY CONTROL OF EXERCISE IN MAN NECESSARY FOR THE VENTILATORY RESPONSE?

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SUMMARY

1. The ventilatory response to electrically induced exercise (E_{EL}) was studied in eighteen normal subjects and compared with the response to performing the same exercise voluntarily (E_V).

2. E_{EL} was produced by surface electrode stimulation of the quadriceps and hamstring muscles so as to cause a pushing movement at 1 Hz against a spring load; this produced no pain or discomfort. Matching of E_V to E_{EL} was achieved by subjects copying a tension signal recorded during E_{EL} and displayed on a storage oscilloscope.

3. There were no differences between the resting states measured before either form of exercise.

4. The ventilatory response (change in ventilation as a ratio of the change in CO_2 elimination) was similar in the two types of exercise. The increases in ventilation and CO_2 elimination were greater with E_{EL}. Small but significant increases in the gas exchange ratio and serum lactate were found for E_{EL} but not for E_V, suggesting an increase in anaerobic metabolism in E_{EL}. End-tidal P_{CO_2} showed little change in either form of exercise. In some runs end-tidal P_{CO_2} rose, but insufficiently to account for the ventilatory response as judged by the response to inhaled CO_2.

5. In two subjects arterial blood samples showed small and inconsistent changes in both P_{a,CO_2} and P_{a,O_2} for E_V and E_{EL}. pH and base excess changes also were consistent with more anaerobiosis with E_{EL} compared to E_V.

6. The first ten breaths of exercise were used to study the on transient. In E_V, expiratory duration shortened and ventilation increased significantly on the first breath but CO_2 elimination did not increase until the second breath; in E_{EL}, these variables did not change significantly until the second breath. For the remainder of the on transient the pattern of the ventilatory response was similar for E_V and E_{EL}. By the end of the on transient both E_V and E_{EL} had reached approximately 80% of their final steady-state values.

7. These results suggest that a normal ventilatory response can occur in the absence of a drive to exercise from the cortex.

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INTRODUCTION

There is still no agreement on the precise roles of 'neural' and 'chemical' drives to breathe in the control of the ventilatory response to exercise (Wasserman, Whipp & Davis, 1981). The term neural includes two separate entities, a cortical component, and a reflex component arising from the exercising muscles transmitted by the spinal cord. These have been analysed in experiments in animals and man, since the pioneer work of Krogh & Lindhard (1913, 1917), but it has not been easy to do definitive experiments in conscious man to ascertain the existence of a cortical component. There are many differing results in the literature on the very existence and importance of reflexes from the exercising muscle in mammals and the literature has been recently summarized (Cross, Davey, Guz, Katona, Maclean, Murphy, Semple & Stidwell, 1982*a*,*b*).

Asmussen, Nielsen & Wieth-Pedersen (1943) studied this problem in the steady state of exercise. They compared the ventilatory response to similar leg movements against a load, either voluntarily controlled or electrically induced. For a comparable increase in metabolism the ventilatory response was the same in the two cases. One subject – the author – demonstrated the matching of ventilation to CO_2 elimination by remaining isocapnic with both forms of exercise. A similar result was obtained in a tabetic subject who in spite of an absence of postural sensation from the legs could nevertheless exercise. The results suggested the primacy of chemical control of the ventilatory response to exercise. The problem has been to explain how this comes about while P_{CO_2} and pH apparently remain unchanged with moderate exercise when anaerobic metabolism does not occur.

The plan of the present study was to use the methodology of Asmussen *et al.* (1943) in subjects unacquainted with respiratory physiology, and to document the dynamics and the steady state of the ventilatory response to the two forms of exercise. The objective was to ascertain whether a cortical drive to breathe could be documented.

METHODS

Voluntary (E_V) and electrically induced exercise (E_{EL}) were studied in eighteen normal volunteers (age 21–50 years, sixteen male, two female). Subjects were seated in a specially designed chair, the position of which could be adjusted relative to spring-loaded pedals mounted within the same rigid framework (Fig. 1). The pedals were attached to a force transducer (Tephcotronics, Edinburgh) which enabled the approximate level and pattern of the exercise to be recorded. The surface electrodes were either 10×10 cm aluminium foil covered in paper (Edwards, Young, Hosking & Jones, 1977) or carbonized rubber electrodes (Slendertone). Two pairs of electrodes were strapped to the anterior and posterior surfaces of each thigh. A layer of electrode paste was applied to reduce skin resistance and avoid point contacts, thus facilitating even stimulation of the muscle groups; this stimulation is presumed to be transmitted via the peripheral motor nerve fibres. The stimulus wave form consisted of a 60 μs pulse train with a repetition frequency of 40 Hz, modulated by a 1 Hz rectified 'sawtooth' envelope (Fig. 1, inset). Prior experiments established that this pattern caused minimal discomfort whilst producing a push–relax rhythm which closely resembled that seen during 'natural exercise'. The amplitude of the stimulus could be varied from 0 to 100 V. The time sequence in which the muscle groups were stimulated was previously determined from measurements made during surface electromyogram (e.m.g.) recordings while exercise was performed voluntarily. It was found that the best 'copy' of voluntary exercise could be obtained if the posterior muscles were stimulated 40 ms after the anterior muscles, but for the same length of time.

Subjects breathed through a mouth-piece connected to a pneumotachograph (Fleisch No. 2) from

which the following variables were derived (Fig. 1): expiratory time (t_e), respiratory rate (RR), tidal volume (V_T) and ventilation ($\dot{V}_I$). Steady-state values for O_2 consumption ($\dot{V}_{O_2}$) and CO_2 elimination ($\dot{V}_{CO_2}$) were calculated from mixed expired concentrations either obtained from a flow-weighted sample of expired air (Fenyves & Gut, ERGOSTAR), or by passing the expired air through a mixing chamber; appropriate analysers (infra-red and paramagnetic) recorded the CO_2 and O_2 concentrations respectively. The gas exchange ratio (R) was also calculated. End-tidal P_{CO_2} (P_{ET,CO_2}) was measured using a fast-response infra-red CO_2 meter (Beckman LB2).

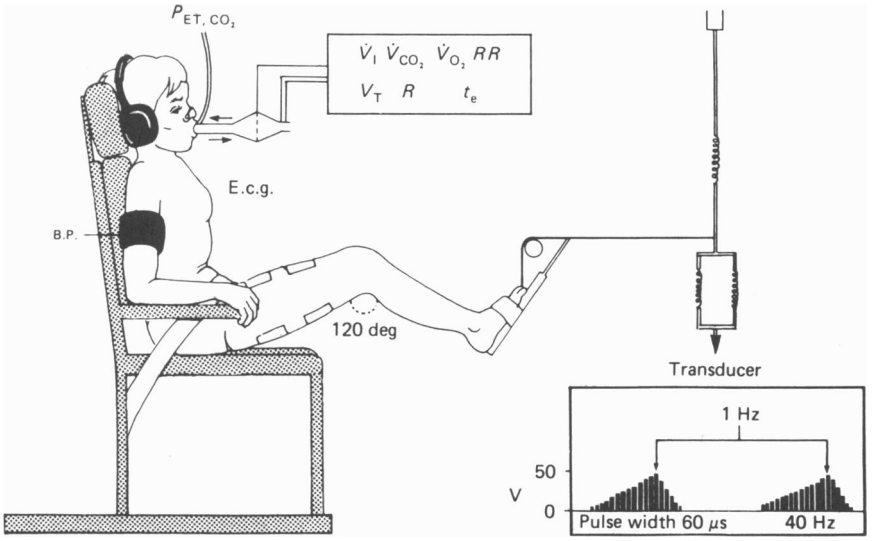

Fig. 1. Schematic diagram of the experimental set-up allowing the same work to be done by the legs voluntarily and with electrical stimulation. The inset shows the stimulus wave form applied to the electrodes shown on the thighs. B.P., blood pressure.

Estimates of $\dot{V}_{CO_2}$ per breath were made by integration of the P_{ET,CO_2} signal as described by Cross *et al.* (1982*a*). The technique was validated by comparison of gas collection measurements in the steady state against the integration method in the same period. This resulted in the following validation: $\dot{V}_{CO_2}$ (steady state) ml $min^{-1} = 0{\cdot}847\,\dot{V}_{CO_2}$ (integration) $+ 62{\cdot}6$, $r = 0{\cdot}88$.

In two subjects catheters (Abocath) were inserted into the brachial artery for estimations of P_{O_2}, P_{CO_2}, pH and serum lactate; in a further subject measurement of lactate only was obtained. Systolic and diastolic blood pressure were monitored regularly using an automatic sphygmomanometer (Arteriosonde) and electrocardiogram (e.c.g.) was recorded continuously. Analog data were recorded on a RACAL STORE 4 FM tape recorder and also simultaneously on a MINGOGRAPH 800 chart recorder for subsequent analysis.

Exercise protocol

Subjects were seated in the chair and their position relative to the pedals was adjusted such that the angle between the upper and lower limbs was approximately 120 deg (Fig. 1). After applying the stimulating electrodes (and monitoring apparatus) the stimulus level to be used during the first experimental run was determined by slowly increasing the voltage to each pair of electrodes until a vigorous level of exercise was obtained with minimal discomfort. Before making any measurements, subjects were given short trials of electrical stimulation and also practised voluntary exercise. Each exercise run was preceded by a 'conditioning' period with the subject attached to the mouth-piece and nose-clip whilst listening to a story through headphones. When the subject was in a relaxed state, as assessed by V_T, P_{ET,CO_2} and heart rate, measurements were made over a 4 min 'rest' period.

This was followed by a 4 min period of either electrically induced or voluntary exercise designed to commence during expiration. With voluntary exercise, the beginning and end were signalled by a light. This method of initiating exercise avoided the ventilatory effects of anticipating the start of exercise. A period of at least 6 min recovery was allowed between experiments during which time the subject was allowed to move freely in the chair and was invited to comment on the study.

In all subjects electrically induced exercise was performed first, followed by a 'matched' voluntary effort. Matching was achieved by instructing subjects to copy, as closely as possible, the tension signal recorded during their electrically induced exercise and displayed on a storage oscilloscope. Thereafter a further period of electrically induced exercise was carried out with an additional 'voluntary' run in some cases.

Steady-state measurements of all variables were made at rest and during the fourth minute of exercise. Breath-by-breath analysis was performed on the ten breaths just before, and immediately following the start of exercise, and also on the last ten breaths of the exercise. The breath in which exercise started was defined as breath 1 of the on transient.

Blood sampling and gas techniques

Arterial blood samples were taken for measurements of P_{O_2}, P_{CO_2}, pH (Radiometer, ABL1) and lactate levels (Boehringer-Ingelheim Kit analyser) during the last 30 s of the rest period and during the last 30 s of the exercise phase in two subjects.

Sampling was done in the following way: the dead space of the catheter and syringe was filled with a saline solution containing 100 u. heparin in 500 ml NaCl (0·15 mol l^{-1}) and before an arterial blood sample was taken for analysis, the dead space was flushed with arterial blood; the volume of blood used for this was at least five times the dead space. Quality checks of the ABL1 on each experimental day were done by tonometry with blood equilibrated with gases calibrated by a Lloyd–Haldane gas analyser. Since this calibration of the ABL1 fell within the limits previously ascertained (Cross *et al.* 1982*a*), all measured values of P_{a,CO_2} and pH were assumed to underestimate the actual levels by 1·7 mmHg and 0·005 units respectively.

Sensitivity to CO_2

Steady-state ventilatory sensitivity to inhaled CO_2 was estimated for each subject whilst breathing a mixture of 2·5–3·0 % CO_2 in air for at least 4 min. This CO_2 concentration was chosen to give increases in P_{CO_2} of about 2–3 mmHg in order to cover the range of P_{CO_2} variation expected during the exercise.

Statistical analysis

The data from the subjects in the steady states, and also for each of ten breaths before and following the onset of exercise were pooled. An unpaired *t* test was used to analyse the steady state. The on transient data were submitted to an analysis of variance, a significant change being assessed using the Least Significant Difference Test of Fisher (Fisher, 1935). In some instances the Mann–Whitney *U* test (Mann & Whitney, 1947) was used. Statistical significance was accepted at the 5 % level in a two-tailed test.

RESULTS

All subjects reported that the electrical stimulus to exercise was acceptable and did not interfere with their listening to the story. They did not think that they were co-operating with the electrical stimulation by adding a voluntary component. During E_V, no difficulty in copying the recorded exercise pattern was experienced, once the principle had been understood. Voluntary and electrically induced exercise were studied in eighteen normal subjects; thirty-six runs were available for analysis with E_V and forty-six runs with E_{EL}. Some of the subjects were studied more than once on separate days, so that the number of runs each subject completed was variable. With E_V the number of runs ranged from one to seven with nine of the subjects completing more than one run; with E_{EL} the number ranged from two to

TABLE 1. Respiratory and circulatory variables at rest and the changes with exercise in the steady state for E_V and E_{EL}

Variable		Voluntary (E_V)			Electrical (E_{EL})			Significant difference in ΔE between E_V and E_{EL}
		n	Rest	ΔE	n	Rest	ΔE	
RR	(min^{-1})	36	16·6 (3·1)	4·4 (3·0)	46	15·8 (2·9)	4·8 (2·7)	N.s.
V_T	(ml)	36	500 (86)	183 (137)	46	512 (92)	233 (147)	N.s.
$\dot{V}_I$	(l min^{-1})	36	8·11 (1·15)	5·90 (2·42)	46	7·85 (1·03)	7·59 (3·16)	$0{\cdot}005 < P < 0{\cdot}01$
$\dot{V}_{CO_2}$	(ml min^{-1})	36	234 (40)	218 (96)	46	229 (39)	287 (143)	$0{\cdot}01 < P < 0{\cdot}025$
$\frac{\Delta \dot{V}_I \times 10^3}{\Delta \dot{V}_{CO_2}}$		—	—	28·1 (4·8)	—	—	28·5 (7·4)	N.s.
P_{ET,CO_2}	(mmHg)	35	37·7 (2·3)	1·2 (1·8)	46	38·0 (2·2)	0·9 (1·4)	N.s.
$\dot{V}_{O_2}$	(ml min^{-1})	35	296 (52)	284 (115)	45	286 (46)	265 (135)	N.s.
R		36	0·79 (0·05)	−0·01 (0·06)	45	0·80 (0·08)	0·13 (0·08)	$P < 0{\cdot}001$
Lactate	(mmol l^{-1})	10	1·10 (0·37)	−0·19 (0·17)	11	0·83 (0·22)	1·34 (0·68)	$P < 0{\cdot}001$
Heart rate	(min^{-1})	36	73 (12)	20 (10)	46	71 (11)	21 (11)	N.s.
S.B.P.	(mmHg)	28	134 (16)	11 (10)	39	132 (15)	19 (16)	$0{\cdot}01 < P < 0{\cdot}025$
D.B.P.	(mmHg)	28	87 (10)	6 (7)	39	86 (9)	5 (14)	N.s.

R is the gas exchange ratio. ΔE indicates change with exercise. S.B.P., systolic blood pressure. D.B.P., diastolic blood pressure. Values are means with S.D. in parentheses.

seven. Whilst each subject had at least one run for each type of exercise on each occasion, not all the runs were included in the final analysis, due to technical failures.

Control Measurements

There were no significant differences in any of the circulatory or respiratory variables measured before the start of either voluntary or electrically induced exercise (Table 1). This suggests that adequate time was allowed between runs for the circulatory and respiratory systems of the subjects to return to their resting states.

Exercise: steady state

The changes in the circulatory and respiratory variables in both types of exercise are shown in Table 1. O_2 consumption was nearly doubled in both forms of exercise, so it is likely that the work achieved was similar. In both forms of exercise there were significant increases in the mean values of $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$, RR, V_T and $\dot{V}_I$; mean P_{ET,CO_2} rose in both forms of exercise but only in E_V was this rise significant. In E_{EL} but not in E_V the rises in the respiratory exchange ratio (R) and lactate were significant. In both E_V and E_{EL} the increase in heart rate and systolic blood pressure was significant; there was in addition a significant increase in diastiolic blood pressure in E_V.

The final column of Table 1 records whether there is any significant difference in the changes in circulation and ventilation *between* E_V and E_{EL}; i.e. tests of significance were made between the mean changes of columns 4 and 7 in Table 1. Although the patterns of the ventilatory response there to the two forms of exercise were the same, was a greater mean rise in $\dot{V}_I$ and $\dot{V}_{CO_2}$ for E_{EL} as opposed to E_V. However, the mean ventilatory equivalent for CO_2 ($\Delta\dot{V}_I/\Delta\dot{V}_{CO_2}$) is the same for both forms of exercise. This is illustrated graphically in Fig. 2, which shows the relationship between $\dot{V}_I$ and $\dot{V}_{CO_2}$ obtained in exercise; the Figure contains all the control and exercise values of all runs for E_V and E_{EL}. The intercepts and slopes of the two regression lines calculated for each type of exercise are nearly identical and both have highly significant correlation coefficients. There is a positive intercept on the ventilatory axis for both E_V and E_{EL}.

Serum lactate and R rose in E_{EL} but fell in E_V and these differences were significant. At the same time $\dot{V}_{CO_2}$ rose significantly more for E_{EL} than for E_V although the increase in $\dot{V}_{O_2}$ was similar in both forms of exercise. These results suggest that E_{EL} was achieved with more anaerobiosis than with E_V.

Systolic blood pressure rose significantly more in E_{EL} than E_V, although changes in mean diastolic blood pressure were very similar.

Acid–base and blood gas levels in arterial blood

These were measured in eleven exercise runs in two subjects during E_V (five runs) and E_{EL} (six runs). The changes in P_{a,CO_2} were small (mean +0·5, S.D. 1·4, range −0·9 to +3·8 mmHg) and were not different in the two types of exercise. $P_{a,CO_2}-P_{ET,CO_2}$ (mean −1·1, S.D. 1·3, range −3·2 to +1·9 mmHg) fell in all except one exercise run and this fall is what would have been anticipated from previous studies in exercise (Jones, Robertson & Kane, 1979). No arterial hypoxia was found in any of the exercise runs. The trend in the changes in the other variables supports the view that

metabolism was more anaerobic in E_{EL} than E_V; thus pH consistently fell in E_{EL} and base excess fell more frequently in E_{EL} than E_V. The mean change in pH for E_V was +0·004 units (S.D. 0·012, range −0·011 to +0·023) and for E_{EL} was −0·014 units (S.D. 0·010, range −0·008 to −0·032). The corresponding changes for base excess were +0·3 mmol l^{-1} (S.D. 0·9, range −0·7 to +1·7) and −0·5 mmol l^{-1} (S.D. 0·9, range −1·4 to +1·0) respectively.

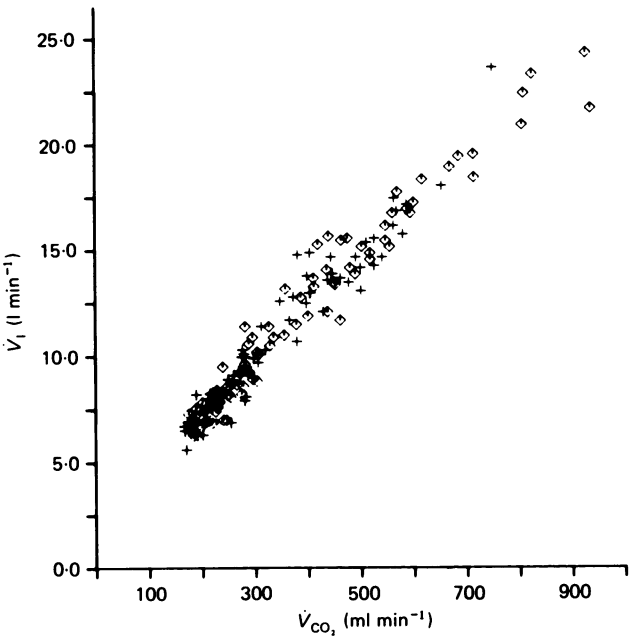

Fig. 2. Control (rest) and steady-state exercise values of $\dot{V}_I$ and $\dot{V}_{CO_2}$ in E_V(+) and E_{EL}(◇). For E_V: $\dot{V}_I = 0{\cdot}0258\ \dot{V}_{CO_2} + 2{\cdot}22$, $r = 0{\cdot}97$. For E_{EL}: $\dot{V}_I = 0{\cdot}0242\ \dot{V}_{CO_2} + 2{\cdot}64$, $r = 0{\cdot}98$.

On transient of exercise

All the variables studied in the steady state were recorded for the first ten breaths of exercise. Twenty-three exercise runs were available for analysis for E_V and thirty-one for E_{EL}. The number of runs used are less than in the steady state because in some instances it was found when analysing the record that exercise had been inadvertently started in inspiration and not expiration; as it was important to determine the precise breath number in which each variable had changed in the two forms of exercise, it was essential that exercise always started in the same phase of the respiratory cycle.

Fig. 3 shows the mean values for P_{ET,CO_2}, $\dot{V}_{CO_2}$ and $\dot{V}_I$ for the ten breaths before and after the start of exercise for both E_V and E_{EL}; Fig. 4 shows the corresponding values for t_e and V_T. In E_V, there were significant changes in the first breath for t_e and $\dot{V}_I$ followed by significant increases in $\dot{V}_{CO_2}$ and V_T on the second breath. In E_{EL}, $\dot{V}_I$, $\dot{V}_{CO_2}$ and t_e changed significantly by the second breath and V_T by the third breath. With E_V the significant rise of $\dot{V}_I$ in the first breath clearly precedes any rise in $\dot{V}_{CO_2}$.

By the second breath of E_V and the third breath of E_{EL}, $\dot{V}_I$ and $\dot{V}_{CO_2}$ reach values which are little different from the mean values for the remainder of the on transient. The increases in V_T occur one breath after t_e, but it must be remembered that the exercise cannot influence V_T on the first breath because exercise is started in

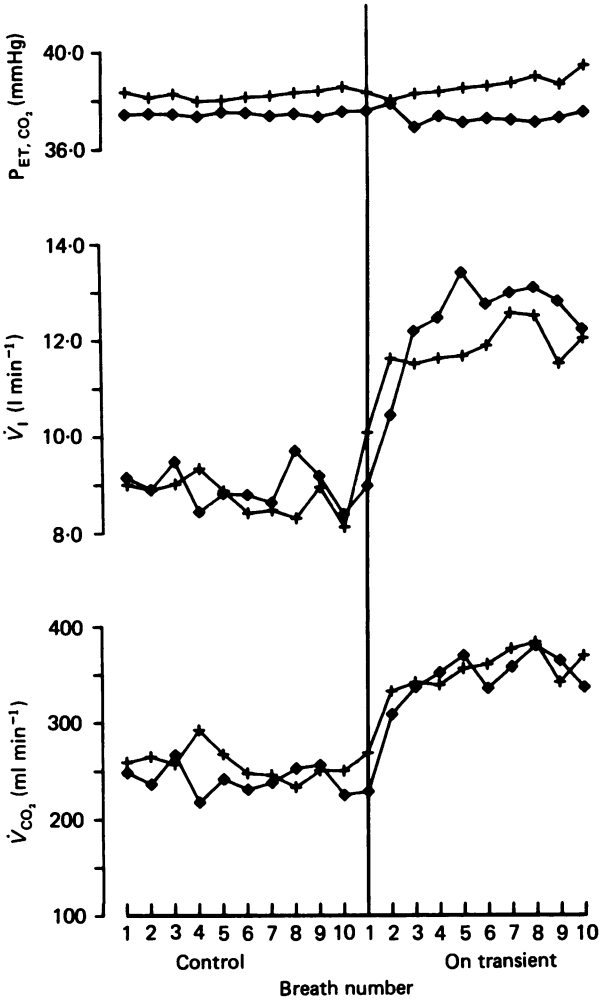

Fig. 3. Mean values for each breath during the control period and on transient for P_{ET,CO_2}, $\dot{V}_I$ and $\dot{V}_{CO_2}$ during E_V(+; $n = 23$) and E_{EL}(◆; $n = 31$). The vertical line indicates the breath (during expiration) in which exercise began. Analyis of variance shows that the first significant changes from control in $\dot{V}_I$ are breath 1 for E_V and breath 2 for E_{EL}; for $\dot{V}_{CO_2}$ the first significant change is in breath 2 for both E_V and E_{EL}; for P_{ET,CO_2} there were only significant changes in breath 8 and 10 for E_V and in breath 3 for E_{EL}.

expiration. There is considerable variation in the mean levels of V_T for E_V but less so for E_{EL}, in which only small changes were seen after the fourth breath of exercise. Despite these changes in the ventilatory variables, P_{ET,CO_2} showed no consistent change in E_V or E_{EL}. Heart rate rose significantly from the first breath onwards for both E_V and E_{EL} following a similar pattern in each case.

Comparison of E_V and E_{EL} during the on transient of exercise

The analysis of the on transient has been further extended to examine more closely if there is a difference between E_{EL} and E_V. Although t_e and $\dot{V}_I$ showed a significant change *from control* on the first breath of E_V and the second of E_{EL}, this finding does

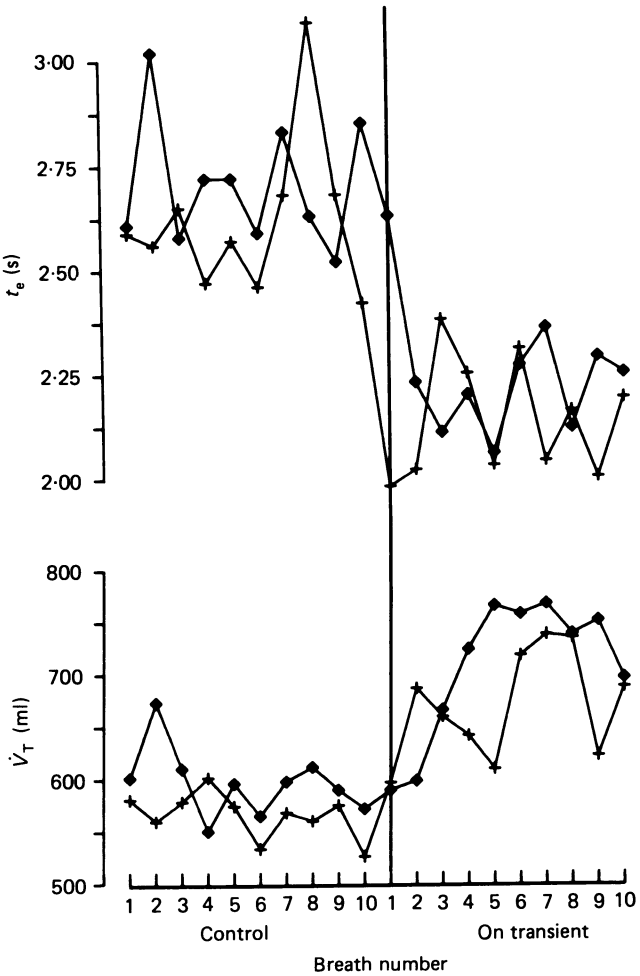

Fig. 4. Mean values for each breath during the control period and on transient for t_e and V_T, during E_V (+ ; $n = 23$) and E_{EL} (◆; $n = 31$). The vertical line indicates the breath (during expiration) in which exercise began. Analysis of variance shows that the first significant changes from control in t_e are breath 1 for E_V and breath 2 for E_{EL}; for V_T the first significant changes are breath 2 for E_V and breath 3 for E_{EL}.

not, on statistical grounds, prove that there is a significant difference *between* E_{EL} and E_V on the first and second breath. The changes in $\dot{V}_I$, t_e and $\dot{V}_{CO_2}$ have therefore been compared at the first two breaths of exercise using an unpaired t test. There was a significant difference for t_e on the first breath between E_V and E_{EL} ($0{\cdot}005 < P < 0{\cdot}01$) but not on the second breath. There was no significant difference betweeen E_V and E_{EL} for $\dot{V}_I$ and $\dot{V}_{CO_2}$ for these breaths.

In order to determine if the rate of increase of CO_2 elimination and ventilation during the on transient was the same for both forms of exercise, a five-point running average was determined for the two variables at each breath number. This method of analysis provides greater precision in determining the mean level of CO_2 elimination and ventilation reached by the end of the on transient in that it 'smooths out' the fluctuations in mean levels between breaths due to the large breath-by-breath variation between and within individual subjects. Whilst the running average is a good method for determining the trend of any change during the on transient, it is of no use for determining abrupt changes as at the start of exercise on the first and

TABLE 2. Mean $\dot{V}_{CO_2}$ and $\dot{V}_I$ of breaths 7 and 8 after onset of exercise derived from smoothed data

	$\dot{V}_{CO_2}$			$\dot{V}_I$		
	E_V	P	E_{EL}	E_V	P	E_{EL}
Percentage increase from control	44 (31)	N.S.	48 (35)	37 (23)	N.S.	44 (22)
Percentage of late exercise	89 (25)	N.S.	84 (40)	87 (18)	N.S.	88 (24)

Values are means with S.D. in parentheses ($n = 23$, E_V; $n = 31$, E_{EL}).

second breaths. Table 2 shows that at the end of the on transient there was no difference between the response in E_V and E_{EL} in that both $\dot{V}_I$ and $\dot{V}_{CO_2}$ had increased by approximately 40% of control values and had reached about 80% of the final steady-state values. These percentages are derived from the mean of breaths 7 and 8 using the smoothed data; a five-point running average precludes calculation of a mean value for breaths 9 and 10, although the data on these last breaths are used in the calculation of the mean level of $\dot{V}_I$ and $\dot{V}_{CO_2}$ of breath 8.

CO_2 sensitivity

Estimation of inhaled CO_2 sensitivity produced a mean value of 1·56 l min^{-1} mmHg^{-1} (S.D. 0·64, $n = 17$). On exercise, P_{ET,CO_2} was unchanged or fell in twelve out of forty-two runs with E_{EL}, and three out of thirty-four runs with E_V. Thus in fifteen runs the 'apparent' sensitivity to CO_2 (Cross *et al.* 1982*a*) was infinite. Where P_{ET,CO_2} rose, the apparent sensitivity to CO_2 during exercise was 12·1 l min^{-1} mmHg^{-1} (S.D. 19·6, $n = 30$) for E_V, and 13·8 l min^{-1} mmHg^{-1} (S.D. 17·7, $n = 31$) for E_{EL}. If P_{a,CO_2} is used where available, then for E_V, apparent sensitivity was infinite for four runs and 6·5 l min^{-1} mmHg^{-1} for one. For E_{EL}, apparent sensitivity was infinite for two runs and was 1·9, 6·0, 4·5 and 9·0 l min^{-1} mmHg^{-1} for the remainder.

DISCUSSION

This study shows that, in man, a ventilation appropriate to CO_2 elimination can be obtained with leg exercise in the presence or absence of a cortical drive to exercise. We cannot show any differences in the ventilatory response except for a definite shortening of t_e during the first breath of voluntary exercise. Our conclusions, which essentially confirm the early work of Asmussen *et al.* (1943), are only valid for the low levels of exercise that we were able to study, which, on average, did no more than double $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

Methodology

The validity of the conclusion depends entirely on whether we can be certain that during E_{EL} the subjects did not voluntarily activate their leg muscles in rhythm with the electrical stimulus, i.e. whether there is an *absence* of cortical drive to movement. We found this difficult to prove with objective evidence. An attempt was made to see if voluntarily induced e.m.g. potentials in the leg muscles could be recorded during the phase of electrical stimulation, but this was not successful because of the large size of the stimulus artifact. When the current was switched off between stimuli, with the subject kept in ignorance of what had been done, a voluntary contraction at the appropriate time might have been expected if the subject was driving the muscles in rhythm with the stimulator; this was never seen either on the tension or e.m.g. records. At the subjective level, all subjects denied 'co-operating' with the stimulus. Nevertheless we cannot exclude the remote possibility that electrical stimulation of the muscles may have evoked a reflex reinforcement, with involvement of pathways within the central nervous system.

The voltage used was always kept below the level that would induce pain. In very similar experiments performed in the anaesthetized dog Cross *et al.* (1982*a*) considered it likely that electrical stimulation of the leg muscles to produce 'exercise' might stimulate afferent fibres concerned with pain transmission. With an intact cord a highly abnormal pattern of ventilatory airflow resulted particularly during the on transient of exercise, when the level of stimulation was increased to produce changes in $\dot{V}_{CO_2}$ over 120%. In the present study, where increases of $\dot{V}_{CO_2}$ were usually less than 120% no abnormal pattern of airflow was ever seen, nor was pain felt with the voltages used. We could produce pain in the legs by increasing the voltage, and then irregular breathing with hypocapnia could be seen. The ability to produce adequate exercise with relatively low voltages suggests that small nerve fibres rather than muscle fibres, were being stimulated. This is certainly true for the comparable studies in the dog (Cross *et al.* 1982*a*) where this point has been proved with the use of gallamine triethiodide to block neuromuscular transmission.

Differences between E_V and E_{EL}

The patterns of exercise and limb movements achieved were remarkably similar with E_V and E_{EL}; this was a cardinal feature of the study by Asmussen *et al.* (1943). It is unlikely that in E_{EL} the development of tension in the quadriceps and hamstrings can have the same fine control expected with a voluntary contraction. This may explain the finding that anaerobiosis occurs to a small extent with E_{EL} even though $\dot{V}_{O_2}$ has only doubled. The production of lactic acid with E_{EL} presumably explains the higher $\dot{V}_{CO_2}$ for a given $\dot{V}_{O_2}$, i.e. an increased R during the steady state; it does not appear that any significant metabolic acidosis occurs during the on transient since $\dot{V}_{CO_2}$ in the two types of exercise does not appear different. Since $\dot{V}_I$ had one unique linear relationship with $\dot{V}_{CO_2}$ in both E_V and E_{EL}, we did not think the steady-state difference was important, especially since arterial pH changes were small. Systolic blood pressure rose more with E_{EL} than with E_V, but there were no differences in heart rate or diastolic blood pressure. Since no continuous measurements of cardiac output were available, we cannot say if this difference is due to a greater increase of cardiac output or a smaller reduction of peripheral resistance, with E_{EL}. It is

possible that group III and IV afferents within muscle might have been activated with E_{EL} when all the tension development occurs in only two muscles, and this could have had cardiovascular effects (Mitchell, Mierzwiak, Wildenthal, Willis & Smith, 1968; McCloskey & Mitchell, 1972).

Neural and chemical drives to breathe during exercise

The concept of a neural drive to breathe has remained controversial and confused over the last 70 years (Dejours, 1959; Astrand & Christensen, 1963; Cunningham, 1963; Wasserman *et al.* 1981). The confusion has arisen because authors have often not been able to distinguish between a neural drive from the exercising muscles, and one originating in the cortex.

The mechanism involving afferents from the moving limbs was thought to be very significant in the dog by Kao (1963) and Kao *et al.* (1979), but this could not be substantiated in the same species by Cross *et al.* (1982*a*). This aspect of neural control as far as man is concerned has not been examined in the present paper but relevant studies are reported in the succeeding paper (Adams, Frankel, Garlick, Guz, Murphy & Semple, 1984). Krogh & Lindhard (1913) proposed that 'irradiation' from the neural centres involved in voluntary exercise, to the pons and medulla, was responsible for the increase in ventilation with exercise. This hypothesis was based on their finding that the increase in ventilation at the onset of electrically induced exercise was slower and smaller than that observed when exercise was started voluntarily. Their experimental design did not use the same form of exercise for E_{EL} and E_V. The only other comparison of E_V with E_{EL} in man has been the study of Asmussen *et al.* (1943), where only the steady state was examined and no differences were found, as in the present paper.

The role of 'irradiation' has been further studied in the cat by Eldridge, Milhorn & Waldrop (1981) and Di Marco, Romaniuk, von Euler & Yamamoto (1983). These authors used the high decerebrate cat which spontaneously developed episodes of co-ordinated walking movement (Shik, Severin & Orlovsky, 1966, 1967; Orlovsky, 1969). It was found that electrical stimulation of two locomotor integrating centres in the subthalmic and mesencephalic regions produced locomotion in the animals, with ventilatory increases that occurred at or just before the onset of locomotor activity. It was thought that ventilation had increased prior to any possible increase in exercise metabolic factors. One of the problems with the interpretation of these experiments is that the ventilatory increase consists primarily of a tachypnoea and results in hypocapnia. Thus these experiments do not show the matching of ventilation to CO_2 elimination so typical of the natural ventilatory response to exercise.

The remarkable similarity between the ventilatory response in the two forms of exercise suggests that in man the cerebral cortex in the conscious state is not necessarily required to achieve matching of ventilation to CO_2 elimination. It would seem unlikely that the amount of ventilation is determined by some form of 'learned' response, but there is evidence to support the concept of 'irradiation' to the respiratory centres from the cortical drive to exercise. This effect, however, seems small, and is confined to the breath in which exercise starts.

REFERENCES

ADAMS, L., FRANKEL, H., GARLICK, J., GUZ, A., MURPHY, K. & SEMPLE, S. J. G. (1984). The role of spinal cord transmission in the ventilatory response to exercise in man. *Journal of Physiology* **355**, 85–97.

ASMUSSEN, E., NIELSEN, M. & WEITH-PEDERSEN, G. (1943). Cortical or reflex control of respiration during muscular work? *Acta physiologica scandinavica* **6**, 168–175.

ASTRAND, P. O. & CHRISTENSEN, E. H. (1963). The hyperpnoea of exercise. In *The Regulation of Human Respiration*, ed. CUNNINGHAM, D. J. C. & LLOYD, B. B., pp. 515–534. Oxford: Blackwell Scientific Publications.

CROSS, B. A., DAVEY, A., GUZ, A., KATONA, P., MACLEAN, M., MURPHY, K., SEMPLE, S. J. G. & STIDWELL, R. (1982*a*). The role of spinal cord transmission in the ventilatory response to electrically induced exercise in the anaesthetized dog. *Journal of Physiology* **329**, 37–55.

CROSS, B. A., DAVEY, A., GUZ, A., KATONA, P., MACLEAN, M., MURPHY, K., SEMPLE, S. J. G. & STIDWELL, R. (1982*b*). The pH oscillations in arterial blood during exercise; a potential signal for the ventilatory response in the dog. *Journal of Physiology* **329**, 57–74.

CUNNINGHAM, D. J. C. (1963). Some quantitative aspects of the regulation of human respiration in exercise. *British Medical Bulletin* **19**:1, 25–30.

DEJOURS, P. (1959). La regulation de la ventilation au cour de l'exercise masculaire chez l'homme. *Journal de physiologie* **51**, 163–261.

DIMARCO, A. F., ROMANIUK, J. R., VON EULER, C. & YAMAMOTO, Y. (1983). Immediate changes in ventilation and respiratory pattern associated with onset and cessation of locomotion in the cat. *Journal of Physiology* **343**, 1–16.

EDWARDS, R. H. T., YOUNG, A., HOSKING, G. P. & JONES, D. A. (1977). Human skeletal muscle function: description of tests and normal values. *Clinical Science & Molecular Medicine* **52**, 283–290.

ELDRIDGE, E. L., MILHORN, D. E. & WALDROP, T. G. (1981). Exercise hyperpnea and locomotion: Parallel activation from the hypothalmus. *Science* **211**, 844–846.

FISHER, R. A. (1935). *The Design of Experiments*. Edinburgh: Oliver & Boyd.

JONES, N. L., ROBERTSON, D. G. & KANE, J. W. (1979). Difference between end-tidal and arterial P_{CO_2} in exercise. *Journal of Applied Physiology* **47**(5), 954–960.

KAO, F. F. (1963). An experimental study of the pathways involved in exercise hyperpnoea employing cross-circulation techniques. In *The Regulation of Human Respiration*, ed. CUNNINGHAM, D. J. C. & LLOYD, B. B., pp. 461–502. Oxford: Blackwell Scientific Publications.

KAO, F. F., MEI, S. S. & KALIA, M. (1979). Interaction between neurogenic exercise drive and chemical drive. In *Central Nervous Control Mechanisms in Breathing*, ed. VON EULER, C. & LAGERCRANTZ, H., pp. 75–89. Oxford: Pergamon Press.

KROGH, A. & LINDHARD, J. (1913). The regulation of respiration and circulation during the initial stages of muscular work. *Journal of Physiology* **47**, 112–136.

KROGH, A. & LINDHARD, J. (1917). A comparison between voluntary and electrically induced muscular work in man. *Journal of Physiology* **51**, 182–201.

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

MANN, H. B. & WHITNEY, D. R. (1947). On a test of whether one of two random variables is stochastically larger than the other. *Annals of Mathematical Statistics* **18**, 50–60.

MITCHELL, J. H., MIERZWIAK, D. S., WILDENTHAL, K., WILLIS JR, W. D. & SMITH, A. M. (1968). Effect on left ventricular performance of stimulation of an afferent nerve from muscle. *Circulation Research* **22**, 507–516.

ORLOVSKY, G. N. (1969). Spontaneous and induced locomotion of the thalamic cat. *Biofizika* **14**, 1095 (English transl. pp. 1154–1162).

SHIK, M. L., SEVERIN, F. V. & ORLOVSKY, G. N. (1966). Control of walking and running by means of electrical stimulation of the midbrain. *Biofizika* **11**, 659 (English transl. pp. 756–765).

SHIK, M. L., SEVERIN, F. V. & ORLOVSKY, G. N. (1967). Brain stem structures responsible for evoked locomotion. *Fiziologicheskii Zhurnal SSSR IM I M Sechonova* **53**, 1125.

WASSERMAN, K., WHIPP, B. J. & DAVIS, J. A. (1981). Respiratory physiology of exercise. Metabolism, gas exchange and ventilatory control. In *International Review of Physiology, Respiratory Physiology III*, vol. 23, ed. WIDDICOMBE, J. G., pp. 149–211. Baltimore: University Park Press.