Comparison of arterial potassium and ventilatory dynamics during sinusoidal work rate variation in man

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1. The mechanisms underlying the exercise hyperpnoea have been difficult to define. Recently it has been suggested that exercise ventilation ($\dot{V}_E$) changes in proportion to changes in arterial potassium concentration ($[K^+]_a$). Similar $\dot{V}_E$ and $[K^+]_a$ time courses following work rate changes have been cited as supporting evidence. This study compared $[K^+]_a$ and $\dot{V}_E$ dynamics during moderate exercise in man.

2. We observed $\dot{V}_E$ and gas exchange responses in five healthy men to sinusoidal work rate variation between 25 and ~105 W. Tests of ~30 min duration were performed at sinusoidal periods of 9, 6 and 3 min and in the steady state. In each test, during two or three sine periods, arterial blood was sampled (24 per test) and analysed for $[K^+]$ and blood gases. Response amplitude and phase (relative to work rate) were determined for each variable.

3. $[K^+]_a$ fluctuated in response to sinusoidal work rate forcing with mean-to-peak amplitude averaging 0·15 mmol l^{-1}. However, among tests, $\dot{V}_E$ amplitude and phase were not highly correlated with $[K^+]_a$ ($r = 0{\cdot}36$ and 0·67, respectively). Further, average $[K^+]_a$ amplitude in the 9 and 6 min sinusoidal studies tended to exceed the steady-state amplitude, while average $\dot{V}_E$ amplitude fell progressively with increasing forcing frequency. The dissimilar dynamics of $[K^+]_a$ and $\dot{V}_E$ seem inconsistent with a major role for $[K^+]_a$ as a proportional controller of ventilation during non-steady state moderate exercise in man.

4. Among tests, $\dot{V}_E$ and CO_2 output ($\dot{V}_{CO_2}$) amplitude and phase were closely correlated ($r = 0{\cdot}87$ and 0·94, respectively). Further, arterial CO_2 pressure (P_{a,CO_2}) and arterial pH (pH_a) did not fluctuate significantly in ten of twenty and thirteen of twenty studies, respectively. In tests where sinusoidal fluctuation was detected, amplitude averaged 1·1 mmHg and 0·008 units, respectively. Thus $\dot{V}_E$ demonstrated a close dynamic coupling to CO_2 output, with consequent tight regulation of P_{a,CO_2} and pH_a.

Definition of the stimulus–response relationships underlying the profound increase in ventilation seen with moderate exercise has proven extremely elusive. We have yet to find identifiable sensors that unequivocally stimulate ventilation ($\dot{V}_E$) whose environment changes during steady-state exercise below the lactic acidosis threshold. The arterial chemoreceptors have been thought to be good candidates for mediating at least a portion of the exercise hyperpnoea since they are responsible for the ventilatory response to other stimuli (e.g. hypoxic or hypercapnic inhalates). However, the levels of the most apparent stimuli to the arterial chemoreceptors, P_{CO_2}, P_{O_2} and pH, do not differ measurably between rest and moderate exercise in man (Wasserman, Whipp & Casaburi, 1986). For many years, there has been a search for a 'factor X', a substance in the arterial blood that rises during moderate exercise and stimulates the respiratory chemoreceptors.

Several investigators have recently postulated that 'factor X' has been found and that it is the potassium ion (K^+) (Band, Linton, Kent & Kurer, 1985; Busse, Maassen & Konrad, 1991; Paterson, 1992). An appreciable body of evidence has been presented to support this postulate. Following exercise onset, arterial K^+ concentration ($[K^+]_a$) rises promptly and substantially; during heavy exercise $[K^+]_a$ can reach 7–8 mmol l^{-1} (Paterson, Robbins & Conway, 1989; Medbo & Sejersted, 1990). Recordings from the carotid sinus nerve of cats reveal that the carotid bodies are stimulated by increases in $[K^+]_a$ in the physiological range and that the response is rapid (Band & Linton, 1986). Studies in the cat reveal that denervating the carotid and aortic chemoreceptors eliminates the stimulatory effects of increases in arterial $[K^+]$ on $\dot{V}_E$ (Band *et al.* 1985). Finally, studies in man have shown that the time course of $[K^+]_a$ and $\dot{V}_E$ following the onset and cessation of exercise are

similar, with $\dot{V}_E$ changing in direct proportion to $[K^+]_a$ (Band, Lim, Linton & Wolff, 1982; Paterson *et al.* 1989; Busse, Scholz, Saxler, Maassen & Boning, 1992).

It is this latter finding we felt worthy of further study. Starting with the work of Krogh & Lindhard (1913), the time course of ventilatory response has been used to infer the candidacy of a number of potential mediators of the exercise hyperpnoea. In the 1970s, studies from this laboratory established that there was a very close relation between the dynamics of CO_2 output ($\dot{V}_{CO_2}$) and $\dot{V}_E$ during exercise (with $\dot{V}_{CO_2}$ slightly leading $\dot{V}_E$) implying that the exercise hyperpnoea was in some way linked to a CO_2-related stimulus (Casaburi, Whipp, Wasserman, Beaver & Koyal, 1977; Casaburi, Whipp, Wasserman & Stremel, 1978). We reasoned that if a close dynamic relation existed between arterial $[K^+]$ and $\dot{V}_E$ (i.e. with $\dot{V}_E$ in close proportion, but lagging $[K^+]_a$ slightly) credence would be lent to the possibility that arterial $[K^+]$ plays a role in the exercise hyperpnoea. We chose to utilize sinusoidal work rate forcings, since they elicit a continuously non-steady-state response. Responses to successive sinusoidal periods can be observed to accentuate the underlying physiological responses. Further, if responses to sinusoidal forcings of a variety of periods are observed, techniques of frequency response analysis can be applied to test mathematical models describing the dynamics of the stimulus–response relationships (Casaburi *et al.* 1977; Wasserman *et al.* 1986).

METHODS

Subjects

This protocol was approved by the Human Subjects Committee of Harbor-UCLA Medical Center. Five healthy young men gave written informed consent for participation in this study. Their physical characteristics were (mean ± S.D.): age, 23·2 ± 5·0 years; height, 171·4 ± 5·3 cm; and weight, 62·2 ± 7·2 kg. Each performed a preliminary incremental exercise test to exhaustion on the cycle ergometer; work rate was increased at a rate of 25 W min^{-1} following 3 min of unloaded pedalling. Ventilatory and gas exchange responses were examined to determine the peak $\dot{V}_{O_2}$ (as the average $\dot{V}_{O_2}$ over the final 30 s of exercise) and the lactic acidosis threshold (by the modified *V*-slope technique (Sue, Wasserman, Moricca & Casaburi, 1988)). Peak $\dot{V}_{O_2}$ was 3·33 ± 0·38 l min^{-1} and lactic acidosis threshold was 1·77 ± 0·42 l min^{-1}.

Experimental procedures

During these studies, subjects exercised on an electromagnetically braked cycle ergometer (Excaliber, Lode, Groningen, Netherlands). The work rate profile was generated by a personal computer that drove the cycle ergometer via a digital-to-analog converter. Subjects respired through a mouthpiece with noseclip in place. Ventilatory and gas exchange responses were measured breath by breath by a digital computer-based system (2900, Sensormedics, Yorba Linda, CA, USA) using previously described algorithms (Beaver, Wasserman & Whipp, 1973). In this system, expired airflow is measured by a hot wire flow meter; respired P_{CO_2} and P_{O_2} are measured by infrared and zirconium oxide analysers, respectively. Prior to exercise, a catheter was introduced into the left brachial artery by the Seldinger technique (Seldinger, 1953) after local anaesthesia with 1% xylocaine solution. The catheter was flushed between samples with heparinized saline.

Each subject performed four exercise tests over a 5 h period with a 45 min rest period between tests. The order of tests was randomized among subjects. In one test, the responses to steady-state exercise were determined; subjects exercised for 8 min at 25 W, immediately followed by 8 min at a work rate which elicited a $\dot{V}_{O_2}$ approximately equal to 90% of that at the subject's lactic acidosis threshold (105 ± 5·5 W). During the final 4 min at each work rate, four arterial blood samples (approximately 2 ml) were drawn into 5 ml glass syringes heparinized with lyophilized sodium heparin. In the other three tests, work rate was varied sinusoidally between the two work rates chosen for the steady-state test. In these tests, 4 min of a work rate equal to the mean value of the sinusoid was followed by 24–27 min of sinusoidal exercise. Three sinusoidal periods were employed in the three tests: 9, 6 and 3 min (with 3, 4 and 9 cycles in each test, respectively). In the later portion of each of these three tests, twenty-four blood samples were drawn from the arterial catheter at evenly spaced intervals. In the 9 min test, samples were drawn every 45 s over two sinusoidal periods. In the 6 min tests, samples were drawn every 30 s over two periods. In the 3 min tests, samples were drawn every 22·5 s over three periods. Note that these sampling intervals yield twelve, twelve and eight samples per sinusoidal period, respectively, assuring good characterization of the sinusoidal response waveforms which have the same period as the work rate forcing.

The timing of blood samples was meticulously co-ordinated by two investigators (one sampling blood and one recording sampling times) so that the phase relation of the blood gas and electrolyte fluctuations to the work rate variation could be accurately determined. A stop-watch was started precisely at the mid-point of the upswing of the work rate sinusoid. Five seconds in advance of each scheduled sampling time the stopcock connected to the arterial catheter (dead space, 0·3 ml) was opened and approximately ¾ ml of blood was allowed to flow into gauze to clear the cannula of flush solution. The investigator stated 'start' and 'stop' as the sampling of approximately 2 ml of blood began and ended – these times were recorded to the nearest second. The sampling duration was approximately 4 s and the sample time was assigned as the mid-point of the interval. In subsequent analysis, the actual sample time, rather than the scheduled time, was used, although these values generally differed by 3 s or less.

Blood samples were immediately degassed, capped and immersed in an ice slurry pending analysis. Samples were analysed by a blood gas-electrolyte analyser (BGE, Instrumentation Laboratories, Lexington, MA, USA) which was used to measure P_{O_2}, P_{CO_2}, pH and potassium and sodium concentrations. Samples from a given test were analysed in the order they were collected by one of two identical analysers. These analysers underwent automatic one point calibration before each sample. Three levels of quality control ampules were employed prior to and following each day's testing. Approximately 12% of the blood samples drawn in this study were introduced into both analysers; no systematic bias between machines for any analyte was observed. Whole blood tonometry was performed to confirm accuracy of the P_{O_2} and P_{CO_2} measurements on several occasions during this study. Each blood

sample was also analysed for lactate concentration (YSI-2300, Yellow Springs, OH, USA); an automated calibration was performed every four samples.

Data analysis

The breath-by-breath ventilatory and gas exchange data from each study were digitally transferred to a general purpose spreadsheet program (Microsoft Excel). Analysis of blood gas samples was manually entered into the spreadsheet program. For the steady-state test, responses to the two work rates studied were determined by averaging the last 4 min of data. The steady-state response amplitude was defined as half of the difference between the response to the work rates corresponding to the upper and lower limits of the sinusoidal fluctuation.

For a discussion of the theory underlying analysis of sinusoidal response data, please see our previous publication (Casaburi *et al.* 1977). When the relationship between the work rate forcing and the responding variables is approximately linear, the response will be a sinusoid of the same period as the work rate input. Therefore, for each variable and for each sinusoidal exercise test, the response data were fitted by the relation:

$$y(t) = A \sin(360\ t/T + \phi),$$

where $y(t)$ is the model response at time t (in s), A is the mean-to peak amplitude, T is the sinusoidal forcing period (in s) and ϕ is the difference in phase (in deg) between the response and the work rate forcing. For each fitting, the values of the parameters A and ϕ were derived that minimized the summed-square difference between the data points and the model curve. This analysis assumes that a linear dynamic system links the work rate forcing to the responding variables. We determined whether the data had a significant sinusoidal fluctuation by comparing the summed-square error for the sinusoidal fit to the summed-square error for a flat line corresponding to the mean value of the sinusoid utilizing an F test (Motulsky & Ransnas, 1987). For the ventilatory and gas exchange data, prior to fitting it was necessary to omit from the calculation the initial transient following the application of the sinusoidal work rate forcing. For the variables examined, the initial transient persists for under 5 min (equal to several time constants of response for these variables); thus the first sinusoidal period was omitted for the 6 and 9 min tests and the first two periods were omitted from the 3 min test.

Comparison of response dynamics

Frequency response analysis utilizes the amplitude and phase relationships of a given response variable as a function of the period of the work rate forcing to determine the dynamic relation of the response variable to the work rate forcing and, by inference, the dynamic linkages among response variables. We employed three approaches to use the sinusoidal response data to discern linkages among response variables. The first (simplest) approach seeks strong linear correlation of response amplitude and phase between two variables as forcing frequency is varied (utilizing the Pearson product–moment correlation coefficient and linear regression analysis). The second approach considers the trends in amplitude and phase lag as a function of forcing frequency of the measured variables to the constant amplitude work rate forcing. Physiological variables which are responding to the sinusoidal work rate forcing with similar response dynamics should have similar trends in amplitude and phase lag as the work rate forcing frequency is increased. The third approach involves fitting the response data to empirical mathematical models which express the dynamic relation between the forcing function (work rate) and the response. Comparison of the model parameters among response variables may suggest similar (or dissimilar) response dynamics. For a given response variable the amplitude and frequency response data for the three sinusoidal tests and the steady-state response were fitted to selected mathematical models by adjusting model parameters to minimize the summed-square difference between response and model. This was accomplished by an interactive computerized routine. Superiority of a more complex mathematical model was established by considering the size of the reduction in summed-square fitting error and the number of parameters contained in the two models (Motulsky & Ransnas, 1987).

All values are expressed as the mean ± 1 S.D., unless otherwise specified. Statistical significance is accepted if $P \leqslant 0{\cdot}05$.

RESULTS

Figure 1 shows the responses of one of the subjects (no. 4) to the three sinusoidal work rate forcings. For purposes of display, successive sinusoidal responses have been superimposed, allowing the amplitude and phase relationships of the variables shown to be easily discerned. For the ventilatory and gas exchange variables clear fluctuations are seen in response to the work rate fluctuation. Superimposed on the response data are sinusoids of best fit. It can be seen that these response data are well described by a sine wave. This allows description of the response of each variable as an amplitude and a phase lag with respect to the work rate forcing. However, the more rapid the work rate fluctuation, the smaller the response amplitude and the greater the phase delay for each of these variables. For the measurements from arterial blood sampling (P_{O_2}, P_{CO_2}, pH and $[K^+]$), distinct fluctuations are also apparent in most variables. An easily discernable fluctuation in P_{a,O_2} is seen; P_{a,CO_2} and pH_a fluctuation is detectable at some (but not all) forcing frequencies. Importantly, arterial $[K^+]$ has a clear sinusoidal fluctuation at all three work rate periods; the amplitude of the fluctuation is 0·13, 0·20 and 0·08 mmol l^{-1} for the 9, 6 and 3 min sinusoidal periods, respectively. The clear sinusoidal response of the gas exchange variables, ventilation and $[K^+]_a$ tends to validate the assumption that a linear dynamic system links the work rate forcing to these variables.

Table 1 presents the amplitude and phase lag of response to sinusoidally varying work rate and also the steady-state response for each of seven variables presented in Fig. 1, for each of the five subjects. It can be seen that in all subjects, at all frequencies, statistically significant fluctuations were seen in $\dot{V}_E$, $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$ and $[K^+]_a$. Of the twenty studies, significant fluctuations were seen in fourteen for P_{a,O_2}, ten for P_{a,CO_2} and seven for pH_a (see below).

Not shown in Table 1 are the amplitude and phase lag of response of arterial lactate and sodium. Blood lactate was found to have a significant fluctuation in thirteen of fifteen sinusoidal studies. However, the amplitude of fluctuation was only $0{\cdot}10 \pm 0{\cdot}04$ mmol l^{-1} and the mean value around which blood lactate fluctuated was $0{\cdot}73 \pm 0{\cdot}09$ mmol l^{-1}, consistent with the intention that the exercise be restricted to work rates below the lactic acidosis threshold. Arterial sodium fluctuated significantly in only three of fifteen sinusoidal studies; in these three, amplitude was only $0{\cdot}9 \pm 0{\cdot}3$ mmol l^{-1}.

Figure 2 compares amplitude and phase lag of three of the responding variables ($\dot{V}_{CO_2}$, $\dot{V}_{O_2}$ and $[K^+]_a$) to the amplitude and phase lag of $\dot{V}_E$ for each of the sinusoidal and steady-state responses of the five subjects. As can be seen, there is a high correlation for both amplitude and phase lag of response between $\dot{V}_E$ and $\dot{V}_{CO_2}$ ($r = 0{\cdot}87$ and 0·94,

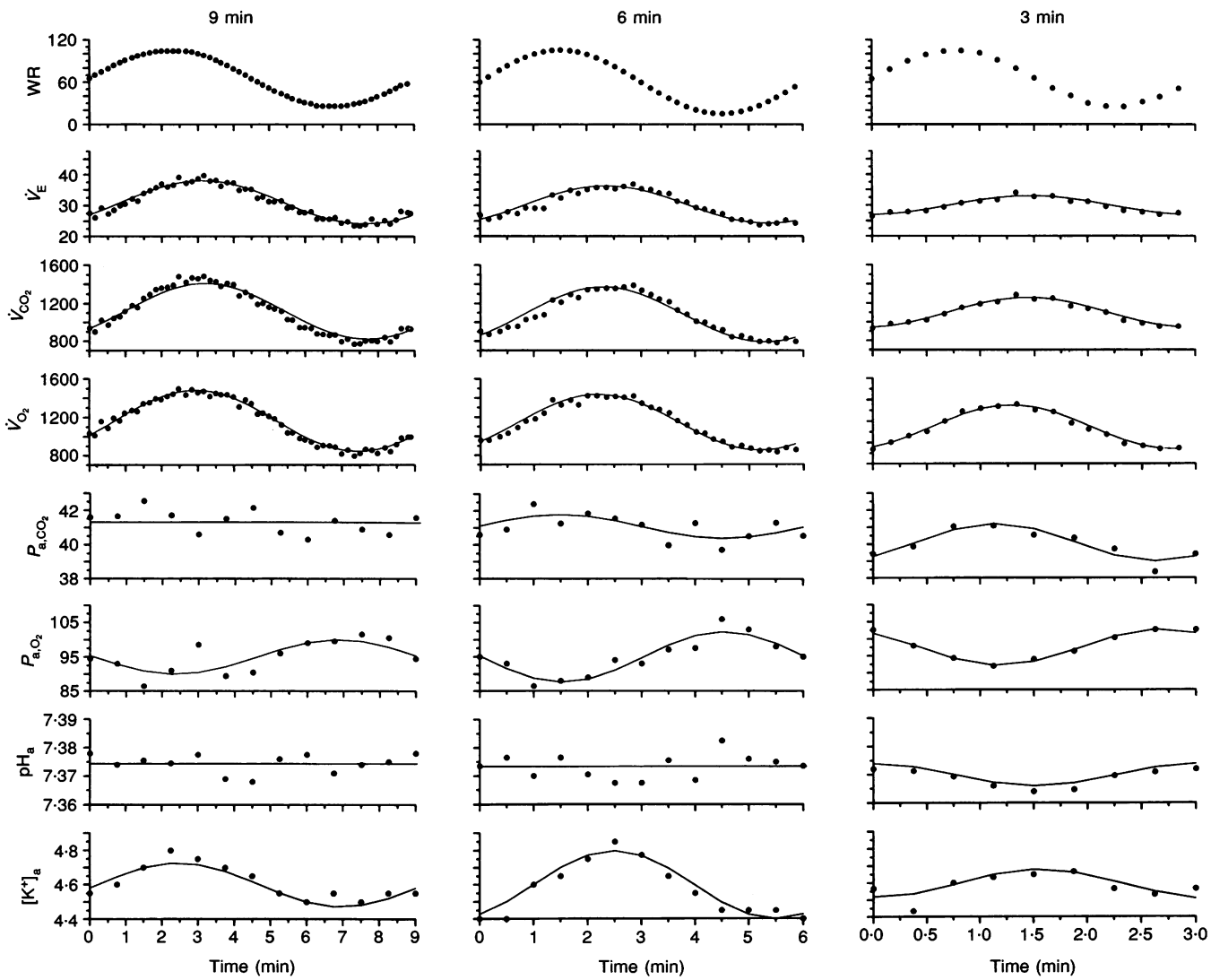

Figure 1. Responses of one subject to sinusoidal work rate variation

Responses of subject no. 4 to sinusoidal work rate forcings with periods of 9, 6 and 3 min. For purposes of display, successive sinusoidal responses have been superimposed. For the ventilatory and gas exchange data, this was accomplished by calculating 10 s averages from the breath-by-breath data. Superimposed on the response data are sinusoids of best fit, which facilitate definition of the amplitude and phase of each response for each variable. WR, work rate (W); $\dot{V}_E$, ventilation (l min^{-1}); $\dot{V}_{CO_2}$, CO_2 output (ml min^{-1}); $\dot{V}_{O_2}$, oxygen uptake (ml min^{-1}); P_{a,CO_2}, arterial CO_2 tension (mmHg); P_{a,O_2}, arterial O_2 tension (mmHg); pH_a, arterial pH; $[K^+]_a$, arterial potassium concentration (mmol l^{-1}).

Table 1. Amplitude and phase lag of response to sinusoidal work rate variation

Subject	Period	$\dot{V}_E$		$\dot{V}_{CO_2}$		$\dot{V}_{O_2}$		P_{a,O_2}		P_{a,CO_2}		pH_a		$[K^+]_a$	
		A	ϕ	A	ϕ	A	ϕ	A	ϕ	A	ϕ	A	ϕ	A	ϕ
	(min)	(l min^{-1})	(deg)	(ml min^{-1})	(deg)	(ml min^{-1})	(deg)	(Torr)	(deg)	(Torr)	(deg)	(units)	(deg)	(mmol l^{-1})	(deg)
1	SS	6·73	—	243	—	259	—	*	—	*	—	*	—	0·18	—
	9	6·66	−50	213	−45	256	−35	3·6	172	*	*	*	*	0·14	−30
	6	4·54	−38	192	−36	224	−30	3·9	159	*	*	*	*	0·14	−19
	3	3·26	−59	113	−66	172	−59	4·1	116	*	*	*	*	0·11	−80
2	SS	7·05	—	311	—	244	—	*	—	*	—	*	—	0·10	—
	9	5·27	−31	260	−31	247	−26	3·5	161	1·1	−32	0·008	128	0·24	−35
	6	5·39	−37	277	−36	266	−32	*	*	*	*	*	*	0·18	−53
	3	3·45	−111	171	−86	184	−79	*	*	*	*	*	*	0·18	−74
3	SS	6·25	—	350	—	337	—	*	—	*	—	*	—	0·21	—
	9	7·96	−39	361	−36	383	−30	4·8	160	1·1	−28	0·005	137	0·24	−35
	6	4·05	−61	253	−56	302	−43	8·2	157	1·7	−66	0·011	111	0·21	−57
	3	5·13	−105	243	−91	291	−80	7·5	129	1·2	−46	*	*	0·17	−79
4	SS	9·20	—	425	—	362	—	−3·3	—	*	—	−0·012	—	0·15	—
	9	6·90	−35	324	−34	317	−28	5·0	−185	*	*	*	*	0·13	−8
	6	6·02	−51	291	−48	293	−38	7·3	−182	0·7	1	*	*	0·20	−59
	3	3·02	−86	160	−83	205	−64	5·3	128	1·1	−47	0·004	88	0·08	−98
5	SS	6·95	—	318	—	216	—	*	—	1·4	—	−0·011	—	0·14	—
	9	4·16	−2	223	−16	236	−8	4·2	171	0·9	−20	*	*	0·09	−28
	6	4·15	−21	255	−24	305	−24	5·2	133	1·2	−87	0·011	80	0·11	−32
	3	2·92	−37	142	−61	214	−41	5·2	117	0·8	−75	*	*	0·08	−84

A, amplitude. SS, steady-state amplitude is one-half the difference between responses to steady exercise at work rates corresponding to peak and trough of sinusoidal fluctuation; sinusoidal amplitudes are the means to peak. ϕ, phase lag with respect to work rate sinusoid. $\dot{V}_E$, ventilation; $\dot{V}_{CO_2}$, CO_2 output; $\dot{V}_{O_2}$, O_2 uptake; P_{a,O_2}, arterial O_2 tension; P_{a,CO_2}, arterial CO_2 tension; pH_a, arterial pH; $[K^+]_a$, arterial potassium ion concentration. * Amplitude of fluctuation was not significantly different from zero.

respectively; left panels). This confirms our previous work which found that ventilation is closely correlated to the rate of CO_2 output at the lung (Casaburi *et al.* 1978). In comparison, the amplitude and phase lag of $[K^+]_a$ is considerably less well correlated with $\dot{V}_E$ ($r = 0{\cdot}36$ and $0{\cdot}67$, respectively). The linear correlation coefficient relating $\dot{V}_E$ and $[K^+]_a$ amplitude is not significantly different from zero which suggests that $\dot{V}_E$ is not responding in proportion to $[K^+]_a$.

Further evidence of the dynamic linkage of ventilation to CO_2 output can be discerned from the blood gas and pH responses listed in Table 1. Significant variation in P_{a,CO_2} and pH_a with the work rate forcing was seen in only ten and seven of twenty studies, respectively. In those cases where a statistically significant fluctuation was detected, the amplitudes of P_{a,CO_2} and pH_a were $1{\cdot}1 \pm 0{\cdot}3$ mmHg and $0{\cdot}008 \pm 0{\cdot}003$ units, respectively, indicating a close dynamic regulation of these variables. Importantly, P_{a,CO_2}

Table 2. Average first-order with delay model parameter values

	$\dot{V}_E$ (l min^{-1})	$\dot{V}_{CO_2}$ (ml min^{-1})	$\dot{V}_{O_2}$ (ml min^{-1})	$[K^+]_a$ (mmol l^{-1})
A_o	6·84 ± 1·53	322 ± 70	284 ± 59	0·16 ± 0·05
τ	42·9 ± 20·6	43·6 ± 13·5	23·9 ± 12·2	23·7 ± 12·3
T_D	7·6 ± 15·3	7·2 ± 9·5	13·0 ± 9·1	22·7 ± 5·4

Parameter values are the means ± S.D. of 5 subjects. A_o, steady-state amplitude; τ, time constant (s); T_D, time delay (s). For other abbreviations, see Table 1.

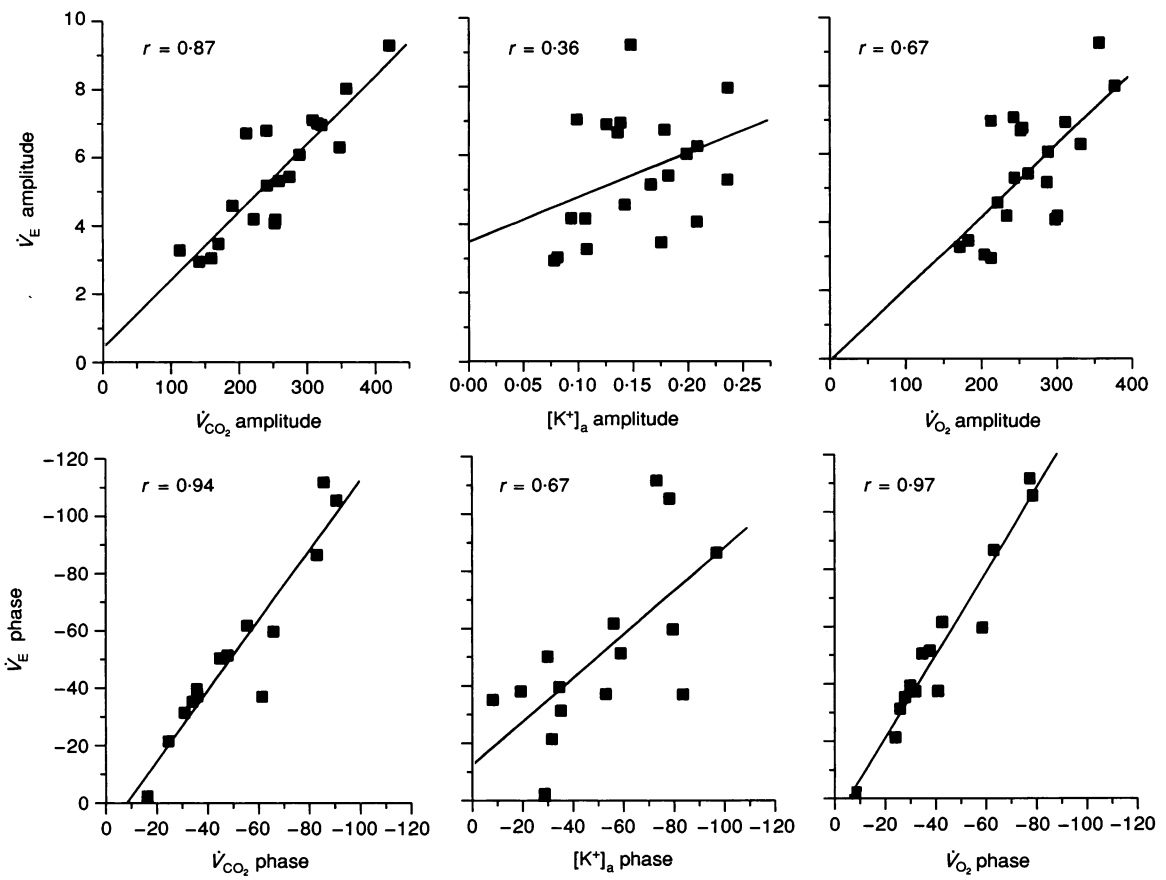

Figure 2. Correlation of amplitudes and phases of response

Comparison of amplitude (top panels) and phase (lower panels) of ventilatory ($\dot{V}_E$) response with CO_2 output ($\dot{V}_{CO_2}$), O_2 uptake ($\dot{V}_{O_2}$) and arterial potassium concentration ($[K^+]_a$). Amplitudes of $\dot{V}_E$, $\dot{V}_{CO_2}$, $[K^+]_a$ and $\dot{V}_{O_2}$ are in units of l min^{-1}, ml min^{-1}, mmol l^{-1} and ml min^{-1}, respectively; phase is expressed as the difference (in deg) from the phase of the work rate fluctuation. Each point represents one of 4 tests (one steady-state plus 3 sinusoidal tests) in each of 5 subjects. Superimposed lines were determined by linear regression. Amplitude correlations are highest for $\dot{V}_E$ *vs.* $\dot{V}_{CO_2}$, intermediate for $\dot{V}_E$ *vs.* $\dot{V}_{O_2}$ and lowest for $\dot{V}_E$ *vs.* $[K^+]_a$. Further, the $\dot{V}_E$ *vs.* $[K^+]_a$ amplitude relation does not extrapolate through the origin. The phase relations show that $\dot{V}_E$ *vs.* $\dot{V}_{CO_2}$ and $\dot{V}_E$ *vs.* $\dot{V}_{O_2}$ are highly correlated but the $\dot{V}_E$ *vs.* $[K^+]_a$ phase angles are less strongly correlated.

was high and pH was low when $\dot{V}_E$ was high (phase differences of 4 ± 42 and 156 ± 32 deg in the sinusoidal studies, respectively). This suggests that (in those studies where significant P_{a,CO_2} or pH_a fluctuations are seen) the coupling between $\dot{V}_E$ and $\dot{V}_{CO_2}$ is inexact during sinusoidal work rate change, with $\dot{V}_E$ lagging $\dot{V}_{CO_2}$ so that, as $\dot{V}_{CO_2}$ rises, arterial P_{CO_2} transiently increases and pH falls.

Figure 3 presents the mean (± S.E.M.) of the five subjects' amplitude (normalized to the steady-state amplitude) and phase lag of response of $\dot{V}_E$, $\dot{V}_{CO_2}$ and $[K^+]_a$ as a function of the forcing frequency. The amplitude of $\dot{V}_E$ and $\dot{V}_{CO_2}$ both decline monotonically with rising forcing frequency; however, the average amplitude of $[K^+]_a$ tends to be higher for the 9 and 6 min forcing periods than for the steady-state test (averaging 1·07 and 1·08 of the steady-state value, respectively). By paired analysis of the fifteen sine wave studies, the fraction of the steady-state amplitude for the sinusoidal studies was higher for $[K^+]_a$ than for $\dot{V}_E$ ($P < 0{\cdot}02$). This indicates a dissimilarity of $\dot{V}_E$ and $[K^+]_a$ dynamics. Average phase lag increases progressively with forcing frequency for each of these three variables.

We chose to fit the sinusoidal response data of $\dot{V}_E$, $\dot{V}_{CO_2}$ and $[K^+]_a$ to a mono-exponential model incorporating a delay, as this has been shown to provide satisfactory fitting of responses to stepwise forcings (Whipp, Ward, Lamarra, Davis & Wasserman, 1982). The corresponding form of this relation in response to stepwise stimuli is:

$$y(t) = A_0(1 - e^{-(t - T_D/\tau)}),$$

where A_0 is the steady-state amplitude, τ is the time constant of the response and T_D is the time delay. Table 2 presents the mean parameter values for the five subjects. It

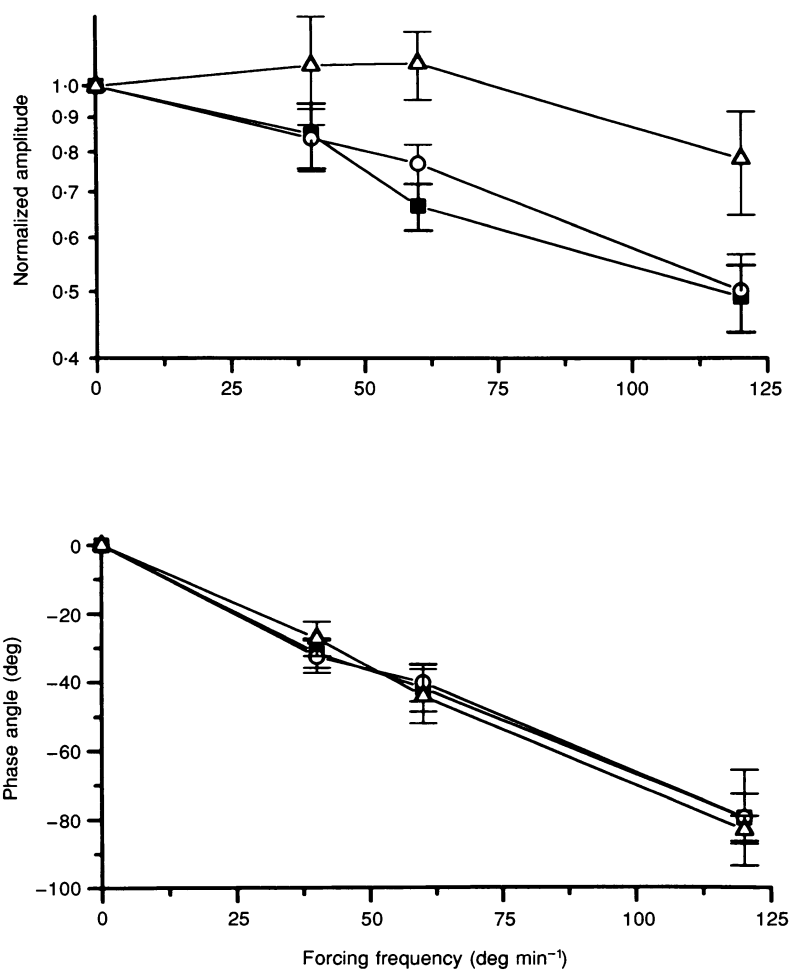

Figure 3. Frequency response of ventilation ($\dot{V}_E$), CO_2 output ($\dot{V}_{CO_2}$) and arterial potassium concentration ($[K^+]_a$)

Bode plot (Milhorn, 1966) of the mean (± S.E.M.) responses of the 5 subjects at each of the 4 forcing frequencies studied. Top panel, average ratio of amplitude to the steady-state amplitude plotted on a semi-logarithmic scale. Bottom panel, phase of response, with respect to the work rate sinusoid. The normalized amplitude response of $\dot{V}_E$ is similar to that of $\dot{V}_{CO_2}$, but not to $[K^+]_a$ (see text). △, $[K^+]_a$; ○, $\dot{V}_{CO_2}$; ■, $\dot{V}_E$.

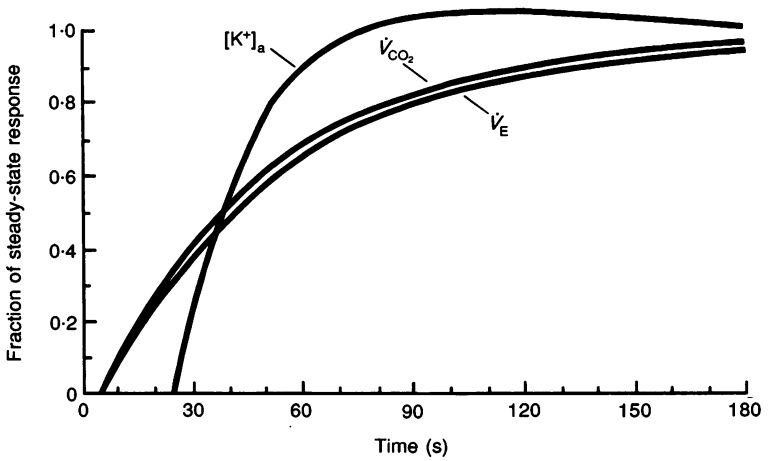

Figure 4. Predicted responses to a stepwise change in work rate

Predicted normalized response to the abrupt transition from 25 to 105 W of ventilation ($\dot{V}_E$), CO_2 output ($\dot{V}_{CO_2}$) and arterial potassium concentration ($[K^+]_a$), based on the frequency response characteristics shown in Fig. 3. Response kinetics of $\dot{V}_{CO_2}$, but not $[K^+]_a$, are similar to $\dot{V}_E$ (see text).

can be seen that $\dot{V}_E$ and $\dot{V}_{CO_2}$ responses are characterized by very similar time constants of response and small time delays. In contrast, fitting of the $[K^+]_a$ data to this model consists of a time constant and time delay of almost equal magnitude. Moreover, the $[K^+]_a$ response data are not well described by this model (for which response amplitude decreases monotonically with forcing frequency).

A better description of the $[K^+]_a$ response data is as a second order underdamped system incorporating a delay (the response to a stepwise forcing for such a system is composed of the sum of a rising and a falling exponential with the falling component having the longer time constant):

$$y(t) = kA_0(1 - e^{-(t-T_D/\tau_1)}) - (1-k)A_0(1 - e^{-(t-T_D/\tau_2)}),$$

where $k > 1$ and expresses the degree of 'overshoot' of the steady-state value and T_1 and T_2 are the time constants of the rising and falling exponentials, respectively. Fitting this model to the mean $[K^+]_a$ data resulted in a 56% reduction in summed-square error in comparison with the mono-exponential model and yielded the following parameter values: $k = 1{\cdot}3$, $A_0 = 0{\cdot}16$ mequiv l^{-1}, $T_D = 25{\cdot}0$ s, $\tau_1 = 22{\cdot}3$ s and $\tau_2 = 75{\cdot}0$ s. Though the reduction in summed-square error is appreciable, it does not achieve statistical significance (the reduction in summed-square error must be sufficient to 'justify' the additional two parameters (Motolsky & Ransnas, 1987)). Thus the superiority of the higher order model cannot be considered to be established. In contrast, fitting this model to the average $\dot{V}_E$ and $\dot{V}_{CO_2}$ data did not result in a reduction in summed-square error compared with the mono-exponential model. To appreciate better the differences in the response kinetics, Fig. 4 presents the normalized predicted response of $[K^+]_a$, $\dot{V}_{CO_2}$ and $\dot{V}_E$ to a stepwise increase in work rate, derived from the best-fitting model responses. While the three variables have superficially similar kinetics (rapid rise of response within the first minute and assumption of a steady state within approximately 4 min), it is clear that $\dot{V}_E$ and $\dot{V}_{CO_2}$ show close kinetic coupling but the $[K^+]_a$ and $\dot{V}_E$ responses do not suggest that $\dot{V}_E$ responds in proportion to $[K^+]_a$.

DISCUSSION

The present studies were undertaken to test the hypothesis that $\dot{V}_E$ changes in direct proportion to changes in arterial $[K^+]$ during moderate exercise. Sinusoidal work rate forcings were used to produce sinusoidal variations in $[K^+]_a$ and $\dot{V}_E$. By observing four different periods of work rate forcings (with identical amplitudes), it was possible to observe the resultant amplitude and phase relation of the oscillations of $[K^+]_a$ and $\dot{V}_E$. The responses we observed are not consistent with a proportional relationship between arterial $[K^+]$ and $\dot{V}_E$ response during moderate exercise.

Dynamic analysis has proven to be a valuable tool in evaluating mechanistic inter-relations underlying the exercise hyperpnoea. The response to stepwise forcings have been utilized for much of this research, but the stepwise forcing has discernable disadvantages. Following changes in work rate (over the range of moderate work rates), information relevant to the dynamic response is restricted to the first 3–4 min of the response; thereafter a steady state is achieved. Physiological 'noise' in breath-by-breath ventilatory and gas exchange data, and measurement 'noise' in assays of relevant variables from blood sampling, limits the ability to discern temporal correlations from this limited time period. Sinusoidal forcings have advantages in this regard in that a continuously dynamic response is induced; resolution can be improved (without limit) the longer the responses are observed. Further, for a system that is substantially linear

(when examined over a delimited range), there exists mathematical machinery that can predict responses to other forcing functions based on the responses to sinusoidal inputs (Wasserman *et al.* 1986). This requires observation of a range of forcing frequencies for full description of the response dynamics. For example, it has been established that, unless very high sinusoidal frequencies are included, hypotheses concerning rapid components of the exercise hyperpnoea cannot be evaluated (Engeman, Swanson & Jones, 1983). Our experimental design was guided by the observation that there were no rapid components in $[K^+]_a$ response following exercise onset (Paterson *et al.* 1989). The range of sinusoidal forcing frequencies we employed was designed to yield good resolution of the slow component of the exercise response.

Since we observed the time courses of blood gases and pH, this investigation provided insights in addition to the main focus on the relation of arterial $[K^+]$ to the exercise hyperpnoea. Specifically, we were able to define further the relationship of CO_2-related variables to $\dot{V}_E$ during moderate exercise (Whipp, Wasserman, Casaburi, Juratsch, Weissman & Stremel, 1978). As previously reported (Casaburi *et al.* 1978), there is a close correlation of $\dot{V}_{CO_2}$ and $\dot{V}_E$ kinetics. Table 1 shows that this results in tight control of P_{a,CO_2} and pH_a. In the face of substantial fluctuation in CO_2 production, there was no measurable fluctuation in P_{a,CO_2} or pH_a in ten of the twenty tests, and no measurable fluctuation in pH_a in three of the remaining tests. In those tests where P_{a,CO_2} or pH_a fluctuation was discerned, the fluctuation amplitudes were only 1·1 mmHg and 0·008 units, respectively (though, based on known sensitivities of the ventilatory chemoreceptors, these fluctuations may well have a measurable influence on $\dot{V}_E$). Importantly, in these tests P_{a,CO_2} was high and pH_a was low at a time when $\dot{V}_E$ was high, indicating that the $\dot{V}_E$ response was not quite adequate to effect acid–base homeostasis. This is a reflection of slightly slower $\dot{V}_E$ kinetics compared with $\dot{V}_{CO_2}$ kinetics. It is worth noting that the size of the P_{a,CO_2} and pH_a fluctuations did not vary appreciably as a function of the period of the work rate forcing. This is probably the result of offsetting influences: any lag of $\dot{V}_E$ with respect to $\dot{V}_{CO_2}$ would tend to yield larger P_{a,CO_2} and pH_a fluctuations for higher forcing frequencies; on the contrary, since $\dot{V}_{CO_2}$ fluctuations are smaller as forcing frequency rises, for a given degree of dynamic mismatch, P_{a,CO_2} and pH_a fluctuation would be smaller.

We observed consistent and reproducible fluctuation in arterial potassium concentration in response to work rate fluctuation, confirming that exercise is associated with alteration in $[K^+]_a$. The amplitude of the fluctuations in $[K^+]_a$ was 0·15 mequiv l^{-1}. This amplitude must be considered in the light of the fact that day-to-day variability of plasma $[K^+]_a$ in healthy subjects well exceeds this amount and that substantial therapeutic adjustments in $[K^+]_a$ yield no apparent changes in $\dot{V}_E$. On this basis it seems hard to accept that small fluctuations in $[K^+]_a$ could be major contributors to the exercise hyperpnoea. Indeed, the recent study of Qayyum, Barlow, O'Connor, Paterson & Robbins (1994), in which oral KCl ingestion increased $[K^+]_a$ by approximately 0·8 mequiv l^{-1} but did not alter $\dot{V}_E$ significantly during moderate exercise, casts doubt on the ability of slowly developing $[K^+]_a$ changes to influence $\dot{V}_E$. (However, it is conceivable that the $\dot{V}_E$ response to $[K^+]_a$ changes that occur over a period of hours might show complete adaptation, though this has not been demonstrated.) Moreover, we have presented three lines of evidence that the kinetics of $[K^+]_a$ and $\dot{V}_E$ during moderate exercise are substantially dissociated. Figure 2 shows that both amplitude and phase lag of $[K^+]_a$ and $\dot{V}_E$ are poorly correlated. Figure 3 demonstrates that the amplitude of $[K^+]_a$ tends to rise over steady-state values for both 9 and 6 min forcing periods, while $\dot{V}_E$ amplitude progressively falls. Figure 4 presents the results of fitting empirical mathematical models to the sinusoidal forcing data to predict stepwise responses of $[K^+]_a$ and $\dot{V}_E$; distinct differences are seen. The predicted $[K^+]_a$ step response can be compared with those previously measured, with the proviso that high frequency components are probably lacking in the simulation. The overshoot of the steady-state value is an interesting feature of the simulation. Paterson *et al.* (1989) did not observe an overshoot in $[K^+]_a$ following the onset of 100 W exercise, though an undershoot following the offset of heavy exercise was seen. Medbo & Sejersted (1990) have also observed a $[K^+]_a$ undershoot following exercise offset. Further, we have observed an overshoot in $[K^+]_a$ following onset of moderate exercise in several subjects (Stringer, Wasserman & Casaburi, 1994).

Though our results seem to rule against a $\dot{V}_E$ response in proportion to $[K^+]_a$, it is worth considering whether other, less direct, control linkages might be consistent with these data. A component of the response related to the rate of change of a variable has been observed in physiological systems and, in fact, this control mode has previously been postulated to be involved in the exercise hyperpnoea (Grodins & James, 1963). However, were $\dot{V}_E$ to increase in response to increases in the rate of change of $[K^+]_a$, the amplitude of the $\dot{V}_E$ response should have been higher, not lower, for the 9 min sine wave forcing than in the steady-state tests (Fig. 3). However, it must be acknowledged that other less direct linkages of $[K^+]_a$ to $\dot{V}_E$ cannot be ruled out.

In summary, an examination of the response kinetics of $\dot{V}_E$ and $[K^+]_a$ revealed distinct differences. This finding seems inconsistent with the role for potassium in the exercise hyperpnoea that has been previously postulated: a component of the $\dot{V}_E$ response in proportion to $[K^+]_a$ change. Importantly, however, we cannot rule out a role for $[K^+]_a$ in the hyperpnoea of heavy exercise (McLoughlin, Linton & Band, 1994). Our analysis also reinforces the close dynamic coupling of $\dot{V}_E$ to $\dot{V}_{CO_2}$ with the consequent tight regulation of arterial P_{CO_2} and pH.

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