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VENTILATION AND CARDIAC OUTPUT DURING THE ONSET OF EXERCISE, AND DURING VOLUNTARY HYPERVENTILATION, IN HUMANS

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SUMMARY

1. Three normal subjects performed rest–exercise transitions on a cycle ergometer, from rest to unloaded pedalling (0 W), 50, 100 and 150 W. Each experiment was performed in triplicate, with randomized work load order, in two sessions. Ventilation was obtained breath-to-breath by integration of a pneumotachygraph signal, and cardiac output beat-to-beat by a new development of the Doppler technique. Results were bin-averaged in 4 s bins over the first 20 s, and compared to resting values.

2. Both ventilation and cardiac output increased significantly in the first 2 s. This initial rise in ventilation was due entirely to an increase in rate, the subsequent rise mainly to increase in tidal volume. Cardiac output increased predominantly through change in rate with smaller increases in stroke volume.

3. A striking feature was a tendency for ventilation and cardiac output responses to be biphasic with an initial rise followed by a slight fall at the 14 s mark, and a subsequent rise, at all work loads. Overall correlation between ventilation and cardiac output was therefore high ($r = 0{\cdot}92$).

4. Six normal subjects hyperventilated for 45 s voluntarily, (a) at rate 24/min and normal tidal volume; (b) at normal rate and tidal volume of 1·5 l; (c) at rate 24/min and tidal volume of 1·5 l. Cardiac output, averaged over 10–45 s, rose by 0·4, 0·5, and 1·0 l min^{-1} respectively, with falls in end-tidal P_{CO_2} of 4, 6, and 8 mmHg.

5. Six normal subjects hyperventilated for 60 s with rate 24/min and tidal volume of 1·4 l, and end-tidal P_{CO_2} maintained at 38 ± 2 mmHg. Cardiac output, averaged from 10–60 s, rose by 1·0 l min^{-1}.

6. With increased rate and tidal volume, whether isocapnic or hypocapnic, cardiac output responses showed an overshoot with a peak value at about 30 s.

7. The hypothesis of 'cardiodynamic hyperpnoea' considers a possible effect of increasing cardiac output on ventilation. The effects of ventilation on cardiac output must also be considered. We propose an extended hypothesis involving stable positive feed-back.

INTRODUCTION

Since the early observations of Krogh & Lindhard (1913) the abrupt increase in ventilation at the onset of exercise has been much discussed (Comroe & Schmidt, 1943; Asmussen & Neilson, 1948; Dejours, 1959; D'Angelo & Torelli, 1971). The increase usually occurs in two phases: phase I, the rapid increase occurring within the first breath and lasting several breaths and phase II which is the more gradual increase beyond the immediate response continuing into the steady state (Wasserman, Whipp & Davis, 1981; Whipp, 1981).

In attempting to explain this increase in ventilation, some experimenters have proposed a neurogenic theory while others believe that the ventilatory response is accounted for by a rapid neurogenic component and a slower humoral component (Dejours, 1959). Still others have suggested that humoral mechanisms might be mediating part of the phase I response (Ward, Whipp, Koyal & Wasserman, 1983). Wasserman, Whipp & Castagna (1974) suggested that the increase in ventilation at the onset of exercise is 'cardiodynamic', proposing that the rapid increase in cardiac output is closely followed by a rise in ventilation so that the increased CO_2 load arriving at the lungs is cleared with little change in arterial CO_2 levels.

In order to test their hypothesis, it is first essential to make breath-to-breath measurements of ventilation and beat-to-beat measurements of cardiac output. Standard techniques for measuring cardiac output (direct and indirect Fick, dye dilution, soluble gas rebreathing) are not applicable. We have developed the non-invasive pulsed Doppler technique to measure aortic flow beat-to-beat (Darsee, Walter & Nutter, 1980; Loeppky, Greene, Hoekenga, Caprihan & Luft, 1981; Alverson, Eldridge, Dillon, Yabek & Berman, 1982; Mehta, Iyawe, Cummin, Bayley, Saunders & Bennett, 1985). We report here measurements of ventilation and cardiac output during the first 20 s of exercise in normal man, the first time these transient changes have been simultaneously measured in this phase.

Second, since the Wasserman hypothesis takes changes in ventilation as following or dependent on changes in cardiac output it would be important to test also whether voluntary changes in ventilation with no great alteration in metabolic rate are accompanied by changes in cardiac output. Previous work (McGregor, Donevan & Anderson, 1962) suggests that there is an increase in cardiac output with voluntary hyperventilation which is small if P_{CO_2} is kept constant (as it is in moderate exercise): however, measurements of cardiac output were not made until 45 s after hyperventilation began.

We therefore averaged cardiac output beat-to-beat during brief periods of voluntary hyperventilation with various breathing patterns and under both hypocapnic and isocapnic conditions.

METHODS

Exercise experiments

Three healthy adult volunteers, all unfamiliar with exercise physiology, all aged 24, took part in the study. They came to the laboratory and practised the experimental protocol a day before the first of two sessions. Each session was on a separate day during which a subject performed six rest–exercise transitions. The subject sat on the cycle ergometer (Siemens-Elema 380B) throughout

the session which lasted for about 1 h. During each experiment the subject cycled for 1 min only, then rested for 10 min before starting the next. The order of work load was randomized so that each subject did triplicate experiments for each of four different work loads ranging from zero-load pedalling (0 W) to 150 W. A typical protocol was:

Day 1:	100 W,	50 W,	0 W,	100 W,	0 W,	150 W
Day 2:	100 W,	150 W,	50 W,	0 W,	150 W,	50 W

The experimental sequence proceeded as follows. At the start, the subject put on a nose clip, and breathed through a low-resistance valve, Rudolph (no. 2700). The Doppler transducer was placed at the suprasternal notch and a gentle probing was made until good velocity signals appeared on a monitoring oscilloscope (Mehta *et al.* 1985). At the end of 3 min rest breathing through the mouth piece, cardiorespiratory variables were recorded on a Gould 6-channel recorder (2600 S). Before exercise, the ergometer flywheel was manually accelerated to a speed of 60–80 rev min^{-1}, with the load pre-set. Data were also collected during the flywheel movement. The subject was then asked to start pedalling at a constant rate of 60 rev min^{-1}. The command to start was transmitted verbally without prior warning.

Inspiratory air flow was recorded continuously with a Fleisch no. 4 pneumotachygraph (Statham Gauge PM 15) and the resulting signals were converted by an Electronics for Medicine IRD.7 integrator to inspiratory tidal volume. The Fleisch head was calibrated before and after each experiment over 0·5 to 3·0 l with a 6 l syringe. Ventilation was calculated from tidal volume and the total breath time T_{tot}.

In determining the time course of the ventilation response, derived values for each breath were plotted as occurring at the mid-point in time of the breath in question. The onset of the ventilation response was taken as the beginning of the first complete respiratory cycle after the signal to start exercise (Ingemann-Jensen, Vejby-Christensen & Petersen, 1972).

Aortic root blood velocity values were determined using a bidirectional continuous wave Doppler velocity meter (Bach Simpson Ltd. BVM 202). The transducer frequency was 2·2 mHz with a penetration capability of 6–14 cm.

The ascending aortic velocity signals obtained were traced manually off-line with a digitizer (Numonics Digitizing Pad) linked to a mini-computer development system (CED System-ALPHA) (Mehta *et al.* 1985). The mini-computer calculated and tabulated the following: (1) mean velocity; (2) systolic velocity integral and (3) heart rate. During signal processing, any beats for which mean velocity or systolic velocity integral was less than 75 % of control were excluded and less than 4 % of the data was excluded by so doing.

Aortic root cross-sectional area was measured with an M-mode echocardiogram (SKI Ekoline 21) of the aortic root. The average systolic diameter ($\bar{D}$) was determined by planimetry and a systolic cross-sectional area ($\bar{A}$) of the aortic root was calculated as $\pi\,(\bar{D}/2)^2$.

The Doppler derived cardiac output was then determined for each heart beat:

$$\text{cardiac output} = (\text{mean velocity} \times \bar{A} \times 60)/1000.$$

Stroke volume was derived from cardiac output and heart rate.

Hyperventilation

Six healthy subjects (age range 24–32) were studied. They practised the experimental protocol several times before the actual experiments. They breathed into a closed-circuit spirometer, allowing a few minutes to stabilize at normal rate and tidal volume. Then they hyperventilated according to one of the following protocols, the order of which was randomized: (A) rate 24/min, normal tidal volume; (B) normal rate, tidal volume 1·5 l; (C) rate 24/min, tidal volume 1·5 l.

We used a standard spirometer with a CO_2 absorber in the expired line (Morgan Transfertest Model C). Rate was controlled by the subject listening to a metronome. Tidal volume was controlled by the subject's observation of the recorder pen moving between two fixed lines on the chart paper. Pure O_2 was injected into the breathing circuit to maintain an inspired concentration of 20·9 %O_2.

In a separate study, a slightly different group (five from the previous group and one new subject) repeated protocol C above, but with end-tidal P_{CO_2} kept as constant as possible by manual addition of pure CO_2 to the inspiratory line (protocol D).

All four protocols were repeated three times by each subject. The records were analysed for a control period of 30 s followed by 45 s hyperventilation (protocols A–C) or 60 s (protocol D).

End-tidal P_{CO_2} was analysed continuously at the mouth by a Centronix MGA 200 mass

spectrometer. The Doppler flow signals were collected and treated as for the exercise studies, except they were automatically, rather than manually, digitized by an A–D converter with PDP 11/23 computer.

Data handling

(*a*) *Averaging*

(i) *Ventilation.* In the exercise studies, on the average, subjects made five breaths within the 20 s studied (i.e. one breath in 4 s). Therefore values for breath-to-breath ventilation were bin-averaged every 4 s for each work load. The corresponding tidal volumes were also averaged and breath rate obtained from mean ventilation and tidal volume.

(ii) *Cardiac output.* Beat-to-beat cardiac output, heart rate and stroke volume were similarly averaged in 4 s bins for comparison with ventilation measurements.

(*b*) *Correlation*

The sequential values for ventilation at rest and during exercise were compared with Doppler derived cardiac output values. Correlation analysis was used to establish a relation between these values at the four levels of exercise. Linear regression with correlation coefficient, slope and S.D. of estimations were computed for each subject and then for the mean of all the subjects and work loads.

RESULTS

Exercise

An example of a rest–exercise transition is shown in Fig. 1.

Ventilation, tidal volume, and breath rate. There was a sudden increase in ventilation at the start of exercise. Within the first 4 s (i.e. first breath), the increase was due to a rise in instantaneous breath rate only. Fig. 1 is atypical in this respect. From

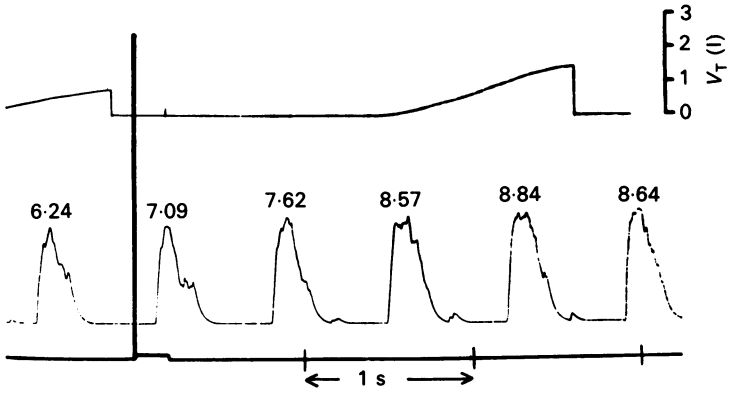

Fig. 1. Experimental record of a rest–exercise transition. Upper trace – tidal volume (V_T). Lower trace – Doppler output. Cardiac output figures (l min^{-1}) are appended for each heart beat.

the second breath, the increase in tidal volume became significant ($P = 0{\cdot}01$) while breath rate rapidly lost any significant contribution to the increase in ventilation (Table 1).

At 0 and 50 W an initial increase in ventilation reached a maximum at 6 s followed by a slight fall. At 100 and 150 W, an initial peak at 10 s was followed by a fall and a second rise at 18 s (Fig. 2*A*). Changes in ventilation were not significantly different for 0 and 50 W.

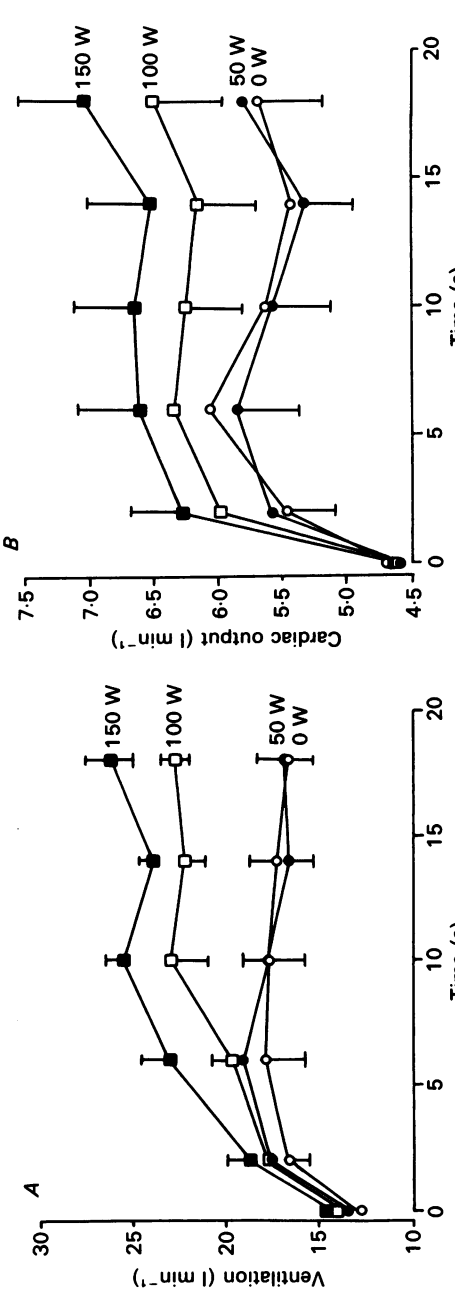

Fig. 2. Changes in mean ventilation (*A*) and cardiac output (*B*) at four work loads. Bars indicate one S.E. of mean.

Fig. 3. Contribution of stroke volume (V_s) and heart rate (H.R.) to changes in cardiac output ($\dot{Q}$), *A*, at 50 W and, *B*, at 150 W.

TABLE 1. Mean tidal volume (V_T), breath rate (B.R.) and ventilation ($\dot{V}$) and percentage changes, at the four chosen work loads

	Time (s)	V_T (l)	V_T (%)	B.R. (min^{-1})	B.R. (%)	$\dot{V}$ (l min^{-1})	$\dot{V}$ (%)
0 W	0	0·96	—	13	—	12·9	—
	2	0·87	−9·4	19	46·2	16·7	29·5
	6	1·12	16·7	16	23·1	18·0	39·5
	10	1·28	33·3	14	7·7	17·8	37·9
	14	1·07	11·5	16	23·1	17·4	34·9
	18	1·32	37·5	13	0·0	16·8	30·2
50 W	0	0·93	—	15	—	13·6	—
	2	0·87	−6·5	20	33·3	17·7	30·1
	6	1·11	19·4	17	13·3	19·2	41·2
	10	1·15	24·0	15	0·0	17·8	30·9
	14	1·15	24·0	15	0·0	16·8	23·5
	18	1·52	63·4	11	−26·7	17·0	25·0
100 W	0	0·97	—	14	—	14·0	—
	2	0·97	0·0	18	28·6	17·9	27·9
	6	1·40	44·3	14	0·0	19·8	41·4
	10	1·51	55·7	15	7·1	23·1	65·0
	14	1·55	59·8	14	0·0	22·4	60·0
	18	1·49	53·6	15	7·1	22·9	63·6
150 W	0	1·07	—	14	—	14·6	—
	2	0·90	−15·9	21	50	18·7	28·1
	6	1·37	28·0	17	21·4	23·2	58·9
	10	1·49	39·3	17	21·4	25·6	75·3
	14	1·44	34·6	17	21·4	24·0	64·4
	18	1·60	49·5	16	14·3	26·3	80·1

TABLE 2. Mean stroke volume (V_s), heart rate (H.R.) and cardiac output ($\dot{Q}$) and percentage changes, at the four chosen work loads

	Time (s)	V_s (ml)	V_s (%)	H.R. (min^{-1})	H.R. (%)	$\dot{Q}$ (l min^{-1})	$\dot{Q}$ (%)
0 W	0	60·2	—	78·0	—	4·7	—
	2	63·5	5·5	86·3	10·6	5·48	17·0
	6	66·0	9·6	91·5	17·3	6·07	29·0
	10	62·2	3·3	90·4	15·9	5·63	20·0
	14	63·6	5·6	85·5	9·6	5·44	16·0
	18	66·5	10·5	85·6	9·7	5·69	21·0
50 W	0	59·0	—	78·0	—	4·6	—
	2	61·8	4·7	90·4	15·9	5·59	21·5
	6	63·7	8·0	92·0	17·9	5·86	27·4
	10	60·9	3·2	91·6	17·4	5·58	21·3
	14	59·9	1·5	89·0	14·1	5·33	15·9
	18	64·7	9·7	89·8	15·1	5·81	26·0
100 W	0	61·0	—	76·0	—	4·64	—
	2	65·0	6·6	92·0	21·0	5·98	28·9
	6	67·1	10·0	94·5	23·7	6·34	36·6
	10	63·5	4·1	98·5	29·6	6·25	34·7
	14	62·6	2·6	98·4	29·5	6·16	32·7
	18	67·5	10·7	96·3	26·7	6·50	40·0
150 W	0	58·0	—	80·0	—	4·65	—
	2	66·1	14·0	95·0	18·8	6·28	35·1
	6	66·1	14·0	100·0	25·0	6·61	42·2
	10	63·3	9·1	105·0	31·3	6·65	43·0
	14	61·5	6·0	106·0	32·5	6·52	40·2
	18	67·0	15·5	105·0	31·3	7·04	51·4

Cardiac output, stroke volume and heart rate. There was an abrupt increase in cardiac output, significant at 2 s (Table 2). The overall increase in cardiac output was due to contributions from both stroke volume and heart rate, predominantly the latter. The percentage increase in cardiac output would have been underestimated if heart-rate alone had been used as an index of cardiovascular response. The time related response was definitely biphasic for 0 and 50 W, peaking at 6 s, falling to a trough at 14 s, and rising again. (Again there was no significant difference in cardiac output at these two work levels.) A less marked biphasic tendency is seen also for cardiac output at 100 and 150 W (Fig. 2*B*). The biphasic nature of the stroke volume response is very prominent (Table 2, Fig. 3), and is mainly responsible for the biphasic response in cardiac output.

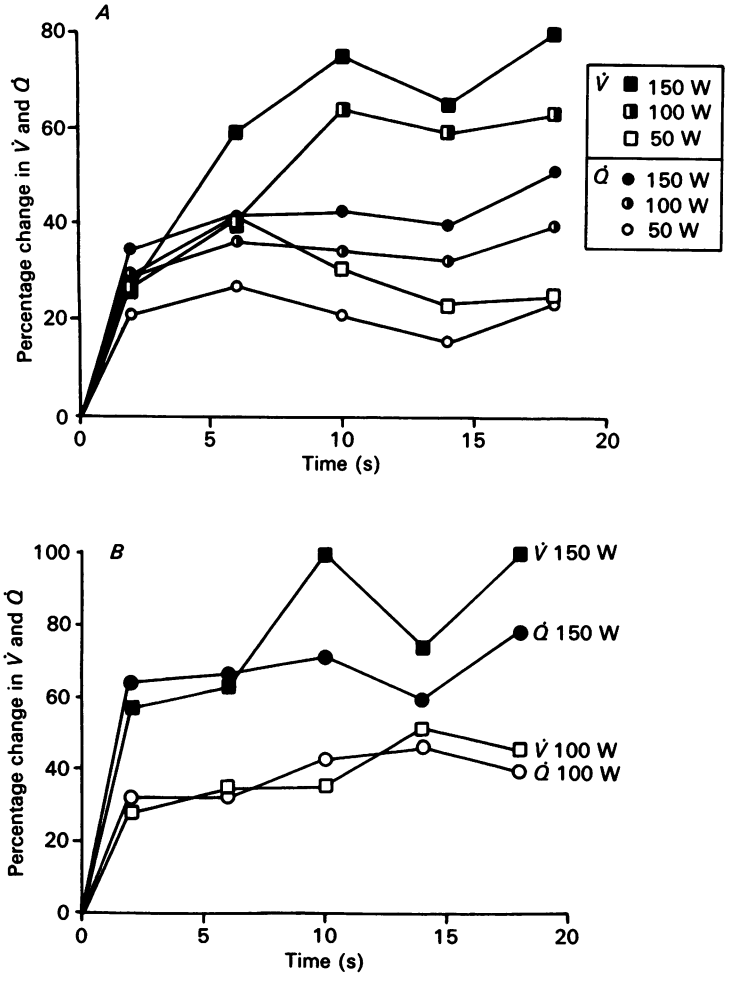

Fig. 4. *A*, percentage changes in mean ventilation ($\dot{V}$) and cardiac output ($\dot{Q}$) for 50, 100 and 150 W. Changes at 0 W were not significantly different from those at 50 W. *B*, percentage changes in mean ventilation and cardiac output for 100 and 150 W in subject SI.

Comparison of time courses of cardiac output and ventilation. When plotted as percentage changes (Fig. 4*A*) the similarity in the shape of response is striking, in that for both ventilation and cardiac output there is an initial peak at 6 or 10 s, and in every case the 14 s value is less than the values at 10 and 18 s for both variables. This was not necessarily true in individuals, as for example in subject SI where there was no trough at 14 s for the 100 W work load: but ventilation and cardiac output still followed closely similar paths, this time with a peak at 14 s followed by a fall (Fig. 4*B*). These shape similarities in the time course produce a high correlation

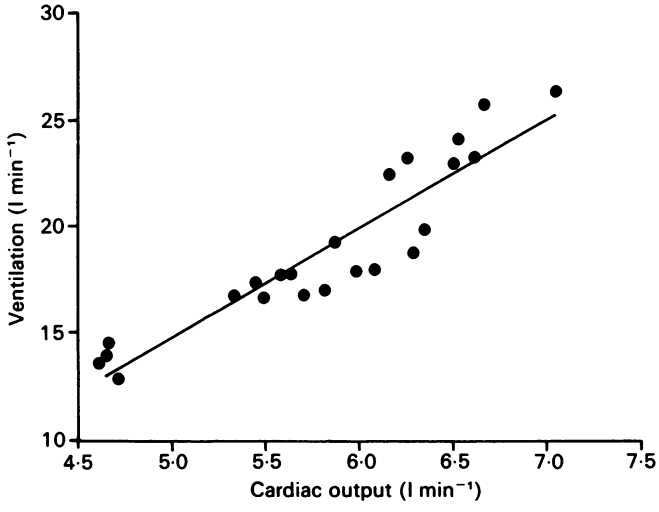

Fig. 5. Regression of mean ventilation on mean cardiac output for exercise tests. $R = 0{\cdot}92$, $P < 10^{-5}$.

TABLE 3. Ventilation and end-tidal P_{CO_2} changes with the four hyperventilation protocols

Protocol		$\dot{V}$ control (l min^{-1})	$\dot{V}$ hyperventilation (l min^{-1})	Δ End-tidal P_{CO_2} (mmHg)
A	↑B.R.	8·5±1·6	13·0±2·2	−3·7±0·5
B	↑V_T	8·3±1·8	23·3±2·6	−6·4±0·5
C	↑B.R.↑V_T	8·7±2·0	36·0±0·8	−8·1±0·5
D	↑B.R.↑V_T Isocapnia	8·9±1·5	36·0±0·6	+0·05±2·0

coefficient (0·92, $P < 10^{-5}$) between ventilation and cardiac output overall (Fig. 5). The linear regression equation is $\dot{V} = 5{\cdot}1\dot{Q} - 10{\cdot}6$, with $s_{y,x}$ (standard deviation of y about x) of 1·5, where $\dot{V}$ is ventilation and $\dot{Q}$ is cardiac output. Even so a tendency can be seen (Fig. 5) for cardiac output to increase more than ventilation at lower cardiac output ($\dot{Q} < 6$ l min^{-1}) and less than ventilation at the highest work load ($\dot{Q} > 6{\cdot}5$ l min^{-1}).

Hyperventilation

Changes in ventilation and end-tidal P_{CO_2} caused by the various hyperventilation protocols are shown in Table 3. The cardiac output results were bin-averaged

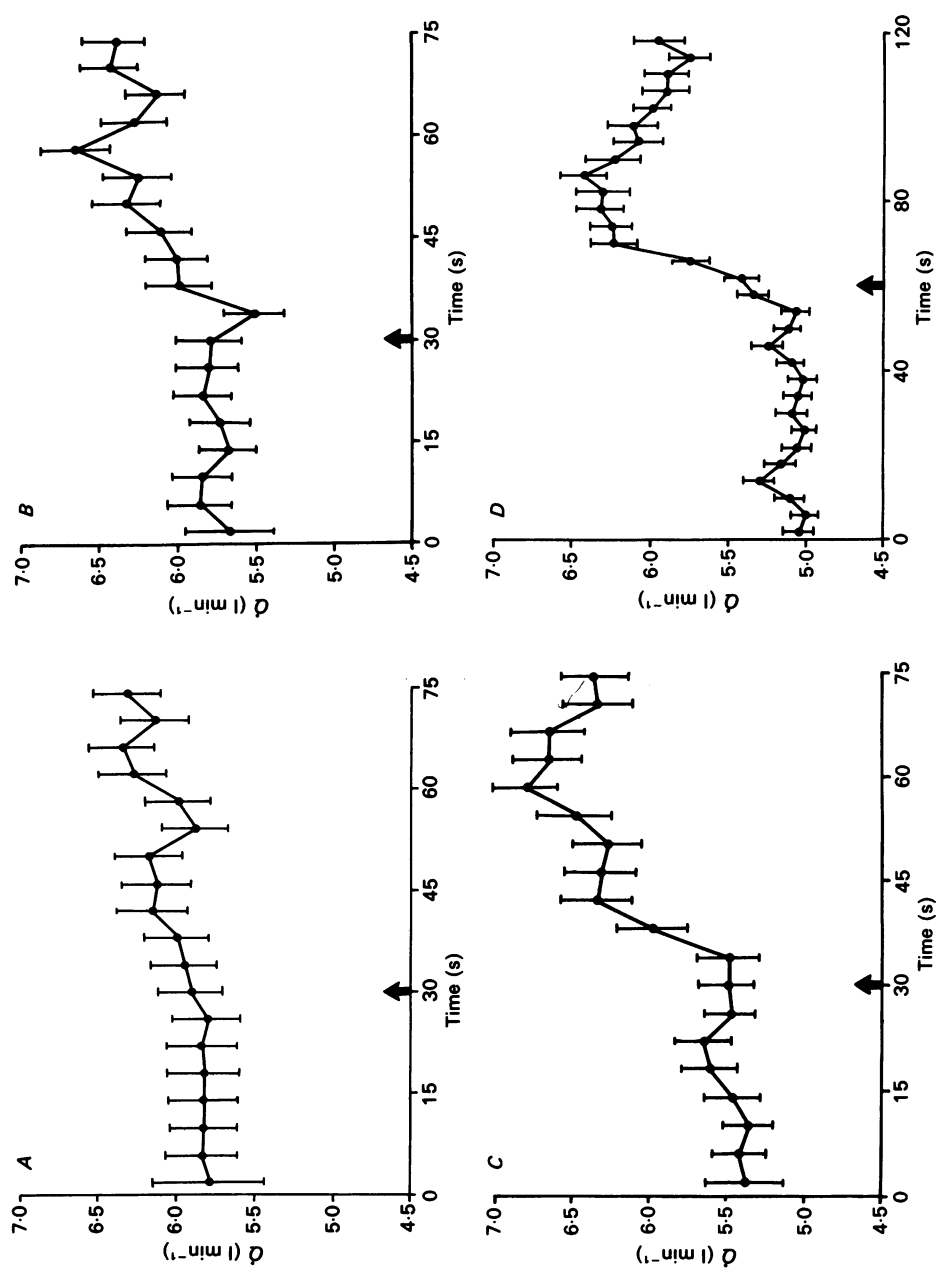

Fig. 6. Cardiac output changes, with standard error bars, during voluntary hyperventilation, which begins at the arrow. *A*, with increased rate; *B*, with increased V_T; *C*, with increased rate and increased V_T; *D*, as for *C* with isocapnia.

(4 s bins) for each protocol for the eighteen experiments (six subjects, each protocol repeated three times). Cardiac output increased significantly for all four protocols (Figs. 6 and 7). From the results of protocols A–C, and Table 3, it appeared that the overall change in cardiac output might be correlated with the fall in end-tidal P_{CO_2}, but in protocol D, with isocapnia, there was still a large increase in cardiac output (Fig. 6). The time course of cardiac output was also similar for protocols C and D, reaching a peak about 30 s after hyperventilation, and falling off thereafter.

The significance of changes in cardiac output was tested by analysis of variance, taking values from the control period, and from the hyperventilation period

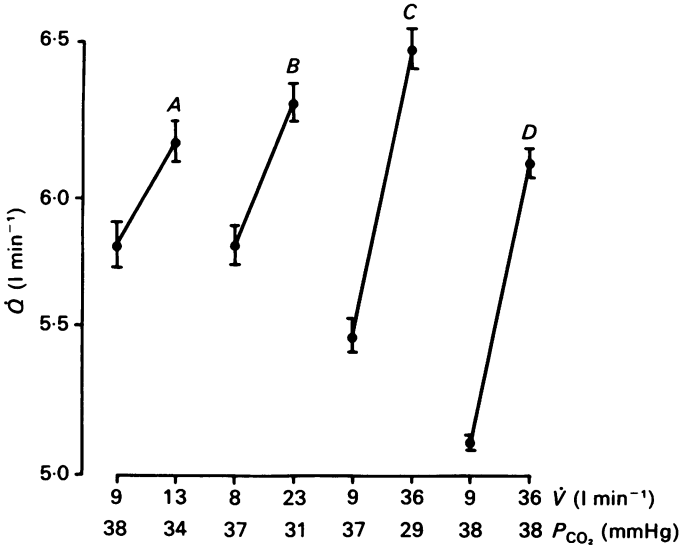

Fig. 7. Mean cardiac output changes from control with standard error bars, during hyperventilation $P < 0{\cdot}01$, *A* and *B*; $P < 0{\cdot}001$, *C* and *D*. *A*, with increased rate; *B*, with increased V_T; *C*, with increased rate and increased V_T; *D*, as for *C* with isocapnia.

excluding the first 10 s. Increases in cardiac output were significant at the 1 % level for protocols A and B and at the 0·1 % level for protocols C and D (Fig. 7).

Changes in cardiac output, heart rate and stroke volume are shown in Fig. 8 for the experimental periods only. For protocol A (increased breath rate), the small changes in cardiac output were mainly attributable to parallel changes in stroke volume. For all protocols (B–D) with increased tidal volume, changes in cardiac output were associated more obviously with changes in heart rate.

DISCUSSION

It is agreed that during moderate exercise below the anaerobic threshold in man, end-tidal P_{CO_2} and P_{O_2}, and the gas respiratory exchange ratio, remain surprisingly constant during the rapid initial increase in ventilation, phase I (Weissman, Jones, Oren, Lamarra, Whipp & Wasserman, 1982). Wasserman, Whipp & Castagna (1974) coined the term 'cardiodynamic hyperpnoea' to describe a possible mechanism for

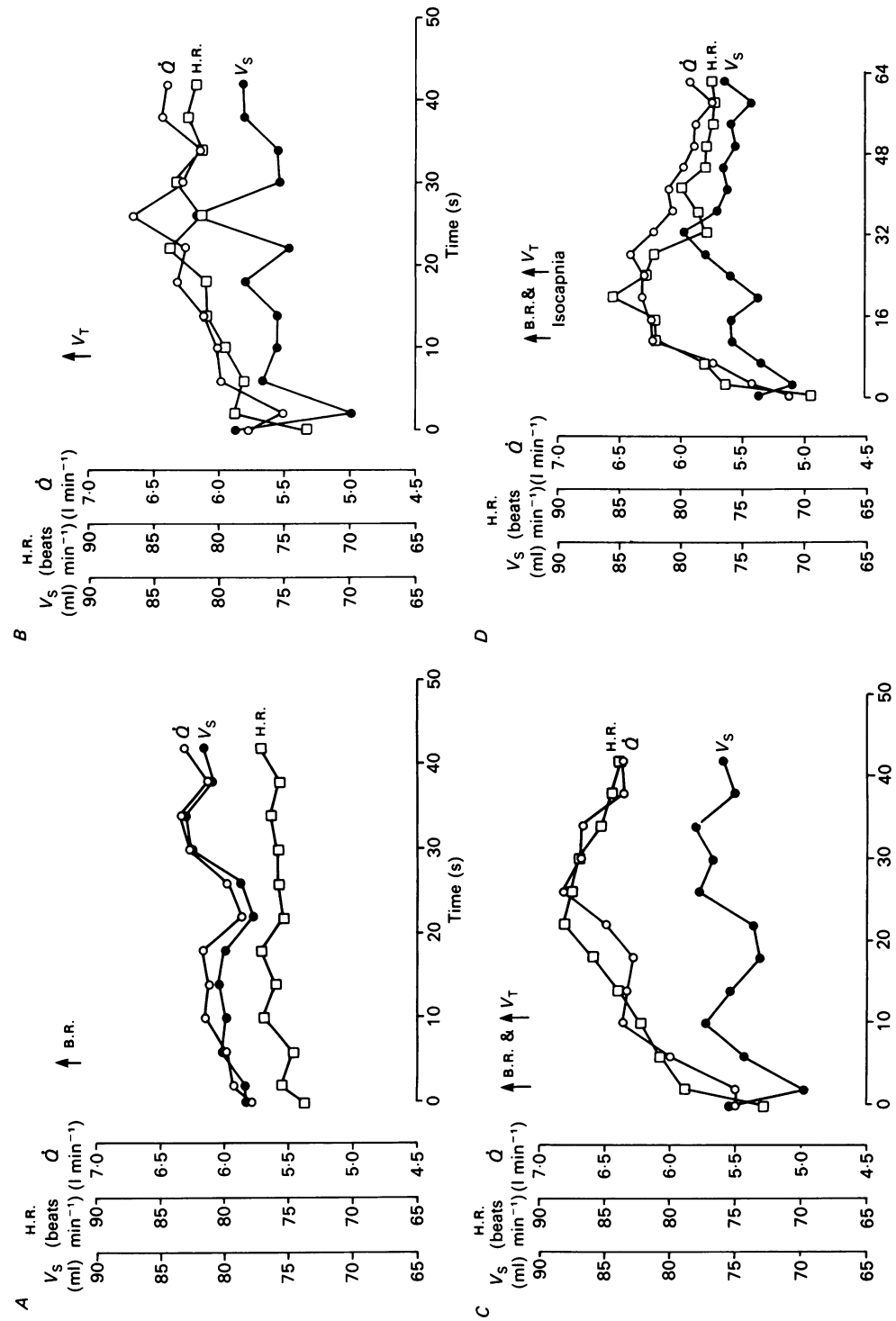

Fig. 8. Mean changes in cardiac output, stroke volume, and heart rate during hyperventilation (control period not shown). *A*, with increased rate; *B*, with increased V_T; *C*, with increased rate and increased V_T; *D*, as for *C* with isocapnia.

control of P_{CO_2} in the first 10–20 s of exercise, postulating that ventilation is linked, in some way, to instantaneous CO_2 inflow to the lungs (Wasserman, Whipp, Casaburi, Beaver & Brown, 1977). Since mixed venous CO_2 levels will not change during this time (Edwards, Denison, Jones, Davies & Campbell, 1972), changes in ventilation should be proportional to or at least highly correlated with simultaneous changes in cardiac output (Whipp & Ward, 1982). We have therefore studied the first 20 s of exercise as phase I, the period during which mixed venous P_{CO_2} does not change and an initial rapid increase in ventilation occurs, but before the onset of the mono-exponential increase to steady-state ventilation (Whipp, Ward, Lamarra, Davis & Wasserman, 1982).

There is certainly much data in man which (by analysis of ventilation, end-tidal P_{CO_2} and CO_2 output records) suggests a close link between cardiac output and ventilation in early exercise even though cardiac output is not measured. Not all the available evidence is in favour. In static exercise, it seems that the increase in ventilation is accompanied by a fall in P_{CO_2}, and that if P_{CO_2} is maintained constant, ventilation is unaffected (Muza, Lee, Wiley, McDonald & Zechman, 1983). Hughson & Morrisey (1982) have found dissociation of ventilation and CO_2 output kinetics in transition from light to heavier exercise, as opposed to rest–exercise transition. In ponies (Pan, Forster, Bisgard, Kaminski, Dorsey & Busch, 1983) and dogs (Favier, Desplanches, Frutoso, Grandmontagne & Flandrois, 1983) there is initial hypocapnia, and in dogs, it was found that the initial fast rise in ventilation was independent of work load, and hence the CO_2 flux (Szlyk, McDonald, Pendergast & Krasney, 1981). In contrast, striking results were obtained by Green & Sheldon (1983) in the anaesthetized dog with isolated pulmonary and systemic circulations, when increasing pulmonary blood flow was accompanied by an increase in ventilation.

It is to be expected that an increase in CO_2 transfer to the expired air would occur rapidly, within the first or second breath, and this was confirmed by experiments in man using exercise with ventilation voluntarily maintained at control levels during the first few breaths (Weissman *et al.* 1982). Jones, French, Weissman & Wasserman (1981) again showed close links between ventilation and cardiac output in man using pacing to change cardiac output in both directions, and subsequently developed a theory linking ventilation to cardiac output through changes in right ventricular load (Jones, Huszcuk & Wasserman, 1982).

We leave the controversy at this stage, commenting only that while there appears to be much evidence suggesting a close causal link between ventilation and cardiac output during early exercise, the exact physiological mechanism (more probably mechanisms) involved are at present obscure. It seems likely that there may be central parallel drives to locomotion, ventilation and blood flow (Eldridge, Millhorn & Waldrop, 1981), but that precise matching of these variables is achieved by one or more feed-back mechanisms.

The work presented here relates to two aspects of the problem. First, there is an important phenomenological gap, namely in the measurement of cardiac output in early exercise in man, and our Doppler techniques enable us to define these changes and relate them to simultaneous transients in ventilation. Second, the concept of cardiodynamic hyperpnoea refers purely to changes in ventilation consequent on changes in cardiac output. We examine also the beat-to-beat changes in cardiac

output caused by voluntary hyperventilation with little change in metabolic rate.

Clearly a precise relation between ventilation and cardiac output cannot be obtained unless cardiac output is measured non-invasively, beat-to-beat. Recent improvements in Doppler techniques make possible, for the first time, reliable beat-to-beat measurement of cardiac output during exercise (Loeppky *et al.* 1981; Mehta *et al.* 1985). The method is non-invasive and harmless, and appears to apply over a wide range of cardiac outputs. There is no assumption about the adequacy of pulmonary function, as rebreathing methods require, and no possibility of spurious correlation which might occur with a ventilation-dependent technique. Using the Doppler technique, we have shown a high correlation between changes in ventilation and cardiac output in the first 20 s of exercise up to the level of 150 W. To avoid obscuring changes by inter-individual variation, we preferred to do multiple experiments on few subjects rather than the reverse. This high correlation is to be expected, since both variables are bound to increase, and is in itself of little interest.

What is more important is the strikingly biphasic nature of the response in both ventilation and cardiac output, seen not only in the massed data (Fig. 4*A*) but in individual records (Fig. 4*B*). It is possible that the trough seen in the ventilation records represents the transition between phases I and II. If so, cardiac output seems to follow both phases.

In short, this part of the work adds striking new evidence concerning the close relation between ventilation and cardiac output in early exercise in normal man. It says nothing about the linking mechanisms.

There is a large literature concerning the effects of voluntary hyperventilation on cardiac output. Results differ both qualitatively and directionally, due in some part to wide variation in subject, species, protocols and experimental techniques for measuring cardiac output. We refer to three papers which try to assess effects shortly after the onset of hyperventilation in man, since it is the parallel with the first 20 s of exercise which we wish to explore (Donevan, Anderson, Sekelj, Papp & McGregor, 1962; McGregor *et al.* 1962; Matalon, Dashkoff, Nesarajah, Klocke & Farhi, 1982).

Donevan *et al.* (1962) used a relatively non-invasive dye-dilution technique (Coomassie Blue and ear-piece oximeter) in normal subjects at a light back-ground work load of 25 W. The dye-curve was inscribed 10 s after the onset of uncontrolled voluntary hyperventilation. They found an increase, on the average, of 0·04 l min^{-1} in cardiac output for every 1 l min^{-1} increase in ventilation ($\Delta\dot{Q}/\Delta\dot{V}$). According to our results (Fig. 6*C* and *D*), these dye-curves would have been inscribed during a sharp transient in cardiac output, and since they take about 30 s to record, both the main body of the curve and the necessary extrapolation to exclude recirculation would have been distorted. They also did experiments to match the extra respiratory work of hyperventilation with extra work due to breathing through an external resistance and this latter procedure caused no increase in cardiac output. McGregor *et al.* (1962) studied normal subjects at rest by the same techniques for measuring cardiac output. They compared the effect of spontaneous hyperventilation with that of hyperventilation with end-tidal P_{CO_2} held constant by adding CO_2 to the inspired air. They again found $\Delta\dot{Q}/\Delta\dot{V}$ of 0·04 during hypocapnic hyperventilation, but a much smaller value, 0·15, when CO_2 was held constant. We also find $\Delta\dot{Q}/\Delta\dot{V}$ of about 0·04 for a hyperventilation of 36 l min^{-1} (Table 3, Fig. 7) but we find no change with

isocapnia. The two main differences between our studies and those of McGregor and colleagues (1962), apart from the method of measuring cardiac output, are first that they inscribed their dye-curves beginning at 45 s for the hypocapnic series, and at 60–100 s for the isocapnic series. Our results (Fig. 6*C*, *D*) were taken only to 45 s (*C*) and 60 s (*D*) after the onset of hyperventilation. It is possible that cardiac output would have decreased subsequently. Second, their level of hyperventilation was much greater than ours, about 50 l min^{-1} (Δ end-tidal P_{CO_2} 16 mmHg) for the hypocapnic series and 70 l min^{-1} during isocapnia. Since our comparison was carried out at the same level of hyperventilation (36 l min^{-1}, Table 3) and our cardiac output measurements were made continuously over an identical time course of 0–45 s, with a technique that can record transient changes in cardiac output, we believe that our conclusion (opposed to theirs), that changes in cardiac output are *not* related to end-tidal P_{CO_2} is a more reliable one. More worrying, at first sight, are the contrasting results of Matalon *et al.* (1982). They studied the effect of hyperventilation at very similar levels to those in our experiments (tidal volume 1·5 l, rate 20; and tidal volume 1·5 l, rate 30), recording cardiac output from 0–60 s. Their technique for measuring cardiac output (infusion of a solution of hydrogen at constant rate) was far from ideal for following transients, but certainly should be capable of detecting changes over a 20 s period. Nevertheless, they found no change in cardiac output. They used a rebreathing technique, so that end-tidal P_{CO_2} fell about 10 mmHg at 15 s, and then rose to control level at about 30 s, and higher thereafter. Our results suggest that this should not affect cardiac output one way or the other. The answer probably lies in the curious fact that in their experiments there was hardly any change in heart rate (2–4/min) during hyperventilation. Yet an increase in heart rate during voluntary hyperventilation has long been recognized (Grollman, 1930; Kety & Schmidt, 1946) as in our results. Since the increases in cardiac output we found at comparable levels of tidal volume and breathing rate (Fig. 8*B*, *C* and *D*) were due to changes in heart rate, it is not surprising that Matalon *et al.* (1982) did not find such changes. We suggest three possible reasons for the discrepancy: their subjects were older (age range 30–62); they were not normal subjects (eight of fifteen had coronary artery disease); and perhaps most importantly they were studied in the prone position.

Several hypotheses have been put forward to explain an increase in cardiac output with hyperventilation. First, it has been suggested that the extra work for the respiratory muscles, as in exercise, results in a central command to increase cardiac output. We doubt this, since the increase in oxygen uptake by the respiratory muscles at 23–36 l min^{-1} (Table 3) is very small, and in any case Donevan *et al.* (1962) found no change in cardiac output when respiratory work was increased to a comparable level with external resistances.

Secondly, because of the previous possibility that cardiac output changes are dependent to an extent on P_{CO_2}, chemosensitive mechanisms have been postulated. Our results are strongly against this. Thirdly, it seems very likely that rhythmic energetic respiratory movements may pump blood mechanically, sucking blood into the thorax on inspiration and pumping it out during expiration. We find it difficult to be more precise than this, nor do we find any more precise description of such a mechanism in the literature, since the following complications need consideration.

Despite unidirectional valves, flow need not necessarily be unidirectional on the systemic venous side, nor, in the presence of capacitance vessels (pulmonary veins) or chambers (atria) will increased filling pressure automatically produce instantaneous increases in net forward flow. Moreover, the net filling pressure for the right atrium will depend on both intrathoracic and intra-abdominal pressures and these depend on the potentially optional uses of thoracic and abdominal muscles. We accept however that a mechanical pumping action is likely.

Fourthly, there is considerable evidence in animals for a cardiac accelerator response to lung inflation with inflation pressure of less than 14 mmHg (Hainsworth, 1974; Angell-James & de Burgh Daly, 1978; Kauffman, Iwamoto, Ashton & Cassidy, 1982) and to distension of the pulmonary vein–atrial junction (Ledsome & Linden, 1964). The topic has been recently reviewed by de Burgh Daly (1985). This is a most attractive mechanism to explain our results, since in all three protocols where tidal volume was increased (Fig. 8*B*,*C*,*D*) the increase in cardiac output was due to an increase in heart rate, whereas in the single protocol where respiratory rate, but not tidal volume, was increased (Fig. 8*A*), the increase in cardiac output was due to a change in stroke volume, not rate. In the latter case, we surmise that the pumping action of hyperventilation increased venous return, stroke volume and cardiac output by the Starling mechanism.

The implications for combined control of ventilation and cardiac output are considerable. Let us assume first that increasing ventilation does cause a secondary increase in cardiac output by cardio-accelerator reflexes and a direct pumping action on venous return. Then assume, from direct evidence in dogs with isolated pulmonary circulations (Green & Sheldon, 1983) that increasing cardiac output causes a reflex increase in ventilation. There is now positive feed-back. Theoretically, this may be perfectly stable, provided the loop gain is less than one (Milhorn, 1966). It would provide a powerful method of linked amplification of both variables in a controlled manner. We would also predict that experimentally it should be very difficult to produce, not only changes in ventilation without changes in cardiac output as in this study, but also changes in cardiac output without changes in ventilation, and initial results changing cardiac output with posture (Cummin, Iyawe, Mehta & Saunders, 1984) and anti-G suits (Iyawe, Cummin, Mehta & Saunders, 1984) bear this out. We wish therefore to extend, or replace, the concept of 'cardiodynamic hyperpnoea' by that of a stable positive feed-back loop involving ventilation and cardiac output mediated both reflexly and mechanically.

Finally, what are the overall implications for control of ventilation in exercise? We accept that there is a central feed-forward drive for both ventilation and cardiac output (Eldridge *et al.* 1981). The difficulty is to explain how the gain of this system is calibrated to control P_{CO_2} levels so precisely in moderate exercise. We have already suggested (Saunders, 1980) that chemosensitivity acts as the calibrator, and that during exercise the gain of the CO_2 response, over a narrow range, may be high or even infinite (Cummin, Iyawe & Saunders, 1983). We now put forward positive feed-back as a further regulating mechanism during the controlled amplification of both ventilation and cardiac output which must occur in exercise. The combination of feed-forward drive with both negative and positive feed-back loops is, as far as we know, a novel suggestion.

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