J. exp. Biol. (1982), 100, 175–193
With 4 figures
Printed in Great Britain

CARDIOPULMONARY COUPLING DURING EXERCISE

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SUMMARY

Muscular exercise imposes the most potent sustained stress to cellular energetics. At work rates below the anaerobic threshold (i.e. no sustained lactic acidosis), the ventilatory and cardiovascular responses regulate arterial P_{CO_2}, $[H^+]$ and P_{O_2} at or close to their resting levels in the steady state. However, dynamic forcing and systems-analytic techniques reveal two phases of the non-steady-state response dynamics. In the first phase, increased gas flow to the lungs results solely from increased pulmonary blood flow ($\dot{Q}$), with alveolar gas tensions being maintained at their resting levels by a coupled increase in ventilation ($\dot{V}_E$): evidence for cardiopulmonary coupling being provided by experimentally-altered $\dot{Q}$ in man and dog. Arterial chemoreception does not impose humoral feedback control in this phase. Rather, rapid feedforward mechanisms operate, with both intrathoracic (largely cardiac) and exercising-limb mechanoreception proposed as afferent sources. In the second phase, cardiogenic gas flow to the lungs is augmented by altered mixed venous blood gas contents; ventilation responding exponentially with a time constant (τ) which is an inverse function of carotid body gain. The close dynamic coupling of $\dot{V}_E$ with CO_2 output ($\tau_{\dot{V}_E} \lesssim \tau_{\dot{V}CO_2}$) in this phase results in arterial P_{CO_2} and $[H^+]$ being maintained close to their resting levels. However, the kinetic dissociation between $\dot{V}_E$ and O_2 uptake, with $\tau_{\dot{V}_E} \gg \tau_{\dot{V}O_2}$, leads to an appreciable transient fall of arterial P_{O_2}. The respiratory compensation for the sustained lactic acidosis at higher work rates is predominantly mediated by the carotid bodies in man: the aortic bodies subserving no discernible role. Control of the respiratory and circulatory responses to exercise is therefore mediated by both neural and humoral mechanisms: and an important control link appears to couple the responses, via feedforward ventilatory control of cardiac origin.

INTRODUCTION

Muscular exercise is a process which depends upon the transformation of the biochemical energy of ingested food into the mechanical energy of muscle contraction and work. The substrate free energy, however, is not used directly to fuel these reactions; rather, adenosine triphosphate, with its high free energy of hydrolysis, is the obli-

gatory intermediary. To maintain the fluid milieu of the contracting muscle in a state compatible with sustained exercise performance, an effective interaction of numerous physiological systems is required.

However, during normal volitional daily activity, steady states of cardiopulmonary function are rare. And yet, our current concepts of ventilatory control and arterial blood gas homeostasis are based predominantly upon ensured steady-state conditions. As large and rapid changes in metabolic rate are common, the ventilatory system must respond both promptly and precisely to obviate significant variations of arterial blood gas and acid-base status.

We believe that it is not useful to consider 'exercise' as a single specific state with respect to ventilatory and cardiovascular control. The determinants of the responses are likely to change both with time and intensity. We prefer to consider three temporal and three intensity domains of the work.

Temporal domains

Phase 1 ($\phi 1$) lasts from the onset of the work to when the gas tensions in mixed venous blood entering the pulmonary capillaries start to change. Increased rates of pulmonary gas exchange in $\phi 1$ therefore reflect alterations of pulmonary blood flow and its distribution, without altered mixed venous composition (Fig. 1). This can therefore be considered the 'cardiodynamic' phase.

Phase 2 ($\phi 2$) is the dynamic phase following $\phi 1$, in which the new steady state is approached, associated with changing mixed venous blood composition. The duration of $\phi 2$ can therefore vary for different functions such as cardiac output ($\dot{Q}$), mixed venous O_2 and CO_2 concentrations ($C_{\bar{v},O_2}$, $C_{\bar{v},CO_2}$), ventilation ($\dot{V}_E$), CO_2 output ($\dot{V}_{CO_2}$) and O_2 uptake ($\dot{V}_{O_2}$).

Phase 3 ($\phi 3$) is the steady state of the response.

Intensity domains

Moderate incorporates the range of $\dot{V}_{O_2}$ in which there is no sustained elevation of arterial blood lactate concentration, and thus lies below the anaerobic threshold, θ_{an} (Wasserman *et al.* 1973). We shall regard the responses to moderate dynamic exercise to be the 'basic' responses with additional perturbations being imposed by the higher work intensities.

Heavy refers to the range in which there is a sustained elevation of arterial blood lactate, namely between θ_{an} and the maximum $\dot{V}_{O_2}$ ($\mu\dot{V}_{O_2}$), but with the lactate concentration not continuing to increase systematically with time. In this intensity domain, $\phi 2$ is prolonged considerably resulting in the delayed, though eventual, acquisition of a steady state.

Severe is restricted to work rates greater than those requiring $\mu\dot{V}_{O_2}$, at which arterial blood lactate continues to increase throughout the work period.

We shall firstly consider the temporal patterns of ventilatory response within these domains.

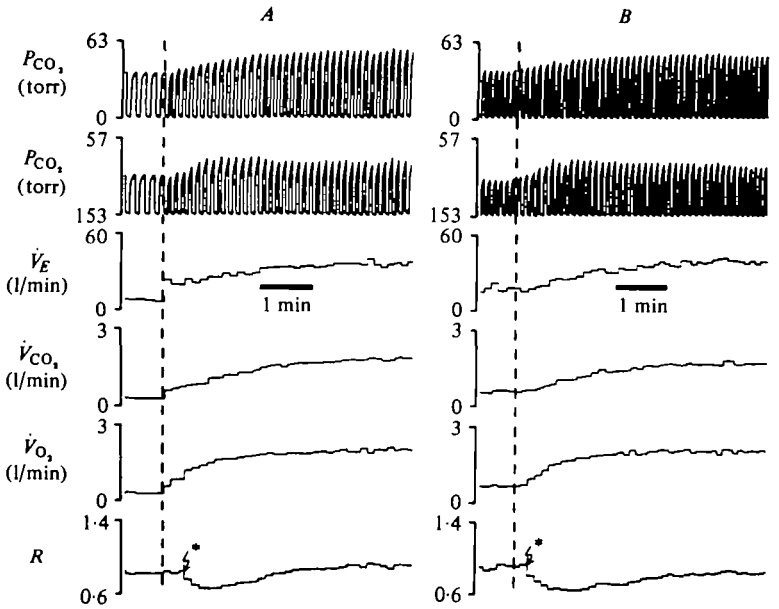

Fig. 1. Ventilatory and pulmonary gas exchange responses to 125 watts cycle ergometer exercise beginning either from rest (*panel A*) or from a baseline of unloaded cycling (*panel B*). Arrow indicates end of phase 1. P_{CO_2} and P_{O_2} are CO_2 and O_2 partial pressures in respired air; $\dot{V}_E$, $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$ and R represent ventilation, CO_2 output, O_2 uptake and the gas exchange ratio. Note that a large, abrupt hyperpnoea at exercise onset is evident from prior rest but not from prior mild exercise, and that in neither case is the phase 1 response hyperventilatory (i.e. end-tidal P_{CO_2} decreasing and R increasing).

VENTILATORY RESPONSES

Moderate exercise

Phase 1. The response patterns of $\dot{V}_E$, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are qualitatively different if the exercise begins from a control state of rest or from prior mild exercise (Fig. 1). Abrupt increases are observed from rest, whereas considerably slower ones are evident from mild exercise (Broman & Wigertz, 1971; Casaburi *et al.* 1978). The $\dot{V}_E$ response in $\phi 1$ is conventionally considered to be controlled by somatic receptors in the exercising limbs (Kao, 1963; Dejours, 1964, 1967; Tibes, 1977) and possibly from supra-bulbar regions (Krogh & Lindhard, 1913; Eldridge, Millhorn & Waldrop, 1981). However, while stimulation of skeletal muscle somatic afferents can increase $\dot{V}_E$ and (consistent with an increase of cardiac output) both heart rate and systemic arterial blood pressure (McCloskey & Mitchell, 1972), spinal cord section at the lower thoracic or upper lumbar level does not significantly affect the $\phi 1$ $\dot{V}_E$ response in animals during electrically-induced exercise (Weissman *et al.* 1979; Brewer *et al.* 1980). Furthermore, we contend that, as both $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ change with the same kinetic characteristics during $\phi 1$ (with consequent stability of alveolar gas tensions and the gas exchange ratio, R, across the transition: Fig. 1), a specific neural control of $\dot{V}_E$, solely, is effectively ruled out as it would evoke hyperventilation with a consequent increase in

end-tidal P_{O_2} (P_{ET,O_2}) and R and decrease in end-tidal P_{CO_2} (P_{ET,CO_2}). Rather, there must be a tight coupling beteeen the $\phi 1$ ventilatory and pulmonary blood flow responses. The mechanism of this coupling remains to be resolved but, as discussed below, a common mechanism to both systems is highly likely, or a rapid and precise response of one system to the other. The carotid bodies, the sole functional peripheral ventilatory chemoreceptors in man (Lugliani *et al.* 1971; Wasserman & Whipp, 1976; Whipp & Wasserman, 1980) appear not to control the $\phi 1$ response: its magnitude in man is unaltered by hypoxia, hyperoxia, hypercapnia (Cunningham, 1974) or by bilateral carotid body resection (Wasserman *et al.* 1975*b*). Furthermore, the lung–carotid body transit time during moderate exercise is some 4–6 s (Petersen *et al.* 1978), whereas the $\phi 1$ $\dot{V}_E$ response begins in virtual synchrony with the onset of the work (Dejours, 1964; Whipp *et al.* 1971; Jensen, Vejby-Christensen & Petersen, 1972; and Fig. 1).

Phase 2. In this phase, $\dot{V}_E$, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ all change as a simple mono-exponential function (Casaburi *et al.* 1977; Whipp, 1981). The associated $\phi 2$ time constant, τ, however, is different for each function: some 35–40 s for $\dot{V}_{O_2}$, 50–60 s for $\dot{V}_{CO_2}$ and $\dot{V}_E$. That $\tau\dot{V}_{CO_2}$ is longer than $\tau\dot{V}_{O_2}$ (Fig. 1) reflects the transient storage of CO_2 in the body stores; and the slow $\tau\dot{V}_E$ presumably reflects the influence of this storage, although central respiratory dynamics have also been suggested (Eldridge, 1977). Thus, in $\phi 2$, $\dot{V}_E$ is highly correlated, not with the rate at which CO_2 is produced in the tissues, but rather with the rate at which it exchanges at the lung (Whipp, 1981). The $\dot{V}_E$ response, however, has been described as slightly lagging the $\dot{V}_{CO_2}$ response (Casaburi *et al.* 1977) during sinusoidal forcing of work rate (i.e. sustained $\phi 2$). As a consequence, the peak of the sinusoidal $\phi 2$ $\dot{V}_E$ response was associated with an elevated P_{ET,CO_2} and arterial P_{CO_2} (P_{a,CO_2}), and a decreased arterial pH (pH_a) (Casaburi *et al.* 1977; Whipp, 1981). Clearly, although $\dot{V}_E$ and $\dot{V}_{CO_2}$ were highly correlated dynamically during the exercise, the coupling was not sufficiently tight to obviate small fluctuations in arterial P_{CO_2} and $[H^+]_a$. Our findings raise the interesting possibility that the increase in P_{a,CO_2} and $[H^+]_a$ in $\phi 2$ may provide a source of humorally mediated control information. Or, alternatively, one must consider whether it is just a consequence of the time constant disparities, and only modulates a more basic control mechanism. Square-wave and incremental work-rate forcings, however, suggest an even tighter coupling between $\dot{V}_E$ and $\dot{V}_{CO_2}$ (Fig. 2).

Several lines of evidence demonstrate the importance of the carotid bodies in controlling $\phi 2$ $\dot{V}_E$ in man: (i) the onset of $\phi 2$ is delayed by O_2-inhalation (Cunningham, 1974); (ii) the kinetics of $\phi 2$ are slowed by O_2-inhalation (Casaburi *et al.* 1978); (iii) the kinetics of $\phi 2$ are appreciably slower than normal in a group of subjects who had previously undergone bilateral carotid body resection (Wasserman *et al.* 1975*b*); and (iv) increasing the gain of the carotid chemoreflex by hypoxia (Griffiths *et al.* 1980) or chronic metabolic acidosis (Oren, Whipp & Wasserman, 1980) results in faster $\phi 2$ kinetics.

It is not currently known whether, or to what extent, neural mechanisms control $\phi 2$ $\dot{V}_E$ kinetics. Eldridge, however, has suggested a central neural component of $\phi 2$ kinetics, with the 'respiratory centre' neural dynamics (Eldridge, 1977) or a hypothalamic mechanism (Eldridge *et al.* 1981) determining ventilatory dynamics, rather

than the peripheral sensing of a stimulus which operates through the respiratory centre without significant temporal modulation. Tibes (1977) has also suggested that neural mechanisms, expressly from the exercising limbs, might account for the slow ventilatory response in $\phi 2$, noting the high correlation between $\dot{V}_E$ and $[K^+]$ in the venous effluent from the exercising muscles (K^+ is predominantly a stimulant of non-myelinated muscle afferents, as demonstrated by Hnik *et al.* 1969). While this proposal would be consistent with observations from the early cross-circulation experiments performed by Kao (1963) in dogs, more recent results from our laboratory (Weissman *et al.* 1979) and from Brewer *et al.* (1980) reveal that interruption of somatic afferent traffic from exercising hindlimbs by thoracic or upper lumbar spinal cord section has no discernible effect on $\phi 2$ $\dot{V}_E$ kinetics, especially when related to the gas exchange responses. It appears, therefore, that somatic neural afferents do not subserve an obligate role for 'normal' $\phi 2$ $\dot{V}_E$ kinetics, and *may* not be involved.

Phase 3. The arterial isocapnia of the exercise hyperpnea is usually taken to reflect crucial humoral control in $\phi 3$. In addition, besides the various neural mechanisms described earlier, it has been suggested that pulmonary blood flow itself may mediate an element of the control (Brown, Wasserman & Whipp, 1976; Stremel *et al.* 1979).

The proportional contribution of the carotid bodies to $\dot{V}_E$ appears to be somewhat greater than at rest: some 15% in moderate exercise, 10% at rest. Subjects who had previously undergone bilateral carotid body resection, however, had a steady-state response to moderate exercise which was not different from normal with respect to blood gases or ventilation (Lugliani *et al.* 1971; Wasserman *et al.* 1975*b*). One explanation for this is that other (presumably central) mechanisms 'take over' the normal carotid body component. This clearly needs resolution as it is crucially related to the understanding of the integrative function of the respiratory center.

Presently, central chemoreceptor mechanisms are believed not to be involved, based upon the failure to discern a recognizable stimulus in the cerebrospinal fluid in the steady state of moderate exercise (Leusen, 1965; Bisgard *et al.* 1978). However, there is a preliminary report (Spode & Schlaefke, 1975) that blocking Region 'S' on the ventral surface of the medulla actually abolished the exercise hyperpnea in peripherally-deafferented cats. This suggests either that central chemoreceptor afferents (thought to course through Region 'S': Schlaefke & Loeschcke, 1967) do play a significant role in the exercise hyperpnoea or that some other afferent excitatory influence can be inhibited by this regional block. Further consideration must, however, await detailed report of these experiments.

Heavy and severe exercise

There is quite convincing evidence that the compensatory hyperventilation which attends exercise in these intensity domains results from carotid body stimulation in man (Wasserman *et al.* 1975*b*; Whipp & Wasserman, 1980). Thus, in response to work-rate increments of 4 min duration or more, P_{a,CO_2} begins to decrease at the anaerobic threshold, θ_{an} (Wasserman & Whipp, 1975). For shorter duration (1 min or less) increments, however, P_{a,CO_2} does not decrease at θ_{an} (Wasserman & Whipp, 1975). There exists, rather, a domain of work rates within which $\dot{V}_E$ changes faster than $\dot{V}_{O_2}$ but in precise proportion to the additional CO_2 evolved from the bicarbonate-

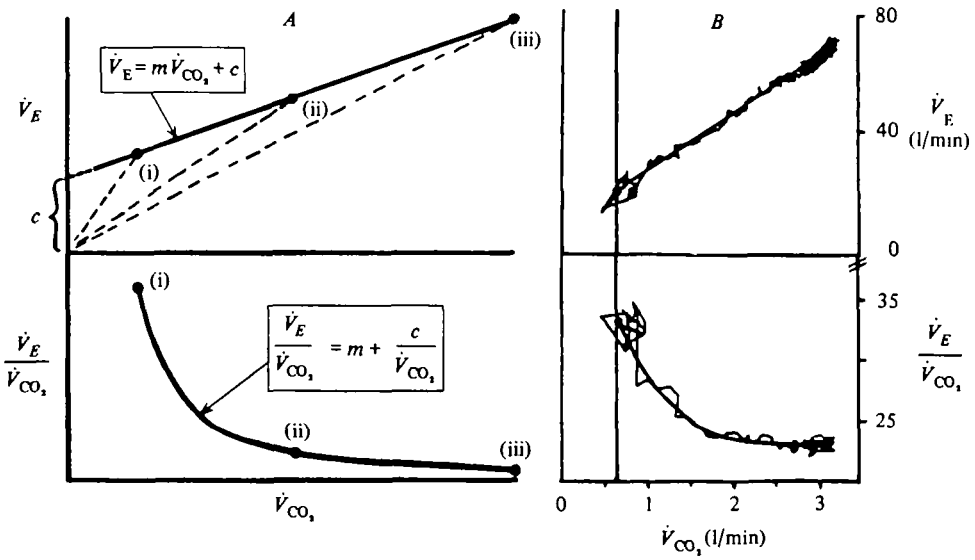

Fig. 2. Schematic representation (*panel A*) of the responses of ventilation ($\dot{V}_E$) and the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) to the increased CO_2 output ($\dot{V}_{CO_2}$) during the course of a bout of moderate constant-load exercise, and the actual responses (*panel B*) of these functions during the transition from unloaded cycling to 250 watts in a fit subject (i.e. below the anaerobic threshold). Points (i), (ii) and (iii) on the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship in panel A represent predicted $\dot{V}_E$, $\dot{V}_{CO_2}$ responses at three arbitrary times during the course of the work; and the slopes of the dashed lines joining these points to the origin define the corresponding $\dot{V}_E/\dot{V}_{CO_2}$ responses (c.f. lower panel). Note that the actual $\dot{V}_E/\dot{V}_{CO_2}$ response fits well the predicted hyperbolic decrease through the transition. See text for further details.

buffering of the lactic acid. This domain has been termed 'isocapnic buffering' (Wasserman *et al.* 1977). It is puzzling that the carotid bodies appear not to respond to the decrease of pH_a within the duration of these short work-rate increments, even though they respond to exogenous H^+ with a time constant or less than a second (Ponte & Purves, 1974).

Inter-relationships between ventilation and CO_2*-related variables*

As the exercise hyperpnea appears to be so crucially related to some control function which is proportional to CO_2 output ($\dot{V}_{CO_2}$), both in the steady- and non-steady state phases of moderate exercise (Fig 2), it is important to recognize certain inherent relationships between 'CO_2' and $\dot{V}_E$.

For example, as alveolar ventilation ($\dot{V}_A$) is related to $\dot{V}_{CO_2}$ and P_{a,CO_2}:

$$\dot{V}_A = 863\,\frac{\dot{V}_{CO_2}}{P_{a,CO_2}} \qquad (1)$$

(where 863 is the constant which ensures that all the quantities are referred to a normal body temperature and pressure, i.e.

$$\frac{273+37}{273} \times \frac{760}{760-47} \times [\text{barometric pressure} - 47]),$$

then $\dot{V}_A$ will change as a linear function of $\dot{V}_{CO_2}$ at any constant level of P_{a,CO_2}. The absolute value of this increase in $\dot{V}_A$ is dictated by the regulated level of P_{a,CO_2}: the lower the P_{a,CO_2}, the greater is the ventilatory requirement for a given change of $\dot{V}_{CO_2}$. However, the neural output of the brainstem respiratory centre effects changes in total ventilation ($\dot{V}_E$). Consequently, the physiological dead space (V_D) confers an additional degree of freedom on the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship. Thus

$$\dot{V}_E = \frac{863.\dot{V}_{CO_2}}{P_{a,CO_2}(1 - V_D/V_T)}, \tag{2}$$

where V_D/V_T represents the ratio of the physiologic dead space to the tidal volume. However, the form of equation (2) does not appear, at first sight, to cohere with the widely described observation that $\dot{V}_E$ changes as a linear function of $\dot{V}_{CO_2}$ (Fig. 2A):

$$\dot{V}_E = m.\dot{V}_{CO_2} + c, \tag{3}$$

where m is the slope of the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship ($d\dot{V}_E/d\dot{V}_{CO_2}$) and c is the $\dot{V}_E$ intercept. Rearranging equation (3) in terms of the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) and substituting for m yields:

$$\frac{\dot{V}_E}{\dot{V}_{CO_2}} = \frac{d\dot{V}_E}{d\dot{V}_{CO_2}} + \frac{c}{\dot{V}_{CO_2}}. \tag{4}$$

Note that the ventilatory equivalent exceeds the *slope* (by the variable factor $c/\dot{V}_{CO_2}$), but approaches it asymptotically at high levels of $\dot{V}_{CO_2}$ (Fig. 2). It is important, therefore, that if values of the ventilatory equivalent for CO_2 are to be used for characterizing a subject's ventilatory response to exercise they should be reported together with the values of $\dot{V}_{CO_2}$ at which they were obtained. Or, better still, both the slope and intercept parameters of the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship should be defined.

Equation (2) is, in fact, the equation of a straight line for moderate exercise when P_{a,CO_2} is regulated at its resting value (e.g. 40 mmHg). Two patterns of V_D/V_T behaviour during moderate exercise would be compatible with a linear $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship and regulation of P_{a,CO_2}. Were V_D/V_T to be constant, independent of work rate, $\dot{V}_E$ would be constrained to increase as a linear function of $\dot{V}_{CO_2}$. Alternatively, were V_D/V_T to decline hyperbolically with respect to $\dot{V}_{CO_2}$, i.e.

$$\frac{V_D}{V_T} = 1 - \frac{863}{P_{a,CO_2}\left[m + \frac{c}{\dot{V}_{CO_2}}\right]} \tag{5*}$$

then, again, the relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ would be linear.

This second V_D/V_T pattern of response actually occurs. Thus, V_D/V_T has been repeatedly demonstrated to fall in response to increases of work rate, the largest changes being evident at low work rates as equation (5) predicts (Jones, McHardy & Naimark, 1966; Whipp & Wasserman, 1969). Indeed, if V_D/V_T were not to decline in this hyperbolic fashion with respect to $\dot{V}_{CO_2}$, then nonlinearities would obtain in the $\dot{V}_E/\dot{V}_{CO_2}$ relationship *or* P_{a,CO_2} would not be regulated, *or* both.

* This equation is obtained by substitution for $\dot{V}_E$ from equation (2) into equation (3).

Extending the range of work rates beyond the anaerobic threshold introduces further complexity into the interpretation of the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship. This results from the compensatory hyperpnoea, which serves to constrain the fall of pHa during the metabolic (lactic) acidosis by lowering P_{a,CO_2} (Whipp & Wasserman, 1969; Wasserman *et al.* 1973; Sutton, Jones & Toews, 1976). As these effects assume greater prominence with increasing work rates above θ_{an}, the steepening $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship departs progressively from the linear form that it exhibited during moderate exercise.

CARDIOVASCULAR RESPONSES

The increase in cardiac output ($\dot{Q}$) during dynamic exercise is a linear function of the increase in O_2 uptake ($\dot{V}_{O_2}$), with rapid changes occurring at the onset of the work. In upright man, the changes are predominantly mediated by increased heart rate with stroke volume also contributing, though only over the lower third of the range of exercise $\dot{V}_{O_2}$ (Astrand & Rodahl, 1970). Cardiac output at a particular $\dot{V}_{O_2}$ does not change with training but is achieved with a higher stroke volume and, consequently, a lower heart rate (Astrand & Rodahl, 1970). And as maximum heart rate is not altered by short-term training (i.e. that does not induce an effect due to simultaneous aging), then the improvement in cardiac output results from the increased stroke volume. Values for $\dot{Q}$ for 30 l/min at maximum work are not uncommon in trained endurance athletes. This, coupled with an increased maximum arterio-to-venous (a–$\bar{v}$) O_2 difference results in the maximal $\dot{V}_{O_2}$ ($\mu\dot{V}_{O_2}$) also being increased by training (Astrand & Rodahl, 1970).

The highly linear relationship between $\dot{Q}$ and $\dot{V}_{O_2}$ for dynamic exercise in normal adults (exercising at sea level and in a cool environment) is well described by the equation:

$$\dot{Q} = m.\dot{V}_{O_2} + c, \tag{6}$$

where m is the slope and c is the $\dot{Q}$ intercept, both having values of approximately 5 when $\dot{Q}$ and $\dot{V}_{O_2}$ are expressed in l/min. (The values of 5 are quite representative when the resting values are not included in the regression.) Consequently, the (a–$\bar{v}$) O_2 difference will increase hyperbolically as $\dot{V}_{O_2}$ increases, conforming to the approximation equation:

$$(a\text{–}\bar{v})\ O_2 = \frac{20\ \dot{V}_{O_2}}{1 + \dot{V}_{O_2}}, \tag{7}$$

where the (a–$\bar{v}$) O_2 difference will have the conventional units of ml/100 ml of blood.

The increase of cardiac output during exercise results from increased mean systemic pressure which raises the pressure gradient for venous return, local vasodilatation in the contracting muscles, and autonomic effects on the heart itself (e.g. Guyton, Jones & Coleman, 1973). The vasodilatation in the contracting muscle, which leads to the increase in $\dot{Q}$ being distributed preferentially to these muscles (Rowell, Blackman & Bruce, 1964; Bevegard & Shepherd, 1967), results predominantly from the effects of locally released metabolites on the pre-capillary resistance vessels (Folkow & Neil, 1971; Guyton *et al.* 1973). Little or no changes are apparent in the post-capillary vessels (Kjellmer, 1965), although a reduction in venous compliance

has been demonstrated (Bevegard & Shephard, 1965), which functions to reduce the time constant for venous return. The resulting increased capillary pressure increases the fluid filtration force which, coupled with the increased osmotic gradient into the muscle, results in a fluid flow into the contracting fibres (Astrand & Rodahl, 1970). This is seen as a decreased plasma volume and increased hematocrit during the work.

Although the precise mechanism of the exercise-induced vasodilatation remains a topic for debate, the most prominent contenders appear to be potassium ions (Skinner & Powell, 1967), with the effect being potentiated by the decreasing local P_{O_2}, and hyperosmolality (Mellander *et al.* 1967). In addition, other factors such as H^+ (especially at high work rates), temperature and adenosine compounds resulting from high-energy phosphate transfer may exert a dilator influence (Guyton *et al.* 1973). Neural vasodilatation in the contracting muscle mediated by local reflex effects of nerves in the vascular wall (Honig, 1979) and also possibly from sympathetic cholinergic influences (Uvnäs, 1960) especially at the onset of, or in anticipation of, the work (although the importance of this mechanism in man has not been conclusively established) may also be involved. However, such influences are thought to be less crucial than metabolic vasodilators in controlling the blood flow to the contracting muscles during dynamic exercise.

The diffuse adrenergic sympathetic nervous system discharge induced by exercise, which for example increases splanchnic vascular resistance and thus decreases the splanchnic flow (Rowell *et al.* 1964), does not to any significant extent modulate the metabolically induced vasodilatation in the working musculature. Thus, the blood flow to the intact and sympathectomized limbs of a conscious, exercising dog was virtually identical, as was the $(a\text{–}\bar{v})$ O_2 difference (Donald, 1980). Furthermore, stimulation of the sympathetic nerves to the exercising limbs of anesthetized dogs has been shown to be relatively ineffective in inducing vasoconstriction. This lack of effect has been termed 'the sympatholysis of exercise'. In conscious dogs, however, such electrical stimulation has been shown to be capable of reducing blood flow in the exercising limb, but with the proportional effect being less at higher work rates.

The net effect of the vasodilatation and capillary recruitment in the working muscles is an increase in capillary surface area, though capillary permeability appears to be unaffected. Thus, a greater diffusive flow of O_2 to the working muscle fibres is ensured. Whether this effect is enhanced as a result of endurance training is not clear, however. Thus, while it has been demonstrated that the capillary – muscle fibre ratio is increased by endurance training (Saltin *et al.* 1977), as the fibre diameter also typically increases it remains to be convincingly established that an improved distance for diffusion results.

The efferent autonomic influences which enhance cardiac output during exercise have been widely studied and reviewed (Astrand & Rodahl, 1970; Folkow & Neil, 1971; Guyton *et al.* 1973). It is clear that the heart rate increases during exercise result from both reduced vagal impulses to the heart and also increased sympathetic discharge; the latter mechanism also increasing cardiac contractility, as do circulating catecholamines. Total denervation of the heart results in only a modest reduction of maximal work rate and cardiac output ($\dot{Q}$), with little evidence of impairment at submaximal work rates in the steady state. However, $\dot{Q}$ kinetics during the non-steady

state were appreciably slowed by this procedure (Donald, 1980), as they were also shown to be when peripheral vascular resistance was not allowed to fall (utilizing constricting cuff on the descending aorta) during treadmill exercise in the dog (Topham & Warner, 1967). (Unfortunately, in neither of these experiments were the ventilatory dynamics reported.) In contrast, following both cardiac denervation and β-adrenergic blockade to inhibit the effects of adrenal catecholamines, work tolerance was significantly constrained and the cardiac output increase was limited to some 2–3 times the resting value (resulting from the 'Frank–Starling' effect). Beta-adrenergic blockade, alone, resulted in little impairment of maximum exercise function. Thus, both the sympathetic nervous system and the effects of circulating catecholamines are necessary to sustain cardiovascular function during high-intensity exercise.

The sensory mechanisms responsible for initiating and maintaining the neurally-mediated cardiac response to exercise remain conjectural. Possible candidates include reflexes originating in the exercising limbs activated by mechanical events or alterations in the local chemical environment (McCloskey & Mitchell, 1972); reflexes originating in the heart and adjacent vasculature activated by the increased venous return (Ledsome & Linden, 1964; Vatner & Pagani, 1976; Ledsome, 1977); and influences arising in higher centres of the brain, such as the cerebral cortex (Krogh & Lindhard, 1913) or the hypothalamus (Folkow & Neil, 1971).

CARDIOPULMONARY COUPLING

In order that arterial blood gas and acid-base homeostasis be maintained, ventilation is required to change as a function of both the actual blood flow through the lungs and its composition.

Based largely upon the temporal response characteristics of $\dot{V}_E$, numerous investigators (but most concertedly Dejours, 1964, 1967) have posited that as the initial rapid responses (Fig. 1) occurred well before any metabolite formed in the exercising limbs could reach a known site of chemoreception (the peripheral and central chemoreceptors) the response must be neurogenic, originating in the limbs and/or the cerebral cortex. And as Kao (1963) demonstrated with complete spinal section or lateral-column section in his cross-circulation experiments in the dog; McCloskey & Mitchell (1972) with blockade of the small-diameter myelinated and non-myelinated afferents in the dorsal roots from the exercising limbs in the cat; and Tibes (1977) with cold-block of the afferent fibres from the limbs of the dog, that the 'neurogenic' mechanism could be abolished, further credence was provided for such a mechanism. Furthermore, drugs which stimulate the muscle spindles (Gautier, Lacaisse & Dejours, 1969) could be shown to cause hyperpnoea, and drugs which suppress spindle activity (Flandrois *et al.* 1967) could reduce ventilation. And as the second mono-exponential increase of $\dot{V}_E$ to its steady state only began after a time commensurate with the transit time for exercise-induced metabolites to reach the arterial chemoreceptors and that the time of onset of this second phase was lengthened when the arterial chemoreceptors were functionally inactivated by hyperoxia (Cunningham, 1974), the mechanistic basis for the neurohumoral control theory of the exercise

hyperpnoea appeared to be firmly established. And while, more recently, Eldridge *et al.* (1981) have described a possible hypothalamic source of the transient ventilatory responses to exercise, its functional significance for the exercise hyperpnoea appears questionable. Thus, electrical stimulation of the hypothalamic motor area in the cat induced rapid ventilatory and gas exchange responses. These, however, appear quite unlike those of spontaneous volitional exercise, i.e. a profound and rapid hyperventilation ensued, apparently consequent to the stimulation of extrapyramidal pathways to the respiratory muscles; and hence this procedure may not be a useful analog of exercise.

Wasserman and his associates (Wasserman *et al.* 1977; Whipp, 1981), however, noted significant inconsistencies with the traditional neurohumoral theory of the exercise hyperpnoea. These included: (i) that throughout the early phase (which they termed 'phase 1' as a temporary expedient to minimize any implied control mechanism) end-tidal P_{O_2} and P_{CO_2} and also the gas exchange ratio R did not typically change (Fig. 1) – were $\dot{V}_E$ to change by an obligatory neurogenic mechanism, then hyperventilation would be expected with R and P_{ET,O_2} increasing and P_{ET,CO_2} decreasing; (ii) that stimulation of the muscle spindle afferents by high-frequency, low-amplitude vibration (a potent spindle stimulus) failed to induce significant hyperpnoea in the cat, in the experiments of Matthews (1972); and that Hornbein, Sorensen & Parkes (1969) could detect no change in the dynamic ventilatory response to exercise when the γ-efferent system to the legs was blocked in man by infiltration of the lower lumbar peridural space with lidocaine; (iii) when complete spinal section at L1 was performed in the dog, no appreciable change in the dynamics of the exercise hyperpnoea could be seen, or at least none out of proportion to any altered metabolic dynamics (Weissman *et al.* 1979; Brewer *et al.* 1980); (iv) that the rapid phase 1 response in $\dot{V}_E$ was only discernible if the work were instituted from rest (Broman & Wigertz, 1971; Casaburi *et al.* 1978; and Fig. 1) – when performed against a background of mild exercise, $\phi 1$ $\dot{V}_E$ was considerably slower and virtually merged into the phase 2 response, although still discernible in certain studies (Swanson, 1978; Whipp *et al.* 1980; Bennett *et al.* 1981); (v) the $\phi 1$ hyperpnoea was markedly attenuated by prior moderate hyperventilation (Ward *et al.* 1981); (vi) and that there appears to be little or no difference in the response characteristics between $\phi 1$ and the exponential $\phi 2$ or even the steady-state phase, if a different frame of reference were considered, this being the CO_2 flux to the lungs (the product of pulmonary blood flow and the mixed venous CO_2 content).

These investigators recognized that as cardiac output and, therefore, pulmonary blood flow increased rapidly at exercise onset (consequent to increased venous return, heart rate and cardiac contractility), the pulmonary CO_2 flux would increase despite no change in mixed venous gas tension (for the duration of $\phi 1$). Any such increase that was not matched by an appropriate increase in alveolar ventilation would necessarily result in a downstream error signal in pH, P_{CO_2} and P_{O_2} which could be sensed by a rapidly responding chemoreceptor, thereby providing a humoral stimulus to the early hyperpnoea of exercise (Wasserman, Whipp & Castagna, 1974). In an attempt to test this hypothesis, these investigators induced primary changes in $\dot{Q}$ in both awake and anesthetized dogs either by electrically 'pacing' the right atrium or by small intravenous bolus injections of the β-stimulant isoproterenol. When $\dot{Q}$ rose (and not

before), $\dot{V}_E$ increased consequently, with little or no change in P_{a,CO_2} or P_{ET,CO_2}. They therefore termed this response a 'Cardiodynamic Hyperpnoea'. And, as previously cited (Whipp, 1981), the poet George Meredith proved to be remarkably prescient when, in his poem 'Hymn to Colour', he questioned 'shall man into the mystery of breath, from his quick-beating pulse a pathway spy?'.

Subsequently, Winn, Hildebrant & Hildebrant (1979) and Eldridge & Gill-Kumar (1980) concluded that a 'cardiodynamic' mechanism for the isoproterenol-induced hyperpnoea was unlikely from their experiments on cat and rabbit, and asserted that the ventilatory response was simply a result of direct stimulation of the peripheral chemoreceptors by the drug. This contention, however, conflicted with the further experiments of Wasserman *et al.* (1979) in the cat which reaffirmed cardiodynamism.

The conflict may be resolved, in large part, by the studies of Juratsch *et al.* (1981) who demonstrated that when the carotid and central chemoreceptors were temporally dissociated from the thorax by interposing long delay loops to both carotid and vertebral arteries (with vessel flows being precisely maintained at control levels by means of pumps), thereby resulting in transit delays of some 2–4 min, an early 'cardiodynamic' response to intravenous isoproterenol clearly preceded the subsequent direct effect upon the chemoreceptors; the separate responses being normally difficult to distinguish owing to the temporal proximity of the heart and the arterial chemoreceptors. Furthermore, Jones *et al.* (1981) induced increased $\dot{Q}$ by raising the paced heart rate in patients with permanent cardiac pacemakers for the management of atrioventricular block. Their results demonstrate that 'exclusive' primary changes in $\dot{Q}$ can result in a consequent hyperpnoea. These investigators judiciously point out, however, that cardiopulmonary coupling during exercise is likely to be much more complex.

Moreover, several groups have diverted a portion of the normal venous return from the venae cavae into the aorta, and utilized a gas exchanger to attempt to 'arterialize' the returning blood (Galletti, 1961; Rawlings *et al.* 1975; Stremel *et al.* 1979). These experiments have a strikingly similar result (despite considerable differences in specific methodology); this being that as the flow through the heart and lungs is reduced, so a hypopnoea develops, even inducing apnoea with sufficient thoracic hypoperfusion. These experiments, however, were performed in the resting state in experimental animals. And so Brown *et al.* (1976) attempted to determine whether such a cardiodynamic mechanism might be operating in the steady-state of exercise in man. When these investigators infused the β-blocking drug propranolol in this condition, ventilation decreased as $\dot{Q}$ fell. Interestingly, however, this isocapnic hypopnoea (i.e. the subjects did not hypoventilate) only persisted until mixed venous CO_2 content rose sufficiently to return pulmonary CO_2 flux back to normal (i.e. $\downarrow\dot{Q}_c$, $\uparrow C_{\bar{v},CO_2}$), as evidenced by CO_2 output at the lung returning again to the exercise level. Consequently, a cardiodynamic mechanism for a component of the exercise hyperpnoea appears likely.

The mechanism responsible for mediating the cardiodynamic component of the exercise hyperpnoea, however, is not likely to involve 'downstream' chemoreception via the peripheral and central chemoreceptors. Whipp (1978, 1981) questioned this concept of the mechanism on theoretical grounds, based upon the known transit

delays from the lungs, the likely change in the error signal and the chemoreflex gains. Furthermore, Wasserman *et al.* (1975*b*) showed that, in man, the magnitude of the phase 1 component of the exercise hyperpnoea was not systematically different in subjects who had undergone bilateral carotid body resection (but were otherwise normal) from control subjects. And as neither hypoxia, hyperoxia nor hypercapnia appear to affect the phase 1 magnitude (Cunningham, 1974), an important role for the known chemoreceptors downstream of the lungs appears remote. Whipp *et al.* (1981), however, designed an experiment expressly to discern whether the cardiodynamic phase of the exercise hyperpnoea involved the chemoreceptors. In the temporally-isolated chemoreceptor preparation in the dog described above (and including, on occasion, bilateral cervical vagotomy), these investigators induced muscular exercise. They could document no slowing of the phase 1 ventilatory response, despite any chemical signals generated at the lungs (by transient $\dot{V}_A/\dot{Q}$ imbalance) being delayed to the chemoreceptors by an average of 2 min.

Therefore, a fundamentally new approach may be required to understand the coupling of ventilation to cardiovascular changes during exercise, and it seems that the mechanism should not be unrelated to 'CO_2'. But, although it has been proposed that ventilation during exercise changes as a function of the CO_2 flux to the lung ($\dot{Q} \times C_{\bar{v},CO_2}$, or $\dot{Q}_{CO_2}$), the response characteristics required to regulate arterial P_{CO_2} throughout the non-steady-state phases of exercise (i.e. both $\phi 1$ and $\phi 2$) have not been formally presented previously. And when these relationships are analysed, there are interesting implications for the necessary coupling of cardiovascular and ventilatory responses. For example, assuming arterial P_{CO_2} equals alveolar P_{CO_2}, then:

$$\frac{\dot{V}_A}{\dot{Q}} = \frac{863\,(C_{\bar{v},CO_2} - C_{a,CO_2})}{P_{a,CO_2}} \tag{8}$$

or

$$\frac{\dot{V}_A}{\dot{Q}} = 863\left[\frac{C_{\bar{v},CO_2}}{P_{a,CO_2}}\right] - \left[\frac{C_{a,CO_2}}{P_{a,CO_2}}\right] \tag{9}$$

And as $C_{a,CO_2}/P_{a,CO_2}$ is a constant (α) by definition and neglecting the proportional constant 863 for simplicity, then (as shown in Fig. 3*a*):

$$\frac{\dot{V}_A}{\dot{Q}} = \beta - \alpha, \tag{10}$$

where β equals $C_{\bar{v},CO_2}/P_{a,CO_2}$. That is, in phase 1 of exercise (in which $C_{\bar{v},CO_2}$ is unaltered) alveolar ventilation must change in precise proportion to the actual pulmonary blood *flow*. Dividing equation (10) through by $C_{\bar{v},CO_2}$ yields:

$$\frac{\dot{V}_A}{\dot{Q} \times C_{\bar{v},CO_2}} = \frac{1}{P_{a,CO_2}} - \frac{\alpha}{C_{\bar{v},CO_2}} \tag{11}$$

And, hence, in phase 2 of exercise (when $C_{\bar{v},CO_2}$ changes), the relationship $\dot{V}_A/\dot{Q}_{CO_2}$ therefore increases hyperbolically with increasing $C_{\bar{v},CO_2}$, as shown in Fig. 3*b*, *c*.

This analysis suggests, therefore, that any direct cardiopulmonary coupling during

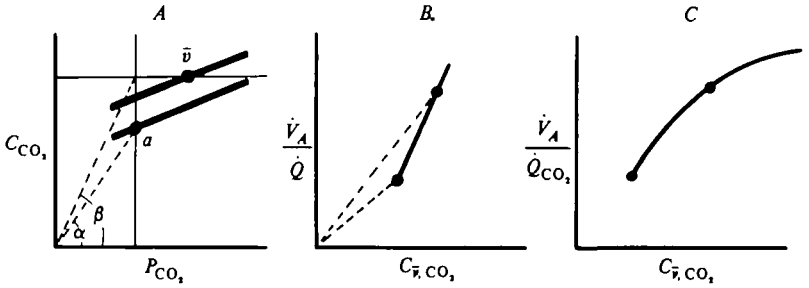

Fig. 3. Representation of the relationship linking alveolar ventilation ($\dot{V}_A$) to the pulmonary CO_2 flux ($\dot{Q}_{CO_2}$) during exercise, with arterial isocapnia assumed. *Panel A* is the blood CO_2 dissociation curve relating CO_2 content (C_{CO_2}) to partial pressure (P_{CO_2}); *a* and $\bar{v}$ representing the arterial and mixed venous points, respectively. The difference between the variable β ($C_{\bar{v},CO_2}/P_{a,CO_2}$) and the constant α ($C_{a,CO_2}/P_{a,CO_2}$) defines the ventilation-to-perfusion ratio ($\dot{V}_A/\dot{Q}$). In *panel B*, $\dot{V}_A/\dot{Q}$ is plotted as a function of the mixed venous CO_2 content ($C_{\bar{v},CO_2}$). Note that prior to $C_{\bar{v},CO_2}$ changing (i.e. phase 1), $\dot{V}_A/\dot{Q}$ remains constant despite both $\dot{V}_A$ and $\dot{Q}$ increasing. However, when $C_{\bar{v},CO_2}$ increases (i.e. phase 2), the ratio of alveolar ventilation to the pulmonary CO_2 flux ($\dot{V}_A/\dot{Q}_{CO_2}$) does not remain constant but rather is required to increase hyperbolically, as shown in *panel C*. See text for further details.

exercise will be manifest largely in phase 1, with an additional component operative in phase 2.

As argued above, this cardiopulmonary coupling in $\phi 1$ appears unrelated to a feedback mechanism mediated by humoral control via the arterial chemoreceptors. Rather, feedforward mechanisms are likely. And, consequently, three potential coupling links deserve consideration:

(i) Feedforward control of ventilation with $\dot{Q}$ changing proportionally as a direct consequence. And although the ventilatory 'pump' can enhance venous return, the rapid changes in $\dot{Q}$ at exercise onset are also largely controlled by altered peripheral vascular resistance and autonomic influences (Guyton *et al.* 1973; Donald, 1980), and of course can occur in the absence of hyperpnoea. Furthermore, when ventilation is increased volitionally, a rapid alkalotic hypocapnia ensues.

(ii) A rapid primary increase in $\dot{Q}$ might itself provide the feedforward control of $\dot{V}_A$ (e.g. Fig. 4A), presumably by cardiac or, possibly pulmonary vascular, mechanoreception. As described above, this appears a likely candidate. Thus, the cardiodynamic hyperpnoea would operate in a manner different from that originally proposed. Rather than the initial alteration in $\dot{Q}$ leading to a downstream error signal which is proportional to the altered pulmonary CO_2 flow, it is likely that the heart provides an increased CO_2 flow which is proportional to the feedforward signal which induces the hyperpnoea. And, as a consequence of this coupling, arterial P_{CO_2} and $[H^+]$ would be regulated in phase 1 of exercise.

(iii) Control of both ventilation and cardiac output could be mediated via neural afferents from, for example, the exercising limbs (Fig. 4B). Such a mechanism is suggested by the results of McCloskey & Mitchell (1972) who demonstrated that when the impulse traffic transmitted from the 'exercising' limbs of the cat in small myelinated and non-myelinated fibres was interrupted by anaesthetic blockade of the dorsal

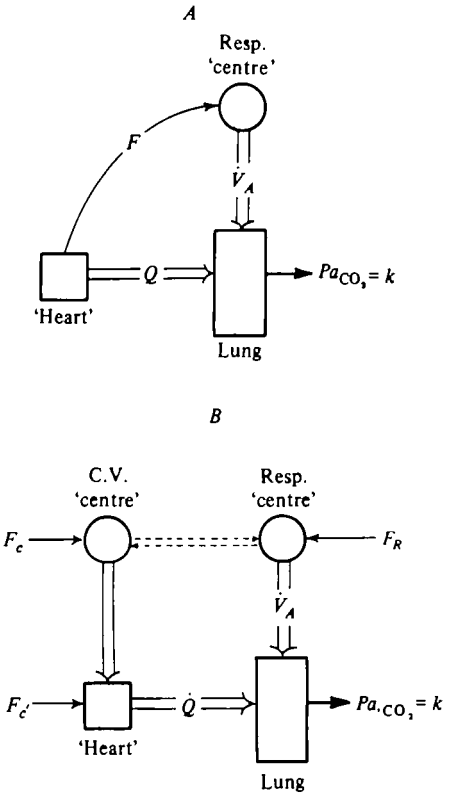

Fig. 4. Simplified representation of two control schemes (A, B) capable of maintaining arterial P_{CO_2} and $[H^+]_a$ relatively constant in response to rapid changes in cardiac output. F represents neural feedforward mechanisms to respiratory (R) and cardiovascular (C) control centres; *C'*, other non-neural mechanisms inducing rapid cardiac output changes (e.g. increased venous return); and $\dot{V}_A$ and $\dot{Q}$, alveolar ventilation and cardiac output. See text for further details.

roots, both the ventilatory *and* the cardiovascular responses were largely abolished. Similarly, of course, any component mediated via hypothalamic or limbic neurogenesis would be likely to incorporate parallel drives.

In this light, and recognizing that the chemical-control model of the cardiodynamic hyperpnoea was untenable in accounting for the dominant proportion of the phase 1 component of the exercise hyperpnoea, Huszczuk, Jones & Wasserman (1981) hypothesized that there might, in fact, be a mechanical source of control information. These investigators demonstrated that changes in the right ventricular moving-average pressure (i.e. a functional analogue of right ventricular load) were highly correlated with both the magnitude and the temporal characteristics of the ventilatory response to changes in cardiovascular dynamics. And, further, that these effects could be dissociated from changes in cardiac output *per se*, or in pulmonary artery or left-side cardiac pressures. The afferent mechanism of this apparent mechanically mediated reflex appears not to be vagal (although bilateral cervical vagotomy did seem to alter

the set-point for the mediation). Neurophysiological evidence for the mediation of information from the heart into ventilatory responses has been obtained from experiments in which cardiac afferent fibres were electrically stimulated (Uchida, 1976) and also when the right ventricle was distended (Kostreva *et al.* 1979), the latter presumably operating through stretch receptors in the ventricular wall (Kostreva *et al.* 1975*a*). Other possible candidates may include reflexes from pulmonary artery distension (Ledsome, 1977) or from altered regional ventilation-to-perfusion relationships (Bartoli *et al.* 1974; Juratsch *et al.* 1982), or other less detailed mechanisms of thoracic origin (Kostreva *et al.* 1975*b*; Levine, 1978) may also be involved.

This concept therefore shifted the focus of the site of the rapid feedforward component of the exercise hyperpnoea from a peripheral source, which is largely independent of respiratory gas flow to the lungs, to a central cardiac mechanism which is (normally) obligatorily coupled to pulmonary CO_2 flux.

However, experiments which utilize extra-corporeal gas exchangers in experimental animals to load or unload CO_2 into or out of the venous blood, either at rest or during exercise, have resulted in highly inconsistent findings. Thus, support has been provided for the ventilatory changes being isocapnic (Yamamoto & Edwards, 1960; Wasserman *et al.* 1975*a*; Stremel *et al.* 1978; Phillipson, Duffin & Cooper, 1981), reflecting an infinite gain of the ventilatory control system with respect to arterial P_{CO_2} and $[H^+]$; and the ventilatory changes indicating a system gain which is higher than (Linton, Miller & Cameron, 1976) and also similar to the gain of the ventilatory response to CO_2 inhalation (Lamb, 1966; Lewis, 1975; Greco *et al.* 1978; Shors *et al.* 1980). It is, at present, not possible to reconcile these disparate responses into a unified theory but, as feedforward cardiac control appears so important, one wonders whether the differences may not involve variations in the involvement of this mechanism.

In conclusion, investigations into the control of cardiovascular or respiratory function during exercise have failed to explain adequately the individual control characteristics of the systems, especially with regard to their non-steady-state behaviour. However, the mechanisms which couple the responses of these systems to the metabolic requirements of the work have received little attention and, hence, are largely obscure, providing a tantalizing challenge to those interested in the control of cardiopulmonary function during exercise.

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