

SYMPOSIUM REVIEW

Tracking pulmonary gas exchange by breathing control during exercise: role of muscle blood flow

Philippe Haouzi

Department of Medicine, Division of Pulmonary and Critical Care Medicine, Penn State University College of Medicine, Hershey, PA, USA

Abstract Populations of group III and IV muscle afferent fibres located in the adventitia of the small vessels appear to respond to the level of venular distension and to recruitment of the vascular bed within the skeletal muscles. The CNS could thus be informed on the level of muscle hyperaemia when the metabolic rate varies. As a result, the magnitude and kinetics of the change in peripheral gas exchange – which translates into pulmonary gas exchange – can be sensed. We present the view that the respiratory control system uses these sources of information of vascular origin, among the numerous inputs produced by exercise, as a marker of the metabolic strain imposed on the circulatory and the ventilatory systems, resulting in an apparent matching between pulmonary gas exchange and alveolar ventilation.

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Corresponding author P. Haouzi: Pennsylvania State University College of Medicine, Department of Medicine, 500 University Drive, H041, Hershey, PA 17033, USA. Email: phaouzi@hmc.psu.edu

This review presents and discusses some of the experimental evidence gathered over the last few years (Haouzi *et al.* 2004*b*; Forster *et al.* 2012) supporting the role for a signal originating from the muscle circulation, related to the local metabolic demand, which contributes to the matching between ventilation and pulmonary gas exchange during exercise (Dejours, 1963; Whipp, 1981; Whipp & Ward, 1991; Forster *et al.* 2012).

The term ‘exercise’ refers here to any muscular activity associated with dynamic contractions, consisting of a succession of rhythmic contractions and relaxations such as walking, running or cycling and resulting in an increase in metabolic rate. Static, or isometric, contractions which are to be regarded as an ‘effort’ (Dejours, 1959), i.e. sustaining a constant load such as carrying a weight, produce ventilatory responses different, both qualitatively and quantitatively, from those observed during dynamic

exercise (Poole *et al.* 1988; Imms & Mehta, 1989). These responses will not be discussed here.

The inability of the cardiovascular system to appropriately increase an already high resting level of O₂ supply to the tissues and CO₂ transport to the lungs requires blood flow to be redistributed toward the exercising muscle wherein muscle metabolic rate increases (Astrand & Rodahl, 1977; Guyton, 1987; Laughlin *et al.* 1999). The theory presented in this paper is that the changes in vascular resistance within the exercising muscles produce a specific signal that may prove to be essential for the ‘respiratory neurons’ involved in the coupling between ventilation and peripheral/pulmonary gas exchange. The elements supporting the ‘vascular distension hypothesis’ are briefly described. For more details the reader can refer to the following reviews (Haouzi *et al.* 2004*b*; Haouzi, 2006; Forster *et al.* 2012).

Philippe Haouzi is a physician and a physiologist, Professor of Medicine at Penn State University, College of Medicine, Division of Pulmonary and critical Care Medicine and Professor of Physiology and Medicine at the University H. Poincare, France. His main interest has been, for the last 20 years, the control of respiration and circulation using large mammals including humans as experimental models. He has received several awards for his work, e.g. Academie Nationale de Medicine, NATO. He is a former fellow of the Japanese Society for the Promotion of Science and has currently a NIH funded research group working on the toxicology of agents altering cellular metabolism and on the prevention of the effects of anoxia.



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Finally, a model will be presented on how this information may be used by the CNS to produce a matching between *alveolar* ventilation (but not *minute* ventilation) and the pulmonary gas exchange rate.

Setting the scene: rate of O₂ and CO₂ transport by the blood and muscle blood flow redistribution

The transfer of molecules of oxygen from the atmosphere to the mitochondria of millions of cells to eventually 'feed' the electron chain, along with the elimination of the molecules of CO₂ produced in the process, relies on a profound interaction between the circulatory and the ventilatory systems (Dejours, 1964; Astrand & Rodahl, 1977).

In resting mammals, including humans, the rate of O₂ delivery by the arterial blood (D_{aO_2}) – the product of the cardiac output and the arterial O₂ concentrations (C_{aO_2}) – is several fold the rate of body O₂ consumption (Astrand & Rodahl, 1977; Dejours, 1981, 1988). For instance, in an average-sized adult human, resting D_{aO_2} is about 1000 ml min⁻¹, assuming an arterial O₂ content of 200 ml l⁻¹ and a cardiac output of 5 l min⁻¹ (Guyton *et al.* 1973), while resting \dot{V}_{O_2} ranges between 250 and 300 ml min⁻¹ (Dejours, 1990). The volume of O₂ delivered per minute in the arterial tree is therefore 3–4 times the volume of O₂ consumed over the same time. As a consequence, D_{VO_2} (the rate of O₂ delivery back to the lungs) is only 25% less than D_{aO_2} (Dejours, 1990). Incidentally, in air-breathing animals, the rate at which CO₂ is transported by the venous system (D_{VCO_2}) is also 3–4 times its rate of production: There is, in addition to the CO₂ produced by all the tissues, about 1 litre min⁻¹ of CO₂ coming for the arterial side which must be transported by the venous system towards the lungs (Dejours, 1981). The latter only eliminates, through alveolar ventilation, the equivalent of the endogenous production of CO₂, 200–250 ml min⁻¹ at rest.

During a dynamic exercise, muscle \dot{V}_{O_2} and \dot{V}_{CO_2} can increase up 20-fold (Astrand & Rodahl, 1977; Dejours, 1990); D_{aO_2} to the muscles must therefore rise to prevent or limit a reduction in muscle P_{O_2} . Similarly, as \dot{V}_{CO_2} must rise by about the same amount as \dot{V}_{O_2} and at a similar rate – or even at a higher rate during heavy exercise – the only way to limit the rise in muscle CO₂ is for the cardiovascular system to allow for an increase in blood flow to (and therefore from) the metabolically active tissues. As O₂ extraction and cardiac output can, at the very best, increase by 3 times each at the peak of a maximal exercise in a trained athlete (Astrand & Rodahl, 1977; Dejours, 1990), a redistribution of blood flow towards the exercising muscles (Saltin *et al.* 1968; Rowell, 1974; Rowell & O'Leary, 1990; Laughlin, 1999) is the only mechanism through which O₂ delivery rate can match the increased rate of O₂ demand in the muscles. This redistribution of muscle blood flow involves

a decrease in vascular resistance in the metabolically active territories, while peripheral conductance decreases in the non-exercising muscles and tissues, for example the skin or the gastrointestinal system (Mitchell, 1990*b*).

The challenge of exercise-induced hyperpnoea: 'matching' peripheral/pulmonary gas exchange

The involvement of the ventilatory system during exercise should be viewed as one of the components of the adjustments described in the previous paragraph, as: (1) the level of breathing must cope with the consequences of an increase in pulmonary gas exchange, (Whipp, 1981; Forster *et al.* 2012), a direct effect of the increase in muscle gas exchange; and (2) the magnitude of the ventilatory response dictates the level of alveolar – and thus arterial – O₂ and CO₂ partial pressures, and contributes to maintaining an adequate rate of O₂ delivery and CO₂ removal (Whipp & Ward, 1998; Haouzi, 2006). Keeping P_{aO_2} and P_{aCO_2} constant will certainly limit the 'circulatory cost' required to raise D_{aO_2} to the exercising muscles.

As the circulatory system is a closed circuit (if, as a first approach, one ignores venous capacitance), the changes in pulmonary blood flow and pulmonary gas exchange mirror the averaged gas exchange occurring in all of the peripheral tissues – unless disrupted by experimental means (see below for the effects of venous *vs.* arterial

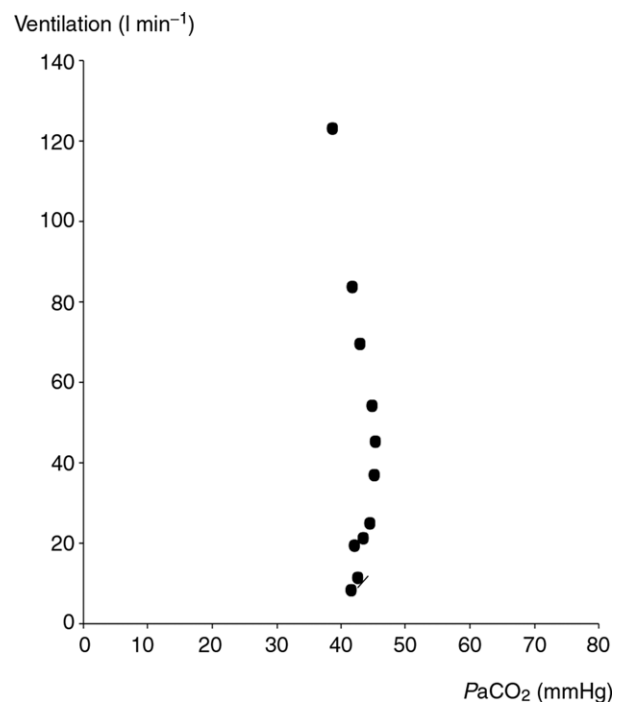


Figure 1. Relationship between arterial P_{CO_2} and minute ventilation during a ramp-like increase in workload in humans (adapted from Sun *et al.* 2001)

Note that ventilation increases with no increase in P_{aCO_2} during a moderate level of exercise, while hypocapnia develops at a higher level of work rate and breathing.

occlusion). Consequently, the convection of a gas in the regions of the lungs wherein gas exchange takes place, i.e. the alveolar regions, must increase to prevent alveolar P_{CO_2} from rising and alveolar P_{O_2} from dropping in proportion to the rate at which peripheral gas exchange increases. To get a quantitative idea of the importance of the adjustment of the convection of gas to the pulmonary gas exchange, consider that a walking human increases O_2 consumption (and CO_2 production) and thus lung gas exchange by about 3 times. As $P_{\text{aO}_2} = P_{\text{iO}_2} - k\dot{V}_{\text{O}_2}/\dot{V}_A$ and $P_{\text{aCO}_2} = P_{\text{iCO}_2} + k\dot{V}_{\text{CO}_2}/\dot{V}_A$, P_{aCO_2} (and P_{aO_2}) will increase by 3 times (up to 120 Torr!) and P_{AO_2} (and P_{aO_2}) would be close to zero, if \dot{V}_A did not increase during this very moderate form of exercise.

As shown in Figs 1 and 2, not only does minute ventilation increase in proportion to the pulmonary gas

exchange, but this ventilatory adjustment has kinetics which seem to 'follow' that of \dot{V}_{O_2} or \dot{V}_{CO_2} during both the onset of and the recovery from any form of dynamic exercise. This remains true whether a step, an impulse, a ramp or a fluctuating change in work load is applied (Fujihara *et al.* 1973a, b; Casaburi *et al.* 1977; Whipp, 1978, 1981; Haouzi *et al.* 2004a). An important point needs to be clarified about P_{aCO_2} homeostatis during exercise: the ventilation tracks in all types of exercise factors related or proportional to the pulmonary gas exchange, but: (1) it is not the pulmonary gas exchange by itself which seems to contain the signal driving breathing; and (2) because the ventilatory kinetics are slower than that of gas exchange, a transient, albeit small, change in P_{aCO_2} does occur in the unsteady state conditions of a step or sinusoidal change in work load (Whipp, 1978). The fundamental question

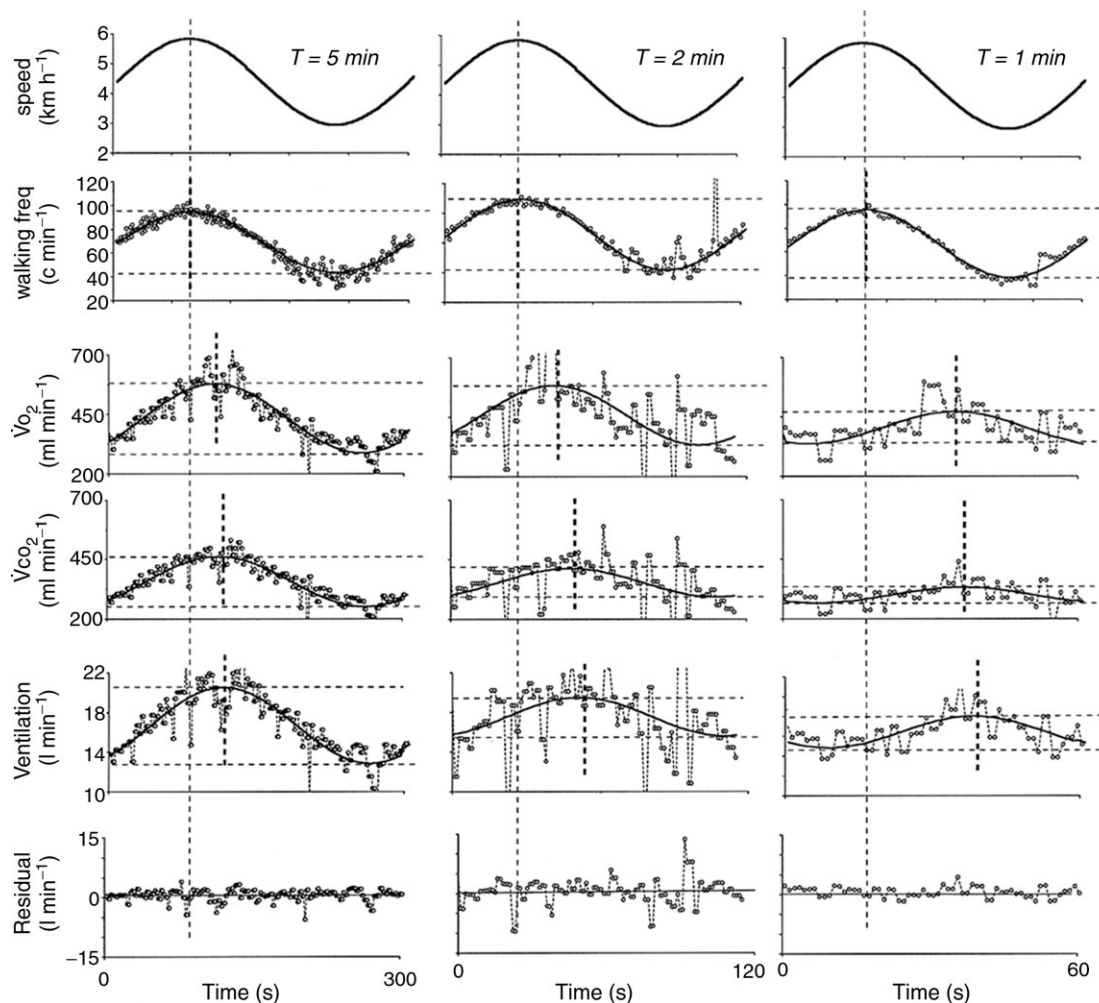


Figure 2. Example of the pulmonary gas exchange and ventilatory response to sinusoidal changes in the speed of walking in a sheep (adapted from Haouzi *et al.* 2004a)

As the period of change in walking speed decreases, the pulmonary gas exchange response becomes dissociated from the motor activity due to a slower time constant response than the locomotor activity, which follows very precisely the change in walking speed. Minute ventilation follows the change in pulmonary gas exchange, with a reduction in amplitude and an increase in phase lag despite unchanged locomotor and motor control. Similar results have long been reported in humans during cycling exercise (Casaburi *et al.* 1977).

of exercise-induced hyperpnoea is therefore to address the mechanisms accounting for the ventilatory–gas exchange matching. In steady-state and unsteady-state conditions, the result of this matching is to prevent (or limit) the rise in P_{aCO_2} (and decrease in P_{aO_2}), which would result from an increase in \dot{V}_{CO_2} (or \dot{V}_{O_2}).

Finally, the evolution of the lung anatomy in air-breathing vertebrates has led to the development of a significant pulmonary dead space (Dejours, 1981), wherein gas circulates between the alveolar regions and the atmosphere without being exchanged. It is alveolar, and not minute, ventilation that controls the levels of CO_2 and O_2 to be exchanged with the blood. The puzzling question is how could alveolar ventilation be regulated while it is minute ventilation (a tidal volume at a given frequency) that is generated by the respiratory neurons. This certainly adds some complexity to the conundrum represented by the mechanism of exercise-induced hyperpnoea.

The ‘peripheral vascular distension hypothesis’

The challenge is not to propose a theory that can account for any rise in ventilation (indeed multiple structures evoked during an exercise can stimulate breathing, for example muscle receptors, chemoreception and supra-medullary structures), but rather to propose a mechanism that can account for the magnitude and time course of the ventilatory response and its link to the pulmonary gas exchange (Whipp & Ward, 1992).

Over the last few years, our group, following the original work of Huszczuk *et al.* (1993), has defended the view that one of the pathways through which the control of breathing may follow metabolic changes in the lungs is to follow metabolic changes in the muscle but based on the neural monitoring of the peripheral vascular events (Haouzi *et al.* 2004b).

Briefly, skeletal muscle afferent fibres are traditionally divided into four groups according to their conduction velocity. The group III and IV muscle afferent fibres (small myelinated or unmyelinated fibres) do increase breathing (McCloskey & Mitchell, 1972; Amann *et al.* 2010). The natural stimuli of these endings, besides ‘painful’ stimuli, include the mechanical distortion of their receptive field (mechanoreception), the accumulation of ‘metabolic by-products’ of the contractions and an increase in local temperature (Hertel *et al.* 1976; Kaufman *et al.* 1993, 2002; Mense, 1996).

Stacey (1969) had already noted that although there is a large range of termination sites within the muscle structures, many group III and IV fibres are originating from the blood vessel adventitia, including the arterioles and venules (Fig. 3). Also, Von Düring & Andres (1990) found striking anatomical relationships between muscle group IV endings and the vessels in the cat. In keeping with these anatomical findings, we found that a

population of these fibres did respond to the distension of the vessels, predominantly at venular level, and could monitor muscle blood flow by encoding the degree of recruitment of the post-capillary network (Haouzi *et al.* 1999). For instance, in 60 slowly conducting afferent fibres present in the dorsal roots coming from the cat triceps surae, we found that 31% of group IV and 15% of group III nerves were stimulated by the vascular smooth muscle relaxant papaverine (2–2.5 mg kg⁻¹; Fig. 4). Sixty-two per cent of them were also stimulated by isoproterenol, and more than half of the fibres that were stimulated by papaverine were also stimulated during an occlusion of the vena cava, suggesting that these fibres are located within or close to the venous or venular structures. Finally, a large number of group IV fibres respond to both dynamic contractions and venous distension or vasodilation (Fig. 4).

In accordance with these neurophysiological findings, reflexes triggering ventilation changes could be elicited when altering muscle circulation. For instance, injection of a vasodilatory agent into the isolated hindlimb circulation of a sheep stimulates breathing (Haouzi *et al.* 1996). This occurs well before the drug could have reached the central circulation and, thus, could have affected the arterial chemo- or baroreceptors. Conversely, total obstruction of the blood flow to and from the limbs at rest or at the cessation of dynamic exercise (Fig. 5) does not stimulate, but actually decreases, ventilation much faster than in control conditions, which decline towards resting levels in humans and in animals (Dejours *et al.* 1957b; Haouzi *et al.* 1993; Fukuba *et al.* 2007). However, impeding, by intravascular occlusion, the circulation from (venous side) or to (arterial side) the hindlimbs during electrically induced

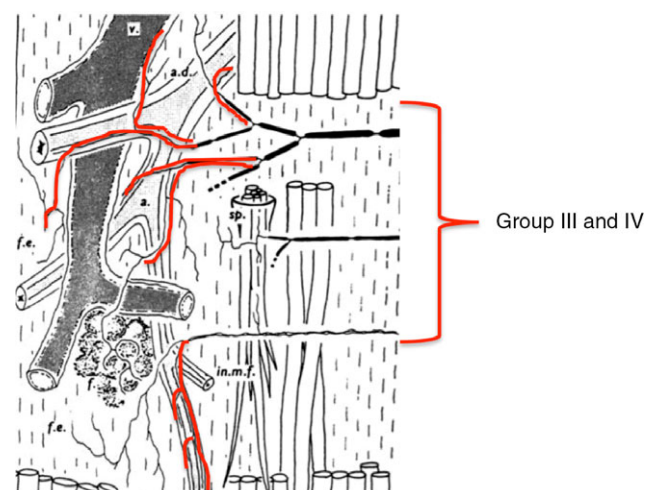


Figure 3. The distribution of the afferent innervation of sympathectomized skeletal muscle in the cat (adapted from Stacey, 1969)

Many group III and IV afferent fibers can be found in association with arterioles and venous structures.

muscle contractions in dogs (Huszczyk *et al.* 1993) leads to opposite ventilatory outcomes, regardless of the circulatory changes occurring in the central circulation. Indeed, despite a similar reduction in O_2 uptake and blood pressure resulting from obstruction of the caudal vena cava or the distal abdominal aorta, ventilation typically rises when the venous side is occluded and decreases when the arterial side is impeded during exercise (Huszczyk *et al.* 1993; Haouzi *et al.* 2004b). Every condition associated with an impediment of the arterial supply prevents the normal

\dot{V}_E response produced both at the onset and during the steady-state response to dynamic contractions in various animal models. A similar reduction in \dot{V}_E response can be observed in patients with peripheral vascular disease of the lower extremities when walking on a treadmill, below their pain threshold (Haouzi *et al.* 1997). Such reduction in breathing during exercise is observed despite all of the other stimuli being present (e.g. control of movements and intensity of contractions). These results also fit with a puzzling observation that whenever the motor act is

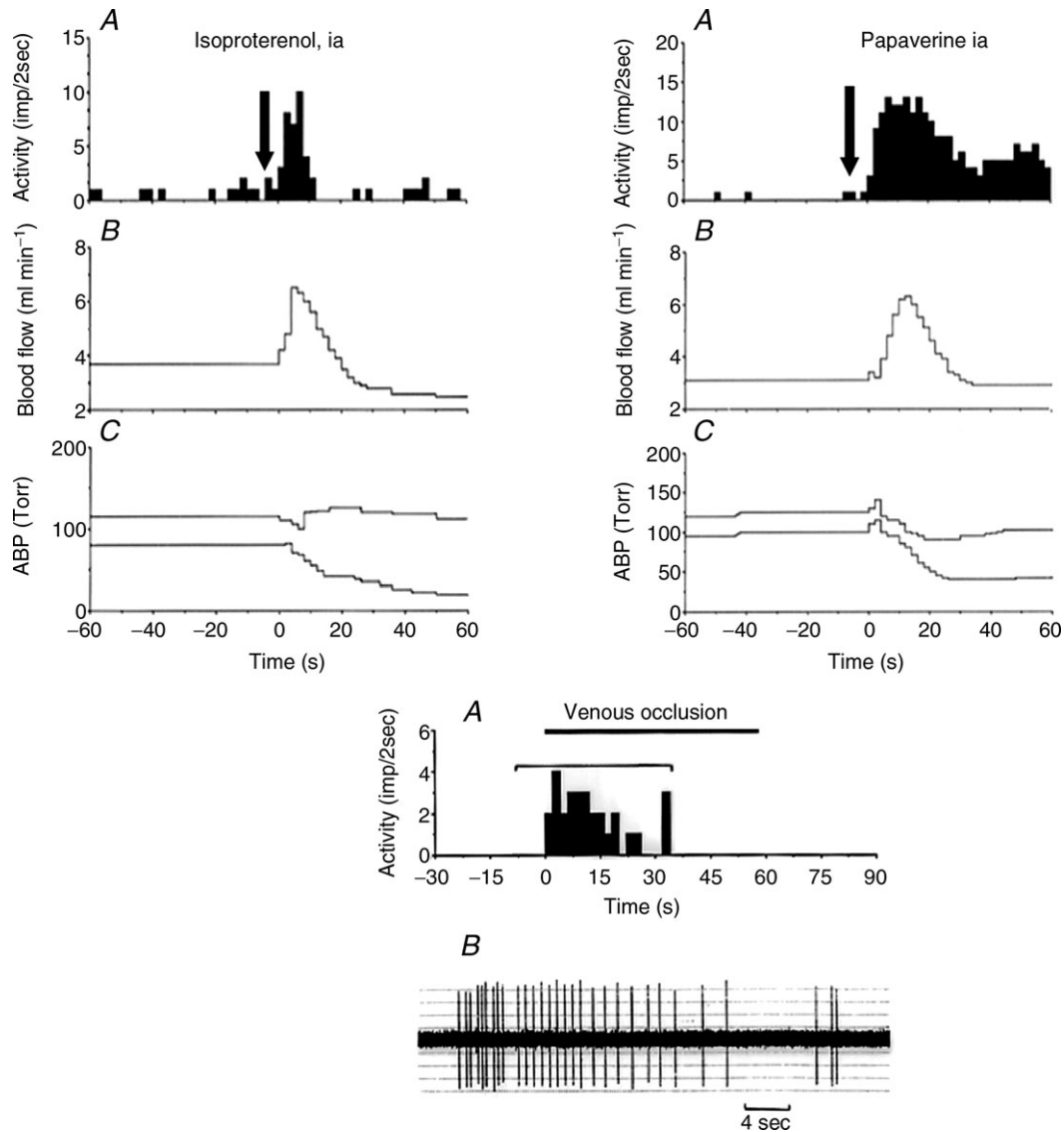


Figure 4. Effects of a intra-aortic injection of isoproterenol, papaverine and venous occlusion on the discharge rate of three group IV muscle afferents of the triceps surae muscles in cat (adapted from Haouzi *et al.* 1999)

Upper panels: A, histogram of activity. B, popliteal blood flow. C, arterial blood pressure (ABP). Arrows indicate the time of injection. Note that the fibre shown at the left responds immediately as soon as blood flow increases. No change was observed during vehicle injection. Lower panel: response to venous occlusion of a group IV afferent fibre, which also responded to papaverine and venous contraction (not shown). The response to the occlusion of the vena cava suggests that the receptive field of this ending is located on the venular side of the muscle circulation.

dissociated from metabolic or gas exchange changes, the strategy adopted by the ventilatory control system is not to follow factors related to the motor activity but to follow, in a systematic and predictive way (Haouzi *et al.* 2004a), factors proportional or related to some of the changes associated with the rate at which CO_2 is exchanged in the lungs (Fig. 2). Any concept that neglects this crucial observation cannot account for the fundamental mechanism of \dot{V}_E control in exercise, as this approach preserves all other inputs to the CNS (Whipp & Ward, 1991).

How to understand the apparent matching between alveolar ventilation and pulmonary gas exchange in exercise

The question is how much the system described in the above section can contribute to the ventilatory response to exercise, wherein minute ventilation can increase by more than 100 l min^{-1} (Dejours, 1964)? Answering this question requires an understanding of how the structures in the CNS involved in breathing control process the multitude of available sources of information reaching

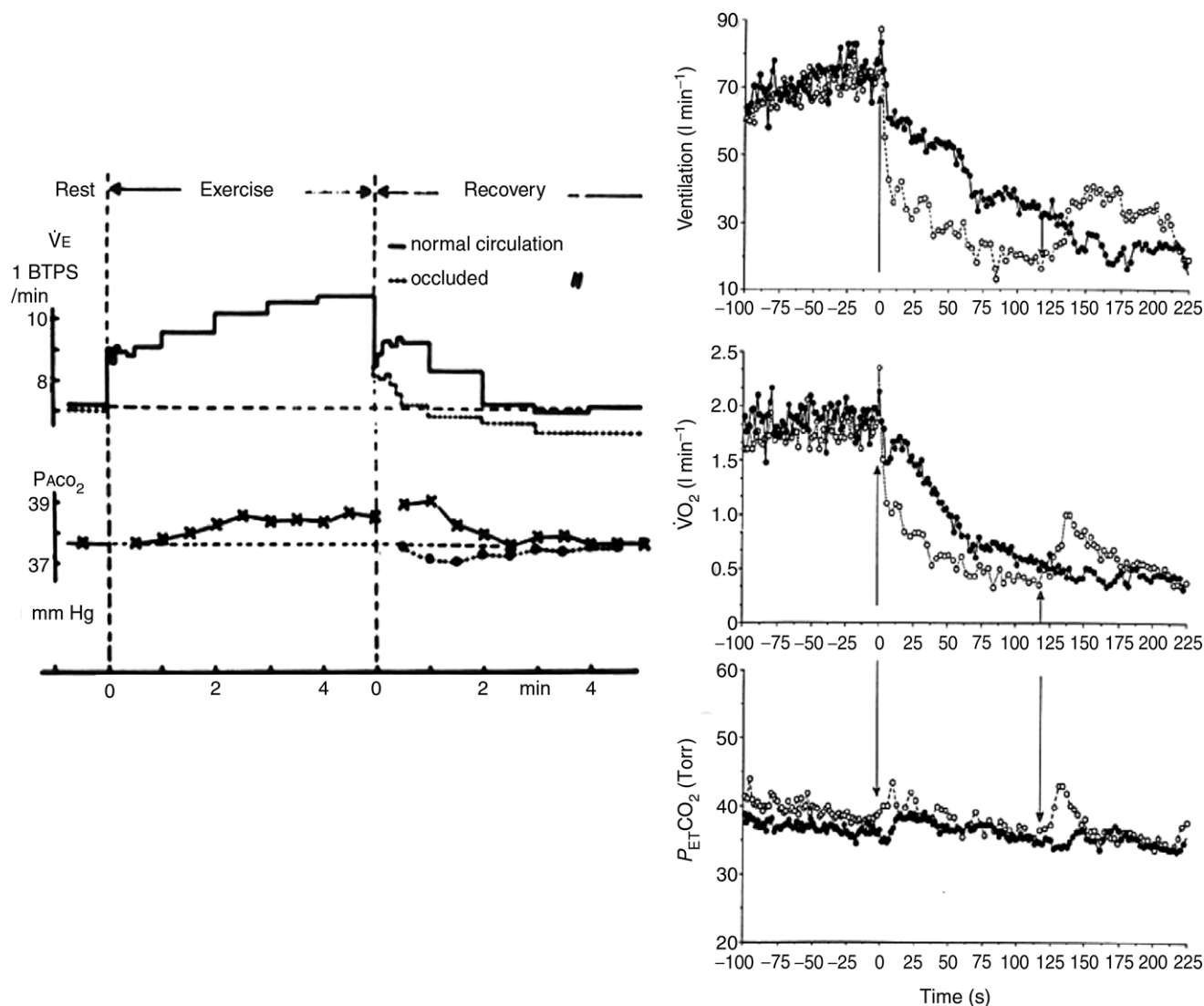


Figure 5 Effects of vascular occlusion during recovery from exercise in humans

Left panel: example of the breath-by-breath minute ventilation (\dot{V}_E), and alveolar P_{CO_2} during recovery from a light level of exercise with intact circulation and while impeding the circulation to the post-exercising legs (Dejours *et al.* 1957). Right panel: Minute ventilation (\dot{V}_E), O_2 uptake (\dot{V}_{O_2}), and end-tidal P_{CO_2} (P_{ETCO_2}) during recovery (filled symbols) from a constant work rate cyclo-ergometer exercise performed above the lactate threshold and during recovery with cuffs inflated for 2 min around the upper thigh (open symbols) (adapted from Haouzi *et al.* 1993). The first arrow indicates the cessation of exercise and cuff inflation; the second arrow indicates the moment of occlusion release. Note that in both studies, the normal ventilatory decline was depressed during cuff occlusion, resulting a large ventilatory deficit, despite expected accumulation of metabolites in the muscle circulation.

the medullary and supra-medullary structures. Although the neurophysiological basis to understand this neuronal processing is still lacking, precious information can still be obtained from what we already know on the \dot{V}_E response to exercise, as presented in the following section.

Exercise is a complex physiological condition, which combines the consequences of a motor activity with those related to an increase in metabolism. Motor activity involves the control and effects of elementary muscle contractions and movements (gate, cycling); the structures implicated in this process include specific cortical (Thornton *et al.* 1998; 2001; Williamson *et al.* 2003) or subcortical regions (Eldridge & Waldrop, 1991; Eldridge, 1994) as well as peripheral inputs related to contractions or movement (Kniffki *et al.* 1978; Mense, 1992; Kaufman *et al.* 2002). The metabolic changes can trigger many different inputs: (1) an increase in CO_2 venous content and venous blood flow (Greco *et al.* 1978; Bennett *et al.* 1984) and a decrease in the mixed venous O_2 content which could in turn affect the arterial chemoreceptors (Phillipson *et al.* 1981); (2) a change in the chemical composition in the muscles (Mense & Stahnke, 1983; Kaufman & Rybicki, 1987) affecting muscle afferents; (3) an increase in local and systemic temperature (Dejours *et al.* 1958; Budzinska, 1975; Hertel *et al.* 1976); and (4) an increase in systemic and muscle blood flow potentially stimulating receptors located in the central (Jones *et al.* 1982; Huszczuk *et al.* 1983) as well as peripheral circulation (Haouzi, 2009), while blood flow decreases in many non-exercising tissues. Despite the fact that all of these inputs, with their different magnitude and time constants, can ‘reach’ the CNS in an almost

infinite number of combinations and can all increase breathing separately, the ventilatory response to exercise seems to follow the metabolism in a rather simple and perfectly predictive manner (Whipp, 1978; Whipp *et al.* 1982). The strategy used by the ‘respiratory neurons’ seems to rely on properties that have more to do with the selection of information and pattern recognition than to the integration of individual inputs. In other words, all of the signals produced by exercise are not *qualitatively* important in translating into an increase in breathing. According to this view, the CNS does not respond in proportion to (or as a function of) a given stimulus, which could be predicted by, for instance, the elementary \dot{V}_E response to CO_2 , hypoxia, a muscle contraction or a change in blood flow. The respiratory control system seems to use all of the various sources of information to determine that an exercise is actually being performed and to select the most relevant sources of information for adjusting breathing (see Fig. 2). Tracking the change in peripheral gas exchange, via the change in circulation, may well be part of this strategy. This is, after all, what the response to ‘sinusoidal’ or ‘impulse’ exercise reveals (Whipp, 1981; Haouzi, 2006). Similarly, when there are antagonist sources of information, such as dissociating venous return to the lungs from the arterial supply, the strategy adopted by the CNS always seems to follow factors associated with an increase in the local vascular response, as if it were the only relevant information for controlling breathing related to exercise (for discussion see Haouzi, 2006). By contrast, the respiratory control system may not be able to recognize that an exercise is being performed when different conditions are created, such as in patients with peripheral vascular disease (Haouzi *et al.* 1997) or, even more dramatically, during a cardiac arrest, resulting in a completely novel and unpredictable \dot{V}_E response (Haouzi *et al.* 2012). With such a view, the matching between \dot{V}_A and pulmonary gas exchange cannot be predicted by any signal considered individually (Haouzi *et al.* 2012)

Finally, the debate over the fact that it is \dot{V}_A and not \dot{V}_E that appears to be regulated while it is \dot{V}_E which is generated could be understood by the constraint imposed on the respiratory system by the ‘non-proportional’ relationship between the amplitude and the duration of any breath (Haouzi *et al.* 2007; Haouzi & Bell, 2009; Haouzi, 2011). Indeed, it is the change in dead space ventilation (\dot{V}_D) and not in dead space (V_D) that can disrupt blood gas during exercise; we have recently proposed that there is an obligatory relationship between the amplitude and duration of any breath – this relationship is not proportional but has a positive intercept of the magnitude of V_D , which results in an apparent regulation of \dot{V}_A (Haouzi *et al.* 2007; Haouzi & Bell, 2009) whatever the level of breathing frequency is adopted. Following such relationship, while it is minute

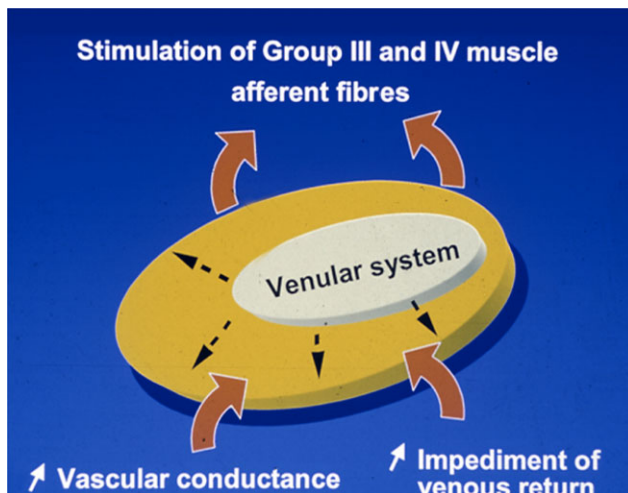


Figure 6. Schematic representation of the ‘vascular hypothesis’ presented in this review

Any event distending the venular system (venous occlusion, hyperemia or mechanical deformation of the receptive field in keeping with volume of blood present) can in turn stimulate group III and IV endings.

ventilation (the product of a tidal volume by the breathing frequency) that is 'generated' by the medullary and spinal respiratory moto-neurons (Mitchell, 1990a), it is V_A that is being regulated.

Concluding remarks

The view presented in this paper is that the volume of blood at the venular level in the muscles could constitute a crucial stimulus informing the CNS that metabolism is changing in peripheral tissue. The CNS produces a ventilatory output that follows the levels of gas exchange but which, intriguingly, appears to neglect other signals, at least in terms of their kinetics. The matching between alveolar ventilation and pulmonary gas exchange observed during exercise may result from a complex process in which the ventilatory strategy chosen by the CNS is determined by (1) the magnitude and kinetics of the vascular response in the muscles; (2) all other inputs produced by exercise, related or not to gas exchange or to one of its circulatory surrogates, which inform the respiratory neurons that an exercise is being performed (see Fig. 2); and (3) the fundamental relationship between the amplitude and the duration of any breath, which results in a regulation of alveolar rather than minute ventilation.

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Additional information

Competing interests

None.