Case study 22.2 Control and co-ordination of respiration and circulation during exercise in mammals

In humans, ventilation, and cardiac output, increase in direct proportion to workload during mild and moderate exercise so that partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and pH in arterial blood remain more or less constant.

At the onset of moderate exercise, an immediate increase in minute ventilation volume ($\dot{V}_E$) (phase I) is followed by a progressive increase for a few minutes (phase II) before it reaches a plateau (phase III). This pattern is shown in Figure A. How are these responses initiated and controlled?

The conventional views concerning the initiation of this response, plus increases in cardiac output, heart rate and blood pressure, in both humans and other species of mammals, are:

- there are outputs to the respiratory-rhythm generating network and cardiovascular-control regions of the brainstem (the central command mechanism) in parallel to the motor output to the locomotor muscles
- and/or Group III and Group IV sensory endings in the exercising limb muscles[1] are stimulated at the onset of exercise by distension of nearby venules as blood flow to the muscles increases. These sensory nerve endings send stimulatory (afferent) information to the relevant regions of the medulla in the brain stem (the afferent feedback mechanism).

These and a number of other proposed mechanisms have been studied, some in great depth, but we still lack a complete understanding of the mechanisms and there is certainly no agreement regarding their relative importance.

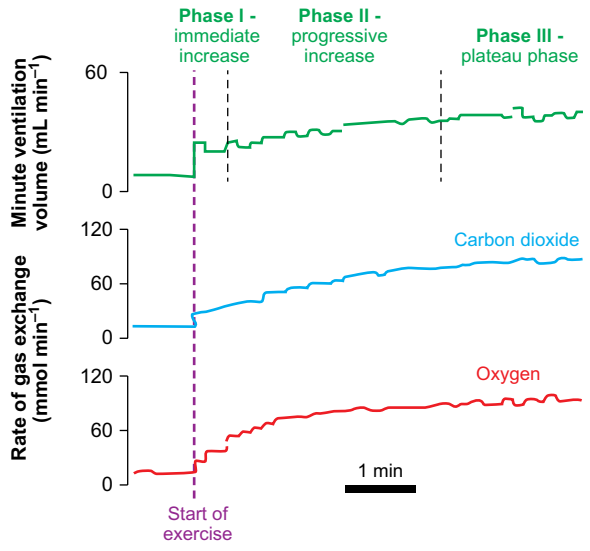

Figure A Ventilatory response to exercise in humans.
There is an immediate increase in minute ventilation volume at the onset of moderate exercise (phase I). This is followed by a progressive increase in minute ventilation volume for a few minutes (phase II) before it reaches a plateau (phase III).
Modified from: Whipp BJ and Ward SA (1982). Cardiopulmonary coupling during exercise. Journal of Experimental Biology 100, 175–193.

In support of the central command hypothesis, electrical stimulation of a region of the hypothalamus in cats shown in Figure B produces locomotor activity as well as proportional increases in ventilation and arterial blood pressure. Although the importance of central command is supported by data from several studies, the evidence for this mechanism is insufficiently strong for it to be universally accepted. Nonetheless, it has been suggested that central command is of major importance at the onset of exercise, during phase I, but that it may be augmented by afferent feedback. It has also been suggested that a group of neurons within the dorsomedial hypothalamus (DMH) may be involved in generating a common output to the cardiorespiratory system for both exercise and the defence-alerting response which we discuss in section 22.5.3.

Afferent feedback becomes more important during phase II when there is a progressive increase in $\dot{V}_E$. These mechanisms become stabilised during the subsequent plateau phase, phase III, when the animal is in a steady-state. As far as the cardiovascular system is concerned, central command seems to play a significant role during mild exercise but other mechanisms are more important during moderate and severe exercise.

The carotid bodies are not thought to be involved in the immediate ventilatory response to the onset of moderate exercise but do seem to be important in the subsequent progressive increase in ventilation in humans. Also, there is little evidence to indicate that the central chemoreceptors are particularly involved in the control of ventilation during moderate exercise in mammals. However, the data in Figure C provide evidence from humans to suggest that ventilation is closely matched to the increase in the rate of exchange of carbon dioxide ($\dot{M}CO_2$) at the lungs during phase II of moderate exercise and to $\dot{M}CO_2$ itself during phase III. The flow of CO_2 to the lungs may be monitored, but exactly how is still a mystery. In contrast to the situation in humans, there is no evidence to indicate that increased flow of CO_2 to the lungs of exercising dogs provides a direct stimulus to ventilation.

What about control of the circulatory system? Although both heart rate and blood pressure increase during exercise, the arterial baroreceptors are still involved in the regulation of blood pressure. This is possible because the set point for blood pressure regulation is increased and there is no change in sensitivity.

At rest, a high level of parasympathetic (vagal) tone acts on the heart so that the initial increase in heart rate at the beginning of exercise results from reduced parasympthatic tone, most likely as a result of central command, as discussed above. As the intensity of exercise increases, the associated increase in heart rate results from a further reduction in parasympathetic activity and increased sympathetic activity. Despite the clear involvement of the autonomic nervous system in controlling the heart during exercise in vertebrates, denervation of the heart of dogs does not decrease their capacity for exercise. This lack of a reduction in capacity is partly the result of an increased concentration of circulating catecholamines; when the action of circulating catecholamines is blocked by administration of β-adrenoceptor antagonists, the exercise capacity of the dogs is reduced.

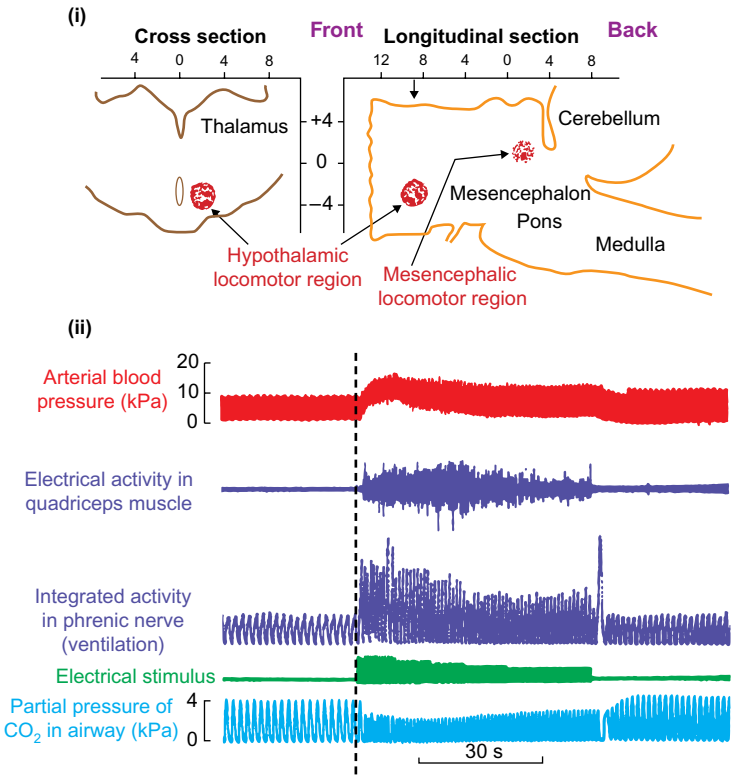

Figure B Locomotor regions of the brain of mammals and the effect of their electrical stimulation on ventilation and blood pressure.

(i) Location of the hypothalamic and mesencephalic locomotor regions in the brain of the domestic cat. Co-ordinates are in mm.

(ii) Effect of electrical stimulation of the hypothalamic locomotor region in an anaesthetised cat on arterial blood pressure and ventilation, as indicated by activity in the phrenic nerve, which innervates the diaphragm. The vertical dashed line indicates when blood pressure and ventilation increase. These occur slightly before the onset of contraction of the locomotory muscles, as indicated by electrical activity in the quadriceps muscle. The reduction in partial pressure of CO_2 in expired gas upon electrical stimulation of the hypothalamus indicates overventilaton

Reproduced from: Eldridge FL et al (1985). Stimulation by central command of locomotion, respiration and circulation during exercise. Respiration Physiology 59, 313-337. Eldridge FL and Waldrop TG (1991). Neural control of breathing during exercise. In: Exercise Pulmonary Physiology and Pathophysiology. Eds Whipp BJ and Wasserman K pp 309-369. Marcel Dekker, Inc, N York.

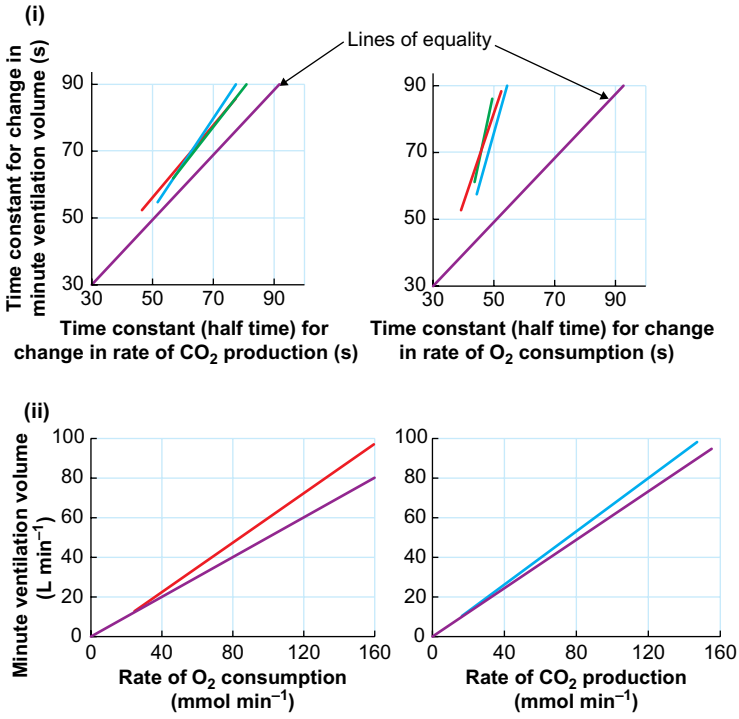

Figure C Role of CO_2 in control of ventilation during phases II and III of exercise in humans.

(i) During phase II, ventilatory kinetics ($\dot{V}_E$) are slower than the kinetics for the rate of CO_2 release ($\dot{M}CO_2$) and $\dot{M}O_2$ but there is a closer relationship between the time constants for minute ventilation volume ($\dot{V}_E$) and $\dot{M}CO_2$ than between those for $\dot{V}_E$ and $\dot{M}O_2$.
Red line is transition from rest to constant work rate on a cycle; blue line is transition from work rate of 25 W to the onset of lactic acid accumulation (anaerobic threshold – discussed in Chapter 15) while pedalling at a constant rate; green line is transition from work rate of 25 W to anaerobic threshold at increasing rate of pedalling.

(ii) During the steady-state conditions of phase III, the ventilatory response to exercise is linearly related to $\dot{M}CO_2$ and $\dot{M}O_2$ until high levels of work are reached but there is less variability when the ventilatory response is related to $\dot{M}CO_2$ (blue line) than when it is related to $\dot{M}O_2$ (red line). This variability is not shown. Purple lines are lines of equality

Based on data from: Wasserman K et al (2011). Respiratory Control During Exercise. In Comprehensive Physiology, R Terjung (ed.).

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[1] Sensory nerve endings in muscles are discussed in section 17.4.4