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Adaptation of rat plantaris muscle to intensity-controlled treadmill running

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Interventions such as chronic electrical stimulation may not realistically replicate the effects of exercise on skeletal muscle. So, we used an animal model of intensity-controlled running, similar to that undertaken by humans, to investigate mechanistic changes induced by exercise.

Wistar rats (312 ± 13 g) were familiarised with running on a motorised treadmill within a metabolic chamber. Ambient air was pumped through the chamber and analysed for concentrations of oxygen and carbon dioxide (Oxymax system; Columbus Instruments, OH, USA), which were used to calculate the animal's oxygen uptake. Each animal's maximum oxygen uptake ($\dot{V}O_2$max) was measured, using an incremental exercise test, before and after the exercise intervention. Rats in the exercise group ran for 30 min at a speed and incline equivalent to 70-75% of their $\dot{V}O_2$max (preceded and followed by 5 min warm-up and cool-down), 4 days per week for 5 weeks. On the same days, control animals undertook the warm-up and cool-down exercise (10 min at a treadmill speed equivalent to 35-40% $\dot{V}O_2$max). Animals were killed 48 h after the final exercise test and their plantaris muscles harvested. Fibre type proportions were determined from myosin-ATPase stained cryosections and changes in the muscle proteome were investigated using 1-D electrophoresis and mass spectrometry (1). Data are presented as means ± SD (n = 5, per group) and significant differences were determined using Student's two-tailed independent t test.

Before the intervention the average $\dot{V}O_2$max was 40.8 ± 2.2 ml kg^{-1} min^{-1} with no significant difference between control and exercise animals. After the exercise intervention the $\dot{V}O_2$max of the trained animals (46.7 ± 0.5 ml kg^{-1} min^{-1}) had increased 11% (P = 0.008) over that of control animals (42.2 ± 2.8 ml kg^{-1} min^{-1}). Exercise did not alter muscle protein content, but there was a suggestion of a greater (25%; P = 0.22) area fraction of slow-oxidative fibres. Densitometry of gel images identified 37 protein bands; one of which (~60 kDa) was significantly reduced (37%; P = 0.056) in plantaris of exercised rats. Database searches (MASCOT; Matrix Science) of the peptide mass fingerprint identified this band as phosphoglucomutase 1, based on 25 matched queries with a MOWSE score of 177 (MOWSE score >63 being significant P<0.05). This enzyme catalyses the reversible reaction glucose 1-phosphate to glucose 6-phosphate, a decrease in the abundance of which signifies a lesser reliance on glycogen metabolism to fuel this intensity of exercise.

In conclusion, intensity-controlled running increased the animals $\dot{V}O_2$max and altered their skeletal muscle metabolism.

Hayter JR et al. (2003). Mol Cell Proteom 2, 85-95.

Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

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Effect of exercise on the expression of metabolic genes involved in glucose transport and oxidation in human skeletal muscle

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A single bout of exercise is known to improve insulin sensitivity for at least 24-48h (Mikines et al. 1988). However, the molecular modulations underlying this effect are not well characterised. The aim of this study was to investigate the effect of prior exercise on basal and insulin mediated changes in the expression of metabolic genes involved in glucose transport (glucose transporter GLUT4, calpain-10) and oxidation (pyruvate dehydrogenase kinases (PDK)-2 and -4). Muscle PDK controls the activity of the pyruvate dehydrogenase compex (PDC), the enzyme which controls the rate-limiting step in glucose oxidation (Randle 1986), whereas calpain-10 has been associated with GLUT4 mediated glucose transport (Paul et al 2003). Eight healthy male individuals (age 24 ± 2years, BMI 24 ± 1, mean ± SEM) underwent a hyperinsulinaemic (80 mU/l) euglycaemic (4.5 mmol/l) clamp for 240min 24h after 90min of one-legged cycling at moderate intensity (~60% of maximal oxygen uptake) while keeping the other leg sedentary (control leg). During the subsequent 24h recovery period, subjects consumed a normal mixed diet (55% CHO, 30% fat, 15% protein). Muscle biopsy samples (vastus lateralis) were obtained from both legs after exercise (day 1), and before and after 4h of insulin infusion (day 2) for the determination of mRNA content of the genes under investigation (normalised to alpha actin) by quantitative real-time PCR using Taqman probes, and protein expression using Western blots. Exercise decreased serum insulin concentrations (7.08 ± 0.79 vs 3.55 ± 0.42 mU/l, P<0.01, 1-way ANOVA, relevant assumptions were verified) and increased plasma FFA levels (0.27 ± 0.05 vs 0.69 ± 0.11 mmol/l, P<0.001). Neither exercise nor insulin affected the mRNA levels of GLUT4 and the diabetes-linked gene calpain-10. However, at the end of exercise, skeletal muscle PDK4 mRNA content was 1.5-fold lower in the exercise leg than the control leg (1.39 ± 0.25 vs 2.14 ± 0.36, P<0.05, 2-way ANOVA). Surprisingly, on day 2, muscle PDK4 mRNA level decreased by 2.2-fold (0.97 ± 0.17 vs 2.14 ± 0.36, P<0.05) in the control leg and was no different from the exercise leg before and after the insulin clamp. On the other hand, prior exercise increased PDK2 mRNA content in the exercise leg only (0.93 ± 0.05 vs 0.74 ± 0.04, P<0.01). However, these exercise-induced changes in PDK2 and PDK4 transcripts did not lead to changes in their mitochondrial protein expression. These results show that a single bout of exercise is associated with significant changes in key genes regulating glucose oxidation but not transport. Furthermore, the exercise-induced downregulation of PDK4 gene expression in both exercised and non-exercised skeletal muscle raises the possibility that an 'extramuscular' factor associated with improvement in insulin sensitivity might be involved in the regulation of PDK4 gene expression in human skeletal muscle.

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This work was supported by BBSRC.

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Angiogenesis in response to graded muscle overload is not due to graded VEGF signalling

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Whilst it is well known that exercise can cause angiogenesis in skeletal muscle low intensity or short duration activity does not cause widespread capillary proliferation, implying that an activation threshold must be overcome for angiogenesis to occur. *In vitro* experiments suggest that specific concentrations of growth factors are needed to produce responses consistent with angiogenesis (Xue & Greisler, 2002), but it is not clear whether these fall inside a physiological range, or if this is indeed the mechanism through which control is exerted. We therefore examined three models of angiogenesis that show a graded response in muscle overload and subsequent angiogenesis. The present study examined whether there was a graded response in vascular endothelial growth factor (VEGF), or its main functional receptor, Flk-1, as VEGF is essential for overload-induced angiogenesis (Williams et al. 2004).

Male Sprague-Dawley rats were anaesthetised with 2% fluothane in oxygen and subjected to either extirpation of the m. tibialis anterior (TA), tenotomy of the main tendon of the TA or ligotomy of the extensor retinaculum, the ligament that holds the TA in place. Animals were randomised with respect to side, and treated postoperatively with analgesics and antibiotics (Temgesic, Duplocillin). These interventions cause a reducing severity of overload of the m. extensor digitorum longus (Badr et al. 2003), which was studied at 3, 7, 14 and 28 days after surgery. Western blots of VEGF and Flk-1, with VEGF ELISA, showed no significant difference in time course or magnitude of response with the degree of overload.

These data suggest that the angiogenic response to graded levels of muscle overload is mediated by a threshold, rather than a graded increase in VEGF and Flk-1. The degree of angiogenesis observed is therefore probably controlled by interactions with other pro-angiogenic stimuli, rather than by a graded response in the primary growth factor alone.

Table 1: Densitometry data for VEGF blots

	Control	3 days	7 days	14 days	28 days
Extirpation	1 ± 0	1.42 ± 0.28	1.68 ± 0.24*	2.38 ± 0.63*	1.48 ± 0.25
Tenotomy	1 ± 0	1.35 ± 0.19	1.62 ± 0.38	2.14 ± 0.42*	1.45 ± 0.35
Ligotomy	1 ± 0	1.18 ± 0.22	1.74 ± 0.33*	1.94 ± 0.51*	1.27 ± 0.45

Data are normalised to control. Mean ± SEM. *P<0.05 vs. control (Student's t-test, n=4)

Table 2: Densitometry data for Flk-1 blots.

	Control	3 days	7 days	14 days	28 days
Extirpation	1 ± 0	1.53 ± 0.32	1.76 ± 0.31*	1.84 ± 0.43*	1.48 ± 0.28
Tenotomy	1 ± 0	1.62 ± 0.39	1.61 ± 0.41	1.91 ± 0.56*	1.44 ± 0.33
Ligotomy	1 ± 0	1.48 ± 0.20	1.59 ± 0.34	1.76 ± 0.27*	1.62 ± 0.24

Data are normalised to control. Mean ± SEM. *P<0.05 vs. control (Student's t-test, n=4)

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This work was supported by the British Heart Foundation.

Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

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The effect of recovery duration on the parameters of the power-duration relationship following exercise to exhaustion

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The tolerable duration (t) of muscular exercise in the very heavy intensity domain has been well described as a hyperbolic function of the external power (P), with an asymptote termed critical power (CP) and a curvature constant W', in units of work (intriguingly), equivalent to a constant amount of work that can be performed above CP (e.g. Poole et al. 1988). This is notionally consistent with the tolerable duration of supra-CP exercise being dependent on the 'utilisation' rate of W', with the tolerable limit being attained when this apparent 'store' is depleted. However, establishing the physiological correlate(s) of this 'store' is complicated by the difficulty in resolving the profile of W' depletion during the exercise. In order gain insight into this issue, we determined the relationship between the recovery kinetics of W' following exhausting exercise concomitantly with those of oxygen uptake ($\dot{V}O_2$) and blood [lactate], and subsequent exercise tolerance. Following ethical committee approval, 6 healthy males (24±4 yr) each performed, on separate occasions, a ramp-incremental and 4 different constant-load (CON) high-intensity exercise tests to the limit of tolerance on a computer-controlled electromagnetically-braked cycle ergometer for determination of CP, W' and $\dot{V}O_{2max}$. Subsequently, a further 3 constant-load tests were performed (REC), each at a different work rate and each preceded by a supra-CP exercise bout to the limit of tolerance (chosen to elicit fatigue in 6 min) with recovery periods of 2, 6 and 15 min at 20W. Gas exchange was measured breath-by-breath, and finger-tip blood sampled at discrete points for [lactate] analysis. Relative to CON, the REC protocols had no significant effect on $\dot{V}O_{2max}$ (CON vs REC (SD): 3.81±0.52 vs 3.71±0.47 l min^{-1}), CP (212±34 vs 213±33 W) or [lactate] at the limit of tolerance (10.11±1.02 vs 10.46±1.22 mM). The hyperbolic P-t relationship was retained in the REC studies, with CP being unchanged but W' being highly dependent on the duration of the intervening recovery phase: i.e. W' recovered to 37±5%, 65±6% and 86±4% of the CON value following 2, 6 and 15-min of recovery, respectively. The recovery kinetics of W' (interpolated $t_{1/2}$ = 234±32s) did not cohere well with those

of $\dot{V}O_2$ ($t_{1/2}$ = 74±2s) or [lactate] ($t_{1/2}$ = 1366±799s). In conclusion, the finding that the P-t relationship remained hyperbolic during REC, with no change in CP, supports the notion that the W' depletion profile 'shapes' the high-intensity exercise tolerance. Comparisons of the utilization and recovery kinetics of W' with those of the metabolic end-products may aid in clarifying not only its role as a parameter determining the tolerance for high-intensity exercise but what, physiologically, it's determinants actually are!

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Structural and functional determinants of mechanical output from human muscle

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In human locomotion the ability to generate and sustain mechanical power output is dependent on the organised variability in contractile and metabolic properties of the muscle fibres that comprise the active muscles.

In studies of human exercise we have used a microdissection technique to obtain fragments of single muscle fibres from needle biopsies before and after exercise. Each fibre fragment is divided into two parts. One part is used to characterize the fibre type in respect of the heavy chain myosin isoform expressed. The other part of the fragment is analysed for high energy phosphate concentration (Sant'Ana Pereira et al. 1996).

Fibres are classified on the basis of expressing either type I, type IIA, or type IIX myosin heavy chain isoforms. It should be noted however that in the type II population many fibres co-express both IIA and the IIX isoforms and we therefore characterize these fibres on the basis of the degree of co-expression. Moreover while there are significant numbers of fibres expressing only the IIA isoform very few fibres are seen in normal healthy subjects which express only IIX.

We were able to show that immediately following 25 s of maximal dynamic exercise, during which power output declined by ~50%, phosphocreatine (PCr) was reduced to zero, or near zero levels in all fibres. ATP was also reduced to 53-34% of resting levels in the type II fibre subgroups, and to ~75% in type I fibres, with concomitant increases in IMP (Sant'Ana Pereira et al. 1996). Subsequently we examined the time course of this dramatic depletion in high energy phosphate using shorter duration cycling exercise (~20 contractions in 10 s; Karatzaferi 2001). In these experiments maximum power ouput decreased by ~23%. Fibre fragments were classified as either type I, IIA, IIAx or IIXa (the latter two classifications of co-expressing fibres having respectively a predominance of type IIA or IIX isoform). Immediately post-exercise PCr content in the four fibre populations decreased to 54, 47, 38, and 41% of resting values. ATP showed no change in type I fibres but decreased to 75, 33, and 30% of resting values in type IIA, IIAx and IIXa fibre groups. There was no detectable IMP in the type I fibres but significant IMP production in type II fibre populations despite the presence of PCr. The results suggest that maximal all-out exercise presented a sequential metabolic challenge to first the type IIX-expressing fibres, then IIA fibres and finally the type I fibres. It is, of course entirely reasonable that during maximal activation those fibre populations with the fastest cross-bridge cycling rates, as determined by myosin heavy chain isoform expressed, will deplete high energy phosphates at the greatest rate resulting in selective fatigue of that population. Thus although the whole muscle mechanical ouput may decrease by only 25% in 20 contractions this may obscure the fact that some fibre populations may be generating very little mechanical ouput while others will be relatively unaffected. The progressive reduction of power during maximal sprint efforts may be interpreted as the cumulative effect of metabolic depletion in successive fibre type populations from IIX to IIXa to IIAx to IIA to I. One important application of the micro-dissection technique is that PCr content may be used as a very sensitive metabolic marker for fibre type recruitment during very short duration concentric, isometric and eccentric exercise (Beltman et al. 2001).

There are of course considerable difficulties in quantifying the contribution of different fibre type populations to mechanical output during whole body exercise not least because of the velocity dependence of both power and efficiency. Nevertheless the issue is of considerable interest having as it does an impact on choice of movement cadence and strategies for improving muscle function including during, e.g. functional electrical stimulation and rehabilitation therapy. In a series of experiments since 1981 we have used cycling as an experimental model and believe that there is good evidence to support the view that under normal conditions human type I fibres will be operating around their optimum for maximum power at a pedalling rate of about 60 rev/min, with type IIA fibres, and those expressing increasing proportions of IIX myosin heavy chain isoform having optima at increasing pedalling speeds, and with related optima for efficiency. It must be recognized however that the contractile and metabolic muscle fibre properties can be transformed both chronically (e.g. by electrical stimulation or training), or acutely by exercise itself, consequent upon fatigue or by changes in muscle temperature (see Sargeant, 1999; Ferguson et al. 2002).

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SA33

Muscle fibre types, mitochondrial function and age

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Muscle fibre types differ in both contractile and metabolic properties. Here we show that muscle fibre types also vary in inherent mitochondrial properties, such as coupling status (ATP/O2 or P/O), and have impact on the pace of mitochondrial and cell aging. Innovative optical and magnetic resonance spectroscopic methods applied to non-invasively measure ATP synthesis and O2 uptake revealed well-coupled mitochondria (P/O=2.3-2.5) in vivo in resting hand (first dorsal interosseus, FDI: P/O=2.7±0.1 SEM, n=10) vs. leg (tibialis anterior, TA: P/O=2.0±0.2 SEM, n=10) in adult subjects (34±4 years). These methods also revealed a significant decrease in coupling correlated with depletion of [ATP] in the FDI but not in the TA in the elderly (74±3 years). The degree of age-related uncoupling

increased with type II muscle fibre content in agreement with the higher reactive oxygen species production in this cell type. This variation in mitochondrial coupling with age and muscle fibre type points to intrinsic cellular factors as critical to mitochondrial function and to the tempo of mitochondrial aging in human muscle.

Thanks go to Lori Arakaki, Wayne Ciesielski, Martin J. Kushmerick, David Niles, and Ken A. Schenkman for their contributions. This work was supported by US National Institutes of Health R01 grants AR 41928, AR 45184, and AR 36281, as well as training grant AG00057.

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Oxygen exchange: muscle-vascular-pulmonary coupling

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During exercise in young, healthy individuals cardinal features of the pulmonary oxygen uptake response (primary component time constant [Grassi et al., 1996], slow component [Poole et al., 1991]) reflect closely events within the exercising muscles. It is tenable therefore that the age-associated slowing of oxygen uptake kinetics (Bell et al., 1999) and also decreased maximal oxygen uptake, (McGuire et al., 2001) might result from impairments in the perfusive (oxygen delivery) and/or diffusive oxygen conductance within muscle. This presentation will examine evidence obtained through investigations in animals for ageing: 1. redistributing exercising oxygen delivery away from highly oxidative muscles and muscle fibers, 2. altering muscle capillary hemodynamics, and 3. reducing the oxygen pressure head within the microcirculation that serves to facilitate blood-muscle oxygen transfer. In many respects, these alterations found in healthy ageing bear a striking resemblance to those present in chronic diseases (diabetes, chronic heart failure) and may help explain the compromised exercise tolerance present in aged individuals. Putative mechanistic insights will be explored within the context of current knowledge and future investigative approaches.

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Supported by: National Institutes of Health grants, HL-50306 and AG-19228.

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SA35

Physiological mechanisms dissociating pulmonary CO_2 and O_2 exchange dynamics during exercise

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There is no convincing evidence that metabolic CO_2 production rate (QCO_2) during muscular exercise of moderate intensity is directly controlled: its rate of change, rather, reflects the influence of the controlled rates of O_2 consumption (QO_2) and the substrate mixture being catabolised. Its response to exercise of moderate intensity (i.e. below the lactate threshold, θ_L) is therefore mono-exponential with a time constant (τ) similar to that for QO_2. Following a delay that incorporates the muscle-lung vascular transit time, the change in QCO_2 is expressed at the lungs (VCO_2) with an appreciably-longer τ (e.g. Whipp, 1987) as a result of the influence of the intervening high-capacitance CO_2 stores: (a) a transient alkalosis caused by proton trapping during phosphocreatine hydrolysis and (b) increased muscle tissue and muscle-venous PCO_2 and bicarbonate concentration ($[HCO_3^-]$). This capacitative effect results in a transient decrease of the respiratory exchange ratio (R) which, with very rapid work-rate incrementation and/or prior CO_2-stores depletion (by volitional or anticipatory hyperventilation) can yield a false positive non-invasive estimation of θ_L ('pseudo-threshold') (e.g. Ozcelik *et al.*, 1999).

Above θ_L, the components of the VCO_2 kinetics are far more complex, reflecting: (a) the translation of the non-linear pulmonary O_2 uptake (VO_2) slow component (e.g. Whipp, 1987) into a corresponding VCO_2 reponse; (b) production of supplemental CO_2 from the *rate* (rather than the *amount*) at which muscle and blood $[HCO_3^-]$ decrease consequent to buffering of the H^+ associated with the [lactate] increase (the amount of CO_2 evolved from these buffering reactions is more than double that of the equivalent aerobic yield); and (c) the time course of the compensatory hyperventilation for the metabolic acidaemia.

For heavy-intensity exercise (i.e. the work-rate range within which arterial [lactate] and $[H^+]$ can be stabilized at constant, although elevated, levels), VCO_2 kinetics often evidence an overshoot before subsequently stabilising (Ozyener *et al.*, 2002). This early overshoot reflects the influence of the rapid phase of the stores wash-out of CO_2 consequent to a rapidly-falling $[HCO_3^-]$, but with little or no early recruitment of compensatory hyperventilation. Despite augmented peripheral chemoreceptor stimulation of ventilation (V_E) at these work rates (from increased $[H^+]$ and $[K^+]$, for example), $PaCO_2$ is typically slightly elevated (e.g. 3-4 mm Hg) during the initial on-transient phase, suggesting that the kinetics of respiratory compensation for the acidosis are long, relative to those of peripheral chemoreceptor responsiveness (Rausch *et al.*, 1991).

At higher work rates (for which arterial [lactate] and $[H^+]$ increase throughout the exercise to the limit of tolerance), VCO_2 kinetics have been shown to revert to a mono-exponential-like form (Casaburi *et al.*, 1989; Ozyener *et al.*, 2002), but are slower than for sub-θ_L exercise. Interestingly, no VCO_2 'slow phase' is evident, despite this being clearly discernible in VO_2. This apparent steady state-like behaviour of VCO_2 at these intensities is

associated with the offsetting effects of a slowing of the rate of $[HCO_3^-]$ decrease and the progressive hyperventilatory decline in $PaCO_2$.

In conclusion, therefore, VCO_2 kinetics are not consistently mono-exponential above the lactate threshold, but even when so, they should not be considered reflective of simple-compartment dynamics. Rather, the profile of VCO_2 conflates the influences of the differing rates of HCO_3^- breakdown and degrees of compensatory hyperventilation with that of the underlying aerobic component.

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Ventilatory control: constraints and limitations

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The characteristics of the exercise hyperpnoea in humans are generally agreed upon. During moderate-intensity exercise (i.e. below the lactate threshold, θ_L), ventilation (V_E) correlates closely with pulmonary CO_2 output (VCO_2) resulting in stability of arterial PCO_2, PO_2 and pH. Thus, following an initial short 'cardiodynamic' (or phase 1) component, V_E increases with mono-exponential (or first-order) kinetics (phase 2) to the new steady state. However, at work rates associated with a metabolic acidaemia (i.e. above θ_L), V_E response kinetics become nonlinear and steady states may be unattainable. The development of respiratory compensation causes V_E to increase out of proportion to VCO_2, with the ensuing hypocapnia constraining the fall of arterial pH.

Ventilatory control models have traditionally included proportional feedback (central medullary and peripheral carotid chemosensory) and feedforward (central and/or peripheral neurogenic) elements (e.g. Waldrop *et al.* 1996). However, the precise details of the control process remain unresolved, reflecting technical and interpretational challenges associated with isolating putative control mechanisms in intact humans, and also the challenges to linear control systems theory presented by multiple-input integration (reflective, in part, of the ventilatory and gas-exchange complexities encountered within supra-θ_L exercise intensities). The rapid V_E increase at exercise onset has been argued to be neurally mediated via muscle reflexogenic drives and/or 'central command' (e.g. Waldrop *et al.* 1996). More recently, cardio-circulatory mechanisms influenced by alterations in central circulatory pressures and intramuscular vascular tissue pressure and/or conductance have also been advocated (Haouzi *et al.* 2004). Control of V_E in phase 2 has traditionally been ascribed to chemosensory mechanisms, argued to provide a 'fine tuning' for arterial blood-gas and acid-base regulation. The carotid body chemoreceptors have been shown to exert an important modulating influence on the phase 2 V_E kinetics in humans, interestingly (from a control perspective) with maintained exponentiality of response. Some investigators, however, favour central neural mechanisms of short-term potentiation in phase 2 (e.g. Waldrop *et al.* 1996). The extent to which the central chemoreceptors are involved in the control process is uncertain, as cerebrospinal pH during moderate exercise is reported to remain reasonably stable. Above θ_L, the carotid chemoreceptors appear to be largely responsible for mediating respiratory compensation, although having surprisingly slow kinetics, with additional involvement of the central chemoreflex through a constraining influence on V_E mediated by the hypocapnia.

Interestingly, the ventilatory control process during exercise behaves as if it has appreciable redundancy, with selective inactivation of any one of several putative mechanisms seeming to have little impact on the magnitude of the exercise hyperpnoea. Such observations have fuelled the formulation of innovative control schemes that reflect both spatial interactions and temporal interactions, such as (a) optimisation of humoral and respiratory-mechanical ventilatory 'costs' (Poon, 1983) and (b) memory or long-term potentiation (Mitchell & Babb, 2006).

Ventilatory control can be challenged at very high work rates, as are encountered in elite endurance athletes (e.g. Dempsey *et al.* 2003). For example, the ventilatory demands to clear metabolically-produced CO_2 and to effect respiratory compensation for the metabolic acidaemia can become so great that they approach, or even exceed, the mechanical limits of the lungs and chest wall (an index of which is the maximum voluntary ventilation). In addition, the perfusion 'costs' of the high respiratory-muscle power generation can, at limiting levels, constrain perfusion of the locomotor muscles and thus predispose to earlier fatigue. Furthermore, arterial PO_2 and O_2 saturation can evidence a decrease ('exercise-induced arterial desaturation'), consequent to the compromised V_E response and to pulmonary gas exchange inefficiencies (e.g. truncating of pulmonary capillary transit times; regional ventilation-to-perfusion mismatching).

In conclusion, the challenge is therefore to discriminate between robust competing control models that not only integrate such structures within plausible physiological equivalents, but also account for both dynamic and steady-state system responses over a range of exercise intensities, recognising that respiratory system limits can over-ride the control at very high work rates.

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