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Arterial oxygenation, central motor output and exercise performance in humans

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The studies of Amann *et al.* (2006, 2007) conclude that feedback from fatiguing skeletal muscle during exercise at different F_{IO_2} reduces central motor output to the working muscles "in order to reinvent excessive development of peripheral muscle fatigue beyond a critical threshold or sensory tolerance limit" (Amann *et al.* 2006, p. 950). We suggest that their findings can be better explained by hypoxia-induced changes in central motor output acting in an anticipatory manner.

First subjects began exercise in hyperoxia (F_{IO_2} of 1.0) whilst activating less than 40% of available rectus femoris muscle fibres (Amann *et al.* 2006, Fig. 3; p. 943). If feedback from fatiguing peripheral muscles determines central motor output in order to prevent 'excessive' peripheral fatigue, then subjects should begin exercise whilst activating 100% of the available motor units in their exercising limbs. Sensory feedback from fatiguing muscles would then cause a progressive reduction in central motor output with a progressive fall in exercise performance.

Rather, the finding that athletes began exercise whilst activating less than 100% of the muscle fibres in their exercising limbs indicates the presence of a teleoanticipatory response (Ulmer, 1996) producing the usual pacing strategies that typify all forms of freely chosen exercise (Tucker *et al.* 2006*a*,*b*).

Second, power outputs during exercise at the different F_{IO_2} values were different after only 200 m (Amann *et al.* 2006, Fig. 3*B*) and rectus femoris EMG activities after only 500 m of the 5 km time trials (Fig. 3*A*). It is unlikely that these changes are due to different levels of peripheral fatigue so early in exercise. Rather it seems probable that different arterial P_{aO_2} and S_{aO_2} at different F_{IO_2} values may have influenced central motor output (Kayser *et al.* 1994) as part of an anticipatory feedforward mechanism. Indeed the authors' second study (Amann *et*

al. 2007) shows that in severe hypoxia there is a 'relatively minor involvement of peripheral fatigue in the decision to terminate exercise' (p. 400); thus this decision results from the direct effects of hypoxia on the brain.

Third, neither power output nor EMG activity fell progressively during exercise as must occur if central motor output falls in response to a progressive skeletal muscle fatigue. Instead EMG activity reached its nadir at 2.5 km ($F_{IO_2} = 1.0 \text{and} 0.28$), 4.0 km ($F_{IO_2} = 0.21$) and at 3.5 km ($F_{IO_2} = 0.15$) before rising.

Fourth, subjects showed an 'endspurt' in which power output especially (Amann *et al.* 2006, Fig. 3*B*) and EMG activity (Fig. 3*A*) increased at the end of exercise. As a result higher power outputs were achieved at the end of exercise at F_{IO_2} values of 1.0 and 0.28 than at the beginning. This 'endspurt' disproves the authors' main conclusion that central motor output is regulated principally by feedback from the fatiguing skeletal muscles. For a system acting purely in response to sensory feedback could not allow an 'endspurt' as it could not forecast the extent of the fatigue at the finish of the 'endspurt'. Regulation of this kind requires anticipatory feedforward control by a complex, intelligent system (Tucker *et al.* 2006*c*).

Furthermore, if peripheral fatigue determines central motor output then for an 'endspurt' to occur, peripheral skeletal muscle fatigue must have disappeared at the end of exercise at least at F_{IO_2} values of 0.28 and 0.21 (Amann *et al.* 2006, Fig. 3) as power output and EMG activity in those conditions were either higher than or similar to values measured at the start of exercise. The finding of apparently significant peripheral muscle fatigue at the end of exercise at F_{IO_2} vlaues of 0.28 and 0.21 (Fig. 4) is therefore either a measurement artifact or it disproves the authors' model.

Fifth, the extent of peripheral fatigue was the same in all conditions (Figs 4 and 6) even though EMG activity was quite different (Fig. 3*A*). This disproves the authors' hypothesis that the extent of peripheral fatigue determines central motor output. Indeed our Fig. 1*A* shows that the extent of peripheral fatigue was unrelated to arterial oxygen saturation (S_{pO_2})(data from Amann *et al.* 2006, Fig. 6) whereas the change in EMG activity (data from Fig. 3*B*) was a linear function with a negative slope of the S_{pO_2}. Similarly our Fig. 1*B* shows that the change in EMG activity appeared to be an exponential function of the F_{IO_2}whereas peripheral fatigue was unrelated to the F_{IO_2}. These data might suggest that in hypoxia the extent of EMG activity is the principal determinant of the exercise performance which must be centrally regulated.

Interestingly, the cardiovascular and respiratory responses appeared to be 'submaximal' during exercise at an $F_{IO_2}$of 0.15 compared to those at higher F_{IO_2}values (Amann *et al.* 2006, Table 1). Similar findings were reported in their second study (Amann *et al.* 2007, Table 2) since exercise in severe hypoxia (F_{IO_2} of0.10)terminated at low heart rates and low blood lactate concentrations and ratings of perceived exertion (RPE).

If peripheral fatigue is the 'protected' variable during exercise in hypoxia, then the cardiorespiratory response must be maximal in hypoxia in order to limit skeletal muscle hypoxia (Noakes *et al.* 2004). This finding is not predicted by the authors' model but can be explained if the state of cerebral oxygenation is the 'protected' variable in more severe hypoxia (Noakes & St Clair Gibson, 2004; Noakes *et al.* 2005; St Clair Gibson & Noakes, 2004; Noakes, 2007).

Sixth, the authors assume that electrical stimulation after exercise can accurately measure the extent to which 'peripheral fatigue' developed during exercise. Kabitz *et al.* (2007) have reported that electrically stimulated diaphragmatic force output increased progressively during exercise but fell immediately exercise terminated. The authors concluded that

diaphragmatic fatigue develops after, not during, exercise so that 'the conventional understanding of fatigue might be flawed because it does not distinguish between the sensation itself and the physical expression of that sensation (Noakes *et al.* 2005)'. If the neural regulation of skeletal muscle during and after exercise is similar to that of diaphragmatic muscle, then electrical stimulation after exercise may produce findings that are the opposite of what happens during exercise.

In summary, the first paper of Amann *et al.* (2006) proves that there is an important anticipatory feedforward component to exercise regulation that their model cannot explain. Especially the presence of the endspurt indicates that the control mechanism must be able to predict in advance what will be the level of peripheral fatigue after the endspurt.

In their second paper, Amann *et al.* (2007) used a different exercise model in which the exercising work rate was imposed by the experimenters. As a result the only behavioural choice available to the subjects was the decision when to terminate exercise. It is not clear what information subjects received about the nature of the study since in one experiment 'arterial hypoxaemia was rapidly removed by surreptitiously switching to an F_{IO_2} of 0.30 (hyperoxygenation)' (p 392). The information provided to subjects before exercise has an important influence on the anticipatory, feedforward component of the central motor output since it influences the initial calculation of the expected exercise duration (Ansley *et al.* 2004). Furthermore different brain mechanisms might determine the pacing strategy during self-paced exercise (as in the authors' first study) and the decision when to terminate exercise when the workload is controlled by the experimenter (as in their second study). Thus the two experimental protocols probably investigate different aspects of central motor control.

The authors clearly establish that the decision to terminate exercise in severe hypoxia (F_{IO_2} of 0.10) occurs before peripheral fatigue reaches a critical or 'threshold' value. Rather

exercise in severe hypoxia terminated when the heart rate, capillary lactate concentration and the rating of perceived exertion (RPE) were all submaximal. Thus the authors concluded that there was a 'relatively minor involvement of peripheral fatigue in the decision to terminate exercise in severe hypoxia' (p. 400). Instead the timing of this decision 'indicates the existence of a hypoxia-sensitive source of inhibition of central motor drive outside the contracting muscles' (p. 400). This conclusion is not new (Kayser *et al.* 1994; Noakes *et al.* 2001; Noakes & St Clair Gibson, 2004) but will hopefully end the debate of whether it is the brain (as a result of a reduced central motor command to the exercising limbs) (Noakes *et al.* 2004) or the heart (through a limiting cardiac output) (Wagner, 2000) that causes the termination of exercise in more severe hypoxia (Noakes, 2007).

In contrast, the authors concluded that the decision to terminate exercise in less severe hypoxia occurred as the result of 'a reduction of central motor output in order to prevent further development of peripheral fatigue beyond a critical threshold' (p. 400). But this conclusion is dependant on their incomplete interpretation of their first study. We suggest that much more work is required to prove that the prevention of a critical threshold level of peripheral fatigue is the sole protected variable during exercise since many other possibilities exist (Lambert *et al.* 2005; St Clair Gibson & Noakes, 2004). Importantly whilst the avoidance of a critical level of peripheral fatigue may be a protected variable, peripheral fatigue cannot be the direct cause of the impaired exercise performance. For the presence of skeletal muscle motor unit reserve in the exercising limbs at the point of voluntary fatigue indicates that central motor command could have been increased further to allow the exercise to continue (Noakes & St Clair Gibson, 2004).

Finally, the authors' second study (Amann *et al.* 2007) found that the RPE at the end of the initial exercise bout prior to the introduction of hyperoxia was maximal in exercise at F_{IO_2}

values of 0.21 and 0.15 but not at an F_{IO_2} of 0.10 (Table 2). Furthermore only exercise at the lowest F_{IO_2} was substantially increased by the introduction of hyperoxia at the point of initial fatigue (Table 2). This suggests that a subsequent intervention will reverse 'fatigue' only when the RPE is submaximal.

Since the rate at which the RPE rises during exercise is set in anticipation (Noakes, 2004; Joseph *et al.* 2007; Eston *et al.* 2007) this suggests the following: (i) that the decision when to terminate a progressive maximal exercise test, made early in the exercise bout, is not influenced to any great extent by F_{IO_2} values of 0.21 and 0.15 but that (ii) during exercise at the lowest F_{IO_2}, the brain calculated that the originally anticipated exercise duration was no longer achievable so that the exercise must be terminated before the maximal RPE is achieved. In contrast the unexpected imposition of an altered environment (for example the addition of heat) during self-paced exercise causes the work rate at the same RPE to be reduced almost immediately so that the total work performed during the exercise bout is reduced (Tucker *et al.* 2004, 2006*c*). It seems clear that an understanding of how the RPE is regulated is essential to any understanding of how and when the brain decides to terminate the exercise bout.

In summary, we propose that the exceptional data of Amann *et al.* (2006, 2007) are more logically interpreted as evidence that the central nervous system regulates exercise performance in an anticipatory manner in order to prevent a catastrophic disruption of homeostasis not just in the exercising skeletal muscles (as their model predicts for conditions of mild and moderate hypoxia) or the brain (in severe hypoxia) but in all bodily organs under all environmental conditions (Tucker *et al.* 2006*c*). It is perhaps premature to conclude that peripheral fatigue is the only 'regulated variable' especially during self-paced exercise in which the presence of an endspurt indicates a far more complex control mechanism than can be explained purely on the basis of peripheral sensory feedback.

Furthermore the model must be able to explain why the RPE is always maximal when exercise terminates (Table 1 in Amann *et al.* (2006); Table 3 in Amann *et al.* (2007)). Since the RPE rises as a linear function of the exercise duration (Noakes, 2004; Eston *et al.* 2007; Joseph *et al.* 2007) and is therefore set from the onset of exercise, this outcome cannot be the result solely of feedback from a developing peripheral fatigue. Rather there must be an anticipatory component to this feedforward control.

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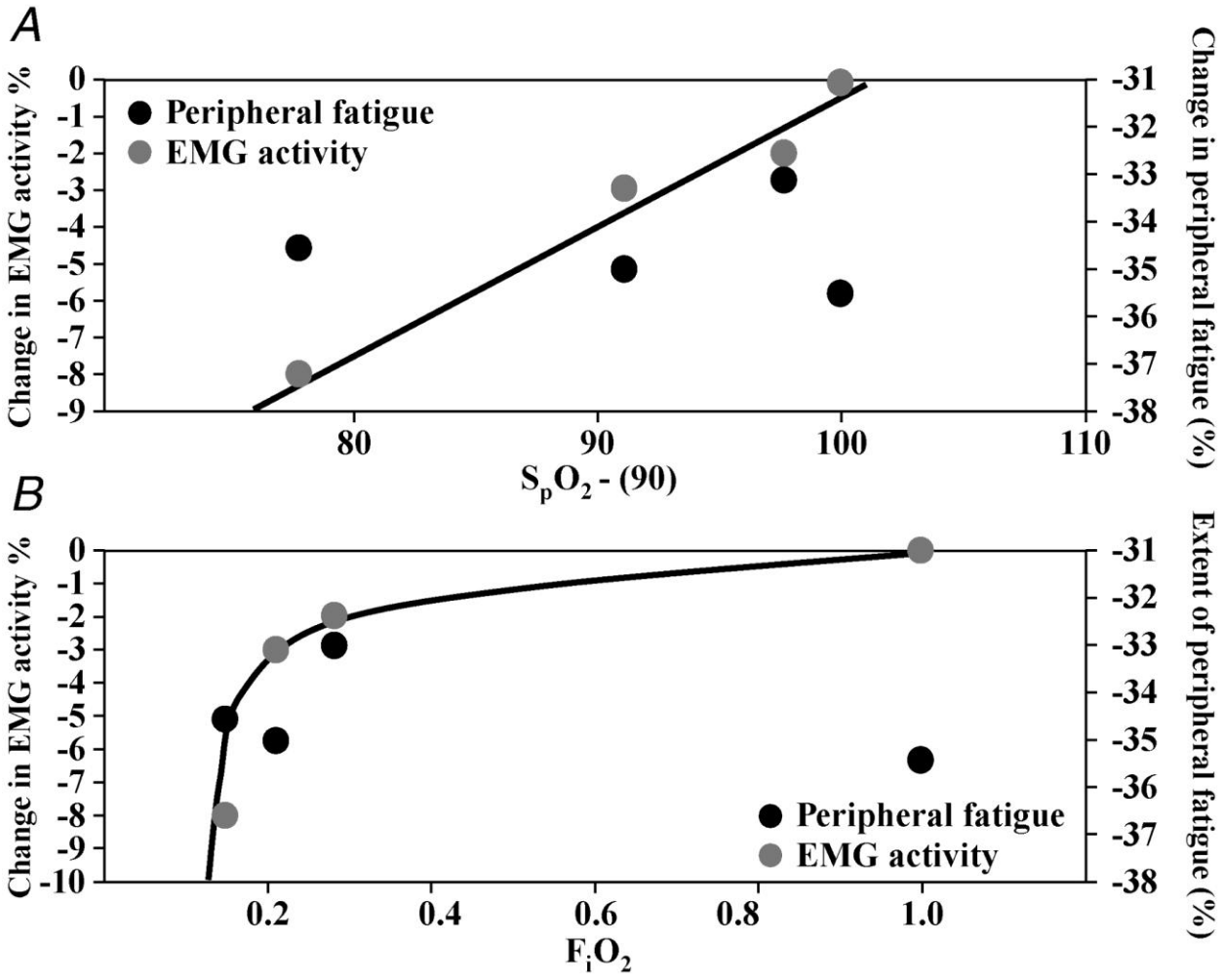

Figure 1

A, changes in peripheral fatigue and in EMG activity with changes in S_{pO2}. Note that whereas there is no relationship between S_{pO2} and the extent to which peripheral fatigue developed, there was a linear relationship with a negative slope between change in EMG activity and S_{pO2}. *B*, changes in peripheral fatigue and in EMG activity with changes in F_{IO2}. Note that whereas there is no relationship between F_{IO2} and the extent to which peripheral fatigue developed, there appears to be an exponential

relationship between change in EMG activity and F_{IO2}. These relationships suggest that the impaired performance measured during exercise at reduced F_{IO2} is due to changes in central motor command and EMG activity rather than in increased levels of ‘peripheral fatigue’ in line with the authors' conclusions. However we argue that changes in central motor command act through a feedforward (anticipatory) control rather than in response to increasing ‘peripheral fatigue’.