

EXERCISE-INDUCED RESPIRATORY MUSCLE WORK: EFFECTS ON BLOOD FLOW, FATIGUE AND PERFORMANCE

J.A. Dempsey, J.D. Miller, L. Romer, M. Amann and C.A. Smith. John Rankin

Laboratory of Pulmonary Medicine, University of Wisconsin – Madison.

In healthy subjects heavy intensity endurance exercise places substantial demands on the respiratory muscles as breathing frequency, ventilation and the work of breathing rise over time. In the highly trained subject working at high absolute work rates the ventilatory demand often causes varying degrees of expiratory flow limitation, sometimes accompanied by lung hyperinflation and therefore increased elastic work of breathing. Time-dependant increases in effort perceptions for both dyspnea and limb discomfort accompany these increased ventilatory demands. Similar responses to endurance exercise but at much lower exercise intensities also occur in patients with COPD and CHF. Note that these responses significantly influence exercise performance times in both health and disease. This effect was demonstrated by the marked reductions in the rate of rise of effort perceptions and the enhanced exercise performance times elicited by unloading the respiratory muscles using pressure support ventilation or proportional assist mechanical ventilation. In healthy fit subjects, unloading the inspiratory work of breathing by about one half, increased performance by an average of 14% (2) and in CHF and COPD patients, performance time more than doubled with respiratory muscle unloading (6). Why are effort perceptions of limb discomfort markedly reduced and exercise performance increased when the respiratory muscles are unloaded? Our hypothesis is shown in Figure 1.

We propose that this effect of respiratory muscle work and intrathoracic pressure development on performance and effort perception begins with the substantial amount of work and metabolic cost incurred by the respiratory muscles during sustained high intensity exercise. Thus, 10 – 15% of the total $\dot{V}O_2$ and cardiac output are estimated to be directed to the respiratory muscles in near maximum exercise (see Reference #1 for review). The substantial force development and high velocity of shortening required during prolonged exercise, combined with the need to compete with limb muscles for the available cardiac output, causes significant diaphragm and expiratory muscle fatigue during heavy intensity exercise. The exercise-induced diaphragm fatigue is prevented by unloading the respiratory muscles via mechanical ventilation.

The major consequences of this respiratory muscle fatigue are cardiovascular in nature. Recordings of electrical activity from metaboreflex receptors in the diaphragm in anesthetized rats show increased activity when the diaphragm is fatigued (via phrenic nerve stimulation) (3). Furthermore, measurements of muscle sympathetic nerve activity

and vascular conductance in the resting limb muscle and blood flow and vascular conductance in exercising humans and dogs (1) show that a supra-spinal metabo-reflex may be activated from the diaphragm via fatiguing contractions and metabolite accumulation which cause vasoconstriction and reduced oxygen transport to the exercising limbs.

How might these reflex effects on limb blood flow affect performance? We think the critical effect here is on peripheral limb fatigue, because of the following lines of evidence. First, evidence from isolated contracting muscles shows that even very small reductions in blood flow diminish muscle force production. Secondly, in humans we used supra-maximal magnetic stimulation of the femoral nerve to quantify force output of the quadriceps before and immediately following exercise and showed that sustained high intensity exercise to exhaustion caused 35 – 40% reductions in force output. With respiratory muscle unloading during exercise (compared to control conditions at the same power output and exercise duration) this exercise-induced peripheral muscle fatigue was reduced by 30 – 35% (7). So, exercise performance and the work of breathing are, at least in part, causally linked via the effects of respiratory muscle work on peripheral fatigue. In turn this local fatigue effect is likely due to the compromised limb blood flow (see above). In addition, there are likely important feedback effects from peripheral fatigue development (of both respiratory and limb locomotor muscles) on the brain's perception of effort of both dyspnea and limb discomfort. In turn, the exacerbation of effort perception would be expected to precipitate a reduction in central motor output or so-called "central" fatigue.

In health, we emphasize that these effects of respiratory muscle work on peripheral fatigue of both respiratory and limb muscles and on performance likely only occur with high intensity sustained exercise. However there are conditions in which we would expect the work of breathing to exert an even greater effect on peripheral fatigue and exercise performance. For example, when healthy subjects exercise in the hypoxia of high altitudes there are marked effects on the work of breathing and on diaphragm fatigue. When the respiratory muscles were unloaded in these conditions (using mechanical ventilation), limb fatigue was reduced to a much greater extent than when unloading was carried out during exercise of similar intensity and duration in a normoxic environment (Amann, unpublished data). Although not directly tested as yet, indirect evidence to date also suggests that the work of breathing during even sub-maximal exercise would be a major determinant of limb blood flow, peripheral muscle fatigue and therefore exercise performance in patients with COPD and CHF (9). These patients have the combined problem of a relatively low oxidative capacity of their limb locomotor muscles, together with hyperventilation and high levels of ventilatory work and expiratory flow limitation during exercise. In addition to these extra loads on the respiratory muscles, CHF patients have a limited cardiac output which would compromise blood flow to the diaphragm and possibly elicit respiratory muscle fatigue even during submaximal exercise.

Finally, it is important to emphasize that in addition to the influence of the work, metabolic and blood flow requirements of the respiratory muscles during exercise there

are also cardiovascular effects resulting from large swings in intra-thoracic pressure that commonly occur in heavy exercise. Using continuous vascular flow probe measurements of cardiac output and limb blood flow in the exercising dog, we have recently observed that the normal negative intra-pleural pressure generated during inspiration is a significant determinant of stroke volume and cardiac output. That is, reducing these negative pressure swings during inspiration (using pressure support ventilation) was shown to *reduce* stroke volume in a healthy animal during mild intensity exercise, but *increased* stroke volume in the animal with CHF (4). This sharp contrast between healthy and CHF animals reflects the importance of intra-thoracic pressures on ventricular pre-load in health and on ventricular after-load in CHF. On the other hand, when intrathoracic pressure on *expiration* is experimentally increased in order to minimize the effects of expiratory flow limitation during exercise, the stroke volume and cardiac output are reduced in both CHF and COPD (5). These cardiovascular effects of inspiratory and expiratory intrathoracic pressure in the exercising dog have also been reported in healthy humans during exercise (9, 1).

In summary, it is important to emphasize that, in health, over a wide range of exercise intensities the ventilatory responses are highly efficient, vitally important to homeostasis of systemic gas transport and contribute little to the limitation of exercise performance. However, in high intensity, sustained exercise in normoxia and in hypoxic environments in health, or in COPD and CHF patients during even submaximal exercise, the cardiovascular effects of the ventilatory response are substantial. Under these conditions, the work and metabolic requirements of the respiratory muscles and the exaggerated intra-thoracic pressures on inspiration and expiration now become significant determinants of cardiac output, limb blood flow, peripheral and central fatigue and ultimately exercise performance.

Supported by NHLBI and the American Heart Association.

References

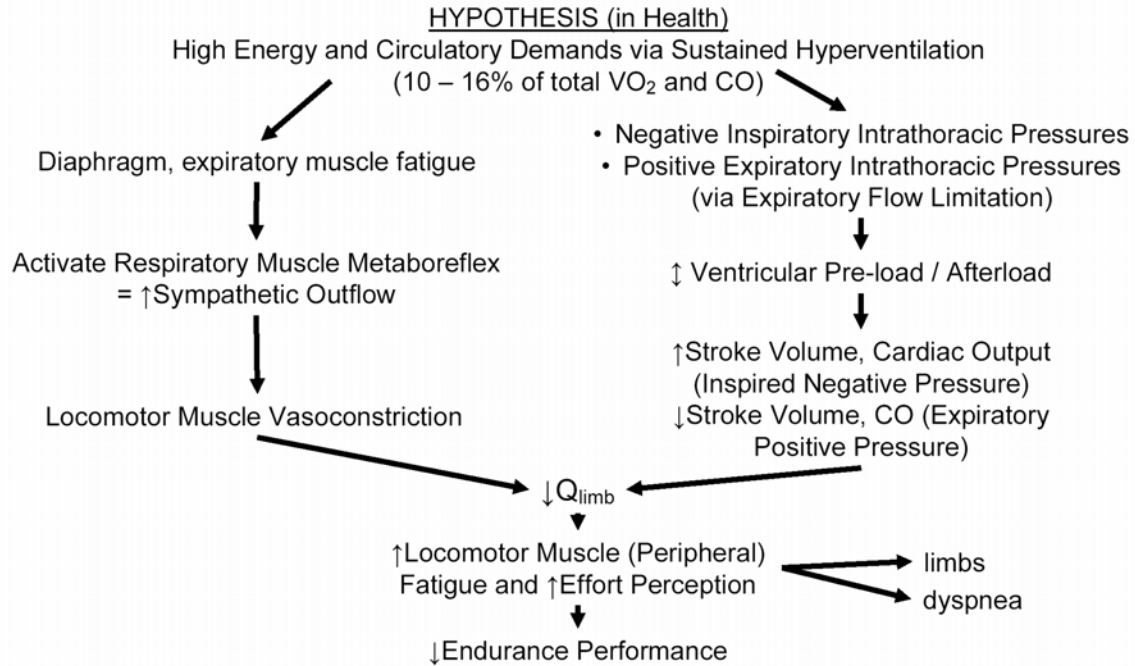
1. J.A. Dempsey, L. Romer, J. Rodman, J. Miller and C. Smith, Consequences of exercise-induced respiratory muscle work, *Respiratory Physiology and Neurobiology*. **151** (2006), pp. 242-250.
2. C.A. Harms, T.J. Wetter, C.M. St Croix, D.F. Pegelow and J.A. Dempsey, Effects of respiratory muscle work on exercise performance, *J. Appl. Physiol.* **89** (2000), pp. 131–138.
3. J.M. Hill, Discharge of group IV phrenic afferent fibers increases during diaphragmatic fatigue., *Brain Res.* **856** (2000), pp. 240–244.
4. J.D. Miller, C.A. Smith, S.J. Hemaure, and J.A. Dempsey, The effects of inspiratory intrathoracic pressure production on the cardiovascular response to submaximal exercise in health and chronic heart failure, *AJP: Heart*, (2006; in press).
5. J.D. Miller, S.J. Hemaure, C.A. Smith, M.K. Stickland and J.A. Dempsey, Expiratory threshold loading impairs cardiovascular function in health and chronic heart failure during submaximal exercise, *J Appl Physiol.* **101** (2006), pp. 213-227.
6. D.E. O'Donnell, S.M. Reville and K.A. Webb, Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* **164** (2001), pp. 770–777.
7. L.M. Romer, H.C. Lovering, A.T. Haverkamp, D.F. Pegelow and J.A. Dempsey, Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans, *J. Physiol.* **271** (2006), pp. 425–439.
8. M. Simon, P. LeBlanc, J. Jobin, M. Desmeules, M.J. Sullivan and F. Maltais, Limitation of lower limb VO₂ during cycling exercise in COPD patients, *J. Appl. Physiol.* **90** (2001), pp. 1013–1019.
9. K.N. Stark-Leyva, K.C. Beck and B.D. Johnson, Influence of expiratory loading and hyperinflation on cardiac output during exercise, *J. Appl. Physiol.* **96** (2004), pp. 1920–1927.

Figure Legends

Figure 1.

Hypothesis: ventilatory requirements DURING sustained, high intensity exercise in healthy subjects leads to diaphragm fatigue and eventually to compromised limb blood flow and fatigue. In addition inspiratory and expiratory swings in intra-thoracic pressure affect ventricular function (see text). The estimate of the fraction of the cardiac output (and $\dot{V}O_2$) devoted to the respiratory muscles during exercise at peak work rate is derived from measurements of muscle blood flow via microspheres in ponies, from the oxygen cost of respiratory muscle work in humans and from the reductions in $\dot{V}O_2$ and CO observed during respiratory muscle unloading in highly fit humans at maximal exercise (see Dempsey et al., 2006 for review).

Respiratory Muscle Work And Intra Thoracic Pressure —Cardiovascular Influences During Exercise—



Relevance to Hypoxic Environments; aging; COPD, CHF