Skeletal muscle hydrogen ion concentration stimulates ventilatory drive through direct neural pathways as shown by ^{31}P MRS

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Introduction: The tight matching of ventilation to metabolism during exercise has been classically explained by a "humoral" mechanism whereby arterial chemoreceptors are stimulated by increased blood concentrations of metabolites such as lactic acid. There has been recent interest in alternative pathways given the observation that patients who are unable to produce lactic acid during exercise (McArdle's Syndrome) have a normal ventilatory response to incremental exercise. One such mechanism is the "skeletal muscle chemoreflex" whereby limb skeletal muscle interstitial fluid metabolites such as H^+ tonically stimulate Group IV spinal afferents, which in turn drive ventilation through phrenic nerve output. ^{31}P Magnetic resonance spectroscopy (MRS) has been used to non-invasively measure skeletal muscle intracellular pH (pHi) and to estimate mitochondria phosphorylation potential. This lab has previously shown a linear relation in the normal exercising human between pHi of vastus medialis and ventilation with and without partial occlusion of lower extremity venous effluent. This study aims to provide more direct evidence of an influence of exercising limb muscle pH on ventilatory drive by measuring the latter. Respiratory drive can be estimated non-invasively in the human by measuring the pressure generated at the mouth during the first 100 ms of an occluded inspiratory effort (P100). P100 has been correlated with phrenic nerve output at rest during hypercapnia, respiratory failure and with exercise. However, no study has attempted to link pHi in exercising muscle and P100 in healthy or disease states. Here we show that exercising limb skeletal muscle pHi stimulates ventilatory drive via a neural pathway in normal subjects.

Materials and Methods: Four healthy subjects performed two bouts of constant load quadriceps exercise, at 35% maximum voluntary contraction (MVC), on each of two separate days. Bilateral lower extremity blood pressure cuffs were inflated during exercise to either 45 Torr, to minimize the possible transport of chemical messengers to central neural circuits and to accentuate the local muscle chemoreflex, or 5 Torr, in a randomized order. The exercise protocol consisted of 2 minutes of baseline rest, 3 minutes of exercise, and 5 minutes of recovery. Simultaneous measurements were made of breath-by-breath expired gases, and minute ventilation. ^{31}P magnetic resonance spectra of the vastus medialis were acquired on a 3T Siemens Trio MRI scanner with a ^{31}P surface coil and a repetition rate of 2 seconds. P100's were measured on a separate day but with the identical exercise protocol as used in the MRS study. MR spectra were averaged in blocks of 7-8 scans to provide a 15 second spectral time window. pHi values for each 15 second window were calculated from the chemical shift difference (Δ) between the phosphocreatine (PCr) and inorganic phosphate (P_i) peaks: $pHi = 6.85 + \log10[(\Delta-3.56)/(5.64-\Delta)]$.

Results and Discussion: Shown in Figure 1 is an NMR spectrum acquired during exercise. The inorganic phosphate (P_i) peak, normally difficult to detect at rest, increases during exercise and is clearly visible above the noise. In contrast, a steady decline in the intensity of the phosphocretine (PCr) peak is observed. Additional signals are observed from the α, β, and γ phosphates of ATP. As shown in Figure 2, the pHi decreases steadily, from approximately 7.2 to 6.7, during exercise. Preliminary data analysis indicates that this decrease in pHi during exercise is correlated ($p = 0.13$, $R = 0.59$) with an increase in P100, as shown in Figure 3.

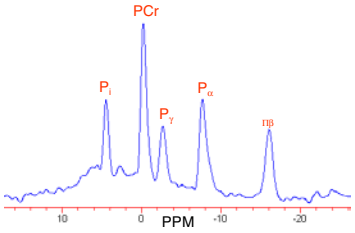

Figure 1: Representative ^{31}P NMR spectrum acquired during exercise. Average of 12 scans with a 25 Hz linebroadening.

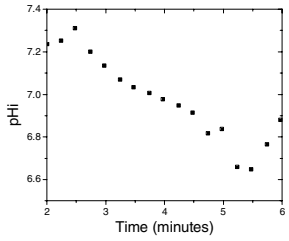

Figure 2: pHi at rest and during exercise as measured by the chemical shift difference between the PCr and Pi peaks for a representitive normal subject.

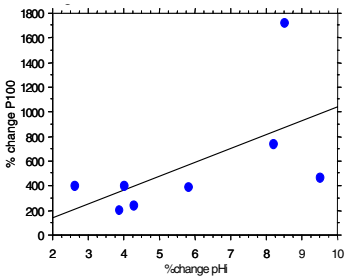

Figure 3: Percent change of the P100 versus percent change of pHi from rest to end-exercise for the 8 exercise bouts (4 patients with 2 exercise bouts/patient).

Conclusions: Respiratory drive, as measured by the change from rest to end-exercise of P100, tended to be related to vastus medialis pHi under both cuff conditions (45 and 5 Torr). Since the high pressure cuff condition should minimize any possible vascular mediated chemical signaling of ventilatory control, these data suggest that skeletal muscle hydrogen ion concentration stimulates ventilatory drive in the normal human directly through neural pathways during exercise.