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Free radical production and diaphragm function in emphysema

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Keywords

Chronic obstructive pulmonary disease, COPD, diaphragmatic contractility, oxygen free radicals

Introduction

Overproduction of free radicals can lead to impaired skeletal muscle (SM) force generation. Antioxidant defenses in SM protect against this effect. Glutathione (GSH) oxidation to GSSG is a major defense mechanism. GSH oxidation increases in acutely loaded diaphragms of the rat, but little is known about chronic loading. This paper's first hypothesis is that impaired diaphragm contractility in emphysema is accompanied by evidence of increased GSH oxidation. The second hypothesis was that training improves contractility, which results in reduced GSH oxidation at rest so that more GSH is available on exertion.

Comments

The data in this paper lend credence to the argument that excess oxidant activity in the diaphragm may lead to decreased contractility and support the contention that antioxidants may be able to improve respiratory muscle function. These data also suggest that endurance training may reverse the detrimental effects of hyperinflation. There are few studies in this area, particularly on endurance training in overinflated lungs. Although this study was performed in hamsters, antioxidants appear to increase task endurance in resistive breathing in normal hamsters (see additional information). This study supports the arguement for a trial determining the effects of antioxidants in patients with severe emphysema.

Methods

Saline or porcine pancreas elastase was administered intravenously to Syrian hamsters, which were studied 6 months after administration.

Fifteen emphysemic hamsters (EH) and 15 normal hamsters (NH) underwent treadmill training for 12 weeks (EH-Tr and NH-Tr). Seventeen of each were used as sedentary controls (EH-sed and NH-sed).

Diaphragm, soleus muscle and liver were studied for GSH, GSSG and citrate synthases (CSis- a marker of oxidant capacity). Peak twitch force (Pt) and peak tetanic force (Po) of the diaphragm were measured, as were fatigability and force-frequency characteristics.

Results

Pt and Po were reduced in EH-sed compared to NH-sed (30% and 15% respectively). Fatigability of the EH-sed was significantly higher than for the NH-sed. Training did not change Pt in NH or EH but it did increase maximum force generating capacity of the diaphragm by 15% (P <0.05). Training abolished the effect of reduced Pt in EH and had a small but beneficial effect on fatigability of the EH diaphragm. EH-sed GSSG was higher than in NH-sed but this 34% increase was not statistically significant. The mean (SD) GSSG/GSH ratio was significantly higher in the EH diaphragm (9.1 ± 0.8) than the NH (5.9 ± 0.6). Endurance training did not affect GSH or GSSG or the GSSG/GSH ratio. Neither emphysema nor training affected soleus GSH, GSSG or the ratio. Diaphragm GSH and GSSH levels were higher than in the soleus muscles for all groups. Liver GSH content was higher than in the muscles. They found an inverse correlation between GSSG/GSH and Pt, indicating that oxidant activity affected contractility (Pearson correlation coefficient -0.48, P <0.001). No correlation was significant for the GSSG/GSH ratio and Po. CS activity, a marker of oxidative capacity of the diaphragm, was unchanged in EH-sed, but it was increased by training in the EH animals (EH-sed 0.98 ± 11 vs EH-Tr 1.35 ± 0.14 P <0.05).

Discussion

In this model, increased load on the respiratory system impaired contractility and was associated with increased GSH oxidation. Although training improved the maximal force generated by the diaphragm in EH, it did not affect the GSH redox status. These results differ from those from previous work by Farkas and Roussos (see additional information), which the authors attribute to differences in experimental design. The authors conclude that emphysema with overinflation induces oxidative stress in the diaphragm, that endurance training results in improved contractile properties of the diaphragm in the emphysemic hamster and that this improvement is not accompanied by changes in GSH redox status. They hypothesize that the explanation may be explained either by increased GSH peroxidase activity in the EH diaphragm with training or by increases in diaphragm superoxide dismutase activity, both of which have been shown by other groups. This would suggest that the diaphragm, after training, is better equipped to sustain increased generation of oxidants such as that imposed with acute exertion.

Additional information

Travaline JM, Sudarshan S, Roy BG, Cordova F, Leyenson V, Criner GJ: **Effect of N-acetylcysteine on human diaphragm strength and fatigability.** *Am J Respir Crit Care Med* 1997, **156**:1567-1571

Four normal subjects were infused with N-acetylcysteine (NAC) or placebo in a randomized double-blind fashion and measurements of diaphragm function were made while breathing against resistive loads. NAC appeared to attenuate low frequency diaphragm fatigue in these normal subjects.

Farkas GA, Roussos C: **Adaptability of the hamster diaphragm to exercise and/or emphysema.** *J App Physiol* 1982, **53**:1263-72

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1. Heunks LM, Bast A, van Herwaarden CL, Haenen GR, Dekhuijzen PN: Effects of emphysema and training on glutathione oxidation in the hamster diaphragm. J Appl Physiol. 2000, 88: 2054-2061.