Detection of Skeletal Muscle Mitochondrial Dysfunction in Pulmonary Arterial Hypertension

M. Hrovat[1], C. Farrar[2], J. J. Tolle[3], P. Gordan[3], G. D. Lewis[3], P. Pappagianopoulos[3], and D. Systrom[3]

[1]Mirtech, Inc., Brockton, MA, United States, [2]Radiology, Massachusetts General Hospital, Boston, MA, United States, [3]Dept. of Pulmonary and Critical Care, Massachusetts General Hospital, Boston, MA, United States

Introduction

Pulmonary arterial hypertension (PAH) is characterized by pulmonary artery vasoconstriction and remodeling. Exercise intolerance, including fatigue and dyspnea, has traditionally been linked to high pulmonary artery pressures and a resulting decrease in cardiac output and arterial oxygen content. Impaired oxygen delivery is thought to deprive the exercising skeletal muscle mitochondrion. Conversely, our laboratory has recently described blunted systemic oxygen extraction at maximum exercise in pulmonary arterial hypertension (PAH)[1] when O_2 delivery is normal or near normal. The purpose of this study is to determine whether intrinsic exercising limb skeletal muscle mitochondrial dysfunction is responsible.

Methods

Patients with PAH (n=6) defined by right-heart catheterization, and controls (n=5), underwent 3 minutes of isotonic quadriceps exercise at 0.5 Hz at 40% of MVC. ^{31}P-magnetic resonance spectroscopy of vastus medialis was performed in a 3T whole-body Siemens magnet utilizing a transmit/receive surface coil. The protocol consisted of a 2 minute rest period, followed by 3 minutes of exercise, followed by a 5 minute rest recovery period. Free induction decays were collected every 2 seconds during the protocol. The data was processed and averaged by utilizing a 12 second sliding window. [Hb] < 10 mg/dl and exercise SpO_2 < 0.90 were excluded. Phosphocreatine (PCr) recovery following cessation of exercise was modeled monoexponentially, and tau (τPCr) was compared by unpaired t-test.

Results

Relative metabolic stress at cessation of exercise was similar for patients and controls, by end exercise intracellular pH (6.92±0.06 vs. 6.90±0.03) and ratio of PCr/Pi (1.37±0.27 vs. 2.19±0.56, p>0.05 for both). τPCr was slowed in PAH vs. controls (57.4±6.3 vs. 33.5±2.7 s, p<0.02). Representative examples are shown in figures 1 and 2.

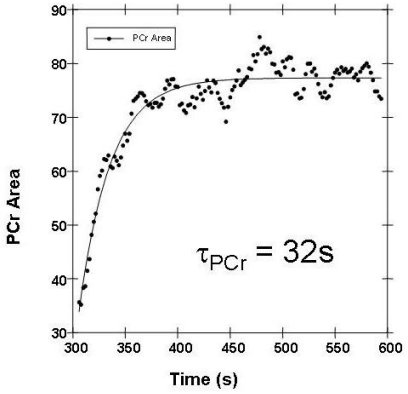

Figure 1. PCr Recovery for a Normal Subject

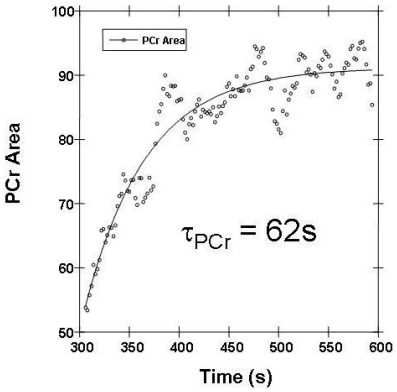

Figure 2. PCr Recovery for a PAH Subject

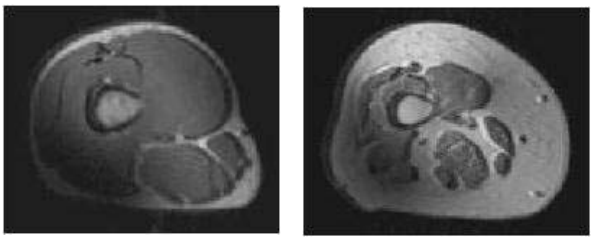

Figure 3. Leg Images of a Normal (left) and PAH (right) subject.

Conclusions

Delayed limb skeletal muscle PCr recovery following exercise with normal arterial O_2 content suggests an intrinsic abnormality of mitochondrial ATP synthesis. Leg images of PAH subjects also show significant muscular abnormalities (Figure 3). It appears that PAH is more of a systemic disease than previously recognized.

References

1. Tolle JJ, et al. Med Sci Sports Exerc. In press