Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension


Background: The mechanisms of right ventricular (RV) failure in pulmonary arterial hypertension (PAH) are poorly understood. Abnormalities in fatty acid (FA) metabolism have been described in experimental models of PAH, but systemic and myocardial FA metabolism have not been studied in human PAH. We hypothesize the FA metabolic defects are present in human PAH and contribute to RV lipotoxicity.

Methods: We used human blood, RV tissue, and non-invasive imaging to characterize multiple steps in the FA metabolic pathway in PAH subjects and controls. Human plasma and RV long-chain acylcarnitines, ceramides, and carnitine palmitoyltransferase I activity were quantified using standard liquid chromatography/mass spectrometric methods. High resolution respirometry was used to measure ex vivo right ventricular oxygen consumption. Proton magnetic resonance spectroscopy was used to quantify in vivo myocardial lipid content.

Results: Circulating FFAs and long-chain acylcarnitines were elevated in PAH patients versus controls after adjusting for multiple comparisons (both p < 0.001). Human RV long-chain FAs were increased and long-chain acylcarnitines were reduced nearly 100-fold in PAH versus controls (p < 0.001). In vivo intramyocyte lipid content was 7-fold higher in human PAH versus controls (Figure 1; 1.4 ± 1.3 %TG vs. 0.22 ± 0.11 %TG, p = 0.02). Ceramide, a mediator of lipotoxicity, was increased in human PAH RVs versus controls (p = 0.006). Using an animal model of heritable PAH (BMPR2R899X), we demonstrated reduced fatty acid oxidation via failure of palmitoylcarnitine to stimulate oxygen consumption in the PAH RV (Figure 2; p < 0.001). Carnitine transporter gene expression and activity were similar between PAH and control RVs.

Conclusions: Abnormalities in fatty acid metabolism can be detected in the blood and myocardium in human PAH and are associated with RV steatosis and lipotoxicity. Murine data suggest that lipotoxicity may arise from impaired fatty acid oxidation. This study highlights specific metabolic pathways of potential therapeutic interest in PAH and establishes a tool to study their activity in vivo.