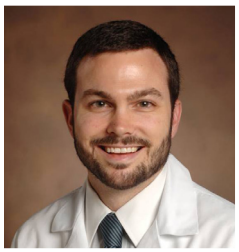
2014 Abstracts



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Dysregulation of Lipid Metabolism and Right Ventricular Function in Pulmonary Arterial Hypertension

Introduction

Right ventricular (RV) failure is the predominant cause of death in pulmonary arterial hypertension (PAH). No RV-specific therapies are available, in part because the underlying mechanisms of RV dysfunction are poorly understood. The development of RV-specific therapeutic targets would represent a major advance in the treatment of PAH.

Preliminary Data

We have found: 1) Elevated circulating free fatty acids (FAs) in PAH patients compared to age, gender, and BMI matched controls. 2) Elevated long-chain acylcarnitines in peripheral blood in PAH patients. 3) Decreased expression of enzymes involved in carnitine shuttling in pulmonary microvascular endothelial cells with BMPR2 mutation. 4) Decreased myocardial acylcarnitines associated with worse RV function and myocardial steatosis in a murine model of PAH. 5) Marked RV lipid deposition detected *in vivo* in patients with PAH and in explanted hearts from humans with PAH. 6) Successful trans-cardiac blood sampling and possible decreased trans-cardiac FA consumption in PAH patients compared to control.

We hypothesize that defects in FA metabolism are common in PAH and contribute to RV failure.

We propose to test this hypothesis with the following specific aims:

1. **To test the hypothesis that defects in FA metabolism are common in PAH and are associated with insulin resistance, RV function, and exercise capacity.** We will perform metabolomics analysis focusing on the long-chain acylcarnitine oleoylcarnitine – the most abundant acylcarnitine in our preliminary data – in 30 patients with idiopathic PAH (IPAH) and 30 matched controls.

2. **To test the hypothesis that trans-cardiac metabolic profiling will demonstrate decreased uptake of FA metabolites and increased glycolysis.** In this aim, we will interrogate *in vivo* FA metabolism by measuring trans-cardiac (pulmonary artery wedge to coronary sinus) metabolite gradients to determine the relationship between substrate metabolism and RV function. We will prospectively sample trans-cardiac FA and glucose metabolite gradients in 20 PAH patients undergoing right heart catheterization and same-day cardiac magnetic resonance imaging (MRI).