**Transpulmonary metabolomics in pulmonary arterial hypertension**

Metabolomic Analysis: NIH Eastern Regional Comprehensive Metabolomics Resource Core (RTI RCMRC)

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**Abstract:**

Pulmonary arterial hypertension (PAH) is a progressive and incurable disease characterized by obliteration of the pulmonary arterioles, elevated pulmonary vascular resistance (PVR), and eventual right heart failure and death. Current medical therapy for PAH is aimed at reducing PVR by targeting pathways involved in vasodilation. Pulmonary vasodilators improve functional capacity but do not target the underlying vascular obstruction. Despite multiple approved therapies, median survival after diagnosis is less than five years, indicating that additional therapeutic targets are needed.

PAH is increasingly recognized as a systemic metabolic disease with life-limiting cardiopulmonary manifestations. PAH patients exhibit abnormalities in glucose and fatty acid metabolism that are associated with disease severity and prognosis. At an organ-specific level, pulmonary vascular endothelial cells from humans with PAH demonstrate increased reliance on aerobic glycolysis, a phenomenon associated with highly proliferative cells such as malignancies. It is unknown whether this change in energy substrate preference is adaptive or maladaptive or could be used as a marker of disease progression or severity. A more detailed understanding of pulmonary vascular metabolic status would address these knowledge gaps and may offer new therapeutic targets for this disease.

In vivo metabolic data in human PAH are limited and no organ-specific data have been published. In preliminary data we have found: 1) markedly increased prevalence of insulin resistance in PAH patients, independent of body mass index. 2) Elevated plasma free fatty acids and long-chain acylcarnitines in PAH patients compared with matched controls. 3) In a proof-of-concept study we demonstrate feasibility of transpulmonary blood sampling with dynamic metabolite changes across the pulmonary circulation.

We hypothesize that transpulmonary metabolomic profiling will demonstrate a PAH-specific metabolic signature. We will examine organ-specific metabolism by measuring blood flowing into (pulmonary artery) and out of (pulmonary artery wedge) the pulmonary circulation at the time of right heart catheterization (RHC). We will compare PAH to patients without PH and to a disease control cohort with PH due to left heart disease.

**Sample Description:**

Plasma was collected from patients during right heart catheterization from the pulmonary artery (PA) and the pulmonary capillary wedge (PCW) position. A total of 154 coded plasma samples were shipped to the NIH RTI-RCMRC on dry ice and immediately stored at -80 °C after being logged in for metabolomics analysis.

The data obtained for the NMR metabolomics analysis can be found in the accompanying files:

Procedures: 1. Brittain Pulmonary Hypertension Metabolomics Procedures.docx

Study Design Tables: 2. Brittain Pulmonary Hypertension Metabolomics Study Design Table.xls

Metadata: 3. Brittain Pulmonary Hypertension Metabolomics METADATA.xlsm

Processed Data: 4.Brittain Pulmonary Hypertension Metabolomics Normalized Binned Data.xlsx

Raw Data: 5. Brittain Pulmonary Hypertension Metabolomics NMR Raw Data.zip

**Notes:**

Full sample preparation and analysis procedures are available in the accompanying document entitled **1. Brittain** Pulmonary **Hypertension Metabolomics NMR Procedures**.

Descriptions of abbreviations for factors are available in the Variable Dictionary in the accompanying file no. **2. Brittain** Pulmonary **Hypertension** **Metabolomics NMR Study Design Table.xls**.

The phenotypic and normalized data are available in the accompanying files: **4. Brittain** Pulmonary **Hypertension** **Metabolomics NMR Normalized Binned Data.xlsx** for normalized binned NMR data. Sample ID and factors can be found in the first 5 columns and other columns in the spreadsheet contain sample metadata and the normalized binned data. If the statistical program does not allow variable names to begin with a number then add a prefix to the column names, for example, bin\_8.98 instead of 8.98.

The Sample ID serves as the unique identifier (Graphical ID) of the individual samples and is used as the NMR folder name in the raw NMR data file **5. Brittain** Pulmonary **Hypertension** **Metabolomics NMR Raw Data.zip**.