ABSTRACT

Heart failure (HF) continues to pose a significant burden to healthcare systems worldwide. Improved risk stratification and diagnostic tools will be essential for improving patient outcomes and reducing costs. Although the pathophysiology of chronic heart failure (CHF) has been well defined, the mechanisms underpinning acute heart failure (AHF) and its clinical management demand further study. AHF is a broadly defined syndrome encompassing a range of clinical presentations spanning from acutely decompensated CHF to refractory CHF and de novo HF. Management of this complex condition is limited in part by the lack of appropriate tools to predict prognosis and guide therapy. The blood plasma compartment provides a minimally-invasive snapshot of systemic pathophysiology, and its utility in disease prognostics and diagnostics has been well established. Consequently we undertook a prospective biomarker study to identify plasma proteomic markers to predict outcomes and identify response to therapy in patients with AHF.

Applying a semi-targeted mass spectrometry approach paired with candidate biomarker analyses, we identified a panel of proteomic biomarkers which could predict 30 day mortality risk, the need for mechanical support or cardiac transplantation, or recovery in patients with severe inotrope-dependent heart failure at the time of hospitalization. Analysis of circulating proteomic responses over the first 30 days of AHF therapy allowed us to characterize the proteomic signature of therapy-specific symptomatic recovery in patients managed medically or with mechanical circulatory support. Pairing our circulating biomarker data with analyses of myocardial tissue samples from patients pre- and post- treatment allowed us to link circulating biomarker signatures with myocardial remodeling.

Further, we used second harmonic imaging to identify biomarker signatures reflective of fibrotic remodeling processes underway within the heart during HF therapy, and subsequently performed in vitro work to identify a potential therapeutic application of vitamin D in inhibiting fibrotic remodeling.

Through this dissertation study we have provided a unique longitudinal data set on a rare patient cohort, and have demonstrated the potential utility of blood derived biomarkers in AHF management. We have identified novel candidate biomarkers of AHF which may also shed light on the complex pathophysiologic mechanisms involved in disease progression, remodeling, and recovery.