Dr. P. Christian Schulze

Project Summary

The prevalence of heart failure (HF) is increasing throughout the world with high morbidity and mortality. Patients with advanced HF develop profound metabolic abnormalities including insulin resistance, cytokine activation and abnormal oxidative metabolism in the failing myocardium. Our previous work has shown accumulation of the toxic lipid intermediates ceramide and diacylglycerol in failing human myocardium and that these toxic lipids induce transcriptional changes, impaired cellular energy metabolism and inhibit insulin signaling. Further, preliminary animal studies revealed accumulation of long-chain ceramides in the failing myocardium. A pro-apoptotic state and enhanced proteolytic protein breakdown known to be associated with toxic lipid intermediates develops in advanced HF. Therefore, accumulation of toxic lipid intermediates such as long-chain ceramides might constitute a key link between altered cellular metabolism and proteolysis leading to impaired function and progressive cardiac remodeling in advanced HF.

The central hypothesis of this application is that lipotoxic accumulation of long-chain ceramide species contributes to structural and functional myocardial changes in HF. We hypothesize that lipotoxicity is a key means of myocardial dysfunction but that distinct characteristics exist defined by the underlying cardiomyopathy. In myocardium from patients with ischemic and non-ischemic cardiomyopathies and nondiseased controls, we will analyze the myocardial lipid composition of ceramides, diacylglycerides, triglycerides, fatty acids, acylcarnitines, lipoxins and resolvins using LC/MS techniques. We also will study the impact of mechanical unloading through left ventricular assist device (LVAD) placement on myocardial metabolic derangements (AIM 1). Further, we will analyze pathways controlling gene and microRNA expression and link these to the results of the lipid composition analyses (AIM 2). Finally, we will analyze the cardiac lipid composition in animal models of human ischemic and non-ischemic cardiomyopathies and test whether pharmacologic and genetic inhibition of the de novo and salvage pathway of ceramide synthesis affects long-chain ceramide accumulation and progressive cardiac remodeling (AIM 3).

In achieving the goals of this proposal, we will expand the understanding of key mechanisms underlying myocardial structural and functional derangements in HF. A major strength of this investigation is the ability to test the impact of long-chain ceramide accumulation on myocardial remodeling. Further, we will define the myocardial lipid pool in patients with advanced HF compared to controls and the impact of mechanical unloading of the failing myocardium. These studies will define new molecular and functional targets in patients with HF. The proposed work will, therefore, lay critical groundwork for broader clinical goals to define and enhance therapeutic strategies to modify molecular and transcriptional patterns of cardiac metabolism in HF.
