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Title: Skeletal Muscle Dysfunction in Diastolic Heart Failure

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Heart failure (HF) prevalence is increasing worldwide with high morbidity and mortality. Most studies of HF focus on patients with reduced ejection fraction (EF), yet more than 50% of chronic HF cases have preserved EF. Heart failure with preserved EF is often referred to as diastolic HF, due to the impairment in cardiac relaxation during diastole. Regardless of phenotype, HF is strongly associated with exercise intolerance and the degree of functional impairment increases mortality risk. Skeletal muscle dysfunction is the best predictor of functional capacity. Beyond exercise impairments, systolic HF patients are shown to develop severe metabolic abnormalities including cytokine activation, changes in gene expression, and abnormal oxidative metabolism in skeletal muscle. The function and morphology of skeletal muscle is directly linked to cellular metabolism and functional load with a tight regulation of anabolic protein synthesis and growth versus catabolic protein breakdown and atrophy. As primarily shown in systolic HF patients, these changes in skeletal muscle lead to progressive muscle wasting and atrophy, causing further impairments in exercise capacity. While numerous studies have examined specific skeletal muscle function parameters and in systolic HF patients, very little is known about skeletal muscle function in diastolic HF patients. Furthermore, little is known regarding skeletal muscle structure and metabolism in diastolic HF, especially in relation to skeletal muscle function. **The CENTRAL HYPOTHESIS of this application is that patients with diastolic HF develop similar impairments in exercise capacity and skeletal muscle function as seen in systolic HF patients, but phenotypic and metabolic changes in the skeletal muscle biopsies will be more impaired in the diastolic HF patients.** In achieving the goals of this proposal, we will elucidate key mechanisms underlying skeletal muscle changes and functional decline in diastolic HF patients. Exploring the metabolic pathways in atrophying skeletal muscle in relation to functional and morphological derangements in diastolic HF is novel. These studies will define molecular and functional targets for diastolic HF patients and therefore, lay critical groundwork for broader clinical goals to enhance therapeutic strategies to modify the HF-related molecular patterns that underlie exercise intolerance and its detrimental effects.