Title: Multiscale modeling of myocardial growth and remodeling

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Heart failure is a worldwide epidemic that contributes considerably to the overall cost of health care in developed nations. The number of people afflicted with this complex disease is increasing at an alarming rate, a trend that will continue as the population ages and life span expands. The objective of this research is to identify the mechanical culprits that dictate the bifurcation from the stable, healthy state into the unstable, failing state. Several geometric parameters, hemodynamic metrics, and molecular biomarkers have been proposed to characterize heart failure; yet, there is currently no established approach to predict heart failure progression. The inherent limitation has been the lack of understanding of the fundamental laws of myocardial growth and remodeling in response to altered hemodynamic conditions, from the microstructural to the macrostructural level. Here, we attempt to predict the propensity to heart failure, by providing insight into the cellular mechanical stimuli and mechanisms that dictate the transition from compensatory growth and remodeling to decompensatory heart failure.

We summarize our mechanistic myocardial growth model that can predict structural alterations in response to mechanical overload across the scales. Specifically, we distinguish between three types of volume overload: global volume overload, global pressure overload, and local overload caused by myocardial infarction. Using chronic swine models for each case, we characterize the effects of overload on cellular-, tissue-, and organ-level structure and function. Unique to this approach is a longitudinal multiscale assessment of heart failure progression, with a systematic data collection at two-week intervals. We correlate mechanical overload on the macroscopic scale with structural alterations on the cellular level, and, vice versa, structural changes on the microscopic scale with functional alterations on the whole organ level. To link the scales, we supplement our study with magnetic resonance images of the heart at its final stage, and create high-resolution mappings of myocardial fiber orientations. This project is currently in its third year, and we discuss recent progress, potential limitations, and future directions.