**MYOCARDIAL INTERSTITIAL FIBROSIS IN HEART FAILURE: BEYOND VENTRICULAR STIFFNESS**

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Accumulation of collagen in the cardiac interstitium termed “reactive interstitial fibrosis” (RIF) occurs in heart failure (HF) with reduced ejection fraction (HFrEF) and in most patients with HF and preserved ejection fraction (HFpEF). In dogs with experimental HF, the volume fraction of left ventricular (LV) RIF ranges between 12% and 16%. When quantified based on extracellular volume in patients with HF, RIF ranges between 25% and 30%. This abnormal deposition of interstitial collagen leads to increased LV stiffness and consequently poor LV filling; the latter a primary abnormality in HFpEF. The adverse impact of RIF on the failing heart, however, is by no means limited to reduced LV compliance. Studies in animals and humans with HF have shown that RIF is associated with coronary microvascular rarefaction. In dogs with HF, myocardial capillary density is decreased by more than 10% compared to normal dogs. Similar findings were reported in HFrEF patients and in the LV subepicardium, midwall and subendocardium of HFpEF patients. In HF dogs, RIF is also associated with a 20% to 30% increase in oxygen diffusion distance, a finding supportive of hypoxia of constituent cardiomyocytes. The likelihood that hypoxia exists in the failing myocardium is supported by the observed significant increase in mRNA and protein levels of hypoxia-inducible factor-1 alpha (HIF-1α). The increase in HIF-1α in the failing heart can trigger increased expression of inducible nitric oxide synthase (iNOS). Increased expression of iNOS in HF has been implicated in 1) cardiomyocyte apoptosis, 2) accelerated fibrosis, 3) suppression of mitochondrial respiration, 4) heart block and 5) sudden cardiac death. The development of RIF in the failing heart, therefore, regardless of the etiology of HF, can trigger a cascade of adverse events that are likely to contribute in a major way to the relentless progression of the HF state and ultimately to intractable HF and death. Targeting RIF in HF with drugs and therapies that can prevent or, at the very least, retard its formation, represents a viable approach to treating this disease syndrome that goes well beyond preservation of LV compliance and filling.