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Background: Patients with congestive heart failure (CHF) experience reduced skeletal muscle exercise tolerance. The mechanism underlying this is not known. Studies have indicated that the extracellular matrix (ECM) may be affected by the CHF condition. The signal from the failing heart that triggers such changes has not been defined, and it is not known to which extent the skeletal muscle itself contributes by sustaining and amplifying a local process. Hence, we have examined various components of skeletal muscle ECM and interstitial fluid (IF) during development of CHF.

Methods: We used a post infarction model of CHF in rats. At various time points (3-112 days) after induction of CHF, IF, blood and muscles were sampled. IF was extracted by wicks inserted in muscles in the hind limb. Cytokines in plasma and IF were analyzed by multiplex technique, while matrix-metalloproteinase (MMP) activity and collagen content in muscle samples were determined with a gelatinase assay and colorimetric assay of hydroxyproline, respectively.

Results: There was a transient increase in MMP activity and collagen content of skeletal muscle at 42 days after induction of heart failure returning to control level at 112 days. Of the analyzed cytokines, vascular endothelial growth factor (VEGF) in IF was significantly lower in CHF compared to Sham at 3 and 10 days, and IL-18 was significantly upregulated in plasma of the CHF animals at 112 days. Both these cytokines exhibited a large gradient from the muscle to plasma, indicating a net production in the muscle.

Conclusions: The reduced exercise tolerance in CHF seems to be associated with MMP-induced alterations in extracellular matrix. A reduced production of VEGF in muscles from the CHF animals may have implications for the development of exercise intolerance in these animals. The high level of IL-18 in the IF compared to plasma, suggests that skeletal muscle may be a major contributor to the systemic level of this cytokine.