Purpose: Inflammatory processes are activated in heart failure (HF), but the regulation of cytokines and their role in the HF pathogenesis are not well understood. The purpose of the present study was to identify cytokines not previously found regulated in HF, and to study selected cytokines regarding their production and effects on cardiac cells.

Methods and Results: Alterations in gene expression during HF progression was screened by micro-array technology in non-infarcted left ventricular murine tissue obtained 3, 5, 7 and 14 days after ligation of the left coronary artery. In total, we identified 14 regulated genes encoding cytokines with no previous association to HF. The strongest up-regulation was found for fractalkine (CX3CL1) (verified by real-time PCR). Myocardial CX3CL1 mRNA expression was also increased in two other experimental HF models; a right-ventricular pressure overload model (constriction of pulmonary artery) and in a cardiomyopathy model (adult conditional cardiomyocyte-specific Serca2 knock-out).

In human failing hearts, we detected a 3-fold increase in CX3CL1 protein production and both cardiomyocytes and fibroblasts revealed strong immunoreactivity of CX3CL1 and its specific receptor CX3CR1. We also found that the circulating level of CX3CL1 was increased in patients with chronic HF in accordance with disease severity (New York Heart Association functional class). In vitro experiments demonstrated that CX3CL1 production could be induced by inflammatory cytokines known to be highly expressed in HF. Using microarray technology we showed that cardiomyocytes stimulated with CX3CL1 had altered expression of genes involved in leukocyte extravasation signaling and cytokine signaling, indicating a direct effect on cardiomyocytes.

Conclusion: Given the increased CX3CL1 production in several different experimental HF models and in patients with chronic HF, as well as direct effects on cardiomyocytes, we suggest that CX3CL1/CX3CR1 interaction could be part of a common pathway in the pathogenesis of HF.