Increased Myocardial Matrix Metalloproteinase Activity in Mice with Systolic and Diastolic Heart Failure

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Background
- Matrix metalloproteinases (MMPs) that degrade extracellular matrix (ECM) play a key role in mediating cardiac remodeling.
- Because there are several MMPs and their inhibitors (TIMPs), assessing net MMP activity has not been possible.
- We used a novel assay to determine net MMP activity in hearts from transgenic mice with contrasting cardiac phenotypes.
- Transgenic mice with cardiac-specific overexpression of Gaq develop left ventricular (LV) dilation with systolic heart failure (SHF).
- In contrast, transgenic mice with cardiac-specific overexpression of Fatty Acid Transport Protein 1 (FATP 1) develop LV hypertrophy with diastolic heart failure (DHF).

Hypothesis
- We tested the hypothesis that net MMP activity is increased in mice models of SHF and decreased in models of DHF.

Methods
- Cardiac fibrosis was confirmed using Masson’s Trichrome staining of paraffin embedded sections of myocardium.
- Net MMP activity was determined using a novel assay based on a fluorogenic substrate (OmmiPMMMP) (Figure 1).
- Steady state mRNA levels of MMPs, TIMPS, and collagens were determined using Taqman real time RT-PCR.

Results

Figure 1: Histological evidence of Interstitial Cardiac Fibrosis between myocytes. (A) Increase in interstitial fibrosis in SHF. (B) Increase in interstitial fibrosis in DHF

Figure 2: Net endogenous MMP activity in whole heart lysates (A) Fluorescence (AU) WT vs DHF. Inhibition of MMPs by EDTA (B) Net MMP activity at 13 weeks. Average WT activity: 1.47 nmoles/mg.min. Average DHF activity: 2.55 nmoles/mg.min. p=.001, n=3 (C) Fluorescence (AU) WT vs SHF (D) Net MMP activity in whole heart lysates at 15 weeks. Average WT activity: 1.28 nmoles/mg.min. Average SHF activity: 2.87 nmoles/mg.min. p=.013, n=3

Figure 3. Changes in steady state mRNA levels of MMPs and TIMPs (A) Decrease in mRNA levels of MMP 13 in DHF 12 weeks. n=3, p=.045 (B) Increase in TIMP 1, TIMP2, and MMP 14 activity in SHF mice at 26 weeks. n=3, p=.05.