**THE TOLL-LIKE RECEPTOR 4 LIGANDS S100A8 AND S100A9 ARE CRUCIAL FACTORS IN VIRAL CARDIOMYOPATHY**

**Poster Contributions**  
**Poster Sessions, Expo North**  
**Sunday, March 10, 2013, 9:45 a.m.-10:30 a.m.**

**Session Title:** New Insights into Heart Failure Pathophysiology  
**Abstract Category:** 16. Heart Failure: Basic  
**Presentation Number:** 1222-293

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**Background:** Various Toll-like receptors (TLRs) are a part of the innate immune system and involved in cardiac immune response after viral infection. Potential endogenous ligands of TLRs and their function in viral myocarditis still remain unclear. In the present study we investigated the role of the alarmins S100A8 and S100A9, identified ligands of TLR4, in Coxsackievirus B3 (CVB3)-induced myocarditis in mice.

**Methods:** S100A8/A9 knockout mice (S100A8/A9-/-) and their wild-type controls (WT) were infected with CVB3 to induce myocarditis. Seven days after viral infection left ventricular (LV) function was estimated by conductance catheter technique as well as cardiac fibrosis, inflammatory response and cardiac apoptosis by immunohistochemistry or PCR. In addition, we examined serum and endomyocardial expression levels of S100A8 and S100A9 in patients with myocarditis and controls.

**Results:** Seven days after infection WT-CVB3 mice displayed an impaired systolic and diastolic LV function, associated with a significant increase in virus load, cardiac fibrosis, inflammation and cardiac apoptosis. In contrast, S100A8/A9 deficient mice showed a definite improvement in systolic (dP/dtmax +26%, SV +30%, SW +42%, CO +63%, EF +29%; P<0.05) and diastolic (dP/dtmin +31%, LVEDP -62%, Tau -44%; P<0.05) LV function. In addition, in S100A8/A9 deficient mice, virus load (P<0.05), inflammatory immune response (e.g. IL-6 2.5-fold, IL-10 2.7-fold, IL-12 2.1-fold, IFN-γ 2.6-fold; P<0.05), cardiac fibrosis (Col I 7.5-fold, Col III 1.4-fold; P<0.05) and cardiac apoptosis (TUNEL 6.4-fold, RACK1 8.1-fold; P<0.05) could be normalized to levels almost similar to uninfected control animals. Exogenous substitution of homodimer S100A8 in S100A8/A9-/- mice led in turn to an exacerbation of CVB3-induced myocarditis. Moreover, patients with myocarditis displayed significantly increased serum and endomyocardial expression levels of S100A8 and S100A9 when compared to controls (P<0.05).

**Conclusions:** The identification of S100A8 and S100A9 proteins as key factors in the pathogenicity of experimental myocarditis might offer a new molecular target and biomarker for treatment of viral cardiomyopathy.