P5443

NOD2 knock down worsens diastolic dysfunction in murine angiotensin II-induced heart failure

I. Mueller, J. Lin, K. Pappritz, C. Tschoepe, S. Van Linthout

Berlin Institute of Health Center for Regenerative Therapies, Berlin, Germany

Background: Heart failure with preserved ejection fraction (HFpEF) is associated with cardiac inflammatory responses, indicating a potential role of the immune system in the pathology of diastolic dysfunction. The cytoplasmatic pattern recognition receptor, nucleotide binding oligomerization domain 2 (NOD2) belongs to the innate immune system and induces among others the NLRP3 inflammasome, known to be involved in myocarditis and coronary heart disease.
Purpose: The aim of this study was to explore the role of NOD2 in Angiotensin II (AngII)-induced diastolic heart failure.
Methods: In NOD2–/– knock down and C57Bl6/j-wild type (WT) mice, diastolic dysfunction was induced by subcutaneous administration of 1.4mg/kg*day^{-1} AngII. Twenty-one days after first AngII administration, left ventricular (LV) function was evaluated by pressure tip catheter. Cardiac fibrosis, inflammation, and the expression of NOD2 and the NLRP3 component Apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) were determined via immunohistochemistry, real-time PCR or Western Blot.
Results: LV NOD2 mRNA expression was 2.3-fold ($p<0.0005$) and 1.9-fold ($p<0.0005$) lower in NOD2–/– control and NOD2–/– AngII mice compared to their respective WT littermates. In parallel, LV protein expression of the downstream NLRP3 component Apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) was 1.5-fold ($p<0.05$) lower in NOD2–/– AngII mice versus WT AngII mice, whereas LV protein IL-1β levels were unchanged. LV diastolic dysfunction was more pronounced in NOD2–/– AngII mice versus WT AngII mice, as displayed by a 19% ($p<0.05$) increased LV relaxation time and 24% ($p<0.057$) impaired dP/dtmin, with no changes in the ejection fraction (EF: NOD2–/– AngII 72.5%±5.4 versus WT AngII 65.6±3.5). In parallel, LV presence of CD68-positive cells was 1.8-fold ($p<0.05$) higher in NOD2–/– AngII compared to WT AngII mice. Concomitantly, NOD2–/– AngII mice displayed 1.3-fold ($p<0.05$) and 1.7-fold ($p<0.05$) higher LV mRNA expression of the chemokine macrophage inflammatory protein (MIP)-2 and monocyte chemotactant protein (MCP)-1 compared to WT AngII mice, respectively. Furthermore, cardiac interstitial fibrosis in NOD2–/– mice with AngII-induced diastolic dysperformance was more pronounced versus the WT AngII group, as indicated by a 2.0-fold ($p<0.0005$), 2.0-fold, and 1.6-fold ($p<0.05$) higher LV ColI/ColIII ratio, and TGF-β and TIMP-1 mRNA expression, respectively.
Conclusion: NOD2–/– deteriorates LV diastolic dysfunction and worsens pathophysiological key mechanisms in mice with AngII-induced diastolic heart failure.