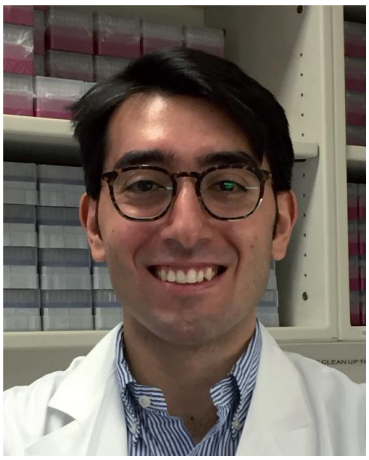
UniversitätsKlinikum Heidelberg

External Seminar Speaker



Gabriele Giacomo Schiattarella, MD PhD
Division of Cardiology,
UT Southwestern Medical Center,
Dallas, Texas, USA

Place: **Analysezentrum 3, 2. OG, Room 02.332**
Date: **Tuesday, February 19th**
Time: **12.00 am**

Nitrosative Stress-dependent Suppression of Xbp1s Drives Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) accounts for ≈50% of all patients with HF and is associated with significant morbidity, mortality and healthcare expenditures. Currently, there are no evidence-based therapies with demonstrated efficacy in HFpEF. This syndrome has proven particularly challenging because lack of informative preclinical models and, in turn, limited insight into its underlying molecular mechanisms. It has been said that HFpEF is the single greatest unmet need in cardiovascular medicine. Manifestly, there is urgent need for mechanistic studies of HFpEF pathogenesis. Cardiac remodeling and dysfunction in HFpEF are driven by the prevalent comorbidities of obesity, diabetes, arterial hypertension and endothelial dysfunction, which together culminate in systemic inflammation. We hypothesized that the convergence of metabolic stress (obesity/ metabolic syndrome) and mechanical stress (hypertension) trigger events leading to HFpEF. We report that simultaneous metabolic and hypertensive stress in mice elicited by a combination of high fat diet (HFD) and constitutive nitric oxide (NO) synthase inhibition uniquely recapitulates the numerous systemic and cardiovascular alterations of human HFpEF. To unravel underlying mechanisms, we evaluated the cardiomyocyte unfolded protein response (UPR), noting that one UPR downstream effector, the spliced form of X-box binding protein 1 (Xbp1s), was reduced in HFpEF mouse hearts and cardiomyocytes. We went on to determine that decreases in Xbp1s resulted from increased inducible NO synthase (iNOS) activity and S-nitrosylation of the endonuclease IRE1α, culminating in a defect in Xbp1 splicing activity. Strikingly, similar molecular alterations were also observed in biopsy specimens of human HFpEF heart. We have developed a novel preclinical model of HFpEF that uniquely recapitulates most of the clinical features of the syndrome, unveiling iNOS-driven dysregulation of Xbp1s as a crucial mechanism of cardiomyocyte dysfunction.

Host: **Prof. Dr. med. Johannes Backs**
Director of the Department Molecular Cardiology and Epigenetics
Department of Internal Medicine VIII
University of Heidelberg