Results: Measures of LA phasic function were more prominently impaired in subjects with HFrEF, than among subjects with HFpEF. In unadjusted Cox proportional hazards models, all measures of phasic LA function and volumes (maximum, minimum and diastatic) were associated with incident events. However, in analyses that adjusted for clinical risk factors, heart failure status, maximum LA volume, left ventricular (LV) mass and LV ejection fraction, measures of conduit and reservoir LA function, but not boosgter-pump function, were associated with incident adverse events. The strongest associations were observed for conduit longitudinal strain (Standardized Hazard ratio=0.66; 95% CI=0.49–0.88, P=0.004), conduit strain rate (Standardized HR=1.59; 95% CI=1.16–2.16, P=0.0035), and reservoir strain (Standardized HR=0.68; 95% CI=0.52–0.89, P=0.0055, Figure).
Conclusions: Phasic LA function measured using MRI feature-tracking is independently predictive of the risk of incident heart failure events, even after adjusting for LA volume and LV remodeling.
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CHRONIC HEART FAILURE – PATHOPHYSIOLOGY AND MECHANISMS

P878
Cardio-renal syndrome type 2: a role of cardiac spinal afferents activation

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Introduction: Cardio-renal syndrome type II (CRS II) is defined as a chronic abnormality in cardiac function (chronic heart failure, CHF) causing progressive and potentially permanent chronic kidney disease. We hypothesized that the cardiac sympathetic afferent reflex (CSAR, a cardiogenic sympatho-excitatory reflex mediated by spinal afferents from the heart) plays a critical role in the pathological development of CRS II. Specifically, we proposed that the CSAR control of sympathetic outflow to the kidneys exacerbates renal hypoperfusion and accelerates renal dysfunction including renal tubular damage in CRS II.
Methods: We examined the effects of acute or chronic activation/inhibition of the CSAR on renal blood flow (RBF), renal vascular resistance (RVR) and renal function in sham-operated and myocardial infarction (MI) rats. Renal function was evaluated by measuring 1) blood creatinine and blood urea nitrogen (BUN) by iSTAT analysis; 2) urinary kidney damage markers such as the kidney injury molecule [KIM]-1 and 3) RNA sequencing analysis (RNA-Seq) in renal tissues.
Results: Acute CSAR activation by epicardial application of bradykinin (BK) in anesthetized, vagotomized rats resulted in augmented blood pressure, heart rate, and renal sympathetic nerve activity responses in MI compared to sham rats. CSAR activation also increased renal vascular resistance (RVR) to a greater extent in MI rats compared to sham rats (Figure 1). We also showed that chronic CSAR ablation with epicardial application of the highly specific TRPV1 receptor agonist resiniferatoxin (RTX), in part, restored the abnormal RBF and RVR in MI rats. Furthermore, epicardial RTX largely prevented the development of renal dysfunction 4–5 months post MI as evidenced by decreased blood creatinine and BUN in MI+RTX rats. RNA-Seq analysis showed that the gene expression of KIM-1 (a specific proximal tubular damage marker) was increased by ~70 fold in whole-kidney tissue of MI rats, whereas it was only increased by ~4 fold in rats treated with RTX. MI rats exhibited much higher concentration of urinary Kim-1 18 weeks post MI, which was largely prevented by RTX treatment.
Conclusion: These data suggest that CSAR ablation by RTX may impart a selective protective effect on renal proximal tubular damage in CHF. Considering the fact that renal proximal tubules are located in the renal cortex where the majority of renal blood flow is distributed, it is very likely that chronic CSAR ablation improves renal proximal tubular damage by partially restoring cortical blood flow in CHF.
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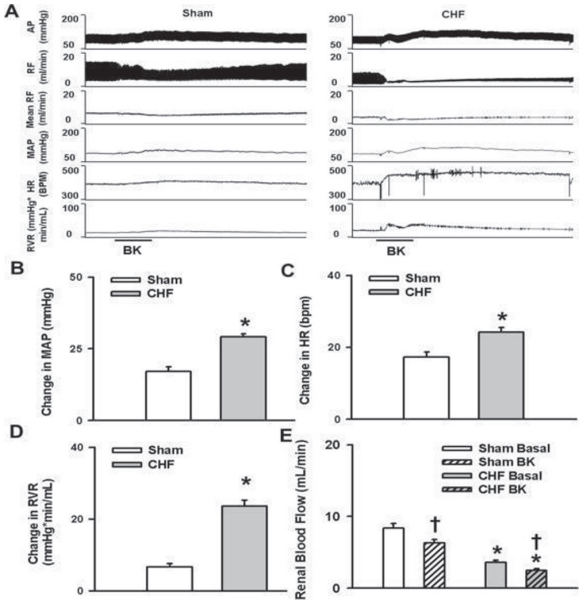

Figure 1

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Myocardial proteomic signatures in end-stage dilated and ischemic cardiomyopathy compared with normal human hearts

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Background: Proteomic studies can provide deeper mechanistic insight in the pathophysiology of heart failure, but those performed on human hearts are scarce.
Methods: Using liquid chromatography-tandem mass spectrometry, we analysed biopsies from explanted human hearts, 15 with ischemic (ICMP) and 14 with dilated (DCMP) cardiomyopathy and 12 healthy donor hearts discarded from implantation (CNT).
Results: Compared with CNT, with Benjamini-Hochberg correction applied, 20/17 down/upregulated proteins retained significance in ICMP and 18/17 down/upregulated proteins in DCMP. In both ICMP and DCMP, the tissue proteomic signature consistently showed higher abundance of proteins involved in the organisation of the extracellular matrix or derived from the circulating blood and lower abundance of mitochondrial proteins. Proteins involved in cell cycle regulation, DNA repair, transcription, calcium fluxes, contractility, signal transduction, the cytoskeleton, protein scaffolding, trafficking and folding and cell migration were either down- or upregulated. In the Ingenuity Pathway Analysis, oxidative phosphorylation and mitochondrial dysfunction were the two top canonical pathways in ICMP and DCMP. The other pathways among the top five, were, clathrin-mediated endocytosis signaling, γ-linolenate biosynthesis and liver X receptor/retinoid X receptor (LXR/RXR) activation in ICMP and γ-linolenate biosynthesis, acetate conversion to acetyl-CoA and pyruvate fermentation to lactate in DCMP, and acute phase response signaling, LXR/RXR and farnesoid-X-receptor (FXR)/RXR activation in the two disease combined. Upstream inhibitors of the pathways associated with ICMP included bone morphogenetic protein 1 (BMP1), ZFHX3 and 20-hydroxyeicosatetraenoic acid and insulin receptor. Rapamycin-insensitive companion was an upstream activator in DCMP. BMP1 and growth hormone 1 were upstream regulators in DCMP without known predicted function.
Conclusions: Our current study translates experimental studies to end-stage heart failure in humans with ICMP and DCMP. Although different in etiology, both cardiomyopathies seem to share similar mechanisms in left ventricular dysfunction and cardiac remodeling, suggesting that both conditions could be treated similarly at the end-stage.

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Rest myocardial blood flow derived from 13N-ammonia positron emission tomography does not differ between stunned and hibernating myocardium in ischemic cardiomyopathy

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Objective: The relationship between normal, stunned, hibernating and scarred myocardium is complex and controversially discussed. While the "smart heart theory" argues that a reduced myocardial blood flow (MBF) at rest is responsible for myocytes to switch into a state of hibernation, others believe that a reduced coronary flow reserve (CFR) is the main reason for hibernation.
Purpose: The aim of the present study was to investigate whether rest MBF as derived from positron emission tomography (PET) differs between stunned and hibernating myocardium.
Methods: This study included 110 patients with ischemic cardiomyopathy (left ventricular ejection fraction [LVEF] <55% and presence of coronary artery disease [CAD]) from the Zurich Quantitative PET Registry. Based on relative distribution of 13N-ammonia (NH3) and 18F-fluorodexoxyglucose (FDG) myocardial uptake as well as on wall motion (WM) assessment obtained from rest transthoracic echocardiography (TTE), myocardial tissue was characterized on a segment-level as a) remote/normal (normal stress perfusion [SP] and WM), stunned (abnormal SP, normal rest perfusion [RP], abnormal WM), hibernating (abnormal RP, normal FDG uptake, abnormal WM) and scarred myocardium (abnormal RP, FDG