Results: LV diastolic dysfunction (E/A; IVRT; Tau), high LV end-diastolic pressure and stiffness parameters were improved in HFpEF compared CTRL upon sGC stimulation. Impaired arterial elastance, arterial stiffening and endothelial dysfunction in HFpEF were corrected upon sGC stimulation. Immunohistochemistry showed increased expression level of cardiac sGC after stimulation. Cardiac fibrosis/collagen gene expression and high oxidative stress/inflammation were reduced upon treatment, which in turn corrected the low NO level, [cGMP] and PKG activity observed in HFpEF. PKG-mediated hypophosphorylation of titin in HFpEF was greatly improved upon sGC stimulation. Accordingly, increased cardiomyocyte stiffness was reduced upon sGC stimulation in HFpEF.
Conclusion: Our data suggest that chronic stimulation of sGC may be a promising treatment option for HFpEF patients.

P4-3

Design of muscle contraction assist devices by liquid crystalline elastomers

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Aims: Loss of muscle contractility occurs in different, life-threatening diseases. Current treatments suggest the need for a new generation of contraction assist devices. Liquid Crystalline Elastomers (LCEs) can work as "artificial muscle", with particular focus on cardiac muscles.
Methods and Results: LCEs are biocompatible materials able to deform reversibly in response to given stimuli. Thin (20-μm) LCEs films were prepared and their light-response and mechanical properties measured from small strips (200–400 μm diameter, 3–4 mm length) isometrically mounted between a force transducer and a linear actuator. LCE film samples maximally activated and relaxed by a green light (200 mW/mm^2), showed a mechanical behavior similar to force responses of isolated human cardiac myofibrils. The nature of material composition and the stimulus intensity modulated mechanical and kinetic parameters.
Conclusions: LCEs are suitable to mimic cardiac muscles. We prepared light-responsive LCEs films, highlighting how different molecular parameters affect different aspects of mechanical functions. Our results open for a new generation of LCE-based contraction assist devices.

P4-4

Crucial role of protein kinase G in regulating Ca2(+)/calmodulin-dependent protein kinase-II phosphorylation and oxidation and thereby diastolic function

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Rationale: Myocardial diastolic stiffness depends in part on signaling pathways and phosphorylation. $Ca^{(2+)}$/calmodulin-dependent protein kinase-II (CaMKII) δ and protein kinase G (PKG) are known to target titin, but it is unknown if PKG phosphorylates CaMKIIδ.
Methods and results: CaMKIIδ phosphorylation by PKG was assessed in recombinant proteins and heart failure (HF) biopsies by autoradiography, immunoblotting and quantified in vivo by mass spectrometry (MS). Unchanged CaMKIIδ phosphorylation and increased oxidation was observed in HF biopsies. PKG-dependent phosphosites were identified within the CaMKIIδ by quantitative MS and confirmed in recombinant human CaMKIIδ. The most highly phosphorylated sites are located in the regulatory domain and the linker region. Acute intravenous injection of PKG stimulator in anaesthetized HF rats significantly improved diastolic function via increased PKG activity, reduced CaMKIIδ auto-phosphorylation and oxidation, and reduced oxidative stress and inflammation.
Conclusion: Our study shows that PKG plays a central role in regulating and maintaining the balance of CaMKIIδ activity and oxidative stress and thereby improving diastolic function.

P4-5

HCM mutation cardiac troponin C A8 V alters cardiomyocyte nucleus structure in a knock in mouse model

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Myopathy-associated mutations in myofilament proteins are most commonly characterized by their effects on Ca^{2+}-sensitivity of muscle function, but also affect other aspects of myocyte structure and function. Considering that thin filament proteins are found not only in the sarcomeres but also in the myocyte nucleus (Asumda and Chase, 2012, Differentiation), we hypothesized that HCM mutations in troponin could alter nuclear structure. To test this possibility, we used a mouse model with Ca^{2+}-sensitizing mutation cTnC A8V (Martins et al., 2015, Circ Cardiovasc Gene) that has been associated in humans with HCM (Landstrom et al., 2008, J Mol Cell Cardiol). We first examined cardiomyocyte nuclei in H&E stained, fixed sections from 18 mo old mice; nucleus area in A8 V heterozygotes was ~ 66% of WT. We next used confocal microscopy to examine nuclei in living cardiomyocytes, isolated from 3 mo old mice and stained with NucBlue and Fluo-5N AM; nucleus area in A8V homozygotes was ~ 66% of WT, and nucleus volume in A8V homozygotes was ~ 50% of WT. Analysis of myocyte contraction suggests that nuclei can resist longitudinal compression, but only up to a point after which they are compressed by sarcomere contraction. Conclusion: an HCM mutation in cTnC affects structure of nuclei in both homo- and heterozygous cardiomyocytes.

P4-7

Cardiomyocytes derived from induced pluripotent stem cells of patient with DiGeorge syndrome show altered beating frequency and irregularity

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