and synthesis (desmosterol), as well as CRP were quantified at baseline and end of study.

**Results:** One hundred and twenty two individuals were included. Atorvastatin alone or combined with ezetimibe reduced both LDL-cholesterol and CRP (P<0.002 vs. baseline); ezetimibe did not modify CRP. Reduction in absorption markers was observed in ezetimibe-based therapies, whereas atorvastatin alone increased these biomarkers (P<0.03 vs. baseline). In addition, ezetimibe also increased desmosterol plasma levels (P<0.004).

**Conclusions:** These results contribute to understand the link between cellular cholesterol homeostasis, inflammation and lipid-modifying therapies. Our findings highlight the broader benefit of combined therapy with a potent statin and ezetimibe decreasing inflammation, and preventing increase in cholesterol biosynthesis, an effect not observed with ezetimibe alone.

P419 I BENCH
Post-infarct administration of erythropoietin-encapsulated liposomes with Sialyl Lewis X (SLX) but not without SLX repairs infarcted myocardium in rabbits
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**Purpose:** We investigated the effect of cardiac-targeting erythropoietin (EPO)-encapsulated liposomes with Sialyl Lewis X (SLX) on myocardial infarct (MI) size, left ventricular (LV) remodeling and function, and its molecular mechanism for repairing infarcted myocardium.

**Methods:** In rabbits, myocardial infarction (MI) was induced by 30 min coronary occlusion followed by reperfusion. EPO-encapsulated liposomes with SLX (L-EPO group), EPO-encapsulated liposomes without SLX (L-EPO without SLX group), liposomes with SLX without EPO (L group), or saline (Saline group) were intravenously administered immediately after MI. The MI size and the number of microvesicles were assessed at 14 days after MI. Prosurvival proteins and signals were assessed by western blot analysis at 2 and 14 days after MI.

**Results:** Confocal microscopy and electron microscopy showed the specific accumulation of liposomes with SLX in the infarcted myocardium. The MI and cardiac fibrosis areas were significantly smaller in the L-EPO group than the other groups. The LV function and remodeling were improved in the L-EPO group. The number of CD68-positive microvesicles was significantly greater in the L-EPO group than in the other groups. Higher expressions of EPO receptors, phosphorylated (p)-Akt, p-ERK, p-Stat3, VEGF, Bcl-2 and pro-MMP-1 were observed in the infarct area in the L-EPO group than in the other groups.

**Conclusions:** The EPO-encapsulated liposomes with SLX selectively accumulated in the infarct area and reduced MI size and improved LV remodeling and function through activation of prosurvival signals and by exerting antiinflammatory and angiogenic effects. EPO-encapsulated liposomes with SLX may be a promising strategy for active targeting treatment of acute MI.

**HEART FAILURE: BASIC MECHANISMS**

P419 I BENCH
The effects of chronic implanted transvenous pulmonary nerve stimulation in central sleep apnea: The remedies® System pilot study
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**Background:** Familial hypertrophic cardiomyopathy (HCM) is frequently caused by mutations in genes encoding sarcomeric proteins. It has been hypothesized that these mutations increase ATP utilization for sarcomere contraction and thereby increase energy demand of the heart. Previous studies in single left ventricular myofibrils from myocardium harboring the first identified causal HCM mutation R403Q in the gene (MYH7) encoding β-myosin heavy chain revealed increased kinetics suggesting a 3-fold increase in energy cost of tension generation. In the present study we investigated if sarcomere contraction is indeed less economic in human hearts harboring the heterozygous R403Q mutation or a homozygous tropinin T mutation (TNNT2/K280N).

**Methods and results:** Force generating capacity and ATP utilization were simultaneously measured at maximal and submaximal activating calcium concentra-tions in multicellular muscle strips to determine economy of sarcomere contraction defined as tension cost (ATP needed for force generation). Measurements in HCM samples with MYH7 (MYH7/R403Q) and TNNT2 (TNNT2/K280N) mutations were compared with control samples from sarcomere mutation-negative patients (HCMsmn) and patients with secondary left ventricular hypertrophy due to aortic stenosis (LVHao). A significantly higher tension cost of sarcomere contraction was found in MYH7/R403Q and TNNT2/K280N compared to HCMsmn and LVHao at maximal and submaximal activation. Exchange of endogenous mutant tropinin T in the TNNT2/K280N sample with recombinant wild-type protein re-stored economy of muscle contraction to values found in the controls. This proves that the mutant tropinin T protein increases ATP utilization to generate a certain amount of force.

**Conclusion:** We provide direct evidence that expression of HCM-associated mutations in the heart decreases the economy of myocardial contraction at the level of sarcomeres. Inefficient contractility may underlie cardiac dysfunction at an early stage of HCM.

P419 I BEDSIDE
Reduction of lymphocyte G-protein coupled receptor kinase-2 (GRK2) after exercise training predicts survival in patients with heart failure
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**Background:** Increased cardiac G-protein coupled receptor kinase-2 (GRK2) expression has a pivotal role at inducing heart failure (HF)-related β-adrenergic re-ceptor (βAR) dysfunction. Importantly, abnormalities of βAR signaling in the failing heart, including GRK2 protein levels, are mirrored in circulating lymphocytes and are directly correlated with HF severity. Exercise training has been demonstrated to exert several beneficial effects on the failing heart, including normalization of cardiac βAR function and GRK2 protein levels. In the present study we evaluated whether lymphocyte GRK2 and its changes after an exercise training program can predict long-term survival in HF patients.
Methods and results: At this aim, we prospectively studied 193 HF patients who underwent a 3-month exercise training program. Lymphocyte GRK2 protein levels, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and norepinephrine were measured at baseline and after training along with clinical and functional parameters (left ventricular ejection fraction, NYHA class, and peak VO2). Cardiac-related mortality was evaluated during a mean follow up period of 37±20 months. Exercise induced a significant reduction of lymphocyte GRK2 protein levels. Importantly, exercise related changes of GRK2 (delta values) robustly predicted survival in our study population. Interestingly, the lack of any significant effect of exercise to reduce lymphocyte GRK2 protein levels identified those HF patients with the poorest outcome.

Conclusions: Our data offer the first demonstration that changes of lymphocyte GRK2 induced by exercise can strongly predict outcome in patients with advanced HF.

P4194 | BENCH
Differential gene expression of cardiac chloride and potassium ion channels in human dilated non-ischemic cardiomyopathy

Purpose: Dilated Cardiomyopathy (DCM) may be induced by different etiologies, but it is known that ion-channel disruptions play an important role. The major ion channels involved in both the depolarization and repolarization of muscle cells are the ones that regulate sodium, potassium, calcium and chloride ion fluxes. The aim of the study is to evaluate the differential gene expression of cardiac chloride and potassium ion channels that represents two ways of ion-flux alterations in DCM patients, compared to normal subjects.

Methods: Experimental material was taken from 42 explanted human hearts. The RNA of 31 heart samples from DCM (n=31) patients undergoing heart transplantation and control donors (CNT, n=11) was extracted to perform a microarray analysis.

Results: We focused on the study of 4 ion channels related genes, since this functional category has not previously been studied. Two chloride (CLCN3, CLCN6) were down regulated (p=0.0001) and two potassium (KCNJ5, KCNJ8) were also down regulated (p=0.0001), in DCM. Validation of the results showed a high degree of consistency with microarray results. We determined whether gene expression changes resulted in alterations at the protein level. Moreover, we observed a significant inverse relationship between the expression of CLCN3 (n=0.7, p=0.05), KCNJ5 (n=0.7, p=0.05) and KCNJ8 (n=0.7, p=0.05) and left ventricular end diastolic dimension in subjects with DCM.

Conclusions: In this study we show that the expression of chloride and potassium-related genes is altered in HF of dilated non-ischemic origin. Furthermore, CLCN3, KCNJ5 and KCNJ8 mRNA levels are closely related with left ventricular end-diastolic dimension in subjects with DCM. These findings could provide a new base for therapeutic oriented studies.

P4195 | BENCH
Association between fetuin A in sarcopenic cardiomyopathy among an elderly cohort echocardiographic survey
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Background: Sarcopenia, an aging condition interpreting the generalized muscle wasting, may be associated with several degenerating processes. With increasing incidence of heart failure among elders, the assessment of sarcopenic status and the aging process in the heart function will be crucial. Fetuin A (FetA), a calcification inhibitor as well as a conjunction in insulin resistance, has been recently observed as a factor for body composition remodeling. We hypothesized that FetA plays a pathophysiological role in Sarcopenic Heart Failure (SHF) via the diastolic or systolic dysfunction process.

Patients and methods: Totally 541 elders were enrolled in an elderly cohort echocardiographic survey in 2012. The sarcopenia was defined by EWGSOP 2010 criteria. We recorded their medical history, measured serologic markers, including egFGR, insulin resistance (HbA1c, HOMA, hsCRP, and FetA. Cardiac echocardiographic parameters, such as Left Ventricular Ejection Fraction (LVEF), diastolic function (E/A) and estimated end-diastolic pressure (E/E') were also obtained. Subjects were defined as Sarcopenia Heart Failure (SHF) once both criteria of sarcopenia and systolic dysfunction were fulfilled.

Results: There were totally 89 (16.4%) patients (80.2±5.9 years of age, male: 30.3%) diagnosed as sarcopenia in this geriatric cohort, among them, 22 (24.7%) were fulfilled as SHF. Compared to control group without evidence of sarcopenia, those sarcopenic subjects showed reduced systolic heart function (LVEF: 68.4±6.6% vs. 64.2±9.3%, p = 0.007), higher end diastolic pressure in E/E' (7.5±2.1 vs. 10.3±4.4, p = 0.001) and higher FetA level (621.1±140.7 vs. 697.3±179 μg/ml, p = 0.0001). Further subgroup analysis revealed significantly high FetA level in SHF compared those sarcopenia with preserved LVEF (664.3±163.8 vs. 788.2±170.2 μg/ml, p = 0.0001). Among non-sarcopenic group, FetA was not different between preserved or impaired LVEF (605.5±142.2, 604.9±104.3 μg/ml, p = 0.05). Multivariable logistic regression showed that existing of coronary artery disease, reduced waist circumference, higher E/E' value and higher FetA level showed independent and significant association to predict SHF, which also indicated the possible mechanism via FetA in the diastolic relaxation maladaptation to the sarcopenic aging process.

Conclusion: In this elderly cohort echocardiographic survey, we found that FetA was significantly higher in sarcopenic elders, especially when their heart diastolic and systolic functions were impaired. These data imply the possible link between FetA and the sarcopenic heart.