plex disease resulting from impaired systolic or diastolic ventricular function. Structural cardiac remodeling induced by alterations in gene expression leads to molecular, cellular, and interstitial changes associated with extensive alterations in cardiac metabolism and essential cellular processes such as energy production.
Purpose: Project goal was to obtain a comprehensive understanding of the holistic metabolic dysregulations at different stages of HF including compensated and decompensated hypertrophy and terminal HF in a left ventricle pressure overload model.
Methods: Male mice were subjected to transverse aortic constriction (TAC) or sham operation and were sacrificed either 2, 4, or 6 weeks post-surgery. Cardiac tissue metabolites were investigated by broad, untargeted metabolomics encompassing GC-MS and LC-MS/MS and compared to results of transcriptional profiling. Since HF is associated with alterations in systemic metabolism, we also investigated metabolic profile changes in plasma, liver, and skeletal muscle.
Results: Progressive alterations of key cardiac metabolic pathways and gene expression patterns confirmed previous reports of cardiac remodeling, impaired mitochondrial beta-oxidation and a "metabolic switch" in failing hearts. We identified similar effects in liver and skeletal muscle, which were also depleted of essential fatty acids and glycerolipids in late stages of HF. Results of cardiac tissue revealed decreased carnitine shuttling and transportation preceding mitochondrial dysfunction. Changes in mitochondrial energy generation may also explain the increase of the onco-metabolite 2-hydroxyglutarate in TAC hearts. Furthermore, levels of betaine and trimethylamine-oxide were elevated in TAC hearts. Lower levels of choline (precursor of betaine) as well as choline-containing lipids in failing hearts are suggested to account for various effects commonly associated with HF. The present mouse model data also reveal novel mechanistic insights into the plasma-based metabolic cardiac lipid panel (CLP) biomarker established for the detection of HF with reduced ejection fraction (HFrEF) in humans. Highly significant discrimination between TAC and sham mice was already found 2 weeks post-surgery, preceding the development of reduced left ventricular function, which strengthens the clinical importance of our results and emphasizes the suitability of the CLP biomarker for the diagnosis of early, asymptomatic HFrEF patients.
Conclusions: Our multi-omics study indicates that metabolic alterations are already present early in compensated pathological hypertrophy and further progress with the development of HF. In addition, our findings support the notion of HF as a multisystemic disorder and may aid diagnostic and therapeutic developments in HF management.
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P3761
Correlation between vascular stiffness and 25-OH vitamin D deficit in heart failure patients

F. Buleu, S. Iurciuc, A. Caraba, N. Pop, M. Valcovici, R. Christodorescu, S. Dragan. *University of Medicine and Pharmacy Victor Babes Timisoara, Timisoara, Romania*

Background: Arterial stiffness has been shown to be a strong predictor of mortality in heart failure. Vitamin D deficiency, highly prevalent in HF patients, also increases risk of mortality and has been associated with increased arterial stiffness. Renal insufficiency, common in these patients, worsens the prognosis. The renal resistive index is a promising marker of renal vascular damage.
Purpose: The purpose of the study was to correlate arterial stiffness represented by vascular calcification marker osteoprotegerin (OPG), 25-OH vitamin D levels and renal resistive index (RRI) with parameters of left ventricular function in heart failure patients.
Methods: This case-control study included 60 patients with ischemic heart failure with angiographically documented CAD, compared with a control group of 60 healthy age-matched subjects (CON). Serum levels of OPG and 25-OH vitamin D were determined by ELISA. Left ventricular volumes (LVTSV, LVTDV) and ejection fraction (LVEF) were measured by echocardiography. Aortic pulse wave velocity (PWV) was determined using the Arteriograph device. RRI was measured by duplex Doppler in the intrarenal segmentary arteries. Peak systolic velocity (PSV) and minimum end-diastolic velocity (EDV) were determined using angle correction and RRI was defined as (PSV-EDV)/PSV. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation. The Spearman correlation test was used for interpretation of results.
Results: The values of OPG were significantly higher in heart failure patients compared to CON (4.7±0.25 vs 1.3±0.67 ng/ml, $p<0.001$). The values of 25-OH vitamin D were significantly lower in heart failure patients compared to CON (20.49±7.31 vs 37.09±4.59 ng/ml, $p<0.0001$). OPG values were significantly correlated with cardiac parameters: LVTDV ($r=0.862$, $p<0.001$), LVEF ($r = -0.832$, $p<0.001$), aortic PWV ($r=0.833$, $p<0.001$) and also with 25-OH vitamin D ($r=-0.636$, $p<0.001$). RRI values were significantly correlated with cardiac parameters: LVTDV ($r=0.586$, $p<0.001$), LVEF ($r=-0.587$, $p<0.001$) and eGFR ($r = -0.488$, $p<0.001$), aortic PWV ($r=0.640$, $p<0.001$) and 25-OH vitamin D ($r=-0.732$, $p<0.001$).
Conclusions: Measurement of arterial stiffness is a convenient, inexpensive and reliable method in heart failure patients. Parameters of arterial and renal stiffness, 25-OH vitamin D and OPG might contribute to prediction of severity and treatment adjustments in these patients.

CHRONIC HEART FAILURE – TREATMENT

P3762
The effect of eplerenone on circulating number of endothelial cell-derived microvesicles in patients with chronic heart failure

A.E. Berezin[1], A. Kremzer[1], I. Mozos[2], T. Berezina[3], T. Samura[1]. *[1]State Medical University, Zaporozhye, Ukraine; [2]University of Medicine Victor Babes, Timisoara, Romania; [3]Private medical center VitaCenter, Zaporozhye, Ukraine*

Background: Recent investigations showed that various stimuli, such as shear stress, inflammation, and vascular damage may raise number of circulating endothelial cell derived microvesicles (EMVs) via secretion from activated endothelial cells and via induction of endothelial cell apoptosis. Although it is well established that reducing the detrimental effects of mineralcorticoids using antagonists in heart failure patients via attenuating inflammation and myocardial fibrosis is associated with improved outcomes, the ability of the drug to alter EMVs is novel and the mechanisms that lead to this effect requires further investigations. The study aim was to evaluate whether the mineralocorticoid receptors (MR) antagonist eplerenone, effects circulating microparticles originated from apoptotic and activated endothelial cells in chronic heart failure (CHF) patients.
Methods: The study population consisted of 252 consecutive patients with CHF who underwent angiography or PCI between April 2010 and June 2016, and post-myocardial infarction subjects. All subjects enrolled in the study were divided into two cohorts: low dose (<50 mg daily) eplerenone treated (n=145) or high dose (50 mg) eplerenone treated (n=107) for 52 weeks. Patients were treated with optimal dose of eplerenone adjusted to plasma potassium. All biomarkers were determined at the beginning (baseline) and at the termination of the study. EMVs were phenotyped by flow cytofluorimetry using a High-Definition Fluorescence Activated Cell Sorter by phycoerythrin (PE)-conjugated monoclonal antibody against CD31, CD144, CD62E, and annexin V. For each sample, 500 thousand events were analyzed. CD31+/annexin V+ and CD144+/CD31+/annexin V+ microparticles were defined as apoptotic EMVs, EMVs positively labeled for CD62E+ as well were identified as EMVs produced due to activation of endothelial cells. Therefore, double-positive EMPs (CD31 and CD144) and triple-positive (CD144+/CD31+/annexin V+) were defined as most specific EMVs.
Results: Total CD144+/annexin V+ phenotyped EMVs were not changed between groups of the patients enrolled in the study. However, CD144+ / CD31+ EMPs were significantly reduced by 19% ($p<0.05$) in patients treated with high daily dose eplerenone compared to low daily dose eplerenon group. In both groups declined CD144+/CD31+/annexin V+ EMPs (by 13.4% and 6.3% respectively) and CD31+/annexin V+ EMVs (by 7.2% and 3.2% respectively) were found ($p<0.05$). In contrast, activated CD62E+ EMV numbers were significantly increased in high daily dose eplerenone group by 24.3% ($p<0.05$) that was associated with increased CD144+/CD31+/annexin V+ EMPs ratio by 35.5% in high daily dose eplerenone group ($p<0.05$) versus by 8.57% in low daily dose eplerenone group ($p=0.46$).
Conclusion: Eplerenone reduced circulating numder of EMVs in CHF patients dose-dependently, suggesting reduced endothelial damage. Circulating EMPs could provide a novel marker for organ damage in CHF patients

P3763
Surrogate decision-making for life-sustaining treatments in patients with heart failure: sex differences in surrogate decision-maker preferences

K. Nakamura, Y. Kinugasa, S. Sugihara, M. Hirai, K. Yanagihara, N. Haruki, K. Matsubara, M. Kato, K. Yamamoto. *Tottori University Hospital, Department of Molecular Medicine and Therapeutics, Yonago, Japan*

Background: Patients with end-stage heart failure (HF) often require surrogate decision-making for end-of-life care owing to a lack of decision-making capacity. However, the clinical characteristics of surrogate decision-making for life-sustaining treatments in Japan remain to be investigated.
Purpose: The present study was performed to clarify the clinical characteristics of surrogate decision-making for life-sustaining treatments in Japanese patients with end-stage HF.
Methods: Among 895 patients admitted to our hospital for HF from January 2004 to October 2015, we retrospectively reviewed the medical records of consecutive 106 patients who died in hospital (mean age: 73±13 years, males, 52.6%).
Results: During hospitalization, attending physicians conducted an average of 2.1±1.4 end-of-life conversations with patients and/or their families. Only 4.7% of patients participated in the conversations and declared their preferences; surrogates made medical care decisions in 95.3% of cases. Most decisions by surrogates (98.1%) were made without the patient's advance directive. During initial end-of-life conversations, 49.4% of surrogates requested cardiopulmonary resuscitation (CPR). However, 72.0% of CPR preferences were changed to Do Not Attempt Resuscitation (DNAR) orders in the final conversation. Female surrogates were more likely to change the preference from CPR to DNAR than male surrogates (47.1% vs. 25.0%, $p=0.023$).
Conclusion: In Japanese patients with end-stage HF, most decision-making regarding life-sustaining treatments was made by surrogates without indication of the patient's preference. Female surrogates wavered more often in their decisions than male surrogates.