P884
Can biomarkers be used to predict cardiopulmonary exercise test performance in patients with chronic heart failure?

M. Fudim[1], J.G. Kelly[1], A. Jones[1], A. Coles[1], S.J. McNulty[1], M. Redfield[2], G. Lewis[3], A.F. Hernandez[1], G.M. Felker[1]. *[1]Duke Clinical Research Institute, Cardiology, Durham, United States of America; [2]Mayo Clinic, Rochester, United States of America; [3]Massachusetts General Hospital, Boston, United States of America*. On behalf of Heart Failure Network

Background: Amino-terminal B-type natriuretic peptides (NTpro-BNP), soluble ST2 (ST2), growth differentiation factor (GDF)-15 and galectin 3 are novel biomarkers of cardiovascular stress and inflammation associated with cardiovascular outcomes in heart failure (HF).
Purpose: Evaluate the association of novel biomarkers in patients with chronic HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) with functional capacity.
Methods: Post-hoc analysis of the RELAX and IRONOUT trial including a HFpEF and HFrEF cohort, respectively. NT-proBNP (filling pressures and wall stress), ST2 (cardiovascular stress and fibrosis), GDF-15 (inflammation) and Galectin 3 (mediator of inflammatory and fibrotic process) were measured at baseline and at 24 and 16 weeks, respectively in a central core laboratory. We assessed the association between all biomarkers at baseline and both VO2 and VCO2 measures at baseline and the association between biomarker and functional capacity change over the course of the study. Analyses were stratified by HF type – HFpEF and HFrEF. RELAX and IRONOUT used a common cardiopulmonary testing protocol. Linear regression models were fit and adjusted for age, gender, body mass index, prior HF hospitalization in past year, systolic blood pressure and blood urea nitrogen. Multivariable adjusted models included all biomarkers.
Results: Of 441 patients, 225 HFrEF (IRONOUT) and 216 HFpEF (RELAX) patients had biomarkers measured at baseline. GDF-15 [median, (25th,75th) HFpEF: 2324 pg/mL (1537, 3713) vs. HFrEF: 1331 pg/mL (875, 2046)] and ST2 levels [HFpEF: 34 ng/mL (27, 47) vs. HFrEF: 28 ng/mL (22, 38)] were higher in the HFpEF cohort, while NTproBNP [HFpEF: 700 pg/mL (283, 1553) vs. HFrEF: 1111 pg/mL (453, 2412)] was higher in HFrEF. Galectin-3 did not differ between populations at baseline. In multivariable adjusted models only GDF-15 (HFrEF $p<0.001$; HFpEF $p<0.001$) and NTproBNP (HFrEF p=0.009; HFpEF <0.001) were associated with baseline peak VO2 in both types of HF (Figure). This relationship was similar for GDF-15/NTproBNP and VE-VCO2 slope. In HFpEF, a change GDF-15 (p=0.040) and NTproBNP ($p<0.001$) was also negatively associated with a change in peak VO2 baseline to 24 weeks (Figure). The relationship between change from baseline in NTproBNP and VE-VCO2 slope was also observed (p=0.014), while a change GDF-15 only trended towards an association with change from baseline in VE-VECO2 slope (p=0.258). Functional capacity was generally unaffected by the assigned treatment group.

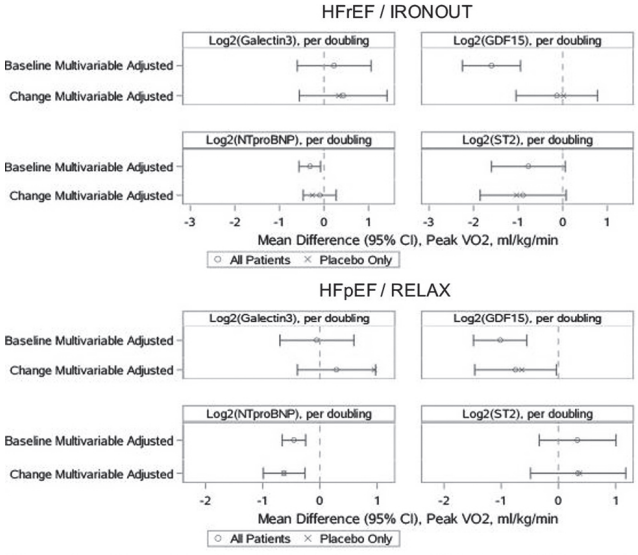


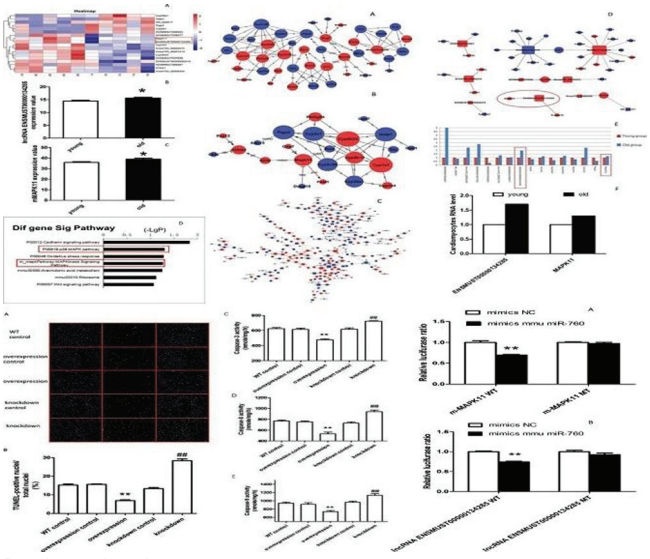
Figure: Association of biomarkers (per doubling) with peak VO_2 by heart failure type/trial.

Discussion: Both GDF-15 and NTproBNP (baseline and a change over time) are strongly associated with functional capacity in HFpEF and HFrEF, suggesting a potential role of inflammation, cardiovascular stress response and cardiac wall stress.
Funding Acknowledgements: National Heart, Lung, and Blood Institute of the National Institutes of Health

P885
The function and mechanism of lncRNA ENSMUST00000134285 in protecting the heart from aging-related myocardial apoptosis

X.C. Yang, D.H. Zhao, J.Y. Tian, Z.C. Cheng, Q. Fan, J.H. Liu. *Beijing Anzhen Hospital, Beijing, China People's Republic of*

Introduction: Aging has been well elaborated in inducing myocardial apoptosis after ischemia/reperfusion, which could accelerate the progression of heart failure. Long noncoding RNAs (lncRNAs) regulate gene expression on multiple levels, but whether lncRNAs could influence the function of aging-related myocardial apoptosis was uncertain.
Purpose: To demonstrate the function and possible molecular mechanism of lncRNAs on the aging-related myocardial apoptosis.
Methods: LncRNAs/mRNAs expression was measured in the myocardium of 5 pairs of 18-month-old C57BL/6 mice and 8-week-old C57BL/6 mice. Combined with the results of KEGG pathway analysis and co-expression analysis, we identified the aging-related lncRNAs which were significantly differential expressed in aging mice. Then realtime RT-PCR was performed to verify their expression levels. Additionally, we detected the apoptotic effect of the target gene by gene manipulation after hypoxia/reoxygenation. We used western blot technique to validate the activity of target protein and apoptosis levels were examined by TUNEL staining and caspase activity assay. Furthermore, dual-luciferase assays were conducted to demonstrate the regulatory network of lncRNA-microRNA-mRNA.
Results: After determination of lncRNA/mRNA microarray and bioinformatics analysis and verification of realtime RT-PCR, we discerned m-MAPK11 and lncRNA ENSMUST00000134285 substantially upregulated in aging cardiocytes and identified them as critical regulatory molecule in aging-related myocardial apoptosis. The function-assay results indicated that transgenic overexpression of lncRNA ENSMUST00000134285 could augment MAPK11 activity levels and attenuate myocardial apoptosis after hypoxia/reoxygenation. Meanwhile, knockdown of lncRNA ENSMUST00000134285 in cardiocytes could reduce MAPK11 activity and enhance myocardial apoptosis after hypoxia/reoxygenation. Furthermore, the results of Dual-luciferase reporter assay indicated that miR-760 may be a mediator between lncRNA ENSMUST00000134285 and m-MAPk11. The relative luciferase activity was significantly inhibited by miR-760 in the m-MAPK11 WT (wide type) vector-transfected cell, whereas miR-760 exhibited no inhibitory effect in cell transfected with the m-MAPK11 MT (mutant type) vector. Similarly, the relative luciferase activity was significantly inhibited by miR-760 in the lncRNA ENSMUST00000134285 WT vector-transfected cell, whereas miR-760 exhibited no inhibitory effect in cell transfected with the lncRNA ENSMUST00000134285 MT vector.



Part of research results

Conclusions: We elucidated that lncRNA ENSMUST00000134285 was upregulated in the aging myocardium and could upregulate the expression of m-MAPK11 by combining with miR-760, which could augment the expression of MAPK11 and reduce cardiomyocyte apoptosis after hypoxia/reoxygenation.
Funding Acknowledgements: National Natural Science Foundation of China (81771494)