Telmisartan, Cyclosporine, or 11RVIVIT attenuated stretch-induced alterations in Ito density and protein expression, and prevented the stretch-induced abbreviation of APD.

Conclusions: The activation of AT1-Calcineurin-NFAT pathway plays an important role in regulating stretch-induced remodeling of Ito and preventing the stretch-induced abbreviation of APD in cultured neonatal rat atrial myocytes.

GW25-e0792

In vivo molecular imaging of plaques in rabbits, using a molecular probe 99mTc-3PEG4-RGD

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Objectives: The extent of neovascularization is closely linked to the inflammatory response and the infiltration of foam cells within atherosclerotic plaques. In this study, we evaluated the feasibility of a radioactive-labeled 99mTc-3PEG4-RGD for vulnerable plaque imaging in vivo by SPECT/CT.

Methods: 15 male New Zealand white rabbits were randomly divided into normal diet group (group A, n=5), vulnerable plaque group (group B, n=5) and stable plaque group (group C, n=5). The animals were treated with the operation of sham separating femoral artery (group A, C) or abdominal aorta balloon injury (group B) after fed for 2 weeks. 99mTc-3PEG4-RGD was injected at key time points of plaque formation (4wk end, 8wk end, 12wk end). images were obtained with SPECT/CT at 0.5, 3, 6, 24h and 72h. The uptake of molecular probe 99mTc-3PEG4-RGD in group B was significantly higher than group A and C. Histopathology results showed that at the end of 12wk, the uptake of molecular probe 99mTc-3PEG4-RGD in group B was significantly higher than group A and C. Histopathology results showed that at the end of 12wk. The uptake of molecular probe 99mTc-3PEG4-RGD in group B was significantly higher than group A and C. The uptake of molecular probe 99mTc-3PEG4-RGD is closely associated with the number of micro-vessels and the severity of vulnerable plaque.

Conclusions: The uptake of molecular probe 99mTc-3PEG4-RGD is closely associated with the number of micro-vessels and the severity of vulnerable plaque. 99mTc-3PEG4-RGD has a certain value for noninvasively evaluating the stabiility of arterial plaques.

GW25-e1428

Metformin attenuates Angiopoietin II induced cardiac fibrosis and cardiac connective tissue growth factor (CTGF) expression through AMP-activated protein kinase activation

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Objectives: In diabetic patients, metformin appears to provide cardiovascular protection that cannot be attributed only to its antihyperglycemic effects. Metformin is also known as the AMP-activated protein kinase (AMPK) activator. Our previous study suggested that metformin inhibits cardiac fibrosis in a mouse heart failure model of pressure overload. Connective tissue growth factor (CTGF) is one of key factors in cardiac fibrosis and is usually induced by Angiopoietin II (AngII) in the pressure overload mouse models. Metformin might play its cardioprotective role through inhibition of cardiac fibrosis and CTGF production. This study investigated the effect of metformin on CTGF production induced by AngII and the underlying mechanisms.

Methods: C57BL/6 wild-type and AMPKα2 knockout were used. (3mg/kg×4day) was infused subcutaneously into mice for 7 days. Adult mouse cardiac fibroblasts were isolated and treated with AngII and/or metformin. Realtime PCR, western blot were performed for the further experiments.

Results: In C57BL/6 mice, metformin inhibits AngII-induced cardiac fibrosis (AngII vs. AngII+Metformin: 12.60±1.97% vs. 7.26±1.30% fibrosis area percentage, P<0.05). In cardiac fibroblasts, metformin inhibits CTGF expression induced by AngII (fold of control mRNA level, AngII vs. AngII+Metformin: 1.376±0.049 vs. 0.997±0.067, P<0.05). In vivo, AMPKα2 deficiency further increases AngII-induced cardiac fibrosis (AngII + wild type vs. AngII+ AMPKα2 knockout: 2.16±0.5% vs. 4.91±1.05% fibrosis area percentage, P<0.05) and CTGF expression (fold of control mRNA level, AngII + wild type vs. AngII+AMPKα2 knockout: 2.551±0.212 vs. 6.245±1.094, P<0.05). Using bioinformatics method, we found that there are putative HNF4α binding sites in the promoter region of CTGF. A 2-fold increased expression of CTGF was found in cardiac fibroblasts infected with HNF4α adenovirus. In cardiac fibroblasts, metformin inhibits HNF4α protein level induced by AngII (fold of control, AngII vs. AngII+Metformin: 4.171±0.818 vs. 2.547±0.903, P<0.05). In vivo, AMPKα2 deficiency further increases AngII-induced HNF4α protein level (fold of control, wild type vs. AMPKα2 knockout: 2.064±0.241 vs. 4.198±0.142, P<0.05).

Conclusions: Metformin inhibits AngII induced cardiac fibrosis and CTGF expression through AMPK activation. The underlying mechanism is that AMPK activation inhibits AngII induced HNF4α and then decreases CTGF expression.

GW25-e3342

Immunoglobulin expressed in mice myocardial tissue and localization in myocardial fibrosis tissue

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Objectives: This study is to demonstrate that Ig molecules can be expressed in myocardial tissue and their classes and localization. Meanwhile, observe the expression and localization of Ig in normal and fibrotic myocardia.

Methods: Wild type mice and B cell deficient mice were used as objects. First, extracorporeal heart perfusion method was used to exclude the contamination of blood. Then we detected the expression and localization of IgM, IgE by Western Blot, RT-PCR, Immunohistochemistry and Immunofluorescence method. We also detected the expression of IgM, IgE in primary cultured cardiomyocyte and HL-1 cells by RT-PCR. Moreover, we analyzed the characteristics of Ig variable region sequences and observed their localization in cardiomyocyte. C57BL/6 mice were divided into two groups: the sham group and the test group. The test group was injected with angiotensin II while the sham group was injected with saline for 14 days through a micro pump post in the back hypothermal. Then the mice were killed, Western Blot and immunohistochemistry staining were taken to detect Ig.

Results: IgM, IgE, IgG. Ig can be expressed in the heart tissue of both wild type and B cell deficient mice and localized mainly on the cross striations, however, IgG can also be observed on the cell membrane and intercalated discs. Furthermore, we detected Ig expression in primary cultured cardiomyocyte and HL-1 cells. We observed that different cell lineage (cardiomyocyte and cardiac fibroblast) showed quite different rearrangement pattern with the same cell line and showed the same pattern. We also observed that the variable region sequences of cardiomyocyte-derived IgM and IgG showed obvious tendency and highly homology. IgM localized mainly on the cell membrane especially on the cell junction. IgE and IgG showed network-like structure in myocardial tissue.

Comparing the fibrosis group with the sham group, Ig expression were up-regulated in myocardial cells. In the fibrosis area, the staining seems to disappear.

Conclusions: This is the first time to demonstrate that mice cardiomyocyte can produce Ig and these cardiomyocyte-derived Ig showed quite different functions comparing with Ig produced by B cells, which demonstrate that these cardiomyocytes-derived Ig may participate in the regulation of myocyte contraction and myocardial fibrosis.

GW25-e5187

The role and mechanism of RAS-MAPK/ERK in right heart dysfunction associated with pulmonary hypertension

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Objectives: To observe in protein expression of AT1R, TGF-β1, and ERK1/2 in pulmonary hypertension related right ventricle remodeling. Methods: 24 male SD rats were randomly divided into: Group 1 (control group), Group 2 (angiotensin II [AngII], Group 3 (Olmesartan Control) and Group 4 (Olmesartan PAH)). After 6 weeks, all survival rats were detected by echocardiography and right catheterization to observe the RVWAd and mPAP, RVSP, Weighted the RV (LV+SVP), to figure out the RVHI. Right ventricles tissue was stained with HE and TEM. The collagen I type I were detected by collagen volume fraction (CVF). Plasma concentrations of AngII was determined by radioimmunoassay. Expressions of AT1R, TGF-β1, and ERK1/2 protein of right ventricles tissue were determined by western blot. Right ventricular cardiac fibroblasts (RCFVs) obtained from neonatal rats were cultured and divided into FBS control group (group 1), AngII group (group 2), Ang-(1-7) group (group 3), U0126 group (group 4), Losartan group (group 5). RCFVs multiplication was detected by MTT colorimetric assay. The expression levels of TGF-β1 were measured by Immunohistochemistry. The expression levels of collagen type I was measured by western blotting.

Results: After 6 weeks, no mortality occurs. Compared with the group 1, RVWAd, mPAP, RVSP and RVHI significantly increased in group 2 (P<0.01) and Compared with the group 2, RVWAd significantly decreased in group 4 (P<0.01). In group 2, the microstructure of right ventricles show cardiac myocyte hypertrophy, interstitial fibrosis lined up in disorder, mitochondria swell, and the Z lines broken. These changes improved to some extent in group 4. CVF in group 2 was significant higher than that in group 1 (P<0.05), and group 4 was significant lower than that in group 2 (P<0.05). Plasma concentrations of AngII markedly increased in group 2 (P<0.05), and there was no significant difference between group 4 and group 2 (P>0.05). AT1R, TGF-β1, and ERK1/2 protein expression markedly increased (P<0.01) in group 2. Compared with group 2, AT1R, TGF-β1, and ERK1/2 protein expression in group 4 markedly decreased (P<0.01). The proliferative capacity of group 2 was significantly increased compared with group 1, while the proliferative capacity of group 3 was significantly decreased as compared with group 2, respectively. The levels of TGF-β1 and collagen type I in group 2 were significantly increased as compared with group 1. Compared with group 2, the levels of TGF-β1 and collagen type I markedly decreased in group 3-5, respectively.

Conclusions: In MCT-induced pulmonary hypertension related RV remodeling rats, AT1R, TGF-β1, and ERK1/2 protein expression of right ventricle were up-regulated, and Plasma concentrations of AngII markedly increased. Olmesartan inhibited the