Otology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were applied to determine the biological function and pathways affected by these differentially expressed genes.

RESULTS We got 3147 differentially expressed genes in total, of which 1891 genes were up-regulated (such as Apoc3, Ace2, and Fasn) and 1256 genes were down-regulated (such as Gna14, Gal, and Ngef). By GO analysis, these differentially expressed genes were classified by molecular function, which were mainly related to NADH dehydrogenase (ubiquinone) activity, cytochrome-c oxidase activity, fatty-acyl-CoA binding and calcium ion binding. From the KEGG analysis, we got 90 pathways altered by the differentially expressed genes, including Focal adhesion, Vascular smooth muscle contraction, Calcium signaling pathway, PPAR signaling pathway, Metabolic pathways and Oxidative phosphorylation.

CONCLUSIONS Due to current study, the mechanism of NTG tolerance is dramatically related to NADH dehydrogenase and cytochrome-c oxidase activity, regulated Focal adhesion and PPAR signaling pathway, which may provide a rational basis for further interpretations of NTG tolerance mechanism.

GW27-e0332

Evodiamine inhibits cardiac fibrosis and endothelial to mesenchymal transition

Xiaohan Jiang,[1,2,3] Qingqing Wu,[1,2,3] Yang Xiao,[1,2,3] Yuan Yuan,[1,2,3] Zheng Yang,[1,2,3] Zhouyan Bian,[1,2,3] Qizhu Tang[1,2,3]
[1]Xiaohan Jiang; [2]Qingqing Wu; [3]Yang Xiao, Renmin Hospital of Wuhan University, Hubei, China

OBJECTIVES Evodiamine is one of the major components of Evodia rutaecarpa and has been demonstrated to restrain atherosclerosis and protect the myocardium against injury induced by ischemia-reperfusion. However, whether evodiamine could protect cardiac fibrosis and attenuate endothelial to mesenchymal transition (EndMT) remians unclear. This study was aimed to uncover the possible mechanism involved in the protecting effect of evodiamine from cardiac fibrosis and EndMT.

METHODS The C57BL/6 mice were randomly divided into 4 groups: control; cardiac fibrosis; low- and high-dose evodiamine (50 mg/kg, 100 mg/kg). Isoproterenol(ISO) was used to induce cardiac fibrosis and evodiamine was gavaged daily at the same time for 14 days. Then the cardiac function was evaluated by echocardiography. The degree of cardiac fibrosis and hypertrophy was assessed by pathological and molecular analyses of heart samples. Microvascular density (MVD) was evaluated by immuno histochemistry. The expression levels of CD31, CD34, α smooth muscle actin (α-SMA) and vimentin were detected by immuno-fluorescence staining and western blot analyses to evaluate the extent of EndMT.

RESULTS After 14 days of ISO injection, the heart weight/body weight ratio(HW/BW) and heart weight/tibia length ratio(HW/TL) revealed no significant difference between ISO group and evodiamine treated group. Echocardiography revealed reduced interventricular septal thickness and left ventricular posterior wall thickness at end diastole in evodiamine treated group. Evodiamine also decreased cardiac fibrosis as accessed by normalization in collagen deposition and gene expression of hypertrophic and fibrotic markers. Evodiamine also prevented EndMT by increasing the expressions of CD31and CD34 while decreasing the expressions of α-SMA and vemintin, which in turn increased the MVD in heart. Furthermore, ISO-induced activation of TGF-β/Smad signal was blunted by evodiamine.

CONCLUSIONS Evodiamine may attenuate cardiac fibrosis and EndMT which is probably mediated by the blockade of TGF-β/Smad pathway.

GW27-e0335

OX40 Regulates Cardiac Remodeling Via CD4 T Cells

Qingqing Wu,[1,2] Qizhu Tang[1,2]
[1]Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, China; [2]Cardiovascular Research Institute of Wuhan University, Wuhan, China

OBJECTIVES Heart failure is a complex syndrome that results from acute injury, such as myocardial infarction or from more long-standing diseases such as pressure and volume overload. The pathophysiological substrate of heart failure during the overall process of heart tissue remodeling includes not only cardiomyocytes but also interstitial tissue, fibroblasts, inflammatory cells, and endothelial cells. More recently, several lines of evidence have involved T lymphocytes in cardiac remodeling. OX40, which belongs to the TNF-receptor family, is a costimulatory receptor that can potentiate T cell receptor signaling on the surface of T lymphocytes. The role of OX40 in non-immune systems, particularly the cardiovascular system, has not been defined. In this study, we explore the role of OX40 in pressure overload induced cardiac remodeling.

METHODS Aortic banding (AB) was performed to induce cardiac hypertrophy in male OX40 global knockout mice and their wild-type littermates. 8 weeks after AB, cardiac function of mice was examined by echocardiography and hemodynamics. The extent of cardiac hypertrophy was also evaluated by pathological and molecular analyses of heart samples. The inflammatory response was evaluated after 2 weeks of AB by real-time quantitative RT-PCR and immunofluorescence staining.

The function of CD4 T lymphocytes from WT mice and OX40 knockout mice spleen were detected by cell counting Kit 8 and ELISA. Neonatal rat cardiomyocytes (NRCMs) co-cultured with the activated supernatant of CD4 T lymphocyte from each group were stimulated with Ang II. The extent of cardiomyocyte hypertrophy was determined by immunofluorescence staining and Western Blotting.

RESULTS A noticeable increase in OX40 expression during cardiac remodeling in rodent heart was observed, while the expression of OX40 in cardiomyocytes was extremely low both under baseline and after stimulation. OX40-KO mice exhibited significantly ameliorated cardiac hypertrophy and fibrosis, inflammation and preserved cardiac function compared with wild-type mice after 8 weeks of aortic banding.

Furthermore, CD4 T lymphocyte proliferation and pro-inflammatory cytokine release were significantly diminished, while anti-inflammatory cytokine release was extremely enlarged in OX40 KO mice compared with wild-type mice as assessed by CCK-8 assay and ELISA. Co-culturing NRCMs with the activated supernatant of CD4 T lymphocytes from OX40 KO mice reduced the hypertrophy response in cardiomyocytes.

CONCLUSIONS OX40 deficiency ameliorates pressure overload-induced cardiac hypertrophy, fibrosis, dysfunction, and inflammation. OX40 alters the pathology of cardiac remodeling via the modulation of CD4 T cell function.

GW27-e0356

Effects of low-level vagus nerve stimulation on ventricular electrophysiological properties in acute myocardial ischemia-reperfusion injury canines

Chen Mingxian,[1] Lilei Yu,[2] Qiming Liu,[1] Zhuo Wang,[2] Songyun Wang,[2] Liping Zhou,[2] Hong Jiang,[2] Shenghua Zhou[1]
[1]The Second Xiangya Hospital of Central South University, Changsha, China; [2]Renmin Hospital of Wuhan University, Wuhan, China

OBJECTIVES Our previous study has been shown that low-level vagus nerve stimulation (LL-VNS) reduces ventricular arrhythmias (VAs) induced by acute myocardial ischemia-reperfusion injury (MIRI). Its potentially biological mechanisms are involving in anti-oxidative stress and anti-apoptosis effects. However, the aim of present study is to investigate the effect of LL-VNS on ventricular electrophysiological properties during acute MIRI.

METHODS Thirteen dogs were randomly divided into 2 groups: MIRI group (2h sham pre-LL-VNS then following by 2h MIRI, N=6) and LL-VNS group (4h LL-VNS plus later 2h MIRI, N=7). MIRI was induced by 1h occlusion and 1h reperfusion of the left anterior descending coronary artery. The left cervical vagal trunk was used to deliver the stimulation with 80% of voltage threshold required to slow the sinus rate. Two multiple-electrode catheters were sutured at right and left ventricular free walls. Monophasic action potentials were recorded from six epicardial ventricular sites. Ventricular effective refractory period (ERP), action potential duration (APD) restitution properties and APD alternans were measured at baseline and after 2h MIRI. VAs were measured.

RESULTS Compared to baseline, MIRI significantly shortened ventricular ERP and APD, but increased the maximal slope (Smax) of the restitution curve ($P<0.05$). However, compared to MIRI group, LL-VNS significantly prolonged ERP, APD, Smax and suppressed APD alternans at each site ($P<0.05$). LL-VNS also significantly decreased the spatial dispersion of ERP and APD ($P<0.05$). The incidence of VAs was significantly lower in LL-VNS group than in MIRI group ($P<0.05$).

CONCLUSIONS LL-VNS prolonged ERP and APD, decreased the slope of restitution curves and suppressed APD alternans during MIRI. It indicates that LL-VNS exerts a protective role for VAs induced by MIRI via modulating the ventricular electrophysiology.