BASIC AND TRANSLATIONAL MEDICINE

BASIC RESEARCH OF CARDIOVASCULAR DISEASE

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Loss of Angiotensin-Converting Enzyme 2 Exacerbates Renal Inflammation and Injury in the Apolipoprotein E-Deficient Mice

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OBJECTIVES Clinical trial evidence indicates that atherosclerosis is considered one of the major risk factors for the chronic kidney diseases (CKD) and the blockade of renin-angiotensin system (RAS) has been shown to delay the progression of CKD to end-stage renal diseases and reduce renal events in patients. Angiotensin-converting enzyme 2 (ACE2) is known as a negative regulator of the RAS, but its role in atherosclerotic renal injury are poorly understood. We hypothesized that ACE2 would exert beneficial effects on renal injury in apolipoprotein E (ApoE)-knockout (KO) mice.

METHODS The 3-month-old wild-type (WT), ApoEKO, ACE2KO, and ACE2/ApoE double-KO mice were used in this study. Systolic blood pressure (SBP) level of mouse was measured non-invasively using the tail-cuff method. We examined changes in pro-inflammatory cytokines/chemokines and adhesion molecules, renal tubule and glomerulus ultrastructure and pathological signaling assessed by real-time PCR, Western blotting, and transmission electron microscope analyses, respectively.

RESULTS Compared to WT control mice, plasma total cholesterol (CHO) and triacylglycerol (TG) concentrations were elevated in both the ApoEKO mice and ACE2/ApoE double-KO mice ($P<0.05$, respectively). ACE2 deficiency was linked with increased circulating Ang II levels and a modest elevation in SBP levels in both the ACE2KO and ACE2/ApoE double-KO mice. Compared with the ApoEKO kidneys, the level of pro-inflammatory cytokines/chemokines and adhesion molecules were increased in the ACE2/ApoE double-KO kidneys, including interleukin (IL)-1beta, IL-6, tumor necrosis factor-alpha (TNF-alpha), TNFRSF1A, RANTES, and intercellular adhesion molecule 1. Renal dysfunction and ultrastructure injury were aggravated in the ApoE/ACE2 double-KO mice associated with increases of plasma creatinine and blood urea nitrogen levels ($P<0.01$, respectively). However, ACE2 deficiency had no effect on renal TNFRSF1B expression and circulating lipid levels in the ACE2/ApoE double-KO mice ($P>0.05$, respectively).

CONCLUSIONS Loss of ACE2 exacerbates kidney inflammation and adverse renal injury in the ApoE-deficient mice via activation of the TNF-alpha/TNFRSF1A signaling pathway. These observations indicate detrimental effect of ACE2 deficiency on inflammation and renal dysfunction and point to ACE2 as a novel target for kidney-protective therapies. Strategies aimed at enhancing ACE2 action may have important therapeutic potential for atherosclerotic renal injury and CKD. This work was supported by Training Program of the National Major Research Plan (91339108), the National Basic Research Program of China (2014CB542300), and the National Natural Science Foundation of China (81370362 & 81170246).

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Optimal Cutoff of the Triglyceride to High-Density-Lipoprotein Cholesterol Ratio to Detect Cardiovascular Risk Factors Among Han Adults in Xinjiang

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OBJECTIVES To determine whether triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C), which has been shown to be an indicator of the metabolic syndrome (MetS) and insulin resistance (IR), can predict cardiovascular risk factors in the Chinese Han population in Xinjiang.

METHODS The Cardiovascular Risk Survey (CRS) was conducted from October 2007 to March 2010. A total of 14618 representative participants were selected using a four-stage stratified sampling method. A total of 5757 Han participants were included in the study. The present statistical analysis was restricted to the 5595 Han subjects who had complete anthropometric data. The sensitivity, specificity, and distance on the receiver operating characteristic (ROC) curve in each TG/HDL level were calculated. The shortest distance in the ROC curves was used to determine the optimal cutoff of the TG/HDL-C ratio for detecting cardiovascular risk factors.

RESULTS The prevalence of hypertension, hypercholesterolemia and hypertriglyceridemia were higher with higher TG/HDL-C ratio for both men and women. The TG/HDL-C ratio was positively associated with systolic blood pressure, diastolic blood pressure and serum concentrations of total cholesterol. The optimal TG/HDL-C ratio cutoffs for predicting hypertension, dyslipidemia, diabetes and $\geq$ two of these risk factors for Han adults in Xinjiang were 1.3, 1.3, 1.4, 1.4 in men and 0.9, 1.0, 1.0, 1.1 in women, respectively.

CONCLUSIONS The evaluation of TG/HDL-C ratio should be considered for one of cardiovascular risk factor predictors among Han adults in Xinjiang.

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Renal Sympathetic Nerve Modulates Ventricular Electrophysiological Characteristics

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OBJECTIVES Recently, renal sympathetic nerve (RSN) has become a hot target for therapeutic intervention in several cardiovascular diseases, including ventricular arrhythmias. However, the role of RSN in the modulation of ventricular electrophysiological characteristics is still poorly understood. The present study aimed to evaluate the effect of RSN activation (RSN-A) or denervation (RSN-D) on ventricular electrophysiology.

METHODS Twenty-one dogs were randomly assigned into RSN-A group (n=8), RSN-D group (n=8) and control group (n=5). Animals in RSN-A group received 3 hours of high frequency stimulation (20 Hz, 2 ms duration) at the voltage required to increase the systolic blood pressure by 10% to simulate a hyperactive state of RSN. RSN-D was achieved by ablating bilateral renal nerves. High frequency stimulation (20 Hz, 2 ms duration, 15 mA, 60s) was applied before and after each ablation to confirm the adequacy of denervation. Ventricular electrophysiological characteristics were measured at baseline and after interventions in each group.

RESULTS Both RSN-A and RSN-D significantly prolonged ventricular effective refractory period (ERP) (RSN-A group: 174 $\pm$ 12 vs 192 $\pm$ 15 ms; RSN-D group: 176 $\pm$ 10 vs 190 $\pm$11 ms, $p<0.05$ for both), action potential duration (APD_{90}) (RSN-A group: 219 $\pm$ 13 vs 240 $\pm$ 16 ms; RSN-D group: 222 $\pm$ 11 vs 238 $\pm$9 ms, $p<0.05$ for both), and QT interval (RSN-A group: 226 $\pm$ 7 vs 249 $\pm$ 9 ms; RSN-D group: 227 $\pm$ 8 vs 246 $\pm$ 8 ms, $p<0.05$ for both). However, RSN-A significantly increased corrected QT interval (QTc) (354 $\pm$ 11 vs 379 $\pm$ 15 ms, $p<0.05$), while RSN-D did not affect it (350 $\pm$ 9 vs 359 $\pm$ 13, $p>0.05$). In addition, RSN-A significantly increased T-peak to T-end (Tp-e) interval (an indicator highly correlated to the dispersion of repolarization) (61 $\pm$ 4 vs 85 $\pm$ 8 ms, $p<0.05$), while RSN-D decreased it (63 $\pm$ 5 vs 52 $\pm$ 6 ms, $p<0.05$). However, no significant electrophysiological change was detected in the five control animals.

CONCLUSIONS RSN-A and RSN-D cause different effects on ventricular electrophysiological characteristics. These results suggest that RSN may play an important role in the modulation of ventricular electrophysiology and arrhythmogenesis.

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Structure, Detect and Evaluate a Tissue-Engineered 3D Cardiac Model Based on Decellularized Heart Scaffold In Vitro

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OBJECTIVES Decellularized extracellular matrix that has naturally occurred three-dimensional structure has been utilized in cardiac