real-time PCR (q-PCR). NADPH oxidase (NOX) 2 and NOX4 mRNA and protein expression of left ventricular tissues was detected using q-PCR and western blot analysis that are associated with oxidative stress.

RESULTS AVE 0991 displayed a significant reduction in the left ventricular weight (15.96±0.68 vs. 22.21±0.75, $P < 0.01$) and left ventricular end-diastolic diameter (3.48±0.19 vs. 4.32±0.20, $P < 0.05$), and a significant elevation in left ventricular ejection fraction (58.16±2.78 vs. 41.82±5.58, $P < 0.05$) when compared to the vehicle-treated AB group. Moreover, we found that the mean myocyte diameter (13.53± 0.56 vs. 15.46 ± 0.21, $P < 0.01$) and the gene expression of the hypertrophic markers atrial natriuretic peptide (ANP) ($P < 0.01$) and β-MHC ($P < 0.01$) were markedly decreased in the AVE0991 group. Furthermore, AVE 0991 inhibited the mRNA and protein expression of NOX 2 ($P < 0.01$) and NOX 4 ($P < 0.01$) when compared to the vehicle-treated AB group.

CONCLUSIONS Our data showed that AVE 0991 treatment could attenuate cardiac hypertrophy and improve heart function, which may be attributed to reducing the oxidative stress.

GW26-e2369

Nicotine Exposure Causes GATA4 and Tbx5 Gene Repression by DNA Hypermethylation during Cardiac Myogenesis

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OBJECTIVES Maternal nicotine exposure caused alteration of gene expression patterns and programming of cardiovascular dysfunction. This study was to investigate effect of nicotine on cardiac gene expression and epigenetic regulation during cardiac myogenesis.

METHODS To study effect of nicotine on cardiac myogenesis, in vitro and in vivo cardiac developmental model were established respectively. Mouse embryonic bodies (EBs) derived from mouse embryonic stem cells were induced to 12-day cardiac differentiation with or without nicotine treatment. As in vivo cardiac myogenic model, pregnant Sprague-Dawley rats were exposed to nicotine through gestation, hearts were isolated from neonatal offspring for further molecular study after echocardiography for heart function.

RESULTS In vitro study shows nicotine exposure selectively inhibited expression of two cardiac genes (GATA4 and *Tbx5*) in both mRNA and protein expression level. Persistent nicotine exposure resulted in up-regulation of 5-methylcytosine, DNMT1 and DNMT3A but decreased GATA4 and Tbx5 gene expression due to promoter DNA hypermethylation. However, no significant effect has been found on mESCs proliferation and two embryonic biomarkers'(Oct4 and Nanog) mRNA expression with nicotine treatment. Nicotine exposure also decreased amounts of beating EBs and reduced GATA4 positive cells at 12-day EBs. This nicotine-induced suppression was reversed by general nicotinic acetylcholine receptors (nAChRs) inhibitor, suggesting the involvement of nAChRs in the direct adverse impact of nicotine on cardiac differentiation. Consistent results of GATA4 and Tbx5 gene suppression and promoter DNA hypermethylation by maternal nicotine treatment were obtained from in vivo cardiac development model. Echocardiography showed impaired cardiac function in offspring including reduced ejection fraction (EF%), systolic and diastolic left ventricular anterolateral wall (LVAW;s and LVAW;d) as well as systolic and diastolic left ventricular posterior wall (LVPW;s and LVPW;d).

CONCLUSIONS This study presents a direct repressive effect of nicotine on cardiac transcriptional factors (GATA4 and Tbx5) by promoter DNA hypermethylation during cardiac myogenesis. Reduction of spontaneous beating EBs and impaired cardiac function in offspring heart has been found with nicotine exposure.

GW26-e3983

Ca2+/calmodulin-dependent protein kinase modulation of torsade de pointes arrhythmogenesis and identification of targeted sites of antiarrhythmic therapy in human Timothy Syndrome arising from a new CACNA1C mutation

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OBJECTIVES Timothy syndrome (TS) is a malignant form of congenital long QT syndrome with excessive cellular Ca^{2+} entry and torsade de pointes (TdP) arrhythmias often triggered by a variety of neurohormonal and second-massager pathways. We sought to explore mechanisms by which Ca^{2+}/ calmodulin-dependent protein kinase (CaMKII) modulates arrhythmogenesis and to identify potential targeted sites of antiarrhythmic therapy in TS arising from a novel mutation (CACNA1C, p.G1911R).

METHODS A 15 mm×15 mm two-dimensional (2D) multicellular transmural tissue model was developed by integrating an anatomically ventricular geometry of the human ventricular tissue sheet and a dynamic human ventricular myocyte model incorporated with a detailed CaMKII module in the format of mono-domain model. To better understand the TS, L-type Ca^{2+} current (I_{CaL}) equations of the myocyte model were modified based on experimental conditions (current density increased ~20%, $V_{1/2}$ of activation shifted ~-5mV, $V_{1/2}$ of inactivation shifted ~+6 mV, tau of inactivation increased ~20%). To explore ionic mechanisms of CaMKII-dependent TdP, proarrhythmic substrates were compared and analyzed. In addition, in order to investigate mechanisms initiating and maintaining TdP, the spatial organization of repolarization and arrhythmogenesis were determined in the 2D transmural tissue model.

RESULTS TS ventricular myocytes exhibited more activated CaMKII(~50%), increased I_{CaL} facilitation (~55%), higher peak Ca^{2+} transient (~83%), augmented frequency of Ca^{2+} sparks (~200%), enhanced maximum SR Ca^{2+} content (~34%), prolonged action potential duration (APD) and afterdepolarizations. On the one hand, CaMKII-dependent SR overload resulted in SR Ca2+ leak for triggering delayed afterdepolarizations (DADs); on the other hand, CaMKII-dependent I_{CaL} facilitation contributed to excessive action potential prolongation in midmyocardial (M) cells (from 413.6 to 1133.9 ms) which favors the generation of early afterdepolarizations(EADs). The excessive prolongation of APD in the M cells caused an abrupt rise in transmural dispersion of repolarization (from 33.06 ms/mm to 52.99 ms/mm) and M cells formed zones of increased refractoriness, producing steep spatial gradients of repolarization that were directly responsible for conduction block and self-sustained intramural reentrant circuits underlying TdP. However, CaMKII inhibition reversed an increase in intracellular Ca2+, normalized action potential and prevented TdP.

CONCLUSIONS These computer simulations suggest that TS-mediated Ca^{2+} influx is an upstream initiating event for arrhythmia phenotypes that are ultimately dependent on CaMKII activation, the M region of TS can increase intrinsic heterogeneities of cardiac tissue and resulte in the generation and maintenance of reentrant excitations underlying TdP, and CaMKII blockers may provide additional antiarrhythmic effect in patients with TS.

GW26-e4017

Intravenous infusion of drag-reducing polymers protects against acute myocardial ischemia and reperfusion injury

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OBJECTIVES Drag-reducing polymers (DRPs) are blood-soluble macromolecules that can increase blood flow and reduce vascular resistance. It has been widely used in petroleum transportation, irrigation, navigation and other industrial pipeline. In recent years, the potential medical application of DRPs had been explored in cardiovascular disease, atherosclerosis, shock and other fields. The purpose of the present study is to observe the effect of DRPs on myocardial ischemia/ reperfusion (I/R) injury in rat model.

METHODS Adult Wistar rats were randomly divided into three groups (n=16): DRP group, Control group and Sham group. Acute myocardial infarction achieved by occluding left anterior descending coronary artery (LAD). After 30 min of ischemia, the LAD was released 120 min to induce I/R injury. Sham animals underwent left thoracotomy only. Rats in DRP group were injected with 5×10^{-5} g/ml DRP solution through the right jugular vein at a constant rate of 3.5 ml/h for 30 min during reperfusion. Saline was administered in control group and sham group. Ejection fraction was measured by echocardiography after 120 min reperfusion. A catheter inserted into left ventricle to measure left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP). Myocardial infarct size were also been measured.

RESULTS All rats in sham group survived through 150 min observation period, the survival rate in DRP group was 81.25% (13/16),

compared to 62.50% (10/16) in control group (P=0.015). After ischemic and reperfusion, DRP treatment significantly increased ejection fraction in this study (DRP group: 40.1±7.2%; Control group: 27.8±9.1%; Sham group: 53.7±7.6%; P<0.01). Our results showed that DRP decreased LVEDP and increased LVSP in DRP group compared with the control group (LVEDP: DRP group 13.46±8.54 mmHg vs. Control group 26.23±13.12 mmHg vs. Sham group 4.83±5.42 mmHg, P<0.01; LVSP: DRP group 87.71±12.68 mmHg vs. Control group 69.90±11.08 mmHg vs. Sham group 113.24±16.76 mmHg, P<0.05). Myocardial infarct size was significantly decreased in DRP group compared with that in the control group (DRP group: 22.03±8.67%; Control group: 29.54±11.36%; Sham group: 0.00±0.00%; P<0.01).

CONCLUSIONS These results suggested that DRPs had a protective effect on cardiac I/R injury of rat hearts and it may offer a new potential approach for the treatment of acute ischemic heart diseases.

GW26-e4786

Protective effects of naringin on diabetic cardiomyopathy in rats through inhibiting p38MAPK pathway

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OBJECTIVES To explore the roles of p38MAPK in diabetic cardiomyopathy. To investigate wheather Naringin protects cardiomyocytes against diabetic cardiomyopathy through inhibiting p38MAPK pathway.

METHODS The 60 male SD rats were randomly divided into normal control group (10 rats), model group (50 rats). Diabetic rats induced by high-sugar and high fat diet and intraperitoneal injection of streptozotocin. Naringin (20/40/80 mg·kg-1·d-1) and SB203580 were administered in diabetic rats for six weeks. Blood glucose were detected every 2 weeks, expression of myocardial t-p38MAPK and p-p38MAPK were tested by Western blotting Assay. Serum BNP were assayed using ELISA kit. Morphology of myocardial cell and myocardial structure were observed by light microscopy and electron microscopy.

RESULTS Naringin could lower blood glucose, BNP and heart to weight index in STZ-induced diabetic cardiomyopathy rat. Morphology of myocardial cell and myocardial structure were analyzed through light microscopy and electron microscopy, which were improved by naringin treatment. Compared with the normal control group, the p-p38MAPK expression of myocardial tissue in DCM rats treated by naringin were decreased similar to the inhibitory effect of a p38MAPK inhibitor SB203580.

CONCLUSIONS Naringin could effectively prevent myocardial remodeling and improve cardiac function via inhibiting p38MAPK pathway.

GW26-e5347

Recovery of Mesenchymal Stem Cells Homing to Rabbit Myocardial Ischemic Infarct Area by Cu-microbubble Treatment

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OBJECTIVES Mobilization and homing of bone-marrow mesenchymal stem cells (BMSCs) were observed in acute myocardial ischemic injury, but disappeared in a long-term ischemic stress along with depressed copper (Cu) concentrations in the heart. Cu is required for hypoxia-inducible transcription factor-1 (HIF-1) regulation of expression of BMSC homing factors. The present study was to test the hypothesis that Cu supplementation recovers BMSC homing signaling system, leading to BMSC homing to the chronic ischemic infarct area of heart.

METHODS Male adult New Zealand rabbits were subjected to coronary artery ligation to generate myocardial ischemia. Six months after myocardial ischemia, a newly developed ultrasound contrast microbubble composed of Cu-albumin surfaced structure was used to specifically deliver Cu to the infarct area. The autologous BMSCs were labeled with fluorescence and injected via i.v. to the rabbits 24 hours before the heart harvest. AMD3100, the specific SDF-1/CXCR4 axis blocker, was used to treat the labeled BMSCs in one group.

RESULTS BMSCs signaling was observed within 7 days after myocardial ischemia and identified in the ischemic area; but six month after myocardial ischemia, the labeled cells were not found in the ischemic area. The ultrasound-Cu-delivering led to homing of the labeled BMSCs to the chronic ischemic infarct area. AMD3100 blocked the recovery of Cu-microbubble-induced homing of BMSCs.

CONCLUSIONS This study thus demonstrated that Cu supplementation reestablishes the signaling pathways for homing of BMSCs to the chronic ischemic area, which involves the role of Cu-activated HIF-1 transcriptional activity.

Supported by National Science Foundation of China (81230004 and 81300109).

GW26-e0735

Cardiac ace2/mas expression and cardiac remodeling in hypertensive rats

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OBJECTIVES The recent discovery of the new components of the renin-angiotensin system (RAS) suggests the importance of the maintenance of cardiovascular structure and functions. To assess the role of the ACE2-Mas axis in the regulation of cardiac structure and function, the present work investigated the expression of ACE2 and Mas receptor in the heart in the cardiac remodelling that occurs in aortic constricted rats.

METHODS Partial abdominal aortic ligation was carried out in Sprague-Dawley rats. Angiotensin AT1 receptor blockade and ACE inhibition were achieved by losartan and enalapril treatment, respectively.

RESULTS Results showed that aortic constriction increased left ventricular hypertrophy, fibrosis, MAP, plasma renin activity (PRA) and cardiac ACE levels, but decreased the expression of cardiac ACE2 and Mas receptor. Losartan treatment significantly decreased MAP, left ventricle hypertrophy (LVH), fibrosis, and increased cardiac ACE2 and Mas expression. Enalapril also improved the cardiac parameters with a rise in cardiac ACE2, but did not change the Mas level.

CONCLUSIONS Aortic constriction results in cardiac hypertrophy, fibrosis and a rise of cardiac ACE expression. Both AT1 receptor blocker and ACE inhibitor play a cardioprotective role in aortic constriction. However, AT1 receptor blocker particularly promotes cardiac ACE2 and Mas receptor levels. ACE inhibitor is associated with the inhibition of ACE and normalization of cardiac ACE2 activity.

ACKNOWLEDGEMENT This study was supported by the Natural Science Foundation of China (No. 81270336).

GW26-e2291

Low Level electromagnetic field suppresses intermittent hypoxia induced atrial fibrillation through autonomic modulating

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OBJECTIVES We tested the hypothesis that low level electromagnetic field (EMF) could suppress intermittent hypoxia induced atrial fibrillation (AF) through autonomic modulating.

METHODS Electrode catheters were attached to atria, and all pulmonary veins. Helmholtz coils were powered by a function generator inducing an EMF. The ventilators were adjusted to simulate the intermittent hypoxia for 1 hour as an acute intermittent hypoxia model. Programmed stimulation determined the effective refractory period (ERP) and the window of vulnerability (WOV), a measure of AF inducibility. 40 ms of high-frequency stimulation (HFS; 100 Hz, 0.01 ms pulse width) was delivered 2 ms after atrial pacing (during the refractory period) to determine the AF threshold (AF-TH) at each site. Other electrodes were attached to the superior left ganglionated plexi (SLGP) and left stellate ganglion (LSG) so that HFS (20 Hz, 0.1 ms pulse width) to these sites induced SR slowing and blood pressure (BP) elevation, respectively. Neural activities recorded from the SLGP, LSG and Renal sympathetic nerve (RSN).

RESULTS

(1) Intermittent hypoxia induced a increase in WOV, a decrease in AF-TH and ERP at all sites (all $P < 0.05$).
(2) The SR slowing response induced by SLGP stimulation and BP elevation induced by LSG stimulation were facilitated by 1 hour intermittent hypoxia.