membrane potential, citrate synthase activity and mtDNA copy number (P<0.05). Furthermore, (2.+) HC cells with decreased SIRT1 expression and PGC-1α acetylation. Additionally, mRNA and protein expression of PGC-1α downstream genes (NRF-1, NRF-2, ERR-2 and TFAM) were reduced in HG group. Resveratrol reversed these changes in HG group, but this effect was diminished in HG+ sh-SIRT1 group.

Conclusions: Resveratrol protects against cardiac apoptosis and improves cardiac function in diabetic mice. High ghrelin biogenesis and function of SIRT1 plays an important role in the resveratrol beneficial effects against diabetic cardiomyopathy.

GW25-e4357

Ghrelin receptor deficiency aggravates instability of atherosclerotic plaque and vascular inflammation in low-density lipoprotein receptor-null mice

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Objectives: Ghrelin has been found to be associated with anti-inflammation, inhibition of atherosclerotic plaque formation and plaque stability in cardiovascular system. We investigated whether ghrelin affected the atherosclerotic plaque and immune inflammation of atherosclerosis.

Methods: We crossed ghrelin receptor knockout mice (GHSR/-/-) into a low-density lipoprotein receptor-null background. In this model, atherosclerotic plaques were promoted by feeding a high-fat, high-cholesterol Western-type diet for 18 weeks, following a standard protocol. Serum lipid levels, atherosclerotic plaque on aortic arches, and the expression of ICAM-1 and VCAM-1, T cell macrophage and smooth muscle cell of atherosclerotic plaque were measured. Results: Serum lipid levels and atherosclerotic plaque area on aortic arches were not significantly different between in GHSR+/+ LDLR-/ mice and GHSR/-/- LDLR-/ mice, the protein expression of ICAM-1 and VCAM-1 in atherosclerosis plaque were increased in GHSR/-/- LDLR-/ mice than that in GHSR+/+ LDLR-/ mice. T cell and macrophage were more, while the smooth muscle cells of atherosclerosis plaque were less in GHSR/-/- LDLR-/ mice than that in GHSR+/+ LDLR-/ mice.

Conclusions: In conclusion, ghrelin receptor deficiency aggravates instability of atherosclerotic plaque and vascular inflammation but not atherosclerotic plaque area, which will provide novel avenues for the treatment of atherosclerotic patients.

GW25-e4400

Study on the relationship between the serum level of GDF15a and infarction area for rats with myocardial infarction

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Objectives: Through detecting the serum level of growth differentiation factor 15a (GDF15a) of the rats with different myocardial infarction area, to explore the relationship between the serum level of GDF15a and myocardial infarction area and the prediction effect of GDF15a on myocardial infarction area.

Methods: 1. Experimental animals: 30 healthy Wistar rats, male, weighing 200 ~ 300 g, were randomly divided into ligature group, ligature and sham operation group with 10 rats in each group. 2. Myocardial infarction model set up: Rats are injected with 10% chloral hydrate and fixed on the operation board, assisted respiration with endotracheal intubation, connected to electrocardiograph (ECG) and monitored. In low ligation group, the coronary arteries are ligated about 3mm from the aortic root which is between the left atrial and pulmonary arterial (ECG) and monitored. In high ligation group, the coronary arteries of rats are ligated about 2 mm from the tip of the left coronary artery ligature point. Blood sampling, heart is harvested, the left ventricular long axis transverse circumference /2 = C2, (C2- C1) / C2 = percentage of patients with QTc prolongation. In conclusion, the percentage of QTc prolongation in the GHSR-/-LDLR-/- mice (40.0% in high ligation group, 38.6%±4.6% in low ligation group and 0 sham operation group. T-test is applied to compare the areas between high ligature group and low ligature group, t=8.7 with P<0.001, which shows that this result also has statistical meaning and infarction area which is higher ligature is significantly larger than the one in low ligation group. Conclusions: The serum level of GDF15a rises for the rats with cardiac obstruction, its level rises with an increasing infarction area, this phenomenon shows that the serum level of the GDF15a has certain prediction effect on the infarction area.

GW25-e4408

Magnolol administration in prehypertension postpones the development of hypertension and the underlying mechanisms

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Objectives: Patients with prehypertension are more likely to progress to manifest hypertension than those with optimal or normal blood pressure. However, the mechanisms underlying the development from prehypertension to hypertension still remain largely elusive and the drugs for antihypertensive treatment in prehypertension are absent. Here, we investigated the effects of magnolol (MAG) on blood pressure and aortic vasodilatation to insulin, and investigated the underlying mechanisms.

Methods: Four-week-old male spontaneous hypertensive rats (SHR) and age-matched normotensive Wistar-Kyoto (WKY) control rats were treatered with vehicle (distilled water) or MAG (100 mg/kg/day, o.g., once daily) for 3 weeks. Additionally, human umbilical vein endothelial cells (HUVECs) were exposed to glucose (25 mM) and a saturated FGF palmitate (16±0.5 500 μM) (HG/FF). After 18 hours and treated with MAG (10μmol/L) for 48 hours.

Results: MAG significantly decreased blood pressure in seven-week-old SHR (SBP: 131±16 vs. 160±11 mmHg in vehicle-treated SHR, DBP: 106±5 vs. 127±8 mmHg, n=8, P=0.01); improved insulin-induced aorta vasodilatation (P=0.04); and NO production (P<0.05). Furthermore, in cultured HUVECs, MAG incubation increased PPARY and decreased TRB3 expression (n=5–6, P<0.05). Moreover, in cultured HUVECs, MAG incubation increased PPARY, decreased TRB3 expressions, and restored insulin-induced phosphorylated Akt and eNOS levels and NO production (P<0.05), which was blocked by both PPARY antagonist and siRNA targeting PPARY (P<0.05).

Conclusions: Treatment of young SHR s with MAG beginning at the prehypertensive stage reduces blood pressure via improving vascular insulin resistance, which is at least partly attributable to upregulated PPARY, downregulated TRB3 and consequently increased Akt and eNOS activations in blood vessels. These results indicate that MAG may be used as an antihypertensive drug early administered at the prehypertensive stage.

GW25-e4516

Genotype-phenotype analysis on a large cohort of Chinese LQTS patients

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Objectives: Long QT syndrome (LQTS) is an inherited cardiac disorder characterized by syncope or even sudden death. Although a variety of clinical index could point to a diagnosis of LQTS, gene-screening remains to be the golden standard for LQTS diagnosis. In addition, while 15 genes have been identified as LQTS causing genes, 90% of the mutations mainly in KCNQ1, KCNH2, SCN5A– the causing genes of LQT1-3. So, in the present study, we aim to evaluate the diagnostic value of the clinical data by analyzing the genetically diagnosed LQTS patients. Besides, we also investigated the mutation spectrum and gene distribution of Chinese LQTS patients.

Methods: 214 LQTS patients, selected from the Chinese Channelopathy Registry Registry, were enrolled into this study. Patients were evaluated based on QT/canonical manifestations. Individuals were clinically diagnosed as LQTS if presenting a prolonged QT interval (QTc>450ms for male; QTc>470ms for female) and/or documented TdP (Torsade de Pointes), ventricular fibrillation as well as cardiac arrest. Molecular screening of KCNQ1, KCNH2, SCN5A genes was performed by PCR and direct DNA sequence analysis. LQTS phenotype were evaluated for all putative LQTS patients.

Results: For the total cohort of the LQTS patients, 173 patients were genotype-positive for LQTS, while 41 negative for any of the known LQTS-causing genotypes by both in two groups. Statistical results indicate that differences of average QTc, Schwartz score, percentages of patients with syncope, and Schwartz score>4 between the two groups are significant (P<0.05), while those of age of first syncpe, gender (female vs. male), percentages of patients with TdP and TdP not (P<0.05).

Overall, 173 of 214 (81%) LQTS patients were found to harbor at least one putative LQTS-causing mutation. Among them, 99 mutations were identified: 42 were in KCNQ1, 54 in KCNH2, 3 in SCN5A. In this set of mutations, 42 were novel, including 15 in KCNQ1, 27 in KCNH2, and none in SCN5A. To be specific, most of mutations (71 of 99, 72%) were missense, while frameshift mutations, splice sites, nonsense and inframe deletions account for 15% (15/99), 5% (5/99), 5% (5/99), 2% (2/99), respectively. Most frameshift mutations (11 of 15, 73%) were found in KCNH2 (representing 20% of all KCNH2mutations), while 80% (4/5) of the splice mutations were identified.
in KCNQ1 (representing 10% of all KCNQ1 mutations). In addition, 4 nonsense mutations were found in KCNQ2, whereas only 1 in KCNQ4 and none in KCNENSA.

**Conclusions:** The present study shows that average QTc, Schwartz score, episodes of syncpe are associated with a higher detection rate of mutations in LQT3 among Chinese patients. In addition, our study indicates that the majority mutations harbored by LQT3 patients are on LQT-1 causing genes and LQT2 is the most common subtype in Chinese patients. The present study also expands the spectrum of LQTS-causing mutations in Chinese.

For Chinese Channelopathy Register Investigators

**GW25±4615**

**Rat cardiomyocytes were isolated enzymatically. Fluorescence dye cGMP. The purpose of this study was to explore the molecular mechanism by which resveratrol activates the cGMP/PKG pathway remains unclear. The intracellular cellular cGMP levels were measured using DAF-FM. Cardiomyocytes treated with resveratrol for 10 min did not show a significant increase in DAF-FM fluorescence intensity, indicating that resveratrol does not produce NO. In contrast, resveratrol significantly reduced PDE5 activity and increased cGMP levels at reperfusion in the heart, indicating that the cardioprotective effect of resveratrol is mediated by guanylyl cyclase activity and is dependent on PDE5. The non-selective PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX) mimicked the cardioprotective effect of resveratrol by reducing infarct size through modulation of the mPTP opening. In addition, resveratrol enhanced the phosphorylation of VASP and GSK-3β, an effect that was partially blocked by PKG inhibitor KT5823.

**Conclusions:** Inhibition of PDE5 leading to the increase in intracellular cGMP accounts for the cardioprotective effect of resveratrol on reperfusion injury through prevention of the mPTP opening via the cGMP/PKG/GSK-3β signaling pathway.

**GW25±5194**

**A protective role of SIRT3 in endothelial function under metabolic stress**

**Yang Lu, Guo Feng**

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**Objectives:** Recent evidence has shown that loss of SIRT3 contributes to the development of the metabolic syndrome but the role of SIRT3 in endothelial dysfunction under metabolic stress has not been identified.

**Methods:** Male SIRT3 KO and age-matched wild type mice were fed with standard chow diet or high fat diet (HFD) for 24 weeks. The vasoreactive responses to phenylephrine, sodium nitroprusside and acetylcholine and ROS production in isolated thoracic aortic segments were determined.

**Results:** Phenylephrine, sodium nitroprusside, and acetylcholine evoked similar vasoreactive responses in SIRT3 KO mice and wild type mice. SIRT3 KO mice fed with HFD. However, compared with the wild type fed with HFD, endothelium-dependent relaxation to acetylcholine was impaired in SIRT3 KO mice fed with HFD. Furthermore, SIRT3 KO mice fed with HFD displayed decreased NO bioavailability and increased mitochondrial superoxide formation compared with the wild type fed with HFD. In human endothelial cells, SIRT3 knockdown exacerbated mitochondrial ROS production while SIRT3 overexpression protected endothelial function against palmitate treatment.

**Conclusions:** Our data have shown that SIRT3 deficiency increases mitochondrial ROS production and exacizes the dysfuncction in mice fed with high-fat diet, indicating a protective role in endothelial homeostasis under metabolic stress.

**GW25±5236**

**Rosuvastatin Attenuates Lps-Induced Adhesion Molecules Expression in Human Umbilical Vein Endothelial Cells**

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**Objectives:** Stable adhesion and transendothelial migration of leucocytes into the vascular wall play an important role in atherogenesis. Cell adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) may be one of the pathogenic mechanisms responsible for the development of AF associated with renal impairment (RI). Renal denervation (RDN) may be one of the pathogenic mechanisms responsible for the development of AF associated with renal impairment (RI). The main objective of the study was to explore the effects of SNS ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters except for embolization. Then animals in RI+RDN group underwent radiofrequency ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters such as effective refractory period were elevated by RI, which were reversed by RDN. Results: We observed 5 main findings. (1) Embolization of small branches of the renal artery in the left kidney led to ischemic RI with mild renal insufficiency. (2) Heart rate and BP were elevated by RI, which were reversed by RDN. (3) Atrial fibrillation developed in RI and AF inducibility in anesthetized beagles with RI. Methods: Unilateral RI was induced in beagles by embolization of small branches of the renal artery in the left kidney using gelatin sponge granules in RI (n=6) and R+RDN group (n=6). The control group (n=6) underwent the same procedure, except for embolization. Then animals in RI+RDN group underwent radiofrequency ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters such as effective refractory period were measured in baseline and after 2 weeks. Levels of angiotensin II, aldosterone, transforming growth factor-β (TGF-β) and fibrosis in atrial tissue were measured after 2 weeks.

**Results:** We observed 5 main findings. (1) Embolization of small branches of the renal artery in the left kidney led to ischemic RI with mild renal insufficiency. (2) Heart rate and BP were elevated by RI, which were reversed by RDN. (3) Atrial fibrillation developed in RI and AF inducibility in anesthetized beagles with RI. Methods: Unilateral RI was induced in beagles by embolization of small branches of the renal artery in the left kidney using gelatin sponge granules in RI (n=6) and R+RDN group (n=6). The control group (n=6) underwent the same procedure, except for embolization. Then animals in RI+RDN group underwent radiofrequency ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters such as effective refractory period were measured in baseline and after 2 weeks. Levels of angiotensin II, aldosterone, transforming growth factor-β (TGF-β) and fibrosis in atrial tissue were measured after 2 weeks.

**Conclusions:** RDN significantly reduced AF inducibility, reversed the atrial electrophysiological changes and inhibited fibrotic pathway in a model of RI by combined reduction of sympathetic drive and renin-angiotensin-aldosterone system activity system.

**GW25±5127**

**The role of PDE5 in resveratrol-induced cardioprotection against ischemia/reperfusion injury**

**X. J. Jinkun, Zhelong Xu**

Department of Physiology and Pathophysiology, Tianjin Medical University

**Objectives:** Resveratrol has been established to be cardioprotective and our previous studies have demonstrated that resveratrol prevents cardiac reperfusion injury by targeting the mitochondrial permeability transition pore (mPTP) through inactivation of GSK-3β via the cGMP/PKG signaling pathway. Nevertheless, the exact mechanism by which resveratrol activates the cGMP/PKG signaling pathway remains unclear. The intracellular cellular cGMP levels were regulated by both guanylyl cyclase that promotes the synthesis of cGMP using NO and phosphodiesterase (PDE) that induces the hydrolysis of cGMP. The purpose of this study was to explore the molecular mechanism by which resveratrol increases intracellular cGMP leading cardioprotection against reperfusion injury, focusing on the roles of NO and PDE5.

**Methods:** Rat cardiomyocytes were isolated enzymatically. Fluorescence dye 4-amino-5-methylamino-2. The role of PDE5 in resveratrol-induced cardioprotection against ischemia/reperfusion injury

**X. J. Jinkun, Zhelong Xu**

Department of Physiology and Pathophysiology, Tianjin Medical University

**Objectives:** Resveratrol has been established to be cardioprotective and our previous studies have demonstrated that resveratrol prevents cardiac reperfusion injury by targeting the mitochondrial permeability transition pore (mPTP) through inactivation of GSK-3β via the cGMP/PKG signaling pathway. Nevertheless, the exact mechanism by which resveratrol activates the cGMP/PKG signaling pathway remains unclear. The intracellular cellular cGMP levels were regulated by both guanylyl cyclase that promotes the synthesis of cGMP using NO and phosphodiesterase (PDE) that induces the hydrolysis of cGMP. The purpose of this study was to explore the molecular mechanism by which resveratrol increases intracellular cGMP leading cardioprotection against reperfusion injury, focusing on the roles of NO and PDE5.

**Methods:** Rat cardiomyocytes were isolated enzymatically. Fluorescence dye 4-amino-5-methylamino-2-fluorescein (DAF-FM) was used to image NO. Fluorescence images were obtained with confocal microscopy. Isolated rat hearts were subjected to 30 min regional ischemia followed by 2 h of reperfusion. Myocardial samples were collected from the risk zone for PDE5 activity, cGMP levels, and western blot analysis. Infarct size was measured by TTC staining. Mitochondrial swelling was measured spectrophotometrically as a decrease in absorbance at 520 nm (A520).

**Results:** Cardiomyocytes treated with resveratrol for 10 min did not show a significant increase in DAF-FM fluorescence intensity, indicating that resveratrol does not produce NO. In contrast, resveratrol significantly reduced PDE5 activity and increased cGMP levels at reperfusion in the heart, indicating that the cardioprotective effect of resveratrol is mediated by guanylyl cyclase activity and is dependent on PDE5. The non-selective PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX) mimicked the cardioproteective effect of resveratrol by reducing infarct size through modulation of the mPTP opening. In addition, resveratrol enhanced the phosphorylation of VASP and GSK-3β, an effect that was partially blocked by PKG inhibitor KT5823.

**Conclusions:** Inhibition of PDE5 leading to the increase in intracellular cGMP accounts for the cardioprotective effect of resveratrol on reperfusion injury through prevention of the mPTP opening via the cGMP/PKG/GSK-3β signal pathway.

**GW25±5238**

**Lycopene protects endoplasmic reticulum stress induced apoptosis against neonatal mouse cardiomyocytes hypoxia/reoxygenation injury**

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**Objectives:** Endoplasmic reticulum (ER) stress induced apoptosis has been implicated as a critical cause in the pathogenesis of myocardial ischemia reperfusion (IR) injury. Our previous studies demonstrated that lycopene exhibits great pharmacological potential in protecting against the IR-injury, but whether its effect is mediated through attenuation of ER stress-induced apoptosis remains unclear. The aim of this study was to investigate the effect of lycopene on hypoxia/reoxygenation (H/R) induced ER stress in primary cultured neonatal mouse cardiomyocytes.

**Methods:** Primary cardiomyocytes were isolated from neonatal C57BL/6 mice and cultured in four groups: H/R, H/R + Lycopene, H/R + Mevalonate, Lycopene treated with lycopene + H/R. Cell viability was assessed using CCK-8 assay in each group.