

microparticles, and the amounts of EMPs from plasma were increased. In ECs, along with TF upregulation, miR-19b release and expression were increased stimulated by TNF- α . Luciferase reporter assays demonstrated that miR-19b bind to TF mRNA. Overexpression of miR-19b inhibited TF expression and procoagulant activity. **Conclusions:** In UA patients, the increase of miR-19b wrapped in EMPs for endothelial dysfunction may partially contributed to the circulating miR-19b elevation. MiR-19b may play an anti-thrombotic role by inhibiting the expression of TF in ECs.

GW25-e0833

Acidic fibroblast growth factor promotes the function of endothelial progenitor cells through Akt/FOXO3a signaling pathway

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Objectives: Endothelial progenitor cells (EPCs) contribute to angiogenesis and acidic fibroblast growth factor (FGF1) gene transfer enhances EPC function. The Forkhead box O transcription factors (FOXOs) play an important role in the regulation of various cellular processes and EPCs mainly express FOXO3a. Here, we aimed to determine whether FGF1 promotes EPC function through Akt/FOXO3a signaling pathway.

Methods: EPCs were cultured from human peripheral blood and transduced with adenoviral vectors expressing a non-phosphorylatable, constitutively active mutant of FOXO3a (Ad-TM-FOXO3a) and the GFP transgene (Ad-GFP) used as control. The Ad-GFP group treated with FGF1 showed the functional improvement including cell survival, proliferation, migration and tube formation, whereas the above promoting effects were reversed after adding Akt inhibitor.

Results: The Ad-TM-FOXO3a group showed the reduced functionality compared with the control and failed to make the functional recovery after FGF1 treatment. Western blotting revealed that FGF1 made EPC functional enhancement through upregulating the phosphorylation of Akt and FOXO3a which could be suppressed by Akt inhibitor.

Conversely, FGF1 failed to rescue EPCs transduced with Ad-TM-FOXO3a from dys-function because the mutant FOXO3a were not phosphorylated by Akt.

Conclusions: FGF1 promoting EPC function is mediated through Akt/FOXO3a signaling pathway. The molecular mechanism of EPC functional improvement we initially explored may provide new ideas for the future to enhance the EPC angiogenic effect and optimize the EPC transplantation therapy.

GW25-e1550

Altered Serum MicroRNAs as Novel Diagnostic Biomarkers for Atypical Coronary Artery Disease

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Objectives: Atypical coronary artery disease (ACAD) is characterized by atypical angina pectoris or silent myocardial ischemia. However, conventional diagnostic techniques are insufficient to identify this subtype of coronary atherosclerotic pathology, and specific and sensitive markers for diagnosing ACAD are still currently lacking. The aim of the present study is to identify a novel serum miRNA expression profile of ACAD patients and evaluate its clinical diagnostic value.

Methods: We enrolled 122 patients who were diagnosed with ACAD and 44 age-matched controls in this study. We examined the levels of a subset of serum miRNAs in both ACAD and control samples. In addition, we sought to predict the potential target genes of the altered miRNAs using bioinformatics methods.

Results: By using TaqMan low density array technology followed by confirmation with quantitative real-time PCR (qRT-PCR), we identified four miRNAs including miR-487a, miR-502, miR-208 and miR-215 that were significantly increased, and one miRNA, miR-29b which was significantly decreased in ACAD patients compared with normal subjects ($P < 0.05$). The area under the ROC curve (AUC) for the five miRNAs ranged from 0.670 to 0.876 ($P < 0.05$), and their panel (0.885) was significantly higher than that of hsTnI (0.627). In addition, target gene prediction showed that these five altered miRNAs are involved in affecting various aspects of cardiac or vascular remodeling, especially in the pathway involving inflammation and fibrosis.

Conclusions: Our findings indicate that the five altered serum miRNAs could be novel non-invasive biomarkers for ACAD and may also represent potential therapeutic targets for atherosclerosis and myocardial ischemia.

GW25-e1723

Protective effects and mechanism of trimetazidine on myocardial structure damaged by pyran adriamycin

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Objectives: To explore the effects of trimetazidine on myocardial structure damaged by pyran adriamycin and to clarify the protection and mechanism of trimetazidine on damaged myocardial structure induced by pyran adriamycin.

Methods: 36 Wistar rats were randomly divided into control group, model group and treatment group. Rats in model group and treatment group were injected pyran doxorubicin 2.5mg/kg (concentration 2mg/ml) by the vena caudal once a week. Control group were injected equivalent normal saline in a coordinative control for 6 weeks. Rats in treatment group were intragastric infuse trimetazidine 5.4mg/kg/d one day before making the model. Control group, model group were injected equivalent normal saline in a coordinative control for 8 weeks. At the end of the experiment, index of heart mass of rats and myocardial enzymes of serum were measured. Systolic and diastolic function were detected with echocardiography. The myocardium tissue were detected by light microscope and electron microscope.

Results: Compared with model group, the level of myoglobin, troponin and alanine transaminase (ALT) in treatment group were decreased ($P < 0.05$). Index of heart mass in treatment group is lower than that in model group and nearly the level of control group. Compared with control group, EF and FS in model group decreased ($P < 0.01$) and LVIDD, LVIDS in creased ($P < 0.05$). EF and FS in Group C is larger than that in Group B ($P < 0.05$), LVIDS, LVIDD in treatment group is lower than model group ($P < 0.05$). Under the light microscope observation, in model group myocardial arranged disorderly, severely damaged structure, multiple visible myocardial, myofibrilament dissolved, fracture, while in treatment group myocardial arranged in order, structure was nearly integrated, partial dissolution, fracture. Under the electron microscope observation, in model group myocardial muscle bundle dissolved fractured, disappeared, mitochondria decreased, cytoplasmic matrix cavitation, while in treatment group, arrangement of cardio myocytes sarcomeres in tow, local myofibrilaments reduced slightly, surrounding mitochondria were oval and arranged in parallel between the muscle bundles.

Conclusions: Trimetazidine can protect the damaged cardiomyocytes and improve the cardiac function caused by pyran adriamycin, and its mechanism may be related to decrease the injury of mitochondria and myocytes

GW25-e3154

Prognostic Value of Mean Platelet Volume to Platelet Count Ratio and White Blood Cell Count in Predicting the Survival in Acute Aortic Dissection

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Objectives: Recent evidence indicates that platelet indices and white blood cell (WBC) are associated with the prognosis of patients with acute aortic dissection (AD). However, there have been no systematic investigations on the utility of baseline mean platelet volume (MPV) to platelet count (PC) ratio (MPV/PC ratio) and WBC for predicting the survival of acute AD. The present study was designed to examine whether the MPV/PC ratio and WBC could predict mortality in acute AD

Methods: Baseline clinical details and hematologic parameters were obtained prospectively in 272 acute AD patients consecutively admitted to a single medical center. The levels of MPV, PC and WBC were determined after their initial admission and evaluated, in concert with follow-up patient survival data, to determine if the MPV/PC ratio and WBC could predict mortality. Between initial measurement and follow-up (medium time: 570 (11-1222.5) days)

Results: Increased levels of plasma MPV/PC ratio (6.3513 (4.6439-8.8730) versus 5.3939 (4.068-6.7415), $P < 0.001$) and WBC (11.90 (8.85-16.03) vs 9.91 (7.46-13.05), $P < 0.001$) were found in dead patients compared with those survived during the follow-up. Multivariable analysis showed that MPV/PC ratio ($P = 0.014$, OR = 1.179, 95% CI: 1.034 to 1.344) and WBC ($P = 0.011$, OR = 1.106, 95% CI: 1.024 to 1.195) was an independent predictor for all-cause mortality during follow-up, respectively. The areas under receiver operating characteristic (ROC) curves of MPV/PC ratio and WBC were 0.618 (95% CI: 0.542 to 0.694) and 0.625 (95% CI: 0.553 to 0.698) for predicting follow-up mortality, with a sensitivity of 39.8%, specificity of 88.1%, cut-off value of 7.55197×10^2 fL (109/L) and a sensitivity of 52.7%, specificity of 68.9%, cut-off value of 11.53×10^9 /L, respectively. While the areas under ROC curves of combination WBC and MPV/PC ratio was 0.674 (95% CI: 0.603 to 0.745) with a sensitivity of 39.8%, specificity of 88.1%. Kaplan-Meier analysis and log-rank test revealed significant survival differences between patients with a MPV/PC ratio $< 7.55197 \times 10^2$ fL (10^9 /L) and a MPV/PC ratio $\geq 7.55197 \times 10^2$ fL (10^9 /L) ($P < 0.001$) and with a WBC $< 11.53 \times 10^9$ /L and a WBC $\geq 11.53 \times 10^9$ /L ($P < 0.001$). Subgroup analysis showed MPV/PC ratio had prognostic value for mortality in patients with type A ($P < 0.001$), surgery ($P = 0.007$) and only medication treatment ($P < 0.001$), no predictive value were found in patients with type B ($P = 0.410$) and endovascular treatment ($P = 0.822$) patients, while prognostic value of WBC for mortality was found in patients with type A ($P = 0.004$) and only medication treatment ($P = 0.004$). **Conclusions:** the elevated MPV/PC ratio and WBC were important risk factors and independently associated with mortality of patients with acute AD. These patients may benefit more from surgical intervention and endovascular treatment.

GW25-e3180

Berberine attenuates cardiac dysfunction, fibrosis, inflammatory in diabetic cardiomyopathy

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Objectives: Patients with diabetes exhibit an increased risk of heart failure. Berberine is a major isoquinoline alkaloid, which is the most abundant constituent of Chinese herb *Rhizoma coptidis*, exerts anti-inflammatory effects in various disease models and prevents diarrheic and inflammation in humans. Berberine may exert cardioprotective effect against myocardial injury and dysfunction in diabetes. In this study, we investigated the effects of berberine on myocardial dysfunction, fibrosis, and inflammation using a rat model of diabetic cardiomyopathy and primary neonatal rat cardiofibroblasts exposed to high glucose and TGF- β .

Methods: Rats were randomized to receiving saline or berberine treatment (200 mg·kg⁻¹·d⁻¹, gavage) for 4 wks. Left ventricular function was measured by echocardiography. Fibrosis and inflammation markers were evaluated by molecular biology/biochemical techniques.

Results: Diabetic cardiomyopathy was characterized by declined LV ejection fractions and decreased LV volumes associated with increased MAPK (JNK and P-38) activation, enhanced expression of adhesion molecules ICAM-1, TNF- α , markers of fibrosis (TGF- β , CTGF, fibronectin, collagen expression, MMP-2 and MMP-9), and diminished AMPK, Akt and ERK phosphorylation. Remarkably, berberine attenuated myocardial dysfunction (91.29±2.93% vs. 76.25±1.66% in diabetic rats, n=4, P<0.01), cardiac fibrosis (TGF- β mRNA, 48.88±5.69% vs. 215±14.65% in diabetic rats, n=3, P<0.05), inflammation and interrelated signaling pathways respectively. Furthermore, berberine also attenuated the TGF- β -induced increased cardiac fibrosis and inflammation signaling pathways in cultured fibroblasts, which berberine effects were blocked by AMPK inhibition.

Conclusions: These results suggested that berberine may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders, by attenuating fibrosis and inflammation.

GW25-e0289

The mechanism research of microRNA-181a regulated H9c2 cell oxidative stress injury induced by hydrogen peroxide

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Objectives: Glutathione peroxidase-1 (Gpx1) is a pivotal intracellular antioxidant enzyme that enzymatically reduces hydrogen peroxide to water to limit its harmful effects. Recent findings indicate that the lack of Gpx1 contributes to the risk of atherosclerosis and cardiovascular disease. This study aims to identify a microRNA (miRNA) targeting Gpx1 to maintain redox homeostasis.

Methods: The cultured H9c2 cells were treated with different concentration of H₂O₂ for 2h. Then, CCK8 assay was used to determine cell viability and the extent of apoptosis was detected by TUNEL assays. Exogenous H₂O₂ induced endogenous Gpx1 expression change in H9c2 cells was assessed by Western blot. Dual luciferase assay combined with mutation and immunoblotting was used to validate the bioinformatically predicted miRNAs. H9c2 cells were transfected with miR-181a mimics or miR-181a inhibitor, H₂O₂ (400 μ M) was added for the last 2 h. H9c2 cells were divided into the following 6 groups. The changes of apoptosis in H9c2 cells were quantitatively assayed with Annexin V and PI double staining by Flow cytometric. LDH and MDA were simultaneously measured. The changes in intracellular ROS was detected by DCFH-DA staining. The measurement of mitochondrial membrane Potential was detected by using JC-1 probe. The expression of Bcl-2, Bax, cleaved caspase-3 in H9c2 cells were detected by Western blotting. Immunofluorescent detection of intracellular cytochrome c localization was used by fluorescent microscopy.

Results: 400 μ M H₂O₂ damage the antioxidant enzymes system resulting in Gpx1 expression decreased (P<0.05). The intersection of three algorithms identified four potential miRNAs candidates: miR-7a, 125a, 181a and 423. At the apoptotic concentration of H₂O₂, only miR-181a expressions were increased compared with normal group, whereas other's expressions decreased (P<0.05). A significant decrease in relative luciferase activity was observed when pmir-RB-Gpx1-3'-UTR was co-transfected with miR-181a mimics as compared with the scrambled miRNAs, and the miR-181a mimics-mediated suppression was abolished by the mutation of the 3'-UTR miR-181a binding site. Compared with anti-CTL group, the release of LDH and the content of MDA, the production of ROS, the apoptosis rates, Bax, cleaved caspase-3 expression and the release of cytochrome c from the mitochondrial intermembrane space into the cytoplasm were significantly decreased in anti-miR-181a group (P<0.05) and the expression of Bcl-2 and mitochondrial membrane potential was correspond increased in anti-miR-181a group while upregulation of miR-181a exacerbated it (P<0.05).

Conclusions: we have demonstrated that the expression of miR-181a is up-regulated in H₂O₂-treated H9c2 cells and that miR-181a inhibitor confers cardiac protection against oxidative stress-induced H9c2 cells apoptosis through directly inhibiting the Gpx1 expression and the ROS generation which maintains mitochondria membrane integrity and inhibits the activation of mitochondrial apoptotic pathway under oxidative stress conditions. These novel findings may have extensive implications for the diagnosis and therapy of a variety of cardiovascular diseases related to ROS such as atherosclerosis, hypertension, restenosis after angioplasty or bypass, diabetic vascular complications, and transplantation arteriopathy.

GW25-e0442

The effect of hematoporphyrin monomethyl ether mediated sonodynamic therapy on rapid delayed rectifier potassium channel and pharmacological activity analysis

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Objectives: Sonodynamic therapy (SDT) is known to decrease multiple cells viability, and nerve stimulation reduces its activity and antagonizes the arrhythmias. The rapid delayed rectifier potassium channel (IKr) is involved in repolarization of cardiac action potential. We investigated the effects of HMME-induced SDT on the biophysical properties of IKr channel and the underlying structure-activity relationships.

Methods: The effects of HMME-SDT were examined on the IKr channels in the stable transfected HEK293 cells using a whole-cell patch clamp technique, western blot analysis and immunofluorescence experiment. The pharmacokinetics and tissue distribution determination of HMME in rats were determined by a validated RP-HPLC method.

Results: HMME-SDT induced decrease of current amplitude in time-dependent. HMME-SDT reduced IKr tail current from 69.5±5.3 pA/pF in control group to 55.6±3.1 pA/pF in the 1 min group, 52.8±1.9 pA/pF (3 min) and 16.7±0.8 pA/pF (5 min); the corresponding current densities of HMME-SDT-treated cells were 39.8±2.9 pA/pF, 31.2±3.0 pA/pF and 15.9±0.7 pA/pF, respectively. HMME had binding affinity for the open and inactivated state of IKr channel. HMME distributed quickly in rats, which was found to be in high concentration. HMME-SDT had no effect on the generation and expression of IKr channels.

Conclusions: In conclusion, HMME-SDT is a potent way to block IKr channels, and may be a potential treatment as an antiarrhythmic method.

GW25-e0548

Effects of arsenic trioxide on cell apoptosis and voltage-gated potassium currents of rat mesenteric arterial smooth muscle cells

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Objectives: Study was designed to determine the changes of voltage-gated K⁺ currents (I_{Kv}) in the mesenteric arterial smooth muscle cells of rat during the gradual apoptosis process by arsenic trioxide treatment.

Methods: Effect of arsenic trioxide on vascular smooth muscle cells was determined by MTT assay. Apoptosis was evaluated by TUNEL method and voltage-gated K⁺ currents were recorded by whole-cell patch-clamp.

Results: Arsenic trioxide reduced vascular smooth muscle cell viability in a concentration-dependent manner after 48h exposure of the cells to 2-32 μ mol/l arsenic trioxide. Arsenic trioxide 8 μ mol/l (48h) induced apoptosis in the cultured mesenteric arterial smooth muscle cells. Apoptosis ratio in arsenic trioxide 8 μ mol/l (48h) incubation group was 21±1.3% vs. 0.9±0.2% in control group (n=5, P<0.05). This concentration was used to treat the primary cultured mesenteric arterial smooth muscle cells for 48h and the voltage-gated K⁺ currents densities (I_{Kv}) was down-regulated. The densities of the I_{Kv} in 8 μ mol/l arsenic trioxide groups were 4.18±0.85 pA/pF vs. 16.86±1.22 pA/pF in the control group at +60mv (n=6, P<0.05).

Conclusions: Chronic As₂O₃ treatment induced vascular toxicity is mediated, at least in part, by apoptosis of cultured mesenteric arterial SMCs. The densities of I_{Kv} in cultured mesenteric arterial smooth muscle cells down-regulated during the gradual apoptotic process maybe a self-protective mechanism to reduce the loss by apoptotic stimuli, and also accelerate vascular disease.

GW25-e4442

Genetic analysis of an SCN5A Mutation in Chinese Patients with Arrhythmogenic Right Ventricular Dysplasia

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Objectives: Arrhythmogenic right ventricular dysplasia (ARVD) is a genetically determined disorder, characterized by two components, cardiomyopathy and arrhythmia. To date, the ion channel-related pathogenesis underlying this phenomenon has been poorly understood. The aim of this study was to systematically evaluate the sodium channel variants in Chinese patients with ARVD.

Methods: Patients meeting the diagnostic guidelines of ARVD revised in 2010 were enrolled. All exons and exon-intron boundaries of the SCN5A gene and desmosomal genes known to be associated with ARVD, including DSC2, DSG2, DSP, JUP, and PKP2 were sequenced by direct DNA sequencing.

Results: A total of 12 unrelated index patients were included. The eight of them developed ventricular tachycardia (VT) and ventricular fibrillation (VF), one of them showed Epsilon wave, one of them showed type 1 Brugada wave, seven of them exhibited syncope or dizziness, and none of the patients had a family history of SCD. A new missense heterozygote mutation, I137M, in SCN5A was found in proband 5 with recurrent palpitations and a high incidence of VT. I137M is in exon 4 of SCN5A, at the S1 segment in domain I of Nav1.5, and predicted a substitution of isoleucine for methionine at codon site 137 (P. Ile137Met, I137M). I137M was not detected in 400 healthy control chromosomes from individuals of the same ethnic background, which indicated that this mutation was a conservative site in the SCN5A gene, and the encoded protein Nav1.5 might have a functional defect resulting in arrhythmia.

Conclusions: This study for the first time systematically evaluated the sodium channel variants in Chinese patients with ARVD, and found a new SCN5A mutation, I137M. The result increases insight to the genetic pathogenesis of ARVD in Chinese patients, and SCN5A genetic screening should be done in patients with ARVD and VT/VF.