Objectives: Orai3 is a store-operated Ca^{2+} channel specific for mammals. Previous studies found that 2-APB, an agonist of Orai3 channel, can either cause or prevent atrial fibrillation in animals. The aim of this study is to determine whether Orai3 mutation is a pathogenetic factor of atrial fibrillation.
Methods: Genomic DNA was extracted from the peripheral blood of 124 patients with atrial fibrillation. The two exons of Orai3 gene were separately amplified from the genomic DNA and sequenced with corresponding primers. The coding sequences were assembled and aligned with the reference sequence from GenBank. Mutation found in the alignment was confirmed by manual check on the original sequencing chromatograms.
Results: Two of the 124 patients were found to carry heterogenic mutation from C to T at position 711 of the nucleic acid sequence. However, this mutation does not lead to any change on translated amino acid sequence.
Conclusions: Due to the lack of non-synonymous mutation in Orai3 gene, we conclude that Orai3 channel is probably not directly involved in the cardiac action potential. The effect of 2-APB on atrial fibrillation is more likely related to other targets of this drug, such as IP_3 receptors.

GW25-e3159

Screening of potassium channel mutations in patients with atrial fibrillation

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Objectives: To identify gene mutations of potassium channels that contributed to the pathogenesis of atrial fibrillation.
Methods: Genomic DNA was extracted from the peripheral blood of 124 patients with atrial fibrillation. The coding regions of genes including KCNE1 (minK), KCNE1L (KCNE5), KCNE2 (MiRP1), KCNE4 (MiRP3), KCNJ2 (Kir2.1) and KCNJ4 (Kir2.3) were amplified from the genomic DNA and sequenced with corresponding primers. The obtained sequences were aligned with reference sequences from GenBank. Mutations found in the alignments were confirmed by manual check on the original sequencing chromatograms.
Results: Mutations leading to changes of amino acids and corresponding mutation rates were found: KCNE1, S37R (0.8%), S38G (92.7%), D85N (0.8%); KCNE1L, Y81H (0.16%); KCNE2, none; KCNE4, M109V (0.8%), D196E (91.1%); KCNJ2, V93I (0.8%); KCNJ4, none.
Conclusions: Genetic mutations on potassium channels are important pathogenetic factors of atrial fibrillation. Among the six genes screened KCNE1 and KCNE4 showed highest mutation rates. The electrophysiological functionality of these mutants needs to be examined in the future to understand their impacts to the cardiac action potential.

GW25-e3168

Sodium tashinoneIIA sulfonate improves tachycardia-induced electrical remodeling of canine

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Objectives: To determine the effects of DS-201 on electrical remodeling of canine and cell membrane potassium ion channels.
Methods: Mongol canines were used for preparation of animal models with AF through rapid pacing left atrial appendage, and then the effect of DS-201 on AF was determined by frequency and duration of AF. And $K_v1.5$ protein expression in atrial myocytes was detected with western blotting.
Results: It was showed that DS-201 significantly reduced both the frequency and duration of AF ($P<0.05$, n=5). The frequency of AF was reduced from 7.2±1.31 to 3.12±1.05, and the duration of AF was lowered from 5.2±2.13 s to 0.89±1.23 s. It is interested that DS-201 did not inhibit $K_v1.5$ protein expression but significantly increase its expression.
Conclusions: DS-201 improves tachycardia-induced electrical remodeling of canine by meliorating the low-level expression of $K_v1.5$ in AF.

GW25-e3173

Inhibition of TRPC channels by the cardioprotective drug sodium tanshinone IIA sulfonate

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Objectives: Sodium tanshinone IIA sulfonate (STS) is a water-soluble derivative of tanshinone IIA, the major lipophilic component extracted from the root of Danshen (*Salvia Miltiorrhiza*). STS is clinically used in the treatment of myocardial infarction, coronary artery disease and other cardiovascular disorders. STS can protect the heart against pathological hypertrophy in laboratory animals. However, the direct molecular targets of STS on cardiomyocytes are still unclear. Here we aim to examine the effect of STS on the activity of TRPC channels, which have been suggested to be important mediators of pathological cardiac hypertrophy.
Methods: Intracellular Ca^{2+} measurement and patch clamp recordings were performed on HEK293 cells stably transfected with human TRPC4 and TRPC5 cDNA. STS was applied to the extracellular solution to test the drug effect.
Results: We found that STS at micromolar concentrations inhibited TRPC4 and TRPC5 channels. The potency of tanshinone IIA on the inhibition of these channels is much lower than that of STS, suggesting the sulfonation of this compound is important for its channel-inhibitory activity.
Conclusions: The inhibition of TRPC channels by STS found in this study is a novel aspect of the cardioprotective pharmacology of this drug. As STS has been used in patients by injection with safety approval, our results suggest that blockade of TRPC channels is a potentially safe strategy for clinical therapy.

GW25-e3207

β1-adrenoceptor Autoantibodies Induce Repolarization Abnormalities and Increase Susceptibility to Ventricular Arrhythmias in Guinea Pigs

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Objectives: The objective of this study was to investigate whether monoclonal autoantibodies against the second extracellular loop of β_1-adrenergic receptor (β_1-AR mAb) induce directly ventricular arrhythmias and to clarify the electrophysiologic mechanisms.
Methods: To identify the function of β_1-AR mAb, the binding of β_1-AR mAb with the β_1-adrenergic receptor (β_1-AR) on the $H9C_2$ by laser scanning confocal microscopy and the effects of β_1-AR mAb on the beat frequency in cultured ventricular myocytes of neonatal rats were observed. A langendorff perfused heart model was used in this study to explore the direct roles of β_1-AR mAb in arrhythmias.
Results: Results showed that β_1-AR mAb may bind with β_1-AR and increase the beat frequency of ventricular myocytes of neonatal rats, which was similar to autoantibodies against the second extracellular loop of β_1-adrenergic receptor (β_1-AA) isolated from patients, thus β_1-AR mAb might be seen as the tool to stuy β_1-AA. β_1-AR mAb induced ventricular premature contractions, and enhanced the excitability of ventricular fibrillation by decreasing the threshold of ventricular fibrillation (β_1-AR mAb group: 9.0±1.5 V; Control group: 11.0±2.1 V, $P<0.05$, n=5/group) and prolonging the duration of ventricular fibrillation (β_1-AR mAb group: 1608.0±135.0 ms; Control group: 1000.0±127.1 ms, $P<0.05$, n=5/group); β_1-AR mAb increased the susceptibility to ventricular arrhythmias as a result of repolarization abnormalities by reducing corrected QT intervals (0 min: 360.0±11.1 ms; 10 min: 333.0±14.0 ms, $P<0.05$, n=5/group) and prolonging late phase repolarization of monophasic action ($MAPD_{90-30}$) (0 min: 360.0±11.1 ms; 10 min: 333.0±14.0 ms, $P<0.05$, n=5/group) in isolated guinea pig hearts.
Conclusions: It is concluded that β_1-AR mAb could induce directly ventricular arrhythmias attributed to the increase of the susceptibility of ventricular arrhythmias by causing repolarization abnormalities.

GW25-e3301

Cardioprotective Effect of Pinacidil on Rats Heart with Transient Hypoxia and Reperfusion Injury

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Objectives: The aim of this study was to evaluate the cardioprotective effect of pinacidil postconditioning on rat hearts with transient hypoxia and reperfusion.
Methods: An acute myocardial anoxia-reperfusion rat model was created by ligating coronary arteries for 10 min and subsequent reperfusion for 60 min. Twenty-four rats in 4 groups received different treatments: normal hearts as control (N=6), anoxia-reperfusion (A/R) only (N=6), pinacidil postconditioning (N=6), and pinacidil plus adenosine triphosphate-sensitive potassium channel inhibitors (glibenclamide) (N=6). The kinetic parameters and electrophysiological properties, including early apoptosis protein expression changes of Bax, Bcl-2, and FN were examined using the isolated perfusion and patch-clamp technique and immunohistochemistry.
Results: The left ventricular systolic pressure and maximum -dp/dt in A/R groups were significantly higher than those in the control group ($P<0.05$). The left ventricular developing pressure, maximum +dp/dt, and heart rate in the A/R group were slightly decreased. The pinacidil-postconditioned group has better cardiac function recovery after ischemia/reperfusion than the A/R group ($P<0.01$). In addition, using the patch-clamp technique, significant differences in the mean open time and conductance value were found in the pinacidil group relative to the A/R group. The expression of apoptosis proteins (Bax, FN) increased during A/R, while the Bcl-2 protein expression decreased. A significant difference was found in the pinacidil treatment group relative to the A/R group.
Conclusions: Pinacidil postconditioning can exert cardioprotective effects on A/R-injured rat hearts, which may indicate a potential application of pinacidil postconditioning to protect A/R-injured hearts.