90A ABSTRACTS - Cardiac Arrhythmias

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1041-11
Significant Association of Renin-Angiotensin System Gene Polymorphisms With Human Atrial Fibrillation
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Background: Activated local renin-angiotensin system (RAS) has been reported to play a role in the pathogenesis of AF. We hypothesized that the RAS genes might be among the susceptible genes of AF, and conducted a genetic case-control study to demonstrate this. Methods and Results: A total of 110 patients with documented AF and 110 controls were selected. The controls were matched to cases by age and sex. The polymorphisms of the renin gene, angiotensinogen gene, and angiotensin II type 1 receptor gene were genotyped in single nucleotide analysis. Results: Single RAS genes were unassociated with AF. However, the frequencies of 22252/A, 6262G/p, and 12217A were significantly associated with AF. The frequencies of M235, G-4, and G-2142 were significantly higher in cases than in controls (p = 0.001, 0.009, and 0.003, respectively). The odds ratios for AF were 3.3 (95% confidence interval CI 1.4-10.0) with M235/M235 plus M235/T235 genotype, 2.9 (95% CI 1.1-7.8) with G/G-4 plus G-4-4 genotype, and 2.0 (95% CI 1.1-5.0) with G-217/G-217 genotype. The associations were significant and not random, and could be explained by our relevant functional studies. In multiscus haplotype analysis, the angiotensinogen gene haplotype profile was significantly different between cases and controls (p < 0.05, p = 0.04). No significant gene-gene interaction was noted by stratification analysis and multivariate analysis. Conclusions: Our study first demonstrates the significant association of RAS gene polymorphisms with AF, and may provide the rationale for clinical trials to investigate the use of renin converting enzyme inhibitor or angiotensin II antagonist in the treatment of AF.

1041-12
Ability of Activation Recovery Interval to Assess Electrical Restitution Properties
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Background: Electrical restitution properties have been proposed as a mechanism for the development of arrhythmias and ventricular fibrillation. The measurement of restitution curves is mainly based on data from monophasic action potentials (MAP), optical, and micro-electrode recordings. We investigated if activation recovery intervals (ARI) derived from unipolar electrograms have a similar ability to assess restitution properties.

Methods: Needles containing 3 KCl MAP electrodes 5 mm apart, each consisting of a KCl electrode and a nearby reference electrode, were inserted into the anterior left ventricular free wall to record transmurally in 6 open-chest pigs. We calculated action potential duration (APD), and ARI at pacemine rates from 400 to 120 ms. APD was defined as the interval from the onset of the action potential to the time for the action potential return to 90% of its maximum value in the MAP electrode recording after the last pacing stimulus. ARI was determined from unipolar recordings of the reference electrode of each MAP electrode pair and defined as the interval between the maximum positive dV/dt of the QRS complex and maximum positive dV/dt of the T wave. Restitution curves were sigmoidal functions fit to these two sets of data.

Results: The ARI values closely correlated with the APD measurements during the different pacing rates (r = 0.94, p < 0.001). The slopes for ARI and APD restitution curves were also correlated closely (r = 0.94, p < 0.001). When the ARI restitution curves were also correlated closely (r = 0.94, p < 0.001).

Conclusion: ARI derived from unipolar electrograms provide an accurate assessment of changes in APD at different pacing rates. Thus, the restitution curves generated from ARI measurements are similar to those measured from tip MAP electrodes. Therefore, the practical usefulness of the unipolar electrogram as a tool for assessing the spatial distribution of restitution properties as well as activation sequences.

1041-13
Inhibition of Calcium Overload by Intracardiac Nitroglycerin as a Major Mechanism for Its Potent Antiarrhythmic Effectiveness
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Background: Intracardiac (IPC) nitroglycerin (NTG), a potent nitric oxide (NO) donor, prevents ischemia-induced ventricular fibrillation in pigs. We hypothesized that a main mechanism of this protection is the capacity of NTG to reduce the proliferative effects of ischemia-induced intracellular calcium overload.

Methods: In 8 closed-chest anesthetized pigs, calcium overload was induced directly by CaCl2 (50-mg bolus) injected into the left main coronary artery both before and at 15-min intervals after IPC NTG delivery through a transcateter catheter. Similarly, in another 4 pigs, 0-sec angiography-balloon inflation of the LAD was performed to induce ischemia associated calcium overload. Vulnerability was measured by T-wave dispersion in pre-cordial electrograms using root-mean-square morphology analysis. Gastrocnemius and motoneuro-motor (1-mg/kg, bolus) were employed to provoke autonomic influences.

Results: IPC NTG significantly blunted calcium-induced dispersion, with a maximum effect at 45 min post-drug. IPC NTG also reduced ischemia-induced dispersion by 30% with a maximum effect at 15 min (p < 0.01). Conclusions: IPC NTG is capable of blunting both calcium- and ischemia-induced dispersion of repolarization, consistent with its previously demonstrated antiarrhythmic effect. Because calcium overload is a significant factor in ischemia-induced arrhythmias, NTG's ability to improve calcium handling appears to be a major mechanism of its protective action.

1041-14
Tyrosine Kinases Inhibit Availability and Open Probability of Single L-Type Calcium Channels in Human Atrial Myocytes
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Background: Human atrial myocytes, the L-channel calcium current is essential for electromechanical coupling and action potential duration. Rapid changes of the current modulate the availability of L-channel calcium current. We investigated the effect of tyrosine kinase inhibitors (TKI) on single human atrial calcium current. Methods: Single LTOC were recorded in the cell-attached configuration of the patch clamp technique in isolated human atrial myocytes. Results: The TKI-inhibitor genistein and the Src kinase inhibitor PP1 significantly enhanced single LTOC peak current average current (I(i)) increasing availability (g(i)) and open probability (P(O)) (genistein: from 18.36% 8.46% fA, fA from 31.22% 7.4 to 42.95% 6.83 %, g(i) from 5.03% 1.43% 5.57% 2.04 %, PP1: from 14.13% 3.46% 31.7x 5.81 fA, fA from 66.06% 7.8% to 78.89% 9.03 %, g(i) from 4.06% 0.00 to 4.06% 0.04 %) PP1 was an inactive analog of genistein, did not influence these gating parameters. Furthermore, bisperoxo-phenoline-vanadate, a tyrosine phosphatase inhibitor significantly increased I(i) (from 20.86% 0.91 to 12.84% 3.01 fA), fA (from 53.20% 8.4 to 56.16% 77.01 %), g(i) (from 6.60% 1.7% to 3.86% 1.57 %). Activation or inhibition of protein kinase A by 8BR-CAMP or Rp8BR-PET-cAMP as well as inhibition of protein phosphatase I and IIb by okadaic acid did not influence the effect of TK on single LTOC activity. However, although genistein increased LTOC activity in the presence of the protein kinase C (PKC) activator PMA, the effect of genistein was abated in the presence of the PKC inhibitors staurosporine or bilirubin. Conclusion: Human atrial myocytes, LTOC availability and open probability are under control of TK, particularly of the Src-family. Furthermore, our results suggest that TK inhibit human atrial LTOC activity cooperatively with PKC.

1041-15
The HMG-CoA Reductase Inhibitor Atorvastatin Prevents Atrial Fibrillation by Inhibiting Inflammation in the Canine Sterile Pericarditis Model
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Background: HMG-CoA reductase inhibitors reduce C-reactive protein (CRP) levels. It has been recently reported that atrial fibrillation (AF) is associated with tissue inflammation, and CRP is elevated in AF patients. We hypothesized that a statin could attenuate the progression of AF in the canine sterile pericarditis model. Methods and Results: Sterile pericarditis was created in 12 dogs, which were randomly assigned to two groups: control group (6 dogs) and atorvastatin treatment group (6 dogs). Atorvastatin was administered orally (10mg/kg/day) from 1 week before the operation to throughout the study. Before and 2 days after the operation, the CRP level, duration of induced AF, atrial effective refractory period (AERP) of the right atrial appendage, and intra-atrial conduction time were determined. Before the operation, there were no significant differences in any of the parameters between the 2 groups. On the 2nd postoperative day, CRP was significantly lower in the atorvastatin group than in the control (Table). Sustained (≥600 sec) AF was induced in all dogs in the control group, but in only 1 dog in the atorvastatin group. The atorvastatin group had a shorter AF duration, a longer AERP, and a shorter intra-atrial conduction time than the control (Table). Conclusions: Atorvastatin can prevent the promotion of AF by inhibiting inflammation in the canine sterile pericarditis model. Atorvastatin may be a novel therapeutic agent for AF.