1041-11 Significant Association of Renin-Angiotensin System Gene Polymorphisms With Human Atrial Fibrillation

Chia-Ti Tsai, Ling-Ping Lai, Fu-Tien Chiang, Jiunn-Lee Lin, Yung-Zu Tseng, National Taiwan University Hospital, Taipei, Taiwan,ROC

Background Activated local atrial renin-angiotensin system (RAS) has been reported to play an important role in the pathogenesis of Afib. We hypothesized that the RAS genes might be among the susceptible genes of Afib, and conducted a genetic case-control study to demonstrate this. ***Methods and Results*** A total of 110 patients with documented Afib and 110 controls were selected. The controls were matched to cases one-by-one regarding age, sex, presence of left ventricular dysfunction, and presence of significant valvular heart disease. Angiotensin-converting enzyme gene insertion/deletion polymorphism; T174M, M235T, G-6A, A-20C, G-152A, and G-217A polymorphisms of the angiotensinogen gene; and A1166C polymorphism of the angiotensin II type I receptor gene were genotyped. In single-locus analysis, M235T, G-6A, and G-217A were significantly associated with Afib. The frequencies of M235, G-6, and G-217 alleles were significantly higher in cases than in controls (P=0.001, 0.005, and 0.039, respectively). The odds ratios for Afib were 3.3 (95% confidence interval [CI] 1.4-10.0) with M235/M235 plus M235/T235 genotype, 2.0 (95% CI 1.1-5.0) with G-6/G-6 plus G-6/A-6 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 multilocus haplotype analysis, the angiotensinogen gene haplotype profile was significantly different between cases and controls (χ^2=35.5, P=0.034). 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 Afib, and may provide the rationale for clinical trials to investigate the use of angiotensin converting enzyme inhibitor or angiotensin II antagonist in the treatment of Afib.

1041-12 Ability of Activation Recovery Interval to Assess Electrical Restitution Properties

Jian Huang, Robert K. Justice, Dennis L. Rollins, Gregory P. Walcott, Raymond E. Ideker, University of Alabama at Birmingham, Birmingham, AL

Background: Electrical restitution properties have been proposed as a mechanism for the development of alternans and ventricular arrhythmias. 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) determined 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 pacing rates from 400 to 120 ms. APD_{90} 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 S1 stimulus. ARI was determined from unipolar recordings of the reference electrode of each MAP electrode pair and defined as the interval between the maximum negative 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 value closely correlated with the APD_{90} measurements during the different pacing rates (r=0.94, p<0.001). The slopes for ARI and APD_{90} restitution curves were also correlated closely (r=0.96, p<0.001).

Conclusion : ARIs obtained 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 from MAP measurements. This demonstrates 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 Intrapericardial Nitroglycerin as a Major Mechanism for Its Potent Antifibrillatory Effect

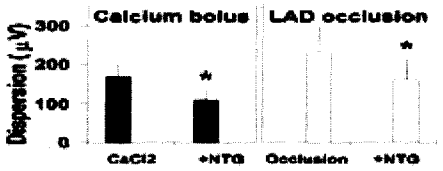
Susan X. Zhao, Veronica O. Busso, Bruce D. Nearing, Kapil Kumar, Richard L. Verrier, Harvard Medical School-MIT Division of Health Sciences & Technology, Boston, MA, Beth Israel Deaconess Medical Center, Boston, MA

Background: Intrapericardial (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 NO to reduce the profibrillatory effects of ischemia-induced intracellular calcium overload.

Methods: In 8 closed-chest anesthetized pigs, calcium overload was induced directly by $CaCl_2$ (50-mg boluses) injection into the left main coronary artery both before and at 15-min intervals after IPC NTG delivery through a transatrial catheter. Similarly, in another 4 pigs, 60-sec angioplasty-balloon inflation of the LAD was performed to induce ischemia associated calcium overload. Vulnerability was measured by T-wave dispersion in precordial electrograms using root-mean-square morphology analysis. Vagotomy and metoprolol (1.5 mg/kg, bolus) were employed to preclude 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 parallel time course. (*p<0.05).

Conclusion: IPC NTG is capable of blunting both calcium- and ischemia-induced dispersion of repolarization, consistent with its previously demonstrated antifibrillatory effect. Because calcium overload is a significant factor in ischemia-induced arrhythmia, 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

Frank Schröder, Gunnar Klein, Tanja Frank, Michaela Bastein, Helmut Drexler, Medical School of Hannover, Hannover, Germany

Background: In human atrial myocytes, the L-type calcium current is essential for electromechanical coupling and action potential duration. Rapid changes are caused by modifications of single L-type calcium channel (LTCC) phosphorylation. A detailed analysis of the effect of tyrosine protein kinases (TK) on single cardiac LTCC gating has not yet been performed. Thus, the present study investigates the influence of TK on single human atrial LTCC regulation. **Methods:** Single LTCC were recorded in the cell-attached configuration of the patch clamp technique in isolated human atrial myocytes. **Results:** The TK-inhibitor genistein and the Src kinase inhibitor PP1 significantly enhanced single LTCC peak average current (I) increasing availability (f_a) and open probability (p_o) (genistein: I from 18.36± 5.77 to 30.34± 6.46 fA, f_a from 31.22± 6.74 to 42.93± 4.63 %, p_o from 5.03± 1.43 to 5.57± 2.04 %, PP1: I from 14.13± 3.46 to 31.7± 5.81 fA, f_a from 55.95± 5.78 to 88.68± 3.03 %, p_o from 2.09± 0.92 to 4.05± 0.98 %) PP3, an inactive analogue of PP1, did not influence these gating parameters. Furthermore, bisperoxophenanthroline-vanadate, a tyrosin phosphatase inhibitor significantly decreased I (from 29.88± 4.91 to 12.84± 3.01 fA), f_a (from 53.29± 8.4 to 36.16± 77.01 %), p_o (from 6.62± 1.77 to 3.86± 1.57 %). Activation or inhibition of proteinkinase A by 8Br-cAMP or RP8BrPETcAMPs as well as inhibition of protein phosphatase I and IIa by okadaic acid did not influence the effect of TK on single LTCC activity. However, although genistein increased LTCC activity in the presence of the proteinkinase C (PKC) activator PMA, the effect of genistein was abated in the presence of the PKC inhibitors staurosporin or bisindoylmaleimide.

Conclusion: In human atrial myocytes, LTCC availability and open probability are under control of TK, particularly of the Src-family. Furthermore, our results suggest that TK inhibit human atrial LTCC activity cooperatively with PKC.

1041-15 The HMG-CoA Reductase Inhibitor Atorvastatin Prevents Atrial Fibrillation by Inhibiting Inflammation in the Canine Sterile Pericarditis Model

Koichiro Kumagai, Hideko Nakashima, Keijiro Saku, Fukuoka University, Fukuoka, Japan

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.

	Control		Atorvastatin	
	Before operation	After operation	Before operation	After operation
CRP (mg/dL)	0.1±0.2	11.8±1.3	0.1±0.3	8.2±0.6**
AF duration (sec)	5.5±4.2	540±351	6.1±4.6	82±84*
AERP (msec)	140±10	122±4	142±10	139±13*
Conduction time (msec)	44±11	56±7	42±11	46±5*

* p<0.05, ** p<0.001 compared with control.