Conclusion . hsCRP levels above 0.12 mg/dl are associated with a longer QTc interval in apparently healthy subjects. This suggests that systemic inflammation may alter the duration of QTc interval on the surface ECG.

ORAL CONTRIBUTIONS

825 Cardiac Electrophysiology and Arrhythmia Mechanisms

Monday, March 31, 2003, 2:00 p.m.-3:30 p.m.
McCormick Place, Room S405

Cardiac Arrhythmias

2:00 p.m.

825-1 Transmural Action Potential Repolarization Heterogeneity Develops Postnatally in the Rabbit

Salim F. Idriss, Patrick D. Wolf, Duke University Medical Center, Durham, NC

Background: Studies in adult hearts have shown that action potential (AP) prolongation in the mid-myocardium creates AP heterogeneity that is arrhythmogenic. We hypothesize that mid-myocardial AP properties change with age. This study's purpose was to compare transmural APs at different developmental ages in the rabbit.
Methods: Isolated arterially-perfused left ventricular wedges were studied in 20 rabbits at 3 ages: 2 wk (n=7 341±125gm), 7 wk (n=7 1600±193gm), adult (n=6 4273±189gm). APs were recorded with microelectrodes from epi and endo surfaces and from subepi, mid, and subendo sites (>1mm below cut surface) during endo S1 pacing. AP duration at 90% repolarization (APD90) was measured for S1 cycle lengths: 500ms, 1000ms, 2000ms.
Results: At 2wks, there were no transmural differences in APD90. At 7wks and adult, AP prolongation from mid to endo created a transmural AP gradient. In adults at all cycle lengths, there was a smooth increase in APD90 from the epi to endo. At 7wks, subendo APD90 was significantly longer than endo at 2000ms cycle length and caused a heterogeneous transmural distribution of APD.

APD90 (mean±se ms)

Age	Wedge QT	Epi	Subepi	Mid	Subendo	Endo
2wk	194±7	152±2	149±2	154±2	156±2	158±2
7wk	240±11	172±2#*	175±2*,#	194±2*	204±2*,#	193±2*
Adult	226±7	157±3#	166±3#	174±3#	185±3*	190±3*

Cycle length 2000ms p<0.05 (* vs 2wk, # vs endo)

Conclusions: Transmural AP heterogeneity is age dependent. In the rabbit, a transmural AP gradient is not present at 2wks, is present and heterogeneous by 7 wks, and is homogeneous by adulthood. Age-dependent changes in the transmural AP gradient may influence arrhythmogenesis during childhood and may in part account for age-related differences in arrhythmia incidence in hereditary and acquired LQTS.

2:15 p.m.

825-2 Gender-Based Transmural Differences in Canine Cardiac Repolarization

Ling Xiao, Denis Chartier, Wei Han, Zhiguo Wang, Stanley Nattel, Montreal Heart Institute, Montreal, PQ, Canada

Introduction: Clinically, female gender is a very important risk factor for drug-induced Torsades de Pointes (TdP). Little is known about gender-based differences in transmural cardiac repolarization and transmural ion-channel function. Methods: We applied standard microelectrode techniques to record transmural action potentials (APs) in perfused canine left ventricular tissues and whole-cell patch-clamp techniques to study transient-outward (Ito) and inward-rectifier (IK1) K+-currents in cardiomyocytes isolated from cardiac Purkinje fibers (PCs), epicardium (Epi), mid-myocardium (M) and endocardium (Endo). Results: No significant differences in action potential duration at 90% repolarization (APD90) were observed between female and male dogs. However, after E-4031 (5 μM) perfusion, female dogs exhibited significantly longer APD90 than male dogs (eg, at 1 Hz: Epi, female 297±17 ms (n=12) vs. male 248±9 ms (n=14); M, female 373±19 ms (n=12) vs. male 304±7 ms (n=14); Endo, female 437±10 ms (n=9) vs. male 344±10 ms (n=24); p<0.05). Female dogs had a substantially smaller Ito in Endo than male dogs (eg, at +70 mV: female: 3.6±0.4 pA/pF, n=16; male: 5.9±0.7 pA/pF, n=23; p<0.05). Ito in Epi was slightly smaller in female dogs (at +30 mV: female: 18.5±0.7 pA/pF, n=46; male: 21.5±1.2 pA/pF, n=38; p<0.05). However, in M cells, females had a slightly larger Ito (at +50 mV: female: 31.2±1.5 pA/pF, n=47; male: 26.8±1.5 pA/pF, n=39; p<0.05). There were no gender differences in IK1 among Epi, M and Endo. In PCs, female dogs had smaller IK1, particularly in the outward direction (eg, at -60 mV; female: 0.3±0.1 pA/pF, n=24; male: 0.8±0.1 pA/pF, n=21; p<0.05), but no differences in Ito. Conclusions: Female dogs are much more sensitive to IKr blocker-induced AP prolongation than male dogs. There are significant, transmurally-determined differences in Ito and IK1, with reduced repolarizing K+-currents in endocardium (Ito) and PCs (IK1), in females. Reduced K+-currents decrease "repolarization reserve" and, along with increased transmural dispersion of cardiac repolarization, may account for the predisposition of females to drug-induced TdP.

2:30 p.m.

825-3 IKs Contributes Importantly to Ventricular Repolarization in Conscious Dogs

Jurren M. Van Opstal, Paul G. Volders, Milan Stengl, E. Martel, Uwe Gerlach, Roel L. Spätjens, Jet D. Beekman, Karin R. Sipido, Marc A. Vos, CARIM, Maastricht, The Netherlands, Centre de Recherches Biologiques, Baugy, France

In large mammals and humans, the exact contribution of IKs to ventricular action potential (AP) is still unclear. We and others have shown in ventricular myocytes that time and voltage domains of the AP limit the generation of significant IKs under baseline conditions, whereas ß-adrenergic receptor stimulation enhances IKs directly and via favorable changes of the AP profile. To assess the role of IKs in vivo, we inhibited the current in conscious and anesthetized dogs.
Methods: The specific IKs blocker HMR 1556 was administered to 10 conscious dogs at concentrations of 3, 10 and 30 mg/kg PO. Regular standard-lead ECGs and Holter recordings were made. In 4 experiments, HMR 1556 (1.5 mg/kg/5 min IV) was given under anesthesia (pentobarbital followed by halothane) and endocardial MAP catheters were placed in the left and right ventricle.
Results: In conscious dogs, HMR 1556 caused a dose-dependent prolongation of the QTc interval. From a baseline interval of 220±5 ms, maximal QTc increases were 11±1, 34±5 and 65±15% at 3, 10 and 30 mg/kg PO respectively. T waves became broad-based and asymmetrical. In one animal, HMR 1556 resulted in SCD due to a tachyarrhythmia during excitement. After 30 mg/kg the maximal plasma HMR 1556 concentration was 2.68±0.55 μmol/l, which is 40 times the IC50 for IKs inhibition according to previous cellular studies. The transition from conscious to anesthetized state already caused QT prolongation, often exceeding 15%. HMR 1556 increased the QTc interval by only 9±1%. The MAP duration changed accordingly in the left (245±35 to 280±40 ms) and right ventricle (220±30 to 245±30 ms). After 1.5 mg/kg IV the plasma concentration of HMR 1556 was comparable to conscious conditions (2.35±0.24 μmol/l). The attenuated effect during anesthesia could be attributed to 1) a diminished adrenergic tone and/or 2) a direct blocking effect of anesthetics on IKs.
Conclusions: In conscious dogs, ventricular repolarization is importantly dependent on IKs, which is a new and clinically relevant observation. During anesthesia the effect of IKs block on repolarization is less prominent, despite similar plasma concentrations.

2:45 p.m.

825-4 Chronic Subthreshold Electrical Stimulation of the Left Stellate Ganglion and a Canine Model of Sudden Cardiac Death

Moshe Swissa, Shengmei Zhou, Che-Ming Chang, Adam W. Cates, Michael C. Fishbein, Lan S. Chen, Peng-Sheng Chen, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Nerve growth factor (NGF) infusion to the left stellate ganglion (LSG) in dogs with complete atrioventricular block (CAVB) and myocardial infarction (MI) induces cardiac nerve sprouting, ventricular arrhythmia and sudden cardiac death (SCD). Subthreshold electrical stimulation is more effective than NGF infusion in inducing nerve sprouting. We hypothesize that subthreshold electrical stimulation to the LSG is more effective than NGF infusion to the LSG in inducing ventricular arrhythmia and SCD in dogs with CABG and MI.
Methods and Results: In dogs with MI and CAVB we induced cardiac sympathetic nerve sprouting by infusion of NGF (n=2) to the LSG or electrical stimulation (n=6) to the LSG. Cardiac rhythm was continuously monitored with an implanted transmitter. Ventricular tissues were harvested for immunocytochemical staining. The results showed a greater magnitude of cardiac nerve sprouting in dogs with LSG electrical stimulation than in dogs with NGF infusion to LSG. Ventricular tachycardia of 8 beats or more, 20 beats or more and non-sustained polymorphic VT episodes were more frequently seen in dogs with electrical stimulation to the LSG compared to NGF infusion to the LSG (36±60 VT, 11±17and 3±3.8 versus 4.7±6.1, 0.1±0.33 and 1±1.2 episodes per day, P<0.05, P<0.03 and P<0.08, respectively). Four out of 6 dogs with LSG electrical stimulation died suddenly.
Conclusions: As compared with NGF infusion, sub-threshold electrical stimulation to the LSG is more effective in inducing cardiac nerve sprouting, VA and SCD in dogs with CAVB and MI

3:00 p.m.

825-5 Chronic Activation of $I_{Cl,}$ Swell in Diseased Human Atrial Myocytes

Dhaval G. Patel, Robert S. Higgins, Clive M. Baumgarten, Medical College of Virginia, Richmond, VA

Background: $I_{Cl,swell}$, an outwardly rectifying swelling-activated Cl current is chronically activated under isosmotic (1T) conditions in animal models of heart failure. We tested the hypothesis that $I_{Cl,swell}$ is chronically activated in diseased human atrial myocytes isolated from patients with evidence of right atrial enlargement (RAE) and/or elevated left ventricular end diastolic pressure (LVEDP).
Methods: Myocytes were enzymatically isolated from right atrial specimens obtained from patients undergoing cardiac surgery. Leak-corrected $I_{Cl,swell}$ was measured under conditions that isolate Cl currents and was identified by either osmotically manipulating cell volume or with tamoxifen (TAM, 10 μm), an $I_{Cl,swell}$ blocker; current density at +40