Conclusions: Prolongation of the QT interval by A is only beneficial if QTpeak and TpTe are increased proportionally. Risk of cardiac death is increased if the QT prolongation is mainly due to an increase in TpTe.

1115-11

Markers of Central Modification of the Sympathetic Nervous System Activity in Humans

Vladimir Shusterman, Peter J. Jannetta, Benhur Aysin, Maksim Glukhovskoy, Irene Ueleke, University of Pittsburgh, Pittsburgh, PA, Allegheny General Hospital, Pittsburgh, PA

Brainstem centers of the sympathetic nervous system activity (SNSA) located in the rostral ventro-lateral medulla (RVLM) play an important role in SNSA homeostasis. We hypothesized that mechanical stimulation of the RVLM neurons would modify SNSA and examined the effects of the stimulation on heart rate (HR) and HRV.

Methods: In 10 patients (age: 54±14y, 7 females), the left (7 patients) or the right (3 patients) side of the brainstem was exposed during neurosurgery, and a mechanical tral ventro-lateral medulla (RVLM) play an important role in SNSA homeostasis. We

Conclusions: Central sympathetic stimulation in anesthetized patients with controlled respiration increases HR, but does not change the spectral distribution of HRV as reflected by the ratio LFP/HFP. This suggests that HR is a more reliable marker of central SNSA modifications in this setting than spectral HRV indices.

1115-12

Prevalent Low-Frequency Oscillation of Heart Rate Is the Strongest Risk Stratifier Independent of All Available Mortality Predictors in the Placebo Population of EMIT Trial

Dan Wichterle, Jan Stinek, A. John Camm, Marek Malik, St George's Hospital Medical School, London, United Kingdom, General University Hospital, Prague, Czech Republic

Background: Hormonal and autonomic influences have been proposed to be responsible for the differences in cardiac repolarisation between men (M) and women (F) as manifested by the longer ECG QTc interval in F. To evaluate the effects of hormones, we investigated the changes in cardiac repolarisation from pre- to post cardiac transplantation (OHT) of the donor heart in transgender and same gender recipients. METHODS: ECGS were analysed in 100 OHT patients: 42 transgender (26 F to M and 16 M to F) and 58 same gender (8 F to F and 50 M to M). The donor OHT was measured prior to explanta-

ORAL CONTRIBUTIONS

821 Electrocardiographic Insights Into Cardiac Physiology

Monday, March 31, 2003, 2:00 p.m.-3:30 p.m.
McCormick Place, Room S404

821-1

Autonomic Modulation of the U Wave

Antony R. Magcrn, Sarah Stimler, Camael M. Boccmteescu, Columbia University - New York Presbyterian Medical Center, New York, NY

Background: Increasing evidence supports the hypothesis that U waves visible on the electrocardiogram (ECG) of normal individuals may be caused by afterdepolarizations (AD). Catecholamines are known to increase the amplitude of both ADs and U waves. Beta-adrenergic blockade decreases AD amplitude while alpha-adrenergic stimulation in intact animals increases AD amplitude, but their effects on the U wave are unknown.

Methods: 25 normals underwent esmolol (1mg/kg, then 0.05 mg/kg/min) and phenylephrine infusion (1.4±3.2mg/kg/min). Heart rate (HR), T & U wave amplitude and QT & QU intervals were measured using CPR -based and during drug infusions. Among 24 subjects with U waves on their resting ECG, baseline values were compared with those during drug infusion by paired t-tests.

Results: As expected, HR decreased with both interventions (p<0.001). Mean U wave amplitude increased by 16.3% during phenylephrine (from 83.0 ± 11.1 μV to 96.5 ± 11.0 μV, p<0.001), but decreased by 14.5% during esmolol (from 83.8 ± 11.6 μV to 71.6 ± 13.5 μV, p<0.001) (figure). Mean T wave amplitude increased from 597 ± 280 μV to 692 ± 312 μV with phenylephrine (p<0.001), but decreased from 692 ± 312 μV to 547 ± 251 μV during esmolol (p<0.001). QT & QU intervals increased with both interventions (p<0.001).

Conclusions: U wave amplitude is highly dependent upon autonomic state. The observations that catecholaminergic, beta blockade and alpha-adrenergic stimulation modify ADs and U waves in a similar manner suggest that U wave amplitude may be an ECG reflection of AD amplitude.
ferences in QTc intervals between M and F OHT recipients were also compared.

RESULTS: In the early post OHT period, there was a significant decrease in the QTc interval for the F to M transplantation subgroup which persisted throughout follow-up. QTc Changes Following Transplantation

Group (Donor to Recipient)        2 days  1 week  1 month  1 year
M to M        -15.68  2.36 -6.46  1.40
M to F        2.92  -4.27  0.76  8.26
F to F        -15.49  -6.33 -37.1*  8.31
F to M        -42.58  -23.18  -16.12  -24.62
*p<0.05 for change in QTc

When comparing the QTc among M and F recipients, there was no gender difference in the QTc interval at early follow-up (419±27 vs 420±23 for M vs F at 1 week; 416±31 vs 415±23 at month) but significant (p>0.05) difference at late follow-up (417±26 vs 432±26 for M vs F at 1 year; 429±30 vs 450±25 at >2 year follow-up). CONCLUSIONS: Gender-related QTc changes are evident both immediately and late after OHT. These effects are most consistent with a hormonal etiology and probably not due to autonomic influences.

2:30 p.m.

821-3

SCNSA Mutations in the S5-S6 Region Cause Brugada Syndrome and Cardiac Conduction Disturbances

Hideo Itoh, Masami Shimiizu, Hiroshi Mabuchi, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan

Background: The SCNSA gene encoding the alpha subunit of the human cardiac sodium channel plays a key role in cardiac electrophysiology. Mutations in SCNSA lead to a wide variety of phenotypes, including long QT syndrome, Brugada syndrome, and isolated progressive cardiac conduction defects. Clinically, there appears to be some overlap among these syndromes, as all are associated with a relatively high incidence of nocturnal sudden cardiac death without prior symptoms.

Methods: DNA was isolated from peripheral white blood cells of 40 patients with Brugada syndrome in Japan and analyzed SCNSA mutations by PCR-SSCP and direct sequence methods.

Results: We detected 2 point mutations in the SCNSA gene (Arg282His and Asn406Ser). These mutations were not detected in 200 chromosomes of normal controls and suggested as disease causing mutations. In a 51-year-old man with frequent nocturnal polymorphic ventricular tachycardia, we found the Arg282His mutation in the S6 region of domain I. He had a 36-year-old brother who suffered sudden death. We analyzed 5 family members and detected 3 of the Arg282His mutation carriers and 2 noncarriers. The 2 noncarriers had neither atraumatic sudden death nor electrocardiographic changes. Two of the mutation carriers, excluding the proband, had no syncope or ventricular fibrillation. All 3 mutation carriers had ST-segment elevations in leads V1 to V2. The two of the mutation carriers, excluding the proband, had ST-segment elevations and a widened QRS complex. The PO and QT intervals in all of the patients with the Arg282His mutation were normal. In a 67-year-old man with asymptomatic Brugada syndrome, we found the Asn406Ser mutation in the S6 of domain I. He had 21-year-old father and 27-year-old son with sudden death. Patient and the proband had no syncope or ventricular fibrillation. All 3 mutation carriers had ST-segment elevations but bradycardia, first degree of atrioventricular block, and prolongation of the QRS width.

Conclusions: We suggested SCNSA mutations in the S5-S6 region cause both Brugada syndrome and cardiac conduction disturbances. Both mutations are located in important sites in the S5-S6 or S6 segment that confer ion selectivity and mutations might cause serious clinical phenotypes.

2:45 p.m.

821-4

Cardiac Autonomic Modulation by Estrogen in Female Mice Undergoing Ambulatory Monitoring and In Vivo Electrophysiologic Testing

Samir Saba, Vladimir Shusterman, Irmute Usiene, Barry London, University of Pittsburgh, Pittsburgh, PA

Introduction: Estrogen is an important modulator of cardiovascular risk, but its mechanism of action is not fully understood. In this study, we investigated the effect of ovariectomy and its timing on the cardiac electrophysiology (EP) in female mice, with and without autonomic blockade. Methods: Thirty female mice (age 16.6±3.1 weeks) under underwent blinded in vivo EP testing before and 10 minutes after administration of atropine (0.5 mg/kg, IP) and propranolol (1 mg/kg, IP). Fifteen mice were overatropined pre-puberty (PRE) and post-puberty (POST). We success performed EP testing. Fifteen sham-operated female mice (F) served as controls. A subset of 13 mice (5 PRE, 3 POST, and 5 F) underwent 24-hour ambulatory monitoring prior to the EP testing. Using all mice with exception of those that had lost weight during the 24-hour period. Ambulatory monitoring, the average aorta (200 mmHg), rise to 2-5 mmHg, min, and minimum (systolic vs systolic) at 25 to 30 min, p<0.002 heart rates were significantly slower in the overatropined mice (PRE and POST groups) compared to the F group. At baseline EP testing, there were no significant differences between the overatropined and intact mice in any of the measured parameters. With autonomic blockade, the F group had a significantly younger heart (A) in the atrioventricular (AV) nodal Wenckebach (AVW) periodicity (A AVW = 11 to 12.9 vs 21.1±7.3 ms, p<0.05) and functional refractory period (A FRP = 11.3±2.1 versus 12.2±6.8 ms, p<0.05) compared to the overatropined mice. These results were not altered by the time of ovariectomy (PRE versus POST groups). The weights of the uteri were significantly different among the 3 groups (14.3±6.7 mg, 23.5±10.8 mg, 68.5±17.7 mg for the PRE, POST and F groups respectively, p<0.05 for all comparisons). Conclusion: Our results suggest that estrogen modulates the autonomic inputs into the murine sinoatrial and AV nodes. Lower estradiol, regardless of the time of ovariectomy, dilates the autonomic influence on the heart. These findings, if replicated in humans, might underlie the observed clustering of certain arrhythmias around menstruation and their higher incidence in men and post-menopausal women.

2:45 p.m.

ABSTRACTS - Cardiac Arrhythmias 111A

821-5

Validation of Electrocardiogram Criteria for Pulmonary Hypertension

Khalid Al-Naamani, Thao Huynh, S. Andrews, McGill University Health Center, Montreal, PQ, Canada

Background: Measurement of right ventricular systolic pressure (RVSP) by 2D-echocardio-
graphy (echo) has been shown to have good correlation with cardiac catheterization. We aimed to validate the sensitivity, specificity and predictive values of electrocardiography in patients with elevated RVSP diagnosed by 2D-echocardiography.

Methods: We analyzed all patients who had echo and EKG, within a 1-month interval, at our institution during 2000-2001. The following criteria were studied:

- R wave in V1, 1.7 mm or
- R wave in V1 < 1.7 mm or
- R wave in lead II or
- R wave in V1 > 1.7 mm or
- R wave in V1 = 1.7 mm or
- R wave in V1 = 1.7 mm

Results: There were 365 patients with echo and EKG within a 1-month interval. We evaluated all patients with normal rhythm and poor EKG quality. The above criteria showed very poor sensitivity (0.0% to 13%), negative predictive values (24% to 36%). They had excellent specificity (92% to 100%) with positive predictive values ranging from 64% to 100%.

Although highly specific, these criteria have poor sensitivity and negative predictive values.

Conclusion: The currently available EKG criteria are poorly sensitive for significant pulmonary hypertension. New EKG criteria with better sensitivity should be developed.

821-6

Increased Levels of High-Sensitivity C-Reactive Protein Are Associated with a Longer QTc Interval in Apparently Healthy Subjects

Aya P. Yazdanbakhsh, Bojan Vrtovec, Branislav Radovancevic, Todd T. Schlegel, NASA Johnson Space Center, Houston, TX

Background: QTc interval prolongation is associated with an increased risk of cardiovascular mortality in apparently healthy individuals. Furthermore, healthy subjects with increased levels of high-sensitivity C-reactive protein (hsCRP) are at a higher risk of cardiovascular disease. Whether increased levels of hsCRP are associated with a longer QTc interval has not yet been studied. Methods: In 110 (56 male/54 female) healthy volunteers with a mean age of 36 ± 11 (range 20-65) years, mean QT interval was measured from a standard 12-lead ECG and QTc interval duration was calculated with the Bazett formula. At the time of ECG recordings, plasma levels of hsCRP were measured using the Kalaire assay. Cardiovascular risk stratification included assessment for the presence of hypertension, smoking, and diabetes mellitus, and measurement of serum total cholesterol, LDL, and HDL levels. The 10-year coronary disease risk was calculated according to Framingham risk estimates. Results: The overall mean QTc interval was 399 ± 26 ms (range: 341 - 469 ms) and the mean hsCRP level was 1.15 ± 0.34 mg/dl (range: 0.002 - 2.517 mg/dl). Of 110 subjects, 48 (43%) had an hsCRP level > 0.12 mg/dl, and 62 (57%) had an hsCRP level < 0.12 mg/dl. The subjects with hsCRP > 0.12 mg/dl had a significantly longer QTc interval than those with hsCRP < 0.12 mg/dl (405 ± 23 ms vs. 392 ± 25 ms, p=0.018). In multivariable analysis, hsCRP level > 0.12 mg/dl was associated with significantly longer QTc interval (p=0.047). No other differences in cardiovascular risk factors between the high-hsCRP and low-hsCRP groups were found.

3:15 p.m.