910-111 Relationship Between Measures of Heart Rate Complexity and Maximal Exercise Capacity

Lee A. Fleisher, Brian G. Kral, Lewis Becker. *Johns Hopkins Medical Institutions, Baltimore, MD*

Attention has focused on heart rate variability (as measured by power spectral analysis) and complexity (as mesured by Approximate Entropy) for assessing cardiovascular health and outcome. Previous research has demonstrated reduced complexity in elderly patients. This is thought to reflect a decrease in networking of normal physiologic control systems. Because of the known decrease in physical fitness with age, we postulated that measures of heart rate variability and complexity would decrease with advancing age. Studies were performed in 182 asymptomatic individuals (77 men and 105 women, 30–59 years of age) who were siblings of patients with premature CAD. Exercise testing (ETT), with recordings of maximal metabolic equivalent (MET), and thallium scanning (TL) were done in each person. Total spectral power was calculated from 24 hour Holter recordings using sequential fast Fourier transformations on 2 minute blocks, averaged over 24 hours. Approximate Entropy (ApEn), a measure of complexity, was calculated for 1000 points, using m = 2, r = 20% of the standard deviation (S.D.) and average over a one hour period during the morning. In 163 people with normal ETT and TL, total spectral power decreased with advancing age, while ApEn was not related to age within the range studied in our cohort. MET level was significantly and linearly related to total power only in the cohort of individuals between 40–50 years of age ($p < 0.05$). In patients age > 50 years, total power was significantly lower than in those age < 40 years, and was not influenced by MET level. ApEn was linearly related to MET level with increasing age. The linear relationship between ApEn and MET remained significant when controlled for age. Our results further support the notion that heart rate variability reflected in total spectral power, and complexity (ApEn) measure different underlying control systems. Reductions in ApEn in the elderly may reflect reduced aerobic capacity and decreased resiliency of the underlying control systems.

910-112 Ultra Low Frequency Power Is the Only Power Spectral Measure Not Confounded by Physical Fitness

Rochelle L. Goldsmith, Daniel M. Bloomfield, Richard C. Steinman, J. Thomas Bigger, Jr.. *Columbia University, New York, NY*

Power spectral analysis of RR variability has been shown to predict mortality after myocardial infarction (MI). Compared to other measures of RR variability, ultra-low frequency power (ULF) is the best predictor of mortality after MI and best separates healthy normal subjects from patients with coronary heart disease (CHD). In addition, ULF is the only measure of RR variability that is not significantly influenced by age or sex. We have shown that physical fitness has a strong relationship with high frequency power, but the relationship between physical fitness and ULF is unknown. This study was carried out to determine if physical fitness influences ULF.

We studied 37 healthy volunteers. Physical fitness was assessed by the measurement of maximal oxygen consumption (VO_2max) attained during an incremental bicycle test. RR variability was obtained from 24-hour Holter recordings during which time subjects did not exercise. We calculated the power within four frequency bands of the 24-hour RR interval power spectrum: < 0.0033 Hz, ULF; 0.0033–0.04 Hz, very low frequency (VLF); 0.04–0.15 Hz, low frequency (LF); 0.15–0.40 Hz, high frequency (HF) power. Among the 33 men and 4 women, aged 22–44 years (mean of 30 ± 5), VO_2max ranged from 25–70 ml/kg/min (mean of 45 ± 13).

VO_2max was significantly correlated with HF ($r = 0.72$, $p < 0.0001$), LF ($r = 0.76$, $p < 0.0001$), and VLF ($r = 0.80$, $p < 0.0001$), but VO_2max was only weakly and not significantly related to ULF ($r = 0.30$, $p = 0.07$).

ULF, the best predictor of death after MI of the power spectral components of RR variability, is not confounded by physical fitness. Since ULF power is not significantly affected by age, sex, or fitness, the effect of CHD on ULF can be more easily interpreted.

910-113 Normal Pregnancy Is Associated With Reduced Heart Rate Variability

Michael T. Hagley, Phyllis K. Stein, Patricia L. Cole, Robert E. Kleiger. *Jewish Hospital, Washington University, Saint Louis, Missouri*

To determine the effect of pregnancy on heart rate variability, we used Marquette heart rate variability software to analyze 24-hour electrocardiograms of 26 pregnant subjects and 26 age-matched female controls. Pregnant subjects in the first (13), second (7), and third (6) trimesters were studied.

Reduction in heart rate variability was similar among subjects in all trimesters.

Conclusion: Maternal heart rate variability is reduced in normal pregnancy during all trimesters. This may represent a component of physiologic adaptation to pregnancy.

Table I. Changes in HRV associated with pregnancy

	Pregnant	Control	p value
Number	23	26	
Age	30 ± 5	29 ± 5	NS
Min. Heart Rate	60 ± 7	49 ± 6	0.001
Avg. Heart Rate	90 ± 8	82 ± 7	0.002
Max. Heart Rate	155 ± 18	145 ± 15	0.04
SDNN	94 ± 25	147 ± 38	< 0.001
SDANN	83 ± 24	133 ± 45	< 0.001
SDNN index	46 ± 15	66 ± 17	0.001
rMSSD	27 ± 13	44 ± 17	0.001
pNN50	7 ± 8	16 ± 9	0.003

910-114 Relationship Between Cardiac Autonomic Function and Symptomatic State in Patients With Syndrome X

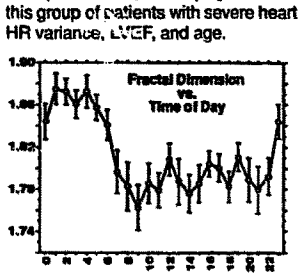
Gaetano A. Lanza, Vincenzo Pasceri, Giuseppe Colonna, Patrizia Pedrotti, Filippo Crea, Attilio Maseri. *Istituto di Cardiologia, Universita' Cattolica del S. Cuore, Roma, Italy*

An increase of both adrenergic activity and sensitivity to painful stimuli have been suggested to play a role in the pathogenesis of syndrome X (SX), but it is not known whether these abnormalities do have any relationship with the frequency of symptoms occuring during daily life in these patients (pts). To address this question, we studied off therapy 23 SX pts (18 women, age 56 ± 8 yrs) by assessing: 1) general sensitivity to pain, by measuring time to forearm ischemic pain (FIP); 2) cardiac autonomic function, by measuring heart rate variability (HRV) on 24-hour Holter recordings, and 3) number, duration and severity (scale 1–5) of anginal episodes occurring in a 4-week period, as reported by pts in an appropriately structured diary. Data showed an inverse correlation between frequency of anginal episodes and time to FIP ($r = -0.48$, $p < 0.05$), and a direct correlation between angina frequency and some time- and frequency-domain HRV indexes specific for vagal activity ($r = 0.43$, $p < 0.05$ for r-MSSD; $r = 0.56$, $p < 0.01$ for pNN50; $r = 0.47$, $p < 0.05$ for HF). Thus, in SX pts a higher frequency of spontaneous anginal episodes is associated to a heightened sensitivity to painful stimuli, but not to an increased adrenergic activity. Indeed, in our pts, the occurrence of anginal episodes was actually correlated to a higher vagal activity, as assessed by HRV analysis.

910-115 Diurnal Variation of Heart Rate Fractal Dimension in Heart Disease Patients

Rachel J. Lampert, Alex J. Denner, K. R. Sreenivasan, Lynda E. Rosenfeld, Forrester A. Lee. *Yale University, New Haven CT*

Alterations in cardiac neural regulation as assessed by heart-rate variability (HRV) correlate with prognosis in patients with heart disease. Circadian rhythms of HRV parameters may provide insight into mechanisms of cardiac events such as MI and VT which are known to occur in circadian patterns. Fractal dimension (FD) is a measure of HRV which is correlated with the 1/f broadband component of the HR spectrum (f < 0.04 Hz). From ambulatory ECG recordings, we analyzed the diurnal variation of FD (computed from the zero crossings of the mean-adjusted HR time series) and standard HRV parameters derived from the power spectrum (high frequency and low frequency components and their ratio). We studied 35 patients with cardiac disease, age = 56 ± 16, LVEF = 22 ± 10%. Comparison of FD in 6-hour time-periods revealed a FD of 1.86 ± 0.01 during the night which was significantly higher than in the morning (1.79 ± 0.01), afternoon (1.80 ± 0.01), or evening (1.80 ± 0.01), ($p < 0.0001$). In multivariable analysis of fractal and standard HRV parameters, FD displayed the strongest correlation with time-period in this group of patients with severe heart disease. FD was independent of HR, HR variance, LVEF, and age.



Conclusions: Fractal dimension, a measure of HR variation which correlates with the 1/f broadband component of the HR spectrum, displays a diurnal variation with highest values during sleep. This suggests an inverse

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relationship between FD and physiologic stress which may aid in evaluation and assessment of prognosis in patients with cardiac disease.

911 Basic Electrophysiology: Ion Channels and Currents

Monday, March 25, 1996, Noon–2:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: 1:00 p.m.–2:00 p.m.

911-61 L-Type Calcium Current in Pediatric and Adult Human Atrial Myocytes

Theresa P. Roca, John D. Pigott, Craig W. Clarkson, Arthur S. Pickoff, William J. Crumb Jr.. *Tulane University School of Medicine, New Orleans, LA*

Several animal studies have documented the presence of marked developmental changes in the properties of the L-type calcium current in cardiac myocytes. In contrast, very little is known about the age-related changes in the L-type calcium current in human. In an effort to understand the postnatal changes which occur in the calcium current in human heart, we characterized the calcium current in atrial myocytes isolated from 14 pediatric (ages 5 days to 17 months) and 14 adult (ages 14–79 years) human hearts using the whole-cell patch clamp technique. In contrast to animal models, we found no evidence for age-related changes in calcium current density, kinetics of current activation, steady-state inactivation, or kinetics of recovery from inactivation, suggesting that in human atrium, calcium channels are in many aspects functionally mature at the time of birth. However, marked differences were found in the kinetics of calcium current inactivation, with calcium current measured in cells isolated from pediatric human atria inactivating approximately two-fold faster than cells isolated from adult hearts. In conclusion, this study is the first to characterize the L-type calcium current in neonatal human heart and suggests a possible role for age-related changes in calcium current inactivation in the shortened action potential observed in pediatric human atrium as compared to adult tissue, as well as, pointing to the hazards of extrapolating data obtained from animal models to human cardiac physiology.

911-62 Localization of Epitopes for Monoclonal Antibodies Generated Against Sodium Channel Protein: Implications for Channel Structure

Sylvia Kolibal, Sabu George, Candace Brady, Weijing Sun, Sidney A. Cohen. *Philadelphia VA Medical Center, Philadelphia, PA; University of Pennsylvania Medical Center, Phila., PA. 19104*

We localized the epitopes for a large panel of monoclonal antibodies generated against purified rSkM1 sodium channel protein using immunoblotting of fusion proteins containing various channel segments. Five major immunogenic regions were identified: the amino-terminus, the interdomain 1–2 region, the mid-interdomain 2–3 region, the far-interdomain 2–3 region, and the carboxyl-terminus. No antibodies had epitopes in the ID 3–4 region. Reexamination of previously published monoclonal-monoclonal competition data and the deduced topologic map of antibody binding sites (J Neurochem 48: 773–778, 1987) provide independent confirmation of selected portions of our recently proposed model of the organization of sodium channel cytoplasmic domains (JBC 270 (39): In Press). These data also suggest that the early N-terminus is closer (< 3.5 nm distance) to the distal-ID 2–3 region than to the mid-ID 2–3 region and that segments of the relatively long ID 1–2 region extend > 3.5 nm away from each of the other channel cytoplasmic segments. Therefore, immunogenic regions of the sodium channel are located on four of the five sodium channel cytoplasmic segments, the topology of monoclonal epitopes provides independent support for our recently proposed model of the organization of sodium channel cytoplasmic domains, and the ID 3–4 segment, modeled to be involved in channel inactivation, has a low surface probability and/or antigenicity, consistent with its short length and proposed interaction with the channel's cytoplasmic surface.

911-63 Localization of Residues Responsible for the Binding of the rSkM1 Amino- and Carboxyl-Termini

Hui Zhang, Sylvia Kolibal, Candace Brady, Weijing Sun, Sidney A. Cohen. *Philadelphia VA Medical Center, Philadelphia, PA; University of Pennsylvania Medical Center, Phila., PA. 19104*

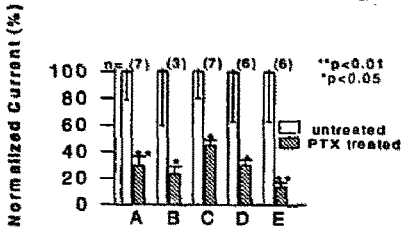
We previously demonstrating the specific binding of a synthetic peptide encompassing the first 30 residues of the rSkM1 N-terminus to a Maltose Binding Protein (MBP) fusion protein containing the rSkM1 C-terminus. In this study, we demonstrate identical binding using an N-terminal fusion protein, further localize the residues responsible for this interaction, and begin to investigate the physiologic significance of this interaction. A fusion protein containing the Flag epitope and the N-terminus of rSkM1 (residues 1–127) bound specifically and with high affinity (Kd of ≈10 nM and 1:1 stoichiometry) to the MBP C-terminal fusion protein. Using both direct and competitive solution phase binding assays, a nested set of peptides encompassing the first 30 residues of the rSkM1 protein were examined for their ability to bind to the MBP C-terminal fusion protein. Peptides 1–30, 7–30, 13–30, and 19–30 bound specifically and with high affinity, to the MBP C-terminal fusion protein identifying residues 19–30 as the region in the N-terminus responsible for binding to the C-terminus. A similar approach using MBP C-terminal fusion protein deletion mutants and either the 1–30 peptide or the Flag-N-terminal fusion protein identified a partially conserved region in the mid-portion of the C-terminus which specifically binds to the N-terminus. The N-terminal 19–30 region contains the epitope for a monoclonal antibody which differentially labels the surface and T-tubular membranes of fast and slow skeletal muscle. We propose that the interaction of N- and C-termini differs in different membrane environments and is involved in the subcellular localization of channel protein.

911-64 G-Protein Coupling of a Novel Recombinant Potassium Channel

Marie-Noelle S. Langan, Kim W. Chan, Jin-liang Sui, Diomedes E. Logothetis. *Mount Sinai School of Medicine, New York, NY*

We have isolated a K channel (KGP) from a human cDNA library. This channel showed a 26 amino acid difference from a rat cardiac clone (rcKATP1/CIR). We have functionally expressed KGP in Xenopus oocytes and recorded membrane currents using two electrode voltage and patch clamp methods. Hyperpolarizing pulses (to −80 mV) yielded measurable baseline current of 1.6 ± 0.45 μA (n = 20). BaCl2 (200 μM) blocked a large component of the KGP generated current (1.0 ± 0.29 μA; n = 20).

Xenopus oocytes coinjected with KGP and hM2 receptor mRNA exhibited significant ACh-induced currents (1.6 μA ± 0.22; n = 23) which were Ba^{2+}-sensitive. This agonist dependent response was diminished by treatment with pertussis toxin (A). Similarly, the magnitude of the Ba^{2+} blocked currents was greatly diminished (B). Interestingly, currents in HK were also diminished (C). PTX treatment of oocytes with KGP alone caused a similar significant reduction in HK currents (D) as well as in Ba sensitive currents (E). Oocytes injected with the voltage gated channel Kv1.1 did not show any PTX effects.



These results strongly suggest that KGP channels can couple to PTX sensitive G proteins not only to elicit agonist dependent but also agonist independent current.

912 Implantable Cardioverter-Defibrillators

Monday, March 25, 1996, Noon–2:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: Noon–1:00 p.m.

912-69 Intracardiac Electrogram Width Measurement for Improved Tachycardia Discrimination: Initial Results of a New Implantable Cardioverter-Defibrillator (ICD)

Johannes Brachmann, Karlheinz Seidl [1], Bernd Hauer [1], Thomas Hilbel, Daniel Lighezan, Wolfgang Schoels, Thorsten Beyer, Jutta Ruf-Richter, Nicola Schwink [1], Jochen Senges [1], Wolfgang Kübler. *University of Heidelberg, Germany; [1] Herzzentrum Ludwigshafen, Germany*

To avoid inappropriate ICD activation due to supraventricular tachycardias (SVT) different sensing algorithms are currently under clinical investigation. A new ICD (Medtronic 7218) allows measurement of intracardiac electrogram (EGM) width for discrimination between ventricular tachycardias (VT) and SVT. In 44 patients (P) with this device intracardiac EGM width could be

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