ELECTROPHYSIOLOGY ARRHYTHMIAS – CLINICAL – VENTRICULAR

901-59 An Estimation of the Spatial Organization of Electrical Activity in the Heart During Ventricular Fibrillation in Humans

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Ventricular fibrillation (VF) is thought to be maintained by multiple, disorganized, wandering wavelets that follow constantly changing reentrant pathways. To estimate the size of the reentrant pathways, we have calculated a spatial length constant from the cross correlation of electrograms recorded during VF in humans for the first time.

Six patients, mean age 61 ± 10 yrs, undergoing implantation of a transvenous cardioverter-defibrillator system were studied. A 36-pole catheter with 4-mm interelectrode spacing was positioned in the LV so that pole 1 was in the antero-basal segment of the LV free wall, poles 16–22 were at the LV apex and pole 36 was in the postero-basal segment of the interventricular septum. A 10-pole catheter in the coronary sinus recorded electrograms from the base of the left ventricle along the mitral annulus. VF was induced by burst pacing or alternating current. Cross correlations were calculated on the two seconds of data collected just before defibrillation shock delivery. The maximum value of the cross correlation between any two channels (Max(R)) versus the distance between the two channels (d) was fitted to $Max(R) = e^{-d/\lambda}$ where λ is the spatial length constant.

The spatial length constant, λ was 9 ± 3 cm. If λ corresponds to the length of the average coherent unit on the endocardium, then reentrant circuits may be about this size. These data suggest that human VF is maintained by only a few activation fronts and that each of these activation fronts extends over a large portion of the LV.

901-60 Is the Response of Catecholamine-Dependent Ventricular Tachycardia to Adenosine Mechanism Specific?

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It has been proposed that termination of ventricular tachycardia (VT) in response to adenosine is a mechanism specific response that identifies cAMP-mediated triggered activity (TA). This is based on adenosine's antiadrenergic effects in ventricular myocardium and its termination of TA in isolated myocytes. Although adenosine has been shown to be ineffective in terminating reentrant VT, its effects on catecholamine-dependent reentry have not been systematically evaluated. We therefore examined the effects of adenosine in 40 consecutive patients with catecholamine-dependent VT, 6 of whom fulfilled criteria for catecholamine-dependent reentry (entrainment). Two patients had arrhythmogenic right ventricular dysplasia, one had cardiac sarcoid, one had idiopathic dilated cardiomyopathy, one had coronary artery disease, and one had no apparent structural heart disease. Patients were between 25–67 years old; there were 5 males. All patients had at least two monomorphic forms of sustained VT induced at cycle lengths of 200–410 ms. No patient responded to Valsalva, edrophonium or verapamil. In addition, adenosine at doses of 24–48 mg had no effect on tachycardia but resulted in either VA block or sinus slowing. Esmolol prevented induction of VT.

Conclusions: Adenosine appears to be a mechanism specific probe for catecholamine-dependent VT. It terminates TA, transiently slows automatic VT, and has no effect on reentry regardless of anatomic etiology. These effects are likely related to the differing cellular substrates of the arrhythmias.

901-61 Sudden Death in Young Competitive Athletes: A Prospective Clinico-Pathologic Study

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Among 232 consecutive cases of sudden death (SD) in young people (≤35 years) which have been prospectively collected in the Veneto Region of Italy from 1979, 46 (20%) were young competitive athletes (41 males and 5 females, mean age 23.6 years). Pathologic findings were related to athlete clinical history, and sport-related SDs were compared with non-sport related events in order to establish which conditions predispose to cardiac arrest during exercise. SD was exercise-related in 37 athletes, and it occurred during (32 cases) or immediately after (5 cases) a sport activity. In 18 athletes, SD was preceded by warning symptoms and/or ECG changes. SD was caused by right ventricular (RV) cardiomyopathy (CM) in 10 cases (25%), atherosclerotic coronary artery disease in 9, congenital coronary anomalies in 7, conduction system pathology in 4, mitral valve prolapse in 4, myocarditis in 3, and hypertrophic CM, dilated CM, pulmonary embolism, aortic rupture, long QT syndrome (one case each). SD was extracardiac in 3 athletes, and remained unexplained in one. Athletes with RVCM more often had a history of warning symptoms and ECG changes, as compared with athletes who died from coronary artery disease, either acquired or congenital ($p < 0.05$). Only RVCM and congenital coronary anomalies were the conditions significantly associated with SD during sport ($p < 0.001$). Thus, SD in young athletes was due to a broad spectrum of cardiac diseases at risk of "arrhythmic" cardiac arrest. In our country, RVCM was the most frequently encountered one, and it appeared to predispose to sport-related sudden cardiac arrest. RVCM can be suspected at preparticipation athletic screening on the basis of prodromal symptoms and ECG signs.

ELECTROPHYSIOLOGY – BASIC

901-62 Optical Mapping of Drug-Induced Torsades De Pointes In the Isolated Rabbit Heart

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Antiarrhythmic drug-induced torsades de pointes (TDP) has been attributed to early after-depolarizations (EADs). However, it has been difficult to link EADs to the undulating electrocardiographic (ECG) patterns of TDP episodes. We hypothesized that drug-induced TDP is the result of activation by multiple subendocardial foci of EADs giving rise to complex patterns of wave propagation. Thus we used a voltage sensitive dye to perform high resolution (≈ 50,000 pixels/frame) video imaging of electrical waves on the epicardial and endocardial surfaces of the Langendorff-perfused rabbit heart. We also recorded a horizontal ECG, as well as monophasic action potentials (MAPs) from the right septal region. Bradycardia was induced by ablation of the AV node. Coronary perfusion of 2 mM KCl Tyrode's plus quinidine (5 μM; n = 5) led to prolongation of the MAP duration (from 206 ± 70 ms to 310 ± 81 ms) and QT interval. Eventually, EADs and triggered activity ensued, giving rise to intermittent episodes of relatively slow (cycle length = 422 ± 109), TDP-like polymorphic tachycardia of variable duration. Epicardial mapping showed no evidence of reentry. Isochrone maps demonstrated well organized plane wave fronts and/or breakthroughs whose site of origin and direction varied on a beat-to-beat basis. Endocardial maps revealed a multiple focal origin of the arrhythmias. Indeed, within a given TDP episode, each beat originated at a different focal site and propagated in a different direction thus giving rise to a polymorphic ECG pattern. In addition the sequence and specific sites of impulse origin could vary from one episode to another. Similar results were obtained when E-4031 (0.5 μM; n = 4) was perfused, but the cycle length of the tachycardia was briefer (328 ± 91 ms), particularly when used in combination with methoxamine (1 μM). These results directly demonstrate that the spatio-temporal patterns of electrical activity giving rise to drug induced TDP are the result of triggered automaticity at multiple subendocardial sites.

901-63 Differential Response to Mexiletine, Catecholamines and Pacing, in a Cellular Model Mimicking the SCN5A and HERG Genes Defect Present in the Long QT Syndrome

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The genes for two forms of Long QT Syndrome (LQTS) have been identified as SCN5A, a voltage dependent sodium channel located on chromosome 3 and HERG, the human potassium channel likely to produce the rapid component (IKr) of the delayed rectifier IK, located on chromosome 7. We developed an in vitro model of LQTS based on the electrophysiologic abnormalities expected based on the genetic defects of ion channels: 1) alteration of the fast inactivation of the INa and 2) partial inactivation of IKr. Guinea pig ventricular myocytes were exposed to anthopleurin 10 nM (Antho), an inhibitor of the inactivation of INa and to dofetilide 1 μM (Dofe), a selective blocker of IKr. Both interventions significantly prolonged Action Potential Duration (APD), by 51 ± 12 and 55 ± 18 ms. Differential responses were observed when cells of the two groups were exposed to mexiletine (Mexi), isoproterenol (Iso) and pacing. In cells pretreated with Antho, APD shortened after Mexi and Iso (from 264 ± 38 to 226 ± 32 ms and from 276 ± 19 ms to 240 ± 20 ms, $p < 0.0001$) and increased adaptation vs Dofe treated and vs control cells. In contrast, in cells exposed to Dofe, APD did not shorten after Mexi and even prolonged (from 268 ± 30 to 300 ± 17 ms, $p < 0.05$) early after exposure to Iso, when early after depolatizations developed. Preliminary data obtained in LQTS patients linked to chromosome 3 (n = 6) and 7 (n = 7) confirm the differential behaviour observed in this cellular model. It is suggested that models of LQTS may now be designed based on genetic information; these models may provide useful insights to devise differential and gene-specific therapeutic approaches.