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IKr is supposed to be atrial selective in pigs and humans. We investigated the effects of different potassium channel blockers, such as IKr-blockers, AVE-0118, S9947 and S20951, in contrast to amiodarone (AM), dofetilide (DO), azimilide (AZ), ibutilide (IB), IKs-blocker HMR 1556, atropine (ATR), flecainide (FL), propafenone (PR), and d,l-sotalol (SO), atenolol (ATE), and esmolol (ES), on left and right atrial and ventricular refractoriness (ERP) and left atrial vulnerability (LAV) in vivo in pigs. In pentobarbital-anesthetized pigs (n = 51) atrial and ventricular ERP were measured with the S1-S2-extrastimulus-method and the QTc-time from electrocardiogram. LAV was assessed after a S2-extrastimulus applied on the left atrium.

All IKr-blockers, AVE 0118 (1mg/kg), S9947 (3mg/kg), and S20951 prolonged left atrial than right atrial ERP (54 ± 7% vs. 23 ± 7%, 56 ± 5% vs. 14 ± 2%, 29 ± 7% vs. 9 ± 2%, all p < 0.05) and did not change QTc-time. All IKr-blockers prolonged predominantly right vs. left atrial ERP (DO: 10μg/kg, 36 ± 4% vs. 23 ± 2%; AZ: 5μg/kg, 33 ± 2% vs. 17 ± 3%; IB: 15μg/kg, 40 ± 9% vs. 23 ± 5%, all p < 0.05) as did IKs-blocker HMR 1556 (1mg/kg, 16 ± 5% vs. 11 ± 5%, n.s.). AM prolonged both atria equally (30 ± 5% vs. 29 ± 5%, n.s.). ATR prolonged left atrial ERP only (12 ± 3% vs. 1 ± 1%, p < 0.05). Pure beta blockers acted predominantly left atrial (ATE: 24 ± 5% vs. 7 ± 2%, ES: 30 ± 5% vs. 11 ± 2%, both 1mg/kg, p < 0.05), as did FL and PR (56 ± 15% vs. 26 ± 5%, 46 ± 5% vs. 17 ± 4%, both 1mg/kg, p < 0.05) while d,l-sotalol acted predominantly right atrial (1.5mg/kg, 41 ± 5% vs. 30 ± 4%, n.s.). IKr-blockers, AVE 0118, S9947 and S20951, ibutilide, and d,l-sotalol significantly decreased LAV (∼100%, −100%, −82%, −53%, −53%, p < 0.05) in contrast to all other drugs studied.

IKr-blockers, AVE 0118, S9947, and S20951, exhibit stronger left atrial effects, not affecting ventricular repolarization. By contrast, IKr-blockers, IKs-blockers, and d,l-sotalol exert predominant right atrial and known ventricular effects. IKr-blockers inhibit atrial tachyarrhythmias stronger than all available drugs, therefore IKr-blockers seem to be promising new atrial selective antiarrhythmic drugs.

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Predicting shapes of transmural filaments of reentrant arrhythmias in the ventricles of the heart
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Reentry is one of the major mechanisms of ventricular arrhythmias. However, mapping studies of such arrhythmias show only rare occurrences of clear reentrant sources on the surface of the heart. This may be explained by an intramural orientation of wave fronts inside the myocardium (Berenfeld, Perestov jib, v.199,383-394,1999). Thus, prediction of filament shapes in myocardium is of great importance for interpreting experimental data on ventricular arrhythmias. In this study we propose a Method for predicting filament shape in cardiac tissue of any geometry and anisotropy. The Method is based on the 'minimal principle for Rotor filaments' proposed by Wellner et al. (PNAS, v.99:8015 8018,2002).

We demonstrate that this principle can be reformulated using the eikonal equation for wave propagation in the same medium in which the 3D reentry rotates. This allows us to find the stable filament position as the minimal path for a wave propagating in a given tissue. We show that this minimal path can be effectively found using wave tracing algorithms, which requires knowledge of arrival times of waves initiated at the boundaries of cardiac tissue. We illustrate our approach in numerical simulations of orthotopically anisotropic cardiac tissue with several types of anisotropy and demonstrate a good correspondence of the predicted and simulated Results.

Because the only information necessary for using our Method is the data on arrival times, our Method can be applied for predicting filament shapes in experimental preparations without requiring any knowledge on the anisotropy of cardiac tissue.

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Basis for the induction of phase two reentry in the Brugada syndrome: Insights from computer simulations
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Introduction: The Brugada syndrome is characterized by a dysfunction of sodium channels that can result in delayed formation of the action potential dome or even complete loss of the dome during phase two in the right epicardial ventricular channels where L_{Na} is large. The repolarization pattern in these cases is believed to give rise to phase two reentry; however, little is known about the specific conditions that allow or suppress its initiation.
Methods: Ionic cell models for normal epicardial, endocardial and M cells were developed in addition to two epicardial Brugada models that reproduced the action potential shape of experimentally measured human Brugada MAPs and the Luo-Rudy dynamic model with Brugada (see figures). These models were used in 1D cables, 2D slabs, and a 3D canine ventricular model to show ST-segment elevation on ECG leads V1-V3 and to study induction of reentry by phase two.

Results: In 1D, phase two reentry can be induced when a region with loss of dome is adjacent to a region with a delayed dome, independent of stimulation site. In 2D, phase two reentry can be initiated when three regions (lost dome, delayed dome, and normal) are present, and sustained reentry initiates following an activation from any stimulus site outside the normal tissue. In 3D, sustained phase two reentry requires taking into account the different resistivity between the epicardial and M cell layers.

Conclusions: The inducibility of phase 2 reentry depends on a number of factors, including I _Na, and resistivity distribution, rate and direction of stimulation, and most importantly, the shape of the late plateau, the action potential duration with loss of dome, and the rate of sodium inactivation.

715 Modelling vortices of electrical waves in mice hearts
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Background: the mouse is the most practical and economical model to carry out genetic manipulations aiming at investigating the molecular mechanisms underlying cardiac death. However, a difficulty currently encountered with such model is that either spontaneous or induced arrhythmias self terminate shortly after initiation.

Objective: Elucidate the cause of arrhythmias self termination in normal and transgenic mice myocardiums.

Method: We simulate impulse propagation in a realistic model of the mouse heart. The reconstruction is based on a fusion of X-ray and confocal imaging modalities. The resulting geometry is meshed with 5 million elements, over which excitation is described with a detailed membrane model. Simulations are performed on massively parallel computers.

Results: The heart reconstruction (8 microns resolution) includes trabeculations, papillary muscles, and a representation of the three-dimensional cardiac fibers arrangement (5 microns resolution) in the entire heart including the above mentioned regions. Vortex activity in the heart is initiated with two point source stimuli. One at the apex and the other one in the free wall of the left ventricle 3 mm above the apex. Adjusting timing between the two stimuli and the circumferential position of the second stimulus vortices are initiated at different locations in the heart. In the majority of cases vortices drift toward the base and terminate when they collide with the latter. Occasionally they stabilize for about 1 second in highly convoluted regions of the heart. Mutations Resulting in an APD prolongation reduce the time of sojourn in stabilizing sites.

Conclusion: self-termination of arrhythmias is the result of vortex drift. Functional anchoring may occasionally occur, but at this time we cannot conclude as to whether it may be permanent.

716 Negative VEP affects activation during diastolic stimulation in the rabbit ventricles
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To further characterize the mechanisms of defibrillation, it is necessary to understand responses to shocks during diastole in the 3D volume of the ventricles. However, the few experimental studies that examined diastolic responses conducted measurements on the epicardium and, recently, on a transmural surface of the LV wall. This study investigates myocardial response to shocks in diastole throughout the volume of the rabbit ventricles using a realistic computational model of stimulation/defibrillation.

Methods: An anatomically accurate 3D bidomain model of the rabbit ventricles was subjected to shocks in diastole. Truncated exponential, 5ms long shocks of strengths in the range 1.5–18.75V/cm were administered via parallel-plate electrodes submerged in the surrounding perfusate.

Results: Total activation time as measured from the start of the shock varied from 26 to 55ms, rapidly decreasing and then slowly increasing as shock strength increased (figure, left panel). Early activation in the LV base was observed for lower (1.5–3V/cm) but not for higher shock strengths. During the shock, the pattern of transmural activation was similar for all mid-range shocks (6–18.75V/cm) and revealed deceleration of the propagating wavefront. We hypothesized that the shock-induced negative VEP caused activation delay and thus, paradoxical increase in activation times for higher shock strengths. Examination of VEP revealed an increase in negative VEP predominantly in the septum and the LV free wall with increase in shock strength (see right panel). The increase in negative VEP inhibited basal activation and slowed propagation for mid to high strength shocks.

Conclusion: During shocks in diastole, negative VEP causes propagation delay for higher strength shocks, Resulting in an unexpected increase in total activation time.

717 Analysis of SCNS5A gene mutation in Japanese patients with arrhythmia
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Objective: SCNS5A gene encodes the a-subunit of voltage-gated cardiac Na channel, which plays an important role in heart excitation/contraction. Mutations in SCNS5A cause distinct and inherited types of arrhythmias: type 3 long QT syndrome (LQTS3), Brugada syndrome (BS), idiopathic ventricular fibrillation (IVF), cardiac conduction disturbance (CCD) and even overlap of them. We analyzed SCNS5A gene mutations and polymorphisms among Japanese patients with inherited arrhythmia.

Methods: Genomic DNA was obtained from 150 probands of arrhythmia patients (congenital and acquired LQTS, BS, IVF, CCD and overlap syndrome) and 110 normal controls. Genetic variants in SCNS5A were screened by using a Denaturing High Performance Liquid Chromatography, and were subsequently determined by a direct DNA sequencing. Several mutations were engineered into the hH1 clone by using a site-directed mutagenesis Method, then expressed in HEK 293 cells, and were studied by a whole-cell mode of patch clamp Method.

Results: Nine SCNS5A mutations (5 novel and 4 reported) were identified (5 in LQTS, 2 in BS, and 2 in overlap syndrome), and were not seen in 220 alleles of normal controls. One novel single nucleotide polymorphism (SNP), L1988R, was also found in 6 patients (0.04%), and in 2 controls (0.02%). Functional assay was conducted in 3 of 5 novel mutations: N1774D mutation was identified in a newborn LQTS, so-called near Sudden Infant Death Syndrome case. The N1774D mutant displayed a significant increase in the late Na current, and simultaneously, it caused a