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Transgenic CCS/lacZ Expression in the Pulmonary Venous Area in Murine Embryos; Source of Atrial Arrhythmias?

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Objectives: Atrial arrhythmias often originate in the pulmonary veins (PV). With the CCS (cardiac conductive system)/lacZ construct it has been possible to delineate the developing and mature cardiac conduction system. Expression in the area of the PV however, has not been described. The aim of this study was to explore the presence of lacZ-expression in the area surrounding the PV. Methods: Analysis of lacZ-expression during sequential stages of cardiogenesis was performed in a line of CCS/LacZ transgenic mice (E 9,5–15,5). Embryos were stained for B-galactosidase activity. An immunohistological staining with the myocardial marker HHF35 was performed to produce a double staining with the lacZ reporter construct. Results were 3-D-reconstructed and morphed to allow optimal insight. Results: Study of the embryos confirmed the presence of lacZ expression in almost the complete embryonic heart tube at stage E 10,5. Thereafter, the expression became gradually confined to the primitive conduction system. Expression was seen in the RA in the sino-atrial node and left and right venous valves, in the right en left atrioventricular ring, His bundle, bundle branches and the moderator band in the RV. Furthermore, LacZ positive cells could be demonstrated in the LA, also encircling the pulmonary venous entrance. These cells were continuous with the left venous valve in the RA. The RV inflow and the distal part of the outflow tract did not show lacZ expression. Conclusion: Lac Z reporter gene expression is able to delineate the developing murine cardiac conduction system. New details have been found, such as the embedding of the PV in an area of lacZ-positive cells, which may be significant in the participation of the PV in atrial arrhythmogenesis.

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Competitive Interactions Between Ectopic Foci and Reentry in Virtual Human Atrium

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BACKGROUND: Although there is considerable experimental evidence to support the multiple wavelet reentrant theory of atrial fibrillation (AF), recent work indicates that a focal origin for the arrhythmia occurs in a significant proportion of cases. As both mechanisms are likely to coexist in many patients, we studied the potential interactions between the 2 in an isotropic virtual model of human atrium. METHODS: A computer model of human atrial action potential (Nygren et al 1998) was incorporated into a 2-D sheet of virtual atrium (area 96 mm^2) using a partial differential equation (PDE). Spiral waves were initiated using an S1-S2 protocol with a diffusion coefficient of 0.3125 cm^2s^{-1} that gave a plane wave velocity of 30 cm s^{-1}: ectopic foci of various rates were modeled using suprathreshold stimuli (4x threshold) to a localised area of the model. RESULTS: The interaction between ectopic activity and reentrant spiral waves is dependent upon the frequency of the ectopic focus f_e, the frequency of spiral reentry f_s, and the critical frequency of the tissue f_t, below which each of a series of ectopic beats can provoke a propagating wave (an inverse measure of refractoriness). If $f_t > f_e > f_s$ (i.e. an ectopic focus firing more rapidly than spiral wave frequency in tissue with reduced or low refractoriness) then the ectopic focus dominates electrical activity, resulting in spiral wave breakdown and persistence of disorganised AF. If fs > fe, the reentry will suppress the ectopic focus and dominate the activity of the whole medium. Depending on the initial distance between the organization center of reentry and ectopic region, the ectopic focus may have no effects on reentry, or perturb the reentry to meander away from the auto-rhythmic region. CONCLUSION: The model supports the view that rapidly firing ectopic foci can acts as "drivers" of AF, promoting breakup of spiral waves and persistence of the arrhythmia, particularly in the setting of reduced refractoriness.

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Differences in Reentry Dynamics Between Two Human Atrial Cell Models

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Introduction: Two detailed ionic models of the human atrial cell, the Nygren et al. model (NM) and the Courtemanche et al. model (CM), have been developed recently. Although both models draw largely from the same experimental data, they exhibit vastly different properties in single cells as well as in tissue. Methods and Results: Simulations of both cell models were performed using simple 2D sheets and an anatomically realistic 3D human atrial structure for as long as several minutes. We found that spiral wave breakup does not occur using the NM, and instead the trajectory obtained transitions over 10–15 minutes from a small circular core to a petal pattern that gradually increases in size. Different transitions occur when some ion concentrations are fixed. With the CM, the stability of reentry depends on the mode of induction. While spiral wave breakup readily occurs after initiation by a premature stimulus, breakup can be reduced or eliminated due to memory if the spiral wave is initiated after exposure to rapid pacing. Reductions in I_{to}, $I_{Ca,L}$, and I_{Kur} to reproduce the physiology of AF-remodeled cells result in a stable spiral. Conclusions: (1) The two models of human atrial cells differ substantially in dynamical properties associated with rate adaptation and reentry stability, and proposed simple changes in current strengths cannot harmonize them. (2) Fixing ion concentrations in these models can affect reentry dynamics. (3) In a realistic 3D atrial anatomy, none of the models, including AF modifications, generate sustained reentry without other modifications, such as dilatation or changes in conduction velocity.

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Action Potential Duration Heterogeneity in the Atrium and Its Effect on Atrial Reentry

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Introduction: The effect of action potential duration (APD) heterogeneity in initiation and maintenance of atrial fibrillation is still unclear. The purpose of this simulation study is to determine the role of varying APD associated with specific atrial structures in the evolution of atrial reentry. Methods: A 2D model of atrial tissue was constructed that incorporates realistic atrial action potentials where the APDs were adjusted to correspond to those of the crista terminalis (CT), atrioventricular rings, and appendage. Insulated boundaries were applied to the inhomogeneous sheet as well as to a sheet with homogeneous APD. A spiral wave (SW) was initiated in each case and its evolution monitored. Phase singularity (PS) traces were generated in order to analyze the effect of APD variations and sheet topology on SW behavior. Results: In the inhomogeneous sheet, the SW anchored on the CT. The PS trajectory of this SW meandered around the CT due to the prolonged refractoriness there. In comparison, the SW in the homogeneous sheet did not survive. The APD variation in the other atrial structures had no significant impact on atrial reentry. Joining the two ends of the sheet to form a cylinder created a continuous surface for the SW to propagate across. In the homogeneous sheet, this resulted in break up of the original SW and sustained reentry. In the inhomogeneous sheet, the PS resulting from the breakup collided with the SW anchored to the CT, and the reentrant activity was extinguished. Conclusions: The prolonged APD of the CT played a major role in the maintenance of the SW. The surface continuity did not affect the movement of the original PS but initiated more waves that created a complex pattern of reentry.