metabolic sink, but only when the sink exceeds a critical size (r>0.4cm). Phase singularity analysis indicates that the fibrillatory activity is initiated at sites close the border zone. The results emphasize the power of integrating cellular electrophysiological, Ca2+ handling, and metabolic subsystems into a multiscale model to simulate emergent macroscopic phenomena in the heart. Moreover, the results provide a proof-of-concept of the metabolic sink hypothesis and a new tool to study its role in arrhythmogenesis and sudden cardiac death.

3428-Pos Board B475

Action Potential Modelling Predicts Electrophysiological and Pharmacological Features of Human Embryonic Stem Cell-derived Cardiomyocytes

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Human embryonic stem cell-derived cardiomyocytes (hES-CM) represent a promising tool for cell therapy and drug screening. Their functional properties must be assessed.

We characterized hES-CM action potentials (AP) at two developmental stages with a combination of electrophysiological, RT-PCR and modelling tools. The AP was simulated on the basis of a model of human adult ventricular cell. The model was modified to incorporate experimentally assessed stage-dependent modifications of ionic currents (e.g. f-current, I_f, inward rectifier, I_{K1}, and delayed rectifier currents, I_{Kr}). Effects of current blockers were simulated by selectively reducing the current maximum conductance.

As we previously showed, changes in AP occur during in-vitro maturation (Early vs. Late): increase in AP duration and amplitude, decrease of slope of diastolic depolarization and rate of spontaneous beating. AP modelling reproduces: (i) experimentally observed changes in AP profile and differential effects of I_{Kr} blockade by E4031 at Early vs. Late stages (Figure A-B); (ii) effects of Ba^{2+} and zatebradine (I_{K1} and I_f blockers, respectively) (Figure C-D). These results suggest that our novel mathematical model can serve as a predictive approach to interpret and refine in-vitro experiments on hES-CM.

3429-Pos Board B476

Stability and Oscillations in a Ventricular Cardiomyocyte Model Studied Using the Tools of Dynamic Systems Analysis and Bifurcation Theory

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Although ventricular fibers of the working myocardium *in vivo* or *in vitro* do not feature pacemaker activity in normal conditions, getting depolarized and contracting only upon receiving current input from the surroundings, in certain pathological states they become prone to generate sustained oscillations. In order to get an insight into the mechanisms underlying these rhythm disturbances, we studied the dynamics and bifurcation behavior of a simple mathematical model of ventricular cardiomyocyte, the Luo-Rudy I model, using numerical and analytical methods, as described by Kurata *et al.* For different configurations of parameters and initial conditions, we found equilibrium points (states where the field of variables vector vanishes). These were further used to compute the eigenvalue vector of the linearized system of differential equations at various values of stimulus current (I_{stim}) in the range of −5 to +5 uA/uF. Doubling the time-dependent potassium conductance (g_{kt}) resulted in sustained self-oscillations in a narrow interval of I_{stim}: (-0.7,+0.3) uA/uF for a reversal potential of the background current e_b=0 mV, and (-3.0,-2.1) uA/uF for the default value e_b=-59.87 mV, while for normal g_{kt} the system reached stable equilibrium over the entire I_{stim} range with either of the e_b values tested. We also demonstrated that, for a given set of parameters, the system admits a maximum of two different equilibrium points, with the same potential but different intracellular calcium concentrations.Acknowledgements to Prof. K. Mubagwa and A. Gwanyanya, PhD from KULeuven for help in initiating experiments on cardiomyocytes in Bucharest.

3430-Pos Board B477

Feasibility of Estimating Maximum Ion Conductance Parameters from the Shape of the Action Potential. A Simulation Study

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Simultaneous measurement of ion currents and transmembrane potential (V(t)) is difficult. We verified whether the V(t) of a myocardial action potential (AP) is sufficient to estimate the cell's ion currents densities. We built a database of 45000 simulated APs by running the Luo-Rudy dynamic model simulator (LRd) on uniform randomly generated parameter sets comprising the maximum conductances for 12 major ion current components in the range of 0.5–2.0 times the default. A 'data' action potential (V_d(t)) was generated randomly in the same parameter interval and we tried to estimate its parameters. Each AP in the database was assigned the same prior probability at step 0. Then, at each of 50 steps spaced at 5 ms, a posterior probability was computed that was used as the prior probabily for the next step. We considered for each step t(j) the difference DV(i,j) between the i'th action potential in the database and the 'data' action potential. Using a normal noise model we calculated the non-conditional probability of DV(i,j), then the post-probability for step j given the prior obtained in step j-1. The highest posterior probability finally obtained identified our estimated parameters in the database.

RESULTS. In 100 such simulated experiments we found a RMSD of 4.14 ± 1.15 mV (mean $\pm$ SD) between estimate V(t) and data, corresponding to a very close resemblance. However, the absolute differences in parameters were large, ranging from 0.30 ± 0.31 for I_Kr to 0.9 ± 0.5 for I_Na.

CONCLUSION. There appears to be insufficient information in the single AP recording to simultaneously estimate the maximum conductances for 12 ion currents, as the same AP can be reconstructed from quite different parameters. Further progress will need taking into account other measurable experimental data.

3431-Pos Board B478

Characterization Of Human Embryonic Stem Cell-derived Cardiomyocyte Action Potentials And Channel Conductances Using A Theoretical Model

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Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) can provide insights into the development of human myocardium and provide a powerful cellular system to investigate the electrical properties of human cardiomyocytes. In this study, we examined the action potentials (APs) of early developing hESC-CMs studied in spontaneously contracting EB outgrowths after 12-15 days of differentiation and modeled the channel conductances/activities responsible for the APs. Intracellular recordings using sharp KCl microelectrodes reveal cellular APs that are similar in basic form to those of early embryonic human cardiomyocytes. Comparison of the AP duration, AP upstroke slope and mean diastolic potential (MDP) show three distinct AP classes: nodal, embryonic-ventricular and embryonic-atrial. To gain a better understanding of the differences in channel activity underlying each AP class and to allow comparison to adult human cardiomyocytes, we used a modified version of a previously developed computational model of the adult cardiomyocyte. The main modification is the addition of a hyperpolarization-activated Na/K channel to represent the observed slow depolarization in diastole. The channels in this model are represented with a Hodgkin-Huxley formalism including parameters describing channel conductance, as well as inactivation and activation gating voltage and time constants. AP time courses are reproduced with this model by varying the various channel conductances (fast Na, rapid delayed rectifier K, etc.) In this manner the three differentiated hESC-CM classes have been characterized in terms of their relative channel conductances for the 12-15 day in culture developmental time point. Our results show that a more active background Na channel is required to adjust for the less polarized MDP seen in the recordings and the slow delayed rectifier K channel activity is greater in the nodal class of APs than is seen in the embryonic-ventricular class.

3432-Pos Board B479

A Novel Computational Model of the Human Ventricular Action Potential and Ca transient

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We have developed a detailed mathematical model for Ca handling and ionic currents in the human ventricular myocyte. Our objective was to implement a model that: 1) accurately reflects Ca-dependent Ca release; 2) uses repolarizing K currents with realistic amplitude; 3) comes to steady state; 4) simulates basic excitation-contraction coupling phenomena; and 5) runs on a normal desktop computer. The model relies on the framework of the rabbit myocyte