Methods:
QTc intervals were measured in 10 week old LDL-receptor (LDLr-/-) and APO1 (APO1-/-) knockout mice, and wild type mice (WT). Action potentials, calcium handling and ion currents were recorded in ventricular myocytes. In perfused hearts regional ischemia was induced by ligating the left anterior descending artery . Arrhythmias inducibility was tested every 30 s by applying premature stimuli followed by a 500 ms pause. The area at risk (AAR) was determined by perfusion with Evans Blue.
Results:
Serum LDL cholesterol was higher in LDLr-/- and serum HDL cholesterol was lower in APO1-/- mice than in WT. Resulting in an increased cholesterol content in ventricular myocytes. The L-type calcium current was increased in LDLr-/- and APO1-/- (12.1 ± 0.7 and 12.8 ± 0.8) compared to WT (9.4 ± 1.1 pA/pF) resulting in altered calcium handling in LDLr-/- and APO1-/- vs WT mice (increased calcium transient and fractional SR calcium release) and prolongation of AP and QTc duration (APD90 102 ± 4 and 106 ± 3 vs 84.4 ± 3.1 and QTc 50.9 ± 1.3 and 52.3 vs 43.8 ± 1.18 ms, respectively.In LDLr-/- and APO1-/- hearts 1.7 and 1.3% of the attempts to induce arrhythmias resulted in VT/VF compared to 6.9% in WT. There was no significant difference in the induction of premature beats although (12.8% in WT vs 15.5 and 15.8 in LDL-/- and APO-/-). The AAR was not significantly different in LDLr -/-, APO1-/- and WT mice.
Conclusion:
Hypercholesterolemia protects against the occurrence of re-entrant arrhythmias during myocardial ischemia due to AP prolongation caused by an increase of the L-type calcium current.

3899-Pos Board B627
Apico-Basal Gradient of Repolarization Over the Left Ventricle Determines Arrhythmia Susceptibility in Mice
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Combined prolongation and spatial heterogeneity of cardiac action potential (AP) duration is proarrhythmic in larger mammals; however the short murine AP suggests a different mechanism underlying arrhythmia induction. Expression of KChIP2 is critical for the stabilization of Kv4.2 in mice, and KChIP2$^{-/-}$ abolishes the transient outward K^+ current, $I_{to,f}$. We have previously shown that KChIP2$^{-/-}$ mice have lower susceptibility to pacing-induced ventricular tachyarrhythmia than normal wild-type mice. Moreover, aorta constriction causing heart failure also lowered proarrhythmia susceptibility in wild-type mice.
In vivo recording of QRS duration from surface ECG suggested comparable conduction velocities in KChIP2$^{-/-}$ and wild-type mice and QRS prolongation associated with heart failure. Next, we used floating microelectrodes to record APs from different regions of the explanted, perfused mouse heart to test the hypothesis that short and spatially heterogeneous AP morphologies contributes to arrhythmia susceptibility in mice. Left ventricular (LV) APs were prolonged in KChIP2$^{-/-}$ (APD_{90}:50 ± 3ms, n=6) compared to wild-type hearts (39 ± 3ms, n=6; $P<0.05$). Right ventricular APs were similar in KChIP2$^{-/-}$ and wild-type hearts, producing a larger left-to-right AP dispersion in KChIP2$^{-/-}$ (17 ± 5 versus 7 ± 3ms, respectively). Importantly, LV apico-basal dispersion of AP duration was smaller in KChIP2$^{-/-}$ hearts than in wild-type hearts (2 ± 1 versus 13 ± 4ms, respectively; $P>0.05$).
Despite prolonged APs in KChIP2$^{-/-}$ and heart failure, arrhythmia susceptibility was low. A large apico-basal AP gradient was found in the proarrhythmic wild-type mice, strongly suggesting that this is an important determinant for arrhythmia vulnerability. Contrary to larger mammals, left-to-right ventricular dispersion of AP duration was not associated with vulnerability to pacing-induced arrhythmia.

3900-Pos Board B628
Effect of Different Currents and Extracellular Potassium Ion Concentration on Anodal Excitation of Cardiac Tissue
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Background:
In order to understand defibrillation completely and thereby to design better defibrillators, we need to understand fibrillation and the effect of electrical stimulation on cardiac tissue. We address this issue by studying anodal excitation applied to the refractory tissue and by measuring the refractoriness of the cardiac tissue through the strength-Interval (SI) curve. The anodal SI curve contains a "dip" in which the S2 threshold increases as the interval increases. Our goal is to find the mechanism of the dip and to determine how calcium currents, sodium calcium exchange (NCX) current and elevated extracellular potassium ion concentration, [K]e, influences the dip in the anodal strength-interval curve.
Methods and Results:
Computer simulations of unipolar stimulation were performed using the bidomain model, with membrane kinetics governed by the Luo-Rudy model. The SI curve is determined by applying a threshold stimulus at different time intervals after a previous action potential. The dip disappears with no NCX current, but is present with 50% and 75% reduction of normal NCX current. The calcium induced calcium release (CICR) current and/or calcium uptake current are not responsible for the dip in the anodal SI curve. High [K]e results in the disappearance of the dip in the anodal SI curve because the tissue remained refractory after the transmembrane potential returned to its resting state.
Conclusions:
Neither NCX nor calcium current is responsible for the dip in the anodal SI curve. It is due to the electrotonic interaction between regions of depolarization and hyperpolarization following the S2 stimulus. The dominance of the electrotonic mechanism emphasizes the importance of the spatial distribution of virtual electrodes during excitation, which ultimately clarifies tissue-shock interactions and optimizes advanced defibrillation protocols.

3901-Pos Board B629
Examination of the Heat-Stress Relationship of Rat Cardiac Trabeculae using an Improved Muscle Calorimeter
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The energetic output of cardiac muscle is closely correlated with its mechanical outputs. Using isolated cardiac preparations (papillary muscles and trabeculae) most investigators have found a linear relation between heat production and developed force, where the heat production at zero force indexes the metabolic cost associated with Ca^{2+} cycling, predominantly by the sarcoplasmic reticulum Ca^{2+}-ATPase. To our knowledge, the heat-stress relationship of cardiac muscle at physiological temperature has not yet been reported. Thus, it is of paramount important to extend previous studies to determine the heat-stress relation at 37°C.
Our flow-through micro-mechano-calorimeter is capable of simultaneously measuring the heat output, length change, and force production of isolated rat cardiac trabeculae, but was restricted to room temperature measurements (22°C). Two modifications to the instrument have been made to allow measurements at physiological temperature. We substituted thermoelectric heat pumps for our thin-film thermopile temperature sensors, thereby reducing light sensitivity and lowering the electrical noise floor. We also added other thermoelectric heat pumps for controlling the temperature of the instrument to a set-point of up to 40°C, with 100 μK resolution. Finite element modelling was used to inform and optimise the choice and position of the heat pumps within the device. The heat-rate resolution of our instrument has thereby been improved ten-fold to 5.8 nW over a 5 Hz bandwidth, corresponding to a temperature change of approximately 0.9 μK.
Using the improved calorimeter, we have determined, for the first time, the heat-stress relation of isolated cardiac trabeculae at 37°C. The value of the heat-intercept is at the vicinity of 1.5 kJ m^{-3} per twitch, which amounts to approximately 25 Ca^{2+} ions sequestered by the sarcoplasmic reticulum Ca^{2+}-ATPase within a sarcomere with each twitch.

3902-Pos Board B630
Sarcomere Length Nanometry in Cardiomyocytes Expressed with α-Actinin-AcGFP in Z-Discs
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Nanometry is widely used in today's biological sciences to analyze the movement of molecules or molecular assemblies in cells and in vivo. In cardiac muscle, a change in sarcomere length (SL) by a mere ~100 nm causes a dramatic change in contractility (i.e., the Frank-Starling mechanism), indicating the need for the simultaneous measurement of SL and intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) in cardiomyocytes at high spatial and temporal resolution. To accurately analyze the motion of individual sarcomeres with nanometer precision during excitation-contraction coupling, we in the present study applied nanometry techniques to primary-cultured rat neonatal cardiomyocytes. First, we developed an experimental system for simultaneous nanoscale analysis of single sarcomere dynamics and $[Ca^{2+}]i$ changes via the expression of AcGFP in Z-discs. We found that the averaging of the lengths