provide an independent support for the theory of optical stimulation of excitable tissue.
Supported by APVV-0721-10 and by VEGA 2/0203/11 and VEGA 2/0197/11.

631-Pos Board B386
Electrophysiological and Structural Left Ventricle Remodelling in Spontaneously Hypertensive Rat Hearts: A Multicellular Study
Samha Alayoubi[1,2], Carolina Pinto Ricardo[1], Junaid Zaman[1], Priyanthi Dias[1], Patrizia Camelliti[1], Magdi H. Yacoub[1], Cesare Terracciano[1].
[1]NHLI, Imperial college, London, United Kingdom, [2]King Fahad Cardiac Center, King Saud University, Riyadh, Saudi Arabia.
The spontaneously hypertensive rat (SHR) is a well-characterised model for studies of hypertension and atrial arrhythmias but little is known about the electrophysiological properties of the left ventricle (LV) and their relation with ventricular arrhythmias in this model. To investigate the mechanisms behind electrophysiological abnormalities in the LV and their links to the morphological substrate we used myocardial slices, a multicellular preparation which allows the investigation of functional and structural properties in the same tissue location. Vibratome-cut myocardial slices (300µm thick) were prepared from 20 month-old SHR and aged-matched control LVs, tangentially to the epicardial surface. Slices were point-stimulated and analysed using a multi-electrode array system; conduction velocity (CV) and field potential duration (FPD), an index of action potential duration, were measured. Longitudinal CV was lower in the SHR compared with controls (SHR: 29 ± 4 cm/s, n=12 slices; C: 45 ± 6 cm/s, n=22 slices; $p<0.05$), but transverse CV was unchanged. FPD was not statistically different between the two groups and showed a similar restitution curve. A high number of fractionated field potentials were observed at similar levels in both groups (SHR: 107 ± 20 ms, n=6 slices; C: 74 ± 2 ms, n=6 slices; $p>0.05$). In support of the lower CV, Western blotting analysis revealed a reduction in the gap junctional protein connexin43 expression in the SHR ($p<0.01$). A high amount of interstitial fibrosis, quantified by Sirius red/fast green collagen quantitative staining kit was found in both groups at similar levels ($P>0.05$) and could be ascribed to aging as this was not detected in slices from 2 month old rats ($p<0.05$). These results suggest that down regulation of connexin 43 and not myocardial fibrosis is associated with electrophysiological LV abnormalities in a rat model of chronic hypertension.

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Alternans in Rabbit Heart During Acute Regional Ischemia: Optical Mapping and Microelectrode Recordings
Irma Martišienė[1], Jonas Jurevičius[1], Ruta Vosyliutė[1], Antanas Navalinskas[1], Rimantas Treinys[1], Regina Mačianskienė[1], Rimantas Benetis[1], Arvydas Matiukas[2], Arkady M. Pertsov[1,2].
[1]Institute of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania, [2]Department of Pharmacology, SUNY Upstate Medical University, Syracuse, NY, USA.
T-wave alternans during acute ischemia have been determined as a precursor of ventricular arrhythmias usually resulting in sudden cardiac death. Optical mapping is often used to investigate the mechanisms of alternans in heart preparations. Several hypothesis exist that may explain the formation of optical alternans. One of them is that optical action potential amplitude (OAPA) alternans may indicate the formation of alternating conduction blocks. In our study by using optical mapping simultaneously with microelectrode recordings we aimed to investigate the occurrence of OAPA alternans during acute regional ischemia and to determine the electrical origin underlying the alternans formation. Experiments were performed in Langendorff-perfused rabbit hearts stained with near-infrared dye di-4-ANBDQBS. Optical signals were registered from left ventricle epicardium. The hearts were stimulated by applying 300 ms, and 200 ms pacing cycle. Results showed that OAP started alternate with high and low amplitudes at 200 ms pacing at early ischemia (4-6 minutes). The alternation zone migrated, shrank and finally disappeared with increasing ischemia time. In order to elucidate the mechanism of this phenomenon two glass microelectrodes were used to examine electrical activity by registering action potentials from subepicardial and deeper (3-5 mm) myocardial layers simultaneously. Microelectrode recordings revealed that OAPA alternans is the result of 2:1 conduction blocks in a certain layer whilst the regular response is held in the other layers. During later ischemia (10-15 minutes) deep myocardial layers lose their excitability remaining optical signals only with low amplitude. It explains the disappearing of OAPA alternans. Thus, our experimental data show that OAPA alternans which arise during the early acute ischemia can be caused by alternation of conduction blocks in a certain myocardial layers.
Research is funded by the European Social Fund under the Global Grant measure.

633-Pos Board B388
Evaluation of Optical Upstroke Morphology in the Rabbit Heart: Optical Mapping and Transmural Microelectrode Recordings
Rūta Vosyliūtė, Regina Mačianskienė, Irma Martišienė, Antanas Navalinskas, Rimantas Treinys, Birutė Vaidelytė, Gintautė Rutkauskaitė, Jonas Jurevičius.
Lithuanian University of Health Sciences, Kaunas, Lithuania.
Last decade optical mapping technique became a widely-used instrument in cardiac electrophysiology. Optically recorded action potentials (AP's) in single cardiac cells precisely match electrically recorded ones. However, this relationship becomes not so direct in myocardium since optical AP (OAP) is the depth-weighted average of propagating AP and is affected by optical-biological processes (absorption, scattering and reflection). The best way to achieve informative results of electrical activity in the heart is to use both, optical approaches in combination with microelectrode technique.
In the Langerdorff-perfused rabbit heart AP's were recorded with glass microelectrodes transmurally across the left ventricle (LV) wall from subepicardium towards subendocardium (3-5 mm, 20-50 steps). Simultaneously we used near-infrared (NIR) voltage sensitive fluorescent dye di-4-ANBDQBS to obtain OAP recordings using EMCCD camera (128x128 pixels, 500 frames/s). OAP's and electrical AP's were recorded using pacing from epicardium and endocardium.
In our experiments we found, that AP activation time dependence on myocardium depth had a different shape, depending on pacing the type, distance, and LV geometry at recording site. The shape of the curve showed electrical transmural inhomogeneity of myocardium, which possibly was caused by histological inhomogeneity and different fibers orientation in different layers of myocardium. For the upstroke of OAP's evaluation, optical signals were compared with electrical AP's, recorded and summated transmurally through LV wall depth. Recordings allowed us to evaluate the role of light scattering and how much tissue inhomogeneity was reflected in the morphology of the upstroke of OAP.
The obtained data could assist for better understanding of the mechanisms of the excitation wave propagation and for proper evaluation of optical signal in LV of the rabbit.
This research is funded by the European Social Fund under the Global Grant measure.

634-Pos Board B389
Mechanisms Underlying Na^+/K^+-ATPase Inhibition-Induced Mitochondrial Dysfunction and Abnormal Action Potentials
Qince Li, **Lufang Zhou**.
Division of Cardiovascular Disease and Comprehensive Cardiovascular Center, University of Alabama at Birmingham, Birmingham, AL, USA.
The proarrhythmic effect of cardiac glycosides has confined their extensive applications in the treatment of heart failure. The detailed molecular mechanisms underlying glycoside-induced arrhythmogenesis are not fully understood. Recent experimental work shows that glycosides (e.g. Ouabain) impair mitochondrial energy metabolism and raise reactive oxygen species (ROS) production, resulting in abnormal action potentials in cardiomyocytes. In the present work, a multiscale cardiomyocyte model that incorporates cellular electrophysiology, mitochondrial energetics and detailed antioxidant system is developed to further investigate how glycosides may lead to mitochondrial dysfunction and abnormal electrophysiology under various physiological/pathological conditions. In the model, the effect of glycoside is mimicked by inhibiting Na^+/K^+ pump (a.k.a NKA) activity. Our simulations show that moderate NKA inhibition (e.g. by 50%-70%) causes cytosolic Ca^{2+} accumulation and blunted mitochondrial Ca^{2+} ($[Ca^{2+}]m$) uptake, especially during the transition of increased workload. The suppressed $[Ca^{2+}]m$ uptake is accompanied with decreased NADH production and increased ROS accumulation. These results are consistent with previous experimental data. Interestingly, model simulations show that under certain conditions (e.g. in stressed cells), blocking NKA can cause mitochondrial depolarization and trigger sustained mitochondrial oscillations. Another finding is that further increasing NKA inhibition (e.g. by 90%) leads to severe ATP depletion and triggers Ca^{2+} and action potential alternans. Finally, simulations reveal that the glycoside-induced mitochondrial dysfunctions can be prevented or alleviated by inhibiting mitochondrial Ca^{2+} extrusion via mitochondrial Na^+/Ca^{2+} exchanger, but not by increasing mitochondrial Ca^{2+} uptake via mitochondrial Ca^{2+} uniporter. These results suggest that impaired mitochondrial Ca^{2+} uptake and energy production are the major factors responsible for NKA inhibition-induced abnormal cellular electrophysiology. This study, using computational modeling, provides new insights into the mechanisms underlying the proarrhythmic effect of cardiac glycosides, and has important implications for developing new glycoside-based therapies of heart failure.