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Variable T-Tubule Density and Organization in Rat Atrial Cardiomyocytes
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T-tubules are invaginations in the cellular membrane of the myocyte. In ventricular cardiomyocytes initiation of excitation-contraction coupling is highly localized near the t-tubules, which span the cell in a predominantly transverse orientation. While t-tubules have traditionally been thought to be virtually absent from atrial cells, recent data indicate that a fairly substantial network is present in the atria of large mammals. We presently compared the t-tubule network of atrial and ventricular cardiomyocytes in 6 week-old Wistar rats. Atrial myocytes were isolated by dicing and agitating tissue in the presence of collagenase, and ventricular cells were isolated by Langendorf perfusion. Cell membrane and t-tubules were stained with di-8-ANEPPS and imaged by confocal microscopy. 100% of ventricular and 37% of atrial cardiomyocytes possessed a measurable t-tubular density (defined as occupying >5% of the cytosolic lumen). In the tubulated atrial cells, t-tubular density was similar to that observed in ventricular myocytes (% cross-sectional area = 16% in atrial vs. 17% in ventricular cardiomyocytes, P=0.76). Surprisingly, 10% of atrial myocytes exhibited an organized, largely transverse structure. Power spectral analysis revealed that this organization was somewhat less homogeneous than that observed in ventricular cells, as atrial myocytes exhibited a higher proportion of longitudinal elements (ratio of peak power to between-peak power = 3.15 in atrial vs. 5.13 in ventricular cells, P=0.02). Neither density nor organization of t-tubules was correlated to atrial cardiomyocyte size. Thus, in contrast to several previous reports, a significant proportion of rat atrial cardiomyocytes possess a t-tubule network which is as extensive as that observed in ventricular cells. Furthermore, in a minority of atrial cardiomyocytes (approximately 10%) the t-tubular network is well organized into a predominately transverse structure.

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Altered Action Potential Heterogeneity in Hypertrophic Right Ventricles of Rats
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Hypertrophy of the myocardium causes electrophysiological remodeling and changes in action potential duration (APD). The right ventricle (RV) becomes hypertrophied and fails under conditions of pulmonary artery hypertension (PAH). The current study evaluated changes in APD heterogeneity in a rodent model of PAH.
Male Wistar rats were given a single i.p. injection of monocrotaline (60 mg/kg) or an equivalent volume of saline. When clinical symptoms of heart failure became apparent (3-4 weeks later) animals were euthanized and the hearts excised. Electrical activity was optically monitored from the epicardial surface of both ventricles in intact hearts using di-4-ANEPPS. The myocardium was stimulated at basic cycle lengths (BCLs) between 80-160 ms. APD at 80% repolarization (APD_{80}) was calculated at the mid-LV, mid-RV and right ventricular outflow tract (RVOT) regions.
At 160 ms BCL, APD_{80} was significantly longer in hypertrophied compared to sham in both RV regions however 8/9 hypertrophied hearts had a longer APD_{80} in the RVOT vs. mid-RV, whilst in 11/11 sham hearts the APD_{80} was shorter in the RVOT. The changes in APD between the two RV regions were significantly different (MCT RVOT - mid-RV +6.6 ± 2.6 ms vs. Sham RVOT - mid-RV −6.8 ± 1.3 ms, p<0.0001 unpaired Student's t-test). APD restitution curves were significantly steeper in the mid-RV and RVOT of hypertrophied hearts than the mid-LV or mid-LV, mid-RV and RVOT of sham hearts.
These data show that electrical remodeling in monocrotaline treated RV was heterogenous. These regionally dependant changes in APD may contribute to the pro-arrhythmic state of hypertensive and hypertrophic RVs.
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Conditional SERCA2 Ablation Impairs Systolic and Diastolic Performance of Isolated Perfused Hearts
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Highly orchestrated contraction and relaxation of the myocardium depends on rapid release and reuptake of Ca^{2+} from the sarcoplasmic reticulum (SR). SERCA2a, a cardiac SR Ca^{2+}-ATPase, is a major contributor to re-sequestration of Ca^{2+} and shows reduced expression with age and in heart failure. Conditional deletion of the *Serca2* gene from the hearts of fl/fl mice results in progressive diastolic dysfunction, heart failure, and death over a period of two months. To gain insight into the interplay between Ca2+-mishandling and the evolution of cardiac pump failure we studied mice at 1 and 4 weeks following cardiac specific cre-mediated deletion of the *Serca2* gene from fl/fl mice. At each time point, isolated hearts were subjected to paced stimulation across a broad frequency range, followed by ischemia/reperfusion injury. At both 1 and 4 weeks, SERCA2a loss resulted in profound contractile deficits and diastolic impairment relative to normal hearts. However, there was no difference in the relative performance of normal and KO hearts following ischemia/reperfusion injury, suggesting that depleting SR Ca^{2+} is not protective from ischemia. Curiously, 1 week after *Serca2* deletion, when 15-20% of baseline SERCA2a protein remains, diastolic performance in response to stepped increases in pacing frequency was impaired to a similar degree as in 4-week KO hearts containing <5% original protein levels. We are further investigating the consequences of SERCA2a loss shortly after gene deletion, at times less than one week after knockout, to construct a detailed dose-response relationship between titrated changes in SR Ca^{2+} handling and contractile function.

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Elevated Plasma Oxidized Lipids in Severe Pulmonary Hypertension are Fully Restored by Estrogen Therapy
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Recently we reported that estrogen (E2) rescues pre-existing severe pulmonary hypertension (PH). PH is associated with pulmonary vascular remodelling. Vascular disorders result from complex interactions between oxidized-lipoproteins, monocytes/macrophages, injured endothelium and smooth muscle cells. Biological oxidation products of arachidonic acid, including prostaglandins (PGs), thromboxanes (TXs), hydroxyeicosatetraenoic acids (HETEs) and hydroxyoctadecadienoic acids (HODEs) play an important role in the pathogenesis of atherosclerosis, yet their role in PH is not fully known. Here we investigated whether PH is associated with increased plasma levels of oxidized-lipids, and if E2 can restore their levels. To induce PH, rats received monocrotaline (MCT, 60mg/kg, s.c.). Severe PH was established 21-days after MCT (PH, n=8). E2 (42.5ug/kg/day, s.c., n=6) was given from day-21 to 30. Saline treated rats served as control (CTRL, n=7). Cardiac catheterization was performed terminally to record RV-pressure (RVP). Plasma HODEs, HETEs, TXs and PGs were determined by mass-spectrometry. p<0.05 was considered significant. Values were mean ± SE. Rats developed severe PH [RVP=68 ± 2 vs. 31 ± 2 mmHg in CTRL, p<0.01). E2 rescued PH (RVP=38 ± 1 mmHg, p<0.01 vs. PH). PH was associated with increased plasma levels (ng/ml of plasma) of 9-HODE (2217 ± 381 vs. 949 ± 255 in CTRL, p<0.05) and 13-HODE (4347 ± 439 vs. 1871 ± 609 in CTRL, p<0.05). E2 reversed PH-induced increase in HODEs (9-HODE=976 ± 259; 13-HODE=2469 ± 531; all p<0.05 vs. PH). PH led to significantly elevated plasma 5-HETE (938 ± 77 vs. 663 ± 15), 12-HETE (9720 ± 972 vs. 6633 ± 522) and 15-HETE (818 ± 62 vs. 534 ± 7; all p<0.05 vs. CTRL). E2 fully reversed the increase in HETEs (5-HETE=708 ± 37; 12-HETE=6981 ± 248; 15-HETE=622 ± 50; p<0.05 vs. PH). PH also led to elevated plasma TXB2 (3.5 ± 0.2 vs. 2.8 ± 0.1), PGD2 (98 ± 11 vs. 35 ± 7) and PGE2 (27 ± 1 vs. 13 ± 2; all p<0.05 vs. CTRL) and E2 restored their levels (TXB2=2.6 ± 0.2; PGD2=54 ± 10; PGE2=19 ± 2; all p<0.05). In conclusion, severe PH is associated with increased plasma levels of oxidized lipids that are fully restored by E2.

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Structural and Hemodynamic Changes Associated with Physiologic Heart Hypertrophy of Pregnancy are Reversed Postpartum
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We have previously characterized pregnancy-induced physiological heart hypertrophy. Pregnancy is associated with ventricular hypertrophy and short-term systolic and diastolic dysfunction due to volume-overload. Here we investigated whether cardiac structural and hemodynamic changes associated with pregnancy are reversed postpartum. Female mice (3-4month, C57BL/6) were used in non-pregnant diestrus-stage (NP), late pregnant (LP), 1-day postpartum (PP1), or 7-days PP (PP7). Echocardiography and cardiac-catheterisation were performed to monitor cardiac-hemodynamics. RT-PCR was performed to determine vascular endothelial growth factor (VEGF) and matrix metalloproteinase-2 (MMP2) transcripts. Trichrome staining for cardiac