P021
REMODELING OF BOVINE DESCENDING AORTA AND AORTIC VALVE DURING PREGNANCY ARE NOT REVERSED POSTPARTUM

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BACKGROUND: The maternal cardiovascular system undergoes dramatic adaptations during the volume overload of pregnancy. Blood volume is increased nearly 40% with enlargement of the cardiac chambers and heart valves. Aortic diameter increases during pregnancy, with even greater increases in multiparous women. How aortic elastin and collagen are altered with this remodeling is poorly understood. Of particular interest is elastin—whose gene is thought to be dormant after development and maturation. Even less clear is how (or if) pregnancy-induced aortic remodeling is reversed post-partum. The objectives of this study were to examine the dimensions, elastin and collagen contents, and collagen thermal stability of the descending aorta and aortic valve in: (i) never pregnant, (ii) pregnant, and (iii) post-pregnant animals.

METHODS AND RESULTS: Tissues were collected from a local abattoir from never-pregnant heifers, pregnant cows, and previously pregnant (i.e. post-partum) cows. Dimensions were measured from isolated aortic rings and aortic valve leaflets. Denaturation temperature (Td) testing provided a proxy measure of collagen thermal stability and maturity. Biochemical assays provided the contents of elastin and collagen (soluble and insoluble). Heart mass increased over 30% in pregnant animals (from non-pregnant) and remained elevated post-partum in previously pregnant animals. Heart volume similarly increased in pregnant animals, which further increases post-partum. Aortic circumference increased by 35% with a relative thinning of the wall that was even more pronounced post-partum. Similarly, the aortic valve leaflet area increased over 80% in pregnant animals from non-pregnant and remained significantly elevated post-partum. Remodeling of aortic collagen and elastin appear to accompany these dimensional changes with pregnancy states. While there was no significant change in aortic collagen content with pregnancy state, there was a trend towards a decrease in the collagen denaturation temperature (Td) in pregnant and previously pregnant animals, suggesting a reduction in thermal stability during pregnancy that does not fully reverse postpartum. Finally, there was a significant accumulation of elastin in the aorta during pregnancy (increasing over 50%), which also remains elevated post-partum.

CONCLUSION: This study has shown for the first time that the dimensional and compositional changes in the descending aorta and aortic valve during pregnancy are not completely reversed postpartum. A widening and thinning of the aorta would elevate wall stress (via Law of Laplace) that, with increased elastin content, may contribute to the increased risk for aortic dissection and other vascular pathologies during and after pregnancy.

	Never Pregnant	Pregnant	Post-Partum (Previously Pregnant)
Heart Mass (kg)	2.12 ± 0.12^{a}	2.92 ± 0.11^{b}	3.07 ± 0.3^{a}
Heart Volume (L)	2.26 ± 0.13^{a}	3.00 ± 0.13^{b}	3.11 ± 0.26^{b}
Aortic Circumference, C (mm)	74.5 ± 2.3^{a}	101.2 ± 3.8^{b}	112.4 ± 4.3^{b}
Aortic wall thickness, h (mm)	6.3 ± 0.1^{a}	6.7 ± 0.2^{a}	5.5 ± 0.2^{b}
Aortic relative wall thickness h/R)	0.35 ± 0.01^{a}	0.29 ± 0.01^{b}	0.24 ± 0.01^{c}
Aortic Collagen T_d(°C)	65.6 ± 0.4	$64.3 \pm 0.3^{\dagger}$	$64.7 \pm 0.3^{\dagger}$
Aortic Elastin (µg/mg)	26.9 ± 4.2^{a}	41.3 ± 3.3^{ab}	43.6 ± 3.7^{b}

Table 1. Heart mass and volume, aortic dimensions, collagen T_d, and elastin content. Values are mean values ± SE. Comparisons between pregnancy groups performed with ANOVA and Tukey's multiple-comparison test. Values labelled with the same letter (a, b) are not significantly different. † = p 0.088.

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P022
SIRT3 PREVENTS DOXORUBICIN INDUCED DILATED CARDIOMYOPATHY VIA REGULATION OF MITOCHONDRIAL PROTEIN ACETYLATION: INVESTIGATING METABOLIC DYSFUNCTION AS A RESULT OF ALTERATIONS TO CARDIAC LIPIDS

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BACKGROUND: Doxorubicin (DOX) is a chemotherapeutic used in the treatment cancer, however it has dose-dependent cardiotoxic side effects such as the development of dilated cardiomyopathy. Previously, we showed that DOX treatment decreases the expression of mitochondrial lysine deacetylase, sirtuin 3 (SIRT3) and alters mitochondrial protein acetylation of enzymes involved in cardiac energy production and oxidative stress in wild-type mice. Cardiac expression of full length mitochondrial localized M1-SIRT3 prevented cardiac remodelling and dysfunction characteristic of dilated cardiomyopathy in female mice. Here, we hypothesize that M1-SIRT3 expression could attenuate DOX-induced cardiac dysfunction by regulating the acetylation of enzymes involved in lipid remodelling and metabolic processes.

METHODS AND RESULTS: DOX (8mg/kg body weight for 4 weeks) was administered to mice with cardiac restricted expression of full length M1-SIRT3 (mitochondrial localized) and short form M3-SIRT3 (lacking the mitochondrial localization sequence) or non-transgenic (Non-Tg) littermates (control groups received saline). Transthoracic echocardiography was performed in male mice from all groups (n=8-13). Cardiac mitochondria were isolated, and a pan acetylated lysine antibody was used to enrich for peptides containing acetylation modifications in M3-SIRT3 and M1-SIRT3 transgenic animals by QTRP LC-MS/MS (n=6). Global lipidomic analysis of cardiac tissue was performed by QTRAP LC-MS/MS (n=6) in all groups. Expression of genes involved in metabolic processes was performed by quantitative PCR (n=6). Radio-labeled

18F-Fluorodeoxyglucose (18F-FDG) was used to examine glucose uptake by PET/MRI imaging (n=6). DOX treatment in Non-Tg male mice caused cardiac dysfunction, whereas expression of M3-SIRT3 and M1-SIRT3 attenuated cardiac remodeling and reduced ejection fraction ($p < 0.05$). Analysis of acetylated peptides revealed that DOX increased the acetylation of several proteins involved in cardiac energy production (e.g. ACO2 and ATP5PB) and lipid metabolism (e.g., HADHA) while M1-SIRT3 expression mitigated these effects. Lipidomic analysis of cardiac tissue identified an increase in proapoptotic lipid markers including gangliosides and phosphatidylserine species and a large decrease in triglyceride lipid species in DOX treated mice. Quantitative PCR identified increases in Cpt1a ($p < 0.05$) and Lipe ($p=0.0518$) in DOX treated Non-Tg mice, but not in M3-SIRT3 and M1-SIRT3 mice. DOX decreased the expression of Fapb3 and Hadha ($p < 0.05$) in all groups. 18F-FDG PET showed increased cardiac glucose uptake in Non-Tg, and M3-SIRT3 DOX treated mice ($p < 0.05$) but remined unchanged in M1-SIRT3 mice.

CONCLUSION: Our data show that increased M1-SIRT3 expression in the heart prevents DOX induced dilated cardiomyopathy. M1-SIRT3 expression altered mitochondrial protein acetylation while DOX decreased cardiac triglycerides and increased glucose uptake indicative of metabolic dysfunction.

Heart and Stroke Foundation of Canada

P023
TARGETING TUMOR NECROSIS FACTOR (TNF) IN ATRIAL STRETCH-DEPENDENT ADVERSE ATRIAL REMODELING AND VALVULAR ATRIAL FIBRILLATION IN A MOUSE MODEL OF AORTIC REGURGITATION

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BACKGROUND: Atrial fibrillation (AF) is the most common sustained supraventricular arrhythmia worldwide with its incidence linked to cardiovascular (CV) disease. Most conditions linked to AF are associated with elevated atrial pressures and atrial stretch, which are powerful stimuli for atrial remodeling. We previously established that the proinflammatory and mechanosensitive cytokine, tumor necrosis factor (TNF), is a key mediator of stretch-related atrial remodeling and AF vulnerability. As TNF is critical factor mediating atrial fibrosis, hypertrophy, inflammation, and arrhythmias in heart disease, we hypothesized that targeting stretch-mediated TNF-dependent signaling may offer a novel therapeutic target in valvular AF patients.

METHODS AND RESULTS: We have developed a clinically relevant mouse model of aortic regurgitation (AR), which is characterized by acute and chronic diastolic volume overload and elevated left ventricular end-diastolic (LVEDPs) and atrial pressures. The effects of pharmacological TNF inhibition with Etanercept (Enbrel®, twice-weekly, 2.5 mg/kg) beginning early (2-days post-AR) or later (1-week post-AR) were examined. Cardiac structure and function as well as electrophysiological properties were assessed using echocardiography, telemetry hemodynamics, histology, immunohistochemistry, in vivo intracardiacs, and ex vivo optical mapping in isolated atria. Results: Four weeks of AR resulted in progressive LV dilatation, functional impairment, and hypertrophy in the absence of ventricular arrhythmias. Moreover, LVEDPs increased acutely and remained elevated with disease progression. In the atria, AR resulted in hypertrophy, fibrosis, and macrophage infiltration as well as decreased conduction velocity, atrial effective refractory periods and action potential durations in wild-type mice. Importantly, AR increased both in vivo and ex vivo AF susceptibility. By contrast, both early and delayed TNF inhibition with Etanercept attenuated AR-induced adverse atrial remodeling and protected against AF inducibility, independent of ventricular changes.

CONCLUSION: Our results establish that stretch-mediated adverse atrial remodeling and AF vulnerability with AR requires TNF, suggesting TNF may offer an important therapeutic target for the prevention and treatment of valvular AF.

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P024
TREADMILL STRESS TEST VENTILATORY PATTERN USING A WEARABLE DEVICE AS AN ADDITIONAL MARKER FOR CV DISEASE

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BACKGROUND: Treadmill stress testing for cardiovascular disease (CVD) is typically done with ECG and blood pressure monitoring alone, with respiratory monitoring via sealed face mask and gas sampling occurring rarely in clinical settings. We sought to examine whether a simple electronic, non-invasive, chest-mounted respiratory monitoring device could successfully be used to reveal clinically useful insights during stress testing.

METHODS AND RESULTS: Twenty-five adult patients referred for treadmill exercise stress testing at an outpatient cardiology clinic were equipped with a small, lightweight, electronic chest band (Airgo, MyAir Inc.) capable of measuring respiratory rate (RR) and minute ventilation (Ve) during completion of an unmodified Bruce protocol stress test. Univariate regression was used to assess patient characteristics such as age, sex, and cardiovascular comorbidities as predictor variables for Ve and RR slope (change in Ve and RR over time). Log transformations were performed for non-normally distributed variables (Ve slope, RR slope, and body mass index, BMI). The mean age of patients was 55.0 years (SD 13.4); 18 males and 7 females. Group mean results (+/- SD): stress test duration 8.6 +/- 3.5