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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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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