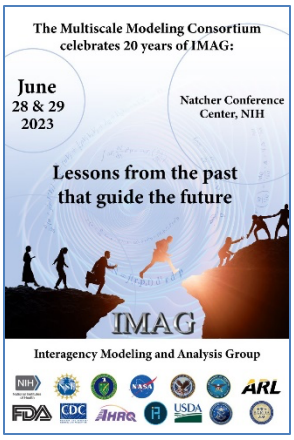

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ABSTRACT FACE PAGE

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MULTISCALE MODELS OF PREGNANCY: HORMONAL & MECHANICAL INTERACTIONS

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BACKGROUND: Pregnancy stands at the interface of biology and mechanics. Throughout nine months of gestation, pregnancy hormones surge as the growing fetus continuously loads the maternal organs. Maternal soft tissues grow and remodel in response to these dynamic biological and mechanical cues. Timely remodeling and proper mechanical function of maternal organs are critical for supporting a healthy pregnancy. For example, the increased demand of pregnancy results in a 45% increase in maternal cardiac output [1]. In response, the maternal heart grows by approximately 30% in mass and volume [2], which reverses after delivery. We previously developed a multiscale computational model incorporating hormonal and hemodynamic changes during pregnancy to predict left ventricular (LV) growth in rats [3]. Here, we assess our model's ability to predict heart growth during postpartum recovery and hypertensive pregnancies.

METHODS: Our multiscale model couples a cell-signaling model that predicts cardiomyocyte hypertrophy in response to reproductive and cardiovascular hormones, as well as cell-level stretch, to a mechanical model of the rat heart and circulation that predicts organ-level LV growth in response to hemodynamic changes. Here, we extended our pregnancy simulations for 21 days postpartum, implementing time-appropriate changes in hemodynamics and hormones. We investigated non-lactating and lactating rats since they exhibit differences in postpartum hormones and hemodynamics, namely an elevated cardiac output in lactating dams. We also simulated three different experimental models of hypertension overlaid on 21 days of normal pregnancy: Angiotensin 2 infusion (+AngII), transverse aortic constriction (+TAC), and reduced uterine perfusion pressure (+RUPP). All experimental studies saw elevated blood pressure and additional heart growth compared to their gestation-day-matched normal pregnant counterparts.

RESULTS: Our model predicted LV mass decrease in non-lactating rats, while the elevated hormones and cardiac output led to LV mass increase in lactating rats, consistent with the available literature (Fig. 1A). Our hypertension simulations correctly captured LV growth in +AngII and +TAC during pregnancy but could not capture reported growth in the +RUPP group (Fig. 1B).

CONCLUSIONS: This work assessed if the mechanisms proposed in our multiscale model of the pregnant heart could predict heart growth 1.) during postpartum remodeling and 2.) during perturbed pregnancies. Our model correctly predicted further LV growth in lactating and regression of LV growth in non-lactating rats postpartum. Additionally, the multiscale model correctly captured cardiac growth in 2/3 cases of hypertensive pregnancies and during postpartum. Further, the simulations indicated dynamic mechanical signals on cardiomyocytes during postpartum, suggesting a key mechanical role in driving heart growth after delivery. In contrast, our hypertensive pregnancy simulations suggest a key hormonal role in cardiac growth during hypertensive pregnancies. An important finding here is the inability of our model to capture the increase in heart growth associated with +RUPP, suggesting the need to include additional mechanisms in the model. We are improving our model to include other key hormones to improve our predictions, specifically for +RUPP pregnancies.

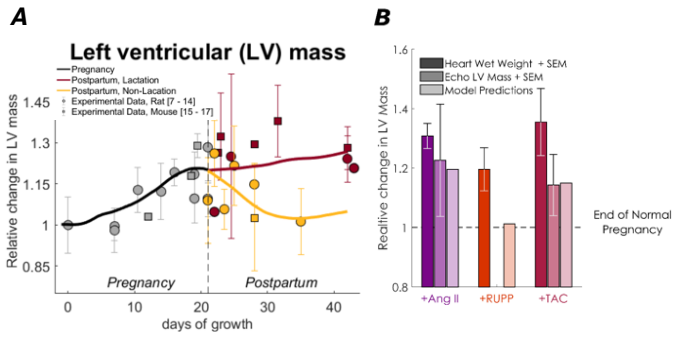

Figure 1 A.) Relative change in LV mass during postpartum in lactating and non-lactating rats. B.) Multiscale model captures LV growth in +AngII and +TAC rats, but not +RUPP

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1. Hunter & Robson. *Br. Heart J.* 68(12): 540-543, 1992.
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