MULTISCALE MODEL OF PREGNANCY-INDUCED HEART GROWTH: INTEGRATING HORMONAL SIGNALING AND MECHANICS

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BACKGROUND: Pregnancy stands at the interface of biology and mechanics. Circulating hormone levels surge by 10 times above nonpregnant levels over nine months of pregnancy, as the maternal cardiac output increases by 50% and left ventricular mass increases by 30% [1,2]. Changes in mechanics and two pregnancy hormones, estrogen (E2) and progesterone (P4), are known drivers of heart cell (cardiomyocyte) growth [3]. Cardiovascular conditions during pregnancy remain as the leading cause of pregnancy-related deaths in the United States [4], highlighting a critical need to understand how hormones and hemodynamics interact and affect the heart during pregnancy. Therefore, the objective of this work is to develop a multiscale cardiac growth model to investigate how biology (hormones) and mechanics (hemodynamics) interact to drive cardiac growth (hypertrophy) during pregnancy.

METHODS: To model the effects of stretch, E2, and P4 on cardiomyocyte hypertrophy, we built an intracellular signaling network model based on *in vitro* studies on neonatal cardiomyocytes treated with E2, P4, and E2+P4 [3] and a previously published model [5]. The growth predicted by this biological model was incorporated into a compartmental growth model of the rat left ventricle (LV) coupled to a lumped-parameter circulation model [6], which was used to model the effects of hemodynamics and cardiac growth on stretch experienced by the cells. The stretch predicted by the mechanical model was fed back into the signaling network model. We first simulated and tuned this multiscale model to individual effects of volume overload (VO), E2, or P4. Next, we simulated the combination of VO + E2. All simulations were compared to published data from *in vivo* studies in rats and mice.

RESULTS: We were able to tune the multiscale model to match the reported time course of growth due to VO in rats, as well as the amount of growth due to P4 and E2 in mice (Fig. 1). When the combination of VO+E2 was simulated, the model predicted a 6% attenuation of growth compared to VO alone at 21 days of growth, which is within the reported range of 5% attenuation at 5 days [7] and 12% attenuation at 56 days of growth [8] in rats.

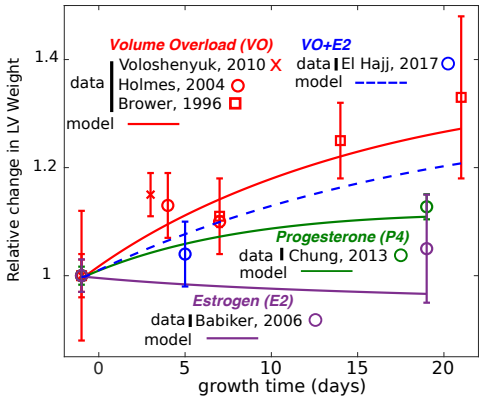

Figure 1: Model comparisons to data for LV growth in response to VO alone (red), P4 alone (green), and E2 alone (purple). Dashed blue line demonstrates attenuated growth predicted by the model for VO+E2. Symbols: experimental data Lines: model predictions.

CONCLUSIONS: We have demonstrated the ability of a multiscale cardiac growth model to capture heart growth due to mechanical overload and pregnancy hormones. Furthermore, the model correctly predicted attenuated growth due to the combination of VO+E2, as reported in previous studies. Future work will focus on incorporating additional intracellular signaling pathways of hypertrophy, as well as experimentally validating model-predicted growth due to the combination of VO+P4. Pregnancy is associated with high levels of P4 and VO, but this combination has not been examined experimentally. After validating this combination, we will incorporate time-varying changes in hemodynamics, E2, and P4, associated with pregnancy, and use the model to inform new therapeutic approaches for pregnancy-induced heart conditions, including peripartum cardiomyopathy. Outside of pregnancy, this model also has potential applications for understanding gender differences in heart failure, including identifying mechanisms through which E2 protects premenopausal women from cardiovascular diseases.

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