Sex Differences in Cardiac Anti-Inflammatory Cytokines in Adult Intrauterine Growth Restricted Rodents

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UNT Health FORT WORTH

BACKGROUND

- Approximately 5-10% of U.S. pregnancies are affected by intrauterine growth restriction (IUGR)
- IUGR is a pathologic condition in which a fetus fails to achieve its optimal growth potential *in utero*
- The most common cause of IUGR in the United States is placental ischemia
- Adults who were exposed to IUGR have a higher risk of developing cardiovascular diseases (CVD), with IUGR males displaying a greater risk of CVD development, morbidity, and mortality
- One plausible mechanism contributing to this outcome is cardiac inflammation
- Multiple studies, such as with humans and surgical models in animals, have shown that IUGR offspring have increased pro-inflammatory cytokines, such as TNF-α, IL-6, and IFN-γ in the heart and circulation
- Furthermore, studies show a sex difference, in which males exhibit a greater inflammatory response, higher rates of left ventricular fibrosis, and hypertension
- However, only a few studies have explored anti-inflammatory cytokines in the hearts of adult IUGR offspring

OBJECTIVE

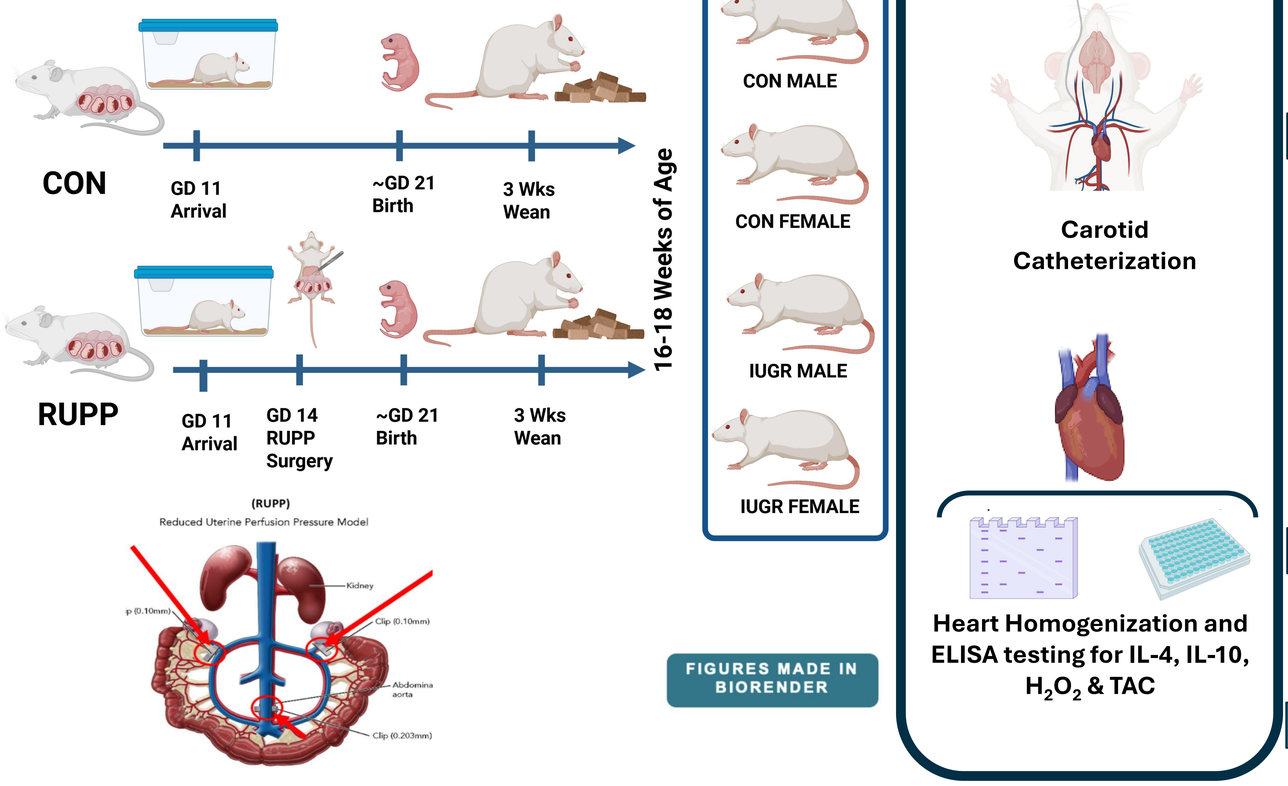
The objective of this study is to investigate the alterations in blood pressure (BP) and cardiac anti-inflammatory cytokines (IL-4 and IL-10) in adult male and female IUGR offspring

HYPOTHESIS

IUGR males will have elevated BP accompanied by decreased levels of cardiac IL-4 and IL-10 , while IUGR females will display no changes in BP and an increase or no change in anti-inflammatory cytokines

METHODS

- Pregnant Sprague Dawley rats were randomly divided into two groups: normal (NP) and placental ischemic (PI) dams
- On gestational day 14, the reduced uterine perfusion pressure surgery was performed to induce PI
- PI dams generated IUGR offspring, while the normal pregnant dams generated control (CON) offspring
- All pups were born naturally and weaned for 3 weeks
- At 16-18 weeks (adulthood), the offsprings' BP was recorded via a carotid catheterization
- Hearts were then collected and homogenized to measure IL-4 and IL-10 levels via ELISAs



ACKNOWLEDGEMENTS

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RESULTS

Figure 1: MAP in CON vs IUGR Offspring

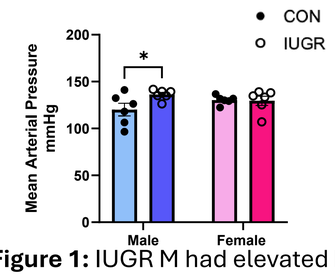

Figure 1: IUGR M had elevated BP vs CON. No differences in IUGR vs CON F. 2-way ANOVA with Fisher LSD Posthoc test. *p<0.05.

Figure 2: Anti-inflammatory IL-10 & IL-4 in Cardiac Tissue

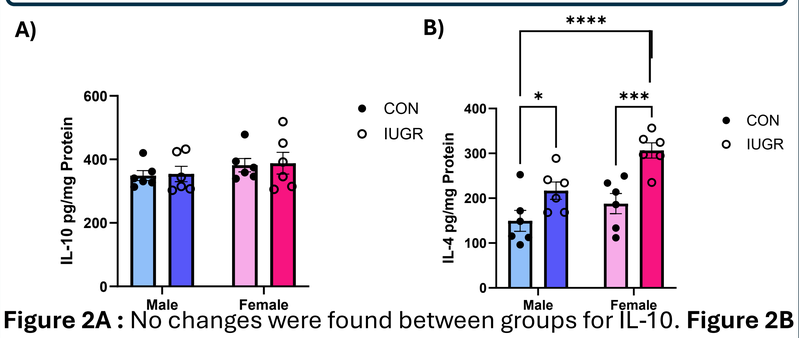

Figure 2A : No changes were found between groups for IL-10. **Figure 2B :** IL-4 was elevated in IUGR exposure for both sexes (p=0.0002). F displayed higher IL-4 levels vs M (p=0.0058). Also, IUGR F displayed the highest amount of IL-4 and greater than IUGR M. 2-way ANOVA with Fisher LSD Posthoc test. *p<0.05, ***p<0.001.

Figure 3 A&B: Oxidative Stress via Total Antioxidant Capacity (TAC) and Hydrogen Peroxide (H_2O_2) in CON vs IUGR Cardiac Tissue

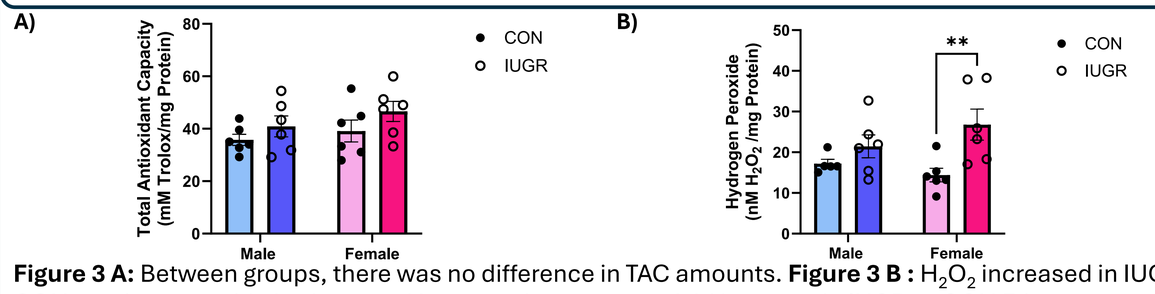

Figure 3 A: Between groups, there was no difference in TAC amounts. **Figure 3 B :** H_2O_2 increased in IUGR vs CON rats (p=0.0058) in both sexes. However, there was a 2-fold increase in IUGR vs CON F (26±4 vs 14±2 nM H_2O_2/mg Protein, p=0.0006). 2-way ANOVA with Fisher LSD Posthoc test. *p<0.05, **p<0.01.

Figure 4 A-C: Correlation Graphs IL-4 & H_2O_2

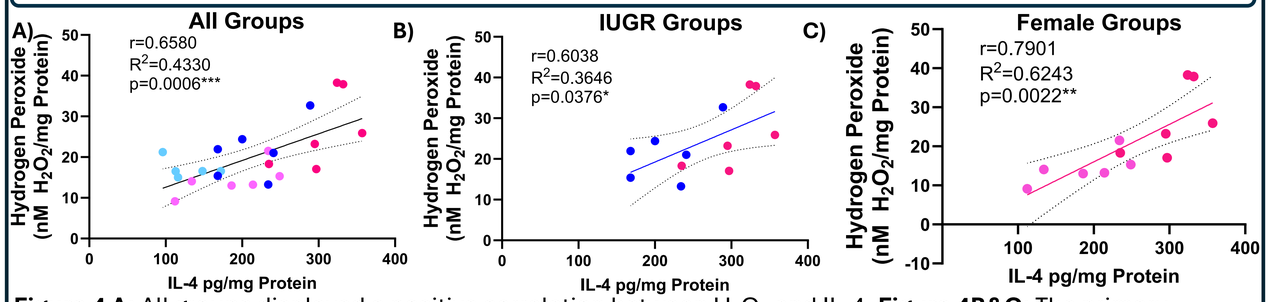

Figure 4 A: All groups displayed a positive correlation between H_2O_2 and IL-4. **Figure 4B&C:** The primary contributors to this trend are F and IUGR groups. 95% CI lines shown with line of best fit. P<0.05*.

DISCUSSION

- IUGR males displayed elevated BP compared to CON males, while females displayed no difference in MAP. This may suggest that IUGR males have an increased risk for CVD
- Surprisingly and contrarily to our hypothesis, IL-4 concentrations were increased with IUGR status regardless of sex and further increased in females compared to males
- H_2O_2 levels were also elevated in IUGR offspring of both sexes, with the greatest increase observed in IUGR versus CON females, while cardiac TAC showed no changes. Together, these findings suggest increased cardiac oxidative stress in adult offspring exposed to IUGR
- Our data show that the increase in IL-4 is correlated with elevated H_2O_2 levels, especially in IUGR and female groups. This potentially contributes to an increased risk of CVD in both sexes following IUGR exposure
- However, despite elevation in IL-4 and oxidative stress, females appear to be protected from increased MAP

CLINICAL RELEVANCE

- Highlights sex differences in CVD risk in adult IUGR offspring
- Explores the role of cardiac IL-4 and oxidative stress in the pathophysiology of CVD in adult IUGR offspring
- Aims to identify targets for prevention and/or treatments for CVDs in males and females exposed to IUGR

FUTURE DIRECTIONS

- Investigate the molecular pathways by which IL-4 and oxidative stress drive sex-specific changes in cardiac structure and function in IUGR offspring
- Elucidate the mechanisms underlying the relative protection from CVD observed in females despite elevated cardiac IL-4 and oxidative stress
- Examine the role of sex hormones in mitigating these cardiac and molecular alterations