Rodents exposed to an impoverished environment during weaning display sex differences in cardiac oxidative stress in adulthood

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BACKGROUND

- **Cardiovascular disease** is the leading cause of death worldwide and early prevention requires understanding childhood risk factors
- Early life stress (ELS) is associated with higher risk of hypertension (HTN) and cardiovascular diseases later in life
- Poverty, is a form of ELS that effects that impacts ~333 million children worldwide
- Oxidative stress, inflammation, and nitric oxide (NO) are key factors in cardiovascular disease development
- Biological sex influences cardiovascular risk and disease outcomes
- Understanding sex differences can provide greater insight into prevention strategies targeting specific sex differences and intervention methods.
- To study the mechanisms connecting early life poverty and cardiovascular disease, we utilized the limited bedding and nesting (LBN) resource deprivation model
- Previous studies, from our lab, have shown LBN male rats have elevated blood pressure while females do not
- Investigating these mechanisms helps clarify sex differences in cardiac response to ELS and potential contributors to HTN

OBJECTIVE

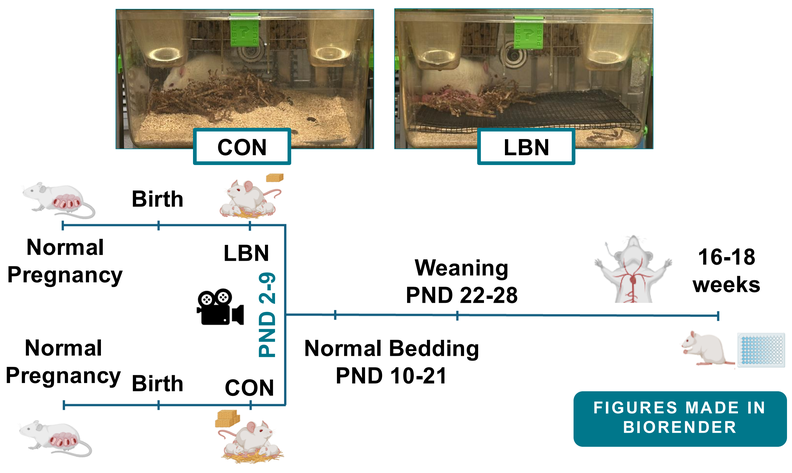
To investigate sex differences in blood pressure, cardiac oxidative stress, inflammation, and NO bioavailability induced by resource deprivation during weaning.

HYPOTHESIS

- Adult LBN male rats will have:
  - Elevated blood pressure
  - Cardiac oxidative stress
  - Increased proinflammatory cytokines TNF-α and IL-17
  - Decreased NO bioavailability
- Adult LBN female rats will display minimal to no changes compared to control (CON) females

METHODS

1. Timed pregnant Sprague Dawley rats gave birth naturally
2. **Postnatal day (PND) 2-9:** Enacted LBN model by removing nesting material, while the CON group remained untouched
3. **PND 2-6:** Recorded maternal behaviors of the dam to validate model
4. **PND 10-21:** Both groups (CON and LBN) received normal bedding
5. **PND 22-28:** Pups from both groups were weaned and separated by sex and treatment
6. Pups were aged to **16-18 weeks**
7. Collected hearts and measured H_2O_2, antioxidant capacity (AC), IL-17 and TNF-α, and metabolic NO concentrations
8. Performed 2-Way ANOVA with a Fisher LSD Post Hoc Test, ***P<0.05**



RESULTS

FIGURES 1A-B: Cardiac Oxidative Stress

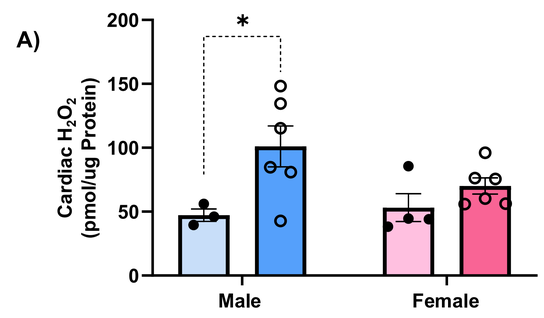


Figure 1A) LBN males had a 2-fold increase in cardiac H_2O_2 vs CON males (101.08 ± 15.95 vs 47.26 ± 4.83 pmol/μg Protein; P<0.05). H_2O_2 was unchanged in females (70.09 ± 6.41 vs 53.14 ± 10.92 pmol/μg Protein; ns).

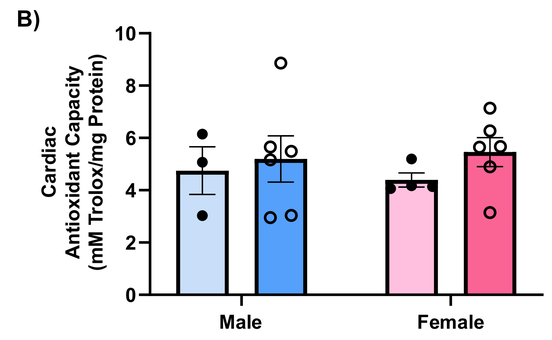


Figure 1B) No changes in antioxidant capacity in males (5.20 ± 0.88 vs 4.75 ± 0.91 mM Trolox/mg Protein; ns) and females (5.46 ± 0.55 vs 4.39 ± 0.27 mM Trolox/mg Protein; ns).

FIGURES 2A-B: Cardiac Inflammation

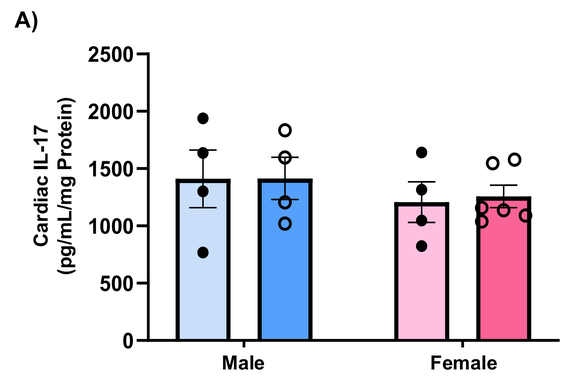


Figure 2A) Cardiac IL-17 concentrations were unchanged in males (1356.23 ± 184.86 vs 1410.90 ± 293.03 pg/mL/mg Protein; ns) and females (1302.28 ± 97.93 vs 1260.58 ± 205.76 pg/mL/mg Protein; ns).

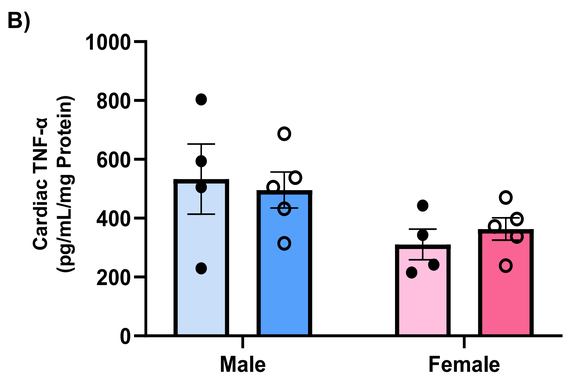


Figure 2B) Cardiac TNF-α concentrations were unchanged in males (495.52 ± 61.34 vs 532.86 ± 118.93 pg/mL/mg Protein; ns) and females (363.11 ± 38.02 vs 310.78 ± 51.84 pg/mL/mg Protein; ns).

RESULTS

FIGURE 3: Cardiac NO Bioavailability

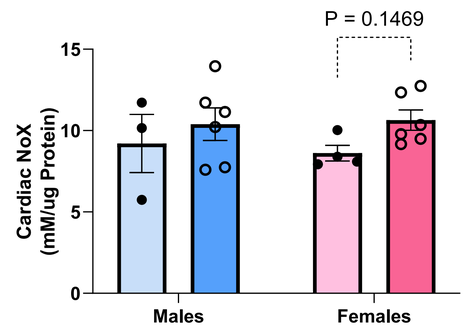


Figure 3) Cardiac NO bioavailability was unchanged in LBN males (10.40 ± 1.00 vs 9.20 ± 1.79 mM/μg Protein; ns), while LBN females showed an upward trend vs CON (10.64 ± 0.62 vs 8.61 ± 0.48 mM/μg Protein; P=0.14).

CONCLUSIONS

- ELS induces oxidative stress in males but not in females
- LBN males may be more sensitive to cardiovascular disturbances
- Antioxidant capacity, inflammatory cytokines, and NO bioavailability were mostly unchanged
- LBN females have an upward trend in cardiac NO bioavailability
- LBN females may have adaptive mechanisms that protect them against negative cardiovascular repercussions

CLINICAL RELEVANCE

- Understanding sex specific responses to ELS may guide prevention and treatment strategies for HTN and cardiovascular disease
- ELS may predispose males to oxidative stress and HTN; suggesting a need for early screening in predisposed individuals
- Protective mechanisms in females could influence future therapeutic strategies expanded to males
- Children exposed to ELS may benefit from early cardiovascular health screenings to address and detect risk factors

FUTURE DIRECTIONS

- Expand sample size to confirm these trends observed
- Assess whether sex-specific cardiac differences become more pronounced with age (middle age vs older adult rodents), since HTN and oxidative stress worsen over time
- Examine estrogen/testosterone pathways to better understand cardiac differences
- Examine more inflammatory markers (IL-6 and IL-10) to better understand inflammatory signaling
- Assess cardiac function and ventricular filling through stoke volume, cardiac output, end diastolic and systolic volume

ACKNOWLEDGEMENTS

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