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## Effects of Neonatal Supplemental Oxygen and High Fat Diet on Weight Gain, Ventricular Hypertrophy and Contractility

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EFFECTS OF NEONATAL SUPPLEMENTAL OXYGEN AND HIGH FAT DIET ON WEIGHT GAIN,  
VENTRICULAR HYPERTROPHY AND CONTRACTILITY

by

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A thesis submitted in partial fulfillment of the requirements  
for graduation with Honors in the Health and Human Physiology

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Spring 2017

All requirements for graduation with Honors in the  
Health and Human Physiology have been completed.

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**EFFECTS OF NEONATAL SUPPLEMENTAL OXYGEN AND HIGH FAT DIET ON WEIGHT GAIN, VENTRICULAR HYPERTROPHY AND CONTRACTILITY**

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**ABSTRACT**

Premature birth represents about 13% of live births each year. Since lungs of these infants are underdeveloped, they receive supplemental oxygen right after birth, but little is known about its effects on the development of normal physiological responses and whether it impacts long-term cardio-metabolic function. Based on previous studies from our lab that showed increased pulse wave velocity in 12 month old rats exposed to neonatal supplemental oxygen, we hypothesized that neonatal exposure to supplemental oxygen causes cardiac hypertrophy and decreased left ventricular contractility. We also hypothesized that these effects to supplemental oxygen would be enhanced by 10 weeks on a high fat diet. To test the hypothesis, we used our rat model of 80% and 21% O<sub>2</sub> exposed rats to FIO<sub>2</sub>=0.80 and 0.21 respectively, for 8 days post-birth. Two months after birth, these 80% and 21% rats were randomly assigned to either a high fat diet (60% of calories from animal fat) or low fat diet (CON) for 10 weeks during which their weights and caloric consumption were monitored. After 10 weeks, a Miller conductance catheter was inserted into the left ventricle to obtain pressure-volume loops and end-systolic pressure volume relationship, which was used to evaluate contractility. 80% rats exposed to CON diet showed higher cumulative weight gain than 21% rats on the same diet. No significant difference was observed between the weights of the left ventricles due to exposure to supplemental oxygen or high fat diet. Neonatal supplemental oxygen exposure decreased contractility whereas the combination of high fat diet and supplemental oxygen exposure reversed this effect. These data suggest that neonatal exposure to supplemental oxygen promotes weight gain and decreased ventricular contractility.

**INTRODUCTION**

Since 1991, approximately 450,000 babies are born prematurely each year. This represents about 13% of live births. The lungs of infants born prematurely (<37 weeks gestation) are underdeveloped – their carotid chemoreceptors are not physiologically equipped to transition from in-utero to ex-utero environment hence requiring exposure to supplemental oxygen immediately after birth (Bates et al. 2013). Although essential to sustain life, mechanical ventilation has been shown to result in significantly higher incidence of respiratory distress syndrome, cardiac arrest, bronchopulmonary dysplasia, seizures, retrolental fibroplasia (Ruiz et al. 1981) and retinopathy of prematurity, in addition to causing oxidative stress. Adult survivors of preterm birth also demonstrate lower pulmonary gas exchange efficiency accompanied by low arterial blood oxygen tension and low power output during exercise when compared with control subjects (Farrell et al. 2015). These findings suggest potential long-term consequences of preterm birth on cardiopulmonary function. However, little is known about the effects of neonatal supplemental oxygen exposure on the development of normal physiological responses and whether it impacts long-term cardio-metabolic function.

Previous studies conducted in our lab have demonstrated that neonatal supplemental oxygen exposure increases aortic pulse wave velocity values significantly in 12 month old rats and humans born prematurely, which is indicative of large elastic artery stiffening and vascular

dysfunction. It was also found that the supplemental oxygen exposure impairs glucose tolerance and causes premature mortality. This led to the question of our current study – given the effects on systemic vasculature, does exposure to supplemental oxygen cause cardiac dysfunction and are these individuals at higher risk of heart disease when exposed to a high fat diet? A common symptom of cardiac dysfunction is decreased left ventricular contractility, which in turn could be a result of thickening of the ventricular muscle, a condition commonly known as left ventricular hypertrophy. To look for evidence of ventricular hypertrophy, we isolated and weighed the left ventricles of the animals studied. The slope of the end-systolic pressure volume relationship (ESPVR) is considered an index of contractility because it does not change with changes in arterial system properties or end-diastolic volume. An increase in the ESPVR slope is thus an indicator of increased ventricular contractility.

To test our hypothesis, we used our rat model of premature birth with supplemental oxygen exposure. We hypothesized that neonatal exposure to supplemental oxygen causes cardiac hypertrophy and decreased left ventricular contractility. We also hypothesized that these effects of exposure to supplemental oxygen would be enhanced by 10 weeks of a high fat diet.

## METHODS

*Animal mode.* Pairs of pregnant dams were obtained from Charles River and monitored daily until delivery of their litters. Male and female rat pups and dams were exposed to  $\text{FIO}_2 = 0.80$  (80%) or 0.21 as a control (21%) for eight days immediately after birth in oxygen control cabinets. The dams were rotated daily to prevent hyperoxic lung injury. The Sprague-Dawley rat model was used because of its many similarities to the premature infant, including saccular-stage (under developed) lungs at birth. At the end of the exposure, rats were returned to normal housing and maintained on standard chow after weaning.

*High fat diet.* Two months after birth, 80% and 21%  $\text{O}_2$  exposed rats were further divided so that these rats were placed on either a high fat diet (60% of calories from animal fat) or a low fat diet for 10 weeks (HFD and CON, respectively). Their daily weight and caloric consumption was monitored throughout this period. As a component of another related study, these rats were fasted overnight on one evening each week.

*Cardiac catheterization.* After 10 weeks, rats were anesthetized with urethane (1.3g/kg, i.p.) and mechanically ventilated with 100%  $\text{O}_2$ . The right common carotid artery was isolated and a Miller conductance catheter was inserted in the left ventricle to obtain pressure volume loops upon occlusion of the inferior vena cava. The end-systolic pressure-volume relationship was used to determine contractility.

*Additional measurements.* The heart, pancreas, liver and gastrocnemius muscle was isolated, weighed, and sections of each were embedded in optimal cutting temperature compound, flash frozen in liquid nitrogen and stored at  $-80^\circ\text{C}$ . The left ventricle was also isolated from the heart, weighed and embedded in optimal cutting temperature compound, flash frozen in liquid and stored at  $-80^\circ\text{C}$ . Tissue blocks were cut into  $4\ \mu\text{m}$  sections and stained. Sections were then evaluated in order to look for evidence of cardiac hypertrophy (thickening of ventricular walls).

## RESULTS

*Weight gain.* There was no significant difference in the absolute weights of the rats in different conditions at the start of the 10 weeks period. No significant difference was observed between the mean absolute weight of 80% HFD and 21% HFD rats, whereas on average 80%

CON rats were heavier than 21% CON rats by the end of week 10 (Fig. 1). 80% HFD and 21% HFD rats showed similar patterns of cumulative weight gain whereas 80% CON rats gained more weight than 21% CON rats over the 10-week period (Fig. 2).

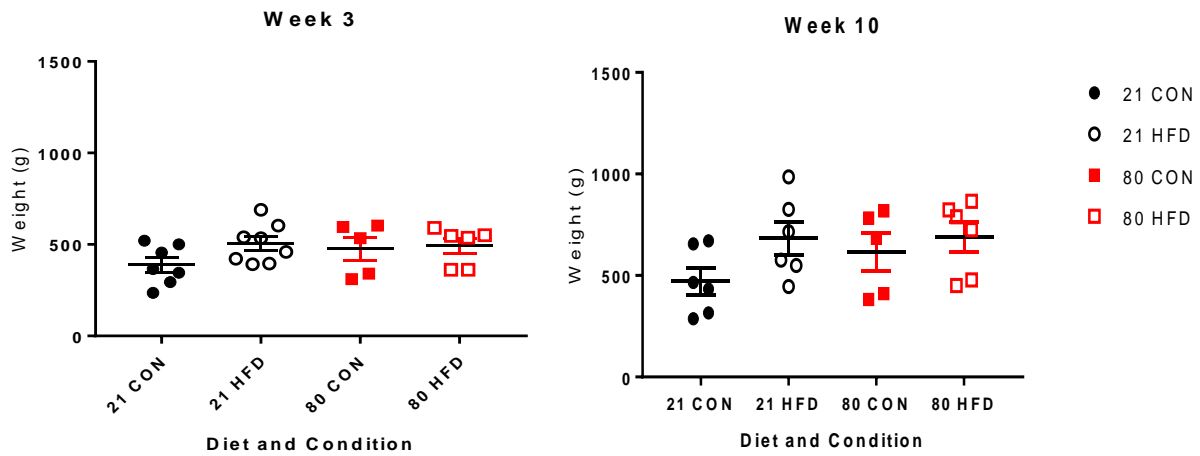


Fig. 1. *Right.* Absolute weight at the end of Week 3 of diet exposure plotted against condition that the rats were exposed to during the study. *Left.* Absolute weight at the end of Week 10 of diet exposure plotted against condition that the rats were exposed to during the study.

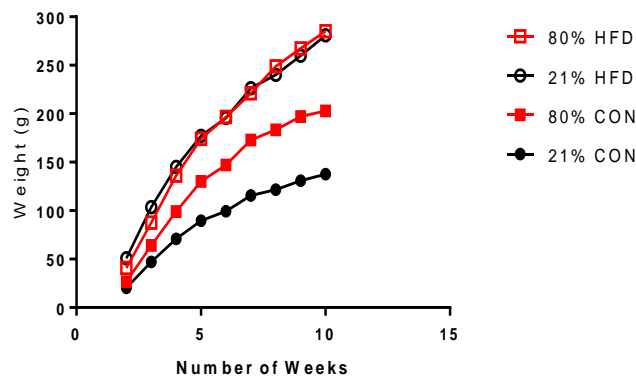


Fig 2. Cumulative weight gained plotted against the number of weeks of exposure to HFD or CON diet. 80% CON rats gained more cumulative weight than 21% CON over the 10-week period while rats exposed to HFD showed similar patterns in cumulative weight gain.

*Left Ventricular Hypertrophy.* No significant difference was observed between the weights of the whole hearts and left ventricles of the rats due to exposure to supplemental oxygen or high fat diet (Fig. 3).

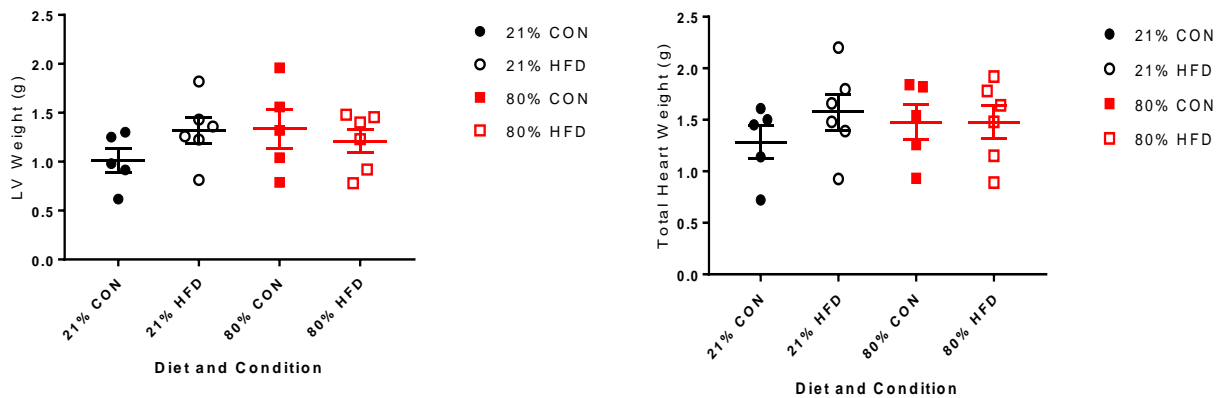


Fig. 3. *Left.* Weight of the heart plotted against different conditions to which the rats were exposed during the study. *Right.* Weight of the LV plotted against different conditions that the rats were exposed to during the study. \* $P > 0.350$ , effect of supplemental oxygen and diet.

**Ventricular Contractility.** Compared to 21% CON rats, 21% HFD rats had lower cardiac contractility as indicated by a lower value of the slope of the end-systolic pressure-volume relationship. The cardiac contractility of 80% CON was also lower than the contractility of 21% CON. These difference were statistically significant. However, rats that were exposed to supplemental oxygen at birth and high fat diet during adulthood had higher contractility than 21% HFD and 80% CON rats.

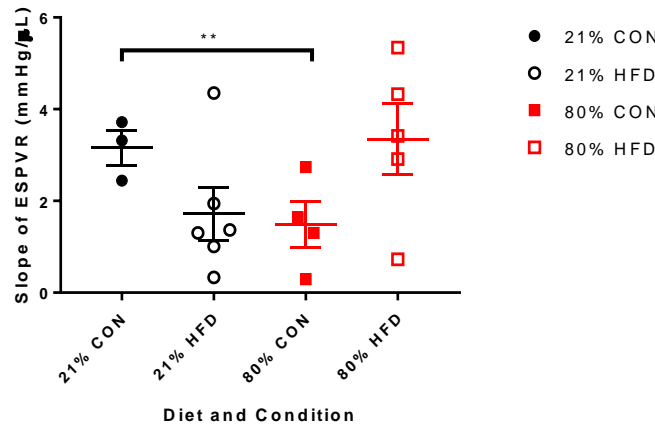


Fig. 4. Slope of the end-systolic pressure volume relationship (ESPVR) plotted against the different conditions the rats were exposed to during the study.

## DISCUSSION

*Neonatal supplemental oxygen exposure increases cumulative weight gained.* Our data showed that neonatal supplemental oxygen exposure increases weight gain even on a low fat diet. However, there was no significant difference in weight gain due to supplemental oxygen when high fat diet was introduced during adulthood. This could possibly mean that the rats have hit a peak weight gain and were physically incapable of gaining any more weight. Further studies in this direction could investigate the changes in weight gain as a result of manipulating the proportion of fat in the diet or duration of exposure to the diet.

*Neither neonatal supplemental oxygen nor high fat diet exposure promotes cardiac hypertrophy.* We did not find any significant difference between the weights of the left ventricles

of rats exposed to different oxygen and diet condition. This could be because we did not account for the fact that the average body weight of rats in each of the groups was different and weight of the heart is a function of total body weight. A difference may become apparent if the weights of the left ventricles are plotted as a fraction of the total body weight.

*Neonatal supplemental oxygen exposure decreases cardiac contractility; an effect that is reversed upon introduction of a high fat diet.* There is extensive literature that demonstrates a decrease in cardiac contractility due to high fat diet in term-born adults (Birse et. al., 2010). We were able to replicate these results by showing that when rats were not exposed to supplemental oxygen, those that were fed a high fat diet during adulthood had lower cardiac contractility than those that were on a low fat diet. Another related study in our lab, demonstrated that neonatal supplemental oxygen causes a modest increase in stroke volume and a large increase in heart rate when exposed to hypoxia during adulthood. Both hypoxia and high fat diet are similar stressors, in that they both result in increased sympathetic tone. An increased sympathetic tone as a result of high fat diet and neonatal supplemental oxygen could be a possible explanation for increased contractility in the 80% HFD rats. This possible mechanism has sparked questions that are grounds for further research in our lab.

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