Chronic Intermittent Hypoxia Adversely Affects Renal Microcirculatory Regulation and Tissue PO_2 in Ovariectomized Female Rats

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Background and Rationale

- Epidemiological evidence indicates that sleep apnea, which increases in prevalence in post-menopausal women, is a major risk factor for development of chronic kidney disease.
- The mechanisms underlying this association are poorly understood, but abnormal renal hemodynamics, neurohormonal activation, and hypoxemia are hypothesized to play prominent roles in this process.
- In this study, we sought to determine if chronic intermittent hypoxia (CIH, a model of sleep apnea) would adversely affect renal microcirculatory regulation and tissue oxygenation (PO_2) in ovariectomized (OVX) female rats.

Hypothesis

- CIH will exacerbate reductions in renal perfusion (RP) and PO_2 in OVX female rats during exposure to hypoxia that will persist after return to normoxia.

Experimental Methods

Ovariectomy

- Adult female Sprague Dawley rats (150-175g), underwent ovariectomy and then were allowed to recover for 4 weeks. At this time rats were randomly assigned to CIH or sham groups.

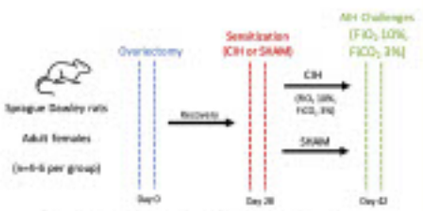

Figure 1. Experimental Protocol

Chronic Intermittent Hypoxia

- CIH animals were exposed to chronic intermittent hypoxia (60 sec. FiO2 10%, 120 sec. FiO2 21% 8h/day) for 14 days. Sham were exposed to air-air cycling for the same period.

Measurement of Renal Perfusion and PO_2

- Following CIH, RP and cortical PO_2 (Oxford Optronics) were measured under isoflurane anesthesia (1.5% in air) during 10 episodes of acute intermittent hypoxia challenges (30 sec. FiO2 10%, FiCO2 3%, 60 sec. FiO2 21%). Renal perfusion was measured using laser speckle contrast imaging (Moor FLPI-2, Moor Instruments).

Data Analysis

- Cortical PO2 and RP data was collected at pre-exposure baseline (average of 300 sec.) and for each AIH baseline and nadir (average of 10 sec. at peak response). Recovery was assessed at 5 and 10 minutes post-AIH (average of 10 sec.). Percent change from baseline was calculated and then averaged for each group. Statistical comparisons were made using unpaired t-tests.

Results

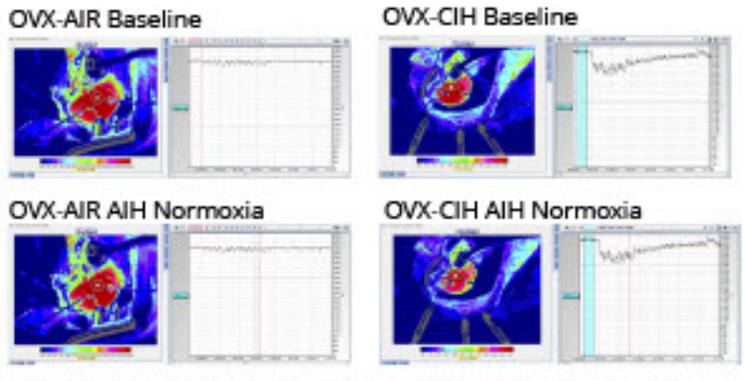

Figure 2. Effect CIH Conditioning on (Normoxic) Renal Perfusion during AIH in OVX and Sham Rats. Shown in the left (OVX-AIR) and right (OVX-CIH) panels above are representative laser speckle contrast images and their respective renal perfusion tracings during baseline and during AIH normoxia. Note the red vertical line in the perfusion tracings denoting point in time laser speckle contrast image was taken.

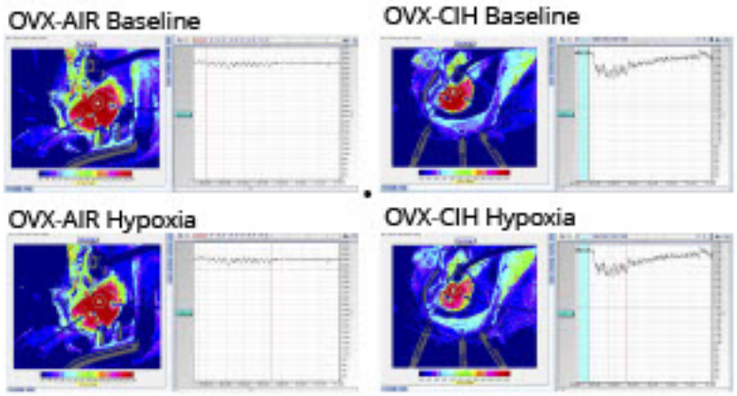

Figure 3. Effect CIH Conditioning on (Hypoxic) Renal Perfusion during AIH in OVX and Sham Rats. Shown in the left (OVX-AIR) and right (OVX-CIH) panels above are representative laser speckle contrast images and their respective renal perfusion tracings during baseline and during AIH hypoxia. Note the red vertical line in the perfusion tracings denoting point in time laser speckle contrast image

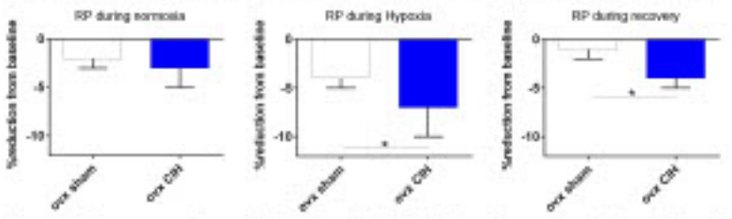

Figure 4. Summary Data of Effects of CIH Conditioning on Renal Perfusion in OVX and Sham rats. Shown in this figure are summary data quantifying the effect of CIH on renal perfusion (RP) in OVX and Sham rats during and after AIH. Note reductions in RP during hypoxia and recovery were significantly greater in OVX-CIH vs. OVX-sham. Results are expressed as mean ± SEM. n=4-6 animals per group. * p < 0.05 vs. sham via t-test.

Results

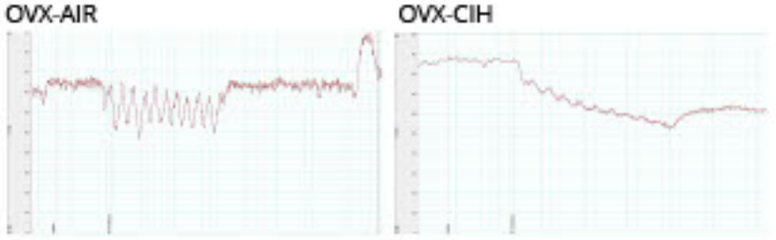

Figure 5. Effect of CIH on Renal Cortical PO2 in OVX Rats. Shown in the left (OVX-AIR) and right (OVX-CIH) panels are representative tracings of cortical pO2 in one OVX-AIR and one OVX-CIH rat. Note that normoxic PO2 remained below baseline after return to normoxia at the conclusion of the AIH protocol in OVX-CIH.

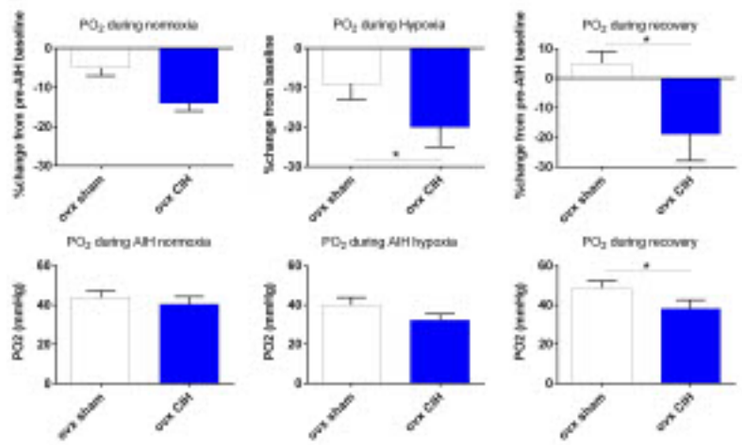

Figure 6. Summary Data of Effects of CIH Conditioning on Renal Cortical PO_2 in OVX and Sham rats. Shown in this figure are summary data quantifying the effect of CIH on renal cortical PO_2 in OVX and Sham rats during and after AIH. Note reductions in PO_2 during hypoxia and recovery were significantly greater in OVX-CIH vs. OVX-sham. Results are expressed as mean ± SEM. n=4-6 animals per group. * p < 0.05 vs. sham via t-test.

Conclusions

- Exposure to CIH in OVX female rats alters renal hemodynamic regulation and tissue PO2 in a manner which may contribute to tissue damage and development of CKD.

Limitations

- Time frame of CIH exposure was relatively short, longer duration exposures may expose more profound effects.
- Estrogen replacement was not performed to confirm a role for estrogen specifically in the observed changes

Support

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