Chronic Intermittent Hypoxia Conditioning Augments Decrements in Renal Microcirculatory Perfusion During Asphyxia

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Background and Rationale

•Sleep apnea (SA) is a chronic condition characterized by repetitive cessation of breathing during sleep.

•SA is a highly prevalent and comorbid disease estimating to affect ~15% of the US population[1], however its prevalence is markedly increased (50-60%)[2] in patients with chronic kidney disease (CKD).

•SA manifests as chronic intermittent hypoxia (CIH), decreased tissue perfusion, oxidative stress, and increased sympathetic activity, all of which have been theorized to potentiate CKD.

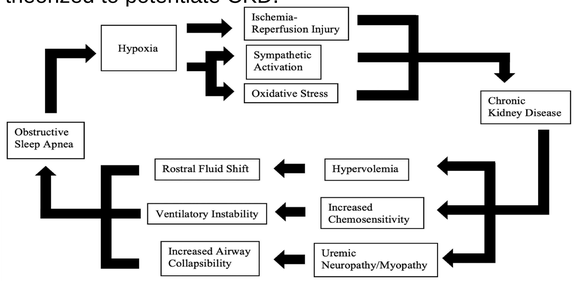

Figure 1. The bidirectional relationship between obstructive sleep apnea and chronic kidney disease.[3]

Purpose

•The effect of intermittent hypoxemia on renal hemodynamic regulation and regional oxygenation has not been extensively studied, therefore the purpose of this study was to determine how CIH alters regulation of renal microcirculatory perfusion (RP) and cortical and medullary tissue oxygenation; Additionally, to investigate gene expression patterns contributing to renal injury.

Hypothesis

•We hypothesized that following CIH exposure, tissue oxygenation (PO_2) and RP would be reduced relative to baseline and decreased to a greater extent in the CIH group vs a sham during an intermittent asphyxia challenge.

•Additionally, we hypothesized that gene programs promoting oxidative stress and fibrosis would be activated by CIH in renal tissue.

Experimental Methods

Chronic Intermittent Hypoxia Exposure

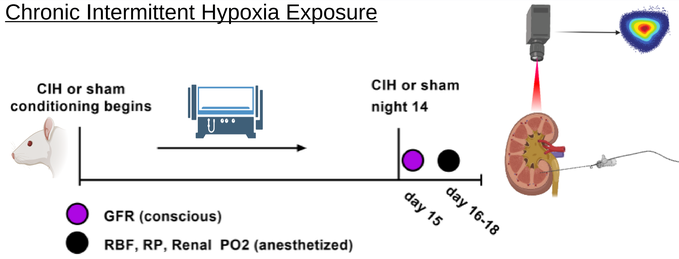

Figure 2. CIH conditioning and study timeline. Adult male Sprague Dawley rats (n=7-12 per group) were exposed to CIH (**60 sec. FiO_2 10%, 120 sec. FiO_2 21%**) or normoxia for 8 hrs/day for 14 days. At the conclusion of this time a conscious resting GFR was taken, followed by physiological measurement of renal blood flow, perfusion, and PO2 the following day (day 16-18).

Global renal microcirculatory perfusion was analyzed via laser speckle contrast imager before and during IA. (as a % of pre-IA baseline).

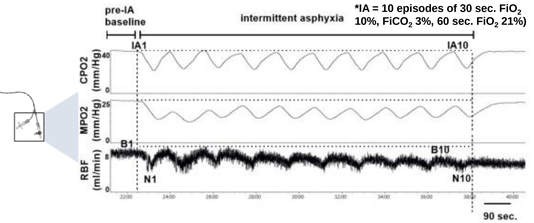

Figure 3. Analysis of response to intermittent asphyxia (IA). Pre-IA baseline (IA1), IA baseline values (1-10), and IA delta values (IA baseline-nadir) measurements were obtained for renal blood flow (RBF), medullary PO_2 (MPO_2), and cortical PO2 (CPO_2). All statistical analysis was performed via unpaired t-test and displayed as violin plots with medians and quartiles.

Results

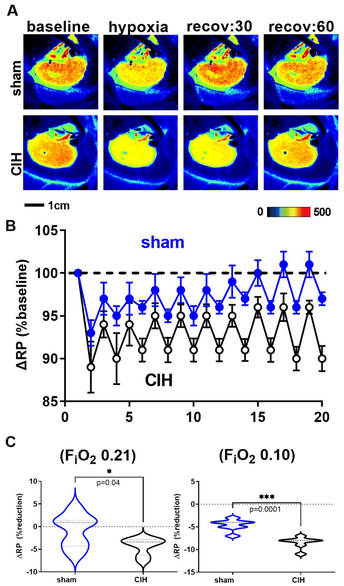

Figure 4. Renal microcirculatory perfusion during asphyxia. Panel (A) shows laser speckle images during IA and recovery. Panel (B) showing composite RP as a percent change from baseline. Panel (C) and (D) show aggregated mean differences (from baseline) in RP under hypoxia and normoxia. *p<0.05, ***p<0.0001

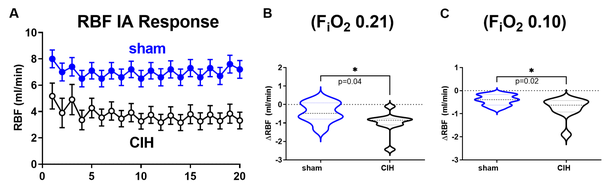

Figure 5. Renal artery blood flow during intermittent asphyxia. 10 bouts of acute asphyxia. Violin plots show average change in RBF during normoxia and during asphyxia. *p<0.05

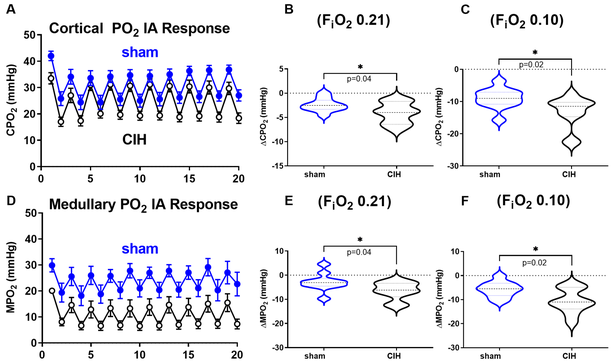

Figure 6. Cortical and medullary oxygenation during IA. Panels (A) and (D) show cortical and medullary PO_2 during 10 bouts of IA. (B) and (E) are aggregated median PO_2 change from baseline during normoxia. Panels (C) and (F) are synonymous plots but during the hypoxia challenge. *p<0.05

Results Continued

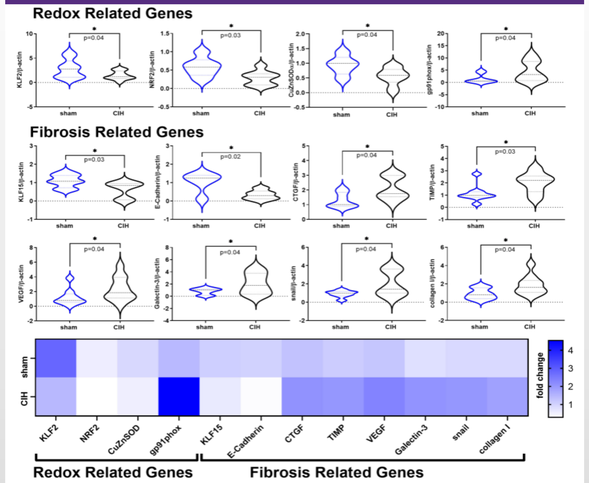

Figure 7. mRNA expression of redox and fibrosis related genes. All tissues are post-treatment and expressed relative to β-actin. The bottom heat map illustrates differences in expression as a fold change relative to β-actin. *p<0.05

•Our results show: **(I)** Both normoxia and hypoxia RBF, RP, CPO2, and MPO2 measures are significantly reduced in CIH vs sham-treated rats, with the CIH exposed group decreasing to a greater extent. **(II)** Pro-oxidative and pro-fibrotic gene programs are activated in renal tissue following CIH.

•This suggests SA contributes to renal dysfunction via stimulating renal hypoperfusion and hypoxia at both physiologic baseline and during apneic episodes.

•There may be therapeutic potential in attenuating tissue hypoxia and perfusion decrements seen in sleep apnea.

•Impact: Renal disease is an independent risk factor for CV mortality. These novel mechanistic findings may provide further insight into the pathophysiological changes seen in the development of other co-morbid conditions of CKD (TIID, HF, & HTN).

Support

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