Effects of Chronic Intermittent Hypoxia on Renal Cortical Antioxidant and Pro-Fibrotic Signaling in Chronic Heart Failure

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Background and Rationale

- A significant proportion of patients with chronic heart failure (CHF) develop co-morbid cardiac & renal dysfunction (i.e. cardio-renal syndrome, CRS).
- CRS is associated with higher morbidity and mortality in patients with CHF.
- Sleep Apnea (SA) is a common comorbidity in patients suffering from CHF and is independently associated with renal dysfunction.
- Carotid body chemoreceptors play a key role in activation of renal sympathetic nerves in CHF and sleep apnea.
- Chronic intermittent hypoxia (CIH, a model of SA) is associated with autonomic dysfunction, abnormal renal hemodynamics, oxidative stress, and inflammation.
- The combination of these insults may underlie renal dysfunction in CHF patients with SA.
- In this study, we sought to evaluate the role of CIH in promoting renal dysfunction in CHF.

Hypotheses

- oxidative, inflammatory, and pro-fibrotic signaling will be increased in kidneys of CHF rats, and this will be exacerbated by CIH.
- carotid body denervation (CBD) will provide a salutary effect.

Experimental Methods

Induction of Chronic Heart Failure

- SD rats (250-300g) underwent permanent ligation of the left anterior descending coronary artery (CAL) for induction of CHF.
- Cardiac function measured via echocardiography
- 4 weeks post-CAL subgroup had carotid body ablation (CBD).

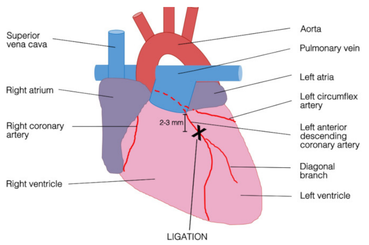

Figure 1. Induction of Chronic Heart Failure. CHF induced via ligation of left anterior descending coronary artery. Illustration from: Lugrin, J. et al. Murine Myocardial Infarction Model using Permanent Ligation of Left Anterior Descending Coronary Artery. J. Vis. Exp. (150), e59591, (2019).

Chronic Intermittent Hypoxia

- A subset of animals was exposed to chronic intermittent hypoxia (60 sec. FiO2 10%, 120 sec. FiO2 21% 8h/day) for 10 days preceding the end of the 8-week experimental period.

Assessment of Oxidative, Inflammatory and Pro-Fibrotic Signaling

- Renal cortical tissue was assessed for mRNA expression using qRT-PCR.
- Data was analyzed using a single factor ANOVA or non-parametric test when appropriate.

Results

Effect of CIH and CBD on Pro-Fibrotic Signaling in CHF

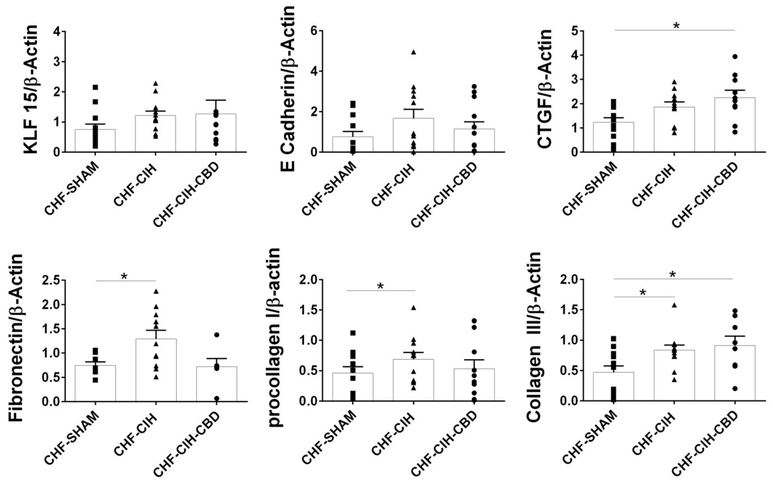

Figure 2. CIH Promotes Pro-Fibrotic Signaling in Renal Cortical Tissue . From top left to bottom right. No significant difference between groups of KLF 15 and E-Cadherin mRNA expression. Fibronectin, Procollagen, and Collagen III mRNA expression was significantly increased in CHF-CIH condition from CHF-SHAM ($p<0.05$). Expression of pro-fibrotic mRNA was not significantly attenuated with addition of CBD. Note that addition of CBD increased pro-fibrotic cTGF and Collagen III expression from CHF-SHAM ($p<0.05$). Results are expressed as mean ± SEM. n=7-10 animals per group. * $p < 0.05$ vs. sham via ANOVA with Sidak-Holm multiple comparison tests.

Effect CHF and CBD on Oxidative Signaling

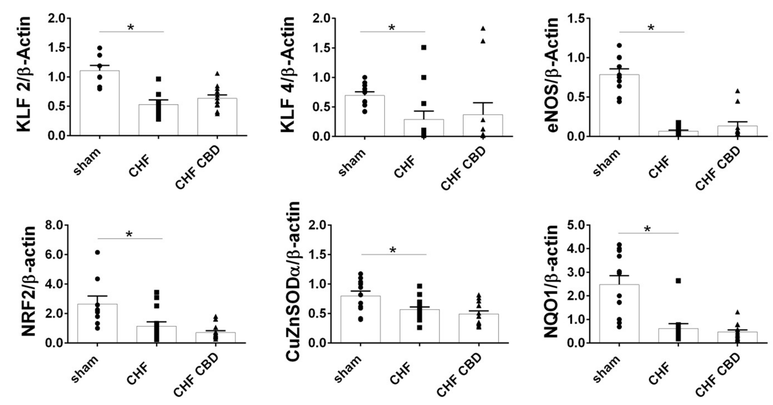

Figure 3. CBD does not Attenuate Reductions in Protective Oxidative Signaling in CHF in Renal Cortical Tissue. From top left to bottom right. Expression KLF 2, KLF 4, eNOS, NRF2, CuZnSOD, and NQO1 mRNA were significantly decreased in CHF from sham ($p<0.05$). Note that addition of CBD did not significantly alter mRNA expression in any marker of oxidative signaling ($p>0.05$). Results are expressed as mean ± SEM. n=7-10 animals per group. * $p < 0.05$ vs. sham via ANOVA with Sidak-Holm multiple comparison tests.

Results

Effect of CIH and CBD on Oxidative Signaling

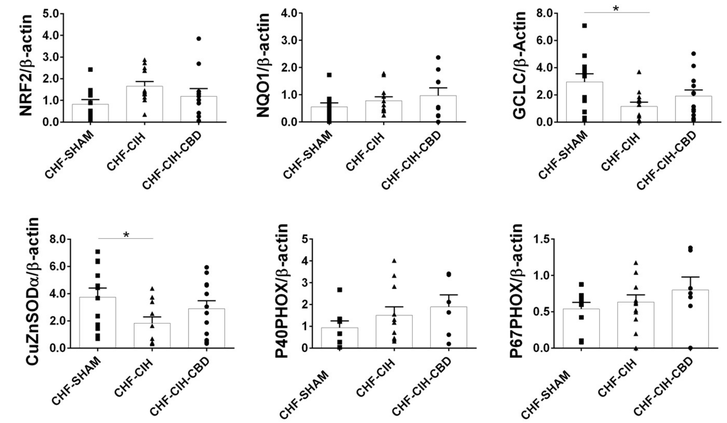

Figure 4. CBD does not Attenuate Reductions in Protective Oxidative signaling in CHF-CIH in Renal Cortical Tissue. CHF-CIH mRNA expression of GCLC, CuZnSOD was significantly decreased ($p<0.05$) from CHF-SHAM condition. Addition of CBD did not significantly alter mRNA expression of oxidative signaling ($p>0.05$). Results are expressed as mean ± SEM. n=7-10 animals per group. * $p < 0.05$ vs. sham via ANOVA with Sidak-Holm multiple comparison tests.

Effect of CIH on Inflammatory, Oxidative, Pro-Fibrotic Signaling

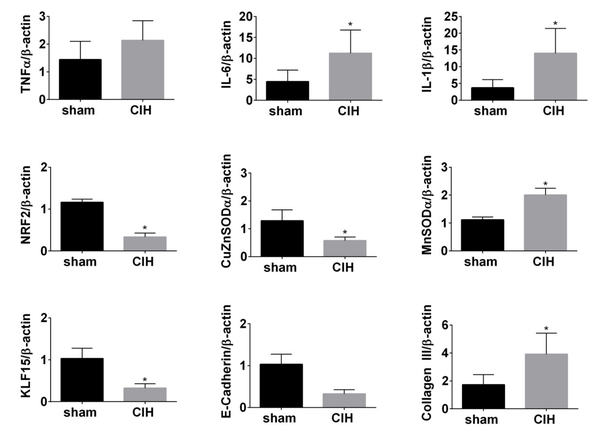

Figure 5. Summary Data of Effects of CIH on Renal Cortical Tissue. From top left to bottom right, CIH significantly increased mRNA expression of IL-6 and IL-1β ($p>0.05$). CIH significantly reduced mRNA expression of NRF2 and CuZnSOD ($p>0.05$). Note that CIH significantly increased mRNA expression of MnSOD from SHAM ($p>0.05$). Expression of KLF15 was significantly decreased in CIH compared to SHAM ($p>0.05$). Expression of Collagen III was significantly increased in CIH compared to SHAM ($p>0.05$). Results are expressed as mean ± SEM. n=7-10 animals per group. * $p < 0.05$ vs. sham via ANOVA with Sidak-Holm multiple comparison tests.

Conclusions

- CIH, a model of SA may promote fibrosis in renal tissue of CHF animals by mechanisms related to downregulation of antioxidant defenses. Whether or not CBD can effectively attenuate tissue damage in these conditions requires further study.

Support

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