Clonidine Does Not Prevent Pulmonary Injury in Conscious Rats Exposed to Hyperbaric Oxygen

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Background

Exposure to hyperbaric oxygen (HBO_2) at > 2 atmospheres absolute (ATA) can cause acute lung injury. When signs of central nervous system (CNS) oxygen toxicity are present, the severity of pulmonary injury is hastened (1). The events that precede pulmonary injury are linked the CNS (2), and include the following:

1. Central sympathetic excitation and catecholamine release
2. Left ventricular dysfunction
3. Pulmonary hypertension
4. Capillary damage/failure (transudation of fluid, protein and red blood cells)

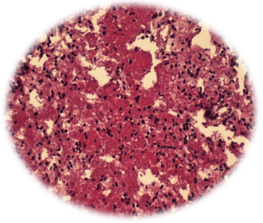

Fig. 1. Light micrograph (20x) of a mouse lung from an animal exposed to 4 ATA of > 99% O_2 for 100 min that displayed symptoms of CNS O_2 toxicity. Pulmonary hemorrhage secondary to hydrostatic rupture of capillary endothelium and alveolar epithelium.

Exploring the efficacy of pharmacological agents that lower central sympathetic output may prove beneficial in preventing acute lung injury during HBO_2. Clonidine is an α-adrenoceptor agonist (preferential affinity for α_2- *vs.* α_1-adrenoceptors) that reduces arterial blood pressure and heart rate primarily by central inhibition of sympathetic nerve activity (reduced norepinephrine release) (3). As such, the ***objective*** of this study was to determine whether clonidine would increase seizure latency and prevent acute lung injury in rats exposed to 5 or 6 ATA of > 99% O_2. Our ***hypothesis*** was seizure latency would be increased and acute lung injury lessened following clonidine administration.

Methods

Animals: Sprague-Dawley rats (270-338 g)
Baseline hemodynamic measurements: Heart rate and mean arterial pressure (MAP) in anesthetized animals administered i.v. clonidine hydrochloride (10 µg/kg)
HBO_2 exposure: 5 or 6 ATA
Clonidine dose: 10 or 30 µg/kg administered i.p.
CNS O_2 toxicity: Seizure latency
Acute lung injury:

- Post-mortem examination:
  1. Absent = 0
  2. Mild = 1
  3. Moderate = 2
  4. Severe = 3
- Bronchoalveolar lavage fluid (BALF):
  1. Lactate dehydrogenase (LDH)
  2. Total protein
  3. Total nitrites and nitrates (NOx)

Results

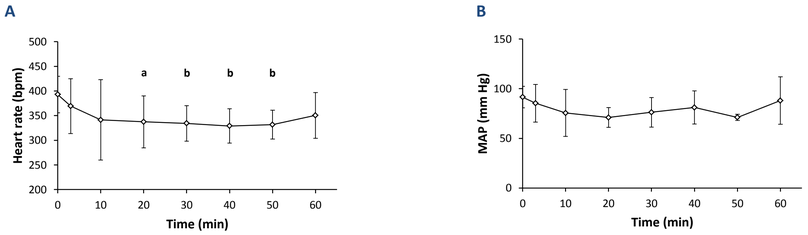

Fig. 2. Heart rate (A) and MAP (B) were measured through a femoral arterial catheter using a pressure transducer in anesthetized rats (n = 3) at baseline (time 0), and then following administration (i.v.) of clonidine hydrochloride (10 µg/kg) over 60 min at 1 ATA. The mean baseline heart rate (± SD) and MAP was 393 ± 37 bpm and 92 ± 11 mm Hg, respectively. A one-way repeated measures ANOVA revealed a significant decline in heart rate (-14%) 20 min following i.v. clonidine (p = 0.014), remaining decreased for an additional 30 min (p < 0.01), while MAP was maintained over 60 min.

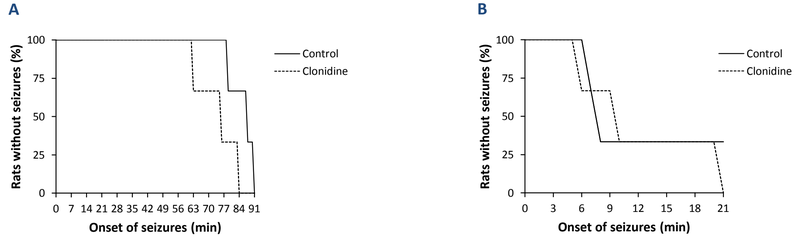

Fig. 3. Time to onset of motor convulsions in rats exposed to 5 ATA of > 99% O_2 (n = 6) for 91 min (A) and 6 ATA of > 99% O_2 (n = 6) for 21 min (B). All animals displayed symptoms of CNS O_2 toxicity at both HBO_2 exposures, and 83.3% of control and 100% of the clonidine animals exhibited tonic-clonic seizures (p > 0.05; Log-rank test).

Group	n	HBO_2	Mean acute lung injury score
Control	3	5 ATA	2
Clonidine (10 µg/kg)	3	5 ATA	3
Control	3	6 ATA	3
Clonidine (30 µg/kg)	3	6 ATA	2

Table 1. Mean acute lung injury score in rats exposed to 5 and 6 ATA of > 99% O_2. The severity of acute lung injury was moderate to severe in both groups following HBO_2 exposures (p > 0.05; Mann-Whitney U test).

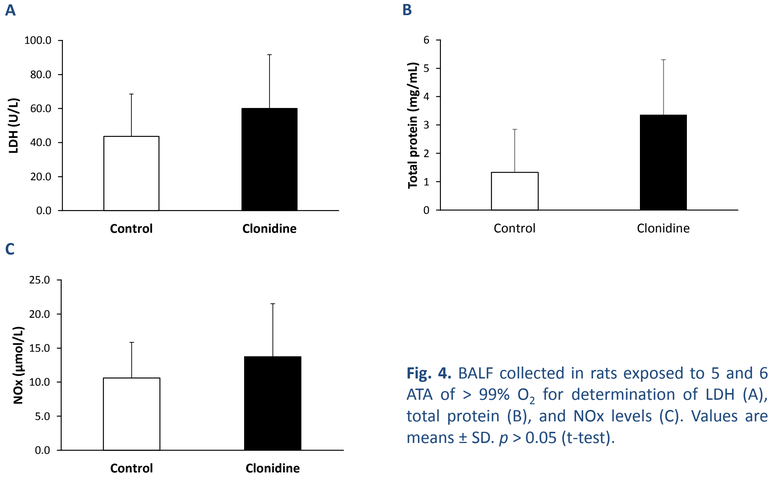

Fig. 4. BALF collected in rats exposed to 5 and 6 ATA of > 99% O_2 for determination of LDH (A), total protein (B), and NOx levels (C). Values are means ± SD. p > 0.05 (t-test).

Summary & Conclusions

- Clonidine administration (10-30 µg/kg) does not protect against symptoms of CNS O_2 toxicity or acute lung injury in rats exposed to HBO_2 at 5-6 ATA.
- These preliminary results suggest that high sympathetic outflow does not shorten seizure latency or act as the sole driver of neurogenic pulmonary damage.

References

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Acknowledgements

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