**Arterial hyperoxemia and acute kidney injury in trauma patients: a retrospective observational study**

**Background:**

Oxygen (O2) is essential for humans and the consequences associated with hypoxemia can be devastating. While O2 has been widely prescribed for therapy in medicine (1), there is an emerging concern that hyperoxemia (increased PaO2) could also embrace potential detrimental systemic effects (2).

Hyperoxemia can induce cellular damage through excess reactive oxygen species and can have negative hemodynamic effects by inducing systemic vasoconstiction (3) (4). Recently, the potentially harmful impact of oxygen has been studied in clinical trials across multiple fields, including cardiopulmonary resuscitation (5) (6), stroke (8), myocardial infarction (9), traumatic brain injury (10) and medical-surgical intensive care (11).

Considering the suggested injurious mechanisms, kidney function could be one of the targets for hyperoxemia toxicity. Animal studies have shown the detrimental effect of hyperoxemia on renal tissue through protein expression associated with inflammation and imbalance of renal oxygen delivery and demand (12) (13). In humans, a strong association between acute kidney injury and mortality (14) was been shown and the potential impact of hyperoxemia on kidney function could be a major concern.

O2 might be the most commonly administered drug in trauma settings. Since significant hypoxemia after trauma can quickly lead to a fatal event, liberal oxygen therapy is provided either in response to or for prevention of hypoxic organ damage. However, the impact of keeping supranormal arterial blood oxygen tensions during the ICU stay on the development of acute kidney injury (AKI) in critically injured patients remains unclear.

**Research Hypotheses:**

We hypothesize that hyperoxemia, as compared with normal oxygen levels is associated with renal dysfunction in trauma patients between 48 hours and up to 7 days of the ICU stay.

**Research Question / Objective:**

The aim of this study is to survey the prevalence and the degree of hyperoxemia among trauma patients in an intensive care unit and to investigate the association between PaO2 and the development of AKI. Our research question is how the time-weighted average PaO2 during the first 24 hours of the ICU stay is associated with the development of AKI.Development of AKI is defined as the primary outcome using Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria (7).The secondary outcomes are all-cause mortality, length of stay in the ICU and hospital length of stay, and duration of mechanical ventilation and start of renal replacement therapy.

**Data Sources:**

**Study Population:**

Inclusion criteria:

* 18 years old and older
* Trauma patients who are defined by using International Classification of Disease, 9th Revision, Clinical Modification codes: 800 – 956 for ICD9
* Patients who, directly or through the operation room, admitted to the ICU
* Patients who stayed in the ICU for at least 48 hours

Exclusion criteria:

* Preexisting chronic kidney dysfunction and hemodialysis
* Patients without ABG measurements, creatinine and/or urine output
* Patients after cardiopulmonary resuscitation
* Patients with Comfort Measures Only (CMO) order

**Covariate(s) of Interest (Exposure):**

Patients will be divided based on quartiles/ quintiles of mean PaO2 levels during the first 24 hours of the ICU stay. This ensures an equal number of participants in each group and is an objective way of classifying exposure levels.

**Confounders:**

We will adjust for the following confounders: age, gender, disease severity (APACHE IV), amount of transfused blood products (blood loss), preexisting kidney disease, preexisting heart disease, diabetes mellitus, chronic lung disease, nephrotoxic medication (NSARS, nephrotoxic antibiotics).

**Statistical analysis**

A Cox proportional hazards models was fitted to evaluate the association of categorized PaO2 levels with the incidence of AKI and secondary outcomes. Time to event was calculated from the day of hospital (all-cause mortality) or ICU (ICU LOS) admission until the experience of the event or until the KDIKO creteria were met (AKI). A multivariable model adjusting for the above-mentioned confounders was fitted. The proportional hazard analysis was tested using Schoenfeld residuals and Schoenfeld’s global test was used to decide whether to reject the proportional hazard assumption. The linearity assumption was tested, and model fit was ensured.

As sensitivity analyses, we used mean PaO2 of the first 6, 12, 24 and 48 hours and observed the effect on the onset of AKI within 48 h and 7 days after ICU admission. We also investigated the effect of changing exposure (mean PaO2) on the onset of predifined secondary outcomes.

All analyses were performed using the open-access software *R* (version 3.4, <http://www.R-project.org/>) and relevant packages. All tests were two-sided and used an alpha-level of 0.05 to determine statistical significance.

**Acknowledgements:**

This manuscript has been produced as part of course HST.953 at the Massachusetts Institute of Technology, Cambridge, MA, USA.

**References:**

1. Bateman NT, Leach RM. Acute oxygen therapy. BMJ. British Medical Journal Publishing Group; 1998 Sep 19;317(7161):798–801.

2. Haines RW, Lin S-P, Hewson R, Kirwan CJ, Torrance HD, O’Dwyer MJ, et al. Acute Kidney Injury in Trauma Patients Admitted to Critical Care: Development and Validation of a Diagnostic Prediction Model. Scientific Reports 2018 8:1. Nature Publishing Group; 2018 Feb 26;8(1):3665.

3. Thomas M, Malmcrona R, Shillingford J. Hemodynamic effects of oxygen in patients with acute myocardial infaction. British Heart Journal. BMJ Publishing Group; 1965 May 1;27(3):401.

4. Cornet AD, Kooter AJ, Peters MJ, Smulders YM. The potential harm of oxygen therapy in medical emergencies. Critical Care 2016 20:1. BioMed Central; 2013 Apr 1;17(2):313.

5. Hope KJ. Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality. 2010 May 19;:1–7.

6. Hope KJ, Jones AE, Parrillo JE, Dellinger P, Milcarek B, Hunter K, et al. Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest, *Circulation*. 2011 April 4;123:2717-2722.

7. Kellum JA. Defining and classifying AKI: one set of criteria. Nephrol Dial Transplant. Oxford University Press; 2008 May 1;23(5):1471–2.

8. Rønning OM, Guldvog B. Should Stroke Victims Routinely Receive Supplemental Oxygen? Stroke. Lippincott Williams & Wilkins; 1999 Oct 1.

9. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Critical Care 2016 20:1. BioMed Central; 2011 Apr 1;15(2):R90.

10. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry. BMJ Publishing Group Ltd; 2013 Jun 20;:jnnp–2013–305505.

11. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. JAMA. 2016 Oct 18;316(15):1583–7.

12. Hinkelbein J, Böhm L, Spelten O, Sander D, Soltész S, Braunecker S. Hyperoxia-Induced Protein Alterations in Renal Rat Tissue: A Quantitative Proteomic Approach to Identify Hyperoxia-Induced Effects in Cellular Signaling Pathways. Disease Markers. Hindawi; 2015 May 27;2015.

13. Pohlmann A, Arakelyan K, Seeliger E, Niendorf T. Magnetic Resonance Imaging (MRI) Analysis of Ischemia/Reperfusion in Experimental Acute Renal Injury. In: Kidney Research. New York, NY: Humana Press, New York, NY; 2016. pp. 113–27. (Methods in Molecular Biology; vol. 1397).

14. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney International. Elsevier; 2008 Mar 1;73(5):538–46.