Linking hyperoxia and harm: Consequence or merely Subsequence?

Mark J Peters [1,2] MD PhD,

1. Respiratory Critical Care and Anaesthesia Unit, UCL Great Ormond Street Institute of Child Health, London, United Kingdom.
2. Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom.

Corresponding author

mark.peters@ucl.ac.uk

Key words

Hyperoxia, cardiopulmonary bypass, oxidative stress, causality, clinical trials

Funding

This work received no direct funding but was supported by the National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Declaration of Interests

I am Chief Investigator of an UK National Institute of Health Research Health Technology Assessment programme funded multiple centre randomised controlled trial of conservative vs liberal oxygenation targets Oxy-PICU ISRCTN92103439

Word count 1063

Humans are highly susceptible to interpreting the timing of events as evidence of causation. Absurd claims based on timing alone abound: Fifth-generation telecommunications networks and pandemics; measles, mumps, rubella immunization and autism; or homeopathy and efficacy. Many doctors are especially prone to this error. Samuel Johnson wrote *"It is incident to physicians, ..., beyond all other men, to mistake subsequence for consequence."* (1)

Intensivists have more data to work with than most physicians. Hence, we may be uniquely prone to spot associations between abnormal physiological parameters and poor outcome. These can become seductive targets for 'treatment'. But some such associations are the opposite of causal; they may be *adaptive*. No benefit, or even harm, is the result when normalisation of non-causal abnormalities are tested in large randomised clinical trials (RCTs). Familiar examples include: pyrexia during infection, low growth hormone, hyperglycemia, hypercarbia or moderate anaemia.(2)

With these warning-bells ringing, consider the association described in this issue of the *Journal*. Beshish and colleagues describe an association between hyperoxia on cardiopulmonary bypass (defined as an average bypass arterial oxygen tension of greater than 41.7KPa [313mmHg]) – and an increased risk of mortality. The effect size is dramatic: odds ratio = 4.3 (95% confidence interval [CI] 1.4–13.2, p=0.008), after adjustment for age, weight and STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) mortality score. (3)

In an accompanying *Statistical Note*, Dr Horvat considers the techniques that may refine the probability of a causal inference (4). However outside of the statistical considerations the context of the observed association is relevant in determining the feasibility of a causal link.

The first relevant context is that similar associations have been made in other conditions. In 2011, hyperoxia was associated with poor outcomes post-cardiac arrest.(5) A U-shaped relationship exists between admission arterial oxygen tension and both crude and risk-adjusted mortality in unselected pediatric critical illness.(6). The most directly comparable data highlight poor outcomes with hyperoxia during support with extracorporeal membrane oxygenation (ECMO).(7)

Next, there are feasible and robust candidate mechanisms linking hyperoxia and harm. The simplest is that hyperoxia is a marker for overtreatment. Using too much pressure and oxygen increases the potential for ventilation-induced lung injury. Or maybe hyperoxia reflects a more generally inappropriate aggressive approach that is harmful via other mechanisms. While appealingly simple, this 'hyperoxia as a marker of general overtreatment' argument does not easily explain the association of death with hyperoxia on cardio-pulmonary bypass as described by Beshish and colleagues (3). Operative bypass is a decrete and shortlived exposure outside of the ICU. The next option is that a high oxygen tension is directly toxic to tissues. In excess, oxygen fuels increased 'reactive oxygen species' (ROS) formation. These oxygen-containing molecules hunt electrons avidly. Antioxidant molecules provide a partial buffer system that can neutralise a modest concentration of ROS. However, these can be overrun, leaving hungry ROS hunting electrons wherever they can find them. This state termed 'oxidative stress' is more precisely defined as "an imbalance between oxidant production and antioxidant and repair defences, resulting in increased steady-state levels of oxidized cellular macromolecules".(8) Oxidation can disrupt all organic molecules (DNA, proteins, and lipids).(9) Enough oxidative damage causes cell death. Sub-lethal oxidative stress may trigger mitochondrial dysfunction-mediated organ 'hibernation' – one theory to explain multiple-organ failure. (10) This is a dynamic process. Recent work confirms that partial pressure of oxygen in an individual cell

influences the rate of ROS production as a by-product of oxidative phosphorylation in the mitochondria.(11) The principle of manipulating inspired oxygen concentration to alter mitochondria ROS production may have merit. There is evidence of a benefit of hypoxia in models of congenital mitochondrial diseases.(12) In short, the basic science context is consistent with hyperoxia causing harm.

Finally, and most importantly for the consideration of causation, there are data from RCTs that link more liberal oxygenation strategies with harm in multiple acute care settings. Liberal oxygenation was associated with a higher mortality than more conservative oxygenation (relative risk 1.21, 95% CI 1.03–1.43) in 16,037 adults across 25 RCTs in a range of acute diseases in adults: emergency surgery, myocardial infarction, sepsis and critical illness. Newer trials in adult critical care provide conflicting results though all have slightly different populations, interventions, comparators and outcomes. Hyperoxia appears to be harmful in sepsis (13) whereas permissive hypoxia may be harmful in acute respiratory distress syndrome (14). No clear signal was apparent in the largest trial to date adult critical illness.(15) There is evidence that lower pulse oximetry oxygen saturation (SpO2) targets (>90%) are safe may have some advantages in terms of rate of recovery in infants admitted to the ward with bronchiolitis.(16). We are conducting the oxygenation targets in critically ill children (Oxy-PICU) trial in 15 centers, recruiting 2040 emergency paediatric intensive admissions receiving invasive mechanical respiratory support (ISRCTN92103439) (17). We are randomising within 6 hours of eligibility to a more restrictive oxygen saturation SpO2 target (88-92%) or standard care (SpO2 >94%). This follows our pilot trial (n=120) with a similar protocol in which no safety concerns were identified. So, generally, trial data are consistent with systemic oxygenation being causally linked to outcome. The caveat is that the majority of trials focus on the benefits of mild hypoxia rather than harm from hyperoxia.

One phase II trial in progress for adults on ECMO, the “Blend to Limit oxygEN in ECMO” (NCT03841084), which will be directly relevant.

Even though the context is supportive for a causal link between hyerpoxia and harm two doubts remain. The possibility is that somehow hyperoxia on bypass reflects clinician and perfusionist concern in a way that is not captured in the adjustment for age, weight and STAT score – an ‘unmeasured confounder’. The other is the huge effect size with an odds ratio of 4.3 for death. If entirely causal this implies we could reduce death in the hyperoxia subgroup by ~80% just by turning down the oxygen flow rate on bypass. This is hardly credible. No intervention in intensive care has ever had an effect of this magnitude. It is both a source of excitement and a worry. We need to explore this urgently.

Psychologist Simon Baron-Cohen argues that the ‘systematizer’ (pattern recognition) trait is key in human creativity, inventiveness and progress.(18) Beshish and colleagues (3) have recognised a clear pattern in their data, which could lead to important progress. Now we need to try to reproduce the association in other populations and to hunt for unmeasured confounders. If the association persists, we must test causation formally in RCTs. In the meantime, we must resist the ‘consequence bias’. No-one should change oxygenation practice on this association alone.

References

1. Johnson S: Review of Dr Lucas's essay on waters. *Literary Magazine* 1756; ii

2. Kox M, Pickkers P: "Less is more" in critically ill patients: not too intensive. *JAMA Intern Med* 2013; 173:1369–1372

3. Beshish AG, Jahadi O, Mello A, et al.: Hyperoxia During Cardiopulmonary Bypass Is Associated With Mortality In Infants Undergoing Cardiac Surgery. *Pediatr Crit Care Med* 2021;

4. Horvat C: Statistical note: confounding and causality in observational studies. *Pediatr Crit Care Med* 2021;

5. Kilgannon JH, Jones AE, Parrillo JE, et al.: Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest. *Circulation* 2011; 123:2717–2722

6. Raman S, Prince NJ, Hoskote A, et al.: Admission PaO2 and Mortality in Critically Ill Children. *Pediatr Crit Care Med* 2016; 17:e444–e450

7. Sznycer-Taub NR, Lowery R, Yu S, et al.: Hyperoxia Is Associated With Poor Outcomes in Pediatric Cardiac Patients Supported on Venoarterial Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2016; 17:350–358

8. Halliwell B: Biochemistry of oxidative stress. *Biochem Soc Trans* 2007; 35:1147–1150

9. Bar-Or D, Bar-Or R, Rael LT, et al.: Oxidative stress in severe acute illness. 2015; 4:340–345

10. Singer M, De Santis V, Vitale D, et al.: Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; 364:545–548

11. Wilson DF: Oxidative phosphorylation: regulation and role in cellular and tissue metabolism. *J Physiol* 2017; 595:7023–7038

12. Mootha VK, Chinnery PF: Oxygen in mitochondrial disease: can there be too much of a good thing? *J Inherit Metab Dis* 2018; 41:761–763

13. Asfar P, Schortgen F, Boisramé-Helms J, et al.: Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respiratory Medicine* 2017; 5:180–190

14. Barrot L, Asfar P, Mauny F, et al.: Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *N Engl J Med* 2020; 382:999–1008

15. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al.: Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med* 2020; 382:989–998

16. Cunningham S, Rodriguez A, Boyd KA, et al.: Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. *Health Technol Assess* 2015; 19:1–172

17. Peters, M.J., Jones, G.A.L., Wiley, D. et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive Care Med 44, 1240–1248 (2018). https://doi.org/10.1007/s00134-018-5232-7

18. Baron-Cohen S: The Pattern Seekers: a new theory of human invention. Penguin Random House, UK; 2020.

Linking hyperoxia and harm: Consequence or merely Subsequence?

Mark J Peters [1,2] MD PhD,

1. Respiratory Critical Care and Anaesthesia Unit, UCL Great Ormond Street Institute of Child Health, London, United Kingdom.
2. Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom.

Corresponding author

mark.peters@ucl.ac.uk

Key words

Hyperoxia, cardiopulmonary bypass, oxidative stress, causality, clinical trials

Funding

This work received no direct funding but was supported by the National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Declaration of Interests

I am Chief Investigator of an UK National Institute of Health Research Health Technology Assessment programme funded multiple centre randomised controlled trial of conservative vs liberal oxygenation targets Oxy-PICU ISRCTN92103439

Word count 1063

Humans are highly susceptible to interpreting the timing of events as evidence of causation. Absurd claims based on timing alone abound: Fifth-generation telecommunications networks and pandemics; measles, mumps, rubella immunization and autism; or homeopathy and efficacy. Many doctors are especially prone to this error. Samuel Johnson wrote *"It is incident to physicians, ..., beyond all other men, to mistake subsequence for consequence."* (1)

Intensivists have more data to work with than most physicians. Hence, we may be uniquely prone to spot associations between abnormal physiological parameters and poor outcome. These can become seductive targets for 'treatment'. But some such associations are the opposite of causal; they may be *adaptive*. No benefit, or even harm, is the result when normalisation of non-causal abnormalities are tested in large randomised clinical trials (RCTs). Familiar examples include: pyrexia during infection, low growth hormone, hyperglycemia, hypercarbia or moderate anaemia.(2)

With these warning-bells ringing, consider the association described in this issue of the *Journal*. Beshish and colleagues describe an association between hyperoxia on cardiopulmonary bypass (defined as an average bypass arterial oxygen tension of greater than 41.7KPa [313mmHg]) – and an increased risk of mortality. The effect size is dramatic: odds ratio = 4.3 (95% confidence interval [CI] 1.4–13.2, p=0.008), after adjustment for age, weight and STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) mortality score. (3)

In an accompanying *Statistical Note*, Dr Horvat considers the techniques that may refine the probability of a causal inference (4). However outside of the statistical considerations the context of the observed association is relevant in determining the feasibility of a causal link.

The first relevant context is that similar associations have been made in other conditions. In 2011, hyperoxia was associated with poor outcomes post-cardiac arrest.(5) A U-shaped relationship exists between admission arterial oxygen tension and both crude and risk-adjusted mortality in unselected pediatric critical illness.(6). The most directly comparable data highlight poor outcomes with hyperoxia during support with extracorporeal membrane oxygenation (ECMO).(7)

Next, there are feasible and robust candidate mechanisms linking hyperoxia and harm. The simplest is that hyperoxia is a marker for overtreatment. Using too much pressure and oxygen increases the potential for ventilation-induced lung injury. Or maybe hyperoxia reflects a more generally inappropriate aggressive approach that is harmful via other mechanisms. While appealingly simple, this 'hyperoxia as a marker of general overtreatment' argument does not easily explain the association of death with hyperoxia on cardio-pulmonary bypass as described by Beshish and colleagues (3). Operative bypass is a decrete and shortlived exposure outside of the ICU. The next option is that a high oxygen tension is directly toxic to tissues. In excess, oxygen fuels increased 'reactive oxygen species' (ROS) formation. These oxygen-containing molecules hunt electrons avidly. Antioxidant molecules provide a partial buffer system that can neutralise a modest concentration of ROS. However, these can be overrun, leaving hungry ROS hunting electrons wherever they can find them. This state termed 'oxidative stress' is more precisely defined as "an imbalance between oxidant production and antioxidant and repair defences, resulting in increased steady-state levels of oxidized cellular macromolecules".(8) Oxidation can disrupt all organic molecules (DNA, proteins, and lipids).(9) Enough oxidative damage causes cell death. Sub-lethal oxidative stress may trigger mitochondrial dysfunction-mediated organ 'hibernation' – one theory to explain multiple-organ failure. (10) This is a dynamic process. Recent work confirms that partial pressure of oxygen in an individual cell

influences the rate of ROS production as a by-product of oxidative phosphorylation in the mitochondria.(11) The principle of manipulating inspired oxygen concentration to alter mitochondria ROS production may have merit. There is evidence of a benefit of hypoxia in models of congenital mitochondrial diseases.(12) In short, the basic science context is consistent with hyperoxia causing harm.

Finally, and most importantly for the consideration of causation, there are data from RCTs that link more liberal oxygenation strategies with harm in multiple acute care settings. Liberal oxygenation was associated with a higher mortality than more conservative oxygenation (relative risk 1.21, 95% CI 1.03–1.43) in 16,037 adults across 25 RCTs in a range of acute diseases in adults: emergency surgery, myocardial infarction, sepsis and critical illness. Newer trials in adult critical care provide conflicting results though all have slightly different populations, interventions, comparators and outcomes. Hyperoxia appears to be harmful in sepsis (13) whereas permissive hypoxia may be harmful in acute respiratory distress syndrome (14). No clear signal was apparent in the largest trial to date adult critical illness.(15) There is evidence that lower pulse oximetry oxygen saturation (SpO2) targets (>90%) are safe may have some advantages in terms of rate of recovery in infants admitted to the ward with bronchiolitis.(16). We are conducting the oxygenation targets in critically ill children (Oxy-PICU) trial in 15 centers, recruiting 2040 emergency paediatric intensive admissions receiving invasive mechanical respiratory support (ISRCTN92103439) (17). We are randomising within 6 hours of eligibility to a more restrictive oxygen saturation SpO2 target (88-92%) or standard care (SpO2 >94%). This follows our pilot trial (n=120) with a similar protocol in which no safety concerns were identified. So, generally, trial data are consistent with systemic oxygenation being causally linked to outcome. The caveat is that the majority of trials focus on the benefits of mild hypoxia rather than harm from hyperoxia.

One phase II trial in progress for adults on ECMO, the “Blend to Limit oxygEN in ECMO” (NCT03841084), which will be directly relevant.

Even though the context is supportive for a causal link between hyerpoxia and harm two doubts remain. The possibility is that somehow hyperoxia on bypass reflects clinician and perfusionist concern in a way that is not captured in the adjustment for age, weight and STAT score – an ‘unmeasured confounder’. The other is the huge effect size with an odds ratio of 4.3 for death. If entirely causal this implies we could reduce death in the hyperoxia subgroup by ~80% just by turning down the oxygen flow rate on bypass. This is hardly credible. No intervention in intensive care has ever had an effect of this magnitude. It is both a source of excitement and a worry. We need to explore this urgently.

Psychologist Simon Baron-Cohen argues that the ‘systematizer’ (pattern recognition) trait is key in human creativity, inventiveness and progress.(18) Beshish and colleagues (3) have recognised a clear pattern in their data, which could lead to important progress. Now we need to try to reproduce the association in other populations and to hunt for unmeasured confounders. If the association persists, we must test causation formally in RCTs. In the meantime, we must resist the ‘consequence bias’. No-one should change oxygenation practice on this association alone.

References

1. Johnson S: Review of Dr Lucas's essay on waters. *Literary Magazine* 1756; ii

2. Kox M, Pickkers P: "Less is more" in critically ill patients: not too intensive. *JAMA Intern Med* 2013; 173:1369–1372

3. Beshish AG, Jahadi O, Mello A, et al.: Hyperoxia During Cardiopulmonary Bypass Is Associated With Mortality In Infants Undergoing Cardiac Surgery. *Pediatr Crit Care Med* 2021;

4. Horvat C: Statistical note: confounding and causality in observational studies. *Pediatr Crit Care Med* 2021;

5. Kilgannon JH, Jones AE, Parrillo JE, et al.: Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest. *Circulation* 2011; 123:2717–2722

6. Raman S, Prince NJ, Hoskote A, et al.: Admission PaO2 and Mortality in Critically Ill Children. *Pediatr Crit Care Med* 2016; 17:e444–e450

7. Sznycer-Taub NR, Lowery R, Yu S, et al.: Hyperoxia Is Associated With Poor Outcomes in Pediatric Cardiac Patients Supported on Venoarterial Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2016; 17:350–358

8. Halliwell B: Biochemistry of oxidative stress. *Biochem Soc Trans* 2007; 35:1147–1150

9. Bar-Or D, Bar-Or R, Rael LT, et al.: Oxidative stress in severe acute illness. 2015; 4:340–345

10. Singer M, De Santis V, Vitale D, et al.: Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; 364:545–548

11. Wilson DF: Oxidative phosphorylation: regulation and role in cellular and tissue metabolism. *J Physiol* 2017; 595:7023–7038

12. Mootha VK, Chinnery PF: Oxygen in mitochondrial disease: can there be too much of a good thing? *J Inherit Metab Dis* 2018; 41:761–763

13. Asfar P, Schortgen F, Boisramé-Helms J, et al.: Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respiratory Medicine* 2017; 5:180–190

14. Barrot L, Asfar P, Mauny F, et al.: Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *N Engl J Med* 2020; 382:999–1008

15. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al.: Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med* 2020; 382:989–998

16. Cunningham S, Rodriguez A, Boyd KA, et al.: Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. *Health Technol Assess* 2015; 19:1–172

17. Peters, M.J., Jones, G.A.L., Wiley, D. et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive Care Med 44, 1240–1248 (2018). https://doi.org/10.1007/s00134-018-5232-7

18. Baron-Cohen S: The Pattern Seekers: a new theory of human invention. Penguin Random House, UK; 2020.