Keywords:
Hyperbaric Oxygenation application, artificial membrane lung, Hyperoxia

ARTICLE

Info Author :
[1] Department of Cardiac Surgery, Anthea Hospital, GVM Care & Research, Bari, Italy

Corresponding author:
Ignazio Condello, PhD
GVM Care & Research, Perfusion Service, Anthea Hospital,
Via Camillo Rosalba 35/37, 70124 Bari, Italy.
Tel. +39 080 5644560
Fax +39 080 5644560
E-mail: ignicondello@hotmail.it

Ignazio Condello [1]

BAROMETRIC AND HYPEROXIA EFFECTS DURING ARTIFICIAL MEMBRANE LUNG

ABSTRACT

Oxygen is one of the most commonly used therapeutic agents.
Injudicious use of oxygen at high partial pressures (hyperoxia) for unproven indications, its known toxic potential, and the acknowledged roles of reactive oxygen species in tissue injury led to skepticism regarding its use. Nevertheless, a large body of data indicates that hyperoxia exerts an extensive profile of physiologic and pharmacologic effects that improve tissue oxygenation, exert anti-inflammatory and antibacterial effects, and augment tissue repair mechanisms.

These data set the rationale for the use of hyperoxia in a list of clinical conditions characterized by tissue hypoxia, infection, and consequential impaired tissue repair. In the world of Perfusion both Cardiopulmonary Bypass (CPB) both Extracorporeal Membrane Oxygenation (ECMO) the application and use of hypobaric or hyperbaric oxygenation and oxygen at high partial pressures (hyperoxia) during artificial membrane lung (aML) is a controversial topic. Gaseous microemboli (GME) may originate from the extracorporeal circuit and enter the arterial circulation of the patient. GME are thought to contribute to cerebral deficit and to adverse outcome after cardiac surgery.

The arterial filter is a specially designed component for removing both gaseous and solid micro-emboli. In different study hypobaric oxygenation approach capitalizes gaseous micro-embolism (GME) reduction to achieve their near-total elimination during cardiopulmonary bypass (CPB). This review summarizes the pros and cons on hyperbaric or hypobaric oxygenation management and hyperoxia during extracorporeal technologies that used membrane lung oxygenators.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9

INTRODUCTION

Oxygen is one of the most commonly used therapeutic agents. Injudicious use of oxygen at high partial pressures (hyperoxia) for unproven indications, its known toxic potential, and the acknowledged roles of reactive oxygen species in tissue injury led to skepticism regarding its use.

A large body of data indicates that hyperoxia exerts an extensive profile of physiologic and pharmacologic effects that improve tissue oxygenation, exert anti-inflammatory and antibacterial effects, and augment tissue repair mechanisms. These data set the rationale for the use of hyperoxia in a list of clinical conditions characterized by tissue hypoxia, infection, and consequential impaired tissue repair. Data on regional hemodynamic effects of hyperoxia and recent compelling evidence on its anti-inflammatory actions incited a surge of interest in the potential therapeutic effects of hyperoxia in myocardial revascularization and protection, in traumatic and nontraumatic ischemicanoxic brain insults, and in prevention of surgical site infections and in alleviation of septic and nonseptic local and systemic inflammatory responses. Although the margin of safety between effective and potentially toxic doses of oxygen is relatively narrow, the ability to carefully control its dose, meticulous adherence to currently accepted therapeutic protocols, and individually tailored treatment regimens make it a cost-effective safe drug [(1)].

In the world of Perfusion both Cardiopulmonary Bypass (CPB) both Extracorporeal Membrane Oxygenation (ECMO) the application and use of hypobaric or hyperbaric and high partial pressure (hyperoxia) oxygenation during membrane lung is a controversial topic [(2)].

Ischaemia-induced tissue injury has wide-ranging clinical implications including myocardial infarction, stroke, compartment syndrome, ischaemic renal failure and replantation and revascularization.

However, the restoration of blood flow produces a 'second hit' phenomenon, the effect of which is greater than the initial ischaemic event and characterizes ischaemia-reperfusion (IR) injury. Some examples of potential settings of IR injury include: following thrombolytic therapy for stroke, invasive cardiovascular procedures, solid organ transplantation, and major trauma resuscitation.
Pathophysiological events of IR injury are the result of reactive oxygen species (ROS) production, microvascular vasoconstriction, and ultimately endothelial cell-neutrophil adhesion with subsequent neutrophil infiltration of the affected tissue. Initially thought to increase the amount of free radical oxygen in the system, hyperbaric hyperoxya (HBO) has demonstrated a protective effect on tissues by influencing the same mechanisms responsible for IR injury.

Nevertheless, there is accumulating evidence that that compared the influence of allogeneic red blood cell transfusion with 100% oxygen ventilation in volume-resuscitated anemic patients after cardiac surgery demonstrated a superior effect of normobaric hyperoxia (NBO) on tissue (skeletal muscle) oxygen tension.in different study hypobaric oxygenation approach capitalizes the reduction of gaseous micro-embolism (GME) to achieve their near-total elimination during cardiopulmonary bypass (CPB) [(3)].
We review the pros and cons on hyperbaric or hypobaric oxygenation management and hyperoxia effects during extracorporeal technologies that used membrane lung oxygenators.

HYPERBARIC OXYGENATION APPLICATION IN ARTIFICIAL MEMBRANE LUNG

Gas transfer is further affected by factors influencing the O2 or CO2 concentration gradient between the blood and the gas compartment.

Pertaining to gas pressures greater than 1 atmosphere of pressure. The term "hyperbaric" is derived from Greek roots: "hyper-" meaning high, beyond, excessive, above normal and "baros" meaning weight.

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
IJPDTM Vol.5 N°2 2022. For personal use only. No other uses without permission.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9

Hyperbaric oxygenation is an increased amount of oxygen in organs and tissues resulting from the administration of oxygen in a chamber at an ambient pressure greater than 1 atmosphere* of pressure. Current perfusion practice generally targets mildly hyperoxic blood gases during aML use [(3)].

This target is achieved by lowering the partial pressure of oxygen in oxygenator sweep gas by dilution with air, thereby engendering the needless side effect of dissolving nitrogen in blood. Design of contemporary oxygenators requires better understanding of the influence of hydrodynamic patterns on gas exchange.

A decrease in blood path width or an increase in intra-oxygenator turbulence for instance, might increase gas transfer efficiency but it will increase shear stress as well.
The effect of additional parameters related to gas transfer efficiency, that is, blood flow, gas flow, sweep gas oxygen fraction (FiO2), hemoglobin concentration, the amount of hemoglobin pumped through the oxygenator per minute-Qhb, and shunt fraction were contemplated as well [(3)].
The design-dependent relationship between shear stress and gas transfer revealed that every oxygenator has an optimal range of blood flow and thus shear stress at which gas transfer is most efficient.

HYPOBARIC OXYGENATION APPLICATION IN ARTIFICIAL MEMBRANE LUNG

Hypobaric oxygenation controls the oxygenator's gas to blood O2 diffusion gradient to achieve desired blood gases without using nitrogen.
The resultant decrease in dissolved blood gases favors aqueous reabsorption of GME, likely explaining the enhanced GME removal observed throughout the CPB circuit. Blood gas undersaturation is more important than denitrogenation alone [(1) (2) (3)].
The difference between a denitrogenated normobaric oxygen control condition and a denitrogenated or undersaturated hypobaric oxygenation condition. Hypobaric oxygenation does not change CPB circuit priming volumes, material composition, or ease of use.
The perfusionist controls Pao2 by adjusting the pressure of pure oxygen sweep gas rather than adjusting the sweep gas oxygen content, while Paco2 is still adjusted by varying the sweep gas flow rate.
As partial pressures of anesthetic vapors are also reduced in proportion to the sweep gas pressure, an adjustment of anesthetic concentration will be necessary to ensure adequate anesthesia [(1)].

As the oxygenator housing must be sealed in order to apply subatmospheric pressures, a suitable pressure relief system must exist to prevent gross air embolism in the event of occlusion of the sweep gas outlet or vacuum failure.
Application of overly negative sweep gas pressures could result in hemoglobin desaturation, the solution for which would be to increase the sweep gas pressure or disconnect the vacuum source.
Hypobaric oxygenation should be used along with, rather than instead of, arterial filtration in the CPB circuit. Among other benefits, arterial filtration reduces the size of GME, thereby increasing the surface-to-volume ratio and promoting rapid reabsorption under conditions of hypobaric oxygenation [(3)].

GASEOUS MICRO-EMBOLI AND BAROMETRIC ASPECTS IN ARTIFICIAL MEMBRANE LUNG

Gaseous microemboli (GME) may originate from the extracorporeal circuit and enter the arterial circulation of the patient. GME are thought to contribute to cerebral deficit and to adverse outcome after cardiac surgery.
The arterial filter is a specially designed component for removing both gaseous and solid microemboli. The arterial circulation receives thousands of 10 to 40 µm gaseous microemboli (GME) during cardiopulmonary bypass (CPB) despite the use of membrane oxygenation and arterial filtration.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9

Vasoocclusive GME cause tissue ischemia and denude endothelium in the brain and other end organs, leading to vascular dilation, increased permeability, activation of platelets and clotting cascades, and recruitment of complement and cellular mediators of inflammation.
As current technologies only partially remove GME from CPB circuits, we sought to develop a novel approach to eliminate GME using well-described principles of gas exchange [(4)].

The study "Elimination of Gaseous Microemboli From Cardiopulmonary Bypass Using Hypobaric Oxygenation" by Keith E. Gipson et al. used a variable subatmospheric pressures were applied to 100% oxygen sweep gas in standard hollow fiber microporous membrane oxygenators to oxygenate and denitrogenate blood.

GME were quantified using ultrasound while air embolism from the surgical field was simulated experimentally and assessed end-organ tissues in swine postoperatively using light microscopy. Variable sweep gas pressures allowed reliable oxygenation independent of carbon dioxide removal while denitrogenating arterial blood. Hypobaric oxygenation produced dose-dependent reductions of Doppler signals produced by bolus and continuous GME loads in vitro. Swine were maintained using hypobaric oxygenation for 4 hours on CPB with no apparent adverse events.

Compared with current practice standards of oxygen/air sweep gas, hypobaric oxygenation reduced GME volumes exiting the oxygenator (by 80%), exiting the arterial filter (95%), and arriving at the aortic cannula (~100%), indicating progressive reabsorption of emboli throughout the CPB circuit in vivo. Analysis of brain tissue suggested decreased microvascular injury under hypobaric conditions.

HYPEROXIA IN NBO AND HBO MANAGEMENT

Oxygen is one of the most commonly used therapeutic agents. Injudicious use of oxygen at high partial pressures (hyperoxia) for unproven indications, its known toxic potential, and the acknowledged roles of reactive oxygen species in tissue injury led to skepticism regarding its use [(5)].
A large body of data indicates that hyperoxia exerts an extensive profile of physiologic and pharmacologic effects that improve tissue oxygenation, exert anti-inflammatory and antibacterial effects, and augment tissue repair mechanisms [(6)] [(7)].

Delivery of oxygen to tissues depends on adequate ventilation, gas exchange, and circulatory distribution. When air is breathed at normal atmospheric pressure, most of the oxygen is bound to hemoglobin while only very little is transported dissolved in the plasma. On exposure to hyperoxia, hemoglobin is completely saturated with oxygen.
This accounts for only a small increase in arterial blood oxygen content. In addition, the amount of physically dissolved oxygen in the blood also increases in direct proportion to the ambient oxygen partial pressure. Due to the low solubility of oxygen in blood, the amount of dissolved oxygen in arterial blood attainable during normobaric exposures to 100% oxygen (about 2 vol%) can provide only one third of resting tissue oxygen requirements.
However, on exposure to oxygen at a pressure of three atmospheres, there is sufficient oxygen dissolved in the plasma (about 6 vol%) to meet the average requirements of resting tissues by means of dissolved oxygen alone without contribution from oxygen bound to hemoglobin [(8)].

This is part of the rationale behind the use of hyperoxia in situations in which the hemoglobin's oxygen-carrying capacity has been impaired (for example, in carbon monoxide poisoning and in severe anemia when transfusion of blood is not possible). Deliberations on the effect of hyperoxia on the availability of molecular oxygen to tissues

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
IJPDTM Vol.5 N°2 2022. For personal use only. No other uses without permission.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9

which are based on changes in arterial blood oxygen content undervalue the main effect of hyperoxia that is related to changes in its partial pressure in the blood. The flow of oxygen into tissues occurs by diffusion. The driving force for diffusion of oxygen is determined by its partial pressure gradient between capillary blood and tissue cells and much less so by increased oxygen content [(9)].
The use of 100% oxygen yields a 5- to 7-fold increase in arterial blood oxygen tension at normal atmospheric pressure and may reach values close to 2,000 mm Hg during hyperbaric exposure to oxygen at 0.3 MPa (3 ATA).

The marked increase in oxygen tension gradient from the blood to metabolizing cells is a key mechanism by which hyperoxygenation of arterial blood can improve effective cellular oxygenation even at low rates of tissue blood flow.
A recent surge of interest in the value of increasing the availability of oxygen to tissues in critical conditions yielded important studies like the one on early goal-directed therapy in sepsis that assessed a resuscitation protocol aimed at increasing tissue oxygenation [(10)].
Regrettably, the specific value of oxygen therapy was not assessed in this study. Yet a recent study that compared the influence of allogeneic red blood cell transfusion with 100% oxygen ventilation in volume-resuscitated anemic patients after cardiac surgery demonstrated a superior effect of normobaric hyperoxia (NBO) on tissue (skeletal muscle) oxygen tension.

PROS OF HYPEROXIA

Recent experimental evidence supports the role of hyperoxia in cerebral ischemic-anoxic insults such as stroke, head injury, near drowning, asphyxia, and cardiac arrest. In the specific case of traumatic brain injury, it has repeatedly been shown that, although hyperbaric hyperoxia (HBO) causes cerebral vasoconstriction, it increases brain tissue pO2 (partial pressure of oxygen) and restores mitochondrial redox potential. NBO has also been shown to decrease intracranial pressure and improve indices of brain oxidative metabolism in patients with severe head injury [(11)].
The availability of oxygen to tissues is also determined by its effects on hemodynamic variables. In healthy animals and humans, oxygen causes a temporary increase in blood pressure by increasing total peripheral vascular resistance secondary to systemic peripheral vasoconstriction. Tissue hypoxia activates a large variety of vascular and inflammatory mediators that trigger local inflammation and may lead to a systemic inflammatory response (SIR) that in many cases culminates in multiple organ dysfunction and multiple organ failure (MOF) [(12)].

The wish to prevent or treat hypoxia-induced inflammatory responses yielded studies that evaluated the effects of hyperoxia on the microvascular-inflammatory response.
Hyperoxia appears to exert a simultaneous effect on a number of steps in the proinflammatory cascades after IR, including interference with polymorphonuclear leukocyte (PMNL) adhesion and production of ROS [(13)] [(14)].
In this regard, HBO has been shown to decrease rolling and adhesion of PMNL in the microcirculation following IR of skeletal muscle, small bowel, skin flaps, heart, and liver as well as after carbon monoxide poisoning.

CONS OF HYPEROXIA

The major limitation confronting a much more liberal clinical use of hyperoxia is its potential toxicity and the relatively narrow margin of safety that exists between its effective and toxic doses.
However, an awareness of the toxic effects of oxygen and an acquaintance with safe pressure and duration limits of its application, combined with the ability to carefully manage its dose, provide an acceptable basis for expanding the current list of clinical indications for its use.
The most obvious toxic manifestations of oxygen are those exerted on the respiratory system and central nervous system (CNS) [(15)].
Oxygen toxicity is believed to result from the formation of ROS in excess of the quantity that can be detoxified by the available antioxidant systems in the tissues.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9

Although mechanisms of free radical damage to a substantial array of cellular systems (proteins, enzymes, membrane lipids, and nucleic acids) have already been characterized, large gaps exist in our understanding of the intermediate stages in the pathophysiologic cascades that follow such reactions and result in functional deficits and clinical phenomena [16].

The Lungs are exposed to higher oxygen tensions than any other organ. At exposures to ambient oxygen pressures of up to 0.1 MPa (1 ATA), the lungs are the first organ to respond adversely to the toxic effects of oxygen. The response involves the entire respiratory tract, including the airway epithelium, microcirculation, alveolar septa, and pleural space [17]. Pulmonary oxygen toxicity is characterized by an initial period in which no overt clinical manifestations of toxicity can be detected – termed the 'latent period'. The duration of this 'silent' clinical interval is inversely proportional to the level of inspired oxygen [18] [19].

CONCLUSION

This review summarizes the barometric and hyperoxia aspects during aML that set the basis for its use in CPB and ECMO. In contrast to a steadily growing body of mechanistic data on hyperoxia, the accumulation of high-quality information on its clinical effects lags behind.
The current list of evidence-based indications for hyperoxia during aML is much narrower than the wide spectrum of clinical conditions characterized by impaired delivery of oxygen, cellular hypoxia, tissue edema, inflammation, infection, or their combination that could potentially be alleviated by oxygen therapy.

Furthermore, most of the available reasonably substantiated clinical data on hyperoxia originate from studies on HBO which usually did not control for the effects of NBO.
Compared with current practice standards of oxygen/air sweep gas, hypobaric oxygenation in literature reduced GME volumes exiting the oxygenator, exiting the arterial filter, and arriving at the aortic cannula (~100%), indicating progressive reabsorption of emboli throughout the CPB circuit in vivo. Analysis of brain tissue suggested decreased microvascular injury under hypobaric conditions.

REFERENCES

1. Bitterman H. Bench-to-bedside review: oxygen as a drug. Crit Care. 2009; 13 (1): 205. doi: 10.1186 / cc7151.

2. Hendrix RHJ, Ganushchak YM, Weerwind PW. Contemporary Oxygenator Design: Shear Stress-Related Oxygen and Carbon Dioxide Transfer. Artif Organs. 2018 Jun;42(6):611-619. doi: 10.1111/aor.13084.

3. Gipson KE, Rosinski DJ, Schonberger RB, Kubera C, Mathew ES, Nichols F, Dyckman W, Courtin F, Sherburne B, Bordey AF, Gross JB. Elimination of gaseous microemboli from cardiopulmonary bypass using hypobaric oxygenation. Ann Thorac Surg. 2014 Mar; 97 (3): 879-86. doi: 10.1016 / j.athoracsur.2013.08.074. Epub 2013 Nov 6. PMID: 24206970; PMCID: PMC4294693.

4. Alex J, Laden G, Cale AR, Bennett S, Flowers K, Madden L, Gardiner E, McCollum PT, Griffin SC. Pretreatment with hyperbaric oxygen and its effect on neuropsychometric dysfunction and systemic inflammatory response after cardiopulmonary bypass: a prospective randomized double-blind trial. J Thorac Cardiovasc Surg. 2005 Dec; 130 (6): 1623-30. doi: 10.1016 / j.jtcvs.2005.08.018.

5. Tibbles PM, Edelsberg JS: Hyperbaric-oxygen therapy. N Engl J Med. 1996, 334: 1642-1648.

6. Borema I, Meyne NG, Brummelkamp WK, Bouma S, Mensch MH, Kamermans F, Stern Hanf M, van Aalderen W: Life without blood. Ned Tijdschr Geneeskd. 1960, 104: 949-954.

7. Weaver LK, Jopkins RO, Chan KJ, Churchill S, Elliot CG, Clemmer TP, Orme JF, Thomas FO, Morris AH: Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002, 347: 1057-1067.

8. Weibel ER: Delivering oxygen to the cells. The Pathway for Oxygen. Edited by: Weibel ER. 1984, Boston: Harvard University Press, 175-210.

9. Rivers EP, Ander DS, Powell D: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001, 345: 1368-1377.

10. Suttner S, Piper SN, Kumle B, Lang K, Rohn KD, Isgro F, Boldt J: The influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. Anesth Analg. 2004, 99: 2-11.

11. Lambertsen CJ: Effects of oxygen at high partial pressure. Handbook of Physiology: Respiration. Section 3. Edited by: Fenn WO, Rahn H. 1965, Bethesda, MD: American Physiological Society, 2: 1027-1046.

12. Bouachour G, Cronier P, Gouello, Toulemonde JL, Talha A, Alquier P: Hyperbaric oxygen therapy in the management of crush injuries: a randomized double blind placebo-controlled clinical trial. J Trauma. 1996, 41: 333-339.

13. Sukoff MH, Ragatz RE: Hyperbaric oxygenation for the treatment of acute cerebral edema. Neurosurgery. 1982, 10: 29-38.

14. Nemoto EM, Betterman K: Basic physiology of hyperbaric oxygen in brain. Neurol Res. 2007, 29: 116-126.

15. Daugherty WP, Levasseur JE, Sun D, Rockswold GL, Bullock R: Effect of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rat. J Neurosurg. 2004, 101: 499-504.

16. Rockswold SB, Rockswold GL, Defillo A: Hyperbaric oxygen in traumatic brain injury. Neurol Res. 2007, 29: 162-172.

17. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR: Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe brain injury. J Neurosurg. 2004, 101: 435-444.

18. Anderson DC, Bottini AG, Jagiella WM, Westphal B, Ford S, Rockswold GL, Loewenson RB: A pilot study of hyperbaric oxygen in the treatment of human stroke. Stroke. 1991, 22: 1137-1142.

19. Nighoghossian N, Trouillas P, Adeleine P, Salord E: Hyperbaric oxygen in the treatment of acute ischemic stroke. A double blind pilot study. Stroke. 1995, 26: 1369-1372.

This article was published on September 30, 2022, at IJPDTM.IT
doi.org/10.30459/2022-9