Hypoxemia During One-Lung Ventilation: Does it Really Matter?

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Abstract

Purpose of Review The human system of oxygen transport and metabolism is complex, and appropriate means to follow its single steps intraoperatively do not exist. Intraoperative tissue hypoxia is one of the leading dangers for patients receiving one-lung ventilation (OLV). Pulmonary, cerebral, or cardiac injuries may be the result. To summarize the current knowledge about the tolerable human limits of hypoxia, inside and outside the thoracic surgery room, is the purpose of this review.

Recent Findings High altitude mountaineers and apnea divers teach us that the healthy human body is able to acclimatize to and cope with severe hypoxemia to prevent fatal tissue hypoxia. The patients receiving OLV for thoracic surgery, however, are lacking adequate time for hypoxic acclimatization. Chronical medical conditions and effects of anesthesia prevent them further from exploiting their full hypoxia defense capacity. Controlled outcome studies on hypoxemia during OLV do not exist.

Summary Patients are no mountaineers. Thus, prevention of tissue hypoxia by avoiding relevant hypoxemia must be still the major goal during OLV. However, if permissive hypoxemia as a protection against perioperative oxygen stress could be tolerable in highly selected patients is the objective of current research.

Keywords Human limit of hypoxia · Acclimatization · Thoracic surgery · Thoracic anesthesia · Permissive hypoxemia · Intraoperative hypoxia

Introduction

Although non-intubated thoracoscopic surgery is currently being re-invented for minor thoracic procedures [1, 2], one-lung ventilation (OLV) in thoracic surgery is still the gold standard to improve access to the operational field. During the procedure, one lung is collapsed and not ventilated, though the perfusion through the non-ventilated lung is partly continuing resulting in a significant intrapulmonary shunt of non-oxygenated blood to a maximal extent of approximately 65% of the cardiac output [3]. This shunt, amongst others,

can result in a relevant hypoxemia in up to 10% of the procedures, rather arbitrarily defined as a decrease in arterial oxygen saturation (SaO_2) of the patient blood below 90% while being ventilated with a inspiratory oxygen fraction (FiO_2) equal or greater than 0.5 [4••, 5•]. However, if this SaO_2 threshold always indicates a life-threatening situation for the patient has to be questioned [6]. Nevertheless, it is not surprising that the rate of hypoxemia during one-lung ventilation is substantially higher as compared with a 1.9% hypoxemia rate, reported for a general surgical collective [7].

Hypoxemia during one-lung ventilation predominantly caused by pronounced shunting is generally difficult to treat [8]. The treatments of choice are either to re-inflate the operated lung or to raise the inspiratory oxygen fraction of the ventilated lung towards 1.0. However, intraprocedural re-inflation of the operated lung impairs the access for the surgeon to the operational field and may reduce the success of surgery. As alternative or rather supplemental approaches either intermittent positive airway pressure [9–11] or differential lung ventilation [12] can be applied to the dependent lung. The extra amount of oxygen in the non-ventilated lung boosts the oxygen content in the shunt.

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Though, excessively the raising of intraoperative FiO_2 with the intention to treat hypoxemia means to replace one evil by another. Oxygen is a powerful vasoconstrictor and the paradoxical situation may arise that hyperoxia (increased arterial oxygen partial pressure) leads to a reduced oxygen delivery to the vascular beds of various organs, especially of the brain or heart [13••]. Moreover, hyperoxia results in increased oxygen stress of the body and in particular of the lungs, resulting in the increased generation of resorption atelectasis [14, 15]. The increase of perioperative oxygen stress is furthermore caused by the generation of reactive oxygen species (ROS) and leads to molecular, cell, and organ damage [16]. However, it has been argued that ROS are not bad as a matter of principle but can be considered beneficial at low to moderate concentrations [17•]. Nevertheless, an increased perioperative risk for cardio-pulmonary complications and for a worse outcome was found in patients who underwent cancer surgery and received a high intraoperative oxygen therapy [18, 19].

Intraoperative oxygen stress represents harm both to the ventilated and predominantly to the collapsed lung and may finally lead to the acute respiratory distress syndrome (ARDS). At the end of the OLV procedure, an ischemia-reperfusion syndrome arises in the collapsed lung which is characterized by pathological capillary leakage and increased rates of leukocyte and platelet activation [20–23]. High inspiratory oxygen fractions, hyperoxemia, and hyperoxia are all known to aggravate the organ damage caused by an ischemia-reperfusion syndrome and should therefore be avoided as much as possible by the treating anesthesiologist.

Surgical procedures including OLV are in particular associated with a liberal oxygen therapy regime [24•]. A generally accepted minimum of SaO_2 below which hypoxemia appears has not been defined and the tolerable limits of hypoxemia during OLV of patients receiving thoracic surgery are not really known. In daily clinical work, the anesthesiologist is left to his own experience regarding at which SaO_2 he thinks hypoxemia starts to threaten his patient. He has to decide how far he accepts the SaO_2 to fall and at which level of hypoxemia, resistant to any therapy, he requests to adjourn or to stop the surgical procedure.

The Clinical Case

A male, 57-year-old, smoking (45 pack years) individual, who was free of other relevant medical conditions, suffered from a B2 thymoma with an UICC stadium IV-A. The large tumor mass in the left mediastinum infiltrated the left brachiocephalic vein leading to occlusion of the vessel and the generation of a distinct net of venous collaterals Fig. 1a. Furthermore, the tumor infiltrated the right cardiac ventricle. In a polysomnographic sleep study performed as part of the preoperative evaluation, the patient showed phases of

desaturation to a SO_2 minimum of 80%. On day of surgery, the patient received a thoracic epidural catheter and continuous epidural anesthesia was maintained with 1.8 mg/h ropivacaine and 1.2 µg/h sufentanil throughout the whole procedure. Total intravenous general anesthesia was induced intravenously with 200 mg propofol, 30 µg sufenanil, and 50 mg rocuronium and maintained with 4–8 mg/kg/h propofol, sufentanil, and rocuronium. The patient was intubated with a 37-French right-sided double lumen tube. One-lung ventilation of the right lung was performed during two subsequent phases throughout the course of the procedure. FiO_2 was always maintained between 0.9 and 1.0.

The resection of the tumor took place in supine position via a median sternotomy in combination with a left lateral thoracotomy. The large tumor mass for the most part, together with the left brachiocephalic vein and the left upper pulmonary lobe, could be removed. A pericardial patch was inserted into the superior cava vein.

The surgical procedure led to an extreme blood loss of approximately 24 L which required a mass transfusion of 36 units of packed red cells, 16 units of fresh-frozen plasm, two units of platelets, and 30 L of crystalloid fluids. Moreover, a continuous infusion of up to 1 µg/kg/min norepinephrine was necessary to maintain a circulation at least on a minimal level Fig. 1b.

Due to the circulatory instability of the patient, the tumor could not be fully removed and hypoxic harm to the brain of the patient caused by the simultaneous appearance of hypoxemic, anemic, and stagnant hypoxias was expected Fig. 1c. Following the procedure, the patient developed a strong systemic inflammatory response syndrome with a subsequent acute delirium. Surprisingly the patient recovered fast and was discharged from the hospital 1 month later without any cognitive sequela. However, the patient reported a significant vision loss of his right eye which had newly occurred after the procedure. A detailed ophthalmological examination revealed occurrence of a bilateral anterior ischemic optic neuropathy (AION). A therapeutically attempt with 1000 mg decortine was not successful. A postoperative computer tomographic angiographic scan of the head was free of any stenosis of the cerebral arteries and showed a regular brain parenchyma without any signs of stroke.

Tolerable Limits of Hypoxia

General Physiological Aspects of the Oxygenation of the Human Body

This case report begs the question of the tolerable limits of hypoxia in patients receiving a thoracic surgical procedure. Whereas this question can be easily answered for the healthy, conscious individual, it is difficult to give a satisfying answer
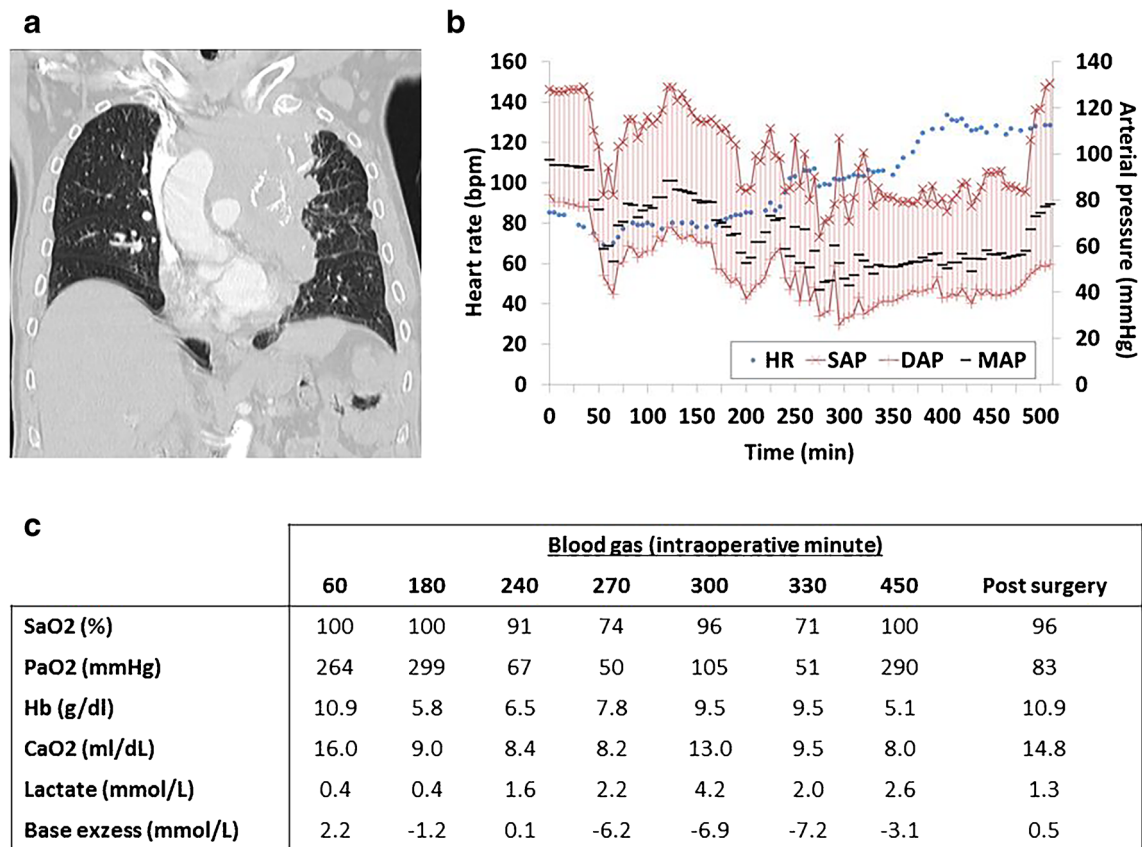
Fig. 1 **a** A computer tomographic scan with contrast agent of the thorax showing a mass (thymome) localized predominantly in the upper and medial left mediastinum. The tumor spreads into the left pleural cave and infiltrates the left brachiocephalic vein and the superior cava vein. **b** The intraoperative circulatory profile is showing a phase of prolonged arterial hypotension during the second half of the procedure (red upper and lower graphs represent systolic and diastolic arterial pressure, black horizontal dashes represent mean arterial pressure) accompanied by tachycardia (blue dots, heart rate). **c** Repetitive arterial blood gas analyses throughout the procedure including the oxygen content of the arterial blood (CaO2)

for the individual with pre-existing medical conditions undergoing a thoracic surgical procedure. In this context, hypoxia stands, in the first line, for tissue hypoxia of the two foremost hypoxia-vulnerable organs of the human body, namely the heart and the brain. First of all, it must be stated that the hypoxemia ($SaO_2 < 90\%$), which the anesthesiologist measures via pulse oximetry during anesthesia and surgery, does not necessarily indicate tissue hypoxia. The cause for a hypoxia is a mismatch between oxygen delivery (DO_2) to and oxygen consumption (VO_2) by the human body, a particular tissue or a yet smaller group of cells, respectively.

Relevant hypoxia appears whenever the oxygen demands of those biological units outweigh their actual oxygen supply. The situation is complicated by the fact that oxygen demand is not stable but highly variable and context sensitive, i.e., hypothermia versus hyperthermia or rest versus exercise. Cell death and severe, irreversible tissue damage are the results of prolonged oxygen under-supply of tissues. Especially the adult human myocardial and brain tissues lack almost from any global regenerative potential which makes their perioperative hypoxic damage in particular devastating [25, 26].

In the context of thoracic surgery, cell oxygen demands depend on several factors like existence of prescribed medication [27, 28], sepsis or systemic inflammation [29], body temperature, and kind and depth of anesthesia [30–33]. Unfortunately, the actual oxygen demand of the body during a thoracic surgical procedure stays largely obscured to the anesthesiologist because appropriate measurement means do not exist for clinical application. How much oxygen reaches the cell rests on the four pillars (I) oxygen transport capacity (blood hemoglobin content), (II) oxygen load of the oxygen carrier (hemoglobin saturation), (III) organ perfusion, and (IV) capillary oxygen partial pressure [34]. Impairments of one or more of these pillars lead to hypoxia, albeit not to a similar extent. Whereas a 50% reduction of the oxygen transport capacity (anemic anemia) is well tolerated under resting conditions, this is less the case for both a 50% reduction of the oxygen load of the hemoglobin (hypoxic hypoxia) and the organ perfusion (stagnant hypoxia), respectively. The least well tolerated kind of tissue hypoxia is caused by a direct reduction of the mitochondrial function (cytotoxic hypoxia) by carbon monoxide poisoning for instance [35].

For the case that several types of hypoxia exist at the same time, it is important for the anesthesiologist to consider that reductions in oxygen transport do not simply sum up but multiply each other. Reductions of 50% of the cardiac output, arterial oxygen saturation, and hemoglobin content each may lead to an overall reduction of oxygen delivery to one-eighth [36].

The Tolerable Hypoxic Limits of Healthy, Conscious, Individuals

For the understanding of the general hypoxemic limits of patients during thoracic surgery, disregarding of any preexisting diseases of these patients, the anesthesiologist can learn substantially from physiological studies of healthy individuals under extreme atmospheric environments [37]. Hypoxia is defined as a decrease of partial pressure of oxygen (pO_2, kPa, or mmHg) in the organ of interest, in contrast to hypoxemia which is the term for only a decrease of blood oxygen content (cO_2, mL/dL). To define the limits of tissue hypoxia, each organ should be looked at separately. The amount of oxygen delivered by blood to an organ is usually regulated via the perfusion of the organ. In the normoxic steady state of an organ, so called physioxia [38], oxygen delivery equalizes oxygen demands. When the oxygen demand of the organ outweighs oxygen delivery, tissue hypoxia appears [38].

The human brain can be seen as the index organ for the effects of hypoxia on the human body. However, the heart and the diaphragm are two other organs which are characterized by their well-known intolerance to hypoxia [39, 40]. Animal studies suggest that myocardial metabolism in hypoxia is maintained when the arterial oxygen content stays above 8 mL/dL [41]. However, sufficient myocardial adaptation to hypoxemia depends greatly on a well-maintained mean arterial pressure [42] and a coronary vasodilatory reserve. The human brain has one of the highest resting oxygen metabolic rates of the organs of the human body (3.5 mL O_2 per 100 g of brain tissue) but has no relevant oxygen stores available. Normal brain oxygenation can be assumed for cerebral tissue PO_2 above 35 mmHg and cerebral blood flow is immediately increased when brain tissue partial pressure of oxygen drops below approximately 30 mmHg. At a SaO_2 of 70% and a PaO_2 of 35 mmHg, respectively, the cerebral metabolism continues to depend almost exclusively on oxidative glucose metabolism without significant lactate accumulation [43]. Remarkably, high altitude mountaineers exceeding 7000 m are defending an alveolar PO_2 of 35 mmHg and avoid a further fall in alveolar oxygen partial pressure by a continuing increase in ventilation [44]. However, coma can result at tissue PO_2 levels below 20 mmHg [45].

The healthy, conscious human brain responds to acute hypoxemia via a rise in blood flow, an accelerated ventilator work, and an increase in oxygen extraction [46–48]. Reduced arterial oxygen content with deoxygenated hemoglobin as the primary oxygen sensor acts as chief regulator of cerebral vasodilation [49]. Thus, assuming a normal blood pressure regulation, the healthy human body is able to maintain oxygen delivery to the brain over a wide range of hypoxemia by increasing brain perfusion.

Interestingly, this response is diminished if arterial oxygen content decreases because of a hemodilution-induced fall of hemoglobin concentration instead of actual hypoxemia [49]. Considering that hemodilution is daily practice in thoracic anesthesia, this might influence the hypoxemic limits of the human brain during one-lung ventilation. When hypoxemia challenges the human, at altitude for instance, several defense mechanisms are activated including hyperventilation, shifting of the oxygen dissociation curve, hemoconcentration, and a rise in cardiac output by tachycardia [50]. Through these adaptation mechanisms, highly trained individuals have proven a fascinating high hypoxia tolerance of the human body. High altitude mountaineers were still able to maintain consciousness and elementary physical performance at an inspiratory PO_2 of 43 mmHg resulting in a mean SaO_2 of only 35% [51].

Cardiac pump function was preserved in subjects who undertook a simulated climb of Mount Everest in a hypobaric chamber [52]. On the actual top of Mount Everest, the arterial oxygen partial pressure in elite climbers, who returned from the summit without any irreversible neurological sequelae, was calculated as low as 28 mmHg [53]. The lowest ever measured arterial oxygen partial pressure and arterial oxygen saturation in a conscious individual were 19 mmHg and 34%, respectively, measured at 8400-m altitude during a summit attempt at Mount Everest [54]. Likewise, very low arterial oxygen saturations in healthy humans (50–70%) were reached in a protected laboratory environment for the purpose of testing of pulse oximetry devices. During these tests, the participants did not show any circulatory impairment or systemic acidosis [55•]. Elite apnea divers, with their lungs filled with room air, were able to stop breathing for up to 435 s resulting in a decrease of PaO_2 and SaO_2 to 23 mmHg and 34%, respectively [56•]. In contrast to hypocapnic hypoxemia in mountaineers, apnea divers develop hypercapnic hypoxemia which may better mimic hypoxemia usually seen in patients with chronic obstructive lung disease or obstructive sleep apnea.

The Tolerable Hypoxic Limits of Patients

It goes without saying that no systematic studies on the limits of hypoxia tolerance of patients or hypoxemic dose-response relationships have been performed due to ethical and safety constraints. The threshold of SaO_2 below which a clinically relevant hypoxemia exists has never been clearly investigated. Based on observations in healthy individuals, SaO2 values between 90 and 75% have been suggested to be safe

[57–59]. For example, the current guidelines for adult respiratory failure of the Extracorporeal Life Support Organization (ELSO) accept a hypoxemia with a SaO_2 of 75% if cardiac output and hemoglobin concentration are adequate [60]. The existence of tissue hypoxia has been suggested for the case that blood lactate concentration would rise above 2.2 mmol/L and central venous oxygen saturation would be less than 70% [61].

Nevertheless, a situation of intraoperative hypoxemia is difficult to interpret, because peripheral oxygen saturation and arterial oxygen partial pressure seem to have only a weak relation with cerebral oxygenation during one-lung ventilation [62]. Technical limitations of the cerebral near infrared spectroscopy technique may, at least in part, be responsible for this weak relationship and drops in cerebral oxygenation during one-lung ventilation could be less than it has been reported so far [63, 64•]. In accordance, a recent study was not able to find a relationship between postoperative cognitive decline and intraoperative cerebral desaturations and the authors question the rationale for avoiding intraoperative decreases in cerebral oxygenation [65]. Further advanced methods to continuously monitor circulation and oxygenation intraoperatively are still not part of clinical routine. In this context, methods for the simultaneous monitoring of parameters of global and local, organ specific parameters of oxygen delivery, oxygen demand, and production of anaerobic metabolites could be a step forward and enable an individualized oxygen therapy. Thus, our actual knowledge on hypoxic limits of patients is small and mainly generated out of clinical outcome experience with patients who suffered therapy refractory hypoxemia, as it is the case in our case report. In a case series of seven patients, no neurological sequelae associated with a therapy with extracorporeal membrane oxygenation and hypoxemia of an average SaO_2 of 79% lasting several days could be found retrospectively [66•]. Although global hypoxic damage of the heart or the brain virtually never happens intraoperatively as long as spontaneous circulation persists, regional hypoxic-ischemic events like stroke or heart attack are common threats [67].

In this regard, it is quite surprising how little is known about the effects on the healthy and diseased heart of hypoxia as opposed to ischemia [40]. Not only macroangiopathic but also microangiopathic diffuse cardiac disease can facilitate myocardial tissue hypoxia [68] but might be easily overlooked during preoperative evaluation. One study elucidating myocardial metabolism under hypoxemia during one-lung ventilation reported no clinically significant signs of myocardial ischemia in patients with multi-vessel coronary disease and drops in arterial partial pressure of oxygen down to levels between 50 and 70 mmHg. Therefore, the authors were unable to define a safety margin of tolerable minimal arterial oxygen partial pressure above the anaerobic threshold of the myocardial metabolism [69••]. This safety margin has to be considered to be clearly patient dependent. The myocardium of aged

humans, for instance, showed a reduced tolerance to ischemia and hypoxia [70]. Low left ventricular ejection fraction and high pulmonary vascular resistance were predictors for hypoxic events ($PaO_2 < 70$ mmHg) in patients undergoing robot-assisted coronary artery bypass grafting and requiring continuous OLV [71]. Several patient trials are currently underway to find a better answer on the question of the "best oxygen content" and if hypoxemia really matters [65, 72, 73].

Conclusions

Hypoxemia ($SaO_2 < 90\%$) happens regularly during anesthesia with a one-lung ventilation technique. Because of a lack of adequate, clinical measurement methods, the anesthesiologist is not able to instantaneously decide whether an intraoperative hypoxemia really matters in terms of the simultaneous existence of a relevant hypoxia of vital organs, like the brain or the heart. This is one of the reasons why the outcome of the patients with intraoperative desaturations during OLV has not been systematically studied yet. Although the healthy, conscious individual with a functioning cardiopulmonary system has a relatively high hypoxemia tolerance, the thoracic anesthesiologist cannot assume a similar hypoxemia tolerance for the majority of his patients undergoing thoracic surgery. Preexisting conditions like chronic heart failure, coronary or cerebral arterial disease, and anemia on the one hand, and the effects of surgery, anesthesia, and mechanical ventilation on the other, may prevent these patients to develop an appropriate physiological response to intraoperative hypoxemic stress. Nevertheless, a high hypoxemia tolerance has also been reported for certain patients, for instance individuals receiving an extracorporeal membrane oxygenation therapy.

The reverse, a too liberal intraoperative oxygen therapy leads to oxygen stress and may either harm the patient directly or boost the surgical induced inflammatory response syndrome. The intention of any oxygen therapy should be therefore the avoidance of a relevant tissue hypoxia, instead to simply treat the "symptom" hypoxemia. From this point of view, the lowest possible intraoperative oxygen therapy would be considered desirable. Though, the question if hypoxemia during one-lung ventilation really matters cannot be finally answered yet. So far, it can be concluded that moderate hypoxemia (SaO_2 90–75%) is tolerable by and maybe even useful in certain patients. However, better studies are urgently needed to investigate an individual "best oxygen content" concept for each patient receiving one-lung ventilation.

Compliance with Ethical Standards

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