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**Review article**

# INTRAOPERATIVE HYPOXEMIA DURING ONE-LUNG VENTILATION: IS IT STILL AN ANESTHESIOLOGISTS' NIGHTMARE? (HYPOXEMIA DURING ONE-LUNG VENTILATION)

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***Sažetak***

*Ventilacija jednog plućnog krila se koristi iz različitih hirurških i ne-hirurških razloga. Ovaj tip ventilacije nosi sa sobom određene rizike za razvoj ventilaciono/perfuzionih poremećaja različitog stepena povezanim sa lateralnim dekubitalnim položajem, jednostranom plućnom ventilacijom i otvaranjem grudnog koša. Kako je hipoksemija jedna od posledica jednostrane plućne ventilacije, različite strategije ventilacije se preporučuju u cilju njene prevencije i lečenja. Strategija uključuje određene manevre na ventilišućem i ne-ventilišućem plućnom krilu kao i upotrebu određenih lekova koji mogu modulirati i intenzivirati fenomen jedinstven za plućnu cirkulaciju- hipoksičnu plućnu vazokontrikciju (HPV).*

***Ključne reči:*** *hipoksemija, jednostrana ventilacija pluća, hipoksična plućna vazokonstrikcija*

***Sumarry***

*Lung isolation is used for various surgical and non-surgical reasons. This type of ventilation carries the risk for various degrees of ventilation/perfusion mismatch associated with lateral decubitus position, one-lung ventilation (OLV) and opened chest. According to this, hypoxemia is common consequence of OLV. Among various recommended ventilation strategies in order to prevent hypoxemia, protective ventilation with lower tidal volumes and applied positive end-expiratory (PEEP) pressure give some promising results. Adequate treatment and possibility to predict hypoxemia during OLV is very important for reducing morbidity and mortality. Treatment includes ventilator strategies on both, ventilated and non-ventilated lung and applied therapy, which can influence and modulate the magnitude of phenomenon unique for lung circulation - hypoxic pulmonary vasoconstriction (HPV).*

***Key words:*** *hypoxemia, one lung ventilation, hypoxic pulmonary vasoconstriction*

## *Pathophysiological mechanism of hypoxemia during one-lung ventilation*

One of the most challenging procedures for anesthesiologist is technique that includes isolation of one lung from ventilation (One Lung Ventilation – OLV). It is not easy to maintain adequate gas exchange during OLV and provide an optimal surgical field, so hypoxemia is an adverse but common consequence of OLV. Hypoxemia during one-lung ventilation (OLV) can be defined as an arterial hemoglobin oxygen saturation of less than 90%, which occurs in 5–10% of patients (that undergo this procedure).[1] The underlying patophysiological cause of hypoxemia is attributed to intrapulmonary shunt. [2]

Basic characteristics during anesthesia with OLV are lateral decubitus position, lung isolation and open chest. Using the double – lumen bronchial tube or bronchial blocker, the lower (dependent) lung is ventilated, whereas the upper (non-dependent) lung is allowed to collapse when opening the chest. Development of hypoxemia (i.e. arterial oxygenation < 90%, or $PaO_2$ < 60mmHg with FiO2=1.0) caused by OLV may be explained by taking into consideration: oxygen storage, dissociation of oxygen from hemoglobin, the relationship between ventilation and perfusion and factors that reduce the effect of hypoxic pulmonary vasoconstriction (HPV). [3]

Factors that potentially increase the risk of hypoxemia during OLV are: right-sided thoracic

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surgery and left side ventilation, high percentage of ventilation or perfusion to the operative lung on preoperative V/Q scan, normal preoperative spirometry, low $PaO_2$ during two lung ventilation (TLV) in lateral position, BMI>30kg/$m^2$, previous lobectomy and contralateral lung collapse surgery.[4]

### *Ventilation–perfusion mismatching*

The lateral position may significantly alter the normal pulmonary ventilation/perfusion ratio. This position in spontaneously breathing patient does not alter the ventilation–perfusion ratio, since the dependent lung receives more perfusion and more ventilation (contraction of the dependent parts of hemidiaphragm is more efficient) than the non-dependent lung. The relationship of ventilation and perfusion changes after induction of anesthesia. During controlled positive-pressure ventilation, in terms of ventilation the upper lung is in more favorable position because its higher compliance, whereas perfusion remains greater in the lower (dependent) lung. Use of neuromuscular blocking agents and opening the chest enhance this effect. Perfusion of the non-dependent lung without ventilation leads to development a large right-to-left intrapulmonary shunt and consequently to hypoxemia and hypercapnia.[5] Due to HPV clinically observed shunt fraction is lower than roughly half of the cardiac output (CO) that normally flows through each lung.[6] It is generally assumed that due to gravity 60% of blood will flow through the dependent lung, with the remaining 40% perfusing through the non-dependent lung. Because total shunt (10% of cardiac output) is roughly equally divided, 55% and 35% of CO participate in gas exchange, respectively. Ventilating the dependent lung only will result in loss of 35% of CO that participates in gas exchange (non-dependent lung). Hypoxic pulmonary vasoconstriction can decrease non-dependent blood flow by 50% (or 17.5% globally), thus the amount of CO available for gas exchange should only fall from 90% to 72.5%. That said, because of abdominal content, paralysis, anesthesia and the weight of mediastinal structures, the dependent lung has reduced FRC and is relatively non-compliant.[7]

### *The impact of ventilation strategy and patient positioning on intraoperative hypoxemia during one-lung ventilation*

In order to prevent acute lung injury (ALI) in thoracic anesthesia procedures, the concept of protective OLV has been widely adopted in the past few years.[8] This ventilation strategy includes the use of lower tidal volumes (5-6 ml/kg), positive end-expiratory pressure-PEEP (5-10cm $H_2O$), lower $FiO_2$ (50-80%) and permissive hypercapnia, The effects of this ventilation strategy on intraoperative hypoxemia still remains controversial [9,10] but it looks like hypercapnia, as part of a protective ventilation, is felt to improve HPV and therefore aid oxygenation.[11] Gao *et al.* showed in their study that therapeutic hypercapnia improves respiratory function, and mitigate OLV-related lung and systemic inflammation.[12] Using lower tidal volumes may be associated with derecruitment, worsening intraoperative atelectasis and intrapulmonary shunt, thus contributing to hypoxemia and hipercapnia.[13] This can be prevented by addition of PEEP which can reduce the incidence of atelectasis by preventing lung collapse. Also, prolonging the inspiratory time and adjusting the I:E ratio can be effective in improving oxygenation and reducing shunt fraction about one hour after starting the OLV.[14]

Although for now, there is not enough evidence about which ventilation mode is preferable, pressure-control ventilation (PCV) is thought to provide more uniform lung aeration and recruitment as well as lower risk of barotrauma by limiting the peak (<35 cm $H_2O$) and plateau airway pressure (<25 cm $H_2O$). Indeed, initial studies comparing PCV and volume-control ventilation (VCV) during OLV found improved oxygenation and shunt fraction with PCV[15], as well as the risk reduction for post-thoracotomy acute lung injury, but subsequent investigations failed to highlight benefit of PCV during OLV.[8, 16-18]

Traditionally, the lateral decubitus position has been found to improve oxygenation during OLV due to gravity redistribution of pulmonary blood flow with diverting roughly 10% of CO to the dependent lung.[19] On the other hand, Yatabe *et al.* found better $PaO_2/FiO_2$ ratios in patients undergoing oesophagectomy in prone position.[20] This finding may be explained by the superior V/Q

matching in the prone position[21] and the lack of compression of the ventilated lung by mediastinal structures.[22] Additionally, supine positioning during some thoracoscopic procedures also tends to increase the risk of hypoxemia during OLV.[23] However, recent animal experiments appear to suggest that anatomic pulmonary vascular factors are more important than gravity *per se* in terms of pulmonary blood flow distribution (it depends on lung volume, body position and PEEP). In the opposite of expectations, the blood flow through the dependent lung can be reduced. One of possible explanation is that the pressure of mediastinal structures could reduces ventilation of the dependent lug. This consequently provokes hypoxic pulmonary vasoconstriction and decreases blood flow.[24]

## *Treatment of hypoxemia*

### *Interventions directed to depended lung*

One of the most efficient ways to treat hypoxemia during OLV is alveolar recruitment maneuver of the dependent lung.[25] It can be applied before starting OLV with 10 breaths limited with plateau pressure of 40 cm $H_2O$ and PEEP in incremental levels of 5-10 cm$H_2O$ with maximum PEEP of 20 cm $H_2O$.[26] This maneuver can be continued on the dependent lung during OLV in a duration of 1 minute and application of 5 cm $H_2O$ PEEP.[27,28] By increasing the area of ventilated lung parenchyma, this maneuver improves gas exchange and arterial oxygenation. Furthermore, in major pulmonary resection, the alveolar recruitment maneuver has improved arterial oxygenation by reducing intrapulmonary shunt and dead space during OLV.[15,29] On the other hand, this strategy may lead to hemodynamic instability by decreasing the left ventricular preload, CO and arterial blood pressure[30,31], and may also cause barotrauma[32] and translocation of pro-inflammatory cytokines from the alveolar space into the systemic circulation.[33] We can conclude that dependent lung recruitment might be effective for arterial oxygenation improvement during OLV, however, its final effect can be transient.[34]

### *Interventions directed to non-depended lung*

When severe hypoxemia occurs, intermittent two-lung ventilation and application of continuous positive airway pressure (CPAP) to the non-dependent lung may be effective. Another advantage of using CPAP is that this maneuver reduces local immune response after OLV, as shown by Verhage *et al.* during thoracoscopic oesophagectomy.[35] However, this technique can interfere with surgical procedure, especially with video-assisted thoracoscopic surgery (VATS) since it impairs the view of the surgical field. This limits the use of CPAP of the non-dependent lung in clinical practice. In order to overcome this limit, modifications of the standard CPAP technique are proposed. These new techniques include a novel method of fibreoptic bronchoscopic selective oxygen insufflation into a bronchopulmonary segment in order to clear the surgical site[36] and intermittent small-volume oxygen insufflations.[37] In cases of disastrous desaturation, clamping the pulmonary artery may improve oxygenation.[38,39]

Making a compression on the nondependent lung by surgeons is one of the additional maneuver for improving oxygenation during OLV. This controversial strategy also decreases CO and systemic oxygen delivery, but Ishikawa *et al*. found that administration of an inotropic agent concomitant with lung compression mitigates the decreases in CO and systemic oxygen delivery, while maintaining the beneficial effect of lung compression on arterial oxygen saturation.[40] High-frequency jet ventilation and high-frequency percussive ventilation also appear successful in treating hypoxemia during OLV without impeding surgical exposure.[41, 42]

### *Medications*

Shunt fraction is the (most important) determinant of oxygenation during OLV and therefore agents which increase the pulmonary blood flow in the ventilated lung may significantly improve oxygenation. Selective vasodilatation of the pulmonary vascular bed may be achieved with inhalational agents. Inhaled nitric oxide (NO) has pulmonary vasodilating, bronchodilating and anti-inflammatory effects. Prostacycline and Alprostadil reduce pulmonary vascular resistance and improve oxygenation, however, all of these agents are expensive and can not be considered a readily available treatment.[43,44,45]

Almitrinine acts as a selective pulmonary vasoconstrictor which increases HPV and decreases

the shunt fraction. Intravenous infusion of 8 μg/kg/min of this agent significantly improves oxygenation. Some authors suggest the combination of almitrinine and NO, however, almitrinine is not yet commercially available in some parts of the world.[46,47]

Epidural dexmedetomidine has been shown to limit the decrease in $PaO_2$ during OLV without affecting systemic or pulmonary hemodynamic parameters.[48] This action of dexmedetomidine may be explained by nitric oxide dependent vasodilatation mediated by endothelial α 2-adrenoceptor activation.[49] Also, aerosolized epoprostenol has been shown to improve arterial oxygenation and decrease mean pulmonary artery pressure in patients with acute respiratory distress syndrome, presumably through dilation of the pulmonary vascular bed in ventilated regions and flow redistribution from shunt areas.[50] Despite limited reports, it seems that epoprostenol may improve critical desaturation during OLV[51] but larger clinical trials are required to establish its safety and efficacy profile during OLV.

### *The influence of anesthetic technique on HPV*

As previously stated, HPV is the most important intraoperative phenomenon in reducing shunt during OLV. This protective physiological reflex occurs with the aim to divert blood flow from hypoxic areas to the regions of better oxygenation and ventilation, and it can decrease the blood flow in non-ventilated lung for about 50%..(7) The stimuli for HPV are the alveolar oxygen tension and the partial pressure of oxygen in mixed venous blood, but it seems that the first one is more important. The threshold for HPV is alveolar oxygen tension of about 80mmHg, and maximum response is with $PaO_2$ of 25mmHg.[52] Various factors (anesthetic agent, CO, acid/base imbalance, lung manipulation, vasodilatators) can modulate the magnitude of HPV in the non-ventilated lung. Also, a series of physiological factors can influence the HPV mechanism, like: extracellular pH and $PCO_2$, temperature, age and iron status. Pulmonary arterial pressure is increased by hypercapnia, acidaemia, hyperthermia, lower age, iron deficiency.[53] Also, surgical trauma may lead to release of vasoactive metabolites and oppose HPV.[54] In animal studies, volatile anesthetics have been shown to impair HPV and to increase intrapulmonary shunt fraction or reduce arterial oxygen tension in a dose-dependent manner[55,56], while propofol does not seem to affect HPV. However, clinical investigations are contradictory regarding the effect of a given anesthetic agent on oxygenation.[57-61]

A combination of almitrin, which reinforces HPV in non-dependent lung areas and nitrous oxide in dependent lung, which reduces pulmonary vasoconstriction, may be useful during hypoxia and OLV. Use of almitirine as a selective lung vasoconstrictor is recommended when other strategies fail to improve hypoxemia.[62]

One of additional saving maneuvers that can be used for improving oxygenation during OLV is extracorporeal membrane oxygenation (ECMO). The major indications are: severe airway obstruction, emergence loss of airway, extended carinal pneumonectomy, severe emphysema undergoing lung volume reduction, acute respiratory distress syndrome undergoing thoracotomy and decortications, tracheoesophageal fistula repair after previous pneumonectomy, oesophagectomy after previous pneumonectomy, segmentectomy after previous contralateral pneumonectomy, thoracotomy after previous single-lung transplantation, thoracotomy with existing contralateral bronchopleural fistula and salvage therapy for severe chest trauma.[4]

## *Prediction of hypoxemia*

### *Capnometry*

The ability to predict which patients are most likely to have impaired arterial oxygenation would allow anesthesiologists to consider applying continuous positive airway pressure (CPAP) to the nondependent lung and positive end-expiratory pressure (PEEP) to the dependent lung at a very early stage in OLV. The percentage of non-dependent lung perfusion, is an important predictor of arterial oxygenation during OLV.[63] On the other hand, capnometry might be used to estimate the balance of blood flow to both lungs and to predict the occurrence of hypoxemia during OLV.[64,65] Two recent studies presented by Fukuoka *et al.* and Yamamoto *et al.* found a significant linear relationship between $ETCO_2$ and the $PaO_2/FiO_2$ ratio af-

ter starting OLV, as $ETO_2$ depends on perfusion, it can be predictable parameter OLV hypoxemia occurance.[61,66]

*Tissue oxygenation*

At present, cerebral oximetry is the only noninvasive monitor available to determine tissue oxygenation during OLV. Decreased levels of cerebral tissue oxygen saturation obtained by noninvasive cerebral oxygen monitoring were found in the majority of patients during OLV.[67] Further research which would determine the final end-organ effects of OLV on other organ systems are necessary and further technical development of noninvasive organ monitors is needed.

***Conclusion***

Besides carrying the risk of developing barotrauma, one lung ventilation (OLV) carries the risk of developing hypoxemia and hypercapnia due to intrapulmonary shunting and dead space ventilation. Both of these can have a significant effect on perioperative anesthesia management and postoperative complications. Today's techniques and medications can mitigate these consequences of OLV, but the problem that still remains is the lack of equipment in some medical centers and the fact that some medications are not available in all countries.

The key point in preventing postoperative complications in thoracic surgery is applying the right ventilatory strategy. There are no published guidelines, however, it seems reasonable to use protective ventilation mode to minimize the risk of lung trauma and acute lung injury (ALI). Despite the growing awareness of the importance of protective ventilation, many clinicians still use tidal volume and PEEP outside the recommended levels in everyday practice.

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