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Retrospective Clinical Study

Intraoperative Hypoxemia in Thoracic Surgery: Impact on early outcome

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ABSTRACT

Intraoperative Hypoxemia in Thoracic Surgery: Impact on early outcome.

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Introduction: Anesthesia for thoracic surgery presents specific challenges since anesthesiologists have to manage patients with several comorbidities, apply One Lung Ventilation (OLV) to facilitate surgery and at the same time they should try to maintain adequate safe oxygen levels. Hypoxemia is a common consequence of OLV. The aim of the present retrospective study was to investigate the impact of intraoperative hypoxia on the early outcome of patients. *Material and Methods:* In this study120 patients were included, who underwent thoracic surgical procedures with OLV and were assigned into two groups of 60 patients in each group. Group A consisted of patients who experienced severe hypoxia (PiO_2/FiO_2<100) during OLV, whereas Group B consisted of those who did not suffer from

hypoxia. ABG samples were collected intraoperatively at four different phases: Ph1: spontaneous breathing without any oxygen supply before intubation, Ph2: after initiation of mechanical ventilation, Ph3: during OLV and Ph4: immediately before being transferred from the operating theatre. Venous blood samples were collected at three phases: Ph1: after initiation of mechanical ventilation, Ph2: at the time of hypoxia occurrence and Ph3: immediately before being transferred from the operating theatre. During ICU stay, ABG samples were taken at four phases: Ph1: immediately after ICU admission, Ph2: before extubation, Ph3: after extubation and Ph4: before ICU discharge. *Results:* Intraoperatively, patients in Group B had better oxygenation compared to Group A at all phases. Moreover, during OLV patients in Group A experienced severe hypoxemia. Intraoperative PO_2/FiO_2 ratio in Group A was 369,8±69,9 / 279,4 ±91,5 / 68,3±11,8 / 324,7± 82,9 and at the corresponding phases the relevant values in Group B were 420,8±68,2 / 373,8±87,5/ 242,9±79,6 / 406,7±64,4. Partial pressure of oxygen in the central venous blood ($PcvO_2$) and Central venous oxygen saturation ($ScvO_2$) differed in a statistically significant manner between the study groups. However, $ScvO_2$ remained at acceptable levels even at the time of hypoxemia in Group A. $ScvO_2$ values in Group A were 78,7±9,1 / 66,8±79,7 / 73,3±5,82 and at the corresponding phases the relevant values in Group B were 87,1±7,2 / 79,8±7,8 / 81,8±7,5. Duration of mechanical ventilation in ICU was longer in Group A compared to Group B (5,34±5,1hrs vs 3,6±2,5hrs), whereas ICU and total hospital stay did not differ between study groups. *Conclusion:* Hypoxemia during OLV in Group A did not have a negative impact on early outcome of patients.

Keywords: Thoracic Anesthesia, One Lung Ventilation, Hypoxemia

INTRODUCTION

The majority of patients scheduled for thoraco-surgical procedures are heavy smokers with respiratory and cardiovascular comorbidities. During the operation, patients remain in lateral decubitus position for a prolonged period and one of the lungs becomes atelectatic. After surgery these patients, who underwent either lobectomy or pneumonectomy, have excess thick mucus and experience difficulties in clearing it from their lungs[1-6]. Respiratory (atelectasis, pneumonia, respiratory failure) and cardiovascular (arrhythmias, myocardial ischaemia) complications are the main causes of perioperative morbidity and mortality associated with cardiothoracic surgery.

One lung ventilation

One lung ventilation (OLV) is a standard approach applied in several operations such as thoracic, oesophagus, aortic and mediastinal surgery. OLV requires double lumen endotracheal tubes (DLT), endobrochial blockers, endobrochial intubation or endotracheal tube[7,8]. During OLV lungs are isolated and the independed upper lung is not ventilated but is per-

fused. The opening of the chest results in loss of negative intrapleural pressure, which causes the collapse of the upper independed lung[9].

In most of the cases volume control mode of ventilation (VCV) is used. Pressure Control Ventilation (PCP) has been also used in several studies. However, it has not been proven to be superior when compared to VCV[10-12].

In the past, mechanical ventilation with high tidal volumes has been used aiming to improve oxygenation since high tidal volumes keep the lungs open independed of whether PEEP was high or low[13].

Recently, according to relevant literature, it has become clear that high tidal volumes during OLV may be associated with an increase of postoperative respiratory complications[14-16].

Current ventilation strategies suggest low tidal volumes <8ml/kg, PEEP application and recruitment maneuvers for both protecting and keeping the lung open. Whereas there is an unambiguous positive effect of low tidal volume ventilation on the degree of lung injury, its effect on oxygenation still remains unclear[17,18].

Respiratory rate is determined to maintain normocapnia. Permissive hypercapnia refers to the ventilation strategy with low tidal volumes applied on ICU ARDS patients aiming to reduce airway pressures and lung injury. This strategy has been also studied in OLV patients with good results[19-21].

Since PEEP application reduces atelectatic regions and contributes to keeping the lungs open, it should be a standard routine in mechanical ventilation both in the setting of OLV and two lungs ventilation. A minimum level of 5cmH_2O PEEP should be applied on all patients. Thereafter, in case of hypoxia, PEEP levels should be titrated. Moreover, endogenous PEEP should always be taken into consideration[22].

Inrtaoperative hypoxemia

OLV has become a standard ventilation practice in daily clinical work. When OLV is applied, anesthesiologists are trying to preserve adequate oxygenation despite the fact that only one lung is ventilated. However, this not always feasible and 40-50% of the patients might experience some degree of hypoxemia. Nevertheless, the rate of severe hypoxemia has declined from 20-25% in the 1970s to 1% today. This is attributed mainly to better education and training of anesthesiologists in DLT placement, to the use of bronchoscope for confirmation of the correct DLT position, to the use of novel inhalational anesthetic agents, which cause a less significant inhibition of the Hypoxic Pulmonary Vasoconstriction (HPV), to better understanding of the relevant pathophysiological mechanisms and immediate application of appropriate management techniques[23].

Several predictive risk factors for hypoxemia have been recognized such as operation on the right lung, poor oxygenation during the period of two lungs ventilation, high ventilation (V) or perfusion (Q) ratio in the preoperative V/Q scan

of the lung which will be operated, normal preoperative FVC and FEV1 values and obesity.

The most significant predictive risk factor is the partial pressure of oxygen in the arterial blood (PaO_2), when patient is in the lateral decubitus position and two lungs ventilation is applied. In addition to that, another important parameter is the rate of PaO_2 deterioration after initiation of mechanical ventilation[24, 25].

Pulse oximetry is used for hypoxia detection but arterial blood gases (ABGs) are necessary for detailed oxygenation assessment[26].

Several strategies are used for hypoxia management such as:

- Confirmation of correct DLT position by the use of bronchoscope.
- FiO_2 increase in the depended lung.
- CPAP application on the independed lung.
- Oxygen insufflation in the independed lung.
- PEEP optimization in the depended lung.
- Intermittent re-expansion of the independed lung.
- OLV cessation and initiation of two lungs ventilation.
- Pulmonary artery occlusion (in lung resection operations)

For the efficient management of hypoxemia, quite often one intervention is not enough[27-33]. The combination of recruitment maneuvers, FiO_2 increase, PEEP increase and CPAP application on the independed lung seem to have the best results[34, 35].

Perioperative lung injury

Since the beginning of thoracosurgery, post-lobectomy or post-pneumonectomy pulmonary edema was recognized as one of the associated postoperative complications. Today this entity is described as perioperative lung injury, is defined as Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS) and is the main cause of death after thoracosurgical procedures[36].

Morbidity and mortality rates related to other postoperative complications such as atelectasis and pneumonia have been reduced over the years. However, this is not the case for lung injury[37, 38].

Lung injury pathophysiological mechanisms are different in the ventilated and the non ventilated lung[39, 40].

High tidal volumes ventilation, low tidal volumes associated atelectasis, hyperperfusion and oxidative stress response have been implicated in the lung injury pathogenesis of the lower ventilated lung[41].

Respectively, atelectasis, recruitment maneuvers, hypoperfusion, ischemia-reperfusion and surgical trauma can cause injury in the upper non ventilated lung. OLV duration is another important risk factor for lung injury. Excessive fluid administration has been associated with lung injury without clear evidence about this

association. Preventive measures could attribute to lower rates of occurrence[42, 43].

The aim of the present retrospective study was to investigate the impact of intraoperative hypoxia on the early outcome of patients.

MATERIAL AND METHODS

In this study 120 patients were included, who underwent thoracic surgical procedures in the Cardiothoracic Department of AHEPA University Hospital, Thessaloniki, Greece. Patients received either open surgery by thoracotomy or Video Assisted Thoracoscopic Surgery (VATS), underwent lobectomy, pneumonectomy or decortication for lung diseases (cancer, pneumothorax, empyema). Anesthesia induction and maintenance was performed by the same anesthetic agents in all patients. OLV by use of DLT was applied in all patients during the operation. Patients were assigned into two groups with 60 patients in each group, Group A & B. Group A consisted of patients who experienced severe hypoxia (PiO_2/FiO_2<100) during OLV, whereas Group B consisted of those who did not suffer from hypoxia.

ABG samples were collected intraoperatively at four different phases: Ph1: spontaneous breathing without any oxygen supply before intubation, Ph2: after initiation of mechanical ventilation, Ph3: during OLV and Ph4: immediately before being transferred from the operating theatre. Venous blood samples were collected at three phases: Ph1: after initiation of mechanical ventilation, Ph2: at the time of hypoxia occurrence and Ph3: immediately before being transferred from the operating theatre.

After the end of the surgery, all patients were transferred to ICU, where they were extubated after a short time period.

During ICU stay, ABG samples were taken at four phases: Ph1: immediately after ICU admission, Ph2: before extubation, Ph3: after extubation and Ph4: before ICU discharge.

Other recorded parameters included, hemodynamic variables, fluid balance, need of any vasoactive support, surgery duration, OLV duration, ICU mechanical ventilation duration, ICU and total hospital stay.

SPSS 25 was used for the statistical analysis. Analysis of variance (ANOVA) was used as a statistical method to evaluate the alterations of recorded quantitative parameters over time. Mean values and standard deviation (SD) were calculated and diagrams depicting the alterations of the parameters over time were created. Statistical significance was set at 0.05 or 5%. Thereafter, values lower than 0.05 were considered statistically significant. In addition to this, 95% confidence intervals which did not overlap were considered to be correlated with mean values that show statistically significant difference. All statistical tests were performed two sided. Chi-square test (x^2) was used for the statistical analysis of quality parameters.

RESULTS

OLV by the use of DLT was applied to all patients. Group A consisted of patients who expe-

rienced severe hypoxia, whereas Group B consisted of those who did not suffer from hypoxia. Demographic data and variables related to the surgical procedure, anesthesia management, ICU and total hospital stay are depicted on Tables 1-3. As far as preoperative variables are concerned, there were statistically significant differences between the study groups on the incidence of diabetes mellitus, on the specific indication for surgery and on the side of surgery (Table 1). With regard to the side of surgery, more patients in Group A were operated on the right lung compared to Group B (Table 2).

Table 1. Patient characteristics and preoperative variables.

Variable	Total	Group A	Group B	P value
Number of patients	120	60	60	
Age	57,8±16,3	58,2±16	58,2±16	0,78
Gender (M/F)	92/28	44/16	48/12	0,38
BMI	26,2±4,7	26,7±4,6	25,6±4,7	0,21
ASA/PS	2=15 3=105	2=10 3= 50	2=5 3=55	0,16
FVC preop	80,1± 17,4	77,7±15,3	81,9±18,9	0,31
FEV1 preop	76,6±17,2	76,3±15,6	76,8±18,5	0,9
Smoking				0,09
Yes	65	31	34	
No	23	16	7	
Former	32	13	19	
Lung Disease				0,003
Lung cancer	78	35	43	
Pneumothorax	21	8	13	
Empyema	12	12	0	
Other	9	5	4	
CO morbidities				
Hypertension	48/72	29/31	19/41	0,06
Coronary artery disease	8/112 16/104	3/57 12/48	5/55 4/56	0,46 0,03
Diabetes mellitus	5/115	4/56	1/59	0,17
Renal failure	35/85	20/40	15/45	0,31
Other				
Medication	61/59	35/25	26/34	0,1

M: male, F: female, BMI: body mass index, ASA/PS: American society of Anesthesiology/physical status, FVC: forced vital capacity, FEV1: forced expiratory volume in one second, preop: preoperatively, p<0,05: statistical significance.

Table 2. Intraoperative Variables.

Variable	Total	Group A	Group B	p value
Number of patients	120	60	60	
Operative technique				
Thoracotomy	99	47	52	0,23
VATS	21	13	8	
Site of operation:				
Right lung/Left lung	78/42	49/11	29/31	0,000
Operation				
Lobectomy	49	24	25	
Pneumonectomy	7	2	5	
Tumor Resection	20	11	9	0,8
Pleurodesis	28	15	13	
Other	16	8	8	
Duration of OLV (min)	160±88,4	144,8±87,3	175,7±87,9	0,59
Duration of operation (min)	264,2±110	244,5±102	284,2±116	0,53
Fluids intraoperative (ml)	5676±1717	5449±1547	5908±1860	0,14
Urine output intraoperatively (ml)	1488±1077	1468±1205	1508±940	0,84
Transfusion Yes/No	19/101	8/52	11/49	0,45
pRBC (Units)	2,1±0,9	2,2±1,2	2,1±0,7	0,7

OLV: One lung ventilation, pRBC: packed red blood cells, p<0,05: statistical significance.

Duration of mechanical ventilation was longer in Group A, whereas ICU stay did not differ statistically significant between study groups.

Three patients in Group A died, one of which suffered massive pulmonary embolism. None of the patients in Group B died (Table 3).

Table 3. Postoperative variables.

Variable	Total	Group A	Group B	p Value
Number of patients	120	60	60	0,08
Mechanical Ventilation (hr)	4,5±4,1	5,34±5,1	3,6±2,5	0,03
ICU stay (hr)	14,1±10,9	13,5±9,4	14,5±12,5	0,62
Hospital stay (day)	8,2±4,2	8,9±4,8	7,5±3,3	0,08
Mortality	3/120	3/60	0/60	

ICU: Intensive Care Unit

PaO_2/FiO_2 ratio showed statistically significant differences both in the way it changed over time and when compared between Groups (Figure 1 & Table 4).

Figure 1: Intraoperative PO_2/FiO_2 ratio alterations.

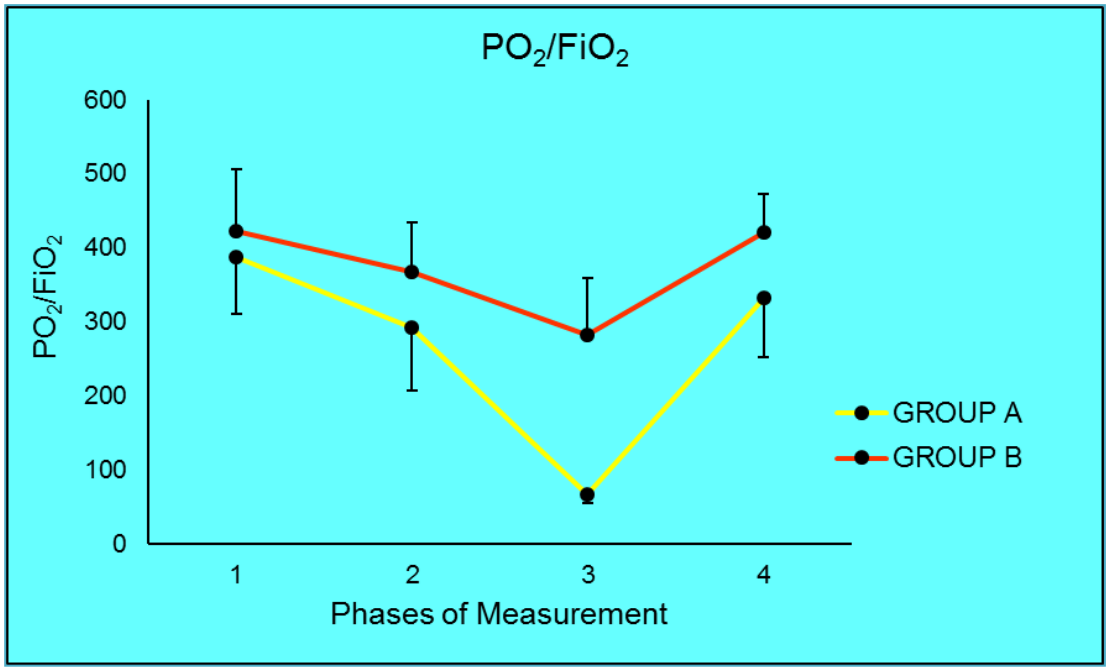


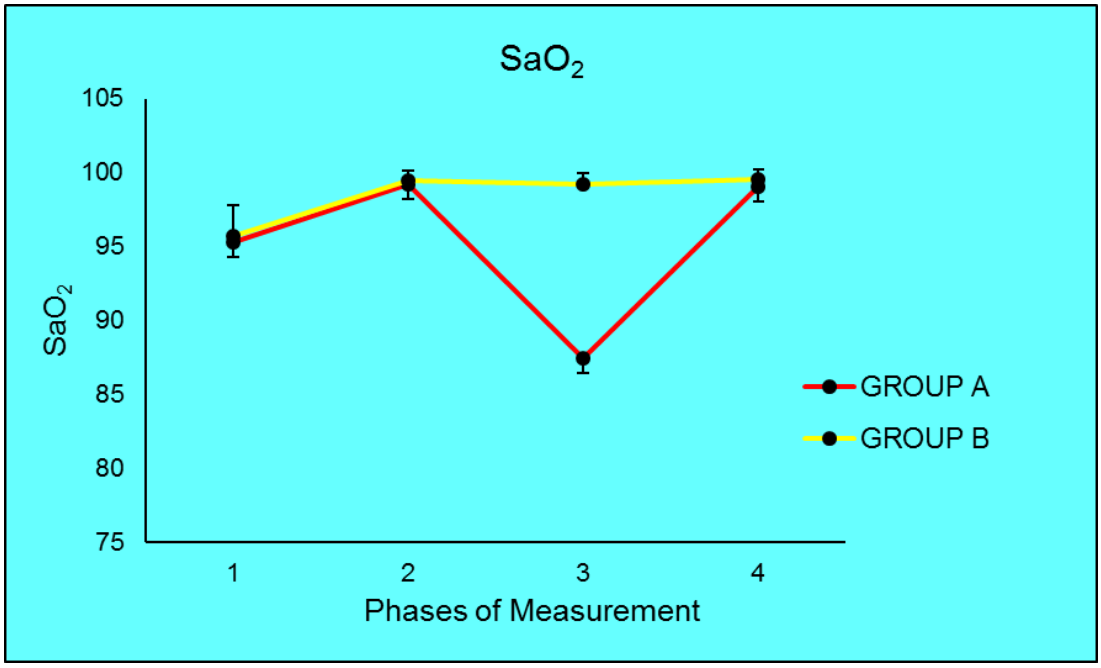
Table 4: Intraoperative descriptive statistics of PO_2/FiO_2 ratio

Phase	Group	Mean	SD	SE	Median	95 Confidence Interval	
						Lower	Upper
1	A	369,8	69,9	9	360,9	351,7	387,9
	B	420,8	68,2	8,8	418,8	403,1	438,4
p value	A vs B	p<0,001					
2	A	279,4***	91,5	11,8	274,5	255,7	303
	B	373,8**	87,5	11,3	386,5	351,2	396,4
p value	A vs B	p<0,001					
3	A	68,3***	11,8	1,5	68,5	65,2	71,3
	B	242,9***	79,6	10,2	229,5	222,3	263,4
p value	A vs B	p<0,001					
4	A	324,7***	82,9	10,7	340	303,3	346,1
	B	406,7	64,4	8,3	412,5	390,1	423,4
p value	A vs B	p<0,001					

*At each phase following comparisons were made: (i) Comparison to corresponding baseline value for each group, (ii) Comparison between study groups. Asterisks indicate statistically significant difference against baseline (*** p<0,001).*

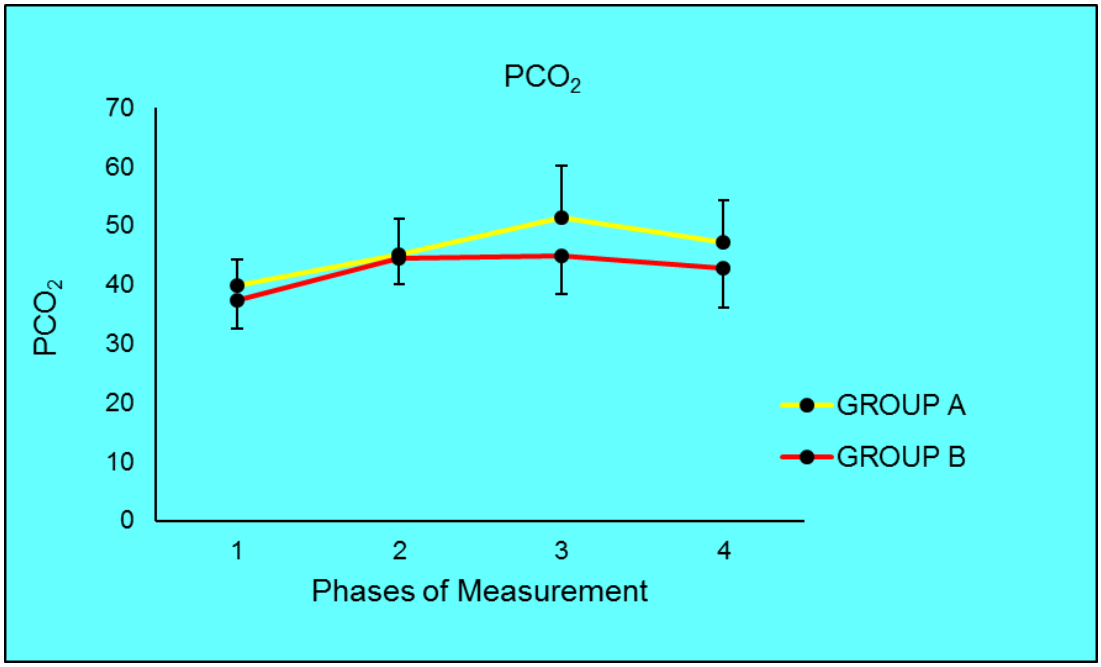
Arterial oxygen saturation (SaO_2) changed in a different way over time. However, hypoxia (<90%) occurred only in Group A at Phase 2 (Figure 2).

Figure 2. Intraoperative SaO_2 alterations.



Partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) showed statistically significant alterations over time. Nevertheless, the difference between study groups was not statistically significant (Figure 3).

Figure 3. Intraoperative $PaCO_2$ alterations.



Alterations of partial pressure of oxygen in the central venous blood ($PcvO_2$) and Central venous oxygen saturation ($ScvO_2$) are depicted on Figures 4 and 5 respectively.

PO_2/FiO_2 ratio during ICU stay changed over time compared to baseline in both groups and there were statistically significant differences at most of the study phases between groups (Table 5). Similarly, $PaCO_2$ and SaO_2 values changed over time compared to baseline in both groups but there were no statistically significant differences at any study phases between groups.

Figure 4. Intraoperative $PcvO_2$ alterations.

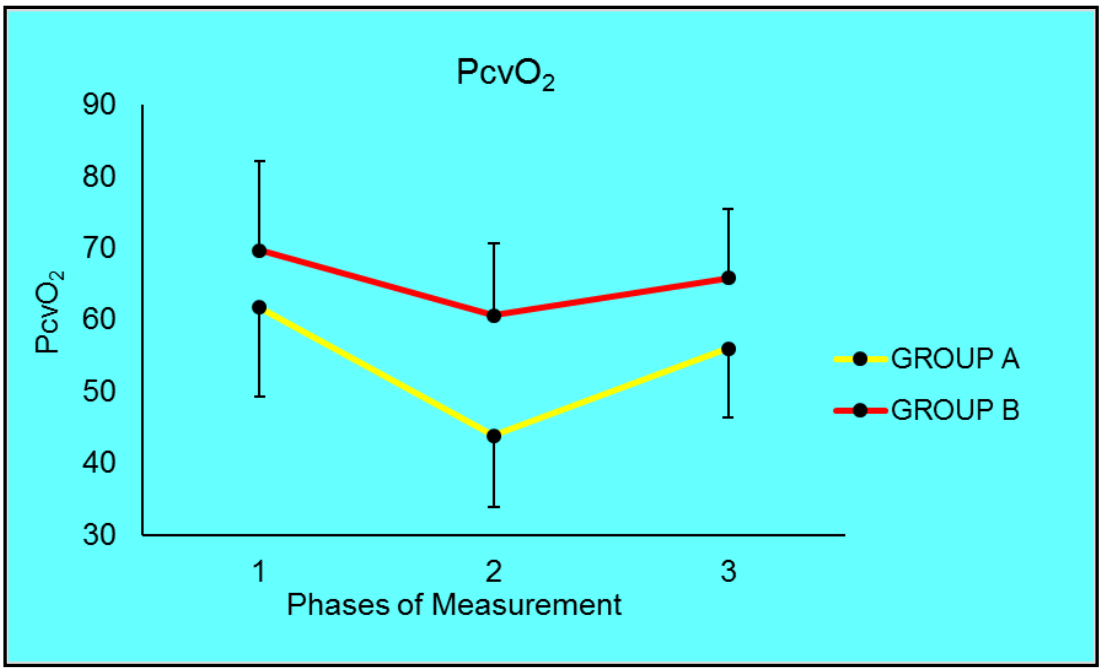


Figure 5. Intraoperative $ScvO_2$ alterations.

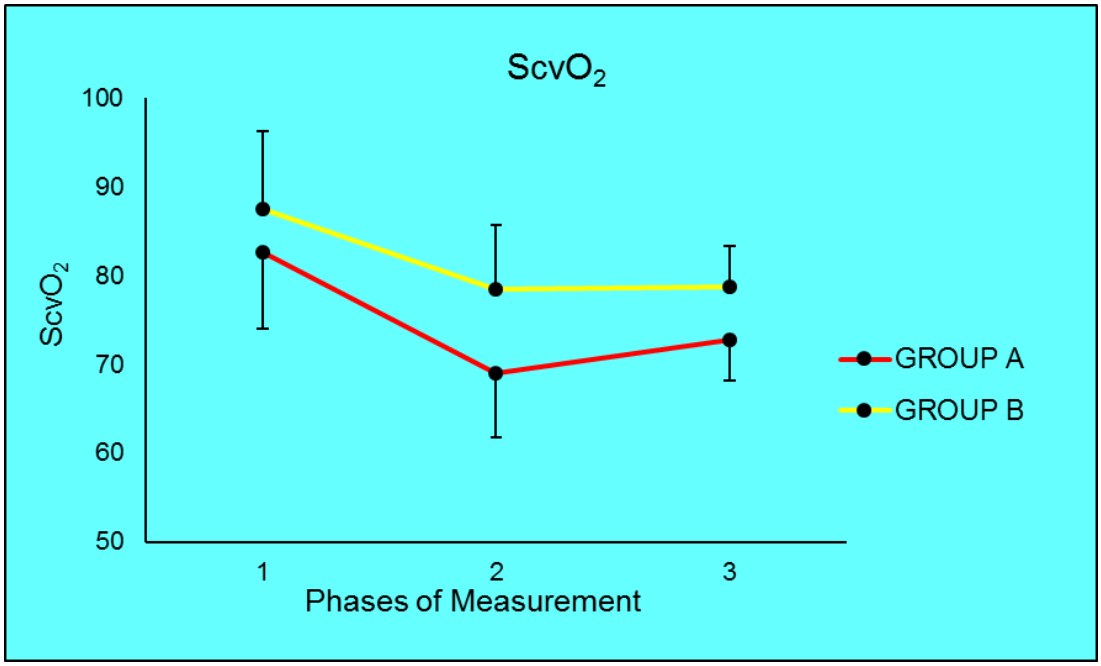


Table 5. Descriptive Statistics of postoperative PaO_2/FiO_2 ratio.

Phase	Group	Mean	SD	SE	Median	95 Confidence Interval	
						Lower	Upper
1	A	361,2	115,6	14,9	369,5	331,3	391
	B	412,5	75,6	9,7	420	392,9	432
p value	A vs B	p=0,05					
2	A	336,3	95,6	12,3	348,8	311,5	361
	B	362,1**	100,2	12,9	378	336,2	388
p value	A vs B	p=0,15					
3	A	306,8**	106,1	13,7	389,2	279,4	334,3
	B	368,8**	112,1	14,5	364,6	339,8	397,8
p value	A vs B	p=0,002					
4	A	330,1	112,2	14,5	300	301,1	359,1
	B	340,1**	65,4	8,4	334,4	323,1	356,9
p value	A vs B	p=0,55					

*At each study phase following comparisons were made: (i) Comparison to corresponding baseline value for each group, (ii) Comparison between study groups. Asterisks indicate statistically significant difference against baseline (** p<0,01).*

DISCUSSION

OLV is an approach which on the one hand facilitates surgery but on the other hand causes oxygenation impairment. It results in collapse of the independed lung and in an increase of the atelectatic regions of the depended lung, which unavoidably lead to intrapulmonary shunt increase and subsequent oxygen impairment[35,44].

OLV has an impact on ventilation and on perfusion of both lungs[45]. OLV diverts ventilation from the upper (independed) lung to the lower (depended) lung), while the independed lung continues to receive perfusion. Nervertheless, due to gravity and to the HPV reflex, the depended lung receives most of the perfusion. In the best case scenario shunt magnitude is 20-25% of the cardiac output[26,46, 47].

Occurrence of hypoxia is common during OLV and is ranging from 5 to 10%. It should be mentioned that to some degree the incidence of hypoxia is influenced by its definition[33,48,49]. Immediately after OLV initiation, oxygenation is impaired but gradually it gets improved by the activation of HPV reflex[47,50,51].

Usually, intraoperative hypoxia is well tolerated by patients on the precondition that there is no

hypoperfusion[52]. However, intraoperative hypoxia has been incriminated as a cause for postoperative complications[53].

A hundred and twenty patients were included in this study, which were assigned into two groups of 60. Patients in Group A experienced intraoperative hypoxia, whereas patients in Group B did not. Patients underwent thoracosurgical procedures for lung diseases under general anesthesia and mechanical ventilation. During the operation OLV was applied by the use of DLT[48,54].

In both groups lung protective mechanical ventilation with the same settings was applied throughout the whole surgery and in the ICU. VCV was selected and ventilation settings entailed a VT of 8ml/kg during two lungs ventilation and 5ml/kg during OLV with the PEEP level set at 5cmH_2O. Protective lung ventilation with low tidal volumes and addition of PEEP is a standard of care for mechanical ventilation during thoracosurgical procedures since it reduces lung injury[55]. Different ventilation modes have been applied in thoracosurgery without any of those having been proven to be superior[10,56].

Hypoxia was defined as PaO_2/FiO_2 ratio<100 (Normal PaO_2/FiO_2 ratio is approximately 400-500mmHg). PaO_2/FiO_2 ratio is used in ARDS for the definition of hypoxia as well as in several severity scoring systems (SOFA, SAPS-II and SAPS-III[57]. The advantage of using PaO_2/FiO_2 ratio is that it is relatively easy to calculate. However, its usefulness is questioned mainly because PaO_2/FiO_2 ratio is not involved in any biological procedure and no human organ is able to detect it[58].

Based on the fact that during OLV oxygenation is impaired, most of the researches define hypoxia as the state of arterial oxygen saturation (SaO_2) below 90% or PaO_2 below 60mmHg on FiO_2=1[33,35].

In the clinical setting, when patients are under general anesthesia it is not possible to determine the exact level of accepted hypoxia for each patient[35,52,59].

As far as demographic data, laboratory tests and spirometry results, there were statistically significant differences between the study groups only on the surgical site, on indication for surgery and on comorbidities. Namely, more patients in Group A were operated on the right lung compared to Group B.

Right sided thoracotomy is one of the three most important factors affecting occurrence of hypoxia during OLV[25,33].

Since the right lung is larger than the left one, oxygenation is expected to be better in left sided thoracotomies, during which the lower (ventilated) lung is the right one[24,25].

Most of the patients in both groups were smokers (either active or former). FVC, FEV1 and preoperative laboratory values did not differ statistically significant between groups.

Similarly, OLV and surgery duration and data related to diuresis and fluid administration did

not show any statistically significant difference between the study groups.

Intraoperative PaO_2/FiO_2 ratio showed a statistically significant change over time against baseline values and moreover differed statistically significant between groups at all study phases. Patients in Group B had better oxygenation both during spontaneous ventilation and during two lungs ventilation. Impaired oxygenation during two lungs ventilation is another risk factor for the occurrence of hypoxia during OLV[25,61]. Application of recruitment maneuvers before OLV could improve oxygenation[13,55,62].

There were statistically significant differences on SaO_2 between the study groups. However, this significance became clinically relevant only during OLV, when SaO_2 was less than 90% in Group A.

$PaCO_2$ showed a statistically significant increase over time during OLV but without any statistically significant differences between groups. Lung protective mechanical ventilation with low VT during OLV causes a $PaCO_2$ increase, which is well tolerated by patients who do not suffer from severe health conditions[20,63]. Special attention should be given to patients with pulmonary hypertension or intracranial pathology.

$PcvO_2$ alterations over time were similar to those of PO_2/FiO_2 ratio.$ScvO_2$ values were kept at acceptable levels in both groups despite the fact that there were statistically significant differences between the study groups. $ScvO_2$ is used instead of SvO_2 and reflects the balance between oxygen delivery (DO_2) and oxygen consumption (VO_2) [64-66]. Actually, it is a global oxygenation indicator.

Oxygenation of patients in ICU differed between study groups only at the time point of ICU admission. Oxygenation was the only indicator of the recorded ABG parameters in ICU which differed statistically significant. At Phase 1 the increase of PiO_2/FiO_2 in Group B was statistically significant but marginal. This difference became really important at Phase 3. Recruitment maneuvers and lung re-expansion at the end of OLV seemed to improve oxygenation in Group A. However, this improvement was not maintained after extubation.

In thoracosurgery, intraoperative recruitment maneuvers are widely used in clinical practice to improve oxygenation. Nevertheless, their positive effect is not maintained after the release of positive pressure[67-69].

Mechanical ventilation duration was longer in Group A, but ICU and total hospital length of stay did not differ between study groups. None of the patients developed ARDS postoperatively.

Postoperative respiratory failure after thoracosurgical procedures is considered to be the most severe complication since it is associated with increased mortality rates, which have not declined over the years[38,39].

Three patients in Group A died, one suffered massive pulmonary embolism, a second patient

was operated for empyema and the third one for lung abscess. Based on the medical history of those patients, deaths cannot be related to perioperative hypoxemia.

Limitations of the study

Group A included 12 patients, who were operated for empyema (one of those had lung abscess). Their oxygenation was impaired due to the underlying pathology. PO_2/FiO_2 ratio calculation is not reliable, when oxygen is being administered via a face mask since it is difficult to determine FiO_2.Oxygen needs, duration of additional oxygen therapy (in case that additional oxygen was supplied) and blood oxygen levels were not recorded after ICU discharge during hospitalization in wards.

CONCLUSION

According to the results of the present study, hypoxia during OLV does not have a negative impact on early outcome of patients undergoing thoracic surgical procedures, on the precondition that there is no underlying pathology.

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Acknowledgements:

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Authors' contributions:

DM drafted the paper and is the lead author. FB contributed to planning and the critical revision of the paper. FCh contributed to planning and the critical revision of the paper. KI contributed to planning and the critical revision of the paper. TS contributed to planning and the critical revision of the paper. AI contributed to planning and the critical revision of the paper. KK contributed to planning and the critical revision of the paper. GV contributed to planning and the critical revision of the paper.

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Availability of supporting data:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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No IRB approval required, patients consent obtained.

Competing interests:

The authors declare that they have no competing interests.

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