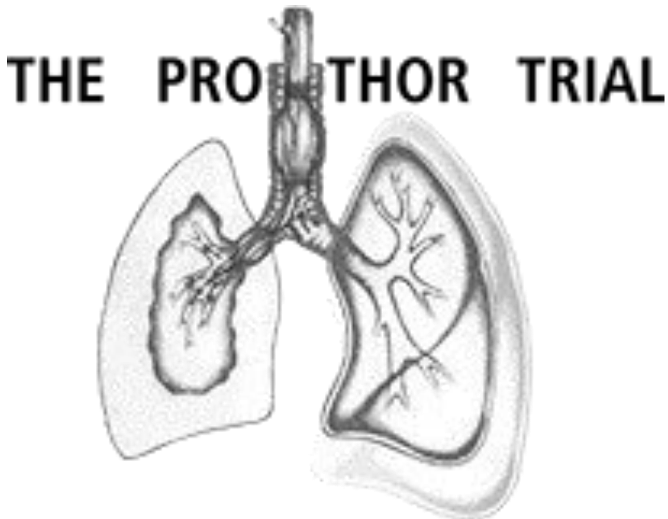
The effect of high PEEP on hemodynamic stability during OLV: a sub-analysis of the PROTHOR Trial.



A sub-analysis

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Abstract

Introduction: During thoracic surgery, one-lung ventilation (OLV) provides a ventilation strategy enabling optimal surgical exposure. However, evidence for optimal mechanical ventilation is scarce. Due to its potential beneficial effect on postoperative pulmonary complications (PPC's), intraoperative high PEEP (10 cmH_2O) with recruitment maneuvers (RM's) versus low PEEP (5 cm H_2O) is compared in the PROTHOR Trial. Higher PEEP is, however, associated with deteriorating intraoperative hemodynamics. This sub-analysis investigates whether higher PEEP in the PROTHOR Trial induces hemodynamic instability (HI) during OLV compared to low PEEP.

Methods: Patients eligible for the PROTHOR Trial were included. A validated HI-score including hemodynamic parameters, fluid therapy and cardiovascular medication was used to compare both cohort groups. At the start of OLV (T_0) the first HI-score was calculated and every hour consecutively. Analysis was conducted for every timepoint (T_X), the mean HI-score and the mean gradient between T_0 and the last T_X to adjust for different durations of surgery.

Results: At the moment of analysis, 33 patients were included of which 32 underwent lung surgery. All included characteristics such as gender, age, weight and ASA-score, total duration of anesthesia and duration of OLV were equally distributed between both groups. No significant variation in HI-score at any individual T_X was found; nor for the mean HI-score (P= 0.602) or gradient (P= 0.375).

Discussion: In this study, HI in the high PEEP group (10 cmH_2O) was comparable to the low PEEP group (5 cmH_2O) during OLV in thoracic surgery. However, many factors are still subject for further study and physicians should act with caution when applying PEEP in OLV.

Abbreviations

AE	Adverse Event
ANOVA	Analysis Of Variance
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CI	Confidence Interval
DLT	Double Lumen Tube
FiO_2	Fraction of inspired oxygen
HI	Hemodynamic Instability
HR	Heart Rate
I:E	Inspiratory-Expiratory rate
MAP	Mean Arterial Pressure
OLV	One Lung Ventilation
PBW	Predicted Body Weight
PEEP	Post End-Expiratory Pressure
P_{IT}	Intrathoracic Pressure
PPC	Postoperative Pulmonary Complication
P_{plat}	Plateau Pressure
PROTHOR	PROtective ventilation with high versus low PEEP during one-lung ventilation for THORacic surgery
RM	Recruitment Maneuver
RR	Respiratory Rate
SAP	Systolic Arterial Pressure
SD	Standard Deviation
TLV	Two Lung Ventilation
VILI	Ventilator Induced Lung Injury
V_T	Tidal Volume

Introduction

While performing thoracic surgery, adequate ventilation of the patient whilst providing an optimal field of surgery can be challenging. One lung ventilation (OLV), introduced by physiologists for application in dogs in 1871, and the usage of a double lumen tube (DLT), concepted in 1889, provides a ventilation strategy for over 80 years.[1]
Despite its extensive practice, OLV is still associated with an increased risk of hypoxemia and postoperative pulmonary complications (PPCs).[2,3]

Mechanical ventilation during OLV includes several determinants that can be adjusted to optimize ones oxygenation and lung protection individually. Examples of these determinants are the ventilation mode, the tidal volume (V_T), the inspiratory-expiratory rate (I:E) and the respiratory rate (RR). But also the fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP) and the use of recruitment maneuvers (RM). Standardized settings for the above-mentioned parameters are used globally with only very limited evidence.[4,5]
Although mechanical ventilation is necessary for patients in respiratory distress or during general anesthesia, it can cause lung injury. This is known as ventilator-induced lung injury (VILI).[6,7] Supposedly this is caused by both atelectrauma - collapsing and reopening of alveoli - and by overdistention of these lung units -, also known as volutrauma.[8] Using lower V_T might lead to reduced volutrauma.[9,10] PEEP is thought to act similarly for atelectrauma. Unfortunately, as before mentioned, evidence for the latter is still scarce.[4,5]

The PROTHOR Trial is an international multicenter randomized controlled trial (RCT). The study compares high PEEP (10 cmH_2O) with recruitment maneuvers to low PEEP (5 cmH_2O) without recruitment maneuvers and low V_T (5 mL/kg predicted body weight) in both groups. The PROTHOR Trial hypothesizes that high PEEP in adult patients undergoing thoracic surgery under standardized OLV prevent PPCs and therefore is superior.[3]

Although its potentially beneficial effect on PPCs both high PEEP and RMs are associated with affecting cardiac output and thus hemodynamics. Therefore, with the PROTHOR Trial, intra-operative hemodynamic instability (HI) is considered one of the most important risks.[3]

Both high levels of PEEP as RM's decrease cardiac output through three different mechanisms: reduced systemic venous return, increased pulmonary vascular resistance and ventricular interdependence.[11]
Increased intrathoracic pressure (P_{IT}) caused by RMs and PEEP is transmitted through the right atrium and the central veins, reducing the systemic venous return and therefore the right ventricular preload. [11,12]
A higher P_{IT} also raises the pulmonary vascular resistance; increasing right ventricle afterload. This could potentially lead to an increase in right ventricular end-diastolic pressure and thus negatively affect the systemic venous return.[11,12]
The lack of right ventricular preload directly alters the supply of blood to the left atrium, resulting in a decreased left ventricular preload and therefore reduced left ventricular cardiac output. Besides a decreased right and left ventricular preload and increased right ventricular afterload, a final mechanism named ventricular interdependence occurs.
Due to overfilling of the right ventricle and the diminished left ventricular preload, the intraventricular septum potentially shifts to the left. Resulting in a larger right

ventricle yet a more limited left ventricle. This leads to a further decrease in left cardiac output and affecting the mean arterial pressure (MAP) consequently. [11-13] RMs are performed by stepwise increasing V_T till a plateau pressure (P_{plat}) of 30 cmH_2O is reached. If necessary PEEP can be titrated so a P_{plat} of 30 cmH_2O can be maintained for 30 seconds.[3]

Extensive research on RMs and their effects on hemodynamics has been conducted. Likewise is known for the effect of high PEEP (>12 cmH_2O) on HI versus lower PEEP (<5cm H_2O). Both RMs as high PEEP proved to have a strong correlation with HI. However, in previous studies comparing a considerable small difference in PEEP, similarly to the only 5 cmH_2O as in the PROTHOR Trial, a significant discrepancy in hemodynamic effects is often not identified.[14,15]

Whether a patient is categorized as hemodynamically stable or unstable is subjective and usually determined by parameters as blood pressure, heart rate and cardiac output. In attempt to objectify HI, Buitenwerf et al. (2019) recently developed and validated an hemodynamic instability score (HI-score).[16]

This sub-analysis investigates whether high PEEP (10 cmH_2O) induces more HI than low PEEP (5 cmH_2O) in adult patients undergoing thoracic surgery while under OLV. We hypothesize that the high PEEP group produces an higher HI-score throughout OLV than the low PEEP group.

Methods

Inclusion

For this sub-analysis of the PROTHOR Trial, patients were prospectively included. and eventually who have written consent for participation in the PROTHOR study were used. Inclusion criteria were patients with an age $\geq$ 18 years and a body mass index <35kg/m^2, who were scheduled for elective thoracic surgery under general anesthesia requiring OLV with a DLT and an expected duration of surgery >60 minutes.[3]

Exclusion criteria were COPD Gold III or IV, NYHA classification III or IV and history with previous lung surgery. As well as documented pulmonary arterial hypertension, neuromuscular disease, intracranial injury or tumor and pregnancy. Patients undergoing surgery as esophagectomy, pleural, mediastinal or chest wall surgery only, lung transplantation, bilateral procedures or any other planned lung separation other than DLT were excluded. Lastly, patient enrollment in another interventional study or presence of an adverse event (AE) before induction were reason for exclusion.[3]

At the start of the sub-analysis 26 patients were already included for the PROTHOR Study. Based on the progress of inclusions in the previous months predictions were that approximately every two weeks a new patient would be included. Therefore another 6-10 patients in the months following were estimated to be included. According to the PROTHOR study protocol, just prior to surgery, patients were randomized for either the control cohort (PEEP 5 cmH_2O) or the intervention cohort (PEEP 10 cmH_2O with RM's). This approach minimized lost to follow-up whilst randomization was already performed.

Predicted potential confounders and effect modifiers were based on their association with PPCs in previous studies. Included were age, gender, weight, American Society of Anaesthesiologists (ASA)-score, duration of total anesthesia and duration of anesthesia while on OLV.[17-19]

Measurements

During lung surgery all patients were under continuous monitoring of their hemodynamic parameters with an artery line and of their FiO_2, CO_2 return, V_T, RR, I:E, P_{plat} and PEEP among other parameters through the mechanical ventilator. Both the control group as well as the intervention group patient's variables were noted at the following specific moments in time: at induction, in final surgical position in TLV, 10 minutes after switching to OLV, every hour in OLV and at the end of surgical procedure in supine position returned to TLV. RM's in the intervention cohort were conducted on similar intervals: after bronchoscopy in TLV, at the start of OLV, every hour in OLV, just before reinflating the operated lung, at the end of surgery in supine position on TLV and following each disconnection from the mechanical ventilator.[3]

Hemodynamic instability score

The beforementioned HI-score by Buitenwerf et al. (2019) takes the following hemodynamic variables: systolic arterial pressure (SAP), MAP and heart rate (HR) into account. The HI-score also focusses on volume therapy and commonly used vasoactive medication: norepinephrine, phenylephrine and dobutamine.
The above mentioned three domains, weighted at 40-30-90 points respectively according to their effect on hemodynamics, produce a score ranging from 0 to 160 points.
The continuous variables do not make a distinction between hemodynamic stability versus instability. Rather do they make it possible to compare different groups on their parameters and need for volume therapy and/or cardiovascular medication. This makes the HI-score ideal for analyzing the two groups in this sub-analysis (fig 1).[16]

Domain	HI-score component	Value	Score
Haemodynamic variables	Maximum SAP (mmHg)	<160	0
		160 to 179	1
		180 to 199	3
		≥200	7
	Time SAP > 160 mmHg (%)	0	0
		0.1 to 1.0	1
		1.1 to 6.6	3
		≥6.7	7
	Minimum MAP (mmHg)	≥60	0
		50 to 59	1
		40 to 49	3
		<40	7
	Time MAP < 60 mmHg (%)	0	0
		0.1 to 1.1	1
		1.2 to 4.1	3
		≥4.2	7
	Maximum HR (bpm)	<100	0
		100 to 119	1
		≥120	3
	Time HR > 100 bpm (%)	0	0
		0.1 to 1.0	1
		>1.0	3
	Minimum HR (bpm)	≥50	0
		40 to 49	1
		<40	3
	Time HR < 50 bpm (%)	0	0
		0.1 to 1.7	1
		>1.7	3
Volume therapy	Volume therapy ($ml\,kg^{-1}\,h^{-1}$)	0 to 84 $ml\,h^{-1}$	0
		≤6.3	2
		6.4 to 9.7	6
		9.8 to 14.3	14
		>14.3	30
Cardiovascular medication	Norepinephrine ($\mu g\,kg^{-1}\,h^{-1}$)	0	0
		>0 to 1.48	5
		1.49 to 2.47	15
		2.48 to 4.14	35
		>4.14	75
	Phenylephrine ($\mu g\,kg^{-1}\,h^{-1}$)	0	0
		>0.0 to 2.06	4
		>2.06	12
	Dobutamine ($mg\,kg^{-1}\,h^{-1}$)	0	0
		>0 to 0.22	1
		>0.22	3
	Total		0 to 160

Fig 1: Composition of the HI-score.
HI-score, hemodynamic instability score; HR, heart rate: MAP, mean arterial pressure; SAP, systolic arterial pressure.[16]

Data extraction

This sub-analysis focusses on the effect of PEEP on hemodynamics during OLV. Therefore the HI-score was calculated at the start of OLV (T_0) and every hour after that (T_1, T_2, T_3 or T_4) . The scores were determined just before performing RMs, hereby superseding the effect of RM's. When the second lung was reinflated in 59 minutes or less for return to TLV, no score was calculated.
At every T_X the score was based on the hemodynamic variables, fluid therapy and

cardiovascular medication in the hour preceding, starting at the previous T_X. Every 15 minutes the fluid and cardiovascular medication was updated in the system, thus the sum of these values was divided by four to obtain an average of that hour. Hemodynamic parameters were measured continuously and were analyzed for violation of the thresholds displayed in fig 1. If so, the maximum value of the trespassing parameter and the amount of time beyond the thresholds was calculated as a percentage of that hour to obtain a score.
At T_0 the variables where used at the end of TLV. Usually OLV was induced in less than an hour after induction. T_0 was considered a baseline measurement of the patient's hemodynamics at the beginning of surgery.

Analyses
To establish equal distribution of the continuous variables over both groups, Gaussian curves were used.
The data was presented as means with standard deviations (SD) when normally distributed. Medians with interquartile ranges were used when data appeared non normally distributed. Either unpaired *t*-tests or Mann-Whitney U Tests were performed for the continuous variables depending on the distribution as a Gaussian or non-Gaussian population, respectively. The binomial variables were tested for significance by the Fisher's Exact Test. Significance was established when $P \leq 0.05$.
HI-scores were assessed and compared between both groups at the individual T_X. Firstly, the Levene's Test for equality of variance was deducted. Significance between the groups was tested with an independent sample *t*-test.
To analyze the overall exposure to high or low PEEP during OLV, an average HI-score was calculated. Both outcomes were assessed with an independent sample *t*-test as well.
Whether the PEEP level increased or decreased the HI in the subjects, the HI-score at the last timepoint (T_{end}) was compared to T_0. This gradient, calculated as $T_{end} – T_0$, in both groups was examined for significance with an independent *t*-test.
These analyses compare the effect of high versus low PEEP on HI at individual timepoints as well as during the whole period of OLV.

Results
At the moment of data analysis, 33 patients were included (fig 2). One patient's operation was cancelled just prior to planned surgery.
The remaining 32 patients were randomized either in the control cohort (N = 17) or the intervention cohort (N = 15). Table 1 shows that variables such as gender, age, ASA-score, duration of total intraoperative anesthesia and duration of OLV were not different between groups.

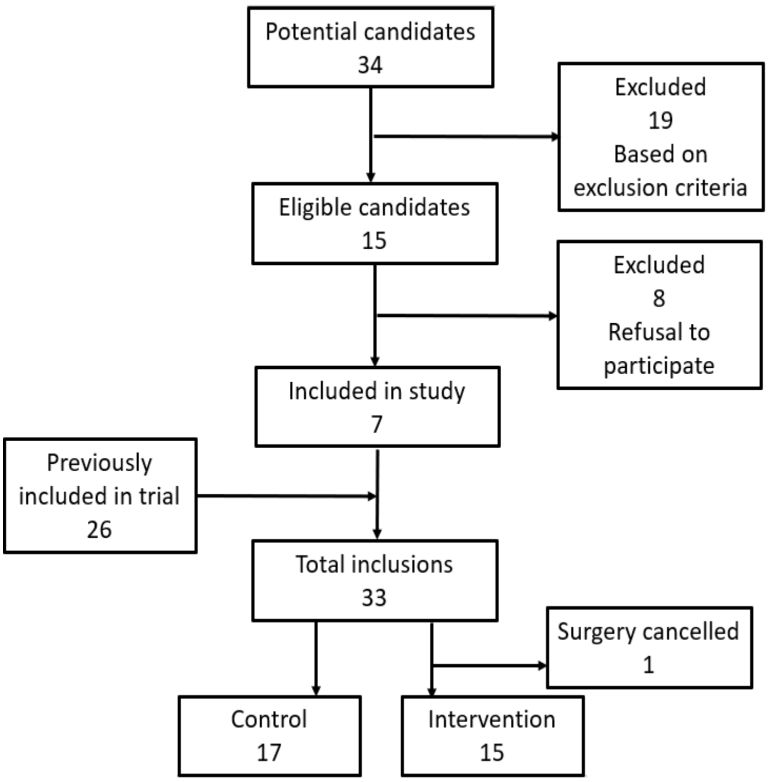


Fig 2: Flow chart of inclusions.

		Baseline characteristics						
		Control group			Intervention group			
		Count N=17	Table N %	Median (P25-P75)	Count N=15	Table N %	Median (P25-P75)	Sig.
Gender	Male	9	28,10%		9	28,10%		.735
	Female	8	25,00%		6	18,80%		
Age (18 - 99 yrs)		17	53,10%	61 (59-73)	15	46,90%	59 (45-71)	.478
Weight (Kg)		17	53,10%	78 (73-88)	15	46,90%	82 (75,8-88)	.655
ASA-score (1-2-3-4)	ASA 1	2	6,30%		0	0,00%		.142
	ASA 2	14	43,80%		11	34,40%		
	ASA 3	1	3,10%		4	12,50%		
	ASA 4	0	0,00%		0	0,00%		
Total anesthesia duration (in min)		17	53,10%	209 (172-254)	15	46,90%	196 (157-238)	.502
Duration of OLV (in min)		17	53,10%	153 (103-189)	15	46,90%	106 (65-161)	.216

Table 1: Baseline characteristics: distribution of variables over both cohorts.
P 25, 25th percentile; P 75, 75th percentile; Sig., significance; yrs, years; ASA, American Society of Anaesthesiologists; OLV, one-lung ventilation.

Table 2 shows the mean HI index, stratified per timepoint. T_4 was only present in the intervention group and therefore not included in further analysis. The mean HI in T_0 and T_3 are higher in the intervention cohort than in the control cohort. In T_1 and T_2, the situation is reversed.

		N	Mean	SD
T_0	Control	16	29	12
	Intervention	15	41	30
T_1	Control	16	49	33
	Intervention	13	36	28
T_2	Control	12	42	32
	Intervention	6	37	34
T_3	Control	7	32	35
	Intervention	3	42	37
T_4	Control	0		
	Intervention	1	7	

Table 2: Average hemodynamic instability scores of both cohorts per T_X.
SD, standard deviation.

Table 3 concludes the independent *t*-test for each T_X, comparing the intervention with the control cohort.
No significant difference in HI between the two cohorts can be established at any T_X; T_0, P = 0.154; T_1, P = 0.254; T_2, P = 0.767, T_3, P = 0.692 and all 95% confidence intervals (CI) include 1, substantiating the non-significance (table 3).
The differences in means reflect whether the control or intervention group averages higher in the HI-score. A negative mean difference signifies a higher HI-score for the intervention cohort over the control at that T_X and a positive mean difference vice versa, as corresponding with the results in table 2.
Table 4 shows the overall HI-score over the OLV period between the two groups. A mean of 43 points for the high PEEP cohort is found versus a mean 38 points for the low PEEP cohort. However, the mean difference is not significantly higher (P= 0.602).

		Levene's Test for Equality of Variances	Independent sample *t*-tests			
		Sig.	Sig.	Mean Difference	95% CI Lower	Upper
T_0	Equal variances not assumed	0,001	0,154	-13	-30	5
T_1	Equal variances assumed	0,296	0,254	13	-10	37
T_2	Equal variances assumed	0,718	0,767	5	-30	40
T_3	Equal variances assumed	0,830	0,692	-10	-66	46

Table 3: Comparison of hemodynamic instability scores per T_X between groups.
Sig., significance (P); 95% CI, 95% Confidence Interval.

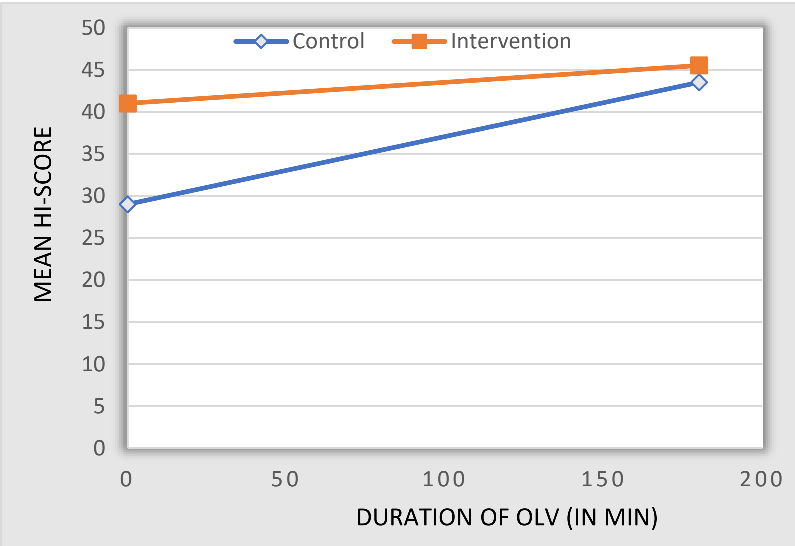
		N	Mean	SD	Sig.
Average HI-score during OLV	Control	16	38	22	0,605
	Intervention	15	43	29	

Table 4: Average HI-scores over the total OLV period and an independent sample *t*-test.
HI-score, hemodynamic instability score; OLV, one-lung ventilation; SD, standard deviation; Sig., significance (P).

		N	ΔMean	SD	Sig.
T_{end} - T_0	Control	16	12	31	0,375
	Intervention	15	4	19	

Table 5: Difference in hemodynamic instability scores between T_0 and T_{end} and an independent sample *t*-test.
ΔMean, difference in mean; SD, standard deviation; Sig., significance (P).

When comparing the course of HI during OLV between T_0 and T_{end}, the control cohort (12 points) has a greater difference (ΔMean) than the intervention cohort (4 points). A higher score indicates a steeper gradient benefiting ones HI-score.
Either the average control patient started with an lower HI-score or they stabilized further than the average intervention patient did. Notably is the standard deviation in the control group greater as well (table 5).
However, no difference between both groups can be found (P = 0.375).
Graph 1 shows clearly the steeper gradient between T_0 (0 in graph) and T_{end} in the control group.



Graph 1: The course of the mean HI-scores at T_0 and T_{end}.
HI-score, hemodynamic instability score; OLV, one-lung ventilation; min, minutes.

Discussion

As demonstrated above no difference can be found in HI during lung surgery while under OLV between low PEEP (5 cmH_2O) and high PEEP (10 cmH_2O) with low V_T during thoracic surgery.
Nor at the start of OLV coming from TLV, nor during surgery and when comparing overall gradients.
Even though the gradient of HI during OLV is three times higher in the control group, the high standard deviation shows great variability within the groups.
Possibly the lack of significant difference in HI-scores between cohorts is caused by the group size of this sub-analysis with only 33 inclusions. Also the relatively small difference in PEEP (5 cmH_2O) between both groups could not differentiate the HI-score significantly. Another reason for these results which is not specific for this study could be the individual reaction to PEEP. The effect on HI of incremental PEEP is known to differ greatly among patients, even on allegedly very high levels of PEEP.

The above findings are in agreement with current literature. Often a greater difference between groups is used, such as PEEP of 4 cmH_2O versus 12cmH_2O and/or include larger research populations. Still significant differences in HI with these criteria is not frequently found.[3,5,14,20]

This sub-analysis has some limitations and therefore could strongly influence the interpretation its results.
A pronounced default of this sub-analysis is its group size. With just 33 inclusions its caliber is too limited to make serious statements about the effect of PEEP on HI during OLV.
Besides this, the statistical analysis is not completely adequate. To analyze all timepoints at the same time while comparing both groups, a Mixed Analysis of Variance (ANOVA) would be appropriate. This test includes both within-subject variables as between-subject variables.
Unfortunately too many missing values, due to different durations of OLV, made this impossible. This resulted in testing between-subject variables at only individual moments of time. Or, as in the last analysis, determining the gradient between two specific moments.

Another limitation is the HI-score used in this sub-analysis. The HI-score consists of intra-operative hemodynamic parameters, fluid therapy and the use of cardiovascular medication. This make this score the most comprehensive score thus far, yet still not all inclusive. For example, during anesthesia in the hospital where this sub-analysis is performed, often cardiovascular medication not included in the HI-score was used. Medication as ephedrine or epinephrine are not covered in the HI-score while these medication affect hemodynamics.
Both adrenergic medications are often bolused in low doses and therefore do not influence the score directly. However, in repeated administration it can significantly alter hemodynamic outcome and therefore should be included in analysis of HI.

This sub-analysis did not present any significant increased HI when administering higher PEEP. Still physicians should act with caution because of the above mentioned limitations of this sub-analysis. This besides the overall patients variability in hemodynamics as a reaction to incremental PEEP.
Hopefully the international RCT PROTHOR Trial will provide a more weighed answer on the effect of high PEEP with RM's on hemodynamics versus low PEEP due to its group size targeting N = 2378.[3]

Furthermore, a more continuous analysis, such as a Mixed ANOVA, is still the preferred method of analyzing HI. This could further support the conclusion of this sub-analysis. Perhaps this type of statistical analysis for HI could be included in the PROTHOR trial.[21]
The variations of HI-scores among patients suggest that one's PEEP level could be optimized by titrating individually. This is possibly the perfect intraoperative ventilation setting for preventing PPC's and avoiding HI.[20,22]
Desirably, different cohorts with different PEEP would be added to the study. Also ones PEEP should be adjusted to its intraoperative HI-score and be analyzed retrospectively. In summary, many opportunities for successive research to be considered and conducted.

In conclusion our hypothesis that the high PEEP group would produces a significantly greater HI-score than the low PEEP group is rejected. In this sub-analysis no significant differences in HI-score at different timepoints as well as during the whole OLV period between a PEEP of 5 cmH_2O versus 10 cmH_2O with low V_T is found.

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