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Effects of PEEP on oxygenation and respiratory mechanics during one-lung ventilation

P. Michelet[1]*, A. Roch[1], D. Brousse[2], X.-B. D'Journo[3], F. Bregeon[5], D. Lambert[1], G. Perrin[1], L. Papazian[4], P. Thomas[3], J.-P. Carpentier[2] and J.-P. Auffray[1]

[1]Département d'Anesthésie Réanimation, Hôpitaux Sud, Marseille, France. [2]Service de Réanimation, Hôpital d'Instruction des Armées Laveran, Marseille, France. [3]Service de Chirurgie Thoracique, Hôpitaux Sud, Marseille, France. [4]Service de Réanimation Médicale, Hôpitaux Sud, Marseille, France. [5]Laboratoire de Physiologie Respiratoire, UPRES EA 2201, Université de la Méditerranée, France

**Corresponding author: Réanimation Polyvalente, Hôpital Sainte-Marguerite, 13274 Marseille Cedex 9, France. E-mail: pierre.michelet@mail.ap-hm.fr*

Background. One-lung ventilation-related hypoxaemia (OLV-RH) can occur in patients with healthy lungs. In this case, PEEP frequently improves oxygenation. The aim of this study was to determine, in a healthy lung model of OLV, whether the increase in PEEP improved oxygenation and whether the mechanisms involved include both inspiratory lung recruitment and an end-expiratory lung volume increase. Since inhaled nitric oxide (iNO) may have a synergistic effect on oxygenation in the case of PEEP-induced recruitment, their association was also tested.

Methods. Twenty pigs were studied during open-chest, left OLV. Arterial blood gases and haemodynamic variables were measured at different levels of PEEP (0, 5, 10 and 15 cm H_2O) applied in random order with or without iNO 4 p.p.m. Pressure–volume curves were measured at each level of PEEP.

Results. $PEEP_5$ and $PEEP_{10}$ improved Pa_{O_2}/FI_{O_2} ratio ($P<0.005$) and shunt ($P<0.005$) regardless of the presence of iNO. $PEEP_{15}$ improved oxygenation and shunt only when it was associated with iNO ($P<0.001$). Whereas $PEEP_5$, $PEEP_{10}$ and $PEEP_{15}$ were associated with a significant increase in end-expiratory volume ($P<0.001$), only $PEEP_5$ and $PEEP_{10}$ were associated with continuous lung volume recruitment ($P<0.01$). Moreover, $PEEP_{15}$ induced a significant decrease in linear compliance ($P<0.001$).

Conclusions. In a healthy porcine lung model of OLV-RH, moderate PEEP can improve oxygenation. This effect implies both expiratory and inspiratory pulmonary recruitment. Co-administration of 4 p.p.m. iNO was ineffective.

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Peroperative hypoxaemia frequently occurs during one-lung ventilation (OLV),[1–4] even in patients with healthy lungs.[5–7] Mechanisms involved in OLV-related hypoxaemia (OLV-RH) include the persistence of perfusion in the non-dependent non-ventilated lung[8] and ventilation to perfusion mismatch in the ventilated lung.[9] Indeed, the dependent lung is prone to collapse during expiration, with consequent worsening in ventilation to perfusion mismatching.[6] In healthy lung patients submitted to mechanical ventilation, PEEP prevents atelectasis but inconstantly improves oxygenation.[10–13] In patients with OLV, it has been reported that the better the underlying lung function the better the response to PEEP.[16] In this situation, the improvement of oxygenation by PEEP 5 cm H_2O was shown to be mainly related to an increase in functional residual capacity (FRC).[6] However, the beneficial effect of higher levels of PEEP remains to be studied. Moreover, it is unknown whether an increase in lung inspiratory volume is also involved in oxygenation improvement related to PEEP. Indeed, a PEEP-related recruitment has been reported above the FRC in acute lung injury[14 15] but never in healthy lungs. We hypothesized that, during OLV-RH, an increase in PEEP could optimize oxygenation and we wanted to determine the distending threshold. We presumed that mechanisms involved

in oxygenation improvement related to PEEP were not only the well-known increase in FRC but also an increase in lung inspiratory volume. Finally, because inhaled nitric oxide (iNO) and PEEP have been shown to potentiate oxygenation when PEEP induces pulmonary recruitment,[16 17] we hypothesized that its association with PEEP could be beneficial during OLV-RH.

The aim of this study was therefore to study the relationship between oxygenation improvement and PEEP during OLV and to test the effectiveness of the addition of iNO 4 p.p.m. in a pig model with intact lungs.

Methods

The study protocol was approved by the IMTSSA veterinary ethics committee. Twenty female pigs 4 months old with a mean (SD) weight of 34 (3) kg were studied.

General procedures

After premedication with i.m. midazolam 2 mg kg^{-1}, anaesthesia was induced and maintained by i.v. infusion of midazolam, fentanyl and pancuronium. Saline solution 7 ml^{-1} kg^{-1} h^{-1} was infused continuously throughout the protocol. Animals were tracheotomized and a tracheostomy cannula (ID 8.0 mm, Mallinckrodt Medical, Hazelwood, MO, USA) was placed. Two-lung volume-controlled ventilation was first performed with a tidal volume of 10 ml kg^{-1}, a $F_{I_{O_2}}$ of 0.4 (oxygen and nitrogen mixture), an inspiration: expiration ratio of 1:2 and no PEEP (Servo 900C; Siemens, Elema, Sweden). Respiratory rate was adjusted to obtain arterial P_{CO_2} between 35 and 45 mm Hg.

After stabilization under two-lung ventilation, the tracheostomy cannula was removed and a single-lumen reinforced tracheal tube with cuff (ID 7.0 mm; Rüsch manufacturing, N. Ireland, UK) was advanced through the tracheostomy orifice. It was blocked in the left main stem bronchus using fibre-optic bronchoscopy in order to exclude the right lung from ventilation. Left OLV was initiated with a tidal volume of 7 ml kg^{-1} and with an inspiration:expiration ratio of 1:2 without PEEP. The respiratory rate was adjusted to obtain arterial P_{CO_2} not exceeding 55 mm Hg. After stabilization, animals were turned left and a right thoracotomy was performed. The right lung was exposed by placing a chest retractor between the fourth and fifth ribs. The effectiveness of right lung exclusion was checked by continuous inspection. The $F_{I_{O_2}}$ was maintained at 0.4 throughout the experiment.

NO in nitrogen was used at a concentration of 450 p.p.m. (Air Liquide®; Meudon, France) and was delivered sequentially during inspiration within the inspiratory limb of the ventilator (Opti-NO; Taema, Antony, France). Intratracheal gas was sampled by continuous aspiration through the endotracheal tube (suction flow 1 litre min^{-1}) so as to allow continuous monitoring of inspiratory, expiratory and mean NO and NO_2 concentrations using a chemiluminescence method (NOX 4000; Sérés, Aix-en-Provence, France). A flowmeter delivering flows within a range of 1 to 999 ml min^{-1} (Air Liquide; Meudon) was set to achieve an inspiratory tracheal concentration of 4 p.p.m. Changes in $F_{I_{O_2}}$ potentially induced by the inhalation of NO were monitored continuously using an oxygen analyser (NOX 4000).

Experimental design

After the onset of baseline left OLV in PEEP 0 cm H_2O, the left lung was ventilated with PEEP levels of 0, 5, 10 and 15 cm H_2O (0 cm H_2O=ZEEP; 5 cm H_2O=$PEEP_5$; 10 cm H_2O=$PEEP_{10}$; 15 cm H_2O=$PEEP_{15}$) in a random order with or without iNO 4 p.p.m. This resulted in eight periods of 20 min with an interval of 5 min at ZEEP between each period.

Data recording and oxygenation measurements

The primary end-point was oxygenation, as assessed by $P_{a_{O_2}}$:$F_{I_{O_2}}$ ratio. Arterial and mixed venous pH, P_{O_2}, $S_{a_{O_2}}$ and P_{CO_2} were measured using a blood gas analyser (278 blood gas system; Ciba Corning, Medfield, MA, USA). Indexed pulmonary vascular resistances (PVRI) and intrapulmonary shunt or venous admixture (Qva/Qt) were calculated using standard formula.

Data recording and pulmonary mechanics measurements

A pulmonary mechanical study of the left lung was performed in semi-static conditions at the end of the PEEP-iNO trial (i.e. after the pigs had been tested with the four levels of PEEP with and without iNO) and for each level of PEEP. In order to do this, the lung volume history was firstly standardized: the level of PEEP was reset at 0 cm H_2O and, after 3 min of mechanical ventilation with unchanged Vt, a recruitment manoeuvre was performed by increasing airway pressure to 45 cm H_2O for 15 s. Thereafter, a pneumotachograph (Hans Rudolf 4813, Kansas City, MO, USA) with an integral pressure transducer was connected on the tracheal tube. Volume changes were obtained by integration of the flow signal recorded on the MP100 data acquisition system (Biopac Systems, Goleta, CA, USA) and analysed using the Acknowledge software program (Biopac Systems).[18] The different pressures were measured with another differential pressure transducer. Dynamic measurements of tidal volume (Vt), respiratory rate (RR), maximal inspiratory pressure (Paw), inspiratory to expiratory ratio (I/E) were recorded continuously. Intrinsic PEEP was measured at the end of a 5 s end-expiratory occlusion.

Variation in FRC was evaluated by measurement of the variation in end-expiratory lung volume (EELVv)[19–21] and performed at each level of PEEP. The EELVv was calculated as the difference between the volume measured during a 6 s prolonged expiration from PEEP to ZEEP and a 6 s prolonged expiration at PEEP (to subtract the volume related to intrinsic PEEP, if any).

A study of the pressure–volume (P-V) relationship was performed at each level of PEEP in order to evaluate the respective lung inspiratory recruitment and potential overdistension related to PEEP. A 2-litre syringe filled with pure oxygen was connected to the tracheal tube at the end of expiration in PEEP. The left lung was inflated in a stepwise fashion with 100 ml increments of oxygen up to a volume of 1500 ml or a maximum plateau airway pressure of 45 cm H_2O.[22] At the end of each increment, an end-expiratory pause of 3 s was held. Plateau airway pressure was defined as the pressure value measured at the 3rd second of pause.[23] At each level of PEEP tested, P-V curves were traced, starting from the pressure point recorded during an end-expiratory occlusion and the corresponding EELVv. Inspiratory lung volume recruited by PEEP was defined as the difference between the volume measured on the curve starting from each level of PEEP and the volume measured on the corresponding curve starting from ZEEP, plotted on the same volume axis.[21] Inspiratory lung recruitment was calculated at several values of plateau airway pressure ranging from 15 to 35 cm H_2O, which represented the range of pressures available for all animals. Measurement of static compliance (Cpl) of the respiratory system was made in the linear segment of the P-V curve.[24]

Data recording and haemodynamic measurements

A 5 F catheter was inserted in the left carotid artery to monitor systemic pressures and arterial blood gases. A pulmonary artery catheter (Baxter Healthcare, Irvine, CA, USA) was inserted via the right external jugular vein to monitor mean pulmonary arterial pressure (MPAP) and cardiac index (CI) by pulmonary thermodilution. Systemic and pulmonary arterial pressures and pulmonary artery occlusion pressure (PAOP) were measured at end-expiration. Cardiac output was measured by injection of three 10 ml boluses of 5% glucose solution at 6 to 10°C via a closed system (Co-set; Baxter Healthcare) at end-inspiration. Study data correspond to the mean of three measurements.

Body surface area (BSA, m^2) was calculated using the following formula: BSA=K/weight $(kg)^{2/3}$, where K was 0.112 for pigs. At the end of the experiment, pigs were killed with an overdose of thiopental.

Statistical analysis

Statistical analysis was performed using the SPSS 11.0 software package (SPSS, Chicago, IL, USA) and distribution of data was confirmed. Results were expressed as mean (SD). Changes in ventilatory settings were assessed with paired Student's *t*-tests. Two-way repeated measures analysis of variance (ANOVA) was used to evaluate the effects of PEEP, iNO and their interaction. The influence of the order of PEEP levels was assessed by a two-way ANOVA taking into account PEEP level and order. Tukey's *post hoc* test was used to compare times and groups when there was statistical significance. For all tests, a *P*-value equal to or less than 0.05 was considered statistically significant.

Results

All animals survived the study period and were in stable physiological, haemodynamic and respiratory conditions before starting OLV. Baseline characteristics of the animals in two-lung and one-lung ventilation are presented in Table 1. Compared with two-lung ventilation, OLV induced a large decrease in Pa_{O_2} ($P<0.05$, *t*-test; Table 1) associated with an increase in pulmonary shunt ($P<0.001$, *t*-test; Table 1) in MPAP ($P<0.001$, *t*-test; Table 1) and PVRI ($P<0.05$, *t*-test; Table 1) whereas CI and MAP were not significantly affected.

Effects of PEEP levels with and without iNO on blood gases

Two-way analysis of variance (ANOVA) showed that PEEP ($P<0.001$) and iNO ($P<0.05$) improved the Pa_{O_2}/FI_{O_2} ratio independently. *Post hoc* tests located the effect of PEEP at $PEEP_5$ and $PEEP_{10}$ ($P<0.005$, *post hoc* Tukey test; Fig. 1A), whereas the interaction between PEEP and iNO was located at $PEEP_{15}$ ($P<0.001$, *post hoc* Tukey test; Fig. 1A).

Although ANOVA showed that PEEP reduced pulmonary shunt ($P<0.001$), it did not show a statistical influence of iNO ($P=0.07$). *Post hoc* tests located the effect of PEEP on pulmonary shunt to $PEEP_5$ and $PEEP_{10}$ ($P<0.005$, *post hoc* Tukey test for each). There was no significant interaction between PEEP and iNO ($P<0.001$, ANOVA), which indicated that the effect of iNO varied with the level of PEEP used. *Post hoc* testing located this effect to $PEEP_{15}$ ($P<0.001$ by *post hoc* Tukey test; Fig. 1B).

Table 1 Respiratory and haemodynamic parameters at baseline during two and one-lung ventilation. Student's *t*-test: **P*<0.01 *vs* two-lung ventilation; †*P*<0.05 *vs* two-lung ventilation

	Two-lung ventilation	One-lung ventilation
Pa_{O_2} (mm Hg)	178 (42)	68 (8)†
Sa_{O_2} (%)	99 (0.6)	87 (3)*
Pa_{CO_2} (mm Hg)	42 (5)	47 (5)*
QS/QT (%)	6 (6)	32 (9)*
Paw (cm H_2O)	15 (3)	23 (3)*
Pplat (cm H_2O)	11 (2)	15 (3)†
VT (ml)	345 (33)	247 (20)*
VT (ml kg^{-1})	10.1 (0.1)	7.1 (0.1)*
RR (min^{-1})	19 (1)	28 (1)*
HR (beats min^{-1})	141 (30)	141 (21)
MAP (mm Hg)	92 (20)	96 (19)
MPAP (mm Hg)	17 (3)	26 (3)*
PAOP (mm Hg)	4 (2)	4 (3)
PVRI (dyne s cm^{-5} m^{-2})	184 (49)	343 (74)†
CI (litre min^{-1} m^2)	5.6 (0.8)	5.3 (1.2)

QS/QT, shunt; Paw, peak airway pressure; Pplat, plateau airway pressure; VT, tidal volume; RR, respiratory rate; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occlusion pressure; PVRI, pulmonary vascular resistances indexed; CI, cardiac index.

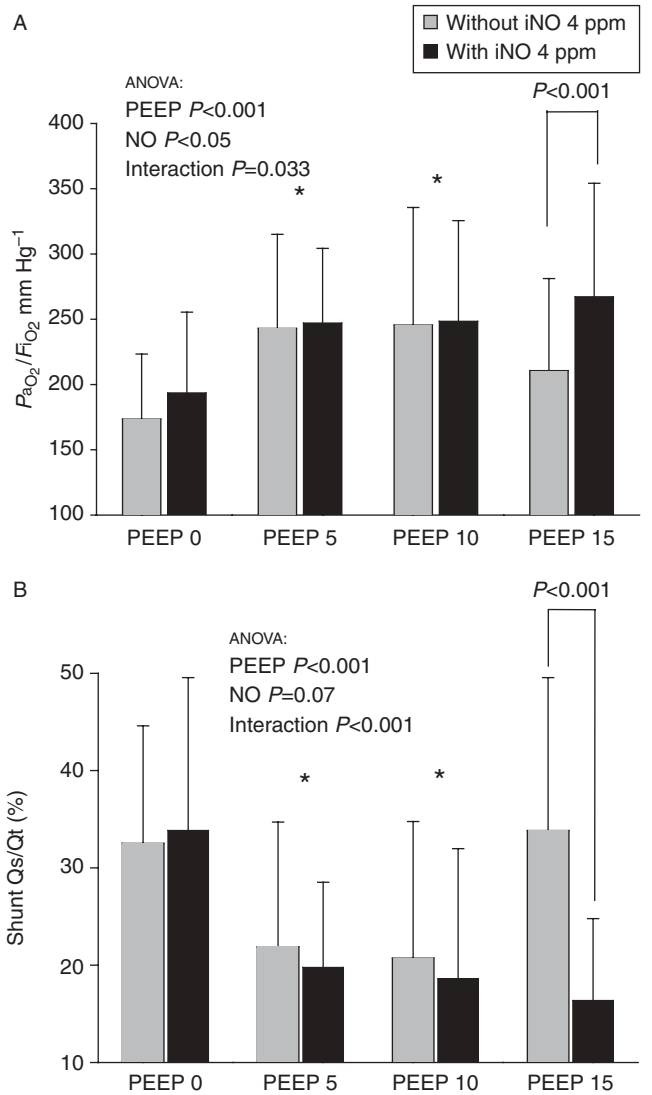

Fig 1 Effects of increasing levels of PEEP alone or in association with iNO on (A) Pa_{O_2}/Fi_{O_2} ratio and (B) pulmonary shunt. *P<0.005 *vs* $PEEP_0$ with or without iNO by Tukey's *post hoc* test.

There was a significant effect of PEEP on Pa_{CO_2} (P<0.001, ANOVA). *Post hoc* analysis revealed that this decrease in Pa_{CO_2} was related to $PEEP_5$ and $PEEP_{10}$ (P<0.001 for each, *post hoc* Tukey test; Table 2). Statistical analysis did not show an effect of iNO or interaction between PEEP and iNO on Pa_{CO_2}.

Effects of PEEP levels on pulmonary mechanics

The linear compliance of the respiratory system was significantly modified by the addition of PEEP (P<0.05, ANOVA). *Post hoc* testing located this effect to $PEEP_5$ (P<0.001; Table 3) with a significant increase, whereas it was significantly decreased at $PEEP_{15}$ (P<0.001, *post hoc* Tukey test; Table 3) with a flat P-V curve, suggesting overdistension (Fig. 2).

The different levels of PEEP resulted in a significant increase in end-expiratory lung volume (P<0.001, ANOVA; Table 3), which resulted from the effect of $PEEP_5$, $PEEP_{10}$ and $PEEP_{15}$ (P<0.001, *post hoc* Tukey test; Table 3).

Similarly, there was a statistical influence of PEEP on lung inspiratory volumes (P<0.001, ANOVA; Fig. 2).

Effects of PEEP levels and iNO on haemodynamic parameters

ANOVA showed that PEEP modified cardiac index (P<0.01), which significantly decreased at $PEEP_{10}$ and $PEEP_{15}$ (P<0.05, *post hoc* Tukey test; Table 2) regardless of the presence of iNO. In addition, ANOVA showed that both PEEP (P<0.05; Table 3) and iNO (P<0.02; Table 3) modified MPAP, which decreased with $PEEP_5$ (P<0.05, *post hoc* Tukey test; Table 2) and with iNO regardless of the presence of PEEP for ZEEP, $PEEP_{10}$ and $PEEP_{15}$ (P<0.02, *post hoc* Tukey test; Table 2). Similarly, the PVRI was influenced both by PEEP (P<0.05, ANOVA; Table 2) and by iNO (P<0.01, ANOVA; Table 2). Whereas $PEEP_5$ was associated with a decrease in PVRI (P<0.05, *post hoc* Tukey test;

Table 2 Evolution of haemodynamic and respiratory parameters. *P<0.05 *vs* $PEEP_0$ and $PEEP_{15}$; †P<0.05 *vs* lower levels of PEEP; ‡P<0.02 *vs* without inhaled NO (Tukey's *post hoc* test)

	$PEEP_0$		$PEEP_5$		$PEEP_{10}$		$PEEP_{15}$		ANOVA
	Without NO	4 p.p.m. NO	Without NO	4 p.p.m. NO	Without NO	4 p.p.m. NO	Without NO	4 p.p.m. NO	
Pa_{CO_2} (mm Hg)	47 (7)	47 (8)	43 (6)*	42 (5)*	44 (7)*	44 (7)*	52 (8)†	51 (6)†	P<0.01
pH	7.39 (0.05)	7.39 (0.08)	7.40 (0.05)	7.41 (0.05)	7.39 (0.06)	7.40 (0.07)	7.37 (0.06)	7.37 (0.06)	NS
Paw (cm H_2O)	23 (3)	24 (3)	21 (4)	21 (3)	25 (7)†	26 (2)†	35 (3)†	36 (3)†	P<0.05
Pplat (cm H_2O)	15.2 (3)	16.1 (3)	16.2 (3)	17.2 (3)	19.4 (2)†	19.8 (2)†	28.4 (2)†	29 (2)†	P<0.001
Int PEEP (cm H_2O)	0.3 (0.1)	0.2 (0.1)	0.3 (0.1)	0.2 (0.1)	0.4 (0.2)	0.3 (0.1)	0.5 (0.2)	0.4 (0.3)	NS
CI (litre min^{-1} m^{-2})	5.3 (0.7)	5.3 (0.7)	5.3 (0.8)	5.5 (0.7)	4.7 (0.7)†	4.8 (0.7)†	4.5 (0.9)†	4.7 (0.8)†	P<0.01
MAP (mm Hg)	95 (13)	94 (14)	94 (14)	93 (15)	92 (18)	92 (22)	90 (12)	89 (24)	NS
PAOP (mm Hg)	4 (2)	4 (5)	3 (2)	3 (2)	5 (2)†	4 (2)†	7 (3)†	7 (3)†	P<0.05
MPAP (mm Hg)	26 (3)	23 (4)‡	24 (3)*	23 (4)	25 (2)	23 (4)‡	28 (3)	24 (3)‡	P<0.02
PVRI (dyne s cm^{-5} m^{-2})	343 (71)	306 (50)‡	311 (41)*	291 (63)	331 (52)	310 (58)	360 (65)	305 (36)†	P<0.01

Paw, peak airway pressure; Pplat, plateau airway pressure; CI, cardiac index; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; Int PEEP, intrinsic PEEP; NS, not significant.

Table 2), $PEEP_{15}$ induced a significant increase compared with $PEEP_5$ ($P<0.05$, *post hoc* Tukey test). iNO induced a decrease in PVRI only at ZEEP and $PEEP_{15}$ ($P<0.02$, *post hoc* Tukey test; Table 2). Mean arterial pressure and heart rate were not affected by PEEP or iNO.

Discussion

The results of this experimental study in pigs showed that $PEEP_5$ and $PEEP_{10}$ increase Pa_{O_2} by 50% during OLV-related hypoxaemia. The novelty of this study is to demonstrate that the improvement in oxygenation by PEEP was associated both with an increase in EELV and in lung inspiratory recruitment. Another important finding was that iNO did not increase oxygenation at the optimal ranges of PEEP ($PEEP_5$ and $PEEP_{10}$). This strategy only improved oxygenation when PEEP was high ($PEEP_{15}$) and associated with overdistension.

Our results are in agreement with previous data showing a beneficial effect of PEEP on oxygenation during OLV.[2,6,25,26] The PEEP-related increase in EELV reported in the current study suggests that an increase in FRC could participate in the improvement in oxygenation. This mechanism has already been suggested in patients by Slinger and colleagues,[6] who demonstrated that $PEEP_5$ increased oxygenation in the case of a PEEP-related increase in plateau end-expiratory pressure towards the lower inflection point of the static compliance curve. A PEEP-related increase in FRC was also described by Cohen and Eisenkraft[1] to explain the oxygenation improvement of several hypoxaemic patients ventilated with $PEEP_{10}$. In addition, and as we hypothesized, we demonstrate here that the increase in oxygenation was associated with a significant lung inspiratory recruitment. Whereas the increase in PEEP leads to a continuous increase in EELV, only $PEEP_5$ and $PEEP_{10}$ induced a significant increase in oxygenation and continuous inspiratory lung recruitment. Conversely, $PEEP_{15}$ was associated with the higher level of EELV but did not further improve oxygenation, whereas it induced limited lung inspiratory recruitment. Therefore, the observation that oxygenation improved only at PEEP levels associated with lung inspiratory recruitment suggests that inspiratory rather than expiratory recruitment is involved in the oxygenation increase. To our knowledge, the effect of lung inspiratory recruitment on oxygenation improvement related to PEEP has not been reported before in this specific setting. Indeed, in injured lungs, the beneficial effect of PEEP on oxygenation has been related both to an increase in FRC and to lung inspiratory recruitment above the FRC.[14,15,23] This phenomenon was explained by an increase in airway and alveolar collapse

Table 3 End-expiratory lung volume variation and linear compliance at different PEEP levels during one-lung ventilation. †$P<0.001$ *vs* respective lower PEEP levels; ‡$P<0.001$ *vs* other PEEP levels (Tukey's test after one-way ANOVA)

	Baseline	PEEP (cm H_2O)			
		0	5	10	15
End-expiratory lung volume variation (ml)	31 (7)	23 (8)	119 (13)†	210 (17)†	395 (16)†
Linear compliance (ml cm H_2O^{-1})	35.8 (1.9)	36.1 (1.8)	40.2 (2.3)‡	34.3 (1.7)	17.2 (1.4)‡

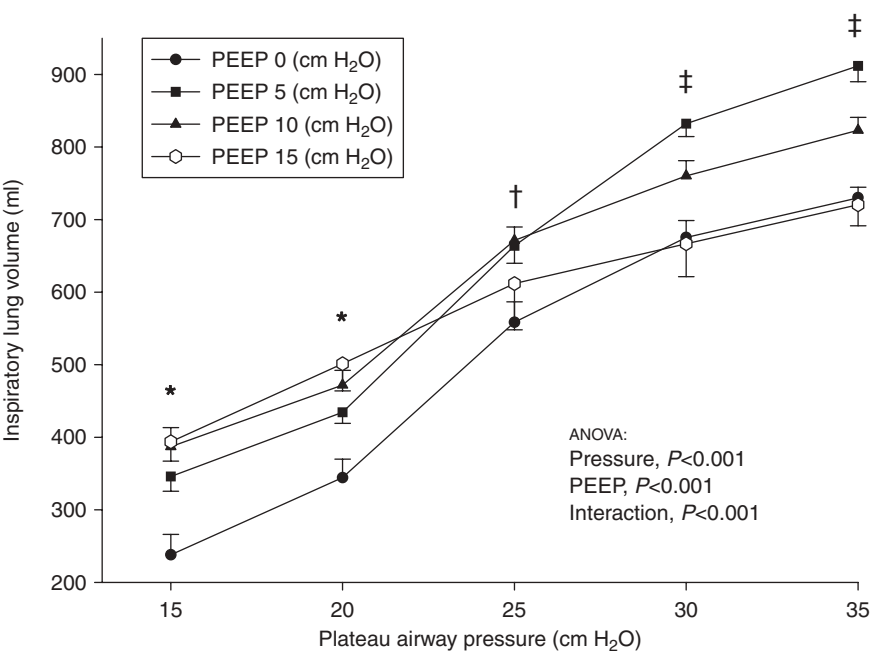

Fig 2 Mean values of lung inspiratory volume against plateau airway pressure (Pplat) for the range of pressure available for all animals at PEEP 0, 5, 10 and 15 cm H_2O (i.e. 15–35 cm H_2O). *For Pplat of 15 and 20 cm H_2O, inspiratory lung volume with $PEEP_0$ lower than with other PEEP levels ($P<0.01$ by *post hoc* Tukey's test); †for Pplat of 25 cm H_2O, inspiratory lung volume with $PEEP_0$ and $PEEP_{15}$ lower than with other PEEP levels ($P<0.01$ by *post hoc* Tukey's test); ‡for Pplat of 30 and 35 cm H_2O, inspiratory lung volume with $PEEP_5$ higher than with other PEEP levels ($P<0.01$ by *post hoc* Tukey's test).

during expiration in ZEEP, with higher pressure needed to reopen the collapsed areas above FRC during the inspiratory phase.[14 15] Conversely, the preservation of FRC in PEEP promotes inspiratory recruitment for the same tidal volume.[14 15 23] However, this mechanism is commonly judged as secondary to the PEEP-induced increase in FRC during OLV.[2 6 25]

The absence of further improvement in oxygenation with $PEEP_{15}$ could be explained by overdistension, which was seen, as in previous reports, as the increase in plateau pressure and Pa_{CO_2} associated with a decrease in linear compliance and a dramatic increase in airway pressures.[14 27–29] As already demonstrated during two-lung ventilation,[27] high levels of PEEP might lead to redistribution of pulmonary blood flow from overdistended lung units to lung areas with a low ventilation:perfusion ratio or pulmonary shunt, resulting in a worsening in oxygenation and pulmonary shunting. Although this mechanism has been reported to explain the discrepancies between studies related to the efficiency of PEEP on oxygenation during OLV,[6] in our study the overdistension was limited to $PEEP_{15}$. The occurrence of this adverse effect only for the higher level of PEEP could result from the tidal volumes used. Our ventilatory strategy included a moderate reduction of Vt at 7 ml kg^{-1} after pulmonary exclusion that has been demonstrated previously to prevent PEEP-related overdistension in an experimental model of OLV in healthy lung.[30] Conversely, the traditional OLV procedure includes the use of tidal volumes almost as high as during two-lung ventilation (i.e. 10–12 ml kg^{-1}).[31] In this setting, the application of external PEEP can promote rapid overdistension during the inspiratory phase with a consequent ineffectiveness PEEP on oxygenation.[30 32] These results led us to consider that a moderate reduction in tidal volume associated with PEEP ranging from 5 to 10 cm H_2O could be the better compromise to optimize oxygenation during OLV in healthy lung. Nevertheless, whereas our study protocol did not include different levels of tidal volume, this interpretation is limited and requires further investigation to test the respective influences of tidal volume and PEEP on oxygenation and lung mechanics.

Recent experimental data suggest that 4 p.p.m. iNO could be efficient for oxygenation during OLV, notably by diverting blood flow from non-ventilated towards ventilated lung.[9] Furthermore, several studies reported that PEEP-induced alveolar recruitment could be considered a factor determining iNO-induced improvement in arterial oxygenation.[16 17] Indeed, iNO could optimize the perfusion of newly recruited areas and reduce the ventilation–perfusion mismatch.[17] Our results do not support this hypothesis in the setting of OLV, since at $PEEP_5$ and $PEEP_{10}$ iNO did not affect oxygenation, while these levels of PEEP were associated with significant pulmonary recruitment. Moreover, the addition of iNO to $PEEP_5$ and $PEEP_{10}$ did not result in a reduction in PVRI compared with PEEP alone. Conversely, the addition of iNO to ZEEP and $PEEP_{15}$ resulted in a significant reduction in PVRI associated with oxygenation improvement for $PEEP_{15}$. Although these results were unexpected regarding our study hypothesis, several factors could explain these observations. For $PEEP_5$ and $PEEP_{10}$, the decrease in hypoxic pulmonary vasoconstriction was probably sufficient to optimize blood flow in the recruited areas, so iNO could not 'overact'. In agreement, iNO-induced reduction in PVRI and improvement in Pa_{O_2} has been correlated with the level of hypoxic pulmonary vasoconstriction.[16] In addition, the increase in PVRI related to PEEP-induced overdistension[25] could have also interacted. This mechanism could explain the lack of PVRI decrease at $PEEP_{10}$ despite a similar oxygenation improvement compared with $PEEP_5$ and the significant increase in PVRI at $PEEP_{15}$ compared with $PEEP_5$ and $PEEP_{10}$. Interestingly, the higher level of PVRI at $PEEP_{15}$ was associated with an effect of iNO on PVRI and oxygenation. As these effects were not associated with a modification in cardiac index, one can presume that the effect of iNO on oxygenation was related to a correction of ventilation–perfusion mismatching induced by overdistension.

Study limitations

During OLV, oxygenation depends on FRC variation and pulmonary recruitment, but also on haemodynamic effects. Our work did not include measurements of the distribution of pulmonary perfusion. Therefore, we could not determine the ventilation–perfusion distribution. Moreover, the goal of mechanical ventilation during OLV is a compromise between the need for alveolar recruitment and the risk of excessive alveolar overdistension. The absence of an evaluation of the distribution of pulmonary recruitment and hyperinflation during the respiratory cycle represents another limitation of our study and should be assessed in further studies, notably by computed tomography.[33 34]

Conclusion

Our results show that, during OLV-related hypoxaemia in a healthy lung model, increasing PEEP should have a beneficial effect on oxygenation, based on its effect on lung inspiratory recruitment and its ability to preserve EELV. Cases of PEEP ineffectiveness during OLV could be related to PEEP-induced overdistension that could probably be limited by reducing the Vt. Whereas the association with iNO did not result in oxygenation improvement in the case of PEEP-related effectiveness, this agent could be useful when overdistension occurs. It is essential to demonstrate the clinical efficiency of such a strategy in clinical studies.

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