Effects of indomethacin and PEEP on oleic acid induced pulmonary oedema in rabbits

K.S. Panaretto, C. Phillips, N. Berend

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ABSTRACT: This study was designed to determine whether indomethacin, a suggested treatment for adult respiratory distress syndrome (ARDS), would inhibit the efficacy of positive end-expiratory pressure (PEEP) in an animal model of ARDS.

Functional residual capacity (FRC), alveolar-to-arterial oxygen difference (A-aPo$_2$) and total lung water were measured in rabbits: 30 controls and 30 with oleic acid induced pulmonary oedema. Within each group, four treatments were administered: diluent (n=12), PEEP (n=6), indomethacin (n=6), or PEEP + indomethacin (n=6). Lung injury was induced at 30 mins and treatment commenced at 45 min.

Oleic acid caused a significant increase at 3 h in % increase in A-aPo$_2$ from baseline (105±12%) attenuated by PEEP (59±17%) and indomethacin (57±7%), with the combination of PEEP + indomethacin preventing a significant increase (26±9%). PEEP increased FRC in both saline and oleic acid animals; this was not reversed by indomethacin. Oleic acid caused an increase in total lung water (5.16 to 6.58±0.16 g), not influenced by any treatment.

These findings suggest that indomethacin did not inhibit the efficacy of PEEP in this model of ARDS.
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The adult respiratory distress syndrome (ARDS) is an increased permeability pulmonary oedema syndrome, resulting from functional disruption to the capillary-alveolar barrier [1]. The pathogenesis of ARDS is not fully understood, but it is thought that accumulation of activated neutrophils in the lung, together with the production and release of free oxygen radicals and arachidonate products, and activation of both the complement and coagulation cascades play important roles [2].

Positive end-expiratory pressure (PEEP) is an established treatment of ARDS [1–3]. It prevents the collapse of alveoli, redistributing extravascular water from the alveolar to the perivascular spaces [4]. Evidence is accumulating that PEEP also results in the release of humoral agents [5], which may be, or may include the prostaglandins [6, 7], some of which are bronchodilators, contributing to the increase in lung volumes seen with PEEP.

The use of cyclooxgenase inhibitors has been shown to improve lung mechanics and gas exchange in several animal models of ARDS [8–12]. Hence, nonsteroidal anti-inflammatory drugs (NSAIDS) have been suggested as possible therapeutic agents for ARDS [2]. However, with regard to the humoral effects of PEEP, the use of

NSAIDS may be counterproductive in the presence of PEEP. It has been demonstrated in sheep and dogs without ARDS [13] that the increase in functional residual capacity (FRC) due to PEEP, can be significantly reduced by indomethacin. However, this effect is not seen in normal human subjects [6].

The purpose of this study was to assess the efficacy of PEEP and indomethacin, both alone and together, in an oleic acid model of ARDS, in rabbits. Oleic acid causes a rapid onset high permeability pulmonary oedema. It causes increased pulmonary arterial pressure, reduced lung compliance and severe hypoxaemia [14–16], thus providing a useful animal model. Lung volumes, blood gases and wet-to-dry lung weight ratios were measured to determine whether indomethacin reversed the beneficial effects of PEEP.

Materials and methods

Animals

Sixty nine healthy New Zealand White male rabbits were used for the study. Their weights ranged from 2.8–3.8 kg. Nine animals died.

Reagents and administration

Oleic acid, approximately 99% pure and bovine serum albumin (BSA) were obtained from Sigma Chemicals. Indomethacin (pure substance) was supplied by Merck, Sharp and Dohme.

Oleic acid, 0.1 ml·kg^{-1}, was administered as a suspension in 0.1% BSA solution, in a ratio of 1:5. The suspension was shaken vigorously immediately prior to administration. In preliminary experiments, 0.15 ml·kg^{-1} of oleic acid was used resulting in a 50% mortality rate, so the dose was lowered to 0.1 ml·kg^{-1} for the study. With this lower dose nine animals died prior to completion of the experiment.

Indomethacin was administered intravenously (i.v.) as a bolus dose, 5 mg·kg^{-1} followed by an infusion of 3 mg·kg^{-1} hourly, dissolved in 8.4% sodium bicarbonate. These doses of indomethacin were chosen based on experience in dogs, where it has been shown to inhibit prostaglandin synthesis [17]. Lower doses than this are known to inhibit cyclooxygenase activity in isolated rabbit lungs [18].

Preparation of animals

The rabbits were anaesthetized with pentobarbital sodium (20 mg·kg^{-1} i.v. initially; maintained hourly with 5 mg·kg^{-1} i.v.) and ketamine hydrochloride (75 mg·kg^{-1} i.m. initially; maintained with 25 mg·kg^{-1} i.m. hourly). A tracheostomy was then performed, and a cuffed endotracheal tube (size 3.5 or 4.0 F) inserted. The animals spontaneously breathed room air. A catheter was introduced into the femoral artery for monitoring blood pressure and collection of arterial blood. Both ear veins were cannulated; one for the delivery of anaesthetic agents and the oleic acid, the other for infusion of indomethacin.

Measurement of lung volumes

The animals were placed supine in a volume displacement plethysmograph. The tracheostomy tube was connected to an external Hans-Rudolph valve (modified to minimize deadspace). Pressure at the airway opening was measured by a Validyne MP45 pressure transducer. Volume was measured with a water-filled Krogh spirometer. The signals were recorded on a Tektronix oscilloscope and Watanabe chart recorder. FRC (for both PEEP and non-PEEP animals) was determined by manually occluding the inspiratory port of the Rudolph valve at end expiration and measuring the lung volume using the Boyle's Law technique. The lung volume was calculated taking the mean of five repeated obstructed breaths. The expiratory port of the Rudolph valve was connected to a tube placed under 5 cm of water to create 5 cmH$_2$O of PEEP.

Experimental protocols

On completion of instrumentation, the rabbits were placed in the plethysmograph and allowed to stabilize. A set of baseline measurements was taken, three replicates of lung volumes and blood gases over consecutive 15 min periods. Half the animals then received oleic acid i.v. through the right ear vein, flushed with 1.5 ml of saline (n=30). The other half, the control animals, received saline only (n=30). Fifteen minutes after administration of the oleic acid or saline a treatment was commenced: saline (n=6), HCO$_3$$^-$ (the diluent for the indomethacin, n=6), PEEP (n=6), indomethacin (n=6) or PEEP + indomethacin (n=6). The HCO$_3$$^-$ animals were included to control for the salt load administered with the 8.4% sodium bicarbonate (3 ml with bolus, and 5 ml with infusion) which may have exacer- bated oedema. However, as the HCO$_3$$^-$ animals did not differ from the saline controls in either the oleic acid or saline the results have been pooled to form a single control treatment subgroup (diluent, n=12). Thus, the control and oleic acid groups have four treatment subgroups: diluent, PEEP, indomethacin, and PEEP + indomethacin.

PEEP was delivered continuously over the treatment period. Indomethacin was administered as a bolus dose (5 mg·kg^{-1}) intravenously, followed by a continuous intravenous infusion (3 mg·kg^{-1} hourly) for the remainder of the experiment.

Fifteen minutes after commencement of the treatment the lung volumes and blood gases were repeated. These measurements were then repeated at hourly intervals for a further two hours. Thus, each experiment was of three hours duration, with monitoring at 30, 90 and 150 min after the administration of oleic acid or saline. At the completion of each experiment each animal was sacrificed with a lethal dose of pentobarbital sodium.

Arterial blood gas samples were collected initially during steady-state conditions as a baseline measurement, then hourly, from the femoral arterial catheter. Oxygen tension (Po$_2$), carbon dioxide tension (Pco$_2$) and pH were measured by an ABL30, Radiometer blood gas analyser. The alveolar-to-arterial oxygen difference (A-aPo$_2$) was calculated using the alveolar gas equation with a fixed respiratory ratio of 0.8. Each set of blood gases for a time point are the mean of three replicates.

Wet-to-dry lung weight ratios were obtained from three samples taken from the left lower lobes, obtained after the animals were sacrificed. The samples were weighed wet, freeze dried (frozen with liquid N$_2$ then vacuum dried for 24 h) and reweighed dry. The final wet-to-dry ratio for each animal being the mean of the three samples.

Statistics

The overall effect of the five treatments in each oleic acid or control group on A-aPo$_2$ or FRC, was evaluated using a mixed model analysis of variance: with

treatment, time and random animal effects. Where differences were found between treatment groups, each time point was considered separately using a one way analysis of variance, with a Student-Newman-Keuls (SNK) analysis to compare the individual treatment means. A p value of <0.05 was considered significant. Variation across time, within each treatment group was analysed using paired tests. A p value of <0.02 was considered significant; this lowering of the p value was due to the number of comparisons being made.

Each control treatment group was compared with its corresponding oleic acid treatment at each time point using unpaired t-tests. Again a p value of <0.02 was considered significant.

The wet-to-dry weight ratios were examined using a one way analysis of variance and a SNK analysis of multiple means.

Results

The blood gas data and FRC data are summarized in tables 1–5. There were no significant differences between treatment subgroups in A-aPo$_2$ or FRC prior to intervention. Consequently, the percentage change in A-aPo$_2$ and FRC from baseline for each animal were analysed, and are presented in figures 1 and 2. All the animals that died did so prior to completion of the experiment. Hence, data from these animals was incomplete and was not included in the analysis.

Blood gas analysis

In the control group there were no significant differences in the % change in A-aPo$_2$ between the treatment subgroups or timepoints (fig. 1).

Table 1. – pH for control and oleic acid rabbits

Treatment groups		Baseline	1	Time h 2	3
Diluent					
	C	7.39±0.01	7.38±0.01	7.39±0.01	7.40±0.01
	O	7.39±0.01	7.42±0.02	7.39±0.02	7.36±0.04
PEEP					
	C	7.37±0.01	7.33±0.02	7.35±0.02	7.34±0.02
	O	7.39±0.01	7.33±0.02	7.21±0.04	7.15±0.05
Indo					
	C	7.37±0.02	7.38±0.02	7.36±0.02	7.37±0.02
	O	7.39±0.01	7.40±0.02	7.36±0.03	7.32±0.03
Indo+PEEP					
	C	7.39±0.02	7.35±0.02	7.33±0.02	7.31±0.03
	O	7.36±0.02	7.36±0.01	7.32±0.01	7.30±0.01

Values are mean±SEM. C: control group; O: oleic acid group; PEEP: positive end-expiratory pressure; Indo: indomethacin.

Table 2. – Pco$_2$ (kPa) for control and oleic acid rabbits

Treatment groups		Baseline	1	Time h 2	3
Diluent					
	C	4.34±0.28	3.77±0.21	3.50±0.26	3.44±0.32
	O	4.77±0.22	3.93±0.25	3.85±0.27	3.59±0.3
PEEP					
	C	4.44±0.16	4.25±0.12	3.68±0.21	3.59±0.3
	O	4.44±0.22	4.43±0.25	4.95±0.27	5.69±0.34
Indo					
	C	5.07±0.33	5.59±0.48	5.66±0.36	5.29±0.38
	O	4.63±0.19	4.39±0.33	4.38±0.44	4.55±0.37
Indo+PEEP					
	C	4.33±0.33	5.17±0.41	5.45±0.61	5.60±0.68
	O	5.00±0.32	5.27±0.33	5.54±0.36	5.44±0.53

Values are mean±SEM. Pco$_2$: carbon dioxide tension. For other abbreviations see legend to figure 1.

Table 3. – Po_2 (kPa) for control and oleic acid rabbits

Treatment groups		Baseline	1	Time h 2	3
Diluent					
	C	10.3±0.46	11.1±0.40	11.9±0.45	11.5±0.46
	O	9.7±0.37	7.5±0.56	6.5±0.47	7.0±0.50
PEEP					
	C	10.5±0.35	10.7±0.38	11.7±0.69	11.7±0.42
	O	10.5±0.63	8.5±0.87	7.7±0.87	7.0±0.58
Indo					
	C	9.6±0.6	8.5±0.38	9.1±0.3	9.9±0.75
	O	9.3±0.36	7.0±0.43	6.8±0.28	6.6±0.38
Indo+PEEP					
	C	10.0±0.68	8.8±0.71	9.1±0.61	9.3±0.88
	O	9.6±0.32	8.5±0.31	8.1±0.15	8.0±0.59

Values are mean±SEM. Po_2: oxygen tension. For other abbreviations see legend to figure 1.

Table 4. – $A\text{-}aPo_2$ (kPa) for control and oleic acid rabbits

Treatment groups		Baseline	1	Time h 2	3
Diluent					
	C	4.3±0.23	4.1±0.33	3.9±0.29	4.2±0.24
	O	4.3±0.24	7.6±0.42	8.7±0.48	8.5±0.44
PEEP					
	C	3.9±0.27	4.0±0.42	3.8±0.54	3.8±0.49
	O	3.9±0.49	5.9±0.72	6.2±0.65	5.9±0.32
Indo					
	C	4.1±0.48	4.1±0.39	3.8±0.62	3.5±0.65
	O	5.0±0.28	7.5±0.23	7.7±0.31	7.7±0.32
Indo+PEEP					
	C	4.6±0.46	4.8±0.52	4.1±0.47	3.7±0.73
	O	4.2±0.3	4.9±0.36	5.0±0.42	5.2±0.34

Values are mean±SEM. $A\text{-}aPo_2$: alveolar-to-arterial oxygen difference. For other abbreviations see legend to table 1.

Table 5. – FRC (ml) for control and oleic acid rabbits

Treatment groups		Baseline	1	Time h 2	3
Diluent					
	C	81.3±2.47	76.5±2.85	79.2±3.45	81.3±2.87
	O	79.1±3.01	70.9±3.90	72.8±3.78	72.8±4.04
PEEP					
	C	85.5±1.22	94.6±2.87	100.0±4.83	103.5±3.11
	O	80.9±5.51	99.5±7.18	102.0±5.95	100.9±6.48
Indo					
	C	82.0±6.08	82.1±4.47	82.0±3.94	83.8±3.93
	O	83.0±2.81	80.7±2.61	78.7±4.0	74.1±2.84
Indo+PEEP					
	C	81.8±1.77	92.7±1.55	93.5±3.43	95.0±4.64
	O	85.3±2.81	107.6±5.35	97.5±3.94	95.8±4.41

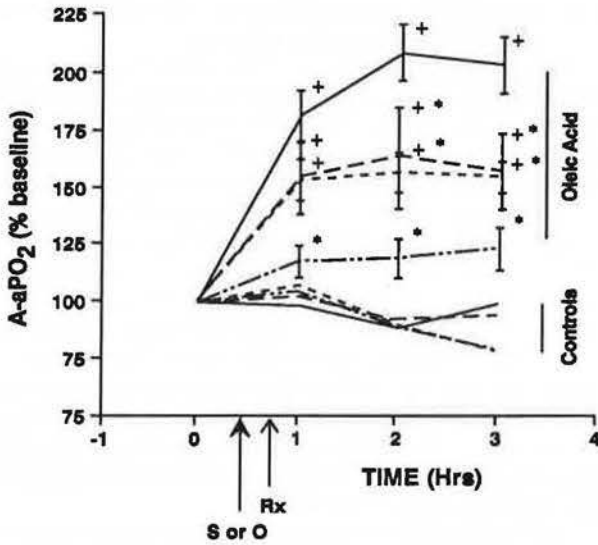Values are mean±SEM. FRC: functional residual capacity. For other abbreviations see legend to table 1.

Fig. 1. – A-aPo₂ as % change from baseline in the saline and oleic acid groups. O: oleic acid; S: saline; Rx: treatment. Group means±SEM (error bars have been omitted for clarity from the control groups. +: significant increase in A-aPo₂ with respect to baseline and respective control treatment subgroup, p<0.02. *: p<0.05 compared to diluent subgroup). ——— : diluent; – – – –: PEEP; - - - -: Indo; —·— ·— · : PEEP + Indo; A-aPo₂: alveolar-to-arterial oxygen difference; PEEP: positive end-expiratory pressure; Indo: indomethacin.
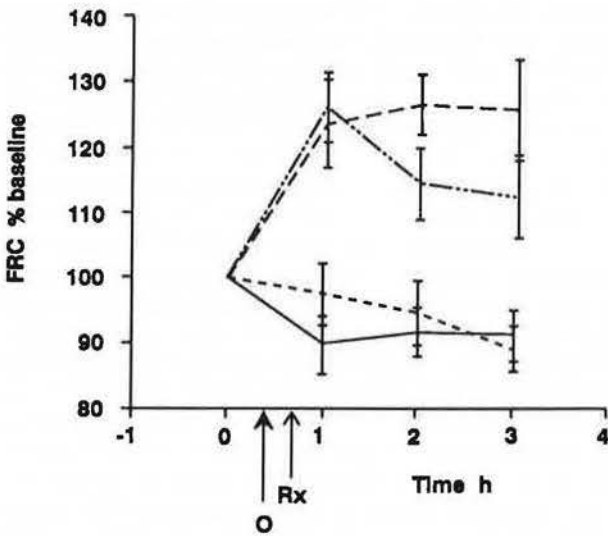

Fig. 2. – FRC as % change from baseline in the oleic acid animals. O: oleic acid; Rx: treatment. Group means±SEM. PEEP caused a significant increase in FRC. *: p<0.05 compared to non-PEEP groups. FRC: functional residual capacity; TGV: thoracic gas volume; PEEP: positive end-expiratory volume. ——— : diluent; – – – – : PEEP; - - - - : Indomethacin; —·—·—· : PEEP + indomethacin.

Oleic acid consistently caused tachypnoea, hypotension, and significant hypoxia. This was accompanied, in the diluent subgroup, by a marked increase in the % change in A-aPo₂ from baseline to the first hour (100 to 182±11.2%, p<0.002) (fig. 1). The A-aPo₂ continued to increase significantly through the second hour stabilizing in the third hour. This increase was attenuated by treatment with PEEP (100 to 155±16.2%), or indometh-

acin (100 to 154±8.9%) alone; these increases from baseline still being significant (p<0.02). The combination of these two treatments, PEEP + indomethacin reduced the increase in A-aPo₂ from baseline (100 to 118±6.8%) to a degree where the increase was not statistically significant at any timepoint (p<0.02).

Comparing the treatment subgroups at each timepoint, at 1 h the increase in A-aPo₂ in the PEEP + indomethacin subgroup was significantly less than that of the diluent subgroup. Treatment with PEEP or indomethacin alone was not different to the diluent subgroup. However, at 2 and 3 h the increase in A-aPo₂ in all of the treatments was significantly less than in the diluent subgroup (p<0.05).

Comparing the control treatment groups with their respective oleic acid treatment groups, oleic acid caused a significant increase in the % change in A-aPo₂ in all treatments except the PEEP + indomethacin groups (p<0.02).

FRC

In the control group, the % change in FRC in the diluent group, and indomethacin groups varied little over the four hours. Application of PEEP caused a significant increase in FRC both from baseline and compared to the subgroups not receiving PEEP (p<0.05).

Oleic acid caused a small fall in the % change in FRC from baseline in the diluent and indomethacin subgroups, which did not reach significance (fig. 2). PEEP caused a significant increase in FRC both alone and with indomethacin both from baseline (p<0.02) and from the non-PEEP subgroups (p<0.05).

Comparing the oleic treatment groups with their respective saline controls, there were no significant differences in any treatment in FRC.
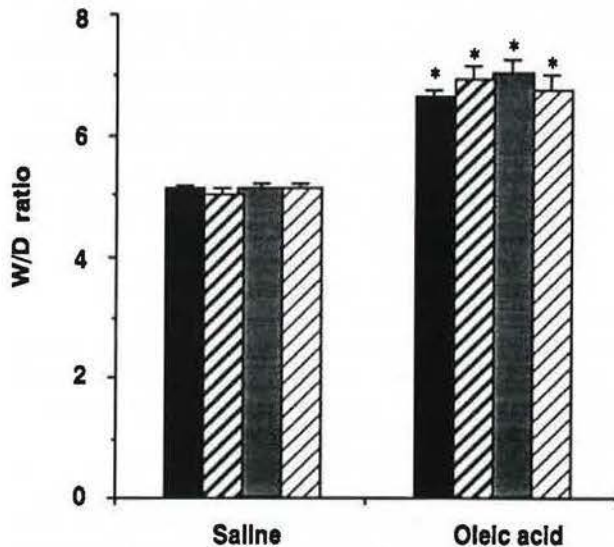

Fig. 3. – Wet-to-dry (W/D) lung weight ratios for saline and oleic acid animals. group mean±SEM. Oleic acid caused a significant increase in wet-to-dry weight ratios. *: p<0.01 compared to saline animals. ■ : diluent; ▨ : PEEP; ■ : Indomethacin; ▨: PEEP + Indo. PEEP: positive end-expiratory pressure.

Total lung water

Oleic acid caused a significant increase in the wet-to-dry lung weight ratios (p<0.01). This increase was not attenuated by PEEP or indomethacin alone or their combination (fig. 3).

Discussion

This study was designed to examine the effect of NSAIDS and PEEP in normal animals and an animal model of ARDS. In particular, these treatment interventions were commenced after the onset of injury, and their effects both alone and in combination were examined.

Oleic acid causes a rapid onset high permeability pulmonary oedema, that has been studied in a number of species [19]. Physiologically, it causes increased pulmonary artery pressure, reduced lung compliance and severe hypoxaemia [14–16]. Histologically, the model is characterized by an acute haemorrhagic alveolitis, with oedema fluid, interstitial leucocyte rich infiltrates and platelet microthrombi [14, 16, 20]. Vascular endothelium and alveolar epithelium are damaged resulting in alveolar flooding. The precise mechanisms mediating these changes remain unclear. Indomethacin, steroids, leucocyte and complement depletion have been found to offer no protection in terms of increased permeability or the histological injury. The role of the neutrophil remains uncertain although this model is thought to be neutrophil independent [19]. However, the reproduction of the physiological features meet the criteria for diagnosis of ARDS in humans, thus providing a useful animal model.

PEEP causes an increase in FRC by mechanically preventing the lung from returning to its resting end-expiratory position, preventing the collapse of flooded alveoli [4, 6, 7]. In addition, the increase in FRC is thought to be due in part to the production of prostaglandins, dilating the peripheral bronchial tree. Thus, it may have been anticipated that a NSAID with PEEP would diminish the increase in FRC achieved with PEEP, thereby reducing its efficacy in ARDS.

With respect to lung volumes, indomethacin did not reverse or inhibit the effects of PEEP. While the indomethacin+ PEEP subgroups did show slightly lower FRC values, the differences were not significant. This may be due to relative lack of smooth muscle in the peripheral bronchial tree in rabbits, as it was a finding common to both the normal animals and those with ARDS. Similarly, the improved gas exchange seen with PEEP was not impaired by indomethacin.

The failure of oleic acid to significantly reduce lung volumes may have been due to the small numbers in our study. In the diluent group FRC fell from 79.1±3.01 ml at baseline to 70.9±3.90 ml at 1 h (p<0.046), and 72.8±4.04 at 3 h (p<0.049), just failing to reach significance with our criteria. If the animals that died are included, the fall in FRC from baseline becomes   significant, Thus, our findings are not inconsistent with a previous study that reported significantly reduced FRC in rabbits given oleic acid (measured by helium dilution), [15] where similar wet-to-dry weight ratios were achieved.

Previous work has shown that meclofenamate and indomethacin improve oxygenation in oleic acid lung injury [9, 21] as have various NSAIDS in endotoxin and ethchlorvynol models of ARDS [10–12]. In all of these studies the NSAID alone prevented falls in arterial oxygen tension (Pa_{O_2}). Our results found that treatment with indomethacin or PEEP alone attenuated the rise in $A\text{-}aPo_2$ from baseline. However, combining the treatments, PEEP + indomethacin significantly prevented the deterioration in gas exchange to the point that $A\text{-}aPo_2$ in this group did not differ from that of its respective control. While this combination was not significantly different to either treatment alone (which may be due to the small numbers used in each group), indomethacin did not prove to reverse the benefits in gas exchange seen with PEEP.

PEEP is thought to reduce intrapulmonary shunt by reinflating flooded alveoli and redistributing extravascular water to the perivascular space, without affecting total lung water [4]. Indomethacin and meclofenamate have been found to reduce shunt fraction in animals with oleic acid lung injury [9, 21, 22]. Based on these findings it has been postulated that cyclooxygenase inhibition prevents the production of dilator prostaglandins (such as prostacyclin), thus maintaining the hypoxic vasoconstriction seen with lung injury and improving ventilation-perfusion matching. However, other work suggests that prostaglandins do not play a major role in modulating normoxic or hypoxic pulmonary vasomotor tone [8, 9] and that indomethacin increases pulmonary vascular resistence by mechanisms other than cyclooxygenase inhibition.

More specifically ALI and DUKE [22] looked at the role of indomethacin followed by PEEP in oleic acid pulmonary oedema in dogs with respect to intrapulmonary shunt. They found that indomethacin decreased perfusion in the injured lobe, by increasing vascular resistance, thus significantly decreasing shunt. The improvement with subsequently applied PEEP was not blocked, the addition of PEEP further decreasing shunt, to a level similar to that achieved with PEEP alone. However, FRC and blood gases were not measured. Thus, although affects of indomethacin on FRC could not be ruled out, it was concluded that the improvements in shunt had a vascular basis, with indomethacin possibly enhancing hypoxic vasoconstriction and that the beneficial effects of PEEP on gas exchange are probably not diminished by indomethacin. Our results now confirm that the use of indomethacin does not inhibit the actions of PEEP and that the improvement in gas exchange seen with the combination of PEEP + indomethacin is not due to indomethacin significantly improving FRC. In addition, although with the small numbers in each group PEEP + indomethacin was not shown to be significantly better than PEEP alone, our results suggest a trend to further improved gas exchange over that achieved with PEEP alone. Thus, PEEP and indomethacin may be acting *via* separate mechanisms, which produce an additive effect when used together to improve gas exchange.

PEEP, meclofenamate and indomethacin have all been found to ameliorate gas exchange but not prevent oedema in animal models of ARDS [9, 22, 23]. Hence, the results of this study where PEEP and indomethacin, alone or together, did not reduce the oedema associated with oleic acid, are consistent with previous work showing that the improvement in gas exchange is not related to the amount of extra vascular water present.

In conclusion, this study shows that in the oleic acid model of ARDS, indomethacin when combined with positive-end-expiratory pressure does not diminish the benefits of PEEP on either gas exchange or FRC. These findings would support the notion that non steroidal anti-inflammatory drugs may have a role in the management of ARDS.

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Effets de l'indomethacine et de la PEP sur l'oedème pulmonaire du lapin induit par l'acid oléique. K.S. Panaretto, C. Phillips, N. Berend.

RÉSUMÉ: Cette étude a été élaborée pour déterminer si l'indomethacine, qui a été suggérée comme traitement pour l'ARDS, pourrait inhiber l'efficacité de la PEP dans un modèle animal d'ARDS.

Nous avons mesuré chez les lapins, FRC, A-aPo₂ et l'eau pulmonaire total: il y eut 30 sujets contrôle et 30 lapins avec oedème pulmonaire induit par l'acid oléique. Au sein de chaque groupe, l'on a administré 4 traitements: l'agent diluant (n=12), PEEP (n=6), l'indomethacine (n=6), et la PEEP + l'indomethacine (n=6). Les lésions pulmonaires ont été induites à la 30e minute, et la traitement commencé à la 45e. L'acide oléique provoque une augmentation significative du % d'augmentation de A-aPo₂ à partir de la ligne de base à la 3e heure (105±12%); cette augmentation fut atténuée par la PEEP (59±17%) et l'indomethacine (57±5%), la combinaison de la PEEP et de l'indomethacine prévenant une augmentation significative (26±9%). La PEEP a augmenté la FRC chez les animaux soumis à la solution saline et à l'acide oléique; ceci n'a pas été redressé par l'indomethacine. L'acide oléique a provoqué une augmentation de l'eau pulmonaire totale (5.16 = 6.58±0.16 g), non influencée par aucun des traitements.

Ces observations suggèrent que l'indomethacine n'inhibe pas l'efficacité de la PEEP dans ce modèle d'ARDS.
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