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Effects of Closed Vs. Open Repeated Endotracheal Suctioning During Mechanical Ventilation on the Pulmonary and Circulatory Levels of Endothelin-1 in Lavage-Induced Rabbit ARDS Model

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Abstract

Background: A growing body of evidence demonstrates discretely the difference of open endotracheal suctioning (OES) and closed endotracheal suctioning (CES) on the respiratory and hemodynamic parameters in acute respiratory distress syndrome (ARDS). Endothelin-1 (ET-1), a mediator of vascular inflammation, cell proliferation, and fibrosis in addition to being a potent vasoconstrictor has been potentially implicated in the pathogenesis of ARDS. Here, we investigated the effects of repeated OES vs. CES during mechanical ventilation on circulatory and pulmonary levels of ET-1 in ARDS.

Methods: Briefly, 22 Japanese White Rabbits were intubated with a 3.5-mm endotracheal tube. Normal saline was instilled into lung and washed mildly. After instillation, rabbits were ventilated at definite setting; OES and CES duration was for 6 hours and performed every 30 minutes from protocol start.

Results: At circulatory level, either OES or CES did not alter plasma ET-1 level compared to the ET-1 level in ARDS before the initiation of endotracheal suctioning (OES 4.7 ± 1.3 pg/ml vs. CES 4.8 ± 1.5 pg/ml, *p*=0.839). In contrast, pulmonary ET-1 level was significantly higher in CES group compared to OES group after 6 hours of repeated suctioning in ARDS (OES 26.9 ± 2.2 pg/mg vs. CES 29.9 ± 3.3 pg/mg, *p*=0.018). This change in pulmonary ET-1 level could maintain a parallel relation with PaO_2 level.

Conclusion: At this moment, we can not clarify the mechanism and effects of the observed change in ET-1 in a rabbit model of ARDS as well as its clinical impact.

Keywords: Acute respiratory distress syndrome; Endotracheal suctioning; Endothelin-1

Abbreviations: OES: Open Endotracheal Suctioning; CES: Closed Endotracheal Suctioning; ARDS: Acute Respiratory Distress Syndrome; VILI: Ventilator-Induced Lung Injury; PEEP: Positive End Expiratory Pressure; ET-1: Endothelin-1; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6; ELISA: Enzyme-Linked Immunosorbent Assay

Introduction

Mechanical ventilation is an important support for patients with acute respiratory distress syndrome (ARDS), although it can cause ventilator-induced lung injury (VILI) [1-3]. The key to a successful clinical management of patients with ARDS is avoidance of further advancement of VILI [1-3]. For this reason, prevention of alveolar over-distension and derecruitment are the goals of recently proposed lung protective ventilation strategies. In order to achieve optimal alveolar recruitment, patients with ARDS are often exposed to high levels of positive end expiratory pressure (PEEP) [3-5]. During disconnect from ventilator, patients may be exposed to unintended sudden withdrawal of PEEP, which may induce harm to ARDS patients by causing lung collapse (derecuritment) and hypoxia.

Endotracheal suctioning is known to be one of the causes of repeated derecruitment during mechanical ventilation [6-10]. There are two methods of endotracheal suctioning based on selection of catheter: open endotracheal suctioning (OES) and closed endotracheal suctioning (CES). More recently, a growing body of evidence demonstrates discretely the difference of OES and CES on the respiratory and hemodynamic parameters in ARDS. The reports suggest

that OES induces alveolar derecruitment because of disconnection of the patients from the ventilator and negative suctioning pressure [6]. Moreover, repeated derecruitment is known to accelerate lung injury during mechanical ventilation [11,12]. In contrast, CES is effective to prevent alveolar derecruitment by avoiding ventilator disconnection, thereby maintaining appropriate oxygenation [6].

It has also been reported that hypoxia up-regulates endothelin-1 (ET-1) in epithelium and mucosal vasculature [13,14]. ET-1 is also a significant inflammatory factor that increases significantly in the plasma and lung tissue of patients with ARDS [15]. ET-1, a mediator of vascular inflammation, cell proliferation, and fibrosis in addition to being a potent vasoconstrictor has been potentially implicated in the pathogenesis of ARDS. The previous reports suggest that the production of ET-1 was increased in plasma and lung tissue in a VILI

model [16]. However, the ET-1 change in mechanical ventilation with endotracheal suctioning is still unknown.

In the present study, we generated a lavage-induced surfactant depleted ARDS rabbit model and investigated the effects of repeated OES vs. CES during mechanical ventilation of applied high PEEP on circulatory and pulmonary levels of ET-1.

Materials and Methods

The animal protocol of the present study was approved by the Ethics Committee of the Animal Resource Center of the University of Tsukuba. The animals were cared for in accordance with the guidelines for ethical animal research.

Animal preparation and induction of lung injury

Briefly, 22 rabbits (2.8-3.5 kg) were initially anesthetized and intubated with a 3.5-mm endotracheal tube. Then, animals were ventilated in pressure-controlled mode with a constant tidal volume (6 mL/kg). Anesthesia and muscle paralysis were maintained by continuous infusion of sodium pentobarbital (5 mg/kg/h) and pancuronium (0.1 mg/kg/h) via infusion pump through the ear vein. Normal saline (3 mL/kg/h) was then continuously infused as maintenance fluid. The right carotid artery was catheterized for blood gas sampling and monitoring of arterial pressure. Heart rate and mean arterial pressure were monitored by using Philips IntelliVueMP50 Patient Monitor (Philips MedizinSysteme GmbH, Böblingen, Germany).

After 30 min of stability, baseline data were recorded. Through the endotracheal tube, 15 mL/kg of saline solution at 38°C was administered into the lung, using a modification of the technique described earlier by Lachmann et al. [17]. Lavage was repeated until the arterial blood gas, drawn 5 mins later, showed $PaO_2 < 100$ mmHg. After we confirmed stable severe lung injury by another arterial blood gas 30 min later ($PaO_2 < 100$ mmHg), the experimental protocol was begun.

Ventilation protocol

After lung injury, intermittent mandatory pressure control ventilation was set up. The fraction of inspired oxygen was set at 1.0. Tidal volume was set at 6 mL/kg, inspiratory time at 0.5 secs, PEEP set at 10 cm H_2O and the mandatory respiratory rate at 30/min. The mandatory respiratory rate was subsequently adjusted to maintain the $PaCO_2$ in the range of 60-100 mmHg when possible, with a minimum rate of 4 /min and maximum of 40/min.

Suctioning protocol

After lung injury, one animal from each pair was randomly assigned to either the CES or OES groups. However, none treated rabbits (no lavage and suctioning) were used as a healthy control (Control). Endotracheal suctioning was performed twice every 30 minute during ventilation. CES was performed using 6 French-closed suctioning catheter (Ballard Medical products, Draper, Utah) connected to endotracheal tube under following conditions: a) a suctioning time and pressure of 10 sec and 140 mmHg, respectively; and b) suction depth of 2 cm (length of adapter) plus length of tracheal tube. OES was performed with the same catheter (Trachcare) under the same conditions, except with a disconnected ventilator circuit from the animal.

Enzyme-Linked Immunosorbent Assay (ELISA)

The concentrations of ET-1, tumor necrosis factor (TNF)-α and

interleukin (IL)-6in lung tissue and plasma/serum were determined by a commercial ELISA kit (R&D Systems, MN, USA). All assays were performed in duplicate.

Histologic analysis

The right lungs were inflated with 4% formaldehyde to a pressure of 20 cm H_2O via trachea and were fixed in 4% formaldehyde for >24 h. Subsequently the lungs were divided into 4 regions with a #11 blade scalpel. Each region was then sectioned, stained with hematoxylin and eosin, and scored by two investigators blinded to experimental conditions. Samples were assigned an injury score in each of the 5 categories (edema, hemorrhage, neutrophil infiltration, bronchiolar epithelial desquamation, and hyaline membrane formation) based on severity (0=not present, 4=severe and present throughout) a previously described [16,17]. Regional composite lung injury scores were calculated by summing the category scores within each lung region. Whole lung injury scores were calculated by summing the regional composite lung scores within each animal.

Statistical analysis

Baseline, hemodynamic, gas exchange variables, ET-1, TNF-α and IL-6 concentrations were expressed as mean ± SD. Intergroup differences were compared by Student's t-test. Repeated-measures analysis of variance was used to determine intra group differences. Specific time points of this difference were determined by using Bonferroni's correction for multiple comparisons. Lung injury score were expressed as medians and interquartile range (25th and 75th percentiles) and the data was analyzed using Mann-Whitney U test. The relationships between the variables were evaluated by the pearson correlation coefficient. A result was considered significant at P<0.05. The data from each group were compared with the previous time point starting from baseline injury by a test of within-subjects contrasts of repeated-measures analysis of variance by IBM-SPSS version19.0 software (IBM-SPSS Inc, Chicago, IL).

Results

Baseline characteristics

Baseline characteristics of the animals in the study groups are shown in Table 1. There were no differences in body weight, hemodynamic variables and gas exchange before the induction of lung injury.

Gas exchange

After lung injury was induced, PaO_2 was reduced to a mean of 66 ± 19 mmHg and 67 ± 14 mmHg for the CES and OES groups,

	OES group n = 9	CES group n = 9	p Value
Wt, kg	3.1 ± 0.2	3.0 ± 0.2	.273
Lavage, times	3.0 ± 0.2	3.0 ± 0.4	.673
MAP, mmHg	125 ± 13	115 ± 13	.081
HR, beats/min	211 ± 50	204 ± 35	.470
RR, breaths/min	24.5 ± 4.6	22.7 ± 6.8	.532
PIP, mmHg	12.3 ± 1.9	13.5 ± 2.7	.091
Arterial pH	7.40 ± 0.22	7.38 ± 0.45	.104
PaO₂, mmHg	470.6 ± 22	485.1 ± 55.4	.588
PaCO₂, mmHg	45.2 ± 4.5	45.6 ± 5.8	.883

OES: Open Endotracheal Suctioning; CES: Closed Endotracheal Suctioning; MAP: Mean Arterial Pressure; HR: Heart Rate; RR: Respiration Rate; PIP: Peak Inspiratory Pressure. Values are mean ± SD

Table 1: Baseline characteristic of experimental animals.

respectively ($p=0.995$). After PEEP levels were increased to 10 cm H_2O, PaO_2 increased to >400 mmHg in both groups. In the CES group, PaO_2 remained 400 mmHg for the duration of the study. However, in the OES group, PaO_2 decreased continuously and dropped to a mean of 300 ± 128 mmHg at 4 hour and to 291 ± 48 mmHg at 6 hour ($p=0.023$ and $p=0.001$ vs. PaO_2 at 1hour after injury). This PaO_2 level was significantly lower than in the CES groups ($p=0.023$ and $p=0.001$ at 4 and 6 hours, respectively) (Table 2).

Heart rate and mean arterial pressure

Overall there was no significant difference in mean arterial pressure and heart rate between both groups (Table 2).

Histologic analysis

No significant differences in histologic variables were observed between CES (median, 6; interquartile range, 2.5-9.0) and OES (median, 8.0; interquartile range, 5.5-14.0) lungs ($p=0.329$).

Circulatory and pulmonary levels of ET-1 in different suctioning groups by ELISA

There was no significant difference observed in the levels of plasma ET-1 between experimental groups at baseline (Figure 1) before the start of lavage ($p=0.916$). After induction of lung injury, but before the start of CES and OES interventions, plasma ET-1 levels of the two groups treated with saline lavage were elevated significantly (CES group; 4.7 ± 1.3 pg/ml, OES group; 5.0 ± 1.0 pg/ml) compared to the baseline variables(no lung injury, all $p<0.001$) (Figure 1). At circulatory level, either CES or OES did not alter plasma ET-1 levels compared to levels (ET-1) observed at the end of the six hours repeated suctioning protocol in ARDS (lung injury) animals. The mean values for ET-1plasma concentrations in the CES and OES groups after 6 hours were 4.8 ± 1.5 pg/ml and 4.7 ± 1.3 pg/ml, respectively ($p=0.839$) (Figure 1). In contrast, ET-1 level of lung tissues was significantly higher in CES group compared to the OES group after 6 hours of repeated suctioning in lavage-induced ARDS. The ET-1 level of lung tissues concentrations in the CES and OES groups were 29.9 ± 3.3 pg/mg and 26.9 ± 2.2 pg/mg, respectively ($p=0.018$) (Figure 1).

Correlation assessment between ET-1 levels and value of PaO_2

No significant correlation was observed either between plasma or pulmonary ET-1 levels and PaO_2, respectively (r=-0.037, $p=0.86$) (r=-0.223, $p=0.26$) in each experimental group, irrespective of the type of suctioning used, in the present study.

Circulatory and pulmonary levels of TNF-α and IL-6 in different suctioning groups by ELISA

There were no significant differences observed in pulmonary and serum protein concentrations of IL-6 and TNF-α between CES and OES groups, as demonstrated by ELISA. Pulmonary and serum concentrations of IL-6 and pulmonary concentrations of TNF-α were higher in all other groups (lung injury irrespective of type of suctioning protocol) compared to the control groups (all $p<0.005$). Mean values for IL-6 pulmonary concentrations (pg/mg) in the CES, OES and control groups were 267 ± 157, $303 \pm 177$and 79 ± 7, respectively. IL-6 serum concentrations (pg/ml) in the CES, OES and control groups were 232 ± 45, 245 ± 52 and 84 ± 20, respectively. The concentrations of pulmonary TNF-α (pg/mg) in the CES, OES and control groups were 654 ± 320, 633 ± 260 and 91 ± 63, respectively. TNF-α serum concentrations (pg/ml) in the CES, OES and control groups were 66 ± 38, $91 \pm 41$and 30 ± 2, respectively.
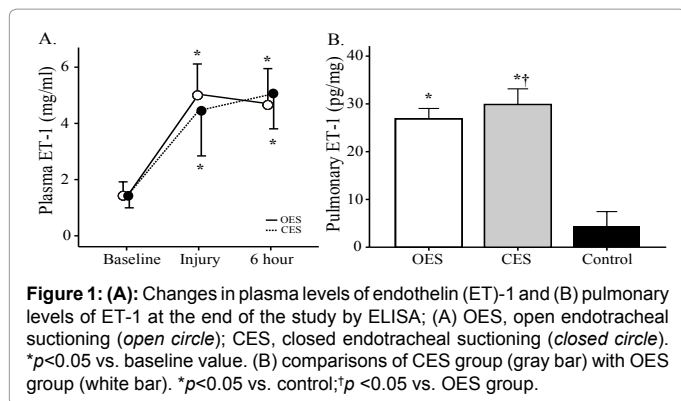
Discussion

The key findings of the present study are that: a) repeated open endotracheal suctioning causes gradual and time-dependent reductions in arterial oxygenation over the course of endotracheal suctioning; b) there was no distinct difference in lung injury severity and extent between OES and CES groups; c) at circulatory level, either OES or CES did not alter plasma ET-1 level. In contrast, pulmonary ET-1 level was significantly higher in CES group compared to the OES group after 6 hours of repeated suctioning in lavage-induced ARDS animals. The changes in ET-1 levels in the OES and CES groups did not correlate with changes in accompanying arterial oxygenation and blood pressure of the current lung injury model.

The lung lavage induced ARDS model is a well characterized and frequently used experimental model of ARDS [18,19]. After the lavage, animals are initially induced surfactant depleted, severe atelectasis and decreased arterial PaO_2. Severe atelectasis then cause lung injury (atelectruma) because of the associated shear stress on the boundary between aerated and collapsed areas oratelectasis per se may promote lung injury through the activation of intracellular pathways that may alter cellular life span [20]. To achieve a large-enough difference between the *in vivo* ARDS models, we used a lung protective strategy combining low VT with high PEEP to minimize further injury. This concept of high PEEP protection was supported by some previous studies illustrating that the use of PEEP could decrease atelectrauma

Variables	group	baseline	injury	2Hr	4Hr	6Hr
PIP , cm H$_2$O	OES	12.3 ± 1.9	18.5 ± 2.8 [b]	22.4 ± 2.6	23.4 ± 2.4[ab]	24.3 ± 2.5[ab]
	CES	13.5 ± 2.7	19.2 ± 2.7 [b]	21.3 ± 2.0	21.2 ± 2.2	21.8 ± 2.3
Arterial pH	OES	7.40 ±0.22	7.03 ± 0.15 [b]	7.14 ± 0.14	7.03 ± 0.11	7.02 ± 0.11
	CES	7.38 ±0.45	7.05 ± 0.12 [b]	7.15 ± 0.11	7.11 ± 0.15	7.14 ± 0.07
Lactate, mmol/L	OES	1.60 ± 0.91	5.46 ± 2.98	5.10 ± 5.40	5.96 ± 6.12	6.07 ± 7.01
	CES	1.46 ± 0.59	6.40 ± 3.29	4.46 ± 3.82	5.38 ± 4.54	6.28 ± 7.61
PaO$_2$, mmHg	OES	470 ± 22	67 ± 14	467 ± 33	300 ± 128[ab]	291 ± 48[ab]
	CES	483 ± 55	66 ± 19	447 ± 54	430 ± 74	434 ± 103
MAP, mmHg	OES	125 ± 13	118 ± 20[b]	103 ± 16[b]	99 ± 23	92 ± 17 [b]
	CES	115± 13	121 ± 17	97 ± 15	91 ± 21	90 ± 17[b]
HR, beats/min	OES	211 ± 50	214 ± 40	210 ± 33	212 ± 41	213 ± 32
	CES	204 ± 35	189 ± 25	217 ± 33	210 ± 35	208 ± 27

OES, open endotracheal suctioning; CES, closed endotracheal suctioning; PIP, peak inspiratory pressure; MAP, mean arterial pressure; HR, heart rate.Values are mean ± SD.[a]p <0.05 vs. CES group; [b]p<0.05 compared with previous value within the same group

Table 2: Sequential changes in variables of lung mechanics and hemodynamics.

Figure 1: (A): Changes in plasma levels of endothelin (ET)-1 and (B) pulmonary levels of ET-1 at the end of the study by ELISA; (A) OES, open endotracheal suctioning (*open circle*); CES, closed endotracheal suctioning (*closed circle*). *$p<0.05$ vs. baseline value. (B) comparisons of CES group (gray bar) with OES group (white bar). *$p<0.05$ vs. control; †$p <0.05$ vs. OES group.

and microatelectatic area. To prevent further injury caused by inappropriate PEEP, the current study adopted an appropriate PEEP of 10 cm H_2O according to a recent rabbits lavage induced ARDS model study which presented that the optimized PEEP was between 9 and 12 cm H_2O [11,12]. Suh et al. [11] showed that repeated derecruitment appeared to cause lung damage during mechanical ventilation with high PEEP in a lavage-induced surfactant-depleted lung injury model [12].

Previous studies reported that levels of circulatory and pulmonary ET-1 are elevated in ARDS models [16,21,22]. The current data are consistent with data from these earlier reports. Thus, collectively, data from the present study and these earlier studies show a significant alteration in levels of both circulatory and pulmonary ET-1 compared to the healthy control subjects in lavage-induced surfactant depleted ARDS models. Secondly, these data suggest validation of the present animal model as a suitable model for ARDS, including the patterns of circulatory and pulmonary ET-1 levels as seen in other frequently used ARDS models [16,21,22].

Endotracheal suctioning is known to be one of the causes of repeated derecruitment, hypoxemia and hemodynamic instability in ARDS subjects [6-10]. While CES is effective in preventing alveolar derecruitment and hemodynamic instability by avoiding ventilator disconnection, thereby maintaining appropriate oxygenation [6], OES has been shown to cause significant hypoxygenation and hemodynamic instability in mechanically-ventilated subjects [6-10]. ET-1, the most potent vasoconstrictor known so far, has been shown to potentially associate with hypoxygenation and hemodynamic change [23] in previous report. However, there is a lack of evidence on the effects of OES on ET-1 levels in mechanically-ventilated lung injury model/subject. Collectively, these facts led us to assume that OES would cause further aggravation in pulmonary ET-1 levels compared to CES in the current study design in lung injury model which had already upregulated ET-1 level compared to the healthy control subject. Further, we assumed that if pulmonary ET-1 levels were more up-regulated in OES group, then there might be a significant correlation between the upregulated levels of ET-1 in lung and the decrease in arterial oxygenation caused by OES in the current experimental setting.

In fact, our present findings on arterial desaturation are similar to those of other groups that have evaluated CES [6,8,24-26]. Consistent to our results, other groups have also found that arterial desaturation related to endotracheal suctioning is greater with OES than with CES [6,8,24-26]. Moreover, the present study demonstrated that PIP levels were higher in the OES group compared to CES groups. This finding suggests that the OES group had decreased lung compliance than that in

CES group. Therefore, it is likely that continuous alveolar derecruitment is responsible for this progressive reduction in oxygenation as observed in OES group. Although arterial desaturation related to endotracheal suctioning is greater with OES than with CES in present study, plasma and pulmonary ET-1 changes did not correlate with changes in reductions in arterial oxygenation of the lung injury model. Further, while ET-1 levels of lung tissue were significantly higher in CES group compared to the OES group, there was no significant difference in lung injury score between OES and CES groups, as demonstrated in the present study. In fact, in our most recent observation [27], using the same model and time points as in the present study, repeated OES and CES failed to cause further up regulation of serum and pulmonary TNF-α and IL-6 in the ARDS model. Thus, this is the first study to show differential expression of potential inflammatory cytokines, such as TNF-α, IL-6 and ET-1 in mechanically-ventilated lung injury models, which depended on the types of endotracheal suctioning, performed.

ET-1 is known to be released during various types of endothelial impairment, such as ischemia, reperfusion and sepsis [28,29]. Also ET-1 enhance the inflammatory response, increase the microvascular leak [30], and exacerbate the lung injury [31]. While ET-1 levels of lung tissue were significantly higher in CES group compared to the OES group, parallel or corresponding changes in lung injury were not observed in the present study. The discrepancies between the present data with the earlier mentioned reports above for now cannot be adequately accounted for. We do, however, know that the human lung is an important site for both ET-1 clearance and production [32]. In a past study, net pulmonary ET-1 clearance was found to decrease early in ARDS, and was reversed in patients who subsequently recovered [33]. In the present study, CES group may have earlier recovery from ARDS and, subsequently, may have higher pulmonary levels of ET-1. At this moment, the underlying mechanism and effects of the observed change in ET-1 in a rabbit model of ARDS as well as its clinical impact are unclear. In addition, throughout the experiment, no significant difference in blood pressure was observed between OES and CES groups, although pulmonary levels of ET-1 in the CES group were increased in animals with lung injury. Because ET-1 is a potent vasoconstrictor that has been implicated in the pathogenesis of hypertension [27], many studies have been able to show the relationship between blood pressure and ET-1 change. For now, the mechanisms underlying the selective and tissue-specific increase in ET-1 levels in pulmonary but not in circulatory level as observed here, also remains unclear.

One of the most important findings of the present study is that, there were no significant correlations between plasma/pulmonary ET-1 levels and the accompanying arterial desaturation in each group of endotracheal suctioning. It is difficult to explain this unexpected finding in the context of alterations observed in other target parameters in the current study, which ranged from morphological injury to other potential cytokine assessment. Future studies are needed to clarify the relationship between ET-1 expression profile and the degree of arterial desaturation in view of the clinical implications of the present findings, where longer duration of suctioning was utilized. Future studies should also focus on more in depth exploration of involvement of various inflammatory cytokines and vaso-active peptides tically engineered experimental animal models. Indeed, biotrauma is known toin the pathogenesis of VILI in ARDS/lung injury subjects undergoing mechanical ventilation using gene potentially contribute to the development and progression of VILI in ARDS subject although this biotrauma field in connection with VILI has just begun to be investigated.

Conclusion

The current observation for the first time reported the involvement of vasoactive peptide like ET-1 underlying the pulmonary changes of endotracheal suctioning during mechanical ventilation in a lavage induced ARDS model. At this moment, we cannot clarify the mechanism and effects of the observed change in ET-1 in a rabbit model of ARDS as well as its clinical impact.

Acknowledgements

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