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# Plasma Soluble Intercellular Adhesion Molecule-1 (sICAM-1) in Pediatric ARDS During High Frequency Oscillatory Ventilation: A Predictor of Mortality

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**SUMMARY** Soluble intercellular adhesion molecule-1 (sICAM-1), an important adhesion molecule that mediates leukocyte-endothelial interaction, has been identified as a marker for the outcome of acute respiratory tract infection. We postulate that plasma ICAM-1 may be a valuable marker for both biological and clinical severity of acute respiratory distress syndrome (ARDS). Sixteen pediatric patients (> 1 month and < 15 years of age) diagnosed with ARDS were recruited from the Pediatric Intensive Care Unit at King Chulalongkorn Memorial University Hospital, Bangkok. The patients were randomized to receive either high frequency oscillatory ventilation (HFOV) or conventional mechanical ventilation. Plasma sICAM-1 was measured by enzyme linked immunosorbent assay (ELISA) on days 1, 3, 5 and 7 of ARDS. Plasma sICAM-1 levels in survivors and non-survivors of the HFOV and conventional treatment groups were compared. Nine and 7 patients constituted the control group receiving conventional treatment and HFOV group, respectively. Overall nine patients survived. The patients in the HFOV group had a better chance of survival compared to the controls (71% versus 31.5%), but it was not statistically significant ($p$ = 0.2). The overall mortality was 45.7%. The mean plasma sICAM-1 levels (n = 13/16) were significantly elevated among non-survival patients as compared to survival patients at all time points, which indicates that an unfavorable outcome in ARDS is related to the degree of epithelial and endothelial alveolar cell injury. The elevation of plasma sICAM-1 on day 3 provided the best predictor of mortality (likelihood ratio 11.9, $p < 0.001$). It was concluded that HFOV facilitated a potentially better outcome compared to conventional treatment and it was associated with less lung injuries evidenced by lower plasma sICAM-1.

Acute respiratory distress syndrome (ARDS) is a clinical and physiopathological disorder characterized by acute and diffuse injury to the endothelial and epithelial surfaces of the lung which leads to respiratory failure. The diffuse alveolar damage is manifested by the breakdown of both the barrier and gas exchange functions of the lung, resulting in proteinaceous alveolar edema and hypoxemia.[1,2] It remains one of the most challenging organ failures in intensive care medicine, and has stimulated research both clinically and in basic science into various ways to try to reduce mortality.[3,4]

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High frequency ventilation treatment (HFV) utilizes below-physiological tidal volumes (1-3 cc/kg) and high ventilation rates (> 300 breaths/minute). Published data on high frequency oscillatory ventilation (HFOV) in pediatric patients with acute respiratory failure are scarce.[5] In 1994, Arnold and colleagues[6] reported the results of a multicenter, randomized trial comparing HFOV and conventional mechanical ventilation in pediatric patients with ARDS. This study demonstrated that application of HFOV resulted in improved survival, less barotrauma and less oxygen requirement at day 30. It appears to be a therapy with great promise for the treatment of acute respiratory failure refractory to management with conventional mechanical ventilation. Several studies have shown that an inflammatory response may be elicited by mechanical ventilation used for recruitment and de-recruitment of collapsed lung units or on over-distended alveolar regions.[7-11] HFOV may minimize lung injury resulting from baro-trauma, volu-trauma and subsequently attenuate inflammatory mediator induction such as cytokines or adhesion molecules. These physiological responses may have implications for the clinical outcome.[12]

The role of cytokines in the pathophysiology of ARDS is well-recognized. Tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-8 (IL-8) play an important role in the early inflammatory response of most patients with ARDS, although other pro-inflammatory pathways may also be involved.[10,13-15] Nevertheless, recent clinical trials have shown some conflicting results as to the role of pro-inflammatory cytokines[16-18] which may suggest that the physiopathology of lung injuries in ARDS patients is indeed complex and requires further investigation. However, the prognostic value of other biological markers of lung injuries in pediatric ARDS has not been thoroughly examined. Recently published data have shown the importance of adhesion molecules especially sICAM-1 in various pulmonary diseases.[19,20] It is found on the alveolar capillary endothelium, epithelium, as well as alveolar macrophages and is released in soluble form in experimental acute lung injuries (ALI).[19-21] Additionally, Flori *et al.*[22] demonstrated that early elevation of sICAM-1 in pediatric patients with acute lung injury is associated with an increased risk of death or prolonged duration of mechanical ventilation.

The purpose of this study was to investigate sICAM-1 in plasma during HFOV and conventional treatment. The sICAM-1 levels measured at intervals were correlated with the clinical course of ARDS. In addition, the overall clinical outcome was compared with that obtained by conventional treatment.

## PATIENTS AND METHODS

### Study population

We recruited 16 pediatric patients (>1 month and <15 years of age) diagnosed with ARDS at the Pediatric Intensive Care Unit, King Chulalongkorn Memorial University Hospital, Bangkok, Thailand, from September 2000 to September 2002. The study was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed and written consent was obtained from the parents prior to the patients' evaluation for HFOV therapy.

Patients were diagnosed with ARDS according to standard criteria[22] and met the following entry criteria: 1) Required PEEP $\geq$ 5cm $H_2O$, 2) $FiO_2$ $\geq$ 0.6 regardless of PEEP level for $\geq$ 12 hours to maintain oxygen saturation $\geq$ 92%, and 3) an oxygenation index (OI) > 15 for $\geq$ 4 hours (OI= $MAP \times FiO_2 / PaO_2 \times 100$; MAP = mean airway pressure).

Patients exhibiting any of the criteria listed below were excluded from the study: pulmonary capillary wedge pressure $\geq$ 18 mmHg, initial CVP $\geq$ 10 mmHg, severe irreversible neurological injury, intractable shock, weight above 35 kg (in HFOV), the underlying disease was deemed irreversible, or ARDS > 48 hours.

### Study protocol

The clinical investigators enrolled and randomized the patients, collected blood and administered the treatment protocol. All adverse effects were recorded accordingly. All patients were intubated, sedated and paralyzed. Cardiopulmonary monitors and pulse oximeters were applied. Pulmonary arterial catheter was not a prerequisite. The following outcome variables were used to access the relative efficacy of HFOV: 1) duration of mechanical ventilation, 2) daily level of mechanical ventilatory support

(Paw, amplitude, $FiO_2$ etc.), 3) daily measurement of OI, $PaO_2/FiO_2$, A-a gradient where applicable, etc., and 4) survival.

The patients in the control group were ventilated with conventional ventilators (CV, Puritan Bennett 7200, Servo 900, Servo 300 or similar ventilators). Time-cycled or pressure-controlled ventilation was performed. High frequency ventilation was delivered by a high frequency oscillator (model 3100, Sensormedics, Yorba Linda, CA). Initial mean airway pressure was selected at 2-3 $cmH_2O$ above the conventional ventilation. The respiratory rate was set at 4-10 Hz according to body weight with an inspiratory time of 33 % and the amplitude was set at 10 $cmH_2O$ above the positive inspiratory pressure (PIP) level of conventional ventilation. Further adjustments in mean airway pressure, $FiO_2$ and respiratory rate were based on arterial blood gas measurements. Metabolic acidosis was aggressively treated by volume replacement and/or inotropes. Additionally, the patients' hemodynamic and physiological variables were maximized maintaining Hct between 32-35 g%, urine output > 1 cc/kg/hour, CI > 4 or capillary refill < 2 seconds. As soon as the patients tolerated endotracheal suctioning without significant changes in saturation after reinstitution of HFOV and the mean airway pressure was 18 ± 3 cm $H_2O$, they were switched to conventional ventilation.

**Oxygenation and ventilation**

Attempts were made to maintain $PaO_2$ above 70 torr or oxygen saturation above 92% at all times. In all patients receiving conventional ventilation, peak inspiratory pressure was limited not to exceed 35 $cmH_2O$ or a pressure plateau ($P_{plat}$) below 30 $cmH_2O$. In addition, the arterial pH was kept at 7.25 or above with the $PaCO_2$ target ranging between 45 and 65 torr. If the patients responded well to the conventional treatment showing improvement in oxygenation, a decrease in $FiO_2$ (until $FiO_2 < 0.6$) took priority over decreasing the positive end expiratory pressure (PEEP) as long as the lung field was not hyperinflated. Patients' outcomes in terms of survival and complications were noted.

**sICAM-1 analysis**

Blood was drawn at specific time points (days 1, 3, 5 and 7) by using EDTA tubes. The plasma was then separated by centrifugation and kept at -70ºC until it was used in the experiment. Levels of sICAM-1 in plasma samples were measured by using commercially available ELISA kits (R&D Systems, MN, USA). This assay employs the quantitative sandwich enzyme immunoassay technique. It has a minimal detectable level of < 0.35 ng/ml.

**Statistical analysis**

Due to unequal numbers of patients at each time point, the importance of determining the effect of HFOV and control on gas exchange, outcome variables, and the irregularity of the data, a non-parametric Wilcoxon's paired test, chi square test and stepwise regression analysis were used for comparison where applicable. A $p < 0.05$ was considered significant. The SPSS program (version 11.0, Chicago, IL) was used for statistical analysis.

## RESULTS

Sixteen patients who met the inclusion criteria were randomized to one of the two treatment groups (random numbers had already been assigned prior to the study without knowing the patients). There was no cross-over between groups except for our last patient, who had initially been assigned to the conventional mode of mechanical ventilation but later developed extensive pneumothorax (Fig. 1). His overall condition rapidly deteriorated. Hence, we decided to switch him from conventional mode to HFOV and terminated our study prematurely. He

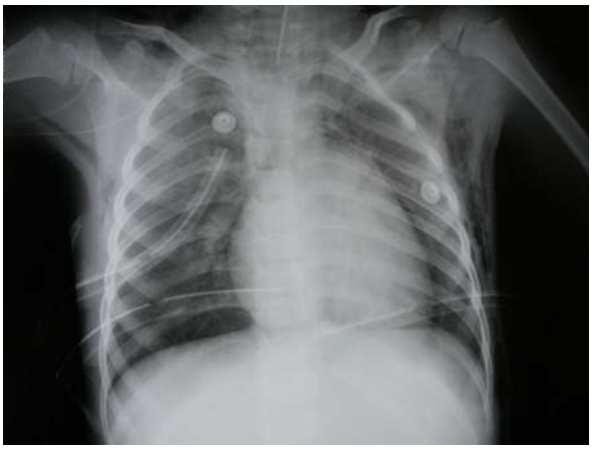

**Fig. 1** A chest x- ray of a patient at second day prior to HFOV.

eventually became one of our survivors. Nine children were randomized to the conventional group and seven were in the HFOV group. Base-line characteristics of patients in both groups are shown in Tables 1 and 2.

Arterial pH, $PaCO_2$, $PaO_2$ and $PaO_2/FiO_2$, and both mean airway pressure and oxygen index values markedly improved within the first 24 hours in the HFOV group compared to CV (data not shown). Survivors in the HFOV group required less days on the ventilator (13.6 ± 4 days [mean ± SEM]) compared to the conventional group (20 ± 4 days; mean ± SEM). Furthermore, the survival rate of patients receiving HFOV was much higher at 71% (5/7) versus 44% (4/9) with CV and overall was at 57.5%. Although the improvement in outcome was obvious, the difference in survival between the two groups did not reach statistical significance ($p = 0.2$, n = 16) due to the low sample size. One of our last patients who had been on CV developed extensive pneumothorax. We also observed that the ones who were on the conventional mode showed evidence of a very early air-leak (pneumomediastinum, small pneumothorax) in spite of a limited PIP (< 35 $cmH_2O$) compared to HFOV at 96 hours after enrollment into the study. Non-survivors in the HFOV group succumbed to the following causes: severe combined immunodeficiency (SCID, n = 2) with septic shock and severe pneumonia, one of them had

**Table 1** Base-line characteristics of patients in both groups

| **Group** | **Age** (yrs) | **Diagnosis and/or under lying disease** | **Days on ventilator** (survival, days) | **Outcome** |
|---|---|---|---|---|
| **Conventional** | | | | |
| Patient No. | | | | |
| 1 | 5 | ALL/Pc | 23 | Survived |
| 2 | 4 | Burkitt lymphoma | - | Expired |
| 3 | 15 | SLE with TB | 14 | Survived |
| 4 | 9 | *Staphylococcus* pneumonia | - | Expired |
| 5 | 3 | Hodgkin's lymphoma | 22 | Survived |
| 6 | 6 | Acute leukemia | - | Expired |
| 7 | 15 | SLE with pneumonia | 21 | Survived |
| 8 | 13 | CML/S/PBM transplant | - | Expired |
| 9 | 6 | HIV/severe pneumonia | - | Expired |
| **Average** (Mean ± SE) | 8.4 ± 1.6 | | 20 ± 4 (s), n = 4 | |
| **HFOV** | | | | |
| Patient No. | | | | |
| 1 | 2.8 | ANLL | 12 | Survived |
| 2 | 0.8 | SCID/BM transplant | - | Expired |
| 3 | 2 | Aspiration pneumonia | 10 | Survived |
| 4 | 0.5 | SCID | - | Expired |
| 5 | 0.8 | Wiskott Aldrich/severe pneumonia | 18 | Survived |
| 6 | 5 | Hodgkin's lymphoma | 10 | Survived |
| 7 | 5.5 | Near drowning | 18 | Survived |
| **Average** (Mean ± SE) | 2.48 ± 0.7 | | 13.6 ± 4 (s), n = 5 | |

SCID, severe combine immune deficiency; ALL, acute lymphoblastic leukemia; Pc, *Pneumocystis carinii*; CML, chronic myeloid

**Table 2** Characteristics of pediatric patients with ARDS compared between conventional and HFOV group at enrollment

| | Conventional (Mean ± SE) | HFOV (Mean ± SE) | *p* value |
|---|---|---|---|
| **1. Oxygen Index at enrollment** | 16.4 ± 1.6 | 23.9 ± 4.3 | NS |
| **2. A-a Gradient at Enrollment** | 480 ± 28.6 | 533.9 ± 46 | NS |
| **3. Initial pH** | 7.4 ± 0.05 | 7.31± 0.09 | NS |
| **4. $PaO_2/FiO_2$** | 131.7 ± 26.06 | 110 ± 30.22 | NS |

**Table 3** The levels of plasma sICAM-1 compared between survivor and non-survivor groups at days 1, 3, 5 and 7.

| Group | **Level of sICAM-1** (Mean ± SEM, ng/ml) | | | |
|---|---|---|---|---|
| | **Day 1** | **Day 3** | **Day 5** | **Day 7** |
| **Survivors** | 538.9 ± 57.5 (n = 8) | 579.6 ± 107.22 (n = 8) | 583.4 ± 101.7 (n = 8) | 323.5 ± 41.2 (n = 4) |
| **Non-survivors** | 1,182 ± 116.49 (n = 5) | 1,339.6 ± 122.2 (n = 5) | 948.8 ± 86.9 (n = 5) | 1,195.6 ± 103.1 (n = 5) |

bone marrow transplantation. Three patients developed pneumothorax while receiving CV. There were a few episodes of hypotension during HFOV that required suctioning to clear secretions responsive to either fluid bolus or inotropes. This complication has been described previously.[23]

Blood of thirteen out of sixteen patients was available for sICAM-1 analysis. The mean plasma sICAM-1 was significantly elevated in non-survival patients both in the conventional and HFOV groups compared to survival patients at all time points (Table 3). Although, the mean level of sICAM-1 was in fact higher in non-survivors (HFOV) than survivors (HFOV) and non-survivors (conventional) compared to survivors (conventional), it did not reach statistical significance (Fig 2). The elevation of plasma sICAM-1 on day 3 (> 1,000 ng/ml) was the most accurate predictor of mortality (92%) with a likelihood ratio of 11.9 ($p < 0.001$) and none of the patients with a plasma sICAM-1 < 1,000 ng/ml at day 3 died, irrespective of group (Fig. 2.2).

## DISCUSSION

High frequency oscillator ventilation is characterized by achieving gas exchange utilizing subdead space tidal volumes and such mechanism may provide a less traumatic method of recruiting and stabilizing lung volumes than other conventional modalities.[5,24] The use of HFOV has increased dramatically in the management of respiratory failure in pediatric patients during the past decade.[5,25] Additionally, animal data convincingly support the concept of reduced lung injury by HFOV.[26] However, few of the previous studies addressed the impact of lung injury and survival rate when comparing between HFOV and conventional methods. Our data indicated that the timing to start HFOV is in fact one of the main factors effecting the success of using HFOV. We found that the earlier we started it, the better the outcome would be. This was also in agreement with a previous study.[24] Furthermore, when we analyzed our subjects treated with HFOV, it became apparent that the one patient who failed from HFOV was

started on it when the disease had already progressed too far. The difference in mean ages between the two groups and the underlying diseases of our subjects may also have contributed to the final outcome. Two of our non-survivors in the HFOV group who had been diagnosed with SCID had overwhelming infection. The mean age in the HFOV group was significantly lower than in the conventional group. In general, mortality in younger patients should be higher than in older ones but not so in our study. This may suggest the benefit of HFOV for smaller individuals. Moreover, there are uncontrollable factors such as fluid management, antibiotics or nutritional supplements that may also contribute to the overall results. To minimize the damage that mechanical ventilation can inflict on the lungs, lung protective strategies have been successfully used in patients with ARDS.[27,28] Conventional ventilation using limited PIP and plateau pressure has previously been shown to improve survival rates in adult ARDS[29] but the outcome in pediatric populations has not been clearly established. Recent reviews suggested that compared to the conventional group, HFOV could reduce lung injury in low birth weight infants and could improve gas exchange in older children with acute respiratory failure although there was no difference in developing BPD.[30] As mentioned earlier, Arnold *et al.*[31,32] conducted a trial to further compare HFOV with CV in pediatric respiratory failure with OI > 13. Their results showed that HFOV could improve the $PaO_2/PAO_2$ ratio at 72 hours whereas the conventional mode could not. Thus, result of our study is in agreement with that of Arnold *et al.*[31,32] HFOV could improve immediate oxygenation and evidently caused less barotraumas than the conventional treatment. Nonetheless our study group had more severe diseases as demonstrated by the oxygen indices at enrollment being above 15 as compared to 13 in the previous study. More importantly, our study has shown the trend in improving survival comparing between HFOV and conventional treatment although it did not reach statistical significance (71% versus 31.5%, $p = 0.2$).

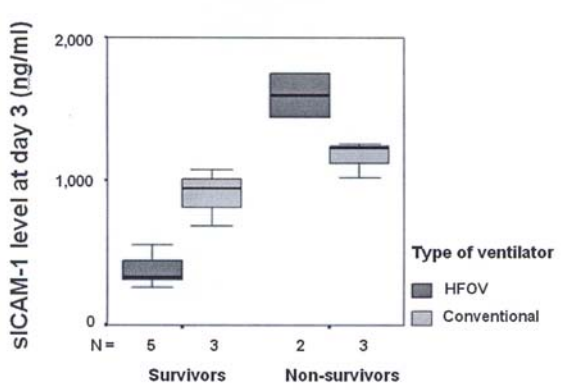


**Fig. 2** Box plot of plasma soluble adhesion molecule (sICAM)-1 levels on day 3 comparing non-survivors (HFOV) versus survivors (HFOV) and non-survivors (conventional) versus survivors (conventional). Horizontal bar represents Mean ± SEM.

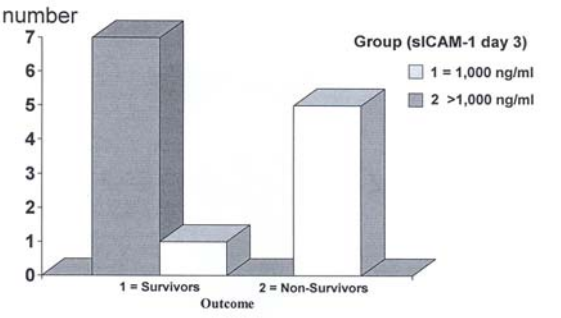


**Fig. 3** Box plot of plasma soluble adhesion molecule (sICAM)-1 levels on day 3. Horizontal bar represents Mean ± SEM. Plasma intercellular adhesion molecule (sICAM)-1 levels on day 3 (< 1,000 ng/ml and > 1,000 ng/ml) *vs* number of survivors with likelihood ratio of 11.9 for dying if the sICAM-1 level > 1,000 ng/ml ($p < 0.001$).

To date, relatively few markers have been identified as reliable outcome predictors in acute lung injuries. A study on bronchoalveolar lavage fluid (BALF) of ARDS patients found that increased IL-8 levels were associated with increased mortality.[3,15] Unfortunately, the lavage procedures were not performed at any fixed time after the onset of ARDS, thus making it difficult to determine whether a single IL-8 level could be used as a prognostic tool.[33] In recent years, ICAM-1, an important molecule that mediates leukocyte-endothelial interaction has been suggested as a contributing factor. It is one of the molecules that contribute to both eosinophil and neutrophil influx into the airway lumen.[21] There has been evidence in human and animal models that

polymorphonuclear leukocytes can participate in the initiation and propagation of lung injuries[34,35] High polymorphonuclear counts in BALF are associated with more severe lung dysfunction.[35] In the present study, we found that sICAM-1 was significantly elevated on days 1 and 3 ($p < 0.001$) when compared between HFOV and the conventional groups. In addition, the level of sICAM-1 could be predictive of the patients' mortality. If the level exceeded 1,000 pg/ml on day 3, almost all the patients (92%, likelihood ratio 11.9, $p < 0.001$) eventually expired. Although our results were limited due to the small sample size and furthermore the increase in sICAM-1 levels may have been induced by some endotoxin, the overall results could still assist in predicting the final outcome. Currently, studies investigating the role of adhesion molecules in conjunction with ARDS are scarce. Boldt *et al*.[36] reported that plasma levels of circulating adhesion molecules were significantly elevated in non-surviving critically ill patients. In addition, Agouridakis *et al*.[37] recently showed the predictive role of serum and BALF adhesion molecules (sICAM-1/sVCAM-1) in adult ARDS but they did not follow the time course of these adhesion molecules. Our findings were in agreement with the previous data reported by Flori *et al.*[22] but their study did not address the important issue of using HFOV in managing pediatric ARDS. In addition our study did demonstrate the importance of this biological marker and its potential benefit in predicting the outcome of pediatric ARDS especially for those on HFOV.

In conclusion, our study supports the use of HFOV in children with acute severe hypoxic respiratory failure based on its potential to alleviate morbidity and mortality. Thus HFOV should be firstly considered for children suffering from ARDS. Moreover, sICAM-1 level is a good prognostic value for the prediction of the ultimate outcome. This new information on the mechanisms of lung injuries may have future applications for novel approaches to the treatment of pediatric ARDS. Clinical trials on a larger scale combined with basic science would be required in order to clarify the unanswered questions.

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