Potent inflammatory cytokine response following lung volume recruitment maneuvers with HFOV in pediatric acute respiratory distress syndrome

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Summary

Objective: Lung volume recruitment maneuver (LVRM) may improve gas exchange but inflating the lungs to nearly vital capacity may cause further lung injuries. Our aim was to determine the potent inflammatory cytokine response following Lung volume recruitment (LVRM) with High Frequency Oscillator Ventilation (HFOV) in Pediatric Acute Respiratory Distress Syndrome (ARDS).

Methods: We prospectively recruited pediatric patients (age >1 month- <15 year old) with a diagnosis of ARDS within 72 hrs of PICU admission. They underwent the LVRM protocol combined with HFOV. Any enrolled subject who had a 20% improvement in PaO_2/FiO_2 (PF ratio) 1 hr after the LVRM we classified as a responder. Baseline clinical data were recorded. Blood was also drawn at baseline, 1 & 24 hrs after LVRM and kept for further sICAM-1, IL-6 & IL-8 analysis.

Results: Eighteen children with ARDS were enrolled. Their mean age was at 6.8 ± 6.1 years (mean±SD). The initial oxygen index (iOI) was at 26.8±17.8 (11.5-84.9). There was no significant differences in sICAM-1, IL-6 and IL-8 levels at baseline; (34 ± 17.5, 121.7 ± 115.15, 601.5 ± 675 pg/ml); 1 hr (39.6 ± 28.7, 99.8 ± 75.5, 617.4 ± 692.5 pg/ml) and at 24 hrs (44.23 ± 34.4, 109.4 ± 63.9, 737.6 ± 922.3 pg/ml) following LVRMs, respectively. However, there was significant difference in the elevation of sICAM-1 levels (%change) from baseline in responders ($-1.8 \pm 12.2\%$) VS non-responders ($47.65 \pm 43.5\%$) at 1 hr. Additionally, sICAM-1 levels were also significantly higher at baseline, 1 hr and 24 hrs in non-survivors as compared with survivors.

Conclusion: There was no significant elevation of potent Inflammatory cytokines that may indicate further lung injuries in the majority of our patients. However, there was significant elevation of sICAM-1 levels in non-responders and in those who did not survive that may indicate more lung injuries in these individuals. *(Asian Pac J Allergy Immunol 2012;30:197-203)*

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Abbreviations

ARDS	=	Acute Respiratory distress syndrome.
CVP	=	Central Venous Pressure (mmHg)
ELISA	=	Enzyme-linked immunosorbent assay
HFOV	=	High Frequency Oscillator Ventilator
IL-6	=	Interleukin-6 (pg/ml)
IL-8	=	Interleukin-8 (pg/ml)
LVRM	=	Lung Volume Recruitment Maneuver

Non-responders = A Non-Responder is defined as any subject who did not have at least 20% improvement in PaO_2/FiO_2 (PF ratio) 1 hr after the LVRM.

Oxygenation index (OI) = Mean airway pressure (mPaw) x FiO_2x100/PaO_2

PaO_2/FiO_2 = P/F ratio

RA = Right atrium

Responder = A Responder is defined as any subject who had a 20% improvement in PaO_2/FiO_2 (PF ratio) 1 hr after the LVRM.
RV   = Right ventricle
RVEDP   = Right Ventricular end diastolic pressure.
RVEDV   = Right Ventricular end diastolic volume.
sICAM-1 = Soluble   intercellular   adhesion Molecule-1 (ng/ml)
TNF-a   = Tumor necrosis factor alpha

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a leading cause of morbidity and mortality in ICUs worldwide. Mechanical Ventilation is the cornerstone of the management of ARDS patients. Low tidal volume combined with adequate PEEP has been shown to reduce mortality.[1-2] However, low tidal volume itself cannot completely prevent tidal hyperinflation, oftentimes causing alveolar de-recruitment. An open lung or lung volume recruitment maneuver (LVRM) is a procedure to reinflate collapsed alveoli. It may be achieved by a brief rise of transpulmonary pressure to higher levels than those achieved during normal ventilation.[3,4] It has been recommended as a useful tool to re-open collapsed lung regions, promoting homogeneity within the lungs and eventually improving oxygenation. A recent review, including our previous work, has shown that using a high frequency oscillator ventilator (HFOV) is better, causing less barotrauma and being unlikely to cause harm as compared with a Conventional Ventilator (CMV).[5-7]

Although several experimental studies have shown a positive effect of LVRM on oxygenation, the results of clinical studies are currently variable. High intrathoracic pressures applied during LVRM to expand the collapsed lung units may cause further barotraumas, as well as biological sequelaes such as cytokine up-regulation and translocation which may cause clinical deterioration following LVRM.[8-9] A recent clinical study, using a CMV with a single high LVRM pressure in pediatric acute lung Injuries (ALI), demonstrated significant increases in pro-inflammatory cytokines (TNF-a, IL-1beta & IL-6).[10] Soluble intercellular adhesion molecule-1 (sICAM-1) is another important potent inflammatory cytokine and has been linked to lung injuries, prolonged mechanical ventilation and mortality.[11,12] Thus, it was our desire to study biological inflammatory markers following LVRM with HFOV.

Methods

Design

A prospective open-label, interventional, clinical trial.

Study population

Eighteen patients (> 1 month to <15 years of age, from January, 2007-October, 2009) with diagnosis of ARDS from the pediatric intensive care unit at King Chulalongkorn Memorial University Hospital who and had no exclusion criteria were recruited for our study. The protocol (ISRCTN 19924570) was approved by our IRB. Informed consents were obtained from the parents prior to their evaluation for HFOV therapy. Before the interventions, all patients received CMV with an FiO_2 of 1, a median PEEP of 12 cmH_2O, fluid resuscitation to maintain a high central venous pressure (range between 8-12 mmHg) and were mostly on either inotropics or vasopressors at the time of transition to HFOV. All patients were deeply sedated and paralyzed. Oxygenation index (OI) = Mean airway pressure (mPaw) x FiO_2 x100/PaO_2

Patients were diagnosed as ARDS by standard criteria and met the following entry criteria: 1) required PEEP $\geq$ 5cmH_2O and 2) FiO_2 $\geq$ 0.6 regardless of PEEP level for $\geq$ 12 hrs to maintain oxygen saturation $\geq$ 92% and 3) an oxygenation index (OI) > 12 for $\geq$ 4 hours. Those patients with any of the exclusion criteria listed below were excluded from consideration.

Exclusion Criteria were: 1. evidence/suspicion of congestive heart failure, or 2. evidence of left atrial hypertension, or 3. severe irreversible neurological injury or intractable shock, or 4. underlying disease deemed irreversible or ARDS > 48 hours, or 5. pre-existing air leak syndrome (eg. pneumothorax or pneumomediastinum) or pre-existing cystic lung disease.

Ventilator strategy

HFOV was delivered with a SensorMedics (3100A/B) oscillator (VIASyS, USA) using a rapid high lung volume recruitment protocol as described in Appendix I.

A Response was defined as a 20% improvement in PaO_2/FiO_2 (PF ratio) at 1 hr after the LVRM.[13] Hypotension was defined as a 25% decreased in baseline mean arterial pressure.

Inflammatory parameters

Plasma Inflammatory cytokines (sICAM-1, IL-6, IL-8) analysis.

Blood samples were obtained from the subjects enrolled and stored in EDTA at baseline, 1 hr and 24 hrs after LVRM with HFOV. The plasma was then separated by centrifugation and kept at -70 ºC for further analysis of sICAM-1, IL-6 and IL-8 using ELISA technique (R&D Systems, MN, USA). The lowest detectable level was < 0.35 ng/ml).

Statistics

All data are presented as means ± SD or median (95% confidence interval) if not normally distributed. They were compared by using non-parametric Wilcoxon sign rank test. A Friedman repeated measures analysis was used for multiple comparisons. A P values less than 0.05 was considered significant. The analysis was performed using SPSS version 13 (SPSS; Chicago, IL).

Result

Eighteen patients (6 females, 12 males) were recruited to our study and followed our LVRM protocol (see appendix I). Four were excluded due to our exclusion criteria. Their baseline demographic clinical characteristics are listed in Table 1. Oxygenation (PaO_2/FiO_2) was significantly higher at 1 hr in responders compared to non-responders after LVRM with HFOV (Figure 1). In addition, their mean age was at 5.8 ± 4.7 (yr) and mean body weight was at 25.6 ± 27 kg.

Cytokines measurement.

There was no significant elevation of sICAM-1 levels (39.6 ± 28.7 vs 44.2 ± 34.4 pg/ml), Interleukin -6 (285.3 ± 424.7 vs 259.5 ± 391.8 pg/ml) and Interleukin -8 (1227.7 ± 2532 vs 1260.2 ± 2556.5 pg/ml) at 1 hr and 24 hr, respectively (Figure 2-4) following LVRM with HFOV.

Responders VS non-responders

sICAM-1

There was significant elevation of sICAM-1 levels in non-responders compared to responders at baseline (59.1 ± 1.7 vs 29.3 ± 14.3 pg/ml, p = 0.004) 1 hr (87.6 ± 27.5 vs 28.5 ± 14.1, pg/ml, p < 0.001) and 24 hrs (94.9 ± 11.2 vs 30.4 ± 23.1 pg/ml, p = 0.001, Figure 5) Their levels were also significantly increased compared to baseline at 1 hr after LVRM when we measured the percent change in the non-responders group (Table 2).

Table 1. Patients' baseline clinical characteristic in this study.

Pt No	Sex	Diagnosis	Pulmonary infiltrates	Out come
1	M	ANLL/Septic shock	Focal	S
2	F	Pneumonia	Bilateral	S
3	M	IAHS/Pneumonia	Bilateral	E
4	M	PWS/Pneumonia	Bilateral	S
5	M	Burkitt's lymphoma/Septic shock	Focal	E
6	M	Leukemia/Septic shock	Focal	S
7	F	SLE/ Pneumonia	Bilateral	E
8	F	Septic shock/Pneumonia	Bilateral	S
9	F	ALL/s/p BMT/Pneumonia	Focal	S
10	M	HIV/Pneumonia	Bilateral	S
11	M	ALL/disseminate varicella	Bilateral	E
12	M	CP/ Aspiration Pneumonia	Bilateral	S
13	M	ALL	Focal	S
14	M	ANLL /Pneumonia	Bilateral	S
15	F	Craniofacial anomaly/ Pneumonia	Bilateral	S
16	F	CRD/Pneumonia	Bilateral	E
17	M	Pneumonia/ANLL	Focal	S
18	M	BA/Septic shock	Bilateral	E

IAHS=Infection associated hemophagocytic syndrome, CP=Cerebral palsy, PWS=Prader Willi syndrome

ALL=Acute lymphocytic leukemia, CRD=Chronic renal disease, BA=Biliary atresia

Interleukin-6

There was no significantly different in IL-6 levels at baseline (239.8 ± 415.9, 697.8 ± 577 pg/ml, p = 0.13) between responders and non-responders. However, their levels were significantly higher at 1 hr (176.3 ± 294.7 vs 757.5 ± 648.2 pg/ml, p = 0.02) and were persistently higher at 24 hrs (145.4 ± 192.1 vs 753 ± 692.1 pg/ml, p = 0.009).

Interleukin-8

There was significantly elevation of IL-8 levels in non-responders compared to responders at baseline (4269.3 ± 5328.4 vs 506.3 ± 612.8 pg/ml, p = 0.01) 1 hr (4257.4±5352.5 vs 528.5 ± 644.5 pg/ml, p <0 .01) and 24 hrs (4810.5 ± 4884.4 vs 440.9 ± 561.1 pg/ml, p = 0.003, Figure 6)
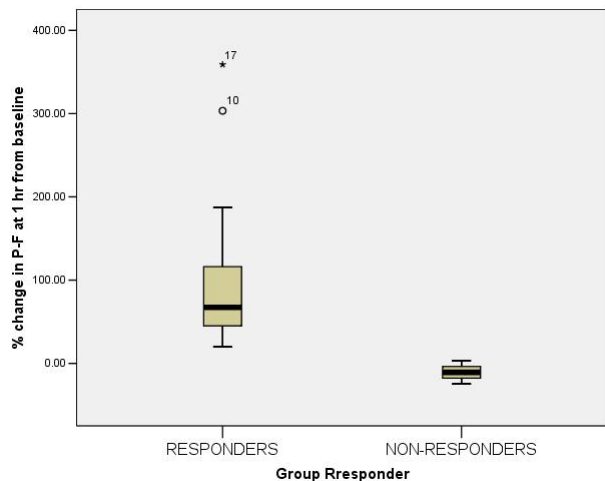
Figure 1. Box-plot demonstrating a significant increase in % change of PaO_2/FiO_2 at 1 hr after LVRM with HFOV between Responders VS Non-Responders (Data shown as Median ± 95% CI, $P < 0.05$).
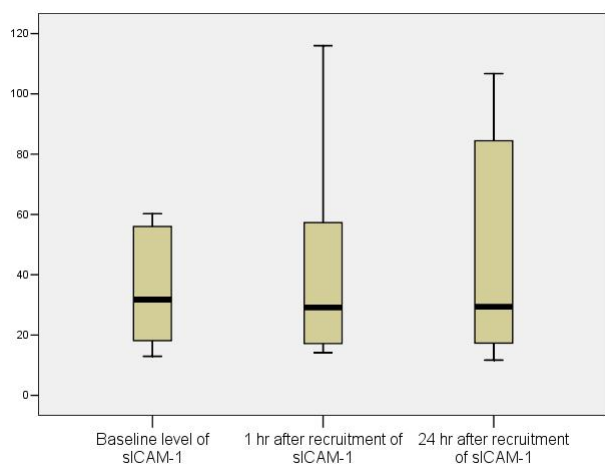
Figure 2. Box-plot demonstrating plasma sICAM-1 levels compared at baseline, 1 hr and 24 hrs after LVRM with HFOV in all patients. (Data shown as Median ± 95% CI, $P = NS$, n = 18).

Survivors VS non-survivors

There was significant elevation of sICAM-1 levels in non-survivors compared to survivors at all three time points (baseline: 49.8 ± 18.2 vs 28.1 ± 15.2 pg/ml, $p = 0.01$, 1hr: 65.3 ± 37.7 vs 27.95 ± 13.7 pg/ml, $p = 0.01$ and 24 hrs: 71.6 ± 37.8 vs 29.1 ± 21.9 pg/ml, $p = 0.02$). IL-8 levels in non-survivors were also significantly higher compared to survivors

at all three time points (baseline: 1288.7 ± 638.5 vs 257.8 ± 366.6 pg/ml, $p = 0.001$, 1hr: 1270.7 ± 635.7 vs 290.7 ± 458.8 pg/ml, $p = 0.004$ and 24 hrs: 1500.1 ± 1050.4 vs 261.1 ± 391.2 pg/ml, $p = 0.01$) . IL-6 levels in non-survivors were higher compared to survivors at all three time points but the differences did not reach statistical significance.

Transition from HFOV to CMV

Fifteen out of eighteen patients (83%) were able to switch back from HFOV to CMV according to our transitional criteria. OI was significantly decreased at 24 hrs. in patients who were able to switch back to CMV compared to those who were not (15.8 ± 7.2, 29.8 ± 29.9, $p = 0.007$).

Complications and outcome

There was one minor case of barotrauma in a patient who developed an isolated small pneumo-mediastinum while he was on mPaw of 30 cmH_2O on the first day of HFOV which resolved after decreasing mPaw. There was no need for chest drain insertion. Most of our patients tolerated the study protocol well. No significant hemodynamic disturbances were observed. Two out of three (66%) in the non-responder group died. The PICU mortality rate was 33 % (6/18). The most common cause of death was multiple organ failure. Patients were on HFOV for a median of 6 days and had 15 total days on a ventilator. No patient was withdrawn from the protocol. One of our patients was given rescue inhaled nitric oxide on day 3 due inability to reduce oxygen requirements.
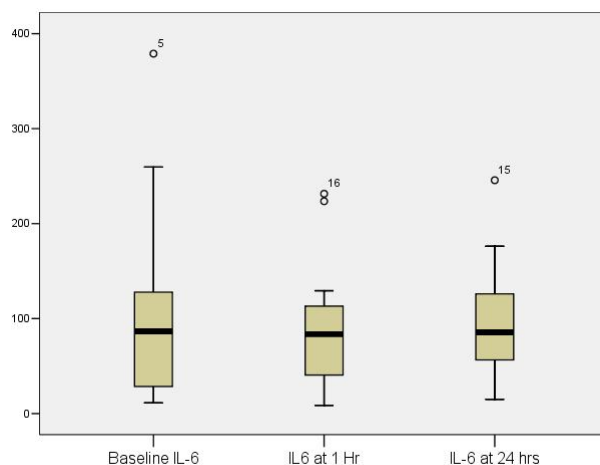
Figure 3. Box-plot demonstrating plasma IL-6 levels compared at baseline, 1 hr and 24 hrs after LVRM with HFOV in all patients. (Data shown as Median ± 95% CI, $P = NS$).
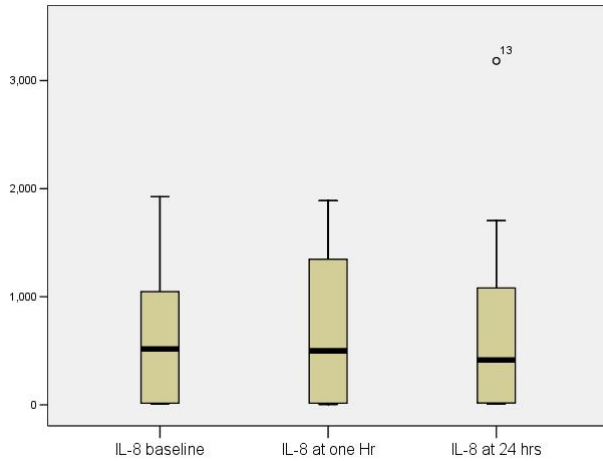
Figure 4. Box-plot demonstrating plasma IL-8 levels compared at baseline, 1 hr and 24 hrs after LVRM with HFOV in all patients. (Data shown as Median ± 95% CI, P = NS).

Table 2. Baseline clinical characteristic compare between Responders & Non-responder group.

Baseline Clinical & Cytokines response	Responders	Non-Responders	p value
Age (Y)	6.3±4.6	2.2±1.6	ns
Gender (M:F)	10:5	2:1	ns
Lung Pathology (EP:P)	11:4	1:2	0.2
iPaw (CmH$_2$o)	20.4 ± 5.4	20.5 ± 1.8	0.4
iOI	31.7±23.4	19.5± 7.9	0.3
iPaO$_2$/FiO$_2$	85±44.9	107.5±47.8	0.3
% change of sICAM-1 at 1 hr following LVRM	-1.8±12.2	47.6±43.5	*0.002
% change of IL-6 at 1 hr following LVRM	106.4 ± 320.6	-9.8 ± 30.2	0.4
% change of IL-8 at 1 hr following LVRM	54.6 ± 140.8	52.7±47.6	0.7
Outcome (S)	67%	33%	0.2

EP:P=Extrapulmonary cause: Pulmonary cause, iOI=initial oxygen index

iPaw= initial Mean airway pressure, S=Survivor

Discussion

To our knowledge, this study is the first prospective trial investigating the immunologic response following HFOV with LVRM in the early phase of pediatric ARDS. We found a rapid and significant improvement in gas exchange evidenced by improving of PaO$_2$/FiO$_2$, A-a gradient and significantly reduced oxygen requirements at 1 hr after LVRM compared to baseline with CMV. These results are in agreement with recent reports from neonatal and adult studies.[14-16] Although there were several reports of clinical responses following LVRM in ARDS patients,[14-15] there are very few in the pediatric population. One recent small clinical trial (n = 7) investigated a single recruitment maneuver in ventilated ALI children with CMV and found significant elevation of pro-inflammatory cytokines with no clinical benefit (10). This could be explained by the difference in the protocol which involved the use of an unusually high PIP/PEEP combination (max 45/30 CmH$_2$O). It could potentially cause disruption of alveolar-capillary integrity, especially in very young children. Compared to our study, however, we did not observe significant elevation of potent inflammatory cytokines (sICAM-1, IL-6 & IL-8) following LVRM with HFOV in the majority when comparing levels at baseline, 1 hr and 24 hrs, respectively.
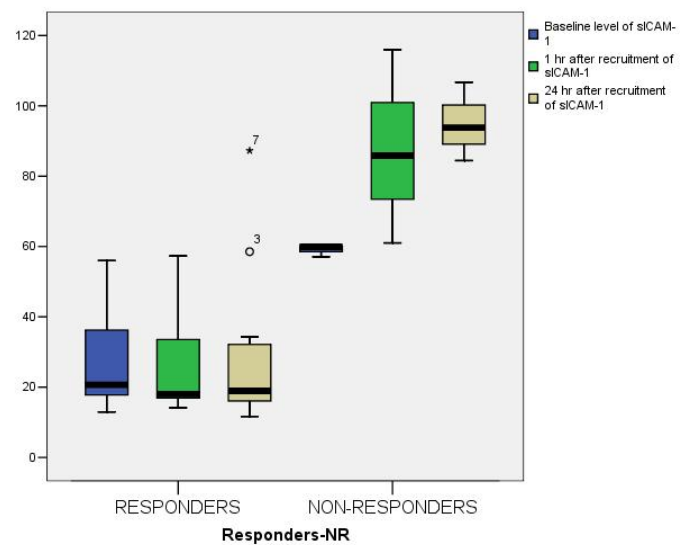
We classified our subjects into two groups, by using oxygenation response following LVRM with HFOV, namely responders and non-responders.

Figure 5. Box-plot demonstrating plasma sICAM -1 levels compared between Responders and Non-Responders at baseline, 1 hr and 24 hrs after LVRM with HFOV. (Data shown as Median ± 95% CI, P =0.004*, 0.001** & 0.001*** respectively).
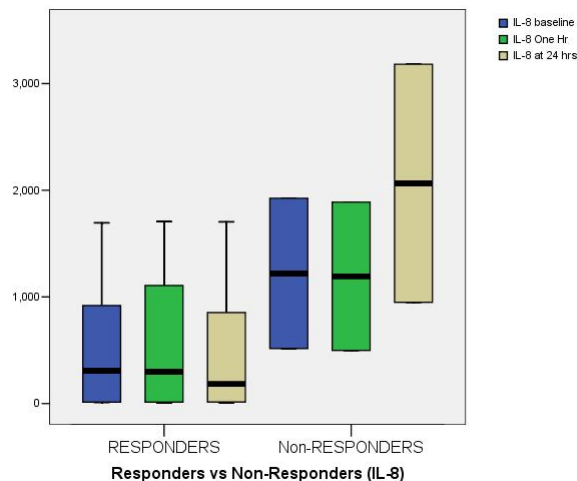
Figure 6. Box-plot demonstrating plasma IL-8 levels compared between Responders and Non-Responders at baseline, 1 hr and 24 hrs after LVRM with HFOV. (Data shown as Median ± 95% CI, P = 0.17, 0.2, 0.02* respectively).

Fifteen (83%) of our enrolled patients were responders and 3 (17%) were non-responders. We found significant elevation of sICAM-1 from baseline when in measurements taken at 1 hr after LVRM with HFOV in the non-responders group, compared to the responders group (% changes). This might indicate that LVRM could potentially cause further lung injuries in this particular group. Furthermore, the non responder group had significantly elevation of IL-8 at 1 hr after LVRM which persisted at 24 hrs. We also observed significant elevation of sICAM-1 at baseline which was sustained in the non-survivor group, when we analyzed them separately. Thus, it is possible that LVRM was not clinical beneficial in this group and caused a further inflammatory response by overdistension the lungs. This may cause disruption of alveolar integrity and might contribute to morbidity in this group.

There is growing evidence that the ventilator strategy used during mechanical ventilation may influence outcomes. A recent animal study comparing different mechanical ventilator modes showed that HFOV with LVRM was at least as beneficial as the best PEEP CMV, in terms of clinical and inflammatory response.[16] Furthermore, in the LPS-injured lung model, HFOV caused less TNF-œ expression than the best PEEP CMV. This may imply that differences in the mode of mechanical ventilation could make a clinical difference. As we known from the previous studies, protective mechanical ventilation strategies can reduce the levels of proinflammatory cytokines.[20-22] Stuber F et al. demonstrated elevation of serum cytokines within one hour in patients ventilated at 5 ml/kg and subsequently changed to 12 ml/kg (17). Another two recent clinical studies in adult ARDS ventilated with LVRM did not show translocation of cytokines in most of the patients (max 40 cmH$_2$O, 30 seconds).[18-19] In addition, the intensity of LVRM defined by the duration, maximum applied transpulmonary pressure, as well as other factors such as alveolar-capillary permeability, degree of inflammation or severity of underlying disease or cells, tissue disruption could translocate pro-inflammatory cytokines to the systemic circulation. Several cytokines can be released from the lungs and contribute to hypercytokinemia. These cytokines have been implicated in multiple organ failure.[20-22]

Conclusions

The HFOV combined with initial LVRM protocol could be a useful therapeutic intervention in the early phase of pediatric ARDS. Following LVRM with HFOV there was no significant immunologic evidence of deterioration in the majority of our patients. Nevertheless, LVRM could result in protracted systemic cytokines increase, especially in the non-responders group that might associated with increased morbidity.

Acknowledgements

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