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Factors associated with survival during high frequency oscillatory ventilation in children

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Abstract

Objectives: To determine indicators of survival in children with severe hypoxic respiratory failure (HRF) after transition to high frequency oscillatory ventilation (HFOV).

Methods: Single center retrospective examination of children with HRF who were transitioned to HFOV. Blood gases and ventilator settings 24 hours prior to and 48 hours after HFOV in survivors and non-survivors were evaluated.

Results: Sixty two children with mean age of 7 years and mean weight of 26 kg were included with an observed mortality of 29%. Mean airway pressures (Paw), oxygenation index (OI), PaO₂/FiO₂ oxygen (P/F) ratio, pH, bicarbonate and PaCO₂ were similar prior to HFOV in survivors and non-survivors. During HFOV, mean OI and P/F ratio improved in both groups with an average Paw increase of ~10 cm of H₂O. Survivors had lower OI than non-survivors (21±0.9 versus 26.5±2.2; p<0.01) beginning 24 hours after HFOV. P/F ratio appears to diverge by 36 hours, with survivors having P/F ratio >200. Survivors had higher pH than non-survivors at 36 hours (7.40±0.01 versus 7.32±0.02; p<0.05), higher bicarbonate levels (27.1±0.7 versus 23.9±1.3 mEq/L) and similar PaCO₂ with less oscillatory support (i.e., hertz and amplitude). Inhaled nitric oxide (iNO) was used in 53% of patients with improvements in oxygenation but with no effect on mortality.

Conclusions: HFOV improves oxygenation in children with severe HRF. Non-survivors can be distinguished from survivors at 24-36 hours during HFOV by higher OI, metabolic acidosis, and higher oscillatory support. These data may assist in prognostication or timing of initiating alternative therapies, such as extracorporeal membrane oxygenation.

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Introduction

The ideal strategy to manage pediatric patients, including children, with severe hypoxic respiratory failure (HRF) is still unsettled and subject to considerable debate [1, 2]. In 2000, the ARDS network published that mortality in adults with acute respiratory distress syndrome (ARDS) managed with conventional mechanical ventilation (CMV) could be reduced by 20% using a low tidal volume (6 mL/ Kg) and low-inspiratory plateau pressure (< 30 cm H₂O) compared to a higher tidal volume (12 mL/kg) [3]. The concept of reducing iatrogenic injury in patients with severe lung disease has led to the development of many ventilatory strategies to reduce volutrauma, atelectrauma, biotrauma and hyperoxia-associated injury, collectively referred to as ventilator-associated lung injury (VALI) [4].

As an alternative approach to CMV, HFOV has the theoretical ability to minimize VALI [1], but data supporting outcome benefits have varied according to the patient population and operator's familiarity with the technology. Trials in pre- and near-term neonates with respiratory failure (including respiratory distress syndrome) have either shown benefit or equivalency of HFOV versus CMV [5, 6]. In adults, HFOV is safe as a rescue therapy in ARDS and may improve oxygenation [7], yet a recent multinational clinical trial in adults with ARDS randomized early to receive HFOV or CMV found a higher mortality in the HFOV-managed arm [8]. Studies in children have not found outcome benefits of HFOV over CMV in those with HRF

or ARDS, but these studies are few and underpowered [9, 10]. Perhaps because of familiarity with the approach from the neonatal experience, HFOV has been adopted as a rescue therapy in many pediatric intensive care units (PICU) for children who have failed CMV [11, 12].

Historically, survival rates in children with HRF managed with HFOV vary from 40-80% [13-16]. To date, there is no universally accepted method to predict who may benefit from and survive this therapy, which could assist in deploying additional treatments in the attempt to improve outcomes. Extracorporeal membrane oxygenation (ECMO) is increasingly used for children with severe HRF, most frequently in those who can no longer be supported by CMV using non-injurious settings. Mortality rates for children with severe HRF, including ARDS, treated with ECMO range from 33-48%. This is considerably lower than the expected mortality without ECMO, since this treatment modality has traditionally been used as a salvage therapy for children likely to die on CMV [17].

Our center has usually initiated HFOV in children with sustained need of high ventilator settings during CMV (PIP consistently > 40 cm of H₂O). Although ECMO capable, in the past we have infrequently employed ECMO for severe “HFOV-resistant” HRF. We hypothesized that, by evaluating our experience, we could identify indicators that could predict outcomes in children with HRF following transition from CMV to HFOV and help to make informed decisions to deploy more invasive modalities, such as ECMO, sooner.

Materials and Methods:

This is a single center retrospective review of children with HRF treated with HFOV who were admitted to the PICU at Riley Hospital for Children between January 2008 and August 2011. The Indiana University institutional review board approved this study with waiver of informed consent. Our unit is a 36 bed tertiary care, combined medical and surgical PICU staffed by pediatric intensivists. All patients older than 1 week of age who were managed with HFOV were included in the study. Patients treated with HFOV for < 12 hours or those with cyanotic heart disease, death within 24 hours of admission, and lack of an arterial catheter were criteria for exclusion. Transition to HFOV and management of children on HFOV was in accordance with our hospital respiratory care policy. Children were switched to HFOV if PIP on CMV was consistently >40 cm of H₂O. Decision to switch from CMV to HFOV and inhaled nitric oxide (iNO) use were at the discretion of the care team. Generally saturations of 86 to 90% were accepted to keep FiO₂ less than 0.6. Children are switched back from HFOV to CMV when Paw is < 22 and FiO₂ is <0.5.

Data Collection

Demographic data included age, weight, gender and primary diagnosis, ICU length of stay (LOS), and disposition (survival to ICU discharge). Clinical and laboratory data included duration of total ventilation, CMV and HFOV ventilator settings, arterial blood gas analysis and the concomitant use of iNO. Clinical and laboratory data were obtained at 6 hour intervals, for the 24 hours prior to transition from CMV to HFOV, and for the 48 hours that followed.

Oxygenation index [(OI) = $P_{aw} \times (F_{iO_2}/P_{aO_2}) \times 100$] and P_{aO_2}/F_{iO_2} (P/F) ratio were calculated for each relevant time point.

Statistical Analysis

Demographic data, duration of mechanical ventilation and LOS are presented as means and ranges, with p-values from Student's t-test or Wilcoxon rank-sum test for continuous variables, depending on the distribution, or Fisher exact tests for categorical variables. Graphical displays of OI, P_{aw} , P/F ratio, pH, bicarbonate and P_{aCO_2} are presented as means and standard error of mean. The data distributions were checked for normality using QQ plots and Kolmogorov-Smirnov Goodness-of-Fit tests. To determine if there were differences between survivors and non-survivors, data were compared using repeated measures ANOVA models with generalized linear mixed models. Auto-regressive covariance structures were used to model within subject variance and models were adjusted for age, gender and weight. To determine at which time points mean values were different between survivors and non-survivors, post-hoc pairwise t-tests were performed using Bonferroni correction. Receiver Operating Characteristic (ROC) curves were also analyzed for OI and pH to determine if there were cutoff points that could accurately differentiate between survivors and non-survivors. Analyses were run using SAS v9.3 (SAS institute, Cary, NC).

Results

Patient demographics and outcomes

Eighty children received HFOV during the study period, but 18 were excluded from this analysis: 5 received HFOV for less than 12 hours, 2 were transitioned to ECMO within the first 12 hours, 7 had cardiac arrest on admission and died within 24 hours, 3 did not have an arterial catheter during the entire data collection period, and 1 had cyanotic heart disease. Data from the remaining 62 children were analyzed. Forty four patients (71%) survived to ICU discharge. Survivors and non-survivors were similar in age, gender, weight, total ventilation and time on CMV before HFOV (Table 1). The average time between initiation of CMV and transition to HFOV in survivors was 1.6 days and 3.4 days in non-survivors. Diagnoses are presented in Table 2.

Ventilatory parameters prior to HFOV

Survivors and non-survivors had similar respiratory data during CMV (Figures 1 and 2, Table 3). In all patients, OI nearly doubled (from ~16 to ~30) with ~30% decrease in P/F ratios (~120 to 80) over the 24 hours leading to transition to HFOV (Figure 1A, B). There were no differences between survivors and non-survivors in the continuous values of Paw, pH, bicarbonate, PaCO₂, OI and P/F ratios in the 24 hours during CMV prior to HFOV (Figures 1 and 2, Table 3). At base line 6 hours prior to transition to HFOV there were no statistically significant differences in any of the analyzed parameters.

Ventilatory parameters during HFOV transition

Ventilatory parameters changed significantly in both survivors and non-survivors immediately after transition to HFOV compared to the CMV parameters and the magnitude of the changes were similar between survivors and non-survivors. Changes in pH, bicarbonate and PaCO₂ were not significant between CMV and HFOV immediately after transition.

Among survivors, OI, P/F ratio and Paw on CMV just prior to HFOV were 30 ± 2 , 75 ± 5 and 21 ± 1 cm of H₂O, respectively. One hour after transition to HFOV, OI, P/F ratio and Paw in survivors were 35 ± 2.3 , 110 ± 11 , 30 ± 1 , respectively ($p < 0.05$ for all compared to CMV). Among survivors, pH, bicarbonate and PaCO₂ on CMV just prior to HFOV were 7.34 ± 0.01 , 24.7 ± 0.7 mEq/L and 47 ± 2 torr, respectively. One hour after transition to HFOV, pH, bicarbonate and PaCO₂ in survivors were 7.31 ± 0.02 , 24.9 ± 0.7 mEq/L and 52 ± 3 torr, respectively ($p=NS$ compared to CMV).

Similarly, among non-survivors, OI, P/F ratio and Paw on CMV just prior to HFOV were 29 ± 3 , 79 ± 9 , and 19 ± 1 cm of H₂O, respectively. One hour after transition to HFOV OI, P/F ratio, Paw in non-survivors were 39 ± 4 , 113 ± 25 , and 31 ± 1 , respectively ($p < 0.05$ for all compared to CMV). Among non-survivors, pH, bicarbonate and PaCO₂ on CMV just prior to HFOV were 7.3 ± 0.02 , 24.2 ± 1.3 mEq/L and 47 ± 2 torr, respectively. One hour after transition to HFOV, pH, bicarbonate and PaCO₂ in non-survivors were 7.27 ± 0.04 , 24.4 ± 1.3 mEq/L and 51 ± 4 torr, respectively ($p=NS$ compared to CMV).

Ventilatory parameters following HFOV transition

Paw in both survivors and non-survivors were similar during 48 hours after transition (Figure 1C). Over this time, average OI was significantly lower in survivors compared to non-survivors (21 ± 0.9 vs. 26.5 ± 2.2 , $p < 0.01$; Figure 1A, Table 3). In point-to-point comparisons, there was a divergence in OI between survivors and non-survivors at 24-hours (20.5 ± 1.9 versus 28.6 ± 4.7 ; $p < 0.05$) and OI remained different between the groups through 48 hours (Figure 1A). Average P/F ratios increased to above 200 in survivors but remained < 200 in non-survivors. Although P/F ratios did not achieve statistical significance either for the course during HFOV or in the point-to-point comparisons, it appeared that a divergence was beginning to become apparent at ~ 36 hours (Figure 1B).

Concerning ventilation, PaCO₂s were not different between survivor and non-survivors (Figure 2B), although survivors were managed with less oscillatory support in terms of amplitude [ΔP] throughout the 48 hours and higher frequency [hertz (Hz)] at later time points (Figure 3). Despite similar PaCO₂s, pH was lower in non-survivors than survivors during HFOV (figure 2A). In survivors, pHs at 36 and 48 hours on HFOV were 7.40 ± 0.01 and 7.41 ± 0.01 which were significantly higher than non-survivors' pHs of 7.32 ± 0.02 and 7.34 ± 0.02 at similar time points ($p < 0.05$). Values of PaCO₂ at the 36 hours and 48 hours in survivors were 46 ± 1.5 and 45 ± 1.4 torr and in non-survivors PaCO₂ at 36 hours and 48 hours were 50 ± 1.5 and 49 ± 3 torr and were not statistically significant. Changes in serum bicarbonate levels were similar to pH changes (Fig 2C). In survivors bicarbonate levels at 36 hours and 48 hours were 27.1 ± 0.7 and

28 ± 0.7 mEq/L. Non-survivors' serum bicarbonate levels at 36 hours and 48 hours were 23.9 ± 1.3 and 24.7 ± 1.5 mEq/l, which were slightly lower compared to survivors ($p < 0.05$).

Outcomes

Children in this study had 29% mortality. In survivors, 31 (70%) patients were ventilator free at 30 days and 39 (88%) patients were ventilator free at 60 days. We computed receiver operating curves (ROC) for survival for OI at 24 hours and pH at 36 hours to evaluate cutoff values to discriminate survivors (Fig 5). $OI < 25$ at 24 hours and $pH > 7.34$ at 36 hours had modest correlation and seems to be helpful to identify survivors during HFOV. The odds ratio (OR) for death with $OI > 25$ at 24 hours during HFOV was 4.6 (95% CI 1.3 to 16.7) and OR for death with a $pH < 7.3$ at 36 hours was 9 (95% CI 2.1 to 39.2). Sixteen (26%) children developed a pneumothorax requiring chest tube placement, 5 during CMV (2 died) and 11 during HFOV (1 died). Out of 44 surviving children, 8 (18%) required tracheostomy and 5 were discharged home on a ventilator. Almost one-third (14) of the surviving children were transferred to an in-patient rehabilitation unit, with average rehabilitation length of stay of 28.3 (7 to 62) days. During the study period 15 children (13 from CMV and 2 from HFOV) were treated with ECMO and 8 (53%) survived.

Inhaled nitric oxide (iNO) data

In this study 33 (53%) children received iNO and 11 (33%) died. iNO was started in 9 children during CMV and in 24 children during HFOV. Seven of nine children in the CMV-iNO group continued to receive iNO during HFOV. P/F ratios and OI improved in both survivors and non-survivors in response to iNO (Figure 4A, 4B). P/F ratio improvements were greater when iNO

was instituted during HFOV vs. CMV, for example, with P/F ratio increase of 34 during HFOV vs. 13 on CMV and 116 during HFOV vs. 35 on CMV at 1 and 24 hours, respectively (all $p < 0.01$; Figure 4C). OI improvement following iNO was similar between CMV and HFOV (Figure 4D). There were no differences in survival in patients who received iNO versus those who did not (67% and 76% respectively, $p = \text{NS}$).

Discussion:

In this study we sought to determine predictors of survival in children with severe HRF managed with HFOV. In pediatric critical care, HFOV is often used to manage children with HRF that is refractory to management with CMV. Determining a method to identify children who may not survive HFOV would assist in developing interventions to improve outcomes in children with severe HRF, such as earlier deployment of more invasive techniques (e.g. ECMO). In this cohort of children with severe HRF treated with HFOV, non-survivors and survivors had similar respiratory parameters during CMV, yet differences in oxygenation, ventilation and acid-base balance became apparent within 48 hours after transition to HFOV. Although OI decreased in both survivors and non-survivors following HFOV, greater improvement was observed in survivors. Specifically, by 24 hours after HFOV, survivors had OIs that averaged ~ 20 or less, while non-survivors had OIs ≥ 25 . Of interest is that these improvements (from OI peaks of 35-40) occurred with an increase in P_{aw} from 20 cm of H_2O to approximately 30 cm of H_2O , which is $\sim 50\%$ increase. P/F ratios also improved in both groups following HFOV, from < 100 to above 200 at 36 hours in survivors, but ranged 150-200 in non-survivors. The P/F ratio differences

were not statistically significant for the whole duration of HFOV or point-to-point comparisons, perhaps reflecting a later divergence of the P/F values, limitations of our sample size, and/or an enhanced sensitivity of OI over P/F ratios in characterizing a patient's oxygenation status since the former takes in consideration the level of ventilatory support (Paw) employed. To detect P/F difference of 50 between survivors and non-survivors with 80% power ($\alpha = 0.05$), we required sample size of 186; if the P/F difference were to be >100 , sample size of 64 would have been sufficient. Our sample size of 62 is adequate enough to detect OI difference of 2.8 and pH difference of 0.032 with 80% power ($\alpha = 0.05$) between survivors and non-survivors.

In addition to oxygenation parameters, our data indicate that ventilation in survivors can be more easily managed than in non-survivors, given the fact that both groups had similar PaCO₂ despite lower amplitude throughout and higher frequency over time in survivors. Survivors also had slightly higher bicarbonate levels than non-survivors. Taken together, non-survivors had modest, but significant, metabolic acidosis compared to survivors.

There are important similarities and differences comparing our results to other studies in this field. There are some recent studies in children and adults which showed the association of improved oxygenation with survival [14, 18-20]. In pediatric studies non-survivors had higher OI (close to 30 or higher) compared to OI of <25 in survivors before transition to HFOV compared to our study where OI was close to 30 in both survivors and non-survivors. In the Babbitt et al study, OI improvement in survivors and non-survivors was similar to our study with OI of less than 20 in survivors and > 25 in non-survivors. Yehya et al, in their elegant studies, have shown that in children with immunocompromised condition (ICC), OI does not improve in non-

survivors whereas in survivors OI improves ~ 50% and OI improvement of < 5% is 100 sensitive and 85% specific in predicting mortality in children with ICC. In their study with mixed population of children, OI improvement in non-survivors was 6% compared to 30% in survivors. In o, OI improvement in survivors during first 48 hours was ~ 35% compared to ~15% in non-survivors. OI improvement in our study is comparable to the above mentioned studies but non-survivors in our study showed slightly higher improvement in OI. In ur study P/F improvement was observed in both survivors and non-survivors and P/F improvement was 100% or more in survivors which is similar to other pediatric studies [14, 18, 19], but P/F improvement in non-survivors was greater compared to those studies and P/F ratio difference could not differentiate survivors and non-survivors in our study contrasted to those studies. A recent study in adults with ARDS who were transitioned from CMV to HFOV found that OIs and P/F ratios only improved in survivors [20], whereas in children these indices improve in both survivors and non-survivors [14, 19], but again with a greater improvement of OIs only in survivors. In adults, differences in OIs and P/F ratios were apparent at 3 hours during HFOV, but we found differences in OIs beginning at 24 hours after transition and what may be the start of differences in P/F ratio at 36 hours. In children OI and P/F improvement has been observed around 4 to 6 hours after HFOV transition [14, 21-22] to 24 hours on HFOV [18, 19]. In adults, lower pH due to higher PaCO₂ correlated with mortality, whereas in our report lower pH, as a consequence of metabolic acidosis, was associated with mortality. In both studies, survivors had OIs less than ~20 and pH higher than ~7.4. In a sub group of children with sepsis during HFOV, metabolic acidosis with of 7.25 is associated with mortality compared to 7.32 in survivors [14]. In our study, survivors had P/F ratios of >200, whereas P/F ratios never improved over 200

in adult survivors, even at or after 72 hours. In other pediatric studies [14, 19] P/F improvement was also noted to be < 200 which is similar to the adult study.

Similar to other reports in adults and children [14, 19, 20], Paw increased by more than 10 cm H₂O with the transition from CMV to HFOV in our study, which suggests that higher PEEP may be beneficial in the management of both adults and children with HRF during CMV. On HFOV, we typically gauge proper lung expansion (i.e. 8 to 10 ribs) by chest X-ray and traditionally advocate increasing Paw by 3-5, whereas patients may require >10 Paw increase while transitioning from CMV to HFOV.

OI has been suggested as a predictor of mortality with OI > 42 at 24 hours during HFOV in pediatric respiratory failure associated with mortality odds ratio of 21 [9] and another study in children reporting OI of > 35 after 24 hours of HFOV being associated with 31 times higher odds of mortality (14), whereas most of our patients had OIs <35 at 24 hours after HFOV. Our data is more similar to a report published from our group which shows that an OI > 25 in hematopoietic stem cell transplant patients with respiratory failure at any time on HFOV is highly associated with mortality (23).

Data on pH during HFOV and outcome are limited. In this study most (90%) survivors had pH >7.3 at 48 hours and children with pH < 7.3 had 9 times higher odds of death. As stated earlier, a subgroup of pediatric sepsis patients treated with HFOV had higher mortality when pH was < 7.32 (14). Our study is unique because it does show that presence of metabolic acidosis (pH <7.34) is associated with decreased survival in children with acute hypoxic respiratory failure, whereas permissive hypercapnia and accepting respiratory acidosis (pH < 7.3) may be beneficial

in some children (24). Differentiating warning signs of persistent metabolic acidosis from acceptable respiratory acidosis is important in clinical decision making.

Although no data currently suggests that iNO impacts outcome in children with HRF or ARDS, about half of our patients received iNO, consistent with a recent survey of pediatric intensivists and their management of pediatric HRF/ARDS [25, 26]. Like others, we show that there is “positive” physiologic response to iNO as evidenced by lower OIs and higher P/F ratios, and greater improvement of these indices while patients were treated with HFOV rather than CMV [27-29]. Consistent with previous reports, iNO did not appear to improve survival, as the mortality rate was 33% in those who received iNO and 24% in those who did not ($p=NS$), although it is possible that iNO is initiated on those, at least subjectively, considered more critically ill. These findings should not negate the potential utility of iNO in severely hypoxemic patients when used for stabilization while bridging to alternative therapies.

Conclusions:

Our study provides additional information for the assessment and management of children with the most severe forms of hypoxemic respiratory failure. Our study suggests that an OI > 25, metabolic acidosis with pH of <7.34, and the inability to reduce ventilatory support in the first 48 hours during HFOV are associated with mortality. In real time scenarios, these data may help caretakers to identify children at risk for death during HFOV within 2 days and may assist in prognostication and earlier consideration of therapeutic alternatives. Data from this study needs to be confirmed in multicenter studies, yet may provide the basis for identifying children

with HRF at the highest risk for death who can participate in clinical trials for alternative ventilator strategies, novel therapeutics or ECMO to improve survival.

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References:

1. Kneyber MC, Van Heerde M, Markhorst DG: Reflections on pediatric high-frequency oscillatory ventilation from a physiologic perspective. *Respir Care* 2012; 57(9):1496-504
2. Sud S, Sud M, Friedrich JO, Wunsch H, Meade MO, Ferguson ND, Adhikari NK. High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome. *Cochrane database Syst Rev* 2013; 2:CD004085
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342 (18):1301-8
4. Pierrakos C, Karanikolas M, Scolletta S, Karamouzou V, Velissaris D. Acute respiratory distress syndrome. Pathophysiology and therapeutic options. *J Clin Med Res* 2012; 4(1):7-16
5. Henderson-Smart DJ, De Paoli AG, Clark RH, Bhuta H. High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term. *Cochrane Database syst rev* 2009(3):CD002974
6. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courteny SE, Dani C, Durand DJ, Gerstmann DR, Henderson-smart DJ, Marlow N, Peacock JL, Pillow JJ, Soll RF, Thome UH, Truffert P, Schreiber MD, et al. Elective high-frequency oscillatory versus conventional

ventilation in preterm infants. A systematic review and meta-analysis of individual patients' data. *Lancet* 2010; 375(9731):2082-91

7. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lawson S, Granton J. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults. A randomized controlled trial. *Am J Respir Crit Care Med* 2002; 166(6): 801-8

8. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368(9):795-805

9. Arnold JH, Hanson JH, Tor-Figuero LO, Gutierrez J, Berens RJ, Anglin DL. Prospective randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 1994; 22(10):1530-9

10. Samransamruajkit R, Prapphal N, Deelodegenavong J, Poovorawan Y: Plasma soluble intercellular adhesion molecule -1(sICAM-1) in pediatric ARDS during high frequency oscillatory ventilation. a predictor of mortality. *Asian Pac J allergy Immunol* 2005; 23(4): 181-8

11. Santschi M, Jouvett P, Leclerc F, Gauvin F, Newth CJ, Carroll CL, Flori H, Tasker RC, Rimensberger PC, Randolph AG: Acute lung injury in children. Therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 2010; 11(6):681-9

12. Randolph AG, Meert KL, O'Neil ME, hanson JH, Luekett PM, arnold JH, Gedeit RG, Cox PN, Roberts JS, Venkataraman ST, Forbes PW, Cheifetz IM. The feasibility of conducting clinical

trials in infants and children with acute respiratory failure. *Am J Respir Crit Care Med* 2003; 167(10):1334-40

13. Fedora M, Klimovic M, Seda M, Dominik P, Nekvasil R. Effect of early intervention of high-frequency oscillatory ventilation on the outcome in pediatric acute respiratory distress syndrome. *Bratisl Lek Listy* 2000; 101(1):8-13

14. Babbitt CJ, Cooper MC, Nussbaum E, Liao E, Levine GK, Randhawa IS. High-frequency oscillatory ventilation in pediatric acute hypoxemic respiratory failure: disease-specific morbidity survival analysis. *Lung* 2012; 190(6):685-90

15. Moniz M, Silvestre C, Nunes P, Abadesso C, Matias E, Loureiro H, Almeida H. High-frequency oscillatory ventilation in children: a 10-year experience. *Jornal de pediatria* 2013; 89(1):48-55

16. Ben Jaballah N, Mnif K, Bouziri A, Kazdaghi K, Belhadi S, Zouari B. High-frequency oscillatory ventilation in paediatric patients with acute respiratory distress syndrome--early rescue use. *Eur J Pediatr* 2005; 164(1):17-21

17. Dalton H, Fortenberry JD, Frenckner B, Palmer P. ECMO for pediatric respiratory failure. In: Annich GM, Lynch WR, Maclaren G, Wilson JM, Bartlett RH, editors. *ECMO: Extracorporeal Cardiopulmonary support in critical care*. 4th edition. Ann arbor, MI: ELSO; 2012: p265-70

18. Yehya N, Topjian AA, Thomas NJ, Friess SH. Improved oxygenation 24 hours after transition to airway pressure release ventilation or high-frequency oscillatory ventilation accurately discriminates survival in immunocompromised pediatric patients with acute

respiratory distress syndrome. *Pediatric critical care medicine: Pediatr Crit Care Med* 2014; 15(4):e147-56

19. Yehya N, Topjian AA, Lin R, Berg RA, Thomas NJ, Friess SH. High frequency oscillation and airway pressure release ventilation in pediatric respiratory failure. *Pediatric pulmonology* 2014; 49(7):707-15

20. Camporota L, Sherry T, Smith J, Lei K, McLuckie A, Beale R. Physiological predictors of survival during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care* 2013; 17(2):R40.

21. Sarnaik AP, Meert KL, Pappas MD, Simpson PM, Lieh-lai MW, Heidemann SM. Predicting outcome in children with severe acute respiratory failure treated with high-frequency ventilation. *Crit Care Med* 1996; 24(8):1396-402

22. Ben Jaballah N, Khaldi A, Mnif K, Bouziri A, Belhadj S, Hamdi A, et al. High-frequency oscillatory ventilation in pediatric patients with acute respiratory failure. *Pediatric critical care medicine: Pediatr Crit Care Med* 2006; 7(4):362-67

23. Rowan CM, Hege KM, Speicher RH, Goodman M, Perkins SM, Slaven JE, Westenkirchner DF, Haut PR, Nitu ME. Oxygenation index predicts mortality in pediatric stem cell transplant recipients requiring mechanical ventilation. *Pediatr Transplant* 2012; 16(6):645-50

24. Rotta AT, Steinhorn DM. Is permissive hypercapnia a beneficial strategy for pediatric acute lung injury? *Respir Care Clin N Am* 2006; 12(3):371-87

25. Rowan CM, Nitu ME, Rigby MR: Inconsistencies in care of the pediatric hematopoietic stem cell transplant recipient with respiratory failure. Opportunity for standardization and improved outcome. *Pediatr Transplant* 2014; 18(2):230-5
26. Santschi M, Randolph AG, Rimensberger PC, Jouvett P. Mechanical ventilation strategies in children with acute lung injury. a survey on stated practice pattern. *Pediatr Crit Care Med* 2013; 14(7):e332-7
27. Afshari A, Brok J, Moller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. *Anesth Analg* 2011; 112(6):1411-21
28. Dobyens EL, Anas NG, Fortenberry JD, Deshpande J, Cornfield DN, Tasker RC, Liu P, Eells PL, Griebel J, Kinsella JP, Abman SH. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. *Crit care Med* 2002; 30(11):2425-29
29. Fioretto JR, Batista KA, Carpi MF, Bonatto RC, Moraes MA, Ricchetti SM, Batistella RF. High-frequency oscillatory ventilation associated with inhaled nitric oxide compared to pressure-controlled assist/control ventilation and inhaled nitric oxide in children: Randomized, non-blinded, crossover study. *Pediatr Pulmonol* 2011; 46(8):809-16

Table 1-Demographic characteristics

	Total (n=62)	Survivors (n=44)	Non-Survivors (n=18)	p-Value
Age in months	83.5 (0.2-398)	82.3 (0.2-398)	86.3 (0.4-249)	0.66
Weight in Kg	25.8 (2.7-93.7)	25.7 (3-93.7)	26.0 (2.7-74)	0.75
Gender				
Male : Female	33 : 29	20 : 24	13 : 5	0.09
Total ventilation (days)	20.9 (1.9-56.9)	22.1 (3.3-56.9)	18.1 (1.9-53)	0.23
CMV before HFOV (hours)	50.9 (4-610)	38.2 (4-187)	81.9 (14-610)	0.65
HFOV Hours	135 (16-503)	129.2 (16-432)	149.4 (25-503)	0.82
CMV after HFOV (days)	13.2 (0-45)	15.1 (2-45)	8.4 (0-45)	<0.01
PICU LOS (days)	27.5 (2-96)	31.3 (5-96)	18.2 (2-58)	0.01
Ventilator free Patients				
Day 30		31(70%)	Not applicable	
Day 60		39(88%)	Not applicable	

Data are presented as mean and range. CMV, conventional mechanical ventilation; HFOV, high frequency oscillatory ventilation; PICU, pediatric intensive care unit; LOS, length of stay.

Table 2-Diagnoses of children treated with HFOV

Diagnosis	Total (n=62)	Survivors (n=44)	Non-survivors (n=18)
Malignancy and complications	14	5	9
Head Injury and trauma	5	4	1
Sepsis with ARDS	10	10	0
Pneumonia viral and bacterial	16	11	5
Post-operative ARDS	4	4	0
Aspiration related respiratory failure	7	5	2
Toxic shock syndrome	3	3	0
Eosinophilic pneumonitis	1	1	0
Pulmonary hemorrhage (Wegener's granulomatosis)	1	1	0
Liver disease	1	0	1

Table 3: Oxygenation Index (OI), PaO₂/FiO₂ (P/F) ratio and mean airway pressure (Paw) during CMV 24 hours prior and 48 hours during HFOV between survivors (S) and non-survivors (NS)

Time(hours)	OI-S	OI-NS	P/F-S	P/F-NS	Paw-S	Paw-NS
-24 (CMV)	17.6±1.5	16.1±3	112±9	130±10	16.0±0.8	16.6±1.4
-18 (CMV)	18.7±1.2	19.3±3.6	101±5	103±9	17.2±0.7	16.2±1.4
-12 (CMV)	21.7±1.5	21.8±2.3	94±6	92±8	18.0±0.7	17.8±0.9
-6 (CMV)	29.8±2	28.6±2.9	76±5	79±9	20.8±0.9	19.2±1.2
+1 (HFOV)	35.3±2.3	38.8±3.9	110±11	113±25	30.4±1.1	31.1±1.0
+6 (HFOV)	28.0±2.1	30.0±4	140±11	163±30	31.7±1.1	31.9±1.0
+12 (HFOV)	25.5±2.2	29.4±3.7	157±12	149±22	31.4±1.2	32.4±1.1
+18 (HFOV)	21.4±1.7	25.3±4.0	185±15	180±27	31.1±1.2	32.4±1.2
+24† (HFOV)	20.5±1.8	28.6±4.6	197±16	181±32	30.6±1.2	32.8±1.1
+30 (HFOV)	18.9±1.9	26.5±4.2	220±19	190±32	30.4±1.1	32.5±1.3
+36 (HFOV)	17.7±1.6	25.0±4.1	233±20	194±30	30.5±1.1	31.7±1.3
+42 (HFOV)	19.5±2.3	27.7±3.9	227±20	164±24	29.9±1.1	32.6±1.1
+48 (HFOV)	20.0±1.9	26.7±3.0	223±20	155±19	29.6±1.1	32.2±1.2

Data are presented as mean \pm SEM. CMV, conventional mechanical ventilation; HFOV, high frequency oscillatory ventilation; Paw (mean airway pressure) in cm of H₂O. †OI is statistically significant ($p < 0.05$) between survivors and non-survivors at or after 24 hours on during HFOV. P/F ratios and Paw are not statistically significant ($p > 0.05$) at any time points.

Figure Legends:

Figure 1: Comparison of oxygenation parameters in children with Hypoxic respiratory failure between survivors and non-survivors before and after transitioning to HFOV. A. Differences in Oxygenation index (OI) between survivors and non-survivors during CMV and HFOV (* $p < 0.05$). B. Differences in $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio between survivors and non-survivors ($\dagger p < 0.05$). C. Mean airway pressure (Paw) settings between survivors and non-survivors during CMV and HFOV. Paw is not significant at all-time points between survivors and non-survivors.

Figure 2: Comparison of PaCO_2 , pH and bicarbonate in children with hypoxic respiratory failure between survivors and non-survivors before and after transitioning to HFOV. A. Differences in pH between survivors and non-survivors before and after HFOV (* $p < 0.05$). B. PaCO_2 (torr) trends between survivors during CMV and HFOV. There is no statistical significance at any time points. C. Bicarbonate (mEq/L) between survivors and non-survivors before and after HFOV (* $p < 0.05$).

Figure 3: Differences in HFOV settings between survivors and non-survivors with Hypoxic respiratory failure. A. Difference in Delta Pressure (ΔP) settings between survivors and non-survivors during HFOV. Overall ΔP settings were higher in non-survivors ($p < 0.01$). B. Differences in frequency (Hz) between survivors and non-survivors. Hz settings were significantly lower ($p < 0.01$) in non-survivors.

Figure 4: Effect of iNO in survivors and non-survivors and changes in P/F ratios and OI during CMV and HFOV. A. Changes in $\text{PaO}_2/\text{FiO}_2$ (P/F) ratios in response to iNO were compared between survivors and non-survivors. B. Oxygenation Index (OI) changes following iNO were compared between survivors and non-survivors. Neither P/F ratios nor OI changes were statistically significant between survivors and non-survivors. C. Changes in $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio before and after inhaled nitric oxide (iNO) during HFOV versus CMV (* $p < 0.05$ at 3 hours and subsequent time points after starting iNO). D. Oxygenation index (OI) changes before and after iNO during HFOV versus CMV. OI changes were statistically not significant between CMV and HFOV at any time points.

Figure 5: Receiver operating characteristic (ROC) curves for Oxygenation index and pH. A. ROC curve to determine survival for oxygenation index (OI) at 24 hours during high frequency oscillatory ventilation (HFOV). B. ROC curve to evaluate survival for pH at 36 hours during HFOV. PPV, Positive predictive value; NPV, Negative predictive value.

Figure 1:

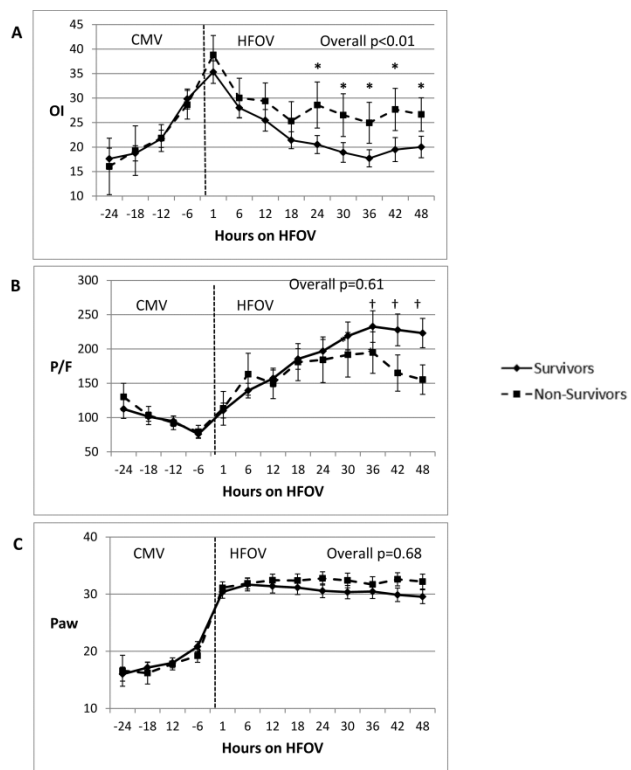


Figure 2:

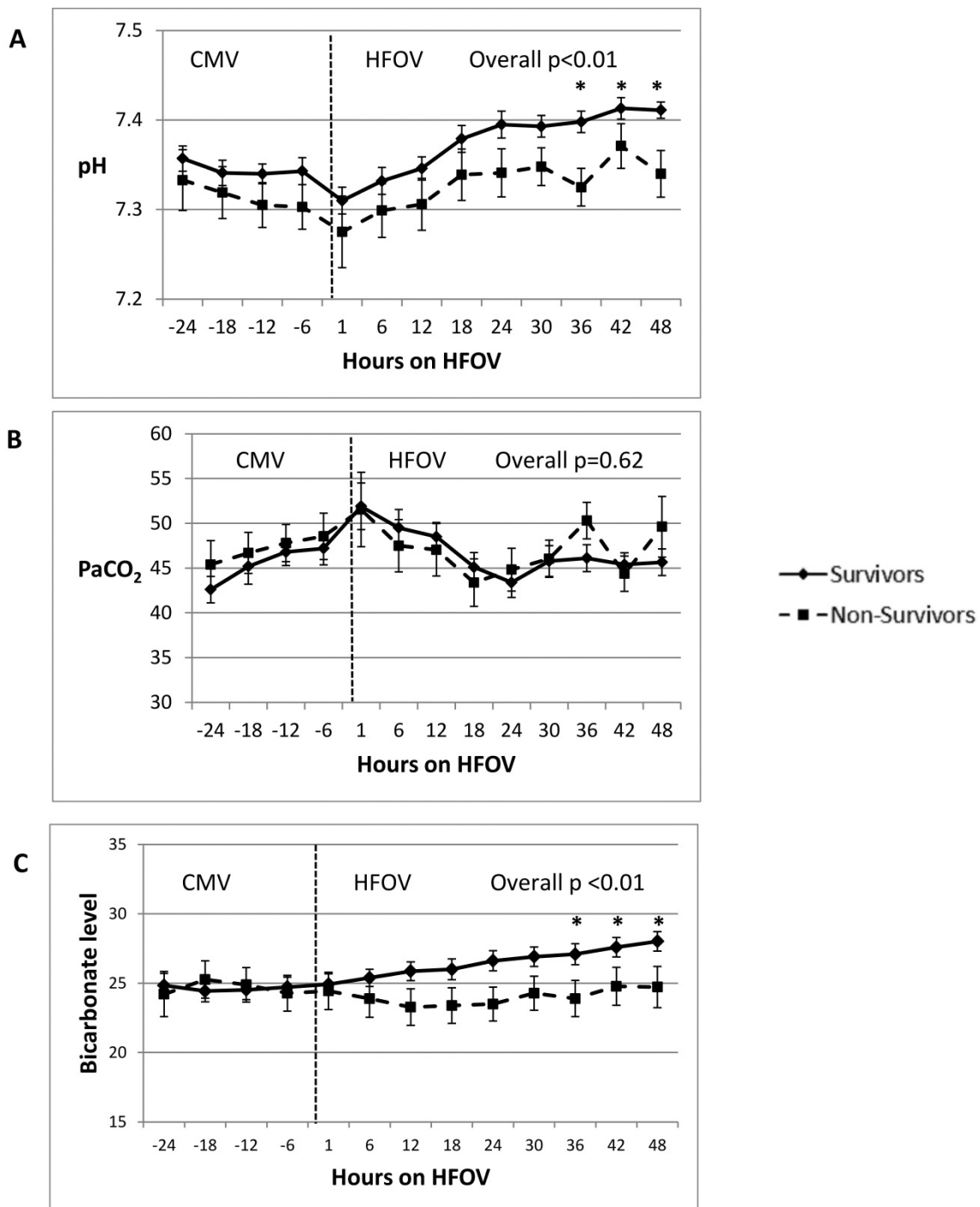


Figure 3:

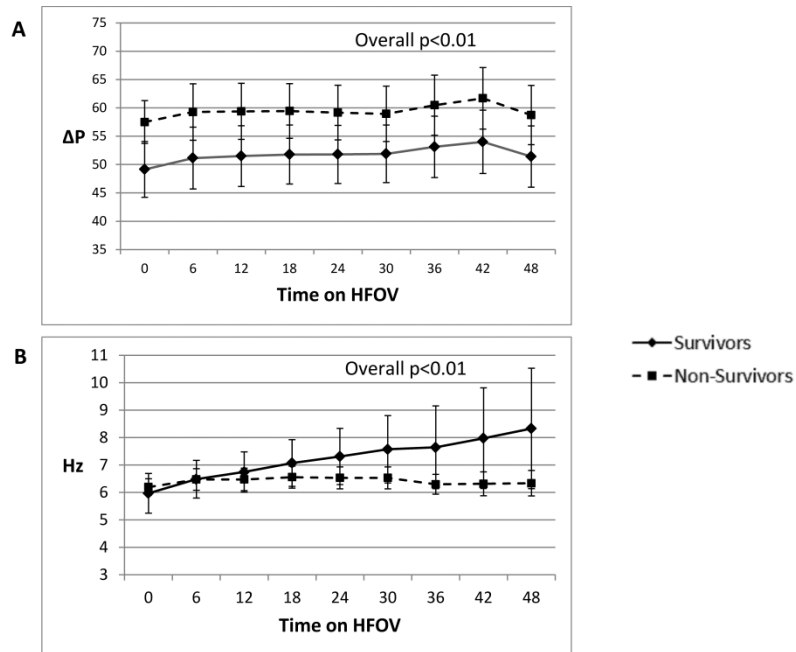


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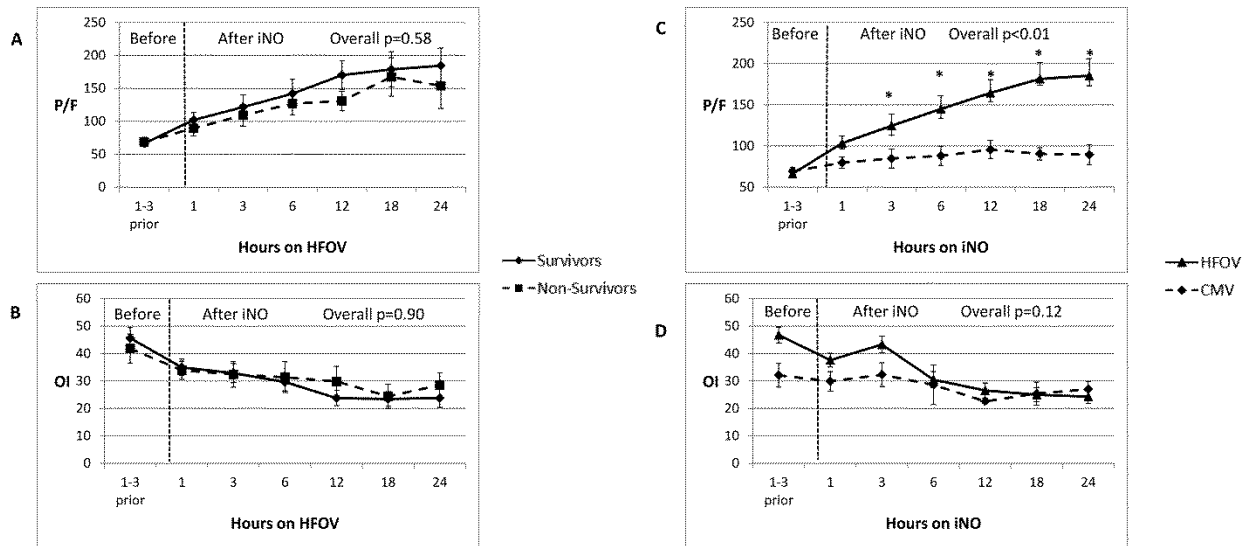
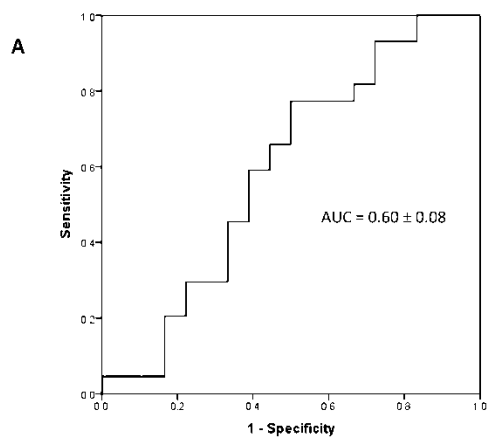
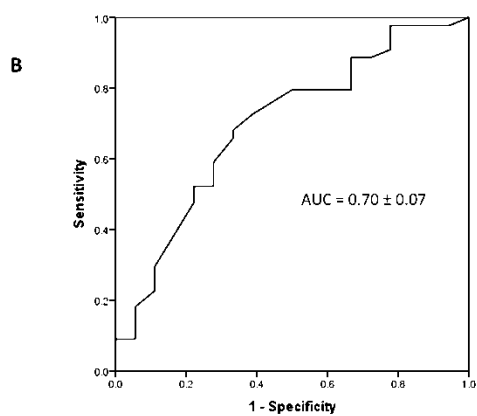


Figure 5:



OI	Sensitivity	Specificity	PPV	NPV
<25	70	50	77	41
<28	77	44	77	44
<30	79	33	74	40
<39	93	22	74	57



pH	Sensitivity	Specificity	PPV	NPV
>7.30	86	33	76	50
>7.34	73	61	82	48
>7.37	66	67	83	44
>7.40	52	78	85	40