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Effect of tidal volume in children with acute hypoxemic respiratory failure

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Abstract *Objectives:* To determine if tidal volume (V_T) between 6 and 10 ml/kg body weight using pressure control ventilation affects outcome for children with acute hypoxemic respiratory failure (AHRF) or acute lung injury (ALI). To validate lung injury severity markers such as oxygenation index (OI), $\text{PaO}_2/\text{FiO}_2$ (PF) ratio, and lung injury score (LIS). *Design:* Retrospective, January 2000–July 2007. *Setting:* Tertiary care, 20-bed PICU. *Patients:* Three hundred and ninety-eight endotracheally intubated and mechanically ventilated children with PF ratio <300 . Outcomes were mortality and 28-day ventilator free days. *Measurements and main results:* Three hundred and ninety-eight children met study criteria, with 20% mortality. 192 children had ALI. Using $>90\%$ pressure control ventilation, 85% of patients achieved V_T less than 10 ml/kg. Median V_T was not significantly different between survivors and non-survivors during the first 3 days of mechanical

ventilation. After controlling for diagnostic category, age, delta P (PIP-PEEP), PEEP, and severity of lung disease, V_T was not associated with mortality ($P > 0.1$), but higher V_T at baseline and on day 1 of mechanical ventilation was associated with more ventilator free days ($P < 0.05$). This was particularly seen in patients with better respiratory system compliance [$\text{Cr}_s > 0.5 \text{ ml/cmH}_2\text{O/kg}$, OR = 0.70 (0.52, 0.95)]. OI, PF ratio, and LIS were all associated with mortality ($P < 0.05$). *Conclusions:* When ventilating children using lung protective strategies with pressure control ventilation, observed V_T is between 6 and 10 ml/kg and is not associated with increased mortality. Moreover, higher V_T within this range is associated with more ventilator free days, particularly for patients with less severe disease.

Keywords Pediatrics · Positive pressure respiration · Lung volume measurements

Introduction

Acute hypoxemic respiratory failure (AHRF), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) result in morbidity and mortality for pediatric intensive care unit (PICU) patients. While contemporary ventilation strategies have improved outcome, mortality

continues at 30–40% for adults [1], and 8–22% for children [2–4] with ALI or ARDS.

Several adult studies demonstrate improved outcome when patients are managed in volume control mode with set tidal volumes of 6 ml/kg predicted body weight, compared to 12 ml/kg [1, 6]. However, differences between adult and pediatric practice regarding modes of

ventilation, tidal volume measurements, and developmental differences bring into question whether such strategies should be embraced universally in pediatrics [5, 13–18]. Moreover, evidence in both adults and children suggests that lung protective strategies should not be one-size fits all, but rather catered to lung disease severity [7, 8]. For further discussion, see Electronic supplementary material (ESM).

We sought to determine the effect of generated tidal volume on outcome for children with ALI or AHRF using historical data from greater than 90% of patients on pressure control ventilation. Additionally, we examined how well lung injury severity measures such as $\text{PaO}_2/\text{FiO}_2$ (PF) ratio, oxygenation index (OI), and a modified Murray pediatric lung injury score (LIS) [19] reflect mortality at various intervals during the initial days of mechanical ventilation [20].

Methods

Patient selection

Retrospective review of all admissions to a tertiary care PICU between January 2000 and July 2007 was conducted. Patients were eligible if endotracheally intubated and mechanically ventilated, and at least one PF ratio was less than 300 within 24 h after intubation. Patients were excluded for evidence of cardiac disease or incomplete ventilation data. All patients met three of four diagnostic criteria for ALI (acute onset, PF ratio <300 , and no left ventricular dysfunction). The presence of bilateral infiltrates on chest radiograph (fourth ALI criteria) was handled separately. Finally, all patients with an endotracheal tube leak greater than 20% were excluded [24].

Variable selection

Data were extracted from two databases: an electronic ICU flow sheet (Philips CareVue®, Waltham, MA), and a patient database (Microsoft Access®, Redmond, WA). From these two databases, information on age, race, gender, weight, primary diagnosis, year of admission, chest X-rays, arterial blood gas values, ventilator settings, and a pediatric risk of mortality (PRISM) Score were extracted [25]. All chest X-rays were read by a pediatric radiologist blinded to the study, and reports reviewed for the presence of ALI criteria.

Ventilator strategy

While this study was non-interventional, a lung-protective strategy was in place in our PICU (see ESM).

Ventilator and arterial blood gas (ABG) variable definition

The initial PF ratio <300 after intubation was defined as “baseline,” where blood gas measurements were extracted. In addition, the closest charted ventilator settings at or prior to the ABG were extracted. Tidal volume (V_T ml/kg) was calculated using exhaled tidal volume (V_{Te}) measured at the ventilator with compensation for tubing compliance and make of the ventilator, divided by actual body weight.

Aggregate variables were created to express time-weighted averages of ventilator settings and blood gas values over the first 3 days after “baseline” (see ESM).

Lung injury severity markers

PF ratio, oxygenation index [$\text{OI} = (\text{mean airway pressure} \times \text{FiO}_2)/(\text{PaO}_2) \times 100$], dynamic compliance of the respiratory system [$\text{Cr}_s = V_T \text{ (ml/kg)}/(\text{PIP}-\text{PEEP})$], and a modified Murray lung injury score (LIS) for pediatrics [19] were determined at “baseline” and then again aggregated over the first 3 days after baseline, as above. The modified lung injury score is a composite of PF ratio, PEEP, Cr_s , and involved quadrants on chest radiograph, with integers from zero to four for each component. Data on quadrants of alveolar consolidation on chest X-ray were not included in this analysis. As a result, the LIS was the average of three, not four, components.

Outcome measures

The primary outcome measure was ICU mortality. Secondary outcome was 28-day ventilator free days (VFDs) [26]. Data on outcome measures were complete and no censoring was necessary.

Statistics

Statistical analysis was performed using Statistica v. 5.5 (StatSoft, Tulsa, OK) and Stata v. 10 (StataCorp, College Station, TX). Continuous variables were analyzed with a Wilcoxon rank-sum test, as assumptions of normality could not always be satisfied. Dichotomous outcomes were analyzed using a Yates-corrected Chi-squared test. Kruskal–Wallis ANOVA was used to examine differences in median tidal volume stratified by categories. Logistic regression analysis was performed to examine the impact of the variables of interest on the outcome of mortality, and control for potential confounding variables, or effect modifiers. A multivariate logistic regression model was built incorporating variables with univariate associations with mortality ($P < 0.2$), with care taken to

avoid terms that were collinear. Overall goodness of fit was assessed using the Hosmer–Lemeshow test and graphical evaluation for influential points. ROC plots were created and overall discrimination ability of the various predictive models was assessed using empirical estimates of the overall area under the curve (AUC).

The outcome of 28-day VFDs had an almost bimodal distribution, as reported previously. Hence, for logistic regression analysis, it was dichotomized to <14 days, or ≥14 days, as previously described [4]. However, when appropriate, comparisons of median number of VFDs between groups were analyzed using a Wilcoxon rank-sum test [26].

For more detailed description of methods and power calculations, please see ESM.

Results

Patient selection

Eight thousand two hundred and forty-six patients <18 years were admitted to the PICU during the study period, and 773 had at least two arterial PF ratios <300. Seven hundred patients were mechanically ventilated and 507 had at least one PF ratio <300 after endotracheal intubation. Nine patients were excluded for incomplete ventilator or blood gas data, 49 patients met cardiac

exclusions, and 51 patients had an endotracheal tube leak >20%.

Three hundred and ninety-eight patients were included in the final analysis, of which 227 were male (57%), 194 were Latino (49%), with a median age of 4.3 years. Eighty patients died, an overall mortality of 20%. One hundred ninety-two patients (48%) had bilateral pulmonary infiltrates on chest X-ray and met full criteria for either ALI or ARDS (Table 1).

Mortality

Univariate results

Associations of diagnostic and demographic variables with mortality are presented in Table 1.

For the entire population, the median PF ratio at baseline was 138 with a lung injury score of 2.33. Patients were managed almost exclusively with pressure control ventilation (>90%, PRVC comprising the rest), with a median PEEP of 6 cmH₂O, V_T of 7.4 ml/kg, MAP of 11 cmH₂O, and PIP of 26 cmH₂O. Eighty-four percent of patients had a PIP ≤ 35, and 94% a PIP ≤ 40. At baseline, patients that died had higher median OI, lower median PF ratio, higher median lung injury score, as well as higher FiO₂, PIP, PEEP, MAP, lower pH, PaO₂, and base deficit. Median V_T was 7.04 ml/kg in deceased and 7.60 ml/kg in survivors ($P = 0.13$). These trends for

Table 1 Univariate analysis by survival

	All <i>n</i> = 398	Survived <i>n</i> = 318	Died <i>n</i> = 80	<i>P</i> value
Weight (kg)	16 (8, 36)	15 (9, 34)	17 (8, 44)	0.73
Age (years)	4.3 (1, 11.5)	3.9 (1, 10.9)	5.9 (0.8, 12.5)	0.73
Race				
Latino	194 (48.7)	157 (49.4)	37 (46.3)	0.71
White	74 (18.6)	56 (17.6)	18 (22.5)	0.40
Black	45 (11.3)	35 (11)	10 (12.5)	0.86
Other	85 (21.4)	70 (22)	15 (18.8)	0.63
Male	227 (57)	180 (56.6)	47 (58.8)	0.83
CXR bilateral infiltrates	192 (48.2)	148 (46.5)	44 (55)	0.22
PRISM Probability of death	0.57 (0.26, 0.86)	0.49 (0.22, 0.79)	0.87 (0.56, 0.97)	<0.001
Admission diagnosis				OR (95% CI)
Parenchymal lung disease ^a	117 (29.4)	92 (28.9)	25 (31.3)	Reference
Other respiratory disease	30 (7.5)	23 (7.2)	7 (8.8)	1.47 (0.57, 3.81)
Shock or sepsis	43 (10.8)	29 (9.1)	14 (17.5)	2.33 (1.08, 5.04)
Trauma	16 (4)	12 (3.8)	4 (5)	1.61 (0.48, 5.41)
Neurologic compromise	50 (12.6)	37 (11.6)	13 (16.3)	1.70 (0.79, 3.65)
Metabolic/renal disease	24 (6)	22 (6.9)	2 (2.5)	0.44 (0.10, 1.99)
Other diagnosis	28 (7)	21 (6.6)	7 (8.8)	1.61 (0.62, 4.20)
Gastrointestinal diagnosis	61 (15.3)	53 (16.7)	8 (10)	0.73 (0.31, 1.73)
Orthopedic diagnosis ^b	29 (7.3)	29 (9.1)	0 (0)	0 (0, 0.27)

Continuous variables expressed as median and interquartile range. Categorical variables expressed as count and percentage

^a Parenchymal lung disease used as baseline group for computation of odds ratios for diagnostic category for admission

^b Orthopedic diagnosis was primarily scoliosis

blood gas, ventilator, and lung severity markers remained consistent over the first 3 days of ventilation (Table 2).

Seventy percent of patients were managed with V_T between 6 and 10 ml/kg throughout the first 3 days of ventilation (Fig. 1). There was a non-significant trend for improved survival with higher V_T . Patients with higher LIS had lower median V_T than those with lower LIS (K–W ANOVA $P < 0.001$, Fig. 2). However, the relationship between V_T and mortality was similar when stratified as a function of LIS (Fig. 3), even though mortality was higher for patients with higher LIS.

Markers of lung injury including PF ratio, OI, and LIS were all significantly associated with mortality at baseline (Table 2) with similar overall classification in a logistic regression model (Table 3). Further, there was a trend for stronger degrees of association with mortality with each additional day the patient remained on mechanical ventilation (Fig. 4). Notably, patients with “severe ARDS,” defined as baseline LIS > 2.5 [16], had significantly higher mortality than those with LIS ≤ 2.5 [53/163 (32.5%) vs. 26/225 (11.5%), $P < 0.001$, Fig. 3]. Respiratory system compliance was associated with mortality when averaged (time-weighted) for days 1–3, although not at baseline.

Bilateral pulmonary infiltrates

One hundred and ninety-two patients had bilateral pulmonary infiltrates and met all four ALI criteria. Patients with bilateral pulmonary infiltrates had higher PIP, PEEP, OI, and lower median V_T (7.13 vs. 7.84 ml/kg, $P = 0.02$) than those without bilateral infiltrates. Moreover, 44/192 (22.8%) patients with bilateral infiltrates died compared to 36/206 (17.5%) without bilateral infiltrates ($P = 0.2$). However, there was no difference between median initial V_T and mortality when limited to patients with bilateral pulmonary infiltrates [$n = 192$, 7.3 (survivors) vs. 7.0 (deceased) ml/kg, $P = 0.27$]. There was also no difference for aggregated V_T over days 1–3 ($P > 0.1$).

Multivariate results

Multivariate logistic regression modeling was performed to determine whether severity of lung disease or systemic illness impacted the relationship between V_T and mortality. V_T was not associated with mortality after controlling for age, Delta P (PIP-PEEP), PEEP, admission diagnosis, and severity of lung disease using LIS, PF ratio, or OI (all V_T coefficients $P > 0.1$, H–L test $P > 0.2$). Moreover, there were no significant interaction effects between V_T and presence of bilateral infiltrates on chest X-ray, diagnostic category of admission, or severity of lung disease as measured by OI, PF ratio, Crs (<0.5 or ≥ 0.5 ml/cmH₂O/kg), or LIS and mortality (all interaction

term P values > 0.1 , see ESM). Finally, due to concerns of collinearity between PRISM score and individual components of the model, a separate model including V_T , PRISM score, age, Delta P, and PEEP was built. It also demonstrated initial as well as day 1–3 V_T had no effect on mortality ($P > 0.1$ all V_T coefficients).

Bilateral pulmonary infiltrates

When limited to patients with bilateral pulmonary infiltrates, V_T had no effect on mortality after controlling for age, Delta P, PEEP, admission diagnosis, and severity of lung disease using LIS, PF ratio, or OI (all V_T coefficients $P > 0.1$, H–L test $P > 0.2$). The same results were seen using the model incorporating PRISM score (all V_T coefficients $P > 0.2$, H–L test $P > 0.2$).

Analysis of non-survivors

For the 80 patients that died, refractory respiratory failure [28] was responsible for death in 29/80 (36%) patients. Twenty-five (31%) patients met neurologic criteria for death or had a hopeless neurological condition. Shock or cardiac arrest not from refractory respiratory failure was responsible for 22 (27%) deaths. Four patients (5%) died from other causes. Fifty-two (69%) patients had at least three dysfunctional organs prior to death. Thirty-four (43%) patients had a documented limitation of care or do not resuscitate order.

28 day ventilator free days (VFDs)

Univariate analysis

The entire cohort had a median of 17.4 VFDs (IQR 0, 24.4). Lower baseline V_T and day 1 V_T were both associated with fewer VFDs (Table 4). Moreover, all variables that had a univariate association with mortality were also associated with fewer VFDs. Except for V_T at baseline and day 1, variables not associated with mortality were also not associated with fewer VFDs (analysis not shown). Patients with bilateral pulmonary infiltrates had significantly fewer VFDs (median 16.4 vs. 20.8, $P = 0.02$), although this was not significant if VFDs were dichotomized at 14 days.

Multivariate analysis

This relationship between lower V_T on day 1 of ventilator management and fewer VFDs held after controlling for age, Delta P, PEEP, admission diagnosis, and measures of lung disease severity such as OI, PF ratio, or LIS ($P < 0.05$ with each measure of lung disease severity).

Table 2 Blood gas, ventilator, and lung severity markers by day of mechanical ventilation, stratified by mortality

	Baseline All n = 398	Baseline Survived n = 318	Baseline Died n = 80	P value	Day 1 All n = 376	Day 1 Survived n = 298	Day 1 Died n = 78	P value
Blood gas								
PaCO ₂	45 (38, 53)	44 (38, 52)	46.5 (38, 57)	0.14	42.6 (37.5, 49)	42 (37.5, 48.0)	45.5 (37.9, 52.1)	0.07
PaO ₂	75 (61, 92)	77 (64, 94)	63.5 (53.5, 80)	<0.01	100 (80, 122)	100 (80, 123)	101.1 (73.6, 117)	0.76
pH	7.35 (7.27, 7.40)	7.35 (7.29, 7.41)	7.29 (7.20, 7.36)	<0.01	7.37 (7.32, 7.42)	7.37 (7.33, 7.42)	7.32 (7.26, 7.38)	<0.01
BE	-2.1 (-5.3, 1.5)	-1.55 (-4.7, 1.85)	-4.6 (-8.8, -0.3)	<0.01	-1.43 (-4.2, 1.73)	-0.89 (-3.51, 1.96)	-3.22 (-6.18, -0.08)	<0.01
Vent support								
FiO ₂	0.6 (0.4, 1)	0.5 (0.4, 0.9)	0.8 (0.5, 1)	<0.01	0.46 (0.4, 0.6)	0.45 (0.40, 0.53)	0.58 (0.43, 0.80)	<0.01
MAP	11 (9, 15)	11 (9, 14)	14 (9, 17)	<0.01	13 (10.2, 17)	12.3 (9.8, 15.7)	17.1 (13.2, 22)	<0.01
PIP	26 (22, 30.5)	26 (22, 30)	30 (24, 34)	<0.01	26.5 (22.8, 31.7)	25.5 (22.2, 30.4)	30.1 (26, 36)	<0.01
PEEP	6 (4, 8)	6 (4, 8)	8 (4, 10)	<0.01	7.4 (5, 10)	6.8 (4.8, 10)	9.5 (6.6, 12.4)	<0.01
V _T	7.45 (5.79, 9.14)	7.6 (5.86, 9.22)	7.04 (5.46, 8.74)	0.13	7.46 (6.08, 9.02)	7.49 (6.24, 9.18)	7.30 (5.53, 8.65)	0.06
Injury marker								
PF ratio	138 (83, 192)	149 (95, 200)	80 (60, 147)	<0.01	196 (140, 268)	209 (148, 271)	168 (96, 248)	0.008
OI	8.1 (5.1, 15.3)	7.4 (4.8, 13.1)	14.3 (7.9, 24.4)	<0.01	6.2 (3.8, 10.6)	5.6 (3.7, 9.2)	10.1 (4.5, 18.2)	<0.01
CRS	0.38 (0.27, 0.50)	0.38 (0.28, 0.51)	0.36 (0.23, 0.47)	0.086	0.40 (0.30, 0.54)	0.42 (0.32, 0.55)	0.35 (0.26, 0.44)	0.001
LIS	2.33 (2, 3)	2.33 (1.67, 3)	3 (2.33, 3.33)	<0.01	2.33 (1.67, 3)	2.33 (1.67, 2.67)	3 (2, 3.33)	<0.01
	Day 2 All n = 343	Day 2 Survived n = 276	Day 2 Died n = 67	P value	Day 3 All n = 290	Day 3 Survived n = 238	Day 3 Died n = 52	P value
Blood gas								
PaCO ₂	42.8 (37.8, 48.6)	42.5 (37.7, 48.3)	43.4 (38.1, 50.5)	0.31	44.3 (38.8, 50.7)	43.5 (38.3, 49.4)	48.3 (40, 55.7)	0.01
PaO ₂	97.2 (78.8, 122.6)	98 (80.4, 122)	95.5 (67.6, 128)	0.26	96 (77.5, 117)	96.4 (79.8, 117.7)	80 (68.1, 114.4)	0.04
pH	7.40 (7.35, 7.44)	7.40 (7.36, 7.44)	7.37 (7.30, 7.43)	0.01	7.40 (7.36, 7.45)	7.41 (7.36, 7.45)	7.37 (7.30, 7.44)	0.002
BE	0.40 (-2.45, 4.42)	0.5 (-2.02, 4.42)	-1.24 (-4.48, 4.35)	0.031	1.65 (-1.1, 5.8)	2.02 (-0.9, 5.71)	0.02 (-2.90, 7.60)	0.14
Vent support								
FiO ₂	0.41 (0.39, 0.52)	0.4 (0.37, 0.47)	0.5 (0.4, 0.65)	<0.01	0.4 (0.36, 0.50)	0.4 (0.36, 0.46)	0.5 (0.4, 0.8)	<0.01
MAP	12.8 (10.1, 26.7)	12 (9.5, 15.2)	16.6 (12.8, 21.6)	<0.01	13.6 (10, 16.6)	12.5 (9.5, 15.6)	16.8 (13.9, 20.8)	<0.01
PIP	26 (21.7, 30.7)	25.1 (21.4, 29.7)	30 (27.1, 35)	<0.01	26 (21.5, 30.6)	24.9 (20.1, 29.6)	30.1 (27, 35.4)	<0.01
PEEP	7.8 (5.7, 10)	7 (5.1, 9.5)	10 (6.8, 12.4)	<0.01	8 (5.8, 10)	7.3 (5.6, 9.9)	10 (7.8, 13.5)	<0.01
V _T	7.17 (5.76, 8.73)	7.20 (5.79, 8.79)	7.01 (5.52, 8.52)	0.38	7.19 (5.88, 8.45)	7.15 (5.88, 8.45)	7.39 (5.98, 8.44)	0.89
Injury markers								
PF ratio	233 (163, 311)	235 (172, 314)	193 (108, 293)	0.01	214 (152, 300)	224 (168, 304)	158 (103, 284)	0.002
OI	5.2 (3.4, 9.5)	4.8 (3.3, 7.6)	8.6 (4.6, 15)	<0.01	5.5 (3.6, 9.8)	5 (3.4, 8)	11 (4.9, 18.3)	<0.01
CRS	0.40 (0.29, 0.52)	0.42 (0.30, 0.55)	0.35 (0.27, 0.48)	0.007	0.42 (0.30, 0.54)	0.43 (0.32, 0.55)	0.35 (0.28, 0.48)	0.017
LIS	2 (1.67, 3)	2 (1.33, 2.67)	2.7 (2, 3.33)	<0.01	2.33 (1.67, 3)	2 (1.67, 2.67)	3 (2, 3.33)	<0.01

Aggregate variables express time-weighted averages of ventilator settings and blood gas values over the first 3 days after “baseline (first PF ratio <300 after intubation).” Day 1–3 values represent independent 24-h periods, not aggregate 48 or 72-h values. Variables expressed as median and interquartile range, and analyzed with a Wilcoxon rank sum test. PaCO₂, PaO₂ in mmHg; BE in mEq/L; pH in Units; MAP, PIP, PEEP in cmH₂O; V_T in ml/kg; Crs in ml/cmH₂O/kg

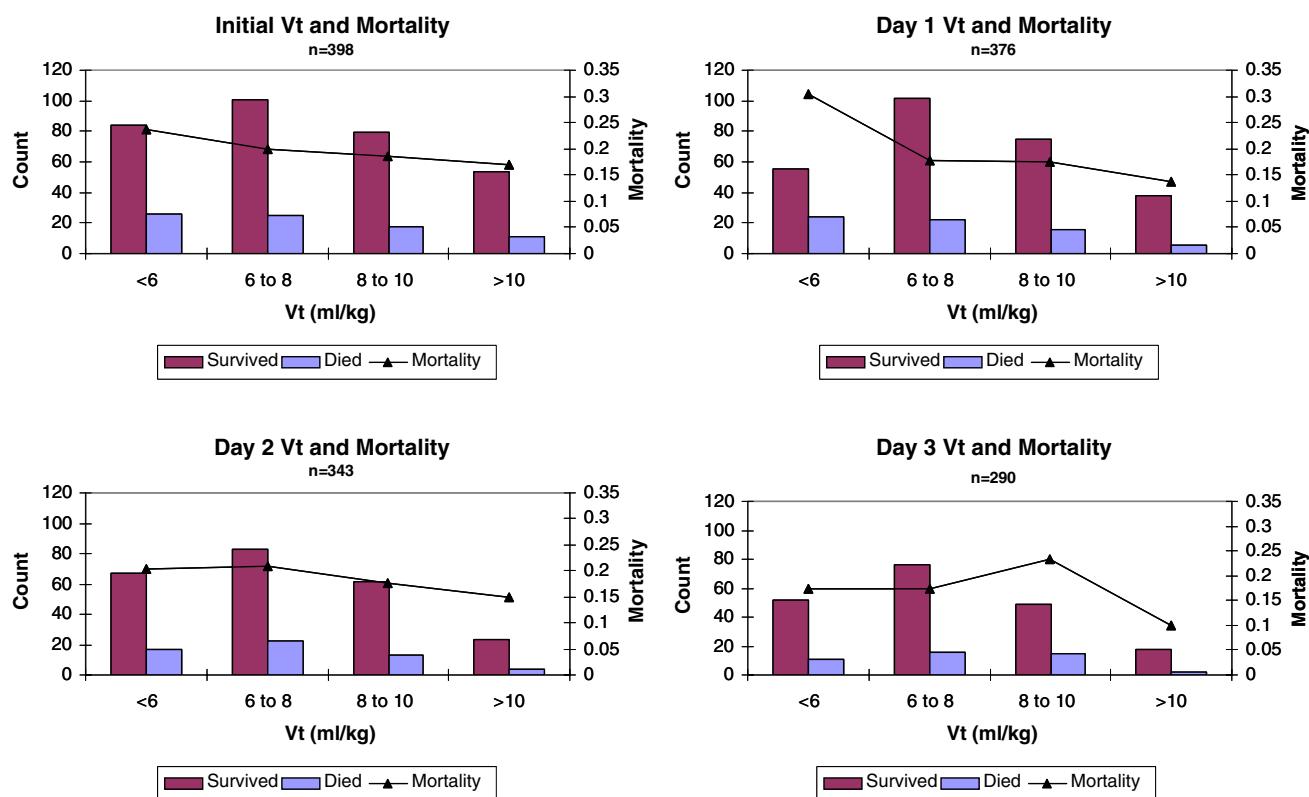


Fig. 1 Tidal volume and mortality by day of mechanical ventilation. There is a general trend for higher mortality with lower tidal volumes both at the beginning of mechanical ventilation, and

throughout the first 3 days. Most patients were ventilated between 6 and 10 ml/kg body weight. Mortality expressed as a proportion

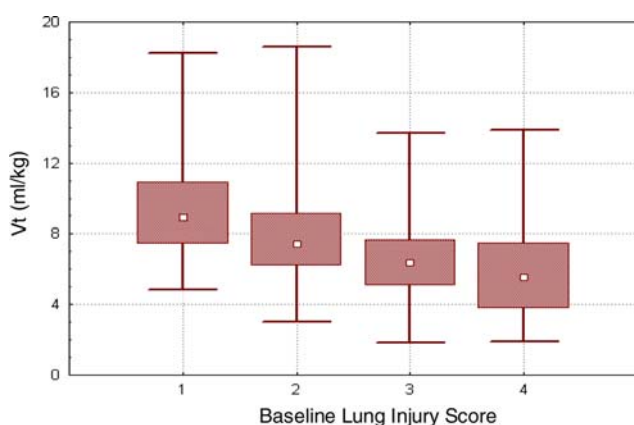


Fig. 2 Median baseline tidal volume by lung injury score. Patients with higher lung injury scores were managed with lower median V_T ($P < 0.001$). Median value, 25–75%, minimum–maximum.

The same results were seen with the multivariate model incorporating PRISM score, age, Delta P, and PEEP [OR = 0.88 (0.78, 0.98)]. Further, when stratifying patients by dynamic compliance of the respiratory system <0.5 or ≥ 0.5 ml/cmH₂O/kg, higher V_T on day 1 was

associated with more VFDs for patients with respiratory system compliance ≥ 0.5 [$n = 76$, OR = 0.73 (0.56, 0.95)] than for patients with compliance <0.5 [$n = 254$, OR = 0.90 (0.80, 1.01)]. This relationship held after controlling for Delta P, PEEP, and LIS [$n = 76$, OR = 0.70 (0.52, 0.95)].

Bilateral pulmonary infiltrates

Finally, when limiting the analysis to the 192 patients with bilateral infiltrates, the association between higher V_T on day 1 and more VFDs held true [OR = 0.82 (0.70, 0.96)]; however this did not reach statistical significance when controlling for age, Delta P, PEEP, admission diagnosis, and LIS [$n = 156$, OR = 0.85 (0.70, 1.03)].

Discussion

This study demonstrates when using a pressure control lung protective ventilation strategy, V_T in the typical range of 6–10 ml/kg measured at the mechanical ventilator does not appear to be associated with mortality for

Fig. 3 V_T and mortality, stratified by lung injury score. Note that while mortality is different stratified by LIS, the trends in the relationship between V_T and mortality are similar (slope of line). Numbers represent patients per point. Mortality expressed as a proportion

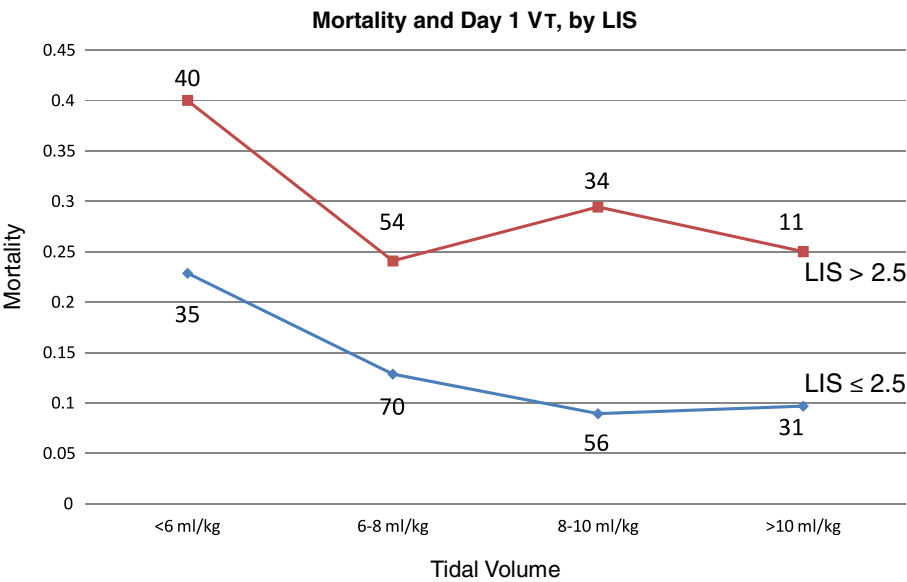


Table 3 Lung disease severity markers and mortality for all patients, and those that had radiographic evidence of ALI or ARDS

Marker of disease	All patients <i>n</i> = 398 OR (95% CI)	All patients <i>n</i> = 398 AUC (95% CI)	CXR criteria <i>n</i> = 192 OR (95%CI)
PF ratio (per 20 pt decrease)	1.23 (1.13, 1.34)	0.693 (0.626, 0.720)	1.19 (1.06, 1.34)
PF ratio <200	2.88 (1.33, 6.24)	23% Sensitivity 91% Specificity	2.32 (0.85, 6.37)
OI (per 1 pt increase)	1.04 (1.02, 1.06)	0.691 (0.628, 0.754)	1.03 (1.00, 1.05)
LIS (per 1 pt increase)	2.32 (1.65, 3.27)	0.68 (0.609, 0.751)	1.81 (1.13, 2.91)

Columns 2 and 4 represent odds ratios per unit change in lung disease severity markers (e.g. a 20-point decrease in PF ratio represents an odds of death of 1.23 for all patients, and 1.19 for patients that meet CXR criteria for ALI). Column 3 represents the classification ability for death in a logistic regression model. An

AUC between 0.7 and 0.8 is acceptable, between 0.8 and 0.9 is excellent, and greater than 0.9 is considered outstanding [27]. PF ratio <200 is a dichotomous outcome, so sensitivity and specificity are reported rather than area under the curve

children with ALI or AHRF. This represents true clinical practice as the ventilator variables are composites capturing patient exposure to particular settings, rather than predetermined intermittent snapshots. This echoes the findings of Flori et al. [4], showing no difference in V_T between survivors and non-survivors with pediatric ALI.

Previous work has shown that a universal approach to V_T selection for patients with ALI may not be best. Higher V_T (>6 ml/kg) may be associated with better outcome for patients with less severe lung disease by improving alveolar recruitment, independent of PEEP. Here, the association between higher V_T on day 1 and more VFDs was seen more clearly in patients with less severe lung disease ($Crs \geq 0.5$ ml/cmH₂O/kg). One can speculate that patients with less severe lung disease may therefore benefit from a higher V_T strategy [7, 8, 12]. We advocate V_T choice be tailored to lung disease severity, rather than universally being 6 ml/kg for all children.

Inherently, pressure control ventilation facilitates changing V_T based on compliance, as patients with poor

compliance attain a smaller V_T for a given pressure than patients with better compliance. This is seen in Fig. 2, where patients with severe disease, measured by LIS, were managed with lower median V_T . Moreover, the decelerating flow of pressure limited ventilation imparts additional benefit over the constant flow of volume modes of ventilation for patients with non-homogenous lung disease [29].

Given the almost universal use of pressure control ventilation and the strategy to limit PIP < 40 cmH₂O, the observed relationship between higher V_T and more VFDs is likely explained by lung disease severity. Patients with severe disease will attain a lower V_T than those with better compliance, given the same Delta P. As such, V_T and compliance really measure the same things: severity of lung disease. We controlled for disease severity using OI, PF ratio, LIS, PRISM, as well as pressure to attain V_T , and found the relationship between higher first day V_T (up to 10 ml/kg) and more VFDs to hold. Short of a randomized controlled trial where different V_T between 6 and 10 ml/kg

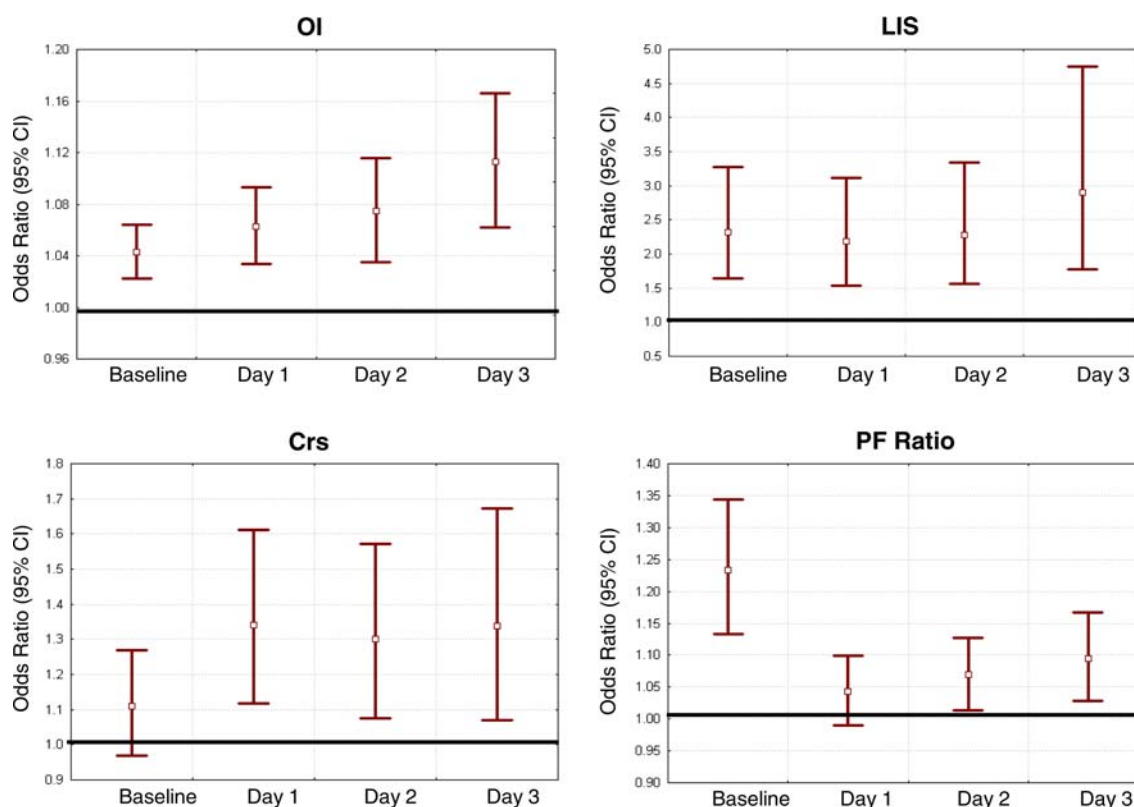


Fig. 4 Lung injury by day and mortality. Odds ratio (OR) for death per one unit increase in OI, one unit increase in LIS, 0.1 unit decrease in Crs, and 20 point decrease in PF ratio. LIS and OI are associated with mortality at baseline and over the first 3 days

($P < 0.05$). Crs over the first 3 days and PF ratio at baseline, second and third day are associated with mortality ($P < 0.05$). 95% CI, ■ odds ratio

Table 4 Tidal volume by day of mechanical ventilation in relation to mortality and ventilator free days

Tidal volume	Mortality	<14 VFD
Baseline	0.94 (0.85, 1.03)	0.91 (0.84, 0.98)
Day 1	0.87 (0.76, 0.99)	0.85 (0.77, 0.94)
Day 2	0.93 (0.80, 1.07)	0.91 (0.81, 1.02)
Day 3	0.97 (0.83, 1.15)	0.97 (0.85, 1.10)

Odds ratio (95% confidence interval) expressed in relation to each 1 ml/kg increase in tidal volume. (e.g. for each one point increase in tidal volume on day 1, the odds of death decreased to 0.87)

are targeted using pressure control ventilation, it is difficult to definitively answer whether higher V_T is in some way protective. However, this data demonstrates a pressure control strategy with a restricted upper pressure limit targeting V_T less than 10 ml/kg measured at the mechanical ventilator, is safe for children with ALI or AHRF.

A caveat to these findings is V_T measurements were not made at the airway using a proximal flow sensor, but rather at the ventilator with compensation for tubing compliance. This could result in overestimation of V_T , particularly for small children [16]. Unfortunately,

proximal measurements were not available for a large number of patients, and such measurements are not routinely used clinically in most ICUs.

With the hope of finding larger variability in ventilator and V_T strategies, we analyzed the presence of bilateral pulmonary infiltrates on chest radiograph separately, although all patients met other diagnostic criteria for ALI. Patients with bilateral infiltrates had more severe lung disease, a trend towards higher mortality, and fewer VFDs than those without bilateral infiltrates. However, the relationship between V_T and outcome was not different in these two groups, and bilateral infiltrates did not confound or modify the relationship between V_T and mortality or VFDs. In fact, the same trends were seen in the 192 patients who met all four criteria for ALI, although some power was lost. With the 192 patients in the ALI group we could detect a 7% reduction in mortality with a power of 0.8, or a 9% reduction in >14 VFDs. With the entire cohort of 398 we could detect a 4.5% reduction in mortality, or a 6.5% reduction in >14 VFDs. While ALI and ARDS represent unique physiologic cohorts, we believe these conclusions regarding V_T and outcome are applicable to patients with either AHRF or ALI.

This study also demonstrates that OI, PF ratio, and a pediatric modification of the Murray lung injury score are all associated with mortality for children with AHRF or ALI. In contrast to adult studies [28, 30–32], initial degree of oxygen impairment is associated with mortality for children, validating previous pediatric results [4, 33]. In general, mortality for ALI in adults is higher, and they tend to die of other organ dysfunction, not irreversible respiratory failure. Approximately 40% of deaths in our study were due to refractory respiratory failure, with 70% of patients having at least three organ dysfunctions at death. This reflects the findings of Trachsel et al. [33], and contrasts with adult studies where mortality from irreversible respiratory failure was responsible for 16% of deaths [28].

Further, OI has a stronger association with mortality each day the patient remains ventilated, as previously reported [33]. This is likely due to alveolar recruitment shortly after intubation, and helps explain why initial measures of lung disease severity often are not robust predictors of outcome. Nonetheless, we have demonstrated that any of these measures (OI, PF, LIS) can be used in future studies on ALI or AHRF to assess disease severity and stratify risk.

There are several shortcomings to this retrospective study. First, V_T measurements were made at the

mechanical ventilator, as discussed earlier. Second, consistency in charting may be variable depending on personnel, patient, or unit acuity. While this cannot be controlled for retrospectively, most information was captured electronically in real-time and human transcription minimized. Third, this was not a randomized trial, so we could not control for all confounding variables.

Conclusions

Ventilating children with ALI or AHRF using a pressure limited strategy with a reasonable upper pressure limit, targeting $V_T < 10$ ml/kg measured at the mechanical ventilator, is safe. Further, severity of lung disease measures such as OI, PF ratio, and a pediatric modification of the Murray lung injury score are all associated with mortality, both on initiation and throughout the first 3 days of ventilator support. This data is retrospective from a single center, and should be confirmed with a multicenter trial.

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