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Higher Pulmonary Dead Space May Predict Prolonged Mechanical Ventilation After Cardiac Surgery

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Summary

Children undergoing congenital heart surgery are at risk for prolonged mechanical ventilation and length of hospital stay. We investigated the prognostic value of pulmonary dead space fraction as a non-invasive, physiologic marker in this population. In a prospective, cross-sectional study, we measured pulmonary dead space fraction in 52 intubated, pediatric patients within 24 hr postoperative from congenital heart surgery. Measurements were obtained with a bedside, non-invasive cardiac output (NICO) monitor (Respironics Novametrix, Inc., Wallingford, CT). Median pulmonary dead space fraction was 0.46 (25–75% IQR 0.34–0.55). Pulmonary dead space fraction significantly correlated with duration of mechanical ventilation and length of hospital stay in the entire cohort (r_s=0.51, *P*=0.0002; r_s=0.51, *P*=0.0002) and in the subset of patients without residual intracardiac shunting (r_s=0.45, *P*=0.008; r_s=0.49, *P*=0.004). In a multivariable logistic regression model, pulmonary dead space fraction remained an independent predictor for prolonged mechanical ventilation in the presence of cardiopulmonary bypass time and ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (OR 2.2; 95% CI 1.14–4.38; *P*=0.02). The area under the receiver operator characteristic curve for this model was 0.91. Elevated pulmonary dead space fraction is associated with prolonged mechanical ventilation and hospital stay in pediatric patients who undergo surgery for congenital heart disease and has additive predictive value in identifying those at risk for longer duration of mechanical ventilation. Pulmonary dead space may be a useful prognostic tool for clinicians in patients who undergo congenital heart surgery.

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Keywords

pulmonary dead space fraction; intubation; congenital heart disease; pediatric; extubation

Introduction

Physiologically, pulmonary dead space is the portion of ventilation that is unable to participate in gas exchange and is essentially wasted. As a ratio of dead space to tidal volume, pulmonary dead space fraction may be a useful estimate of inefficient carbon dioxide excretion. Indeed, dead space fraction has been shown in both adult and pediatric populations to have important prognostic value in acute lung injury[1–3] and congenital diaphragmatic hernia.[4] In addition, lower pulmonary dead space fraction has been predictive of successful extubation in critically ill infants and children.[5] Thus, pulmonary dead space fraction may have potential value as a physiologic marker in other critically ill pediatric populations.

Postoperative congenital heart disease patients reflect a special population with multiple pulmonary factors that may contribute to prolonged mechanical ventilation. Chest wall mechanics are disturbed by thoracotomy, and the use of cardiopulmonary bypass may result in inflammatory damage to the lungs.[6–8] In addition, prolonged mechanical ventilation in these patients has been associated with cost burden and high morbidity with ventilator-associated pneumonia.[9,10] Indeed, children with congenital heart disease who fail extubation have been shown to have a high mortality rate and the longest duration of hospitalization in comparison with other critically ill children.[11,12] Thus, a substantial effort has been made to identify risk factors associated with prolonged mechanical ventilation after pediatric cardiac surgery.[6,13–16]

Identified predictors for prolonged mechanical ventilation in this population include duration of cardiopulmonary bypass time, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), the intraoperative requirement for blood product transfusion, and the volume of fluid intake in the first 24 hr postoperatively.[13] Traditional physiologic indices such as the CROP (compliance, rate, oxygenation, and pressure) index and the RSB (rapid shallow breathing) index in critically ill children in general have had variable results as predictors of extubation outcome.[17–20] Furthermore, these indices involve multiple, potentially uncomfortable measurements with determining maximal negative inspiratory flow against a unidirectional valve.[20]

Thus, we chose to evaluate pulmonary dead space fraction as a non-invasive variable to predict duration of mechanical ventilation in this at-risk population. We hypothesized that pulmonary dead space fraction would be elevated in children following reparative cardiac surgery and would have predictive value for patients at risk for prolonged mechanical ventilation. We therefore carried out a prospective, cross-sectional study to evaluate pulmonary dead space fraction as a physiologic marker in children undergoing surgery for congenital heart disease.

Materials and Methods

Subjects

For a period of 12 months, patients were screened in the University of California-San Francisco (UCSF) Children's Hospital Cardiac Intensive Care Unit, a tertiary university referral center. Intubated, postoperative congenital heart disease repair patients were eligible for enrollment. Non-intubated patients and patients with a tracheostomy were excluded. Informed consent was obtained from the patient, parent, and/or legal guardian, depending on the patient's age and

ability to comprehend the evaluation. The study was approved by the Institutional Review Board at the University of California-San Francisco.

Study Measurements

The non-invasive cardiac output (NICO) monitor (Respironics Novametrix, Inc., Wallingford, CT)[21] was used to measure pulmonary dead space fraction. The NICO monitor measures carbon dioxide (CO_2) elimination and integrates an average of breath to breath measurements over 1 min to calculate mixed expired CO_2 ($PeCO_2$). Using the Enghoff modification of the Bohr equation, $PeCO_2$ and a simultaneous arterial blood gas measurement are used to calculate the physiologic pulmonary dead space fraction:[22]

$$\text{Pulmonary dead space fraction} = \frac{PaCO_2 - PeCO_2}{PaCO_2}$$

Patients were studied in the absence of nursing care activities and were synchronous with the ventilator. Pulmonary dead space fraction measurements were made within the first 24 hr postoperatively in the intensive care unit. The clinical team was blinded to the dead space measurement. Dead space fraction measurements were collected by study personnel, not recorded in the patient's medical record, and not used for clinical decisions including extubation readiness. Extubation readiness was determined by the clinical team per previously established protocol.[23,24] Demographic data included patient age, diagnosis, weight, height, race, and gender. Vital signs, ventilator settings, and respiratory mechanics were recorded at the time of dead space measurement. Outcomes were duration of mechanical ventilation and days of hospital stay. Patients were excluded from the analysis if they remained intubated for a second surgical intervention (e.g., diaphragm plication).

Statistical Analysis

The primary outcome variable was duration of mechanical ventilation in hours and the secondary outcome was length of hospital stay in days. Data analysis was conducted using statistical software (STATA 10.0; College Station, TX). Baseline characteristics of the study population are reported as medians and interquartile ranges for continuous data and number and percentages for dichotomous data. Since pulmonary dead space fraction, duration of mechanical ventilation, and hospital length of stay were not normally distributed, nonparametric methods were used. The Mann–Whitney test was used to compare dead space fraction by mechanical ventilation group. Spearman rank correlation was used to test the association of pulmonary dead space with each outcome. Kruskal–Wallis was used to test for differences among tertiles of dead space fraction.

Logistic regression was used to identify variables that were independently associated with prolonged mechanical ventilation. Prolonged mechanical ventilation was defined as ≥48 hr. The model was adjusted for clinical predictors known to be associated with duration of mechanical ventilation. The area under the receiver operating characteristic (ROC) curve and likelihood ratio testing were used to evaluate whether the sequential addition of pulmonary dead space increased predictive value for prolonged mechanical ventilation. Model fit was assessed with the Hosmer–Lemeshow test.[25] A two-sided P-value <0.05 was considered statistically significant.

Given the potential impact of anatomic mixing on dead space fraction measurement, we performed subgroup analysis of those with and without residual shunt physiology. Subgroups were compared by Mann–Whitney analysis and Spearman rank correlation coefficients were assessed for each outcome in the subgroups. Shunt lesion status was included in the

multivariable model to assess independent predictive value of pulmonary dead space fraction for prolonged mechanical ventilation.

Results

We enrolled 52 patients who underwent surgical repair of congenital heart disease. A diverse group of patients with congenital heart disease was studied (Table 1). Of the 52 enrolled patients, four patients were excluded from analysis because they were maintained on mechanical ventilation for a second surgical procedure other than chest wall closure. Two patients required diaphragmatic plication for phrenic nerve palsy. One patient required thoracic duct ligation secondary to chylothorax, and one patient required laryngeal web resection. Baseline characteristics are summarized in Table 2 for the 48 patients included in the analysis. The average time after ICU admission of pulmonary dead space fraction measurement was 4 hr and 37 min. The median dead space fraction was 0.46 (IQR 0.34–0.55). The median time of mechanical ventilation was 28 hr (IQR 11–95 hr), and the median length of hospital stay was 9 days (IQR 6–17 days). No children died postoperatively prior to hospital discharge.

Pulmonary dead space fraction was significantly higher in patients requiring mechanical ventilation for 48 hr or longer (0.36 vs. 0.51, P=0.0004; Fig. 1). Higher pulmonary dead space fraction significantly correlated with longer duration of mechanical ventilation (r_s=0.51, P=0.0002). Patients were divided into tertiles by pulmonary dead space fraction (Fig. 2). There was a significant trend towards increased median duration of mechanical ventilation across the tertiles, with patients in the highest tertile having the longest duration of mechanical ventilation (P=0.006).

To assess the potential clinical utility of pulmonary dead space fraction, we did *a post hoc* assessment of a cut off value of pulmonary dead space fraction ≥0.50. Using this cut off as a predictor of the requirement of mechanical ventilation for 48 hr or beyond, the sensitivity was 70%, the specificity was 84%, the positive predictive value was 80%, and the negative predictive value was 75%. Thus, the likelihood ratio of a dead space fraction of 0.50 or greater increases the prior odds of prolonged mechanical ventilation of a postoperative congenital heart disease patient by 4.3 times.

Prolonged mechanical ventilation also correlated with longer cardiopulmonary bypass time and lower PaO_2/FiO_2 (r_s=0.54, P=0.0002; r_s=−0.38, P=0.007, respectively). Higher pulmonary dead space fraction was significantly associated with longer length of hospital stay (r_s=0.51, P=0.0002).

In order to test pulmonary dead space fraction as an independent predictor of prolonged mechanical ventilation, we used multivariable logistic regression analysis with known physiologic variables previously shown to be associated with prolonged mechanical ventilation. Pulmonary dead space fraction remained an independent predictor of prolonged mechanical ventilation in a model adjusting for cardiopulmonary bypass time, PaO_2/FiO_2, and presence of a residual shunt lesion (Table 3). Shunt lesion status was not an independent predictor of prolonged mechanical ventilation (P=0.34), and it was removed from the model. For every 0.10 increase in dead space fraction, the odds of mechanical ventilation ≥48 hr increased by 220% (OR 2.2; 95% CI 1.1–4.4; P=0.02). In the subset of patients without residual shunt physiology, pulmonary dead space fraction was still an independent predictor of prolonged mechanical ventilation (OR 2.3; 95% CI 1.0–5.2; P=0.05).

To examine the utility of pulmonary dead space fraction as an independent predictor of prolonged mechanical ventilation, we tested our multivariable logistic regression model with and without pulmonary dead space fraction. The area under the ROC curve increased to 0.91 from 0.85 when dead space fraction was included in the model. Likelihood ratio testing

demonstrated this contribution of pulmonary dead space fraction to the logistic model was significant (P=0.008). The Hosmer–Lemeshow test indicated that the fit of the model was good (P=0.64) (Fig. 3).

Anatomical mixing may have an impact on pulmonary dead space fraction, and 13 of our 14 patients with residual shunt lesions were right to left or bidirectional (Table 1). Thus, we analyzed subgroups of patients with and without residual shunt physiology (Fig. 4). As expected in patients with residual shunt physiology, PaO_2/FiO_2 was lower and pulmonary dead space fraction was elevated (Table 4). There was a trend for prolonged mechanical ventilation and longer duration of hospital stay in patients with residual shunts compared to patients without shunts, but these were not significantly different, likely due to the small number of patients (n=14). There was no significant difference in cardiopulmonary bypass time. A similar spread of duration of mechanical ventilation and dead space fraction was seen in both subgroups. In patients without residual shunt physiology, higher pulmonary dead space fraction significantly correlated with longer duration of mechanical ventilation (r_s=0.45, P=0.008). Similarly, higher pulmonary dead space fraction also correlated with prolonged length of hospital stay (r_s=0.49, P=0.004).

Discussion

We prospectively evaluated the prognostic value of pulmonary dead space fraction, a single, non-invasive physiologic parameter, in patients after congenital heart surgery. Pulmonary dead space fraction is a simple, easy-to-obtain measurement involving a sensor attached in-line to the mechanical ventilator that measures flow, pressure, and CO_2 elimination. We found that patients with a higher pulmonary dead space fraction have a longer duration of mechanical ventilation. Specifically, higher pulmonary dead space fraction independently doubled the odds of prolonged mechanical ventilation (OR 2.2; 95% CI 1.1–4.4; P=0.02). Furthermore, higher pulmonary dead space fraction is associated with longer length of hospital stay.

There are several independent mechanisms that may contribute to elevated pulmonary dead space fraction in congenital heart disease patients. Microvascular thrombosis during cardiac surgery is one mechanism suggested by a recent study that may contribute to elevated pulmonary dead space fraction.[26] Increased microvascular thrombosis may be due to inflammation associated with cardiopulmonary bypass from surface and blood component interactions, non-pulsatile blood flow, regional perfusion disturbances, and ischemia-reperfusion insults.[7,8] In other inflammatory conditions, such as acute lung injury, disordered coagulation and fibrinolysis have been associated with worse clinical outcomes.[27–30] In our study, higher pulmonary dead space fraction was weakly correlated with longer cardiopulmonary bypass time (r_s=0.28, P=0.05), and this correlation was strengthened in the subgroup of patients without residual shunting (r_s=0.40, P=0.02).

Another possible mechanism for elevated pulmonary dead space fraction may be poor pulmonary perfusion from low cardiac output or hypotension. Indeed, most deaths after congenital heart surgery are due to low cardiac output.[31] There were no deaths in our cohort, however. Also, although we used a NICO monitor to determine dead space fraction, cardiac output measurements from this device have not been rigorously calibrated in children. Adult studies have demonstrated a poor estimation of cardiac output from NICO monitors.[32,33] The lack of a direct determinant for the contribution of low cardiac output to elevated dead space fraction is a limitation in many critically ill populations. However, dead space fraction could still be of value in correlating with prolonged mechanical ventilation. Dead space fraction measurement may provide a joint assessment of pulmonary and cardiac physiology to predict prolonged mechanical ventilation. Thus, we believe that the measurement of dead space

fraction may still be useful even though the mechanism of elevation cannot be completely resolved.

Patients with residual shunt physiology may have an elevated dead space fraction as the shunt lesion may prevent some blood from reaching the lung to eliminate CO_2. In patients with intracardiac shunts, pulmonary dead space fraction is indeed significantly elevated (P=0.03). However, there was no significant difference between the subgroups in cardiopulmonary bypass time. Furthermore, there was no significant difference in outcomes of mechanical ventilation duration or length of hospital stay although there was a trend. In fact, elevated pulmonary dead space fraction remained significantly correlated with prolonged mechanical ventilation (r_s=0.45, P=0.008) and longer length of hospital stay (r_s=0.49, P=0.004) when patients with residual shunt physiology were excluded.

A limitation of our study population was the small number of patients with residual shunt physiology. There was no significant correlation of pulmonary dead space fraction with duration of mechanical ventilation or length of hospital stay in these patients. However, we constructed a multivariable logistic regression model of known physiologic variables independently associated with prolonged mechanical ventilation, namely cardiopulmonary bypass time, PaO_2/FiO_2, and presence of an intracardiac shunt. In this model, pulmonary dead space fraction remained an independent predictor of prolonged mechanical ventilation after adjustment for these known clinical predictors. Furthermore, in a parallel model excluding patients with residual shunting, higher pulmonary dead space fraction continues to double the odds of prolonged mechanical ventilation (OR 2.3; 95% CI 1.0–5.2; P=0.05). Also, a similar spread of duration of mechanical ventilation and dead space fraction can be observed in both subgroups (Fig. 4). There were insufficient numbers of patients with residual shunt physiology present to evaluate fully the prognostic value of pulmonary dead space fraction in relation to prolonged mechanical ventilation. Further studies should be done to evaluate pulmonary dead space fraction in this subset of the population.

Another limitation in our study was the lack of direct determinants of cardiac output in contribution to prolonged mechanical ventilation. However, given the difficulty in placing pulmonary artery catheters in children, clinicians do not routinely measure pulmonary artery pressure and cardiac output in critically ill children with congenital heart disease despite the fact that pulmonary hypertension and low cardiac output are known causes of failed extubation.[6,14] Failed extubation in these cases may manifest as an inefficiency in CO_2 excretion, or such as a disrupted state of both pulmonary and cardiac physiology. We believe that pulmonary dead space fraction may be useful as a marker of CO_2 excretion jointly assessing pulmonary and cardiac physiology. As a joint marker, pulmonary dead space fraction could still be of value in correlating with prolonged mechanical ventilation.

Indeed, we were able to construct a model with excellent predictive value using pulmonary dead space fraction as a predictor of duration of mechanical ventilation. Our multivariable model of physiologic variables to predict prolonged mechanical ventilation agrees with the observations of previous investigators identifying independent predictors of prolonged mechanical ventilation and hospital stay.[13,34] In fact, we demonstrated a significant addition of pulmonary dead space fraction (P=0.008) to this model with an impressive area under the ROC curve of 0.91. Furthermore, a pulmonary dead space fraction of ≥0.50 has positive predictive value of 80% to require mechanical ventilation for beyond 48 hr. Thus, we have prospectively shown that pulmonary dead space fraction is an independent, non-invasive, and easily measured physiologic parameter associated with prolonged mechanical ventilation. The results of our study suggest that this physiologic pulmonary measurement may have added clinical utility as a valuable prognostic indicator in children undergoing cardiac surgery.

Conclusions

Elevated pulmonary dead space fraction is associated with prolonged mechanical ventilation and hospital stay in children who undergo surgery for congenital heart disease and is a useful clinical variable. This is the first study to evaluate a single, non-invasive, pulmonary parameter to predict duration of mechanical ventilation following congenital heart surgery in children. A dead space fraction at a threshold of 0.50 or greater has a positive predictive value of 80% for the requirement of mechanical ventilation beyond 48 hr. Also, the combination of pulmonary dead space fraction, cardiopulmonary bypass time, and the PaO_2 to FiO_2 ratio has additive, predictive value in identifying children at risk for longer duration of mechanical ventilation following cardiac surgery. This marker may play a role in a combined clinical index of pulmonary and cardiac physiologic predictors of prolonged mechanical ventilation, but needs validation in a larger cohort. Higher pulmonary dead space fraction may be a useful prognostic tool for clinicians in patients who undergo congenital heart surgery.

Acknowledgments

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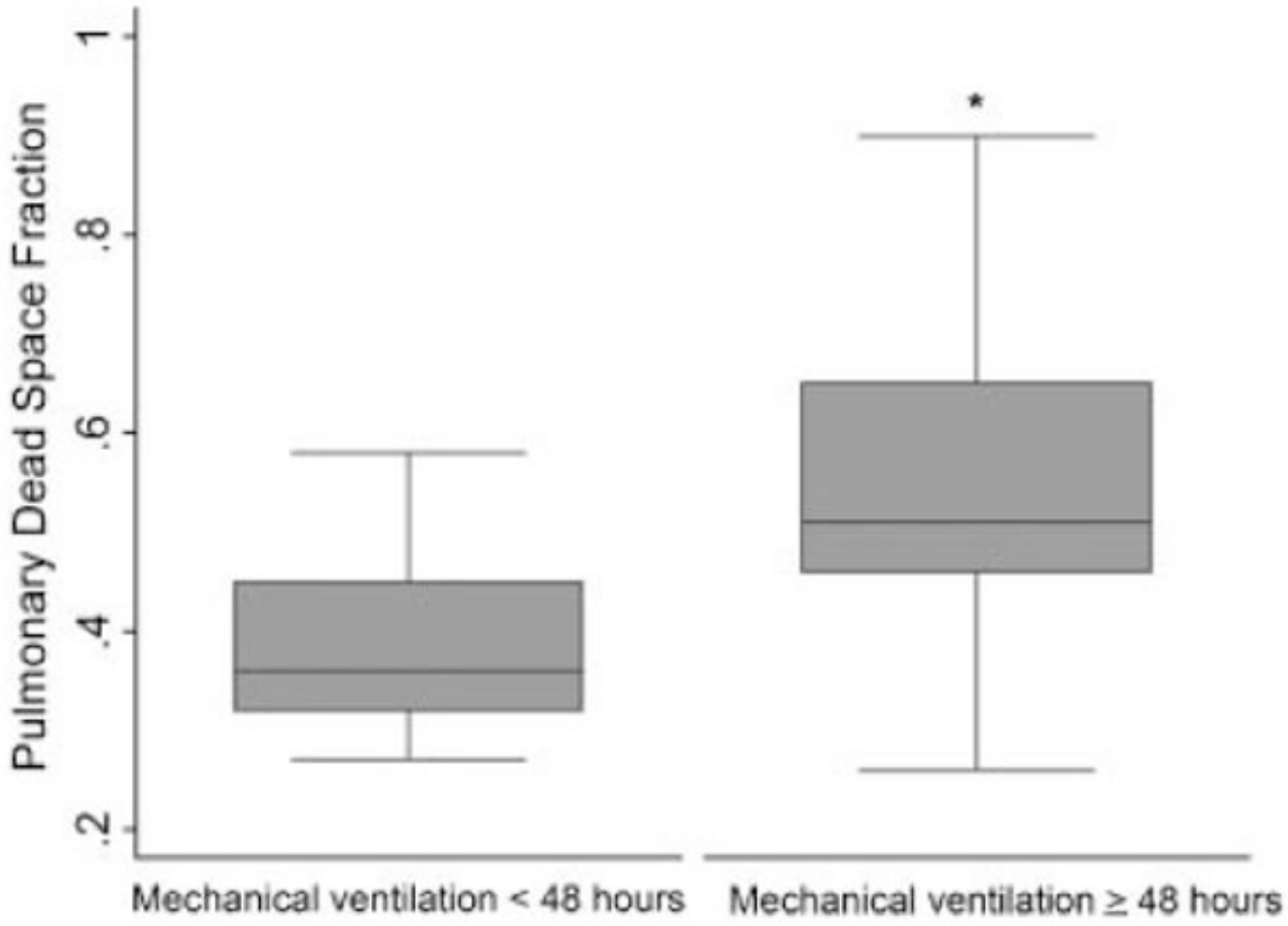

Fig. 1.

Pulmonary dead space fraction is elevated in patients requiring mechanical ventilation for 48 hr or longer. Median pulmonary dead space fraction was compared using Mann–Whitney. (<48 hr, n=25; ≥48 hr, n=23; **P*=0.0004).

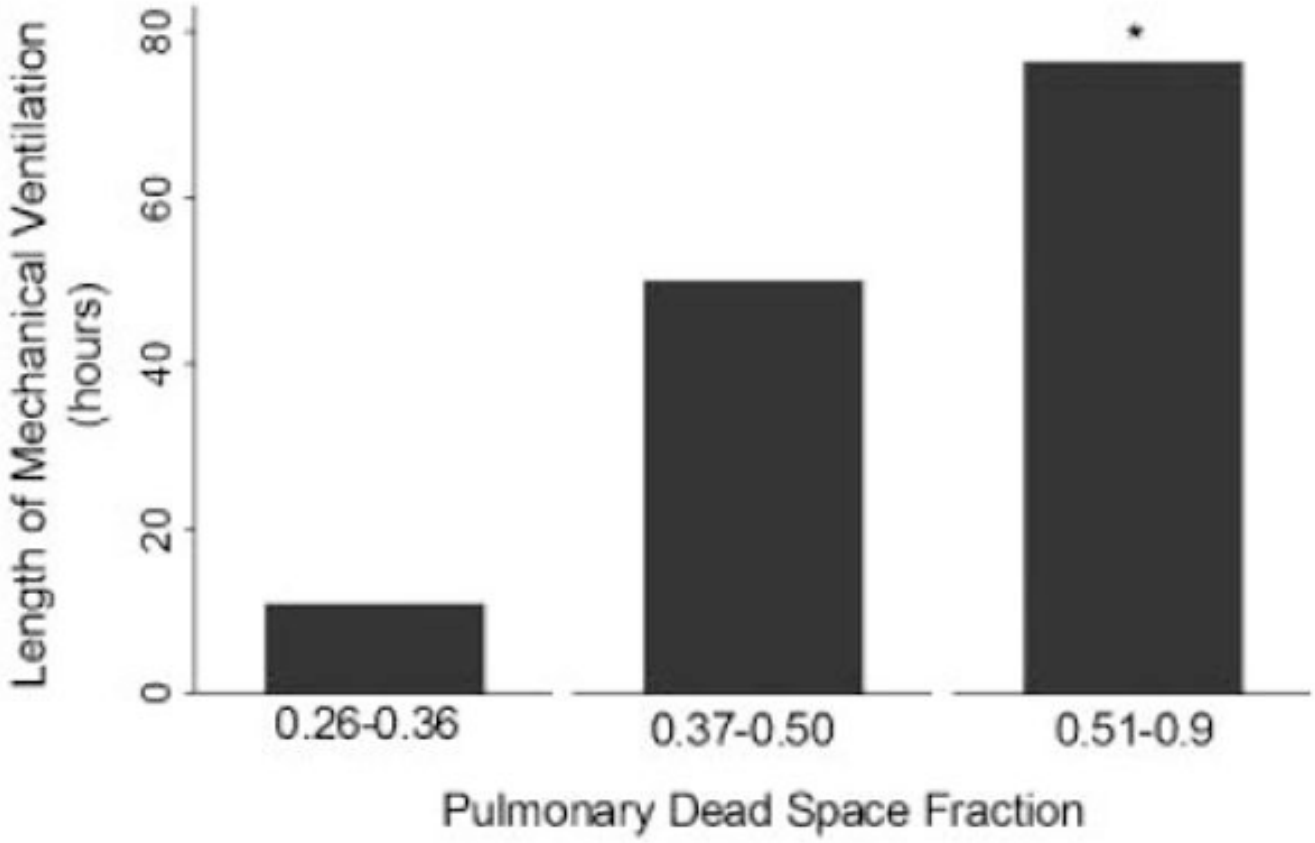

Fig. 2.

Median duration of mechanical ventilation by tertile of dead space fraction. Patients were divided into tertiles by pulmonary dead space fraction. Median duration of mechanical ventilation across tertiles was compared using Kruskal–Wallis. (**P*=0.006).

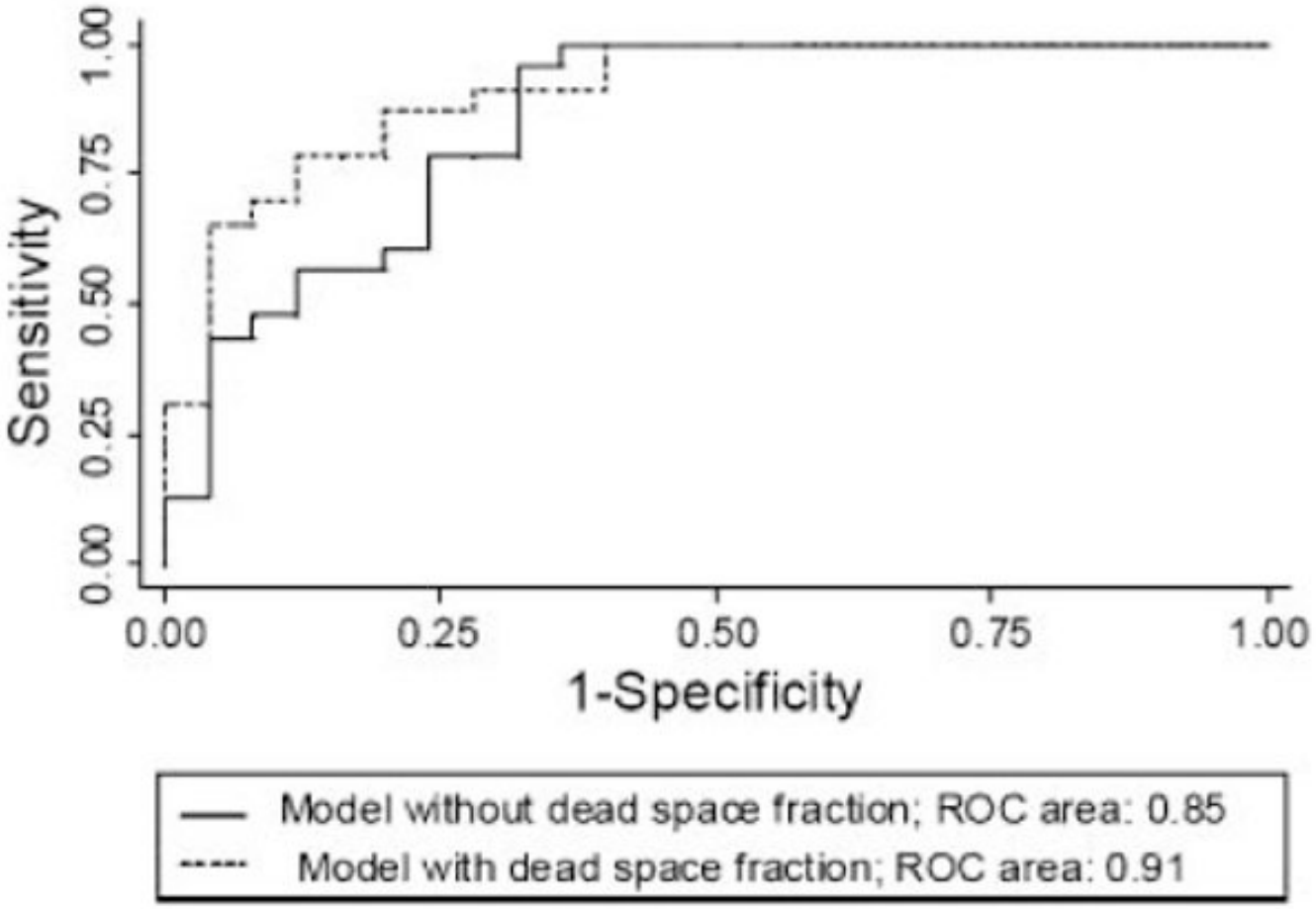

Fig. 3.

Receiver operating characteristic (ROC) curves for predictors of prolonged mechanical ventilation. Solid line model includes ratio of PaO_2 to FiO_2 and cardiopulmonary bypass time (Area under the ROC curve 0.85). Dotted line model includes solid line model plus pulmonary dead space fraction (Area under the ROC curve 0.91). Models were compared with and without pulmonary dead space fraction using likelihood ratio testing (*P*=0.008).

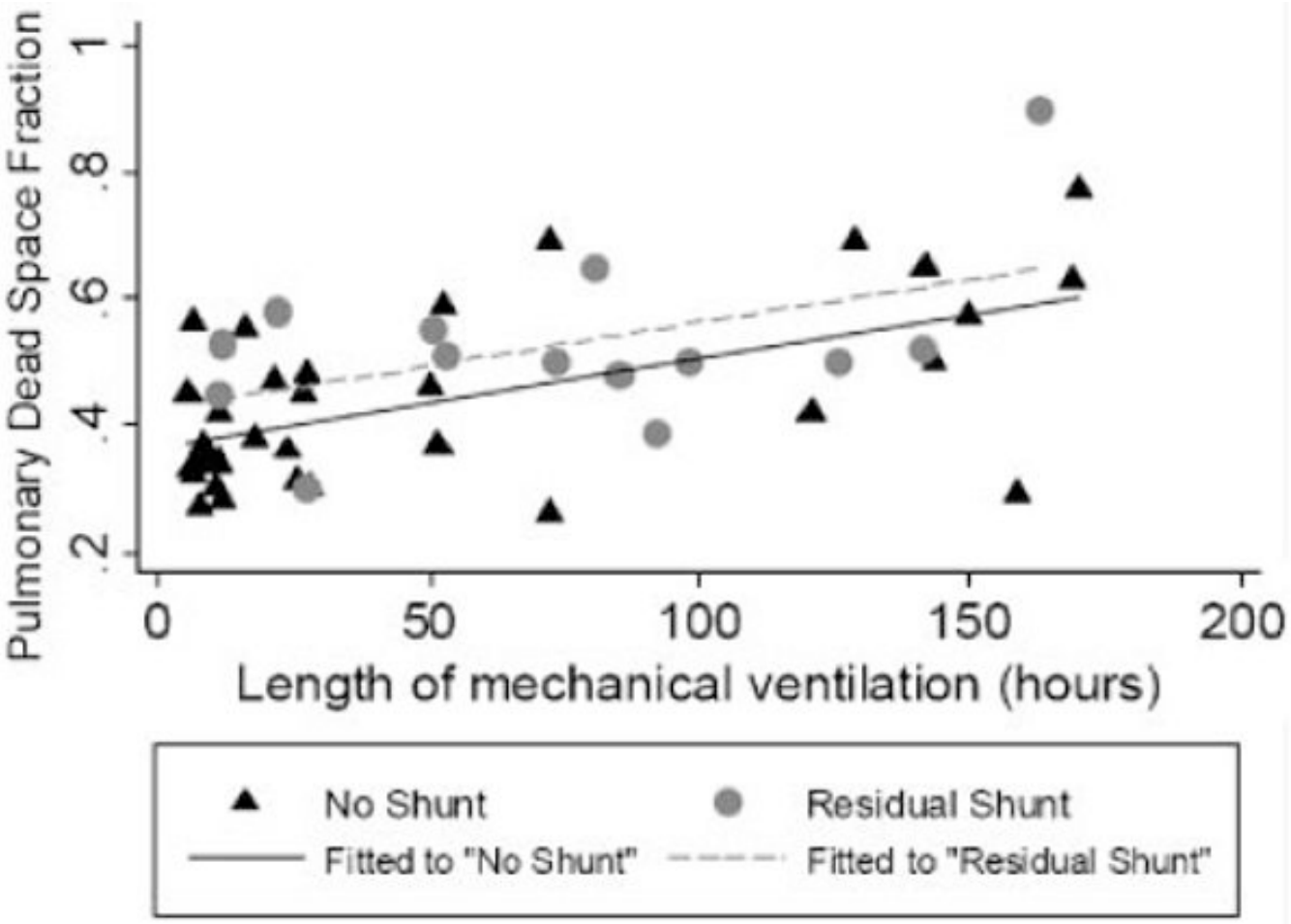

Fig. 4.

Duration of mechanical ventilation by pulmonary dead space fraction in patients with and without residual shunt lesions. A similar slope of fitted lines is seen between patients with and without shunt lesions.

Table 1
Cardiac Lesions in 52 Patients Who Underwent Surgical Repair

Cardiac lesion	Number of patients (%)
Transposition of the great arteries	9 (17)
Single ventricle physiology (right ventricle to pulmonary artery shunt)	6 (11)
Septal defect	6 (11)
Valve insufficiency	6 (11)
Coarctation of the aorta	5 (10)
Single ventricle physiology (Glenn)	5 (10)
Single ventricle physiology (Fontan)	5 (10)
Interrupted aortic arch	4 (8)
Tetralogy of Fallot	2 (4)
Partial anomalous pulmonary venous return	1 (2)
Atrioventricular canal	1 (2)
Total anomalous pulmonary venous return	1 (2)
Truncus arteriosus	1 (2)

Table 2
Clinical Characteristics of 48 Patients With Congenital Heart Disease Repair

Characteristic	Median (IQR) or n (%)
Age (days)	167 (19–1,832)
Male (%)	30 (63%)
Caucasian (%)	25 (52%)
Residual shunt physiology (%)	14 (29%)
Tidal volume (mL/kg)	10 (9–14)
Mean airway pressure (mm H_2O)	8 (7.7–10)
Systolic blood pressure (mm Hg)	87 (72–107)
Intubation duration (hr)	28 (11–95)
Hospital stay (days)	9 (6–17)
Bypass time (min)	70 (45–130)

For dichotomous variables, n=number of patients, %=percentage of the total cohort. Medians reported for continuous variables. IQR=25–75% interquartile range.

Table 3

Odds Ratios for Clinical Variables Independently Associated With an Increased Risk of Mechanical Ventilation ≥48 hr

Risk factor	OR	95% CI	*P*-value
Dead space fraction[1]	2.23	1.13–4.38	0.02
PaO_2/FiO_2[2]	1.85	1.06–3.26	0.03
Duration of CPB[3]	2.50	1.28–4.86	0.007

OR, odds ratio; CI, confidence interval; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; CPB, cardiopulmonary bypass time.

[1] per 0.10 increase.

[2] per 100 decrease.

[3] per 30 min increase.

Table 4

Clinical Characteristics for Patients With and Without Residual Intracardiac Shunt Physiology

Characteristic	Residual shunt physiology (N=14)	No shunt physiology (N=34)	*P*-value
PaO_2/FiO_2	82 (54–118)	381 (328–416)	<0.0001
Tidal volume (cm^3/kg)	10 (9–17)	10 (9–13)	0.74
Pulmonary dead space fraction	0.50 (0.48–0.55)	0.40 (0.33–0.55)	0.03
Intubation duration (hr)	77 (27–97)	25 (10–72)	0.07
Hospital stay (days)	13 (7–21)	8 (5–14)	0.09
Bypass time (min)	76 (40–146)	69 (54–127)	0.67

N, number of patients. Medians reported with 25–75% interquartile range in parentheses. PaO_2/FiO_2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.