Association of dead space ventilation and prolonged ventilation after repair of tetralogy of Fallot with pulmonary atresia

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ABSTRACT

Background: We set out to determine whether patients with tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries (TOF/PA/MAPCA) are at risk for elevated dead space ventilation fraction (VD/VT), and whether this is associated with prolonged mechanical ventilation. We hypothesized that elevated VD/VT (>20%) in the first 24 hours after unifocalization surgery is associated with increased risk for prolonged mechanical ventilation (>7 days).

Methods: All patients with TOF/PA/MAPCA undergoing unifocalization surgery between January 2003 and December 2015 were included in this study. Average VD/VT was calculated over the first 24 hours after surgery. Demographic and surgical data were collected. Outcome data included duration of mechanical ventilation. Patients were separated into 2 groups: elevated VD/VT and normal DVSF. Groups were compared using the Student *t* test, Wilcoxon rank-sum test, and χ^2 test. Univariable and multivariable regression analyses were performed with VD/VT as a continuous variable to test for association.

Results: Of the 265 included patients, 127 (48%) had an elevated VD/VT. The 2 groups did not differ significantly in any demographic characteristic. Patients with an elevated VD/VT had longer cardiopulmonary bypass times ($P = .03$), were more likely to have delayed sternal closure, and more likely to have prolonged respiratory failure (odds ratio, 2.2; 95% confidence interval, 1.2-4.0; $P = .007$). The percent VD/VT was associated with duration of mechanical ventilation in univariable ($P < .001$) and multivariable ($P < .001$) regression analyses when controlled for age, weight and bypass time.

Conclusions: Elevated postoperative VD/VT is associated with prolonged mechanical ventilation in patients with TOF/PA/MAPCA following unifocalization. Elevated postoperative VD/VT may be an early indicator of patients who will require prolonged duration of mechanical ventilation, allowing optimization of medical management to promote better outcomes. (J Thorac Cardiovasc Surg 2018;156:1181-7)

Duration of mechanical ventilation versus 24-hour average VD/VT.

Central Message

Increased dead-space ventilation fraction is associated with prolonged ventilation in patients with TOF/PA/MAPCA after unifocalization and, if identified, may allow caregivers to optimize care and improve outcomes.

Perspective

Children with TOF/PA/MAPCA are at risk for increased dead-space ventilation fraction (VD/VT) following unifocalization, which is associated with prolonged mechanical ventilation. Elevated VD/VT has been associated with poor outcomes in patients with congenital heart disease but has not been described in these patients. Our findings can help predict the postoperative course and allow for treatment optimization.

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The care of patients with tetralogy of Fallot with pulmonary atresia and major aortopulmonary collaterals (TOF/PA/MAPCA) presents both surgical and medical

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Abbreviations and Acronyms

CI	= confidence interval
CPB	= cardiopulmonary bypass
ICU	= intensive care unit
OR	= odds ratio
PaCO ₂	= arterial partial pressure of carbon dioxide
ROC	= receiver operating characteristic
RV	= right ventricle
TOF/PA/MAPCA	= tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries
VD/VT	= dead space ventilation fraction
VSD	= ventricular septal defect

challenges. The surgical procedures (unifocalization/pulmonary artery reconstruction) performed in these patients are often complex, leading to a complicated postoperative course in the cardiovascular intensive care unit (ICU). After surgery, patients may require prolonged mechanical ventilation, impacting the ICU and hospital lengths of stay.¹

Both delayed sternal closure and postoperative respiratory infections have been associated with prolonged mechanical ventilation in this population.¹ Prolonged mechanical ventilation has been associated with poor outcomes in many populations.²⁻¹¹ Numerous postoperative factors have been associated with poor outcomes after congenital cardiac surgery, including renal injury,¹² level of vasopressor support,¹³ and blood transfusions,¹⁴ but few studies¹⁵ have looked at respiratory parameters, such as dead space ventilation fraction (VD/VT). This is the first study to describe the association of VD/VT with postoperative respiratory outcomes in children undergoing unifocalization surgery.

An elevated VD/VT has been described in normal children¹⁶⁻¹⁸ and children undergoing cardiac surgery¹⁹ and has been established as a risk factor for prolonged respiratory failure and increased hospital length of stay after stage 1 single-ventricle palliative surgery.²⁰ The same association was observed in a prospective study of VD/VT in patients with various forms of congenital heart disease undergoing cardiac surgery, with the exception of patients with residual shunt physiology.²¹

The management of patients with TOF/PA/MAPCA includes establishing pulmonary blood flow to all lung segments to achieve the lowest possible right ventricular pressure to optimize the risk of ventricular septal defect (VSD) closure. If it is deemed that the pulmonary vascular bed requires growth and/or the pulmonary arterial pressure

would be too high, a shunt is placed into the unifocalized pulmonary vascular bed.²² Thus, patients undergo either unifocalization with complete intracardiac repair (VSD closure) or unifocalization to a central shunt. No patients underwent unifocalization with placement of a right ventricle (RV) to pulmonary artery conduit without VSD closure. Although this is the end goal, at times there still may be differential perfusion, which could lead to elevated VD/VT. During unifocalization surgery, there is extensive intraparenchymal dissection with resultant airway edema, bronchospasm, and air-trapping, along with arterial vasoconstriction and areas of impaired perfusion. These factors contribute to elevated VD/VT, but the degree and importance of elevated VD/VT in patients with TOF/PA/MAPCA undergoing unifocalization is unknown.

Given the mechanism of injury and high potential for elevated VD/VT in the postoperative period after unifocalization, we hypothesized that elevated VD/VT (defined as >20%) in the first 24 postoperative hours would be associated with prolonged respiratory failure (>7 days) in patients with TOF/PA/MAPCA. If this physiological perturbation is detected and shown to be a risk factor, early interventions, such as bronchodilator or mucolytic therapy, anti-inflammatory agents, inhaled nitric oxide, and modification of ventilation strategies, could be used to improve ventilation-perfusion matching and potentially decrease the duration of mechanical ventilation and ICU length of stay. Our primary aim was to establish the incidence of elevated VD/VT in this patient population and to determine its association with prolonged postoperative respiratory failure.

METHODS**Patients**

All patients age <18 years with TOF/PA/MAPCA old undergoing unifocalization surgery between January 2003 and December 2015 at Lucile Packard Children's Hospital Stanford were included in the inception cohort for this retrospective cohort study. The cohort was established by interrogating a PA/MAPCA REDCap database that is maintained by the Clinical and Translational Research Program of the Heart Center at Lucile Packard Children's Hospital Stanford. Patients were excluded if they underwent only an aortopulmonary window (without dissection of collateral arteries), never underwent unifocalization at Stanford, had preoperative pulmonary hypertension, had undergone tracheostomy preoperatively, were placed on extracorporeal membrane oxygenation in the first 24 postoperative hours, remained intubated for an additional procedure, or had fewer than 3 recorded paired end-tidal CO₂ and arterial partial pressure of CO₂ (PaCO₂) measurements after returning to the cardiovascular ICU after unifocalization. This study was approved by Stanford University's Institutional Review Board.

Data Collection

Demographic data, including age, sex, weight, and length, were recorded. Clinical data collected including cardiopulmonary bypass (CPB) time, aortic cross-clamp time, time to initial extubation after surgery, status of chest (open or closed in the operating room), length of time that the chest remained open, ICU and hospital lengths of stay, number of vessels

unifocalized, RV:left ventricle pressure ratio in the operating room (for those who underwent VSD closure), and paired end-tidal CO₂ and PaCO₂ from an arterial blood gas analysis. To be included as data points in the study, the end-tidal CO₂ and PaCO₂ needed to be obtained within 1 hour of each other. The end-tidal CO₂ and PaCO₂ values were then used to calculate VD/VT using the Enghoff modification of the Bohr equation:

$$\frac{VD}{VT} = \frac{PaCO_2 - PeCO_2}{PaCO_2}$$

where PeCO₂ is the partial pressure of carbon dioxide in the expired (exhaled) air.

Elevated VD/VT was defined ad hoc as >20%. To date, few studies have examined VD/VT in normal subjects, although some studies have suggested that a normal VD/VT is closer to 35%.¹⁹ In truth, the normal value may be widely variable. We chose 20% as a cutoff before data collection for a study of this specific cohort, and this was correlated with the approximate median of the sample.

Data Analysis

Average VD/VT was calculated over the first 24 postoperative hours. The cohort was separated into 2 groups: those with elevated VD/VT (>20%) and those with normal VD/VT. The cutoff value for elevated VD/VT was chosen ad hoc as a clinically relevant level that was near the median for the cohort. Prolonged mechanical ventilation was defined as a duration of mechanical ventilator support for ≥7 days. This duration was chosen ad hoc as a clinically relevant period that also matched the upper quartile of mechanical ventilation use. We tested all collected data for normalcy. Groups were compared using the Student *t*, Wilcoxon rank-sum, and χ² tests, as appropriate. Variables were expressed as either mean with standard deviation or median with interquartile range. Odds ratios (ORs) are presented with 95% confidence intervals (CIs).

Univariable and multivariable regression analysis was performed with VD/VT as a discreet and continuous variable to test for association with outcome. Natural logarithmic transformation was used when the outcome was nonlinear. Variables were selected for entry into the multivariable model based on Pearson correlation (*P* < .10). We also performed subgroup analysis to separately study patients who underwent unifocalization of collateral vessels with placement of an aortopulmonary shunt and those who underwent complete intracardiac repair intracardiac repair with closure of the VSD and RV-to-pulmonary artery conduit placement. A scatterplot of VD/VT and duration of mechanical ventilation was created to identify whether any clinically significant predictors could be identified based on the degree of VD/VT. The scatterplot was also used to establish negative predictive values for prolonged mechanical ventilation. A receiver operator characteristic (ROC) curve was generated for prediction of prolonged mechanical ventilation. Cutpoint analysis was performed to find the level of VD/VT that would result in a sensitivity of at least 70% with a specificity of at least 50%.

All statistical tests were performed with SPSS version 23.0 (IBM, Armonk, NY). A *P* value <.05 was considered statistically significant.

RESULTS

A total of 265 patients met the criteria for study inclusion (Figure 1), including 128 patients with elevated VD/VT and 138 patients with normal VD/VT. The 2 groups were similar with respect to the variables listed in Table 1. All patients included in the study had sufficient data to calculate average VD/VT in the first 24 hours after surgery.

Patients with elevated VD/VT had longer CPB times and were more likely to undergo delayed sternal closure, although the average time with the sternum left open was

similar in the 2 groups (3.9 days for those with elevated VD/VT and 3.6 days with normal VD/VT). They were also more likely than those with normal VD/VT to have prolonged mechanical ventilation (OR, 2.2; 95% CI, 1.2-4; *P* = .007) (Table 2). Using VD/VT as a continuous variable and length of mechanical ventilation as a dichotomous variable (prolonged vs not), we found that for each percentile increase in VD/VT there was a 5% increase in the likelihood of having a prolonged duration of mechanical ventilation (*β* = 5.03; *P* = < .001). Figure 2 depicts the relationship of VD/VT and duration of mechanical ventilation, with bold lines at 7 days of mechanical ventilation and a VD/VT of 20%.

This association was maintained in multivariable regression analysis. When controlling for open chest, weight, unifocalized collaterals, and CPB, an increased VD/VT was significantly associated with prolonged duration of mechanical ventilation (*P* = .021). All of the variables in the multivariable model had complete data.

Our ROC curve (Figure 3) identified VD/VT as a good predictor for prolonged mechanical ventilation, with an area under the ROC curve of 0.712 (*P* < .001). A VD/VT value of 0.187 had optimal predictive properties with a sensitivity of 72% and a specificity of 50%. The negative predictive value of VD/VT of 0.187 was 85.7%, and the positive predictive value was 30%.

Most patients who were intubated for an extremely long duration (≥14 days) had a VD/VT of >20%. Using this analysis, the negative predictive value for prolonged mechanical ventilation of ≥7 days is 83.3%, and the likelihood that the duration will not exceed 14 days is 93.2%.

Fifty-seven patients in the cohort underwent unifocalization with an aortopulmonary shunt rather than complete intracardiac repair with an RV-to-pulmonary artery conduit placement. In a subgroup analysis of this group of patients, those with an elevated VD/VT had an OR of 4.8 for prolonged mechanical ventilation (95% CI, 1.3-16.9; *P* = .014) compared with patients with a normal VD/VT (Table 2). However, this association was no longer significant when controlling for weight and CPB time in multivariable logistic regression (*P* = .23).

A total of 209 patients underwent unifocalization, VSD closure, and RV-to-pulmonary artery conduit placement. Subgroup analysis in this group of patients showed that those with elevated VD/VT had an OR of 1.45 for prolonged mechanical ventilation (95% CI, 1.3-2.92; *P* = .029) compared with patients with normal VD/VT. However, this association was no longer significant when controlling for weight and CPB time in multivariable logistic regression (*P* = .06).

DISCUSSION

We found that patients with TOF/PA/MAPCA are at significant risk of elevated VD/VT in the first 24 hours after

FIGURE 1. CONSORT diagram flowchart for patients included in the study. *ET/CO₂*, End-tidal carbon dioxide; *PaCO₂*, arterial partial pressure of carbon dioxide; *ECMO*, extracorporeal membrane oxygenation.

unifocalization, and that elevated VD/VT is associated with prolonged duration of mechanical ventilation. VD/VT may allow for risk stratification in the postoperative period and targeted intervention to improve respiratory outcomes, as seen in a previous study targeting optimal

positive end-expiratory pressure in patients after cardiac surgery.²³

We performed a subset analysis in patients who underwent unifocalization but not complete repair and had pulmonary blood flow through an aortopulmonary shunt with

TABLE 1. Baseline characteristics for the overall cohort and in the elevated and normal VD/VT groups

Characteristic	Overall	Elevated VD/VT (n = 127)	Normal VD/VT (n = 138)	P value
Age, mo, median (IQR)	7.4 (4.7-16)	8.1 (3.4-43)	7 (5.3-10.8)	.65
Female sex, n/N (%)	142/265 (54)	64/127 (50)	78/138 (56.5)	.35
Weight, kg, median (IQR)	6.7 (5.3-10)	6.7 (4.9-13.1)	6.7 (5.5-8.7)	.88
Bypass time, min, mean ± SD	230 ± 118	247 ± 119	214 ± 116	.03
Previous surgery, n/N (%)	109/266 (41)	54/127 (43)	55/138 (40)	.79
RV pressure, % of LV, mean ± SD*	36 ± 8	36 ± 8	36 ± 8	.74
Unifocalized vessels, mean ± SD	3.2 ± 1.5	3.4 ± 1.6	3.0 ± 1.5	.053
Delayed sternal closure, n/N (%)	68/265 (26)	41/127 (32)	27/138 (20)	.018
Postoperative shunt physiology, n/N (%)	56/265 (21)	36/127 (28)	20/138 (14)	.001
VD/VT, %, median (IQR)	19.2 (13.8-26.3)	26.8 (23.6-32.5)	14 (10.6-16.8)	<.001

VD/VT, Dead space ventilation fraction; IQR, interquartile range; SD, standard deviation; RV, right ventricle; LV, left ventricle. *For those who underwent VSD closure.

TABLE 2. Univariable analysis for associations of clinical factors with prolonged mechanical ventilation

Variable	OR (95% CI) for prolonged mechanical ventilation	P value
Age	0.98 (0.97-1)	.02
Weight	0.88 (0.81-0.96)	.003
Female sex	0.83 (0.47-1.47)	.50
Bypass time	1.002 (1-1.01)	.04
Previous surgery	1.34 (0.74-2.41)	.30
RV:LV pressure ratio	1.32 (0.01-111.87)	.90
Delayed sternal closure	5.46 (2.95-10.13)	.0001
Unifocalized vessels	1.38 (1.15-1.66)	.001
Shunted physiology	2.93 (1.56-5.52)	.001
Elevated VD/VT (dichotomous)	2.22 (1.23-3.97)	.007
Elevated VD/VT (dichotomous) in patients with shunted physiology	4.8 (1.31-16.9)	.014

OR, Odds ratio; CI, confidence interval; RV, right ventricle; LV, left ventricle; VD/VT, dead space ventilation fraction.

persistent mixing and hypoxemia, hypothesizing that these might have different outcomes. Although an association between VD/VT and prolonged mechanical ventilation was present in univariable analysis, the association was no longer statistically significant after adjustment, possibly related to the small number of patients in this cohort. It should be noted that in the presence of a right-to-left shunt (all patients with unifocalization to an aortopulmonary

shunt), the Enghoff modification of the Bohr equation overestimates physiological dead space due to venous admixture.^{19,24-27} Given that the elevated VD/VT in shunted patients might not be due entirely to intrapulmonary dead space ventilation, a different mechanism for prolonged mechanical ventilation must be considered in this subset of our cohort. One possible mechanism is elevated pulmonary blood flow due to a Qp:Qs ratio >1, leading to hydrostatic pulmonary edema and difficulty in weaning from the ventilator. Those who underwent complete repair also showed a significant association of increasing VD/VT with prolonged mechanical ventilation that was no longer significant in the multivariable model. The trend was toward an association and did not reach significance due to diminished power owing to a smaller sample size.

In an effort to provide more a more objective cutoff point for prolonged mechanical ventilation using VD/VT, we constructed an ROC curve and optimized it for the highest possible sensitivity (while maintaining 50% specificity). The VD/VT cutoff that provided the highest sensitivity was very close to the cutoff of 20% that was established ad hoc. When using this data in the clinical setting, it is important to identify as many patients at risk for prolonged mechanical ventilation as possible. This led us to determine the cutoff that provided the highest sensitivity. It should be noted that identifying a patient who is at risk but does not ultimately require prolonged mechanical ventilation would not expose this patient to any further morbidity.

The mechanism of elevated VD/VT in these patients cannot be inferred from the findings of this retrospective

Dead Space Ventilation and the Duration of Mechanical Ventilation

FIGURE 2. Duration of mechanical ventilation versus 24-hour average dead space ventilation fraction (VD/VT). Shunted patients are denoted by a blue cross, and septated patient are denoted by a red X. Dark lines represent the a priori determined cutoffs for prolonged mechanical ventilation (7 days) and elevated VD/VT (20%).

FIGURE 3. Receiver operating characteristic (ROC) curve for dead space ventilation fraction (VD/VT) for the diagnosis of prolonged mechanical ventilation. The area under the ROC curve for VD/VT is 0.72 ($P < .001$).

study. However, one plausible explanation is that patients with longer CPB duration, and thus more extensive pulmonary artery reconstruction, were more likely to develop impaired gas exchange and elevated VD/VT because of extensive lung dissection.

Regardless of the etiology of elevated VD/VT, the clinical implications are apparent. With elevated VD/VT and PaCO₂, patients may develop compensatory tachypnea, which may contribute to the need for prolonged respiratory support and increased metabolic demands. Our findings are consistent with those of Ong and colleagues²¹ and Shakti and colleagues.²⁰ Ong and colleagues²¹ measured VD/VT in patients with various types of congenital heart disease in the postoperative period and found higher VD/VT and prolonged mechanical ventilation in those with residual shunt physiology. Shakti and colleagues²⁰ studied VD/VT after stage I palliation for single-ventricle heart disease and found poorer clinical outcomes in those with elevated VD/VT, such as prolonged respiratory failure, reintubation, and longer hospital stay.

Our finding that elevated VD/VT (>20%) had a negative predictive value of 83% for a duration of mechanical ventilation <7 days and 93% for <14 days may be helpful in immediate postoperative planning and family counseling.

Further prospective investigation is needed to confirm the association between dead space ventilation and outcomes, and also to allow for more robust control of potential biases and confounders. Interventional trials are also indicated to determine whether specific ventilation strategies and/or

VIDEO 1. Author A. Koth explains the complex care of patients with tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries after unifocalization, and describes how the findings of this study may aid in their postoperative care. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31227-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31227-3/fulltext).

medical interventions such as inhaled nitric oxide, which has been shown to decrease VD/VT,²⁸ or enhanced pulmonary toilet with bronchodilator or mucolytic therapy could decrease VD/VT and subsequently reduce the duration of mechanical ventilation.

Limitations

This study is limited by its retrospective design. In retrospective cohort study, there are also issues with missing data. Data in this study were complete with the exception of RV:left ventricle pressure ratio. This variable was used in the univariable analysis but did not meet the criteria for inclusion in the multivariable model and thus was not included. In addition, these findings reflect the experience of a single center that treats a large number of patients with TOF/PA/MAPCAs and as such might not be generalizable to centers with different management approaches. We also recognize the likelihood of overestimating VD/VT in patients with residual shunt physiology as described above. This overestimation may have influenced our results.

CONCLUSIONS

We studied a large, homogeneous cohort and found that elevated VD/VT occurred in approximately one-half of all patients with TOF/PA/MAPCA undergoing unifocalization,

and that those with elevated VD/VT experienced poor postoperative outcomes, including prolonged mechanical ventilation and longer ICU length of stay. The association of VD/VT with prolonged postoperative recovery provides a target for the management of these patients in the cardiovascular ICU that may be modified to improve outcomes (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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