Pulmonary function testing in infants with tetralogy of Fallot and absent pulmonary valve syndrome

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ABSTRACT

Aim : **Absent pulmonary valve syndrome (APVS) is found in 3-6% of patients with Tetralogy of Fallot (TOF). Along with findings of TOF, absence of pulmonary valve tissue results in aneurysmal dilatation of the main and branch pulmonary arteries compressing the trachea, main-stem, and intrapulmonary bronchi leading to obstructive airways disease. Our objective was to review pulmonary function tests (PFT) in TOF-APVS patients.**

Materials and Methods : **Eight PFT were performed on five mechanically ventilated TOF-APVS patients in the intensive care unit. Tidal volume, forced vital capacity (FVC), maximal expiratory flow 25%, resistance and compliance of the respiratory system were measured.**

Results : **Pre-operative PFTs showed markedly elevated airways resistance (R_{RS}) (median 0.45 cmH_2O/mL/sec, range 0.17-0.66) and marked variability of the static compliance of the respiratory system (C_{RS}) (median 0.6 mL/cmH_2O/kg, range 0.25-2.6). Flow-volume loops measured by forced deflation showed flow limitation within the medium to small airways. Post-operative FVC was reduced in four of the five patients (median 46 mL/kg, IQR 42.9 - 48.8 mL/kg). Patients studied with various levels of positive end expiratory pressure (PEEP) showed improvement in tidal volume and reduced obstruction with PEEP greater than 10 cmH_2O. For three patients with pre-operative data available, surgical correction resulted in near-normal post-operative C_{RS} and improved, but still elevated R_{RS} (median 0.14 cmH_2O/mL/sec, interquartile range [IQR] 0.11-0.31).**

Conclusion : **For our patients with TOF-APVS, airway resistance was elevated. Flow limitation was seen in the medium to small airways with a mild reduction of FVC. PFTs may help guide management of mechanical ventilation for TOF-APVS patients.**

Keywords : Congenital heart disease (CHD), compliance of the respiratory system, forced vital capacity (FVC), obstructive airway disease, pediatrics, resistance of the respiratory system, tidal volume

INTRODUCTION

Absent pulmonary valve syndrome (APVS) is a rare malformation that can occur in 3-6% of patients with Tetralogy of Fallot (TOF).[1] The condition is characterized by all the classic findings of TOF (pulmonary stenosis, overriding aorta, anterior malaligned ventricular septal defect [VSD], and right ventricular hypertrophy) along with rudimentary or absent pulmonary valve tissue. Absence of the pulmonary valve causes pulmonary regurgitation and aneurysmal dilatation of the main and branch pulmonary arteries (with right pulmonary artery more frequently dilated than left) that can compress the trachea and main stem bronchi.[2] Vascular compression may even occur among the intrapulmonary bronchi due to abnormal pulmonary artery branching during fetal life predisposing patients to develop varying degrees of more distal obstructive airway disease.[3,4] The extent of the obstructive airway disease contributes to the

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patient's morbidity and mortality before and after surgery.

TOF-APVS patients can be clinically differentiated into two groups; those who present with respiratory symptoms prior to surgery and those who do not. The groups are equally divided and likely represent the severity of the disease process for that individual patient. For TOF-APVS patients who present prior to surgery their respiratory symptoms tend to occur in the first 3 months of life.[5] In contrast, patients without respiratory symptoms follow a course similar to patients with classic TOF. Given the variability in the clinical degree of obstructive airway disease among children with TOF-APVS, objective quantification of the degree of airway obstruction before and after surgery may be helpful for their clinical management and prognosis. To date, there have been no published reports to quantify the degree of airway obstruction in patients with TOF-APVS. The purpose of this study is to present our experience with five patients with TOF-APVS and demonstrate the utility of performing pulmonary function tests (PFT) during the peri-operative period for these patients.

MATERIALS AND METHODS

This is a single-institution, retrospective study describing the clinical outcomes of five patients with TOF-APVS who had pulmonary function tests (PFT). We reviewed each patient's medical record to determine the hospital course including birth history, clinical presentation, surgical procedure, post-operative course, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, and outcome. PFTs were performed as part of routine clinical care while these patients were intubated and mechanically ventilated. The patients were receiving ongoing sedation titrated to need based upon nursing and physician assessments. PFTs were performed in a standardized manner using the SensorMedics® 2600 Infant PFT Cart (CareFusion, Yorba Linda, CA) and calibrated pneumotachometers (PNT). All five patients had PFTs measured post-operatively, and three had pre-operative values available for comparison.

Passive respiratory mechanics include measurement of tidal volume (V_T), flow-volume waveforms, compliance of the respiratory system (C_{RS}), and resistance of the respiratory system (R_{RS}). The C_{RS} and R_{RS} were measured using a single-breath occlusion technique. The patient is observed during mechanical ventilation and an inline shutter/valve is activated close to end inspiration. This temporarily occludes the airflow provoking the Hering Breuer Inflation Reflex. Passive expiratory flow is measured through a PNT with a 0 to 35 L/min flow range (4500B series, Hans Rudolph, Shawnee, KS) and is analyzed for relaxation airway pressure, airflow, and volume, which are used to calculate C_{RS} and $R_{RS.}$ The final C_{RS} and R_{RS} were calculated from the average of ten measured single breath occlusion events. Our measurement passive respiratory mechanics (C_{RS} and R_{RS}) follow the standards set by the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force.[6]

Raised volume-negative pressure forced deflations included measurement of forced vital capacity (FVC) and maximal expiratory flow 25% (MEF25). MEF25 is the forced flow when 25% of the forced vital capacity remains in the lungs. MEF25 (European convention) is therefore equivalent to Forced Expiratory Flow 75% (US convention). The ERS/ATS standard for raised volume forced expiration in infants primarily addresses techniques for non-intubated patients using rapid thoracic compression by means of a jacket surrounding the child with an inflatable bladder. Our measurements of FVC were performed in a different manner by means of a negative pressure forced deflation. This method has been previously described.[7] The patients were manually ventilated with a self-inflating or flow-inflating anesthesia bag connected to wall oxygen and a pressure manometer. The endotracheal tube and anesthesia bag are connected to the side ports of a three-way directional sliding valve (8540 series, Hans Rudolph, Shawnee, KS). The third port is connected to a PNT inline to a 100 Liter reservoir maintained at a constant pressure of –40 cmH_2O. During a measurement, the airway pressure is brought up to + 40 cmH_2O for 3 seconds and the sliding valve is activated. The endotracheal tube is now connected through the PNT to the –40 cmH_2O reservoir. The resulting exhalation is measured by a PNT with a 0 to 100 L/min flow range (4719 series, Hans Rudolph, Shawnee, KS). Exhalation was maintained until expiratory flow ceased or for 3 seconds at which time the slider valve returned to its original position and the manual ventilation resumed.

Results of PFTs obtained were compared to values for normal patients used by our pulmonary function testing laboratory. The normal values for FVC, MEF25, C_{RS}, and R_{RS} reflect those for normal patients obtained from published studies.[7-12]

RESULTS

Summary details of the patient demographics are in Table 1. All patients presented in the newborn period and cyanosis or respiratory failure was the indication for the echocardiogram that led to the diagnosis. Two patients were unable to leave the hospital prior to their surgical correction. Four patients required bronchoscopy for clinical purposes following surgery and showed some degree of bronchomalacia. Four of the five patients survived and were eventually discharged home or transferred to a community hospital after surgery. These four survivors needed total mechanical ventilation ranging from 8 to 68 days (post-operative duration of mechanical

Table 1: Patient characteristics

Patient #	1	2	3	4	5
Gender (F = female, M = male)	M	F	F	F	F
Estimated gestational age (weeks)	36	34	34	37	30
Cause for diagnostic echocardiogram	Cyanosis	Cyanosis	Cyanosis	Respiratory failure	Cyanosis
Discharged home prior to surgery	No	No	Yes	Yes	Yes
Reason for re-admission	n/a	n/a	Respiratory failure	Heart failure	Shock, Resp. Failure
Admission age (days)	1	1	82	85	19
Admission weight (kg)	2.6	2.2	4.2	4.2	2.6
Age at intubation (days)	1	1	85	88	18
Age at 1st surgery (days)	2	31	85	108	22
Number subsequent cardiac surgeries	1	0	0	0	0
Post-operative complications	Seizures, hydrocephalus, candidemia	Rhinovirus, pneumonia	None	Multiple pneumonias, failure to thrive	Pulmonary hypertension, congestive heart failure
Need for tracheostomy	No	No	No	No	Yes
Duration of pre-operative mechanical ventilation (days)	2	30	0	20	4
Duration of post-operative mechanical ventilation (days)	58	20	8	48	225
Post-operative bronchoscopy	Not done	Right upper lobe, bronchomalacia	Left mainstem compression, bronchomalacia	Mild left, severe right, bronchomalacia	Compression of the trachea above the carina
Duration of hospitalization (days)	70	104	22	139	229
Outcome	Lived	Lived	Lived	Lived	Died
Discharged home with oxygen	Yes	Yes	Yes	Yes	n/a
Age at follow-up	Lost	1 year	17 year	13 months	n/a
Supplemental oxygen at follow-up	n/a	No	No	No	n/a
Respiratory symptoms at follow-up	n/a	Yes	No	Yes	n/a

ventilation was 8 to 58 days) and their hospitalization duration ranged from 22 to 139 days. In addition to closure of the ventricular septal defects (VSD), surgical correction of all patients included use of a pulmonary homograft. For patient 1, the pulmonary homograft was placed during the second surgery with revision of a leaking VSD patch. Reduction pulmonary arterioplasty was performed in patients 2 and 3. Anterior translocation of the pulmonary arteries was performed in patients 2 and 4.

Details of their PFTs are in Table 2. Three patients had pre-operative PFTs and all had elevation of their airways resistance (R_{RS}). For two patients the PFTs results led to the use of increased positive end expiratory pressure (PEEP) for lung recruitment and to overcome intrinsic PEEP. Results of the PEEP titration curve are shown in Table 3. Figure 1 shows the results of a forced vital capacity maneuver for one patient with an idealized normal curve superimposed on it. Figure 2 shows a passive deflation flow-volume curves for patient 5. These curves were measured during the exhalation phase of a mechanical ventilator delivered tidal volume breath during a single breath occlusion measurement. Comparison of the flow-volume curves before and after surgical correction of TOF-APVS show increased airflow within the larger airways post-operatively but no changes in airflow within the small airways.

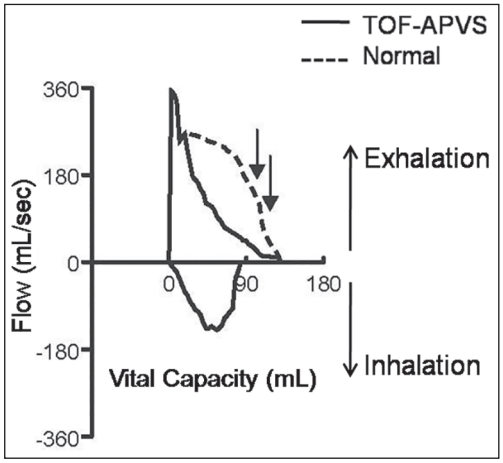

Figure 1: Forced deflation flow-volume curve from pulmonary function testing for Tetralogy of Fallot (TOF)-absent pulmonary valve syndrome (APVS) patients. The flow-volume curve above obtained during a forced deflation maneuver shows marked concavity of the expiratory limb reflecting flow limitation within the medium and small airways. The dotted line approximates a normal forced deflation flow-volume curve and the arrows indicate the markedly decreased flows in TOF-APVS patients at 25% and 10% of forced vital capacity (FVC) compared with normal subjects

DISCUSSION

Despite the fact that obstructive respiratory disease can pose a relevant and serious cause for prolonged ventilator dependence in infants with TOF-APVS, there exists little to no information on the range of lung function abnormalities connected to this malformation and their changes after surgical correction. The patients in our study appear to have a severe form of TOF-APVS. Consistent with other studies[3] all of our patients presented with respiratory symptoms within the first

Table 2: Pulmonary function testing (PFT) results

Patient #	1	2	3	4	5
Pre-operative PFT, days prior to surgery	n/a	11	n/a	13	3
Weight at PFT (kg)		2.2		4.3	2.6
Length at PFT (cm)		48		54	49
ETT size (mmID)		3.5		3.5	3.0
Pre-operative PFT: R_{RS} (normal ≤ 0.133 cmH_2O/mL/sec for 3.0 ETT) (normal ≤ 0.066 cmH_2O/mL/sec for 3.5 ETT)	n/a	0.17	n/a	0.45	0.66
Coefficient of variation % R_{RS} measurement		8.4		*	20.2
Pre-operative PFT: C_{RS} (normal = 0.8-1.2 mL/cmH_2O/kg)	n/a	2.6	n/a	0.25	0.6
Coefficient of variation % C_{RS} measurement		3.5		*	13
Maximal expiratory flow 25% (ml/kg/sec) (normal = 35-45 ml/kg/sec)	n/a	14.1	n/a	n/a	14.4
Pre-operative FVC per kg (mL/kg) (normal 42-60 mL/kg)	n/a	53	n/a	n/a	56.3
Post-operative PFT, days after surgery	48	25	7	20	14
Weight at PFT (kg)	2.7	5.3	4	4.1	2.6
Length at PFT (cm)	47	62	54	54	49
ETT size	3.5	3.5	3.0	3.5	3.5
Post-operative PFT: R_{RS} (normal ≤ 0.133 cmH_2O/mL/sec for 3.0 ETT) (normal ≤ 0.066 cmH_2O/mL/sec for 3.5 ETT)	0.31	0.11	0.14	0.11	0.55
Coefficient of variation % R_{RS} measurement	15.9	6.7	3.2	4.1	31.6
Post-operative PFT: C_{RS} (normal = 0.8-1.2 mL/cmH_2O/kg)	0.96	0.91	0.74	0.73	0.5
Coefficient of variation % C_{RS} measurement	7.3	5.3	2.6	4.5	10.2
Change in C_{RS} from pre-operative PFT (%)		35		292	83
Maximal expiratory flow 25% (ml/kg/sec) (normal = 28 ml/kg/sec)	8.6	7.4	1.8	19.0	9.6
Post-operative PFT: FVC/kg (mL/kg) (normal 42-60 mL/kg)	46	42.9	41.1	64.4	48.8

RRS: Resistance of the respiratory system, CRS: Compliance of the respiratory system, FVC: Forced vital capacity, PFT: Pulmonary function test, *data unavailable

Table 3: Tidal volume measurements with increasing positive end expiratory pressure (PEEP)

Patient	PEEP # 1	PEEP # 2	PEEP # 3
Patient # 2	6	10	16
Tidal volume (ml/kg)	14.8	14.3	16.4
Patient # 4	5	10	15
Tidal volume (ml/kg)	4.1	6.4	7.8

3-months of life. These patients typically need early surgical correction to address the classic abnormalities of TOF and to relieve the airway compression by revision of the dilated pulmonary arteries.[13,14]

We found that all our ventilated infants with TOF-APVS had evidence of severe obstructive airway disease with increased R_{RS}, reduced FVC, and reduced maximal expiratory flows. This represents the expected pathophysiologic changes caused by vascular airway compression of the large and small airways. R_{RS} reached values of comparable or even higher magnitude than we have previously measured in infants with respiratory failure due to severe RSV bronchiolitis (mean R_{RS} 0.37 [0.06] cmH_2O/mL/sec).[15]

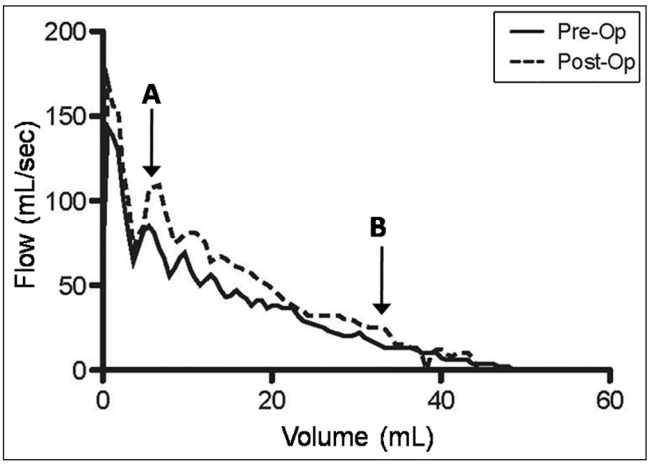

Figure 2: Passive deflation flow-volume curves for Patient # 5 As part of the pulmonary function tests, passive deflation flow-volume curves were measured during the exhalation phase of a single occlusive breath. There is marked expiratory flow limitation demonstrated on both curves. Comparison of the flow-volume curves before and after surgical correction of Tetralogy of Fallot (TOF)- absent pulmonary valve syndrome (APVS) show increased airflow within the larger airways (within the arrows A and B) post-operatively but no changes in airflow within the small airways (represented beyond arrow B)

The one patient who died in our cohort had the most severe degree of obstructive lung disease (Patient # 5, pre-operative R_{RS} 0.66 cmH_2O/mL/sec, post-operative R_{RS} 0.55 cmH_2O/mL/sec) and was mechanically ventilated the longest (for 229 days until the patient's death). In our experience, fixed airway obstructions with such high R_{RS} values are usually incompatible with life. It has to be emphasized that passive mechanics data includes the physical characteristics of the endotracheal tube affecting C_{RS} to a minor and R_{RS} to a much greater extent. Normal R_{RS} in intubated infants have been previously reported by von Ungern-Sternberg *et al.* [12] according to endotracheal tube (ETT) size and were 0.133 (SD 0.034cmH_2O/mL/sec for ETT size of 3.0 mm and 0.066 (standard deviation [SD] 0.017) cmH_2O/mL/sec for ETT of 3.5 mm. The equipment used in our measurements was identical to those of von Ungern-Sternberg *et al.*

We measured a decrease in R_{RS} after surgical correction which is however not reflected in the measurements of forced expiration. Forced deflation may fail to detect improvements in peripheral airway obstruction when bronchomalacia is present and airway collapse occurs during forced expiration. Surgical correction may relieve some of the airway obstruction caused by extrinsic compression but not improve the airway stability in patients with TOF-APVS. However, due to our small sample size, the clinical significance of this improvement in our patients with severe obstructive airway disease remains unclear.

For our patients with TOF-APVS, the information we obtained from PFTs were useful in the patient's post-operative ventilatory care. Adjustment of PEEP

during pulmonary function testing showed improvement in the tidal volume and R_{RS} with PEEP greater than 10 cmH_2O with clinical decrease in the work of breathing (WOB). This demonstrates the beneficial effect of PEEP stenting or stabilizing collapsible airways in patients with TOF-APVS. Interval measurements of PFTs were also helpful for the clinician especially during discussions with the family regarding the patient's clinical status and respiratory prognosis. As expected from pathophysiology, inhaled albuterol did not improve R_{RS} in the one patient where it was tested (data not shown). From our experience, we would recommend performing PFTs in TOF-APVS patients that require respiratory support both before and after surgery. One would hope to identify a reduction in R_{RS} with surgery approaching normal values. If there is no significant improvement that information would be valuable for prognosis. Should the patient have difficulty weaning from mechanical ventilation, we would suggest repeating PFTs during manipulation of PEEP.

The limitations of this study include the retrospective nature of the analysis involving a small cohort of severely ill patients with a rare variant of a cardiac disease. Due to the rarity of the absent pulmonary valve syndrome variant of TOF, it is difficult to make conclusions from the results of a small cohort of patients. Further, it is difficult to make conclusions for the less ill patients with TOF-APVS. To date, this is the only report quantifying the degree of obstructive lung disease using PFTs in TOF-APVS patients. Data from a larger cohort will be needed for a more robust analysis. Potentially, pulmonary function testing may play a role in adjusting the ventilator setting, and assessing the benefit of surgical correction and the evolution of airway obstruction during mechanical ventilation.

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