Cardiac and Cardiovascular Research 2024, 5(2), 2922.
https://doi.org/10.54517/ccr.v5i2.2922

Article

Abnormal spirometry is a predictor of exercise capacity in patients with tetralogy of Fallot

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CITATION

Pexton N, Bhatia R, Temkit H, Sabati A. Abnormal spirometry is a predictor of exercise capacity in patients with tetralogy of Fallot. Cardiac and Cardiovascular Research. 2024; 5(2): 2922. https://doi.org/10.54517/ccr.v5i2.2922

ARTICLE INFO

Received: 5 September 2024
Accepted: 26 September 2024
Available online: 29 September 2024

Abstract: We investigated the association between cardiac factors, spirometry, and exercise testing in patients with tetralogy of Fallot (TOF). Clinical data from patients with TOF performing a cardiopulmonary exercise test (CPET) was collected retrospectively over a 10-year period. 122 patients with TOF were identified, 52 excluded for incomplete exercise, spirometry, or cardiac data for 70 total patients included in the study. There was a male predominance 39 (56%), a mean age of 25 ± 12 years, with 28 (40%) < 18 years of age. The mean number of cardiac surgeries was 2.1 ± 1.2. Most, 46 (69%) had moderate to severe pulmonary valve insufficiency (PI) and 34 (51%) had moderate to severe right ventricular (RV) dilation. Mean forced vital capacity (FVC) was low at 81.8% predicted, and 32 (46%) with low FVC (< 80% predicted). Overall peak VO_2/kg was low with a mean of 58.2 ± 13.2 % predicted. Using multiple regression analysis, a higher number of cardiac surgeries was an independent predictor of lower FVC ($p = 0.01$). Lower FVC was itself an independent predictor of lower peak VO_2/kg and O_2 pulse ($p < 0.05$). Moderate or severe RV systolic dysfunction was an independent predictor of stroke volume response ($p = 0.03$). Higher body mass index (BMI) was an independent predictor of all exercise measures being worse ($p < 0.05$). Low FVC and reduced exercise capacity were common in our population of TOF patients. Low FVC was predictive of low exercise capacity while, of the cardiac measures only RV systolic dysfunction was significant and predictive of stroke volume response. Spirometry may be a valuable screening tool in evaluation of TOF patients.

Keywords: tetralogy of Fallot; congenital heart disease; spirometry; pulmonary function; exercise capacity; peak VO_2

1. Background

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease with a broad range of clinical presentations and repairs. After the initial surgical repairs, the focus of long-term follow-up is generally on the health of the right ventricle (RV), pulmonary valve (PV), and branch pulmonary arteries (PAs). The need for surgical interventions such as PV replacement are largely determined by imaging from echocardiography (echo) and cardiac magnetic resonance imaging (cMRI). Patients who are not symptomatic at rest may have abnormal cardiac and pulmonary response to exercise during cardiopulmonary exercise testing (CPET), which may aid in appropriate timing of PV replacement along with echo and cMRI data. Though CPET is a supplementary testing modality it adds an important piece of the puzzle in management of TOF and the balancing of too-soon/too-late for PV replacement.

The relationship between pulmonary function and exercise capacity (defined as % of predicted peak VO_2/kg) in patients with congenital heart disease (CHD) is complex and incompletely understood [1–3]. Several studies have shown a high incidence of restrictive lung pattern with low forced vital capacity (FVC) in patients with CHD. Almost half of Fontan patients in the Pediatric Heart Network Fontan Study Group had low FVC and that low FVC was associated with decreased exercise capacity [2]. There have been small studies in patients with TOF. One demonstrated that patients with TOF had lower exercise capacity, stroke volume response, and FVC than other patients with two-ventricle CHD. This same series showed a correlation between FVC and exercise capacity, stroke volume response and ventilation perfusion (V/Q) matching. The number of cardiac surgeries was related to incidence of abnormal FVC in patients with TOF and there is evidence that abnormal lung development may occur in-utero [4].

Despite the paucity of information about the pulmonary function in patients with TOF much has been studied about their exercise response. Exercise capacity is variable in children with TOF and may be normal or reduced [5,6]. There is a decline in exercise capacity seen with age in adult patients [7]. Determinants of exercise capacity are complex and multifactorial in most patient populations and TOF is no exception with studies showing relation to right ventricular end diastolic volume (RVEDV) and RV function [8]. RV function has been reported as one of the most predictive of exercise capacity in patients with TOF [9] with a decline in exercise capacity related to a decline in RV ejection fraction. O_2 pulse, a surrogate for stroke volume response [10], can be abnormal in TOF patients and lead to decreased exercise capacity [11]. Ventilation perfusion (V/Q) matching can be frequently abnormal in patients with TOF measured by the V_E/V_{CO2} slope [12,13].

While the exercise response in TOF patients has been extensively characterized there is very little data integrating the role of pulmonary pathology which is common in TOF patients. The goal of this study was to investigate the relationship between exercise response and pulmonary pathology in patients with TOF. Our hypothesis was that patients with TOF and abnormal spirometry (low FVC) will have lower exercise capacity than the TOF patients with normal FVC. Our secondary objectives were to investigate the relationship between pulmonary function and exercise response from O_2 pulse and V_E/V_{CO2} slope. Because of the wide range of clinical presentation and current clinical status at the time of testing we integrated the data from echo and cMRI with respect to RVEDV, RV function, and PV function.

2. Methods

We conducted a retrospective chart review of patients with TOF who had undergone routine clinical CPET over a 4-year consecutive period by querying the exercise records. In cases where patients had multiple visits the most recent was used. We included patients with TOF of all ages who were able to exercise. We excluded patients with absent PV syndrome as this lesion has particular airway anomalies and may bias our assessment of pulmonary disease. We did not include patients with a diagnosis of double outlet right ventricle with TOF type physiology or pulmonary atresia (PA) with major aortopulmonary collateral arteries as number of surgeries and

surgical repairs in these patients can be significantly different from that of TOF with pulmonary stenosis.

2.1. Cardiac history

The electronic medical record was reviewed for the number of prior surgeries and records of the original cardiac diagnosis from initial imaging of the patient. The types of TOF were divided into two categories of 1) TOF with pulmonary stenosis undergoing complete initial repair and 2) TOF with pulmonary stenosis or pulmonary atresia requiring a shunt procedure as their initial palliation.

Imaging data was collected from the imaging study (cMRI or echo) in closest proximity to the CPET as possible; often the echo was from the same day. We did not include the imaging data if it was collected more than one year from the date of CPET or if the patient had an intervention in the interim between when the imaging and CPET were conducted.

The quantitative results from cMRI for RVEDV was classified as normal or mild dilation (<120 mL/m^2), moderate dilation (120–140 mL/m^2), and severe dilation (>140 mL/m^2). RV systolic function was classified as normal or mildly reduced (≥35% ejection fraction) and moderately reduced (<35% ejection fraction). No patients had severely reduced RV function. PI was classified as normal to mild (<20% regurgitant fraction), moderate (20%–40% regurgitant fraction), and severe (>40% regurgitant fraction). PV stenosis and pulmonary artery stenosis were classified as mild, moderate, or severe by their respective echo gradients/criteria.

2.2. Spirometry

Spirometry was performed and reported based on American Thoracic Society guidelines. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were considered normal if the percent predicted calculation was ≥80%. FEV_1/FVC was considered normal if values were ≥80%. Tests with poor effort or short exhalation times were excluded.

2.3. CPET

CPET variables included: Exercise capacity (defined as weight indexed oxygen consumption = peak VO_2/kg and expressed as % of predicted), ventilatory efficiency (defined by V_E/V_{CO2} slope), stroke volume response (defined by oxygen pulse = O_2 pulse and expressed as % of predicted), and oxygen uptake efficiency slope (expressed as % of predicted)).

CPETs were conducted using a Medical Graphics Ultima Medical Cart (MGC corporation, Minneapolis, MN). Three tests were conducted on ergometers while the rest were conducted on treadmills. The respiratory exchange ratio (RER) was reviewed to ensure the exercise tests were conducted with good effort by the participant. Tests were excluded if RER at peak VO_2/kg was <1.0. Two patients had peak RER 1.04 and five others had RER of 1.05–1.09 while all others had RER at peak exercise >1.1. These seven patients were felt to have maximal effort tests by their subjective effort and had heart rates of 82%–92% predicted. Given the wide range of ages in our study population, exercise parameters were reported as percent predicted value using

standardized equations to allow for direct comparison between patients of different sexes and the adults and children in the study group [14]. Breathing reserve was calculated by ((maximal voluntary ventilation (MVV) – peak minute ventilation)/MVV) where MVV = $FEV_1 \times 40$ and classified as normal if >20% or abnormal if ≤20%. Oxygen uptake efficiency slope (OUES), measures how efficiently oxygen is extracted by the lungs and used in the body by comparing VO_2 and the logarithm of the minute ventilation (VE). It does not depend on maximal effort in the exercise test and can also integrate combined cardiac and pulmonary abnormalities which may be present in TOF patients. Slope data from the OUES and V_E/V_{CO2} slope (start to end of exercise) were all obtained directly from the recorded exercise data. OUES predicted values and % predicted OUES values were calculated using equations developed by Sun et al. for adults and Bongers et al. for children [15,16].

2.4. Statistics

Preliminary descriptive statistics consist of providing frequencies and proportions for categorical variables, and mean, standard deviation, for continuous variables. Group comparisons were conducted by the Fisher's exact test and the Wilcoxon rank-sum test. The univariate regression analyses and multivariable models for continuous outcomes were summarized using the regression estimates, corresponding 95% confidence interval (95% CI) *p*-value and the *R* (% variability of the outcome explained by the model). The univariate logistic analyses and multivariable models for categorical outcomes were summarized using the odds ratio (OR), corresponding 95% confidence interval (95% CI), *p*-value and AUROC (Area Under the Receiver Operating Characteristic or C statistic). For the multivariable regression models, we included all predictors from the univariate analysis with a *p*-value <0.1. The significance level is at 0.05. Statistical Analyses were performed using the statistical software packages SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Demographics

We identified 122 potential patients with TOF who underwent exercise testing at Phoenix Children's Hospital during our study period and included 70 patients in our analysis. We excluded 28 patients for incomplete or inadequate effort spirometry data and 20 patients for incomplete or inadequate exercise data. Four patients were excluded for incomplete cardiac histories that could not be confirmed or additional cardiac defects beyond TOF. Three patients had imaging (echo or cMRI) that were greater than one year from the time of CPET, so their imaging data was not included. 32 patients had a recent cMRI that was used, while 35 patients did not have a recent cMRI and data from a more recent echo was used instead. Exercise restriction is sometimes advised for patients by physicians however, none of our patients were exercise restricted [17].

Demographic data is listed in **Table 1**. The study population showed a slight male predominance 39 (56%), a mean age of 25 years, with 28 (40%) < 18 years of age.

There were four patients <18 years in the obese range and eight patients ≥18 years of age in the obese range.

Table 1. Demographic, spirometry, and exercise data.

Variable Description	All	Normal FVC	Low FVC	*p*-value
	(*n* = 70)	(*n* = 38)	(*n* = 32)	
Age, y	25 ± 12	23 ± 11	27 ± 13	0.28
Sex, male	39 (56%)	22 (58%)	17 (53%)	0.81
BMI Z-score (≤ 18yo)	−0.2 ± 0.6 (*n* = 28)	−0.1 ± 0.7 (*n* = 18)	−0.3 ± 1.0 (*n* = 10)	
BMI (> 18yo)	26 ± 2 (*n* = 42)	26 ± 2.0 (*n* = 20)	26 ± 3 (*n* = 22)	
Type of TOF, shunt ± PA	27 (39%)	11 (29%)	16 (50%)	0.09
Number of surgeries	2.1 ± 1.2	1.7 ± 1	2.7 ± 1.3	0.0002
Moderate or severe RV dilation	34 (51%) (*n* = 67)	17 (48%) (*n* = 36)	17 (57%) (*n* = 30)	
Moderate or severe RV systolic dysfunction	6 (9%) (*n* = 67)	1 (3%) (*n* = 36)	5 (17%) (*n* = 30)	0.08
Moderate or severe PI	46 (69%) (*n* = 67)	26 (72%) (*n* = 36)	12 (40%) (*n* = 30)	
Spirometry				
FVC (%)	81.8% ± 17.7%	94.2% ± 10.5%	65.7% ± 10.1%	< 0.0001
FEV_1/FVC ratio	83.5% ± 8.9%	81.3% ± 8.4%	86.1% ± 8.5%	0.09
Both low FVC and FEV_1/FVC ratio	28 (40%)	0 (0%)	28 (88%)	< 0.0001
Exercise Measures				
Low breathing reserve	9 (13%)	7 (18%)	2 (6%)	0.07
Peak VO_2/kg (%)	58.2 ± 13.2	59.8 ± 12.2	53.1 ± 13.3	0.05
O_2 pulse (%)	89.8 ± 16	91.7 ± 13.9	84.5 ± 17.3	0.27
work (%)	59 ± 16.5	61.6 ± 14	53.9 ± 15.1	0.07
VO_2 at AT/peak exercise	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.49
V_E/V_{CO2} slope	32 ± 6.1	30.9 ± 5.2	32 ± 6.9	0.44
OUES (%)	65.9 ± 15.5	67.7 ± 15	63.7 ± 15.9	0.43

FVC, peak VO_2/kg, O_2 Pulse, work, and OUES are all expressed in % of predicted. Values are in *n* (%) or mean ± SD.

27 (39%) required a shunt as their initial palliation. The remainder of the population had a primary TOF repair. Most patients had between one and five cardiac surgeries (mean 2.1 ± 1.2) while one patient had seven. Most of our population 46 (69%) had moderate to severe PI at the time of CPET. Almost half of the study patients 34 (51%) had moderate to severe RV dilation. Most had normal or mildly reduced RV function 61 (91%), 6 (9%) had moderately reduced RV function, and no patients had severely reduced RV function. 6 (9%) patients had PV stenosis and 3 (5%) had moderate to severe PA stenosis. Only three patients had PV replacement in the one year prior to the exercise stress test. The remainder of the study population was undergoing evaluation for PV replacement or a routine surveillance study.

3.2. Spirometry

Spirometry data is also listed in **Table 1**. The mean FVC in our study population

was 81.8% predicted with almost half, 32 (46%) patients, having low FVC (< 80% predicted). Of those with low FVC 9 (28%) also had a low FEV_1/FVC ratio (< 80% predicted) with a mixed restrictive and obstructive pattern. There were no significant differences in age, sex, or BMI between normal and low FVC groups. The TOF sub-types and requirement of neonatal shunting did not reach statistical significance between normal and low FVC groups however, the low FVC group had significantly more cardiac surgeries (2.7 vs. 1.7, $p = 0.0002$). There were no significant differences in RV dilation, RV systolic dysfunction, or PVR between normal and low FVC groups.

3.3. CPET

CPET data is also listed in **Table 1**. The exercise capacity of the study population was reduced at a mean value 58% predicted with only four patients having exercise capacity ≥80% predicted. Female patients had a lower exercise capacity than male patients (51.9% vs. 63.2% predicted, $p \leq 0.001$) though O_2 pulse (88.5% predicted ± 15.4% vs. 91.5% predicted ±16.2%, $p = 0.5$) and V_E/V_{CO2} slope (33.4 ± 5.6 vs. 29.2 ± 6.5, $p = 0.48$) were not significantly different. Along with the low exercise capacity, only nine patients had a normal work rate and only 13 patients had a normal OUES. V_E/V_{CO2} slope was normal in 27 (39%) patients. Most patients had normal breathing reserve with only 9 (13%) having breathing reserve below 20%. Most of our study patients 55 (79%) had a normal O_2 pulse.

Patients with low FVC had significantly lower exercise capacity than those with normal FVC (53.1% vs. 59.8% predicted, $p = 0.05$). Patients with normal FVC had slightly higher O_2 pulse (91.7 ± 13.9% predicted) compared to patients with low FVC (84.5 ± 17.3% predicted) but it was not significant ($p = 0.27$). V_E/V_{CO2} slope was not significantly different between normal and low FVC (30.9 ± 5.2 vs. 32 ± 6.9, $p = 0.44$).

There was no significant difference in exercise capacity between pediatric patients vs. adults (59.2% predicted ± 4.3% vs. 57.5% predicted ± 4.2% $p = 0.34$). O_2 pulse was also not significantly different between pediatric patients and adults (70% predicted ± 5.3% vs. 63.1% predicted ±4.7%, $p = 0.51$). V_E/V_{CO2} slope however was higher for patients <18 years of age 34.8 ± 2.5 than for patients ≥18 years of age 30.1 ± 1.5 ($p = 0.05$).

3.4. Predictors of FVC

Predictors of FVC in the multivariable model are summarized in **Table 2**. The only significant independent predictor of FVC was the number of prior cardiac surgeries. With every surgery, the odds of having low FVC increases (OR 2.4, 1.2–4.8, $p = 0.01$).

Table 2. Predictors of low FVC in the multivariable model.

Variable Description	Odds Ratio	*P*-value	AUROC
Type of TOF, shunt ± PA	1.2 (0.3, 4.6)	0.78	0.77
Number of surgeries	2.4 (1.2, 4.8)	0.01	
Peak VO_2/kg (%)	1 (0.9, 1.0)	0.1	

Peak VO_2/kg is expressed in % of predicted. Values are Odds Ratio (95% CI).

3.5. Predictors of exercise capacity

Predictors of peak VO_2/kg are listed in **Table 3**. Age, type of TOF, number of surgeries, moderate or severe RV systolic dysfunction, O_2 pulse, and V_E/V_{CO2} slope were all considered in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariable model. Severe RV dilation (p = 0.13) was slightly greater than our cutoff of p = 0.1 but given the potential of severe RV dilation to impact exercise capacity, it was included in the multivariable model. In addition, BMI (p = 0.0004), sex (p = 0.0002), % predicted FVC (p = 0.003), and OUES (p = 0.07) were all included from the univariate analysis.

Table 3. Predictors of peak VO_2/kg in the multivariable model.

Variable Description	Estimate	*P*-value	*R*-squared
BMI	−0.6 (−1.0, −0.3)	0.002	0.59
Sex, male	−16.4 (−21.5, −11.3)	<0.0001	
FVC (%)	0.2 (0.1, 0.3)	0.004	
OUES (%)	0.3 (0.1, 0.5)	0.0008	
Severe RV dilation	−4.1 (−9.5,1.3)	0.13	

FVC and OUES are all expressed in % of predicted. Values are Odds Ratio (95% CI).

In the multivariable model exercise capacity was negatively associated with BMI as well as male sex. OUES was a predictor of exercise capacity though this may be a covariate effect due to the integration of VO_2 and V_E to calculate OUES. FVC was also an independent predictor of exercise capacity. Diminished RV systolic function was not significant even in the univariable model (small sample size n = 6). RV size was included in the multivariable model but was not significant.

3.6. Predictors of stroke volume response

Predictors of O_2 pulse are listed in **Table 4**. Age, sex, type of TOF, number of surgeries, severe RV dilation, exercise capacity, V_E/V_{CO2} slope, and OUES were all considered in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariable model. BMI (p = 0.02), FVC (p = 0.007), and moderate or severe RV systolic dysfunction (p = 0.009) were all included from the univariate analysis. Both BMI and FVC were significant predictors of O_2 pulse though moderate/severe RV systolic dysfunction was the strongest predictor in multivariate analysis. RV dilation, number of surgeries and TOF sub-type were not significant in univariate analysis and therefore were not considered for multivariable model.

Table 4. Predictors of O_2 pulse in the multivariable model.

Variable Description	Estimate	*P*-value	*R*-Squared
BMI	0.6 (0.1, 1.1)	0.03	0.23
FVC (%)	0.2 (0.03, 0.4)	0.03	
Moderate or severe RV systolic dysfunction	13.7 (1.5, 25.8)	0.03	

FVC is expressed in % of predicted. Values are Odds Ratio (95% CI).

3.7. Predictors of ventilatory efficiency

Predictors of V_E/V_{CO2} slope are listed in **Table 5**. FVC, type of TOF, number of surgeries, RV function, exercise capacity, O_2 pulse, ed OUES, and severe RV dilation were considered in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariable model. Age (p = 0.002), BMI (0.005), and sex (0.01) were all included from the univariate analysis. Age, BMI, and sex were all significant predictors of V_E/V_{CO2} slope in the univariate analysis. BMI was a significant independent predictor of V_E/V_{CO2} slope in the multivariable model.

Table 5. Predictors of V_E/V_{CO2} slope in the multivariable model.

Variable Description	Estimate	*P*-value	*R*-squared
Age, y	−0.13 (−0.26, 0.01)	0.0702	0.26
BMI	−0.26 (−0.51, −0.02)	0.0356	
Sex, male	−2.8 (−5.6, 0.01)	0.0506	

Values are Odds Ratio (95% CI).

4. Discussion

4.1. Spirometry

Almost half of our study population had low FVC which is consistent with prior studies [4]. A higher number of surgeries was an independent predictor of FVC in the multivariable model and is consistent with prior research [18]. Most patients had normal FEV_1/FVC ratio (along with low FVC) suggesting they did not have an obstructive component to their lung disease. Low FVC can be due to restrictive lung disease and/or air trapping. Number of surgeries was a predictor of low FVC but was not an independent predictor of low exercise capacity probably because it does not account for low FVC due to air trapping. Air trapping in particular can lead to decrease exercise capacity through ineffective ventilation because of increased dead space ventilation. It has been suggested that cardiac surgery leads to significant fibrosis and adhesions that could cause restrictive lung disease and decreased total lung volume. Our findings suggest that apart from the post-surgical changes from sternotomy there may be other lung disease present which may result in air-trapping. Unfortunately, we did not have measurements from a full batter of pulmonary function testing to quantify lung volumes to assess restrictive lung disease (low total lung capacity) and/or air trapping (increased residual volume) as a cause of low FVC. FVC was lower in our patients ≥18 years of age and in our patients with more complex TOF (shunt dependent and/or with pulmonary atresia) but this was not significant in the multivariable model. Older patients and those with more complex TOF may have lower FVC because those factors make it more likely they need repeated cardiac surgeries and cardiac surgeries are one of the drivers of decreased FVC.

We hypothesized that progressive RV dilation would contribute to restrictive lung disease by occupying more space in the chest and compressing the lungs. However, we did not find significant negative effect of RV dilation on FVC even though we had patients with very large RVs including three patients with RVEDV exceeding 200 mL/m^2.

4.2. CPET parameters

The mean exercise capacity of our study population was low at 58% predicted (peak VO_2/kg). Multivariate analysis showed that in our study population lower FVC, higher BMI, female sex, and lower OUES were all independent predictors of lower exercise capacity. Though this relationship has been previously described there is no plausible mechanistic reason in prior studies apart from the relationship with number of sternotomies. Our study also found low FVC as an independent predictor of O_2 pulse (% predicted) which is a novel finding. This result is an interesting relationship between lung function stroke volume response and may be due to cardiopulmonary that have not been delineated.

Females had lower exercise capacity in our study population. Males with TOF have been shown to have impaired ventricular function compared to females at all ages [19]. Our study did not show any sex-based differences in ventricular function. The underlying mechanism for lower exercise capacity in females in our study population is unclear.

4.3. Pulmonary valve insufficiency and RV dilation

Consistent with other studies, we did not find a difference between PI and exercise capacity, likely due to the ability of the heart to compensate for PI with RV dilation to maintain forward pulmonary flow. We hypothesized that we would see a significant impact from RV dilation on exercise capacity as others have, given that we had a wide range of patients from normal RV size to significant dilation >200 mL/M2, but we did not [8]. Our study may not have been powered enough to see this or it's possible that our patients were able to compensate for the decrease in intrathoracic space that a dilated RV causes without decreasing their FVC.

We found moderate or severe RV systolic dysfunction to be an independent predictor of stroke volume response which was expected, though again RV systolic dysfunction was not directly predictive of exercise capacity. Prior publications evaluating lung function and CPET have not integrated echocardiography or cMRI data making our findings unique.

5. Study limitations

Our data is limited by the single center nature of this investigation with a small sample size. Many patients were excluded due to incomplete surgical data. Comparisons across this diverse population of tetralogy are challenging, the absolute values that many are accustomed to seeing in CPET evaluation become less meaningful as there is so much variance in what is normal between the age groups. We reported CPET variables exclusively as % predicted to allow for a more facile comparison within this diverse population. Cardiac testing was variable in our group and not all patients had cMRI to report RV related measures. Despite the size and limitations there are clear relationships between spirometry and physiologic response in exercise.

6. Conclusions

Abnormal spirometry, specifically low FVC is a predictor of not only exercise capacity but also O_2 pulse suggesting there may be a cardiopulmonary interaction between low FVC and stroke volume response in TOF patients (**Figure 1**). There is a relationship between number of cardiac surgeries and low FVC but cardiac surgeries are not predictive of exercise variables suggesting there may be additional pulmonary pathology present. Further workup such as a full pulmonary function test may provide clinical utility if a reversible processes such as air trapping can be identified and appropriate treatment can be initiated.

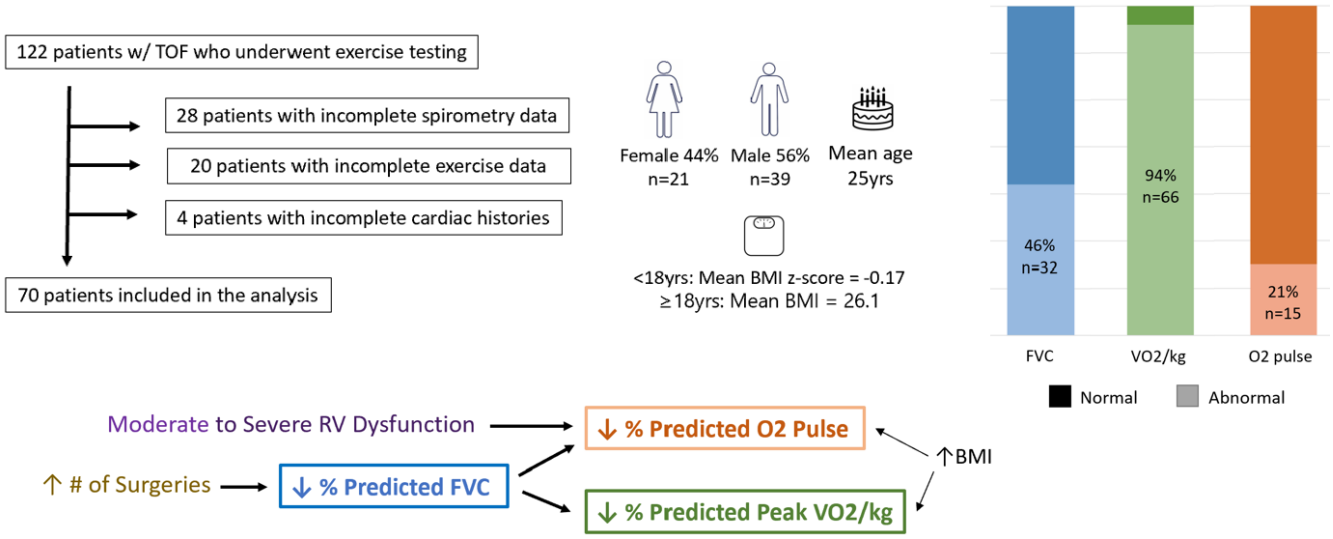

Figure 1. Abnormal exercise and spirometry in tetralogy of Fallot population.

70 patients with tetralogy of Fallot (TOF) included. 46% had abnormal forced vital capacity (FVC). Most had low peak VO_2/kg (94%). FVC was predictive of both O_2 pulse and peak VO_2/kg in multivariate analysis. Body mass index (BMI) was also predictive of O_2 pulse and peak VO_2/kg. RV dilation was not predictive of O_2 pulse or peak VO_2/kg. Right ventricular (RV) systolic dysfunction was only predictive of O_2 pulse.

Age, BMI, sex, moderate or severe RV systolic dysfunction, O_2 pulse, V_E/V_{CO2} slope, OUES, and severe RV dilation were all included in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariate analysis. Type of TOF ($p = 0.07$), number of surgeries ($p = 0.003$), and peak VO_2/kg ($p = 0.05$) were all included from the univariate analysis. Number of surgeries was an independent predictor of low FVC in the multivariate analysis.

Age, type of TOF, number of surgeries, moderate or severe RV systolic dysfunction, O_2 pulse, and V_E/V_{CO2} slope were included in the univariate analysis but had *p*-values of >0.1 and were not included in the multivariate analysis. Severe RV dilation ($p = 0.13$) had $p > 0.1$ but given the potential impact on exercise capacity, it was included. In addition, BMI ($p = 0.0004$), sex ($p = 0.0002$), FVC ($p = 0.003$) and OUES ($p = 0.0736$) were included from the univariate analysis. BMI, sex, FVC and OUES were independent predictors of peak VO_2/kg in the multivariate analysis.

Age, sex, type of TOF, number of surgeries, severe RV dilation, peak VO_2/kg, V_E/V_{CO2} slope, and OUES were all included in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariate analysis. BMI ($p = 0.02$), FVC ($p = 0.007$), and moderate or severe RV systolic dysfunction ($p = 0.009$) were all included from the univariate analysis. BMI, FVC and RV systolic dysfunction are all independent predictors of O_2 pulse.

FVC, type of TOF, number of surgeries, RV function, peak VO_2/kg, O_2 pulse, OUES and severe dilated RV were included in the univariate analysis but had *p*-values of >0.1. Therefore, they were not included in the multivariate analysis. Age ($p = 0.002$), BMI (0.005) and sex (0.01) were all included from the univariate analysis. BMI is an independent predictor of V_E/V_{CO2}.

Author contributions: Conceptualization, NP and HT; writing—original draft preparation, RB; writing—review and editing, RB and AS; supervision, AS. All authors have read and agreed to the published version of the manuscript.

Ethics statement: This study received approval from the Phoenix Children's Hospital Institutional Review Board. All data collection and chart review was done in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

BMI	body mass index
cMRI	cardiac magnetic resonance imaging
CPET	cardiopulmonary exercise testing
Echo	echocardiography
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
O_2 pulse	oxygen pulse
OUES	oxygen uptake efficiency slope
PAs	pulmonary arteries
PA	pulmonary atresia
PV	pulmonary valve
PI	pulmonary valve insufficiency
RV	right ventricle
RVEDV	right ventricular end diastolic volume
TOF	tetralogy of Fallot
V/Q mismatch	ventilation perfusion mismatch
V_{CO2}	carbon dioxide consumption
V_E/V_{CO2}	equivalents of minute ventilation per equivalents of expired carbon dioxide
VO_2	oxygen consumption
VO_2/kg	weight indexed oxygen consumption

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