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ORIGINAL ARTICLE

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Forced vital capacity predicts morbidity and mortality in adults with repaired tetralogy of Fallot

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Abstract

Objective: Abnormal lung function characterized by a reduced forced vital capacity (FVC) is common in adults with repaired tetralogy of Fallot (TOF) and is associated with previous thoracotomies and sternotomies. The impact of abnormal lung function on clinical outcomes in adult patients with repaired TOF is unclear. The aim of this study was to determine the impact of abnormal lung function on the outcome of hospitalization and death in adults with repaired TOF when analyzed with other traditional cardiac risk factors.

Design: Retrospective study of adults with repaired TOF, who underwent spirometry between 2000 and 2014. FVC < 60% of predicted was categorized as moderate-to-severely reduced lung function. Primary outcome measure was the combined clinical endpoint of death, cardiac transplantation, or nonelective hospitalization for primary cardiac or respiratory indication.

Results: A total of 122 patients were included. Average age at spirometry testing was 31 ± 10.1 years. FVC was < 60% predicted in 23 (19%) patients. During a mean follow-up period of 3.97 ± 2.65 years, 23 (19%) patients reached the combined clinical outcome of nonelective hospitalization and/or death. FVC < 60% predicted was independently associated with the risk for the combined clinical outcome (RR 6.68 (95% CI 2.49–17.94), $P < .001$).

Conclusions: Abnormal pulmonary function characterized by reduced FVC is common in adults with repaired TOF. Patients with FVC < 60% predicted had a 6 times higher rate of hospitalization and/or death compared to those with FVC ≥ 60%.

KEYWORDS

forced vital capacity, lung pathology, mortality, restrictive lung disease, tetralogy of Fallot

1 | INTRODUCTION

Abnormal lung function is common in pediatric and adult patients with congenital heart disease (CHD).[1–3] Patients with repaired tetralogy of Fallot (TOF), in particular, have one of the highest prevalence of abnormal lung function, with up to 76% having reduced forced vital capacity (FVC) percent predicted measured with spirometry.[2] The etiology for reduced FVC in this population is likely multifactorial, and includes hemodynamic abnormalities related to the underlying CHD, abnormal pulmonary growth and development, and risk for chest wall or rib cage deformities following cardiac surgery.

Abnormal lung function is associated with reduced exercise capacity in patients with repaired TOF,[4] but its impact on the risk for mortality in this population is unclear. In adults with acquired heart disease, there has been an observed association between low FVC and risk for heart failure and death.[5] One single-center study reported a similar association between low FVC and mortality in a heterogeneous population of adults with CHD.[2] However, no study has examined the relationship of lung function and clinical outcomes specifically in adult patients with repaired TOF. The aim of this study was to determine the relationship between abnormal lung function and the risk for nonelective hospitalization and death in adults with

repaired TOF when analyzed with other traditional cardiac risk factors in this population.

2 | METHODS

2.1 | Population

Adult patients (age ≥ 18y/o) with history of repaired TOF, who underwent pulmonary function measurements with spirometry at the time of cardiopulmonary exercise testing (CPET) between January 1, 2000 and March 31, 2014 at our institution were included in the study. In general, our institution performs cardiopulmonary exercise testing with spirometry for the assessment of symptoms, or every 2 years in asymptomatic patients with residual hemodynamic lesions, such as pulmonary insufficiency after TOF repair. For female subjects, only CPET with spirometry performed during nonpregnancy state were included. The study was approved by the Children's Hospital of Wisconsin Institutional Review Board.

2.2 | Assessment of lung function

Spirometry was performed according to reviewed standards, with measurements of FVC and forced expiratory volume in 1 second (FEV_1) obtained.[6] Values for FVC and FEV_1 were expressed as a percent of predicted for age, sex, and height according to reference values.[7] Lung function was classified categorically based on FVC % predicted as normal (FVC > 70% predicted), mildly reduced (FVC = 60%–70% predicted), and moderate-to-severely reduced (FVC < 60% predicted) based on previous publications.[2,7] An FEV_1/FVC ratio < 0.70 was considered obstructive lung physiology.

2.3 | Data collection and assessment of risk factors

Demographics and clinical data were obtained by retrospective chart review. Variables included number of previous surgeries/sternotomies/thoracotomies, New York Heart Association (NYHA) functional class, and smoking history. Obesity at time of spirometry was defined as body mass index (kilograms/meters^2) ≥ 30. Results from CPET performed immediately following spirometry were collected. CPET was performed using a standard Bruce protocol on a treadmill ergometer with incremental increases in speed and grade to voluntary exhaustion. Peak oxygen consumption (VO_2) was measured electronically on a breath-by-breath basis (CareFusion Corp., Yorba Linda, CA, USA) and was expressed as a percentage of predicted for age, height, and weight.[8] Ventilatory efficiency was calculated as the slope of the regression line between minute ventilation (VE) and carbon dioxide produced (VCO_2) acquired throughout the entire period of exercise. Peak VO_2 and VE/VCO_2 slope measurements were available in 99 (82%) and 95 (79%) patients, respectively. Chronotropic index was defined by the equation (peak heart rate−resting heart rate)/(220−age −resting heart rate), and abnormal chronotropic index was defined as value < 0.80. Cyanosis was defined as oxygen saturation measured with pulse oximetry of less than 90% either at rest or with exercise. Maximum QRS width in any lead was measured from the first to the last sharp vector crossing the isoelectric line on standard 12-lead surface electrocardiogram (25 mm/s and 1 mV/cm) performed at rest just prior to CPET. Left and right ventricular systolic function was assessed by an experienced blinded reviewer based on an echocardiogram performed within 6 months of spirometry and categorized as normal, mildly decreased, moderately decreased, and severely decreased systolic function. Scoliosis was included as clinical risk factor for patients with previous clinical diagnosis that was made based on clinical exam and/or with plain PA chest x-ray identifying spinal curvature with Cobb angle > 10 degrees.

2.4 | Follow-up and outcomes

Assessment of the combined clinical outcome of death and/or nonelective hospitalization for primary cardiac or respiratory indication during the time period following the spirometry was obtained by retrospective chart review. Indications for nonelective hospitalizations included congestive heart failure, arrhythmia, pneumonia, and/or respiratory failure of any etiology. Elective catheterizations or surgeries were not included as part of the outcome data. Follow-up was complete for all patients included in the study during the study period.

2.5 | Statistical analysis

Descriptive statistics such as means with standard deviations for continuous variables and counts with percentages for categorical variables were used to summarize sample characteristics. Cox proportional hazards model was used to identify variables associated with the primary outcome of nonelective hospitalization or death. Kaplan-Meier curve was used to summarize the time to hospitalization or death among patients with normal and mildly reduced lung function versus those who had moderately-to-severely reduced lung function. Log-rank test was employed to compare the two groups of patients. Logistic regression model was used for identifying the risk factors of having moderately-to-severely reduced lung function. All *P* values are two-sided and alpha of 0.05 was used throughout. Analyses were carried out using SAS 9.4 statistical software (SAS Institute, Inc. Cary, NC).

3 | RESULTS

A total of 122 patients, 59 (48%) female, were included in the study (Table 1). The average age at spirometry testing was 31 ± 10.1 years. Median age at complete repair was 28 months (range = 1 month to 13 years). Obesity was a diagnosis in 22 (18%), scoliosis in 10 (8%), and diaphragm paralysis in 3 (2%). Ten patients (8%) were identified as current smokers; 6 (5%) were former smokers; and 106 (87%) were never smokers or had unknown smoking history. NYHA functional class I was documented in 115 (94%) patients, class II in 5 (4%), and class III in 2 (2%). No patient was classified as NYHA functional class IV.

Based on FVC % predicted, lung function was categorized as normal in 76 (61%) patients, mildly reduced in 23 (19%), and moderate-to-severely reduced in 23 (19%). A total of 3 (2%) patients had an FEV_1/FVC ratio less than 0.70 with a normal FVC % predicted suggesting a

TABLE 1 Demographics and baseline characteristics

Characteristics	Number (%)
Age at spirometry (years)	31 ± 10.1
Female	59 (48%)
Lung function	
Normal (FVC > 70%)	76 (61)
Mildly reduced (FVC = 60-70)	23 (19)
Moderate/severely reduced (FVC < 60)	23 (19)
Age at complete repair (months)	28 (0.1-156)*
# Prior cardiac surgeries	
1–2	78 (64)
> 2	44 (36)
# Previous thoracotomies	
0	72 (59)
1	37 (30)
≥ 2	13 (11)
Scoliosis	10 (8)
Diaphragm paralysis	3 (2)
Obese	22 (18)
Tobacco smoking status	
Never or unknown	106 (87)
Former smoker	6 (5)
Current smoker	10 (8)
NYHA functional class	
I	115 (94)
II	5 (4)
III	2 (2)
IV	0
CPET results (N = 99)	
Peak VO_2% predicted	75±19.6
# Peak VO_2 < 60% predicted	23 (23)
VE/VCO_2 slope	25.3±5.6
VE/VCO_2 slope > 40	1 (1)
Chronotropic index	0.79 ± 0.2
# chronotropic index < 0.8	45 (37)
Oxygen saturation measured during CPET	
Resting cyanosis (N = 30)	4 (13)
Exercise cyanosis (N = 29)	6 (21)
Left ventricular systolic function by echocardiogram (N = 88)	
Normal	81 (92)
Mildly decreased	7 (8)
Moderate or severely decreased	0 (0)
Right ventricular systolic function by echocardiogram (N = 91)	
Normal	80 (88)
Mildly decreased	7 (8)
Moderately decreased	3 (3)
Severely decreased	1 (1)
QRS duration (N = 121)	
< 120 ms	34 (28)
120–179 ms	81 (67)
≥180 ms	6 (5)

Data presented as mean ± standard deviation or *median (range). #, number; %, percentage; CPET, cardiopulmonary exercise testing; FVC, forced vital capacity percent predicted; NYHA, New York Heart Association functional class.

primary obstructive lung physiology, while two patients had a reduced FEV_1/FVC ratio and reduced FVC% predicted suggesting mixed obstructive/restrictive pulmonary physiology. Exercise capacity was reduced for the cohort with a mean peak VO_2% predicted of 75%, with 23 (23%) patients having a peak VO_2 < 60% of predicted. Heart rate response to exercise was abnormal in 45 (37%) patients based on a chronotropic index less than 0.80. Of patients with chronotropic index less than 0.80, 23 (51%) were taking beta-blockers at the time of CPET.

During a mean follow-up period of 3.97 ± 2.65 years, a total of 23 (19%) patients reached the combined end-point of nonelective hospitalization (n = 21) or death (n = 2). The indication for hospitalization was for a primary cardiac indication in eight patients, and primary respiratory indication in 13 patients. Cardiac indications for admission included congestive heart failure (n = 5) and arrhythmia (n = 3). Respiratory indications included shortness of breath (n = 8), status asthmaticus or chronic obstructive pulmonary disease exacerbation (n = 2), dyspnea associated with pregnancy (n = 2) and pneumonia (n = 1). Causes of death included congestive heart failure (n = 1) and sudden death (n = 1).

By univariate analysis (Table 2), FVC < 60% predicted, peak VO_2 < 60% of predicted, chronotropic index < 0.80, and QRS duration ≥ 180 ms were all significantly associated with the combined end-point of nonelective hospitalization or death. Reduced left or right ventricular systolic function, NYHA functional class ≥ 2, and VE/VCO_2 slope > 40 were not associated with the clinical outcome.

TABLE 2 Risk factors for combined clinical outcome of nonelective hospitalization or death by univariate predictor models

Characteristics	Relative risk (95% confidence interval)	*P* value
FVC < 60% predicted	4.72 (2.05–10.82)	<.001
Peak VO_2 < 60% Predicted	3.90 (1.58–9.61)	.003
Chronotropic incompetence	2.48 (1.08–5.68)	.03
QRS duration		.11 (2df)
<120	Referent	
120–179	1.38 (0.50–3.82)	.53
≥180	4.38 (1.04–18.46)	.04
Right ventricular systolic function		.16 (2df)
Normal	Referent	
Mildly decreased	3.42 (0.95–12.22)	.06
Moderately decreased	1.99 (0.25–15.87)	.51
NYHA functional class		.53 (2df)
I	Referent	
II	1.83 (0.24–13.78)	.56
III	2.79 (0.37–20.86)	.32
Mildly reduced left ventricular systolic function (vs. normal systolic function)	1.46 (0.33–6.42)	.62
VE/VCO_2 slope > 40	5.47 (0.71–41.69)	.10

df, degrees of freedom; FVC, forced vital capacity; NYHA, New York Heart Association.

TABLE 3 Risk factors for combined clinical outcome of nonelective hospitalization or death by multivariate predictor models

Characteristics	Relative risk (95% confidence interval)	*P* value
FVC < 60% predicted	6.68 (2.49–17.94)	<.001
Peak VO_2 < 60% predicted	3.13 (1.18–8.28)	.02
QRS duration		.0014 (2df)
<120	Referent	
120–179	0.71 (0.24–2.07)	.53
≥180	10.38 (2.12–50.69)	.0038

df, degrees of freedom; FVC, forced vital capacity.

TABLE 4 Factors associated with moderate to severely reduced pulmonary function

Characteristics	Odds ratio (95% confidence interval)	*P* value
# Previous thoracotomies		<.0001
0	Referent	
1	8.52 (2.17–33.35)	.002
≥ 2	76.67 (13.56–433.44)	<.0001
# Prior cardiac surgeries		.0007
1	Referent	
2	1.79 (0.31–10.39)	.52
≥ 3	10.70 (2.27–50.42)	.003
Age < 1 at complete repair	6.25 (1.8–20)	.03
Age at spirometry	0.97 (0.92–1.02)	.29
Scoliosis	3.50 (0.90–13.59)	.07

By multivariate analysis (Table 3), FVC < 60% predicted was an independent predictor for the combined clinical outcome (RR 6.68 (95% CI 2.49–17.94), $P < .001$). Other well known risk factors in this population, peak VO_2 <60% predicted (RR 3.13 (95% CI 1.18–8.28), $P = .02$) and QRS duration ≥ 180 ms (RR 10.38 (95% CI 2.12–50.69), $P = .004$) were also independent predictors (Table 3). Figure 1 demonstrates the difference in freedom from hospitalization or death in patients based on FVC. The freedom from hospitalization or death during the follow-up period was significantly lower for patients with moderate-to-severely reduced lung function defined as FVC < 60% predicted (log rank $P < .001$).

Risk factors for having FVC < 60% predicted included having a history of ≥ 2 thoracotomies ($P < .001$), a greater number of previous cardiac surgeries ($P < .001$), and age at complete TOF repair < 1 year ($P = .03$) (Table 4). There was a nonsignificant trend for patients with a diagnosis of scoliosis ($P = .07$) to also be more likely to have FVC < 60% predicted.

4 | DISCUSSION

This study demonstrates that adults with repaired TOF that have abnormal lung function characterized by FVC < 60% predicted measured with spirometry, have a 6-fold increased risk of death or nonelective hospitalization for a primary cardiac or respiratory indication. In a

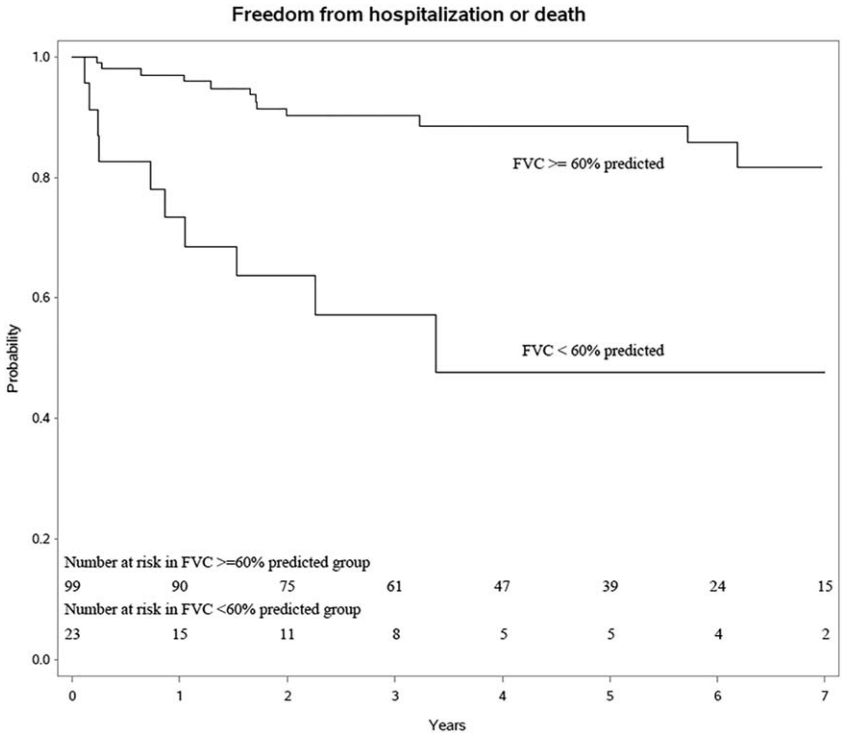

FIGURE 1 Lung function and freedom to hospitalization or death. Patients with FVC ≥ 60% predicted had a lower risk of reaching the combined clinical endpoint of hospitalization or death when compared to patients with FVC < 60% predicted. (Log rank $P < .001$)

single-center study, Alonso-Gonzalez et al. also showed that reduced lung function is associated with a higher risk for mortality in a heterogeneous population of adults with CHD.[2] This study is unique in that it demonstrates a similar relationship between lung function and clinical outcomes specifically in adults with repaired TOF independent of other well known risk factors in this population such as reduced peak VO_2,[9,10] QRS duration,[11] and RV systolic function.[12]

Despite overall good survival and clinical outcomes, adults with repaired TOF are at on-going risk for hospitalization[13,14] and mortality[15–17] due to both cardiac and noncardiac causes. Spirometry is performed routinely with CPET, and the finding of reduced FVC may be an additional clinical risk factor to identify those patients with repaired TOF that are higher risk for worse outcomes. Giardini et al. also demonstrated that reduced peak VO_2 and elevated VE/VCO_2 measurements on CPET provide prognostic information in adults with TOF,[9] and the addition of FVC further enhances the role of CPET during routine follow-up for this growing population.

The mechanisms for this observed relationship between abnormal lung function and risk for mortality in adults with repaired TOF are unclear. Abnormal lung function has a similar impact on clinical outcomes in adults with acquired heart disease, with increased risk for atherosclerosis, hospitalization, and mortality, and it has been hypothesized that this may be due to increased systemic inflammation from certain cytokines and growth factors that may be overexpressed in lung tissue.[5,21–23] Inflammatory markers are also increased in adults with congenital heart disease and may be associated with risk for ventricular dysfunction and congestive heart failure.[24]

This study also demonstrated that patients with TOF that have FVC < 60% predicted are more likely to have a history of multiple thoracotomies and multiple previous surgeries, and to have undergone complete TOF repair before the age of 1 years old. Multiple cardiac surgeries and disruption of the chest wall may result in a restrictive thoracic cage, which can affect lung volumes and pulmonary compliance, thus accounting for the restrictive physiology measured by spirometry.[2–4] Unlike the previous study by Alfonso-Gonzalez et al.,[2] scoliosis was not associated with low FVC in our study, although there was a nonsignificant trend ($P = .07$). We suspect this relationship did not reach statistical significance in our cohort likely due to underdiagnoses of scoliosis in our adult patients with TOF repair and limitations of identifying this variable in a retrospective study.

The association between age of complete repair < 1 years old and risk for abnormal lung function is not entirely clear. Hawkins et al. also found a higher prevalence of restrictive lung disease in children who had cardiac surgery prior to one year of age.[3] We speculate that early age at repair is a marker of those patients who had more severe right ventricular outflow tract obstruction, which in turn resulted in abnormal pulmonary growth and development in the setting of reduced pulmonary blood flow. Right ventricular outflow tract obstruction in TOF is associated with altered alveolar development.[18] Alonso-Gonzalez et al. also found that lung hypoperfusion at birth was a risk factor for low FVC in adults with CHD.[2] Adults with isolated pulmonary valve stenosis were also found to have pulmonary hypoplasia when compared to healthy controls,[19] further suggesting that pulmonary parenchymal growth may be altered by pulmonary outflow tract obstruction early in life. Earlier age at repair may also reflect differences in surgical era and/or use of aortopulmonary shunts. Great number of previous cardiac surgeries prior to complete repair was a risk factor for having FVC < 60%, however the impact of aortopulmonary shunts on long-term pulmonary growth is unclear. Finally, whether earlier age of repair is related to the likelihood of a surgeon employing transannular patch during primary complete repair, and the resultant impact of severe pulmonary insufficiency on pulmonary growth was unable to be elucidated based on our study, and warrants further investigation. Further studies with formal pulmonary function testing with body plethysmography may be useful in this study population to further elucidate the respective role of extrinsic and intrinsic etiologies for the reduced FVC and "restrictive lung physiology" seen in adults with repaired TOF.

4.1 | Limitations

This study was limited by the retrospective design and a relatively small sample size within a single center. In addition, this study is subject to referral bias, as all patients are followed at a tertiary care medical center. Echocardiogram was utilized for assessment of RV systolic function. Magnetic resonance imaging would have provided a more accurate assessment of RV size and function, but unfortunately was not performed on a majority of patients within 6 months of spirometry. Finally, lung function was assessed using spirometry, which is only suggestive, and not diagnostic, of restrictive lung disease. Pulmonary function testing with body plethysmography is needed to confirm the diagnosis of restrictive lung disease by showing a reduction in total lung capacity.[20] Advantages of spirometry, however, are that it is low cost and frequently performed during routine CPET, making it a very clinically useful and widely available screening test.

5 | CONCLUSIONS

Abnormal lung function characterized by reduced FVC is common in adult patients with repaired TOF. FVC provides prognostic information in this population, such that patients with FVC < 60% predicted have a significantly higher rate of hospitalization and/or death. Those patients with repaired TOF that have a greater number of previous cardiac surgeries and thoracotomies may be at higher risk for abnormal lung function in adulthood.

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CONFLICT OF INTERESTS

None of the authors have any potential conflicts of interest, including financial interests or relationships to industry, relevant to the subject matter or materials discussed in the manuscript.

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REFERENCES

[1] Zapletal AA. Lung function in children and adolescents with tetralogy of Fallot after intracardiac repair. *Pediatr Pulmonol*. 1993;716(1):23–30.

[2] Alonso-Gonzalez R, Borgia F, Diller G, et al. Abnormal lung function in adults with congenital heart disease: Prevalence, relation to cardiac anatomy, and association with survival clinical perspective. *Circulation*. 2013;127(8):882–890.

[3] Hawkins SMM, Taylor AL, Sillau SH, Mitchell MB, Rausch CM. Restrictive lung function in pediatric patients with structural congenital heart disease. *J Thorac Cardiovasc Surg*. 2014;148(1):207–211.

[4] Ginde S, Bartz PJ, Hill GD, et al. Restrictive lung disease is an independent predictor of exercise intolerance in the adult with congenital heart disease. *Congenital Heart Disease*. 2013;8(3):246–254.

[5] Sin DD, Wu L, Man SFP. The Relationship between reduced lung function and cardiovascular mortality: A population-based study and a systematic review of the literature. *Chest*. 2005;127(6):1952–1959.

[6] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338.

[7] Lung function testing: Selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis*. 1991;144(5):1202–1218.

[8] Wasserman K, Hansen J, Sue DY, et al. Normal values. In: Wasserman K, ed. *Principles of Exercise Testing and Interpretation*. 5th ed. Pennsylvania, USA: Lippincott Williams & Wilkins; 2012:154–180.

[9] Giardini A, Specchia S, Tacy TA, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2007;99(10):1462–1467.

[10] Müller J, Hager A, Diller G, et al. Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. *Int J Cardiol*. 2015;196:158–164.

[11] Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. *Lancet*. 2000;356(9234):975–981.

[12] Valente AM, Gauvreau K, Assenza GE, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart*. 2013;100(3):247–253.

[13] Kaemmerer H, Fratz S, Bauer U, et al. Emergency hospital admissions and three-year survival of adults with and without cardiovascular surgery for congenital cardiac disease. *J Thorac Cardiovasc Surg*. 2003;126(4):1048–1052.

[14] Opotowsky AR, Siddiqi OK, Webb GD. Trends in Hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol*. 2009;54(5):460–467.

[15] Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med*. 1993;329(9):593–599.

[16] Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000;86(10):1111–1116.

[17] Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30(5):1374–1383.

[18] Johnson RJ, Haworth SG. Pulmonary vascular and alveolar development in tetralogy of Fallot: A recommendation for early correction. *Thorax*. 1982;37(12):893–901.

[19] De Troyer A, Yernault JC, Englert M. Lung hypoplasia in congenital pulmonary valve stenosis. *Circulation*. 1977;56(4):647–651.

[20] Crapo RO. Pulmonary-function testing. *N Engl J Med*. 1994;331(1):25–30.

[21] Beaty TH, Newill CA, Cohen BH, Tockman MS. Spurgeon Effects of pulmonary function on mortality. *J Chronic Dis*. 1985;38:703–710.

[22] Friedman GD, Klatsky AL, Siegelaub AB. Lung function and risk of myocardial infarction and sudden death. *N Engl J Med*. 1976;294:1071–1075.

[23] Schunemann HJ, Dorn J, Grant BJB, Winkelstein W, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest*. 2000;118:656–664.

[24] Sharma R, Bolger AP, Li W, et al. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. *Am J Cardiol*. 2003;92:188–193.

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