

Abnormal Pulmonary Arterial Elastance Is Associated With Reduced Exercise Capacity in Tetralogy of Fallot

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Background—A previous study reported histologic abnormalities in the pulmonary artery (PA) of patients with tetralogy of Fallot (TOF). However, the potential effect of these anatomical findings on PA vascular function has not been studied. We hypothesized that TOF patients had abnormal PA vascular function, and that PA vascular function was associated with exercise capacity.

Methods and Results—This a study of adult TOF patients who had cardiac magnetic resonance imaging and echocardiogram (on the same day) at Mayo Clinic, 2002–2015. In order to test the study hypothesis, we compared PA elastance index (PAEI) between 207 TOF patients and a referent group of 8 subjects without structural heart disease. PAEI was calculated as a quotient of PA systolic pressure and cardiac magnetic resonance imaging–derived right ventricular stroke volume. Mean age was 33 ± 13 and 36 ± 4 years in the TOF and referent groups respectively. TOF patients had higher PAEI compared with the referent group (0.62 ± 0.12 versus 0.48 ± 0.08 mm Hg/mL/m²; $P=0.001$). There was a good correlation between PAEI and peak oxygen consumption (adjusted $R^2=0.73$; $r=0.85$; $P<0.001$). After multivariate adjustment for potential confounders, PAEI was independently associated with peak oxygen consumption (adjusted $R^2=0.69$; $r=0.83$; $P<0.001$).

Conclusions—The high PA elastance in the TOF group may be attributed to abnormal PA vascular function. The association between PAEI and exercise intolerance suggests that PA vascular dysfunction may contribute to exercise intolerance, which is an important clinical problem in this population. Further studies are required to validate our findings and explore potential therapies to improve PA vascular function in this population. (*J Am Heart Assoc.* 2019;8:e011731. DOI: 10.1161/JAHA.118.011731.)

Key Words: pulmonary artery • pulmonary vascular disease • tetralogy of Fallot

Tetralogy of Fallot (TOF) is characterized by a large subaortic ventricular septal defect and right ventricular (RV) outflow tract (RVOT) obstruction.¹ TOF is not just a disease of the RVOT, but it can also involve the pulmonary arteries and capillaries.^{2,3} RV pressure overload can occur after TOF repair, and it is associated with ventricular arrhythmia and cardiovascular mortality.^{4,5} In addition to RVOT obstruction, which is the most common cause of RV pressure overload, other lesions, such as pulmonary arterial (PA) and capillary vascular dysfunction, can also result in RV pressure overload.^{6,7}

Although the deleterious effect of RV hypertension attributed to RVOT obstruction after TOF repair is well known,^{4,5} the potential contribution of PA vascular dysfunction to RV

hypertension has not been studied. Studies conducted in patients with heart failure attributed to acquired heart disease have shown that pulmonary hypertension, either because of PA vascular dysfunction or left ventricular diastolic dysfunction, was associated with RV dysfunction, symptoms, and mortality.^{8–10} A previous necropsy study demonstrated that TOF patients had extensive histological abnormalities of the PA compared with patients without congenital heart disease, but the clinical implications of these vascular abnormalities have not been studied.² Based on these preliminary data, we hypothesized that TOF patients had abnormal PA vascular function, and that PA vascular function was associated with exercise capacity.

Methods

Patient Selection

We will make data, analytical methods, and study materials available to other researchers on request. This a cross-sectional case-control study of patients (age ≥ 18 years) with repaired TOF who underwent cardiac magnetic resonance imaging (CMRI) at Mayo Clinic Rochester, Minnesota from

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Clinical Perspective

What Is New?

- Pulmonary artery elastance is abnormal in patients with tetralogy of Fallot, and it is an independent predictor of exercise capacity.

What Are the Clinical Implications?

- Pulmonary artery elastance can be estimated noninvasively and should be integrated in the clinical workup of tetralogy of Fallot patients with unexplained exercise intolerance.

January 1, 2002 through December 31, 2015. Only patients who had CMRI and transthoracic echocardiogram on the same day were selected for the study. From this cohort, we excluded patients without Doppler assessment of RV systolic pressure (RVSP) or pulmonary valve gradient. We selected a referent group of subjects without any structural heart disease who underwent CMRI and transthoracic echocardiogram on the same day as part of the SIFALD (Sildenafil for Fontan Associated Liver Disease) Clinical Trial (Institutional Review Board #16-008985). The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients who provided research authorization.

Study End Points and Definitions

The primary study objective was to compare PA vascular function between TOF patients and a control group of normal subjects. We used PA elastance index (PAEi) as a measure of PA vascular function. PAEi represents a lumped measure of the total “stiffness” of the arterial system and was calculated as a quotient of Doppler-derived PA systolic pressure and CMRI-derived RV stroke volume index.¹¹ We used CMRI-derived RV stroke volume instead of Doppler-derived RV stroke volume for the calculation of PA elastance because CMRI is the current gold standard for RV volumetric assessment, and the validity of Doppler-derived RV stroke volume in the TOF population has not been studied.^{12,13} In order to assess the feasibility of assessing RV stroke volume using Doppler echocardiography, we calculated Doppler-derived RV stroke volume and used the Doppler-derived RV stroke volume for the calculation of PAEi in a subgroup of patients with echocardiographic images of adequate quality (n=191 [92%]). The secondary objective was to determine the association between PAEi and exercise capacity measured by percent predicted peak oxygen consumption (VO₂). Exploratory analysis was performed to assess the relationship between PAEi and RV function (measured by CMRI-derived RV ejection fraction [RVEF]) and other indices of disease

severity (atrial arrhythmia and NT-pro-BNP [N-terminal B-type natriuretic peptide]). Atrial arrhythmia was defined as current or past history of atrial fibrillation and/or atrial tachycardia/flutter. Only NT-pro-BNP assays performed within 6 months from the time of CMRI and echocardiogram were used for analysis.

Echocardiography

Two-dimensional, M-mode, and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines.¹⁴ Doppler-derived RVSP was calculated using the Bernoulli equation.¹⁴ PA systolic pressure was calculated as the difference between Doppler-derived RVSP and pulmonary valve peak systolic gradient.

RVOT diameter and time velocity integral (TVI) were measured from the parasternal long-axis window. Offline measurements of RVOT diameter and TVI were performed in all patients with adequate echocardiographic images by an experienced sonographer (R.P.), and these measurements were repeated in a random sample of 50 patients by 1 of the investigators (A.C.E.) blinded to the initial measurement performed by the sonographer. Doppler-derived RV stroke volume was assessed using the hydraulic orifice formula (flow rate=cross-sectional area×flow velocity) and calculated as $0.785 \times (\text{RVOT diameter})^2 \times \text{RVOT TVI}$.¹⁴

Cardiac magnetic resonance imaging

The protocol for volumetric assessment using CMRI at this institution has been previously described.¹⁵ Briefly, all CMRI studies were performed on a 1.5-T system (Signa; GE Healthcare, Waukesha, WI) using an 8-element phased-array cardiac coil. Initial scout images were obtained, and this was followed by short-axis cine balanced steady-state free precession images obtained from the atrioventricular ring to the apex and then axial steady-state free precession images. RV and left ventricular volumes were obtained by manual tracing of endocardial borders from axial images at end-diastole and end-systole. RV stroke volume and ejection fraction were calculated from end-diastolic and end-systolic volumes. All volumetric data were indexed to the body surface area.

Statistical Analysis

Data were presented as mean±SD or number (%). Comparison between TOF patients and the control group were made using the Student *t* test for continuous outcomes and Pearson chi-squared tests for discrete outcomes. Simple linear regression was used to assess the association between PAEi and continuous measures such as peak VO₂, RVEF, and NT-pro-BNP. Simple logistic regression was used to assess the association between PAEi and categorical measures such as

atrial arrhythmia. Primary interest is in the association between PAEi and peak VO_2 ; therefore, to control for potential confounders of the relationship between PAEi and peak VO_2 , a multivariable linear regression model was constructed adjusting for atrial arrhythmia history, RVEF, severity of pulmonary regurgitation, TOF-PA diagnosis, age at TOF repair, and current age. These variables were chosen because of their known association with clinical outcomes in the TOF population. We also performed multivariable adjustments for the association between PAEi and other outcomes (atrial arrhythmia, NT-pro-BNP, and RVEF). Given that PA systolic pressure and PAEi are both measures of RV afterload, we assessed the relationship between PA systolic pressure and peak VO_2 using simple linear regression. Linear regression analyses were only performed in TOF patients. $P < 0.050$ was considered statistically significant. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Of 218 TOF patients with CMRI data, we excluded those who did not undergo echocardiogram on the same day ($n=8$) and those without Doppler assessment of RVSP ($n=3$). Among the 207 patients in the study, mean age at the beginning of the study was 33 ± 13 years; median age at time of TOF repair was 4 (2–7) years, and 42 (20%) patients had TOF with pulmonary atresia. Tables 1 and 2 show baseline clinical and hemodynamic characteristics of the cohort. There were 9 control subjects without structural heart disease who underwent same-day echocardiogram and CMRI as part of a different prospective study. Among these 9 control subjects, 8 had Doppler assessment of RVSP, and these 8 patients were selected as the control arm of this study. Mean age of the control group was 36 ± 4 years.

PA Vascular Function Indices and Exercise Capacity

Table 3 compares PA vascular function indices between TOF patients and the control group. The TOF group had higher PA systolic pressure (33 ± 5 versus 18 ± 2 mm Hg; $P=0.001$) and higher PAEi (0.62 ± 0.12 versus 0.48 ± 0.08 mm Hg/mL/m²; $P=0.001$). There was a good correlation between PAEi and peak VO_2 (adjusted $R^2=0.73$; $r=0.85$; $P < 0.001$) and a modest correlation between PA systolic pressure and peak VO_2 (adjusted $R^2=0.50$; $r=0.71$; $P < 0.001$; Figure 1). PAEi also had modest correlation with NT-pro-BNP (adjusted $R^2=0.58$; $P=0.024$) and atrial arrhythmia history (adjusted $R^2=0.61$; $P=0.017$). There was a poor correlation between PAEi and RVEF (adjusted $R^2=0.31$; $r=0.56$; $P=0.082$). After multivariate

Table 1. Baseline Characteristics of TOF Patients

Clinical variables	N=207
Age at beginning of study, y	33±13
Male (%)	87 (42)
Body mass index, kg/m ²	26±6
Body surface area, m ²	1.8±0.3
Age at TOF repair, y	4±2
Past palliative shunt (%)	85 (41)
TOF-pulmonary atresia (%)	42 (20)
Comorbidities (%)	
Atrial fibrillation	31 (15)
Atrial flutter/tachycardia	27 (13)
Hypertension	32 (16)
Hyperlipidemia	64 (31)
Coronary artery disease	9 (4)
Current or past smoker	39 (19)
Diabetes mellitus	27 (13)
Sleep apnea	36 (17)
Previous stroke	15 (7)
NYHA III/IV	28 (14%)
Heart rhythm (%)	
Nonsustained ventricular tachycardia	25 (12)
Sustained ventricular tachycardia	8 (4)
Laboratory tests	
Hemoglobin, g/dL	14.1±1.7
Creatinine, mg/dL	0.9±0.3
Medications (%)	
Diuretics	25 (12)
Beta-blockers	37 (18)
Calcium-channel blockers	6 (3)
ACEI/ARB	38 (18)
Aldosterone antagonist	1 (2)
Warfarin	11 (5)
Direct oral anticoagulants	6 (9)
Aspirin	45 (22)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; TOF, tetralogy of Fallot.

adjustment for atrial arrhythmia history, RVEF, severity of pulmonary regurgitation, TOF-PA diagnosis, age at TOF repair, and current age, there was an independent association between PAEi and peak VO_2 (adjusted $R^2=0.69$; $r=0.83$; $P < 0.001$). After multivariate adjustment for severity of pulmonary regurgitation, TOF-PA diagnosis, age at TOF repair, and current age, there was a poor correlation between PAEi and atrial arrhythmia adjusted ($R^2=0.21$; $P=0.031$), but no

Table 2. Noninvasive Hemodynamic Data of TOF Patients

Echocardiography	N=207 (%)
≥Moderate RV enlargement*	154 (77)
≥Moderate RV systolic dysfunction*	51 (25)
≥Moderate tricuspid regurgitation*	32 (21)
≥Moderate pulmonary regurgitation*	156 (76)
Severe pulmonary regurgitation*	129 (63)
Tricuspid regurgitation velocity, m/s	3.1±0.7
Pulmonary valve peak velocity, m/s	2.4±0.9
≥Moderate RA enlargement*	80 (39)
LA volume index, mL/m ²	29±12
RA pressure, mm Hg	8±4
TAPSE, cm	18±4
RV s', cm/s	10±2
RV end-diastolic area, cm ²	42±13
RV end-systolic area, cm ²	25±8
Fractional area change, %	39±9
Medial E, cm/s	10±4
Lateral E, cm/s	15±5
Medial E/e'	11±4
Lateral E/e'	8±3
LV end-diastolic dimension, mm	46±8
LV end-systolic dimension, mm	30±6
LV ejection fraction, %	58±9
LV mass index, mg/m ²	84±27
Relative wall thickness	0.39±0.08
CMRI	N=207
RVEDV index, mL/m ²	141±43
RVESV index, mL/m ²	79±38
RV stroke volume index, mL/m ²	59±20
RV ejection fraction, %	44±10
PR regurgitant volume index, mL/m ²	18±6
PR regurgitant fraction, %	31±7
LV stroke volume index, mL/m ²	41±11
LV ejection fraction, %	58±8
Cardiopulmonary exercise test	N=92
Peak VO ₂ , mL/kg/min	22±7
Peak VO ₂ , % predicted	64±18

Continued

Table 2. Continued

Cardiopulmonary exercise test	N=92
Peak heart rate, % predicted	82±13
VE/VCO ₂ nadir	27±4

E indicates mitral inflow early velocity; e', tissue Doppler early velocity; LA, left atrium; LV, left ventricle; PR, pulmonary regurgitation; quantitative assessment; RA, right atrium; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; s', tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot; VE/VCO₂, ventilatory equivalent for carbon dioxide; VO₂, oxygen consumption.

*Qualitative assessment.

significant correlations between PAEi and NT-pro-BNP ($P=0.112$) and between PAEi and RVEF ($P=0.463$).

Potential Effect of RVOT Obstruction

PA systolic pressure was calculated as the difference between Doppler-derived RVSP and pulmonary valve peak systolic

Table 3. Comparison of TOF Patients to the Control Group

Clinical variables	TOF (N=207)	Control (N=8)	P Value
Age, y	33±13	36±14	0.128
Body surface area, m ²	1.8±0.3	1.9±0.2	0.214
Echocardiographic data			
Heart rate, bpm	71±11	63±5	0.087
Fractional area change, %	39±9	41±3	0.022
TAPSE, cm	18±4	24±3	0.008
RV s', cm/s	10±2	14±2	0.029
Tricuspid regurgitation velocity, m/s	3.1±0.7	2.5±0.2	0.001
RA pressure, mm Hg	8±4	5±1	0.057
RVSP, mm Hg	48±9	31±3	<0.001
Pulmonary valve peak gradient, mm Hg	16±7	13±2	0.038
PA systolic pressure, mm Hg	33±5	18±2	<0.001
Magnetic resonance imaging data			
Heart rate, bpm	73±13	65±7	0.041
RVEDV index, mL/m ²	141±43	108±16	<0.001
RVESV index, mL/m ²	79±38	53±14	<0.001
RV ejection fraction, %	44±10	56±4	<0.001
RV stroke volume index, mL/m ²	59±20	41±4	<0.001

BPM indicates beats per minute; RA, right atrial; RVSP, right ventricular systolic pressure; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.

P are P values obtained from Student t tests comparing TOF patients to the control group.

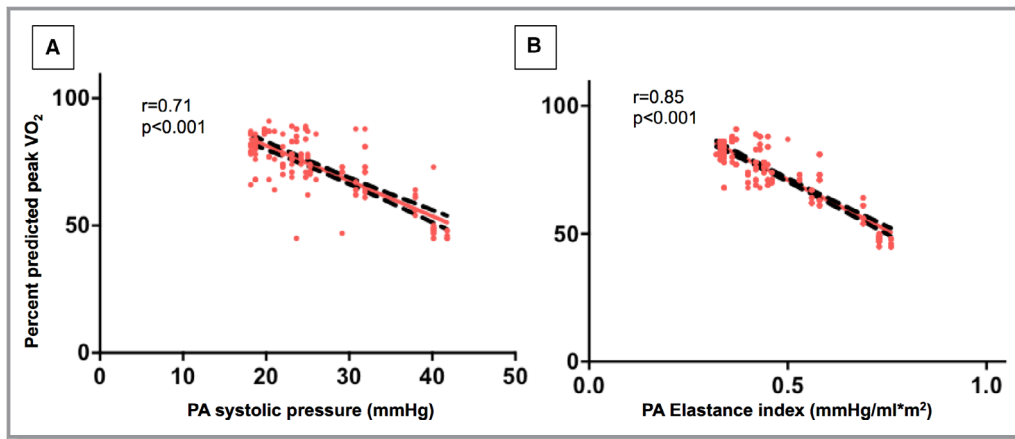


Figure. Unadjusted linear regression of peak oxygen consumptions (VO_2) on PA systolic pressure (A) and PA Elastance index (B). PA indicates pulmonary artery.

gradient, and this may potentially increase the margin of error in the assessment of PA systolic pressure. In order to correct for the assumptions inherent in the use of the simplified Bernoulli equation for assessment of RVOT gradient, we performed stratified analysis in patients with residual RVOT obstruction defined as pulmonary valve systolic gradient of >25 mm Hg (pulmonary valve peak systolic velocity, >2.5 m/s) versus patients without residual RVOT obstruction defined as pulmonary valve systolic gradient ≤ 25 mm Hg (pulmonary valve peak systolic velocity, ≤ 2.5 m/s). There was no significant difference in the calculated PAEI between the 2 subgroups (0.63 ± 0.11 [patient with residual obstruction] versus 0.61 ± 0.013 mm Hg/mL/m² [patient without residual obstruction]; $P=0.413$). There was a good correlation between PAEI and peak VO_2 in both subgroups (adjusted $R^2=0.71$; $r=0.84$; $P<0.001$ [for patient with residual obstruction] and adjusted $R^2=0.73$; $r=0.85$; $P<0.001$ [for patients without residual obstruction]; P interaction, $P=0.644$).

PAEI Assessment Using Doppler-Derived RV Stroke Volume

The assessment of Doppler-derived RV stroke volume was feasible in 191 (92%) patients, and in this patient subset, the mean RVOT diameter and TVI were 2.6 ± 0.4 and 26 ± 5 cm, respectively, in the TOF group. The interclass correlation for RVOT diameter was 0.87 (95% confidence interval, 0.81–0.94) and the interclass correlation for RVOT TVI was 0.88 (95% confidence interval, 0.80–0.95). Mean Doppler-derived stroke volume index was 46 ± 17 mL/m². PAEI calculated using Doppler-derived RV stroke volume was 0.73 ± 0.16 mm Hg/mL/m² and correlated with peak VO_2 (adjusted $R^2=0.66$; $r=0.81$; $P=0.004$). There was no significant difference in slope of the association between PAEI (calculated using CMRI-derived RV stroke volume) and peak VO_2 and PAEI (calculated

using Doppler-derived RV stroke volume) and peak VO_2 (P -interaction=0.218).

Discussion

In this study, we compared PA elastance between 207 TOF patients and 8 normal controls, and our results showed that TOF patients had higher PA elastance compared with the control group. PA elastance is a measure of arterial stiffness and afterload, and a high PA elastance suggests PA vascular dysfunction. An earlier necropsy study demonstrated extensive histological abnormalities in PA of patients with TOF, and these abnormalities were present even in newborns and fetuses.² Extent of PA histological abnormalities was more profound in older patients and in patients with history of palliative shunts. These findings suggest an underlying congenital malformation of the PA, which is exacerbated by hemodynamic injury over time. Clinical significance of these structural abnormalities has not been studied. The abnormal PA elastance noted in the current study suggests that these underlying histological abnormalities likely result in impaired PA vascular function.

We observed an association between PA elastance and exercise capacity in this study. High PA elastance, which is a measure of RV afterload, has been reported as an independent risk factor for exercise intolerance, heart failure, and mortality in patients with acquired heart disease.^{8–10} Clinical relevance of PA vascular function has not been studied in patients with TOF. Our results suggest that PA vascular function (as measured by PA elastance) may contribute to exercise intolerance in this population. In health, the PA will undergo physiological vasodilation during exercise in order to accommodate the obligatory exercise-induced increase in pulmonary blood flow. In the setting of PA vascular dysfunction, there is blunted PA vasodilation resulting in a higher RV

afterload for a given change in pulmonary blood flow.^{8–10} Our data suggest that the higher PAEi (a measure of PA vascular function) in TOF patients and the observed negative correlation between PAEi and exercise capacity may explain (to some extent) the problem of exercise intolerance in this population. We speculate that patients with abnormal PA elastance at rest may have impaired exercise-induced PA vasodilation resulting in a reduced exercise tolerance. Invasive and noninvasive hemodynamic cardiopulmonary exercise testing will be required to test this hypothesis by assessing exercise-induced changes in PA vascular function.

Clinical Implications and Future Direction

RV hypertension is a risk factor for mortality in TOF patients, and the most common cause of RV hypertension is RVOT obstruction based on data from previous studies.^{4,5} The current study shows that abnormal PA elastance, a lumped measure of RV afterload attributed to PA vascular and capillary function and left heart filling pressures, also contributes to RV hypertension in this population. RVOT obstruction can be treated by pulmonary valve replacement,¹⁶ but the appropriate therapies for PA vascular dysfunction, pulmonary vascular disease, and left ventricular diastolic dysfunction are less clear-cut. Pulmonary vasodilators and other novel therapies, such as inorganic nitrite and beta agonist, have been shown to be beneficial in patients with PA hypertension attributed to acquired heart disease, but these therapies have not been studied in patients with congenital heart disease.^{17–19} Further studies are required to delineate the underlying mechanism of PA vascular dysfunction and assess the role of conventional and novel medical therapies in disease modulation in this population.

Limitations

We studied TOF patients who underwent CMRI at a referral medical center leading to a selection bias. RV stroke volume and PA pressure assessments were not performed simultaneously, and changes in loading conditions could have affected our results. However, we controlled for this by studying only the patients who had both CMRI and echocardiogram on the same day. Although CMRI is currently used as the gold standard for RV volumetric assessment, the good correlation between PAEi (calculated using Doppler-derived RV stroke volume) and peak VO_2 show that PAEi may potentially be assessed with echocardiogram alone without need for CMRI. This will eliminate the problem of variation in loading conditions between tests. We did not have invasive hemodynamic data and as a result cannot determine how much of the high PA elastance was attributed to PA vascular dysfunction versus pulmonary

capillaries and left heart disease. Last, we acknowledge that the results of the current study may not be generalizable to all adult TOF patients because of the unique characteristics of the study cohort.

Conclusions

In this study, we demonstrated that TOF patients have elevated PA elastance, suggesting an underlying PA vascular dysfunction in this population. Although presence of PA histological abnormalities have been described in the TOF population, the observed elevation in PA elastance in this study suggests that these anatomical abnormalities may have functional significance manifesting as PA vascular dysfunction. Our results suggest that PA vascular dysfunction may contribute to exercise intolerance, which is an important clinical problem in this population. Further studies are required to validate our findings and explore potential therapies to improve PA vascular function in this population.

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Disclosures

None.

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