Assessment and Implications of Right Ventricular Afterload in Tetralogy of Fallot

Alexander C. Egbe, MD, MPH[a,*], Nathaniel W. Taggart, MD[b], Yogesh N.V Reddy, MBBS[a], Mahir Sufian, BS[a], Keerthana Banala, MD[a], Rahul Vojjini, MD[a], Maria Najam, MD[a], Karim Osman, MD[a], Masaru Obokata, MD[a], and Barry A. Borlaug, MD[a]

Patients with tetralogy of Fallot (TOF) have abnormal right ventricular (RV) afterload because of residual or recurrent outflow tract obstruction, often with abnormal pulmonary artery (PA) vascular function. The purpose of this study was to determine if RV afterload was independently associated with death and/or heart transplant in patients with TOF. This is a retrospective study of TOF patients that underwent cardiac catheterization for clinical indications at Mayo clinic between 1990 and 2015. Invasively measured RV systolic pressure (RVSP) was used to define RV afterload. To explore clinical utility for echocardiographic estimates of invasive data, correlations between invasive and Doppler-derived indices of RV afterload were examined. Among 266 patients with TOF (age 35 ± 14 years, TOF-pulmonary atresia 117 [44%]), RVSP was 72 ± 28 mm Hg, PA systolic pressure 45 ± 19 mm Hg, mean PA pressure 27 ± 10 mm Hg, pulmonary vascular resistance 4.2 ± 3.1 WU, and PA wedge pressure 14 ± 5 mm Hg. Over a mean follow up of 12.9 years, there were 35 deaths and 4 heart transplants. Invasively measured RVSP (hazard ratio 1.25, 95% confidence interval 1.12 to 1.37; p <0.001) and TOF-pulmonary atresia (hazard ratio 1.18, 95% confidence interval 1.08 to 1.41; p = 0.023) were independent risk factors for death and/or transplant. Doppler-derived RVSP was well-correlated with invasive RVSP (r = 0.92, p <0.001), and was also independently associated with the combined end point. RVSP, a composite measure of RV afterload, is independently prognostic in patients with TOF, and can be reliably assessed using Doppler echocardiography. Further study is required to test whether interventions to reduce RVSP can improve outcomes in patients with TOF. **(Am J Cardiol 2019;124:1780−1784)**

Congenital heart diseases represent another important cause of right-sided heart failure (RHF), and in these, tetralogy of Fallot (TOF) is one of the most common etiologies. Even after successful TOF repair, most patients display residual or recurrent hemodynamic lesions, the most common being chronic pulmonary regurgitation.[1] Right ventricular (RV) volume overload due to chronic pulmonary regurgitation causes RV dilation and dysfunction, leading to RHF and arrhythmias.[2,3] Surveillance typically of RV volume and systolic function assessments are important in TOF to determine the timing of intervention.[4−7] RV performance is highly sensitive to changes in afterload.[8] However, there are limited data regarding the impact of abnormal RV afterload on clinical outcomes after TOF repair.[8−10] Based on previous data about the prognostic implication of RV pressure overload in patients with acquired RHF, we hypothesized that high RV afterload would be independently associated with clinical outcomes in patients with TOF.

Methods

This a retrospective cohort study of patients (age ≥18 years) with repaired TOF that received care at Mayo Clinic Rochester, Minnesota from January 1, 1990 through December 31, 2015. Only patients that had right and/or left heart cardiac catheterization and echocardiogram performed within 48 hours between tests were included in this study. Patients with additional sources of pulmonary blood supply such as aortopulmonary collateral arteries were excluded. The Mayo Clinic Institutional Review Board approved this study.

The primary study objective was to determine whether invasively measured RV afterload was independently associated with death and/or heart transplant. RV afterload is the total pressure load on the RV in each cardiac cycle, and it is a composite of pressure load from right ventricular outflow tract obstruction (RVOT) obstruction, pulmonary artery (PA) vascular function, pulmonary vascular resistance, and left heart filling pressure. For the purpose of this study, we used invasively measured RV systolic pressure (RVSP) as the index of RV afterload. We subdivided the cohort into patients with versus without significant RVOT obstruction defined as cath-derived peak-to-peak gradient greater than or less than 36 mm Hg, respectively. The secondary objective was to assess the correlation between invasive and noninvasively measured (Doppler-derived) indices of RV afterload.

Hemodynamic tracings, angiographic images and cardiac catheterization reports were reviewed. Cardiac output (pulmonary blood flow, CO) was determined by the Fick technique.[11]

[a]Department of Cardiovascular Medicine, Mayo Clinic Rochester, Minnesota; and [b]Division of Pediatric Cardiology, Mayo Clinic Rochester, Minnesota. Manuscript received July 18, 2019; revised manuscript received and accepted August 22, 2019.

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*Corresponding author: Tel: (507) 284-2520; fax: (507) 266-0103.

E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

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Effective RV stroke volume (SV_{eff}) was determined by the quotient of CO and HR. Pulmonary vascular resistance was calculated as the quotient of transpulmonary gradient and CO, and left heart filling pressure was assessed using PA wedge pressure. PA compliance was calculated as the quotient of SV_{eff} and PA pulse pressure (systolic minus diastolic). Total pulmonary resistance was assessed using the ratio of mean PA pressure and cardiac output (MPA/CO).

Two-dimensional, M-mode and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines.[12] Offline measurements of RVOT diameter and time velocity integral (TVI) were performed in all patients with adequate echocardiographic images by an experienced sonographer (RP), and these measurements were repeated in a random sample of 50 patients by one of the investigators (ACE) who was blinded to the initial measurement performed by the sonographer.

Doppler-derived RVSP was calculated using the Bernoulli equation.[12] Pulmonary vascular resistance was estimated using the ratio tricuspid regurgitation velocity^2/RVOT TVI, and left heart filling pressure was estimated as the ratio of mitral inflow early velocity and mitral annular tissue Doppler early velocity (E/e'), as previously described.[13,14] PA vascular function was assessed using Doppler-derived PA elastance which is a lumped measure of the total "stiffness" of the arterial system, and calculated as PA end-systolic pressure (PA systolic blood pressure × 0.9)/RV stroke volume index.[15,16]

Data are presented as mean ± standard deviation, median (interquartile range) or number (%). Unpaired *t* test, Wilcoxon rank sum test, or Chi-squared tests were used as appropriate to compare between-group differences. Cox regression was used to assess the relation between invasively measured RVSP and the end point of death and/or heart transplant. First, univariable analyses were performed using explanatory variables chosen *a priori* based on previously described risk factors for adverse outcomes in patients with TOF.[17–19] Then the variables with statistically significant association on univariable analysis were incorporated into the multivariable model. The association between variables and end point was expressed as hazard ratio (HR) and 95% confidence interval (CI).

Pearson correlation coefficient and Bland Altman analysis were used to assess the agreement between invasive and Doppler-derived indices of RV afterload. Intraclass correlation coefficient (ICC) was used to assess the interobserver agreements between measurements of RVOT diameter and TVI. A $p < 0.05$ was considered statistically significant. Receiver operating characteristic curves were used to determine the best cut-off point for medial and lateral E/e' that predicted elevated left ventricular filling pressure defined as PA wedge pressure >15 mm Hg. The predictive value of the different variables we compared using the area under the curve. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, North Carolina).

Results

Of 683 adult TOF patients, 269 underwent cardiac catheterization and 3 of these patients were excluded because of presence of aortopulmonary collateral arteries. Supplementary Tables 1 and 2 show comparisons of the clinical and hemodynamic characteristics of the patient with and without cardiac catheterization. Of the 266 patients, 175 (66%) met the study criterion for significant RVOT obstruction. Supplementary Table 3 shows a comparison of the invasive and noninvasive hemodynamics between patients with versus without significant RVOT obstruction. The indications for cardiac catheterization were RHF (volume overload) (n = 56), atrial arrhythmia (n = 53), exercise intolerance (n = 46), hypoxia (n = 9), abnormal/nondiagnostic echocardiographic data (n = 54), and preoperative evaluation previous cardiac surgery (n = 68). Some patients had more than one indication for cardiac catheterization. Table 1 shows the invasive hemodynamic data obtained at the time of cardiac catheterization.

Table 1
Invasive and noninvasive indices of right ventricular afterload

Catheterization	(n = 266)
Right atrial pressure (mm Hg)	11 ± 6
Right ventricular end-diastolic pressure (mm Hg)	15 ± 6
Right ventricular systolic pressure (mm Hg)	72 ± 28
Pulmonary artery systolic pressure (mm Hg)	45 ± 19
Pulmonary artery diastolic pressure (mm Hg)	13 ± 8
Mean pulmonary artery pressure (mm Hg)	27 ± 10
Pulmonary artery wedge pressure (mm Hg)	14 ± 5
Left ventricular end-diastolic pressure, mm Hg	16 ± 6
Mean left atrial pressure (mm Hg)	14 ± 4
Mean arterial pressure (mm Hg)	86 ± 14
Cardiac output (l/min)	4.2 ± 1.2
Cardiac index (l/min*m^2)	2.3 ± 0.7
Transpulmonary gradient (mm Hg)	13 ± 5
Pulmonary vascular resistance, index (WU*m^2)	7.6 ± 5.2
Total pulmonary resistance (mm Hg/L/min)	6.4 ± 2.3
Mixed venous saturation (%)	67 ± 9
Aortic saturation, %	96 ± 3
Echocardiography	
Tricuspid regurgitation velocity (m/s) [n = 212]	3.7 ± 0.8
Estimated right atrial pressure (mm Hg) [n = 212]	13 ± 4
Right ventricular systolic pressure (mm Hg) [n = 212]	81 ± 22
Right ventricular outflow tract diameter (cm) [n = 131]	2.8 ± 0.4
Right ventricular stroke volume (ml) [n = 131]	126 ± 39
Pulmonary artery systolic pressure (mm Hg) [n = 108]	44 ± 12
Pulmonary artery elastance (mm Hg/ml) [n = 108]	0.31 ± 0.18

The 266 patients who underwent catheterization were followed for 12.9 ± 7.3 years from the time of invasive study. During this period 35 (13%) patients died. Of the 35 patients that died, 27 patients had significant RVOT obstruction whereas 8 patients did not have significant RVOT obstruction. There was no significant difference in mortality between patients with versus without significant RVOT obstruction (8/91 [9%] vs 27/175 [15%], p = 0.129). Mean age at the time of death was 49 ± 14 years. Causes of death were end-stage RHF (n = 14), sudden cardiac death (n = 11), sepsis with multiorgan system failure (n = 3), postoperative death following cardiac surgery (n = 4), major bleeding event (n = 2), and unknown (n = 1). Four patients (2%) underwent heart transplant for end-stage RHF at a mean age of 51 ± 7 years. One of the patients that had heart transplant at age 55 years died 13 months later from multisystem organ failure due to rejection and sepsis.

Table 2
Univariable analysis of invasive RV afterload indices as risk factors for death and/or transplant

Variable	HR (95% CI)	p
Right ventricular systolic pressure (mm Hg)	1.44 (1.38-1.55)	<0.001
Pulmonary artery systolic pressure (mm Hg)	1.02 (1.00-1.03)	0.035
Mean pulmonary artery pressure (mm Hg)	1.03 (1.01-1.05)	0.003
Pulmonary vascular resistance index (WU*m^2)	1.07 (0.95-1.21)	0.236
Pulmonary artery wedge pressure (mm Hg)	1.07 (1.02-1.18)	0.013
Left ventricular end-diastolic pressure (mm Hg)	1.10 (1.04-1.15)	0.001

RVSP and other indices of RV afterload were associated with death and/or transplant on univariable analysis (Table 2). Table 3 shows multivariable analysis of the relation between invasive RVSP and outcomes. Invasively measured RVSP (HR 1.25, 95% CI 1.12 to 1.37, p <0.001) and TOF-pulmonary atresia diagnosis (HR 1.18, 95% CI 1.08 to 1.41; p = 0.023) were independent risk factors for death and/or heart transplant.

The mean RVOT diameter and TVI were 2.8 ± 0.4 cm and 24 ± 5 cm, respectively. The between-observer ICC for RVOT diameter was 0.86 (95% CI 0.81 to 0.93) and the ICC for RVOT TVI was 0.89 (95% CI 0.82 to 0.96). The mean Doppler-derived PA elastance was 0.31 ± 0.18 mm Hg/ml (PA elastance index 0.55 ± 0.21 mm Hg/ml*m^2) and mean Doppler-derived pulmonary vascular resistance (tricuspid regurgitation velocity^2/RVOT TVI) was 0.81 ± 0.55 (Table 1).

There was a good correlation between invasively measure RVSP and Doppler-derived RVSP (r = 0.92, p <0.001; Figure 1). The mean difference between Doppler-derived RVSP and invasively measured RVSP was +6 mm Hg, with 95% CI of agreement, −13 to +24 mm Hg (Figure 1). Doppler-derived RVSP was independently predictive of death and/transplant, though the point estimate was lower than for invasive RVSP (HR 1.08, 95 CI 1.02 to 1.22; p = 0.038).

Discussion

In this study of adults with previous TOF repair, we showed that elevated RVSP, a composite measure of RV afterload, was independently associated with death and heart transplant, whether assessed invasively or noninvasively. TOF patients usually display residual or recurrent right heart hemodynamic lesions, the most common being chronic pulmonary regurgitation. The deleterious effect of chronic pulmonary regurgitation on the RV is well studied, and pulmonary valve replacement, which mitigates RV volume overload, protects the RV from progressive hemodynamic deterioration.[2–7] Historically, the timing of pulmonary valve replacement has been based on RV volumes and systolic function, motivated by outcome data in previous studies.[18,20] The current data suggest that addition of RVSP to the latter indices will also be helpful in risk stratification and decision making regarding structural interventions.

RV afterload has different components, and a high RV afterload may be due to RVOT obstruction, abnormal PA vascular function, increased pulmonary vascular resistance, or left ventricular diastolic dysfunction.[8] All components of RV afterload were found to be elevated in patients with TOF in this study. The prognostic importance of RVSP in the current study is consistent with data from 2 previous studies.[18,20]

Although cardiac catheterization remains the gold standard of hemodynamic assessment, it is not suitable for

Table 3
Multivariable analysis of risk factors for death and/or transplant

	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
RV afterload				
Invasive right ventricular systolic pressure, mmHg	1.44 (1.38−1.55)	<0.001	1.25 (1.12−1.37)	<0.001
Clinical				
Age, years	1.86 (1.24−2.03)	0.002	1.16 (0.88−1.85)	0.097
Age at tetralogy of Fallot repair, years	0.98 (0.96−1.01)	0.132		
Tetralogy of Fallot-pulmonary atresia	1.29 (1.18−1.53)	<0.001	1.18 (1.08-1.41)	0.023
Prior palliative shunt	1.06 (0.61−1.85)	0.837		
Atrial fibrillation	1.84 (1.06−3.17)	0.029	1.45 (0.28−3.65)	0.418
Coronary artery disease	1.40 (0.26−2.47)	0.254		
Hypertension	1.47 (0.81−2.57)	0.192		
Creatinine, mg/dl	0.98 (0.61−1.87)	0.195		
Diuretics	1.25 (0.71−2.16)	0.441		
Beta and/or calcium channel blockers	1.66 (0.90−2.44)	0.269		
Nonsustained ventricular tachycardia	0.86 (0.48−1.51)	0.615		
QRS duration >180 ms	1.09 (0.68−1.98)	0.214		
Echocardiography				
≥Moderate right ventricular dysfunction	1.29 (0.97−1.61)	0.063		
≥Moderate RV enlargement	1.14 (0.48−3.61)	0.517		
Right ventricular s', cm/s	0.83 (0.56−2.75)	0.214		
Fractional area change, %	0.98 (0.94−1.01)	0.098		
Tricuspid annular plane systolic excursion, cm	0.87 (0.35−1.74)	0.417		
Left ventricular ejection fraction <50%	1.39 (1.08−2.31)	0.031	1.06 (0.71−1.85)	0.285

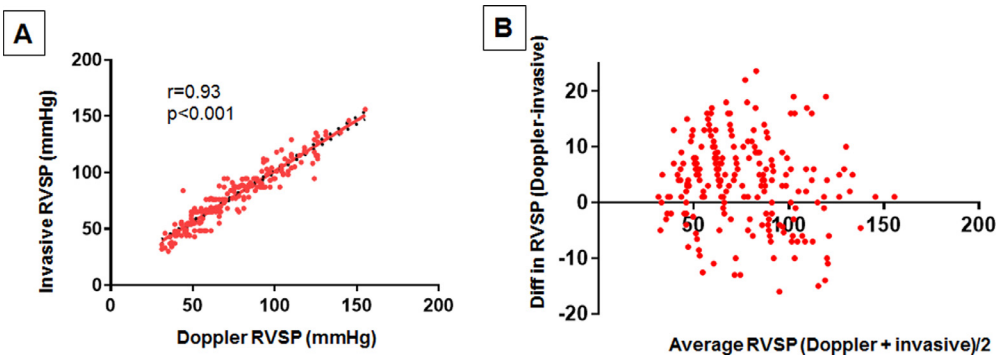

Figure 1. (*A*): Linear correlation of invasive right ventricular systolic pressure (RVSP) vs Doppler-derived RVSP. (*B*): Bland-Altman plot showing the mean difference between invasive RVSP and Doppler-derived RVSP. The mean difference was +6 (95% confidence interval of agreement, −13 to +24).

longitudinal monitoring and serial assessments. Doppler echocardiography provides robust noninvasive hemodynamic assessment and it is readily accessible and easy to perform.[12] We observed an excellent correlation between Doppler-derived RVSP and invasively measured RVSP, even though these assessments were not performed simultaneously (but were contemporaneous, within 48 hours). Importantly Doppler-derived RVSP was also independently associated with outcomes in our cohort, and as a result can be used for risk stratification and longitudinal monitoring.

The current data suggest that therapies to normalize (or at least reduce) RV pressure overload might reduce the burden of RHF and improve outcomes in patients with TOF. All components of RV afterload were abnormal in this study, and this may be related to congenital malformation of the PA as well as PA distortion and pulmonary capillary remodeling from previous palliative shunts.[9,10] Although RVOT obstruction can easily be addressed by pulmonary valve replacement, 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 acquired heart disease, but these therapies have not been studied in patients with congenital heart disease.[21−23] The prognostic importance of RV afterload in this study further highlights the knowledge gaps about the underlying mechanism and pathophysiology of this disease. There is need for more studies to better understand the effect of exercise on RV afterload since exertional fatigue and dyspnea are common symptoms in this population, and the potential role of conventional and novel medical therapies in disease modulation in this population. Such studies will guide clinical practice and intervention aimed at reducing long-term mortality and morbidity after TOF repair.

This study was based on a selected cohort of patients that underwent clinically indicated cardiac catheterization, and their clinical characteristics will likely differ from that of the general TOF population, hence limiting generalizability of ours results. Echocardiographic assessment of RV dimension and systolic function was not simultaneously performed at the time of cardiac catheterization, and change in loading condition is therefore a potential confounder. Notwithstanding these limitations, the study highlights the importance of RV hypertension on clinical outcomes, and also showed that Doppler echocardiography is a reliable tool for RV afterload assessment in this population.

Patients with TOF have abnormal RV afterload, and in this study we observed abnormal values of all components of RV afterload in our cohort. Invasively measured and Doppler-derived RVSP is prognostic, suggesting that these indices should be used for risk stratification and to guide treatment decisions in this population to mitigate or prevent development of RHF and improve outcomes.

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Disclosures

The author has no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.035.

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