Usefulness of Right Ventricular Volumetric and Afterload Indices for Risk Stratification in Patients With Tetralogy of Fallot

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Right ventricular (RV) volume overload due to chronic pulmonary regurgitation is the common mechanism for hemodynamic deterioration after tetralogy of Fallot (TOF) repair. As a result, RV volumetric indices are used for clinical risk stratification in this population. Since RV afterload is a determinant of RV hemodynamic performance, we hypothesized that afterload-adjusted RV volumetric indices will have a better correlation with disease severity compared with RV volumetric indices alone in patients with TOF. Cross-sectional study of adults with previous TOF repair that received care at Mayo Clinic, 2002-2015. We defined disease severity as atrial arrhythmia and/or impaired exercise capacity. We created afterload-adjusted RV volumetric indices by indexing these indices to RV systolic pressure (RVSP) as follows: RV end-diastolic volume (RVEDVi)/RVSP, RV end-systolic volume (RVESVi)/RVSP, and RV ejection fraction (RVEF)/RVSP. The RV volumetric indices were: RVEDVi 141 ± 43 ml/m^2, RVESVi 79 ± 38 ml/m^2, and RVEF 44 ± 10%, and RVSP was 48 ± 9 mm Hg. RVESVi was the only RV volumetric parameter that was associated with disease severity (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.01 to 1.32, p = 0.041) with area under the curve (AUC) of 0.612. In contrast RVEF/RVSP (OR 0.73, 95% CI 0.38 to 0.92, p = 0.037, AUC 0.649), and RVESVi/RVSP (OR 1.28, 95% CI 1.14-1.55, p = 0.008, AUC 0.798) were associated with disease severity. Compared with RV volumetric indices alone, the combined RV volumetric and afterload indices had better correlation with disease severity as measured by AUC. Afterload-adjusted RV volumetric indices had better correlation with disease severity, and may potentially improve risk stratification in this population. **(Am J Cardiol 2019;124:1293−1297)**

Right ventricular (RV) systolic dysfunction due to chronic pulmonary regurgitation is the most common pathway that ultimately leads to cardiovascular mortality in patients with tetralogy of Fallot (TOF). As a result, pulmonary valve replacement is the preferred therapy to prevent irreversible RV dysfunction due to chronic volume overload.[1,2] Cardiac magnetic resonance imaging (CMRI) is the gold standard for RV volumetric assessment because the complex geometry of the RV limits the use of echocardiography for volumetric assessment, and also because the predominant lesion is regurgitation and hence pressure overload is not considered a significant problem.[3,4] Afterload is an important determinant of systolic function, and the RV is sensitive to changes in afterload.[5] Several studies in patients with heart failure due to acquired heart disease have shown that RV pressure afterload is an independent predictor of RV hemodynamic performance and clinical outcomes.[6−8] Similarly, a few studies suggest that RV afterload may be prognostic in the TOF population.[9,10] Based on these data that support the importance of RV afterload, we hypothesized that the combination of RV volumetric and afterload indices will have a better correlation with disease severity compared with RV volumetric indices alone in patients with TOF.

Methods

This a retrospective study of patients (age ≥18 years) with repaired TOF that underwent CMRI at Mayo Clinic Rochester, Minnesota from January 1, 2002 through December 31, 2015. Only patients that had CMRI and transthoracic echocardiogram on the same day were selected for the study. From this cohort we excluded patients without Doppler assessment of right ventricular systolic pressure (RVSP). The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization.

The purpose of this study was to test the hypothesis that combined RV volumetric and afterload indices have a better correlation with disease severity compared with RV volumetric indices alone in patients with TOF. To test this hypothesis, first we assessed the relationship between RV volumetric indices and disease severity. Next, we assessed the relationship between combined RV volumetric and

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afterload indices and disease severity. We then compared the ability of RV volumetric indices alone vs combined RV volumetric and afterload indices to predict disease severity.

For the purpose of this study, we defined disease severity as the occurrence of atrial arrhythmia and/or impaired exercise capacity. Atrial arrhythmia was defined as a history of atrial fibrillation, atrial flutter or atrial tachycardia. Impaired exercise capacity was defined as percent predicted peak oxygen consumption <50%. We only analyzed data from symptom-limited cardiopulmonary exercise testing using treadmill ergometer performed within 6 months from the time of CMRI. The protocol for cardiopulmonary exercise testing at this institution has been described.[11,12]

CMRI was used for RV volumetric assessment, and the detailed protocol for performing CMRI at this institution has been described.[13] RV end-diastolic volume indexed to body surface area (RVEDVi) and RV end-systolic volume indexed to body surface area (RVESVi) was obtained by manual tracing of endocardial borders from axial images at end-diastole and end-systole respectively. RV stroke volume and ejection fraction (RVEF) were calculated from these volumes as previously described.[13] We selected 3 CMRI-derived RV volumetric indices for this study, and these indices were RVEDVi, RVESVi, and RVEF.

Doppler-derived RVSP was used as a measure of RV afterload for the purpose of this study. Doppler-derived RVSP was calculated using the Bernoulli equation ([4 x tricuspid regurgitation velocity^2] + estimated right atrial pressure based on respirophasic changes of inferior venae cava dimension).[14] We created combined RV volumetric and afterload indices by adjusting the preselected RV volumetric indices for afterload as follows: RVEDVi/RVSP, RVESVi/RVSP, and RVEF/RVSP. In order to control for the effect of RV outflow tract obstruction, we performed a separate analysis is the subgroup of patients without RV outflow tract obstruction defined as pulmonary valve peak velocity <2.5 m/s.

Data were presented as mean ± standard deviation, median (interquartile range) or number (%). We assessed disease severity as binary outcomes, and the patients with atrial arrhythmia and/or impaired exercise capacity were coded as "yes" whereas the patients without atrial arrhythmia or impaired exercise capacity were coded as "no". Logistic regression was used to measure the association between RV volumetric indices (RVEDVi, RVESVi, and RVEF) and disease severity (occurrence of atrial arrhythmia and/or impaired exercise capacity). Receiver operator characteristic curves were constructed to determine the optimal cut-off point for the RV volumetric indices that predicted disease severity. Logistic regression and receiver operator characteristic curves were also used to measure the association between RV volumetric and afterload indices (RVEDVi,/RVSP, RVESVi/RVSP and RVEF/RVSP) and predict disease severity. The correlation between disease severity and RV volumetric indices vs the correlation between disease severity and combined RV volumetric and afterload indices were then compared using the area under the curve (AUC). A p <0.050 was considered statistically significant. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC).

Results

Out of 218 TOF patients with CMRI data, we excluded patients that did not undergo echocardiogram on the same day and patients without Doppler-derived RVSP data (n = 11). Based on these inclusion-exclusion criteria, we selected 207 patients for the study, and the mean age at the time of CMRI was 33 ± 13 years. The baseline clinical and hemodynamic characteristics of the cohort are shown in Tables 1 and 2.

There were 31 (15%) patients with history of atrial fibrillation and 27 (13%) patients with history of atrial flutter/tachycardia. Some patients had more than one type of atrial arrhythmia and altogether there were 41 (20%) patients with history of atrial arrhythmia. Cardiopulmonary exercise test data was available in 92 (44%) patients, and among these, 20 (22%) had impaired exercise capacity. Based on the predefined criteria for disease severity, there were 58 (28%) patients with atrial arrhythmia and/or impaired exercise intolerance.

The mean RV volumetric indices were RVEDVi 141 ± 43 ml/m^2, RVESVi 79 ± 38 ml/m^2, and RVEF 44 ± 10%, and RVSP was 48 ± 9 mm Hg. There was association between RVESVi and disease severity (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.01 to 1.32, p = 0.041) with AUC of 0.612. However, RVEDVi (OR 1.16, 95% CI

Table 1
Baseline characteristics

Variable	N = 207
Age at beginning of study (years)	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 (years)	4 (2-7)
Prior palliative shunt	85 (41%)
TOF-pulmonary atresia	42 (20%)
Atrial fibrillation	31 (15%)
Atrial flutter/tachycardia	27 (13%)
Hypertension	32 (16%)
Hyperlipidemia	64 (31%)
Coronary artery disease	9 (4%)
Current or prior smoker	39 (19%)
Diabetes mellitus	27 (13%)
Sleep apnea	36 (17%)
Prior stroke	15 (7%)
NYHA III/IV	28 (14%)
Nonsustained ventricular tachycardia	25 (12%)
Sustained ventricular tachycardia	8 (4%)
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%)

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

Table 2
Noninvasive hemodynamic data

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%)
RVSP (mm Hg)	48 ± 9
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**
RVEDVi, (ml/m^2)	141 ± 43
RVESVi, (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
Peak heart rate (% predicted)	82 ± 13
VE/VCO_2 nadir	27 ± 4

RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; LV = left ventricle; RA = Right atrium; LA = left atrium; TAPSE = tricuspid annular plane systolic excursion; RVSP = right ventricular systolic pressure; E = mitral inflow early velocity; e' = tissue Doppler early velocity; s' = tissue Doppler systolic velocity; Quantitative assessment; VO_2 = oxygen consumption; VE/VCO_2 = ventilatory equivalent for carbon dioxide; RVEDV = right ventricular end-diastolic volume indexed; RVESVi = right ventricular end-systolic volume indexed; PR = pulmonary regurgitation; LV = left ventricle.

0.53 to 2.38, p = 0.279), and RVEF (OR 0.98, 95% CI 0.61 to 2.34, p = 0.308) were not associated with disease severity.

The combined RV volumetric and afterload indices were RVEDVi/RVSP 3.1 ± 1.1, RVESVi/RVSP 1.8 ± 0.6, and RVEF/RVSP 1.0 ± 0.4. RVEF/RVSP was associated with disease severity (OR 0.73, 95% CI 0.38 to 0.92, p = 0.037, AUC 0.649), and RVESVi/RVSP was also associated with disease severity (OR 1.28, 95% CI 1.14 to 1.55, p = 0.008, AUC 0.798). There was no association between RVEDVi/RVSP and disease severity (OR 1.12, 95% CI 0.76 to 1.98, p = 0.136). Compared with RV volumetric indices alone, the combined RV volumetric and afterload indices (RVEDVi/RVSP, RVESVi/RVSP, and RVEF/RVSP) had better correlation with disease severity as measured AUC.

Of the 207 patients, 149 (72%) patients did not have RV outflow tract obstruction defined as pulmonary valve peak velocity <2.5 m/s. In this subgroup of patients, RVEF/RVSP (OR 0.71, 95% CI 0.32 to 0.95, p = 0.040, AUC 0.0.632), and RVESVi/RVSP (OR 1.24, 95% CI 1.11 to 1.57, p = 0.012, AUC 0.763) were also associated with disease severity.

Discussion

In this study, we reviewed the noninvasive hemodynamic and clinical data of 207 TOF patients, and our results show that combined RV volumetric and afterload indices had a better correlation with disease severity compared with RV volumetric indices alone. Of the 3 RV volumetric indices studied, only RVESV was associated with disease severity, in contrast to afterload-adjusted RVEF and RVESV that had better correlation with disease severity. Most of the outcomes studies have focused on RV volumetric indices for presurgical risk stratification in TOF patients with chronic pulmonary regurgitation.[1,2,15] Preoperative RVEF and RVESV have consistently been shown to be associated to postoperative RV reverse remodeling.[1,2,15−18] Unlike these previous studies, the current study showed that the integration of RV volumetric and afterload indices provides better risk stratification.

Studies from patients with heart failure due to acquired heart disease have consistently shown that pulmonary artery pressure, a measure of RV afterload, was associated RV hemodynamic performance, exercise capacity, heart failure symptoms, and mortality.[6−8] However, there are only a few studies that have assessed the effect of RV afterload on clinical outcomes in patients with TOF. In one of the studies, Valente et al[9] reviewed outcomes of 873 children and adults TOF patients, and reported that RVEF, Doppler-derived RVSP and RV hypertrophy (a secondary effect of chronic RV pressure overload) were risk factors for death and sustained ventricular tachycardia. Another study, which is a recent update from the same cohort, showed that preoperative Doppler-derived RVSP and RVEF were predictors of adverse outcome even after pulmonary valve replacement.[10]

Residual or recurrent RV outflow tract obstruction can occur after TOF repair.[19] RV pressure overload due to RV outflow tract obstruction is a known risk factor for adverse outcomes.[9,10] The current study showed that the relationship between RV afterload and disease severity was not limited to the patients with RV outflow tract obstruction but was also present in patients without RV outflow obstruction. This highlights the importance of the other components of RV afterload such as pulmonary artery elastance, pulmonary vascular resistance, and left heart filling pressure.

These proposed indices in this study may improve the current risk stratification models that are based predominantly on RV volumetric indices (preload) by adjusting for the effect of afterload. RV wall stress, which is conceptually tied to RV systolic dysfunction and myocardial injury, has a direct relationship with RV chamber dilation and afterload, and this is consistent with the results of this study.[20] RVSP is a routine Doppler parameter that is obtained as part of a comprehensive echocardiograpm.[14,21] It is easy to assess and is also highly reproducible.[14,21] As a result, the afterload-adjusted indices of RV volumetric assessment proposed in the current study should be easy to implement in clinical practice since it does not involve any additional tests.

TOF is not just a disease of the RV outflow tract but it can involve the pulmonary arteries and capillaries.[22,23] Patients with TOF can sometimes have left ventricular cardiomyopathy that can result in left ventricular diastolic dysfunction.[9] Additionally, previous palliative shunts and the effect of cyanosis before TOF repair can potentially affect pulmonary artery elastance and pulmonary vascular resistance.[22,23] All these factor can result in high RV afterload. The potential clinical and hemodynamic importance of RV afterload, demonstrated in the current study, calls for more in-depth invasive and noninvasive hemodynamic studies to better understand the different causes of RV pressure overload (in addition to RV outflow tract obstruction) and the potential therapies to address these problems. There is also a need for prospective cohort studies to determine whether medical and surgical interventions based on afterload-adjusted RV volumetric indices will lead to a reduction in cardiovascular mortality in TOF patients. Considering the relatively low annual cardiovascular mortality rate of about 1%,[9,10,24] such cohort studies will require very long follow-up (which is not ideal) or involve multi-center collaboration to increase sample size.

This is a retrospective single center study of patient with CMRI data, and is therefore prone to selection bias. The differences in the clinical characteristics of this selected cohort compared with the general TOF population may limit generalizability of the results of this study. Although we demonstrated an association between afterload-adjusted RV volumetric indices and disease severity indices, the cross-section design does not allow for any inference about causality.

Combined RV volumetric and afterload indices, that provides afterload-adjusted RV volumetric assessment, has a better correlation with disease severity compared with unadjusted RV volumetric indices. The novel indices proposed in the current study should be easy to implement in clinical practice since it does involve any additional tests. The potential importance of RV afterload on clinical outcomes, highlight the knowledge gaps about pulmonary vascular function in TOF patients. Further studies are required to better understand the role of pulmonary vascular dysfunction in disease progression, and potential benefits (or lack thereof) of performing medical and surgical intervention based on afterload-adjusted RV volumetric indices.

Disclosures

The authors have 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.2019.07.025.

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