Pathophysiologic and Prognostic Implications of Right Atrial Hypertension in Adults With Tetralogy of Fallot

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Background—Right atrial pressure (RAP), a composite metric of right ventricular diastolic function, volume status, and right heart compliance, is a predictor of mortality in patients with heart failure due to acquired heart disease. Because patients with tetralogy of Fallot (TOF) might have abnormal right atrial and ventricular mechanics caused by myocardial injury and remodeling, we hypothesized that RAP would be associated with disease severity and cardiovascular adverse events in this population.

Methods and Results—We performed a cohort study of adults with TOF who underwent right heart catheterization at the Mayo Clinic Rochester between 1990 and 2017. The objective was to determine the association between RAP and multiple domains of disease severity in TOF (percentage of predicted peak oxygen consumption, atrial or ventricular arrhythmia, and heart failure hospitalization), as well as cardiovascular adverse events, defined as sustained ventricular tachycardia, resuscitated or aborted sudden death, heart transplantation, or death. Among 225 patients (113 male; mean age: 39 ± 14 years), mean RAP was 10.7 ± 5.2 mm Hg and median was 10 mm Hg (interquartile range: 7−13 mm Hg). Increasing RAP was associated with atrial or ventricular arrhythmias (odds ratio: 5.01; 95% CI, 1.22−23.49; $P<0.001$), heart failure hospitalization (odds ratio: 1.47; 95% CI, 1.10−2.39; $P=0.033$) per 5 mm Hg, and worsening exercise capacity (peak oxygen consumption; $R^2=0.74$, $r=-0.86$, $P<0.001$). RAP was a predictor of cardiovascular adverse events (hazard ratio: 1.28; 95% CI, 1.10−1.47; $P=0.028$) per 5 mm Hg.

Conclusions—In symptomatic patients with TOF, increasing RAP correlates with multiple domains of disease severity (risk stratification) and predicts future cardiovascular events (prognostication). These data have potential clinical implications in the target population of symptomatic TOF patients. (*J Am Heart Assoc*. 2019;8:e014148. DOI: 10.1161/JAHA.119.014148.)

Key Words: diastolic dysfunction • exercise capacity • mortality • right atrial pressure • tetralogy of Fallot

C ongenital heart disease is an important but understudied cause of heart failure and arrhythmia, and tetralogy of Fallot (TOF) is one of the most common congenital heart disease diagnoses in adults.[1] Right ventricular (RV) systolic dysfunction frequently develops in adults with repaired TOF[2,3] and is one of the criteria used to guide the decision for pulmonary valve replacement.[4,5] RV systolic dysfunction in TOF is believed to be caused by cyanosis and RV pressure overload before TOF repair[6] and RV volume and/or pressure overload caused by residual or recurrent hemodynamic

lesions after TOF repair.[7] RV diastolic dysfunction typically precedes systolic dysfunction,[8,9] suggesting that this might be an earlier indicator for ventricular dysfunction, but the assessment of RV diastolic function is challenging, and there are no validated noninvasive indexes of RV diastolic function in the TOF population.

Although there are robust invasive and noninvasive hemodynamic studies of left ventricular (LV) diastolic function,[8,9] the prevalence and clinical implications of RV diastolic dysfunction based on invasive hemodynamic data have not been studied in adults with TOF. Right atrial pressure (RAP) is a composite metric of right heart function that is related to RV diastolic function, volume status, and right atrial (RA) compliance. Increased RAP is a predictor of mortality in patients with heart failure due to acquired heart disease.[10,11] It seems likely that TOF patients might have abnormal RA and RV mechanics caused by myocardial injury and remodeling because of prior surgical and ongoing hemodynamic insult, thus causing abnormal RAP. We hypothesized that RAP, as assessed by the gold standard of invasive hemodynamic assessment, would be associated with disease severity and cardiovascular adverse events in adults with TOF.

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Clinical Perspective

What Is New?

- Right atrial pressure is the main determinant of left heart filling pressures, and it correlates with disease severity and mortality in patients with tetralogy of Fallot.
- In tetralogy of Fallot patients with elevated pulmonary artery wedge pressure, right atrial pressure (and not pulmonary artery wedge pressure) was an independent predictor of cardiovascular adverse events.

What Are the Clinical Implications?

- Elevated right atrial pressure is a hemodynamic characteristic of patients at high risk for adverse outcomes and thus can potentially be used to guide therapy in this population.

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Methods

Patient Selection

The data that support the findings of this study are available from the corresponding author on reasonable request. This is a retrospective cohort study, and the target population is symptomatic patients with repaired TOF. The Mayo Clinic institutional review board approved this study and waived informed consent for patients who provided research authorization. The MACHD (Mayo Adult Congenital Heart Disease) Registry was interrogated to identify all adults (aged ≥18 years) with repaired TOF who underwent right heart catheterization at the Mayo Clinic Rochester (Minnesota) from January 1, 1990, through December 31, 2017. Patients with tricuspid valve prostheses were excluded.

Study End Points and Definitions

The primary study objective was to determine the association between RAP and disease severity indexes, assessed across 3 clinical domains: (1) aerobic capacity (percentage of predicted peak oxygen consumption [Vo_2]), (2) arrhythmias, and (3) heart failure hospitalization. Atrial/ventricular arrhythmia was defined as documented atrial fibrillation, atrial flutter/tachycardia, or nonsustained ventricular tachycardia.[12] Heart failure hospitalization was defined as admission for volume overload (pulmonary congestion and/or peripheral edema) requiring intravenous diuretics.[13] The secondary study objective was to determine the association between RAP and cardiovascular adverse events, defined as sustained ventricular tachycardia, resuscitated or aborted sudden cardiac death, heart transplantation, or all-cause mortality.

Exploratory analysis was performed to determine the correlation between RAP and echocardiographic indexes of RV diastolic function endorsed by the American Society of Echocardiography.[14] These indexes are (1) tricuspid inflow early diastolic velocity/tricuspid inflow late diastolic velocity (E/A), (2) tricuspid inflow early diastolic velocity/tricuspid annular tissue Doppler early systolic velocity (E/e′), (3) tricuspid inflow deceleration time (DT), and (4) inferior vena cava (IVC) size. We included only patients in sinus rhythm and had less-than-moderate tricuspid regurgitation for this exploratory analysis.

Cardiac Catheterization

All studies were performed with patients on chronic medications in the fasted state and mild sedation using 7-Fr fluid-filled catheters. Catheter position was confirmed by appearance on fluoroscopy, characteristic pressure waveforms, and oximetry. Systemic arterial pressures and saturations were assessed at the time of left heart catheterization or via femoral or radial arterial cannulation in patients who did not undergo concurrent left heart catheterization. Pressure measurements were recorded at end expiration and represent an average of 3 beats for patients in sinus rhythm and 5 beats for patients in atrial fibrillation.[15] Cardiac output was determined by the Fick technique using assumed O_2 consumption and directly measured O_2 contents in pulmonary and systemic circulations.[16] Total pulmonary resistance was calculated as mean pulmonary artery (PA)/pulmonary blood flow index, PA compliance index by the ratio of RV stroke volume index/PA pulse pressure, and pulmonary elastance by the ratio of PA systolic pressure/stroke volume index.[17,18] LV transmural pressure, which reflects the net distending pressure that favors LV filling, was calculated as PA wedge press minus RAP, given that RAP is an accurate estimate of pericardial pressure.[17,19] These variables were indexed to body surface area. Hemodynamic pressure tracings were recorded, digitized (240 Hz), and stored for offline analysis. Offline review of hemodynamic tracings, angiographic images, and cardiac catheterization reports were performed in all patients.

Echocardiography

Two-dimensional, M-mode, and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines,[14,20] and only echocardiograms performed within 7 days from the time of cardiac catheterization were analyzed for this study. Offline measurements of tricuspid inflow and tissue Doppler indexes (apical view) and IVC size (subcostal short axis) were performed in all patients by an experienced sonographer. Dilated IVC was defined as IVC >21 mm, and reduced collapsibility during inspiration was defined as <50% decrease in IVC diameter during inspiration.[14]

Outcomes Assessment

Percentage of predicted peak Vo_2 was assessed using upright treadmill cardiopulmonary exercise testing, with maximum effort defined as respiratory quotient >1.1.[21] All exercise tests were required to be performed within 6 months from the time of cardiac catheterization. Atrial/ventricular arrhythmia and heart failure hospitalization status were ascertained in 100% of patients as of December 31, 2017, using the date of the last clinic visit. All-cause mortality was ascertained using the Mayo Clinic registration database and Accurint, an institutionally approved location service, in 100% of patients as of December 31, 2017.

Statistical Analysis

Data are presented as mean±SD, median (interquartile range), or number (percentage). Between-group comparisons were performed using the Fisher exact test, *t* test, or Wilcoxon rank sum test, as appropriate. Linear regression analysis was used to assess the relationship between RAP and RV afterload indexes (PA elastance, capacitance, and total pulmonary resistance), LV transmural pressure, and peak Vo_2. We also used logistic regression and receiver operating characteristic curves to determine the optimal cutoff point of RAP that predicted a cardiovascular adverse event with the best sensitivity and specificity. For the exploratory analysis, logistic regression was used to assess the performance of the echocardiographic indexes of RV diastolic function to detect elevated RAP, defined as RAP >10 mm Hg. Cox regression was used to assess the correlation between RAP and cardiovascular adverse events, defined as sustained ventricular tachycardia, resuscitated or aborted sudden cardiac death, heart transplantation, or all-cause mortality. Schoenfeld residual was used to assess Cox proportional hazards assumptions.

All regression models were adjusted for age at the time of catheterization, age at the time of TOF repair, TOF–pulmonary atresia diagnosis, severity of RV systolic dysfunction, tricuspid regurgitation, and pulmonary regurgitation, using manual backward stepwise model selection based on likelihood ratio *P* value. These variables were chosen a priori because of

Table 1. Baseline Clinical Characteristics

	N=225	RAP ≤10 mm Hg (n=134)	RAP >10 mm Hg (n=94)	*P* Value
Age at beginning of study, y	34±16	33±12	35±13	0.136
Male	113 (50)	63 (47)	50 (53)	0.105
Age at TOF repair, y	6 (3–14)	5 (3–10)	7 (4–17)	0.092
Prior palliative shunt	141 (62)	78 (58)	63 (67)	0.412
TOF–pulmonary atresia	87 (39)	48 (36)	39 (41)	0.341
Transannular patch repair	122 (54)	74 (55)	48 (51)	0.534
Prior pulmonary valve replacement	161 (72)	92 (69)	69 (73)	0.348
Prior heart failure hospitalization	26 (12)	8 (6)	18 (19)	0.003
Loop diuretics	47 (21)	18 (13)	29 (31)	0.005
RAAS antagonist	56 (25)	22 (16)	34 (36)	<0.001
β-Blocker	35 (16)	12 (9)	23 (24)	0.004
Comorbidities				
Atrial fibrillation	63 (28)	21 (16)	42 (45)	<0.001
Atrial flutter/tachycardia	56 (25)	26 (19)	30 (32)	0.026
Chronic kidney disease	17 (8)	8 ()	9 (105)	0.323
Hypertension	71 (32)	37 (28)	34 (36)	0.481
Hyperlipidemia	95 (42)	49 (37)	46 (49)	0.287
Coronary artery disease	25 (11)	12 (9)	13 (14)	0.375
Current or prior smoker	45 (20)	22 (16)	23 (25)	0.346
Diabetes mellitus	33 (15)	8 (6)	25 (27)	<0.001
Obesity	52 (23)	28 (21)	24 (26)	0.219

Data are presented as mean±SD, median (interquartile range), or number (%). Chronic kidney disease is defined as stage ≥3 (creatinine clearance <60 mL/min). RAAS indicates renin–angiotensin–aldosterone system; RAP, right atrial pressure; TOF, tetralogy of Fallot.

known association with clinical outcomes in patients with TOF.[2,3,22] In addition, we adjusted for the effect of indication for cardiac catheterization, era effect, and pulmonary valve replacement during follow-up in the Cox regression model assessing the relationship between RAP and cardiovascular adverse events. The indication for cardiac catheterization was modeled as a categorical variable (preoperative evaluation versus others), and the procedure era was also modeled as categorical variable (before January 2004 versus others). Kaplan–Meier analysis was used to assess the relationship between RAP and cardiovascular adverse event, and between-group comparison was performed with a log-rank test. The time of cardiac catheterization was used as the baseline for time-to-event analyses. $P<0.050$ was considered statistically significant. All statistical analyses were performed with JMP software (v14.0; SAS Institute).

Results

Clinical and Hemodynamic Data

A total of 231 ambulatory patients with TOF underwent right heart catheterization within the study period. Six were excluded because they had tricuspid valve prostheses. The indications for cardiac catheterization were preoperative evaluation (n=134, 60%), congestive heart failure (n=46, 21%), arrhythmia (n=75, 33%), and aborted sudden cardiac death (n=4, 2%). Age at the time of cardiac catheterization was 39±14 years, and 87 patients (39%) had TOF–pulmonary atresia (Table 1).

Right Heart Filling Pressures

Mean RAP was 10.7±5.2 mm Hg, and median RAP was 10 mm Hg (interquartile range: 7–13 mm Hg; Table 2). There was good correlation between RAP and RV afterload, as measured by PA compliance, PA elastance, and total pulmonary resistance (Figure 1), but no correlation between RAP and RV outflow tract (RVOT) obstruction ($r=0.003$, $P=0.218$). Similarly, RAP correlated with LV transmural pressure and cardiac output (Figure 1). Because Fick-derived stroke volume measures the net stroke volume (forward minus regurgitant flow) rather than the total stroke volume, sensitivity analyses were performed in the subset of patients without significant pulmonary regurgitation (excluding moderate or greater pulmonary regurgitation), and these analyses demonstrated similar correlations.

RAP and Disease Severity Indexes

Of 225 patients, 95 (42%) experienced atrial/ventricular arrhythmias (63 with atrial fibrillation, 56 with atrial flutter/

Table 2. Invasive and Noninvasive Hemodynamic Data

	Results (N=225)
Echocardiography	
Moderate or greater tricuspid regurgitation*	51 (23)
Moderate or greater pulmonary regurgitation*	121 (56)
Moderate or greater RV enlargement*	161 (73)
Moderate or greater RV systolic dysfunction*	75 (34)
RVSP, mm Hg	64±23
Tricuspid regurgitation velocity, m/s	3.6±0.8
Assumed RAP, mm Hg	10±4
Pulmonary valve peak velocity, m/s	2.9±1.0
RA volume index, mL/m^2	59±22
Moderate or greater RA enlargement*	131 (59)
LA volume index, mL/m^2	31±8
Moderate or greater LA enlargement*	36 (16)
Medial E/e′	11±4
Lateral E/e′	7±3
LV ejection fraction, %	59±10
Catheterization	
RAP, mm Hg	10 (7–13)
RVEDP, mm Hg	14 (11–17)
RVSP, mm Hg	62 (50–86)
PA systolic pressure, mm Hg	41 (31–52)
PA diastolic pressure, mm Hg	11 (7–16)
Mean PA pressure, mm Hg	23 (17–30)
PAWP, mm Hg	14±5
PA compliance index, mL×m^{-2}/mm Hg	1.46 (0.94–2.07)
PA elastance index, mm Hg/mL×m^2	1.01 (0.72–1.58)
TPR index, mm Hg/L×min^{-1}	10.2 (7.2–14.3)
PVR, index, WU×m^2	3.6 (2.4–6.6)
LV transmural pressure, mm Hg	3 (2–5)
Cardiac index, L/min×m^2	2.3±0.7
MAP, mm Hg	86±15
Mixed venous saturation, %	69±8
Aortic saturation, %	96 (94–98)

Data are presented as mean±SD, median (interquartile range), or number (%). E indicates mitral inflow early velocity; e′, tissue Doppler early velocity; LA, left atrium; LV, left ventricle; MAP, mean arterial pressure; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure; TPR, total pulmonary resistance; WU, Wood units.
*Qualitative echocardiographic assessment.

tachycardia, and 50 with nonsustained ventricular tachycardia) during the follow-up period. RAP was associated with atrial/ventricular arrhythmia occurrence (odds ratio: 5.01; 95% CI, 1.22–23.49; $P<0.001$ per 5-mm Hg increase in RAP).

An exploratory analysis was performed to assess the correlation between RAP and ventricular arrhythmias. Again, we noted an association between RAP and ventricular arrhythmia occurrence (odds ratio: 3.22; 95% CI, 1.09–16.12; P=0.024 per 5-mm Hg increase in RAP). There were 26 patients (12%) with heart failure hospitalizations, and RAP was associated with heart failure hospitalization (odds ratio: 1.47; 95% CI, 1.10–2.39; P=0.033 per 5-mm Hg increase in RAP). Of the 128 patients (57%) with exercise test data, the mean peak Vo_2 and percentage of predicted peak Vo_2 were 21±6 mL/kg per minute and 62±15%, respectively. There was an inverse correlation between RAP and percentage of predicted peak Vo_2 (R^2=0.74, r=−0.86, P<0.001; Figure 2).

RAP and Cardiovascular Adverse Events

Mean follow-up from the time of cardiac catheterization was 7.3±5.8 years, yielding total follow-up of 1642 patient-years. In total, 97 patients (43%) underwent pulmonary valve replacement during follow-up. During this period, there were 28 cases of sustained ventricular tachycardia, 4 cases of aborted sudden cardiac death, 4 patients who underwent heart transplant, and 35 patients who died. The cause of death was end-stage heart failure (n=20), arrhythmic death (n=6), postoperative death after cardiac surgery (n=3), bleeding- or stroke-related death (n=1), malignancy (n=1), sepsis (n=1), and unknown (n=3). A cardiovascular adverse event end point occurred in 55 patients (24%), yielding an event rate of 3.2 per 100 patient-years.

The 10-year rate of freedom from cardiovascular adverse events was 74% for the entire cohort. RAP >10 mm Hg provided the best prediction of cardiovascular adverse events (area under the curve: 0.752; sensitivity: 74%; specificity: 76%). Patients with RAP >10 mm Hg had lower event-free survival compared with those with RAP ≤10 mm Hg (54% versus 85%, P<0.001; Figure 3). RAP was a statistically significant predictor of cardiovascular adverse events (hazard ratio: 1.28; 95% CI, 1.10–1.47; P=0.028; Table 3).
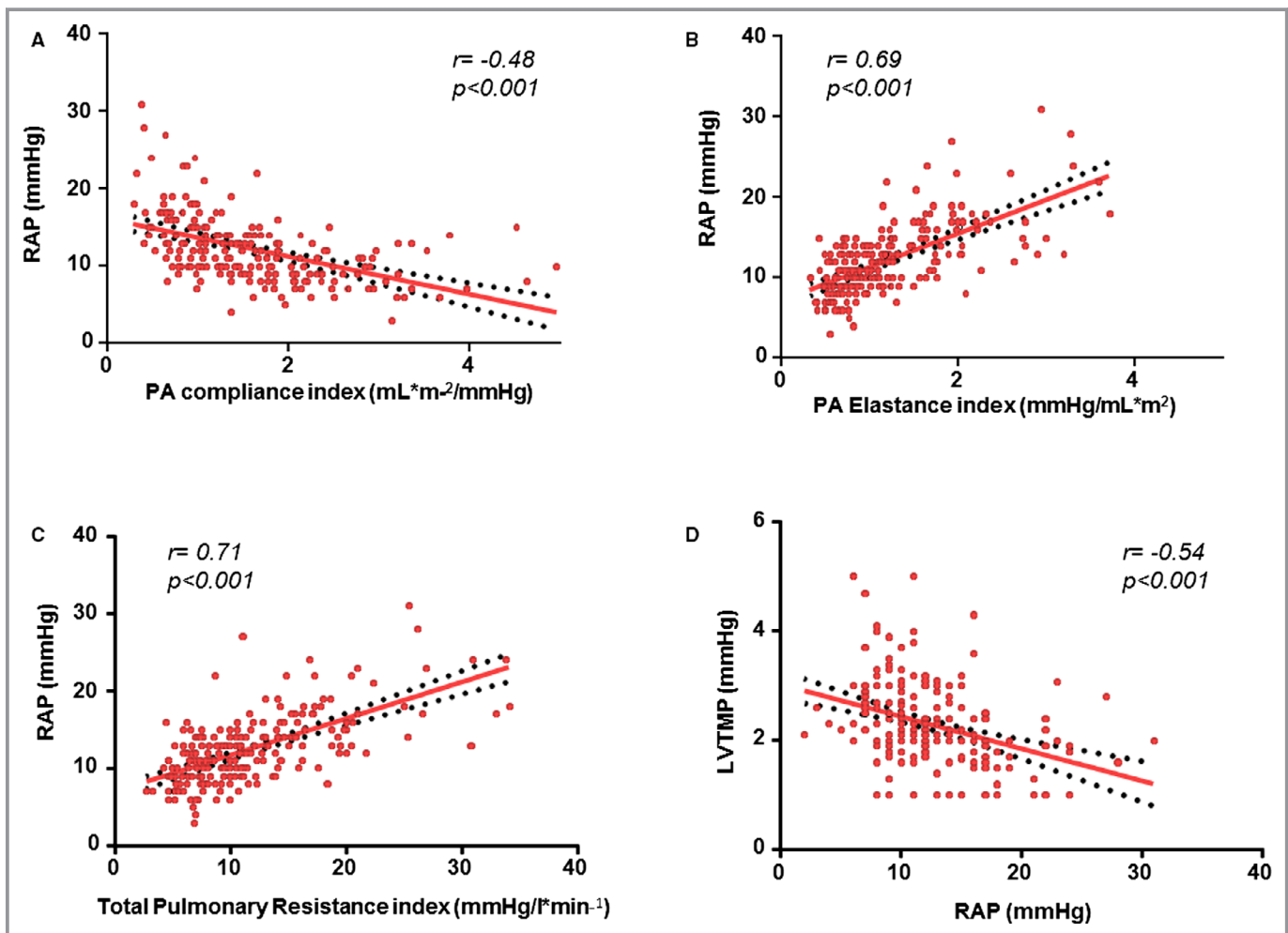
Figure 1. Linear regression of right atrial pressure (RAP) and pulmonary artery (PA) capacitance index (**A**), PA elastance index (**B**), total pulmonary resistance (**C**), and left ventricular transmural pressure (LVTMP) (**D**). Note that increase in PA elastance index and total pulmonary resistance denote increase in right ventricular (RV) afterload, whereas decrease in PA compliance denotes a decrease in RV afterload.
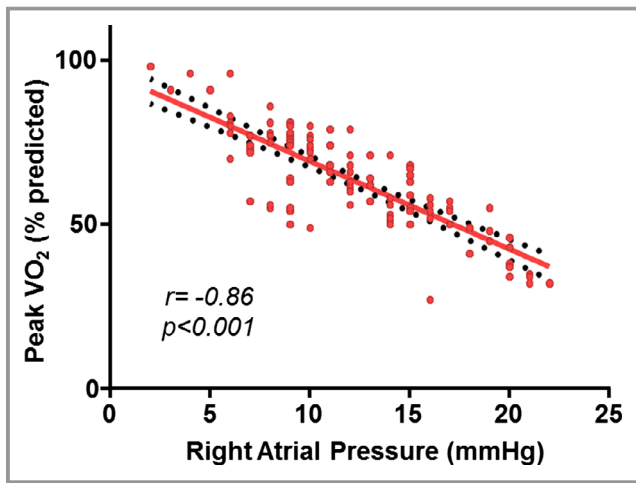
Figure 2. Linear regression of right atrial pressure and peak oxygen consumption (Vo_2).

Echocardiographic Predictors of RAP

Of the 231 patients in the study, 135 (58%) met the inclusion criteria for exploratory analysis, and the echocardiographic indexes of diastolic function are shown in Table S1. Of all diastolic function indexes assessed, IVC size and collapsibility provided the best detection of elevated RAP (RAP >10 mm Hg) based on area under the curve (Table S2). Dilated IVC had the best sensitivity to detect elevated RAP (sensitivity: 93%; specificity: 58%; area under the curve: 0.766), whereas dilated IVC with reduced inspiratory collapse had the best specificity to detect elevated RAP (sensitivity: 77%; specificity: 98%; area under the curve: 0.742).
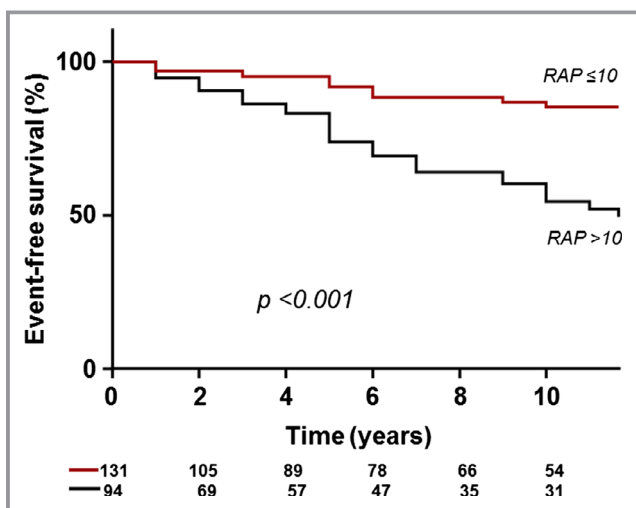
Figure 3. Kaplan–Meier analysis showing event-free survival. RAP indicates right atrial pressure.

Of the 129 patients with IVC size and collapsibility data, 44 (33%) had normal IVC size and collapsibility, 55 (41%) had dilated IVC or reduced collapsibility, and 36 (27%) had dilated IVC and reduced collapsibility, and median RAP was significantly different among the 3 groups: 6 mm Hg (interquartile range: 4–7 mm Hg), 9 mm Hg (interquartile range: 6–11 mm Hg), and 14 mm Hg (interquartile range: 12–16 mm Hg), respectively; $P<0.001$). Similarly, the 10-year event-free survival rate was significantly different among the 3 groups (88%, 64%, and 57%, respectively; $P<0.001$; Figure S1).

Discussion

In this study of symptomatic patients with TOF who underwent right heart catheterization, increasing RAP—an integrated measure of right heart compliance—was associated with worsening exercise capacity disease severity and cardiovascular adverse events. These data suggest that RAP can be used for risk stratification in symptomatic TOF patients and can have potential clinical implications regarding type and timing of intervention. Furthermore, assessment of IVC size and collapsibility can be used for noninvasive estimation of RAP and correlated with event-free survival.

The prevalence of RV diastolic dysfunction in the TOF population is unknown but is likely common considering the cumulative effect of myocardial injury caused by cyanosis before repair, hypoxic injury at the time of surgery, and residual or recurrent hemodynamic lesion after repair.[7] In a multicenter study of 556 adult TOF patients, RV diastolic dysfunction—defined based on tricuspid inflow and tricuspid annulus tissue Doppler indexes—was present in 52% of patients.[23] In a study of 38 TOF patients, Gatzoulis et al[24] defined restrictive RV physiology (advanced RV diastolic dysfunction) by the presence of diastolic forward flow in the PA during atrial systole. Based on this definition, the authors identified restrictive RV physiology in 53% of the participants. Subsequent studies using the same definition have reported restrictive RV physiology in 20% to 40% of TOF patients.[23–28] In contrast to prior studies that defined RV diastolic function on the basis of noninvasive indexes, the current study assessed right heart filling pressures in symptomatic TOF patients based on invasive hemodynamic data.

RAP and Prognosis

RAP correlated with exercise capacity, arrhythmias, and heart failure hospitalization, which are validated markers of cardiovascular disease severity.[21,29,30] RAP was also an predictor of all-cause mortality. Chronic pulmonary regurgitation is the most common hemodynamic lesion in the adult TOF population.[30] Consequently, current risk stratification indexes are

centered around RV volumetric assessment.[4,5] Some studies have demonstrated an association between RV afterload and mortality,[30] and thus the guidelines recommend RV systolic pressure as one of the criteria for RVOT intervention.[4,5] In contrast, the relationship among RV diastolic function, symptoms, and clinical outcomes has not been extensively investigated. The available literature on RV diastology has mostly centered on noninvasive markers of restrictive RV physiology,[23–28] but the correlation of these noninvasive indexes with invasive hemodynamic data has not been investigated in a robust way. The current study shows that right heart filling pressures, as defined by the gold standard of invasive hemodynamic assessment, correlated with current disease severity indexes and predicted future outcomes. This novel finding has potential clinical implications, such as improvement of the current risk stratification metrics, and provides a potential therapeutic target to improve outcomes.

Potential Mechanism for the Detrimental Effects of High RAPs

Unlike the intuitive chain of causality between RV systolic dysfunction and adverse outcomes, the relationship between RV diastolic dysfunction and adverse outcomes is less clear-cut. We postulate that high RAP in TOF reflects greater pericardial restraint from right heart overload, which is then coupled with reduction in LV transmural pressure. LV transmural pressure, which can be estimated as the difference between intracavitary LV pressure and pericardial pressure, more accurately reflects the distending pressure that determines true LV preload or end-diastolic volume.[17,19] RAP is a close estimate for intrapericardial pressure,[19] so as RAP increases at a given LV filling pressure,

there is progressive "underfilling" of the LV, which may impair stroke volume and cardiac output reserve according to the Frank-Starling principle. This may explain the robust relationship we observed between RAP and peak Vo_2; the latter is defined as the product of cardiac output and arteriovenous O_2 content difference, according to the Fick principle. We speculate that high filling pressures and cardiac output limitation in TOF patients with high RAP explain the reduced exercise capacity, arrhythmia, heart failure hospitalization, and cardiovascular adverse events observed in this study.

Clinical Implications and Future Directions

The current guideline recommendations for RVOT intervention are based on symptoms, RV volumes, RV ejection fraction, and the severity of RV outflow lesion.[4,5] The current study showed significantly worse outcomes in patients with high RAP (RV diastolic dysfunction and/or RA dysfunction) despite having similar severity of RVOT lesion (pulmonary regurgitation and stenosis). These data suggest that RAP might be considered when deciding on timing of RVOT intervention in patients with borderline indications for intervention, especially when symptoms (exercise intolerance, arrhythmia, and heart failure) seem disproportionate to the severity of RVOT lesion. Furthermore, RAP may also be considered during sudden death risk stratification because of its correlation with occurrence of ventricular arrhythmia occurrence.

It is important to highlight the lack of correlation between RAP and outflow tract obstruction, suggesting that the association between RAP and RV afterload is more likely due to pulmonary vascular dysfunction (both PA and capillaries) and left atrial hypertension. Therefore, in addition to identifying and

Table 3. Multivariable Predictors of Cardiovascular Adverse Events

	Full Model		Final Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
RAP (per 5 mm Hg)	1.34 (1.05–1.69)	0.035	1.28 (1.10–1.47)	0.028
Age at cardiac catheterization (per 1 y)	1.05 (1.01–1.07)	0.016	1.04 (1.01–1.07)	0.014
Age at TOF repair (per 1 y)	0.99 (0.97–1.01)	0.534	…	…
Indication for cardiac catheterization	1.17 (0.86–2.14)	0.133	…	…
Procedure era before 2004	1.08 (0.73–4.66)	0.234	…	…
PVR during follow-up	1.13 (0.64–3.55)	0.298	…	…
TOF–pulmonary atresia diagnosis	1.02 (0.56–1.79)	0.881	…	…
Moderate or greater RV systolic dysfunction	1.83 (0.95–3.53)	0.074	1.81 (1.00–3.04)	0.046
Moderate or greater tricuspid regurgitation	1.73 (0.84–3.84)	0.151	…	…
Moderate or greater pulmonary regurgitation	1.62 (0.48–2.52)	0.286	…	…

HR indicates hazard ratio; PVR, pulmonary valve replacement; RAP, right atrial pressure; RV, right ventricle; TOF, tetralogy of Fallot.

treating branch PA stenosis, the current data raise the possibility that medical therapies targeting the pulmonary vasculature tested in acquired heart diseases may also hold promise in TOF.[31–34]

Limitations

The current study was based on a selected cohort of patients who underwent cardiac catheterization, and this approach may limit the generalizability of the results. Although this study will not be appropriate for describing the prevalence of diastolic dysfunction, the clinical implications of RV diastolic dysfunction reported in this study are still pertinent when dealing with symptomatic patients. A disproportionately large number of patients had TOF–pulmonary atresia—more than would be expected in a contemporary TOF cohort. We adjusted for TOF–pulmonary atresia diagnosis in our statistical models, but this difference in population demographics may affect the gener-alizability of our results. Finally, our risk model was based on qualitative echocardiographic indexes of right heart function (RV dysfunction, tricuspid and pulmonary regurgitation) rather than quantitative cardiac magnetic resonance imaging data.

Conclusions

In adults with repaired TOF, increasing RAP correlates with worse exercise capacity and greater disease severity including arrhythmic burden and risk of heart failure and also predicts future cardiovascular adverse events. These data provide new insight in the pathophysiology of disease progression for symptomatic patients with TOF and can be used to improve risk stratification in this population.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Echocardiographic Indices of Right Ventricular Diastolic Function.

Indices	N	value
Tricuspid E, cm/s	103	58±19
Tricuspid A, cm/s	82	37±13
Tricuspid DT, ms	94	151±44
Tricuspid E/A	82	1.6±0.6
Tricuspid e', cm/s	114	9±5
Tricuspid E/e'	96	6±3
IVC size/collapsibility	129	---

N: Number of patients with variable assessed
IVC: Inferior vena cava; E: tricuspid inflow early velocity; A: tricuspid inflow late or atrial velocity;
e': tricuspid annular tissue Doppler early velocity; DT: Deceleration time

Table S2. Echocardiographic Predictors of RAP >10 mmHg.

	AUC	p
Tricuspid E, cm/s	0.516	0.611
Tricuspid A, cm/s	0.505	0.684
Tricuspid E/A	0.521	0.480
Tricuspid DT	0.529	0.285
Tricuspid e', cm/s	0.579	0.102
Tricuspid E/e'	0.624	0.014
Dilated IVC	0.766	<0.001
Dilated IVC +reduced collapse	0.742	<0.001

RAP: Right atrial pressure; AUC: Area under the curve

Figure S1. Kaplan Meier curves comparing event-free survival based on inferior vena cava size and collapsibility (IVC hemodynamics).