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ORIGINAL RESEARCH ARTICLE

Prognostic implications of inferior vena cava haemodynamics in ambulatory patients with tetralogy of Fallot

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Abstract

Aims Right atrial pressure (RAP) provides a composite measure of right ventricular diastolic dysfunction, right atrial compliance, and volume status, and these three variables are typically abnormal in adults with repaired tetralogy of Fallot (TOF). RAP is a well-established prognostic metric in patients with pulmonary hypertension, and recent data suggest that RAP is associated with clinical outcomes in TOF. The purpose of this study was to determine the role of inferior vena cava (IVC) haemodynamics (size and collapsibility) for the assessment of RAP and its potential application for risk stratification and prognostication in the TOF population.

Methods and results Adult TOF patients with echocardiographic assessment of IVC haemodynamics were divided into patients with (derivation cohort, n = 256) and without (validation cohort, n = 492) cardiac catheterization data. We assessed the correlation between IVC haemodynamics, RAP, and disease severity indices [arrhythmias, peak oxygen consumption (VO_2), and heart failure hospitalization] in derivation cohort and compared it with the correlations in the validation cohort. IVC haemodynamics correlated with RAP (r = 0.52, P < 0.001), with disease severity indices {atrial arrhythmias [area under the curve (AUC) 0.81], ventricular arrhythmias [AUC 0.67], heart failure hospitalizations [AUC 0.78], and peak VO_2 [r = 0.53]}, and with transplant-free survival in the derivation cohort. Similar correlations between IVC haemodynamics, disease severity indices, and transplant-free survival were also observed in the validation cohort.

Conclusions These findings suggest that IVC haemodynamics can potentially be used for risk stratification and prognostication in TOF patients and can complement the current risk models that are based predominately on right ventricular volumes and systolic function.

Keywords Tetralogy of Fallot; Right atrial pressure; Inferior vena cava; Right ventricular diastolic function; Clinical outcomes

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Introduction

Right heart failure is the most common cause of mortality in adults with tetralogy of Fallot (TOF).[1,2] The pathogenesis of right heart failure after TOF repair typically starts with chronic pulmonary regurgitation, which subsequently leads to right ventricular (RV) volume overload and dysfunction, arrhythmias, heart failure symptoms, and then cardiovascular death.[3,4] Pulmonary valve replacement is an effective therapy in this population, and the best outcome is achieved when it is performed at the onset of RV dysfunction, in order to prevent progressive RV dysfunction and cardiovascular death.[2,4,5] RV systolic function is routinely assessed in clinical practice, and it is a central metric in deciding on the timing of intervention.[4] RV diastolic function, an equally important component of right heart performance, is not often used in clinical decision-making in this population. This is because of the lack of validated metrics for the assessment of RV diastolic function and the conflicting data about the relationship between RV

diastolic function indices and clinical outcomes in the TOF population.[6,7]

Right atrial pressure (RAP) is a composite metric of right heart function and reflects RV diastolic function, right atrial (RA) compliance, and volume status.[8] RAP is a well-established prognostic metric, and it is routinely used to guide clinical decision-making in patients with pulmonary arterial hypertension and other acquired forms of heart failure.[8–10] Although the clinical utility of RAP has not been systematically explored in the congenital heart disease population, a recent study showed that invasively measured RAP correlated with disease severity and all-cause mortality in symptomatic TOF patients.[11] Right heart catheterization is not routinely performed in asymptomatic patients, thereby limiting the clinical application of this metric for risk stratification in ambulatory TOF patients.

The American Society of Echocardiography recommends the assessment of inferior vena cava (IVC) for the estimation of RAP.[12] However, the prognostic performance of non-invasively estimated RAP using the IVC has not been evaluated in the TOF population. Because RAP is a barometer of right heart function, and right heart function is the critical factor in the natural history of TOF, data about non-invasive assessment of RAP and its potential prognostic implications would be important for clinical practice. The purpose of this study was to determine the role of echocardiographic evaluation of IVC for the assessment of RAP and its potential application for risk stratification and prognostication in the TOF population.

Methods

Study population

This is a retrospective review of adult (age $\geq$ 18 years) TOF patients who underwent transthoracic echocardiogram at Mayo Clinic. The data were derived from the MACHD (Mayo Adult Congenital Heart Disease) Registry, which contains data of all adults with congenital heart disease who received care at the Mayo Clinic Enterprise from 1 January 1985 through 31 December 2018. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients who provided research authorization. Patients with inadequate echocardiographic assessment of the IVC and patients with tricuspid valve prostheses were excluded. We defined adequate IVC assessment as having 2D echocardiographic images of sufficient quality to measure IVC diameter throughout a full respiratory cycle on the same clip.

From this population, we identified patients who underwent right heart cardiac catheterization within 7 days from the time of baseline echocardiogram. The patients with right heart cardiac catheterization data were considered as the 'derivation cohort', while the rest of the patients constituted the 'validation cohort'.

Study design

We hypothesized that IVC haemodynamics (size and collapsibility) was a robust estimate of invasively measured RAP and that IVC haemodynamics correlated with disease severity indices and transplant-free survival in patients with repaired TOF. The primary study objective was to test this hypothesis in the derivation cohort using three methods: (i) assess the correlation between IVC haemodynamics and invasively measured RAP; (ii) compare the robustness of the correlation between RAP and disease severity indices vs. IVC haemodynamics and disease severity indices; and (iii) compare the robustness of the correlation between RAP and transplant-free survival vs. IVC haemodynamics and transplant-free survival.

The secondary objective was to assess the performance of IVC haemodynamics for risk stratification and prognostication in the validation cohort using these methods: (i) assess the correlation between IVC haemodynamics and disease severity indices at the time of baseline echocardiogram and (ii) assess the correlation between IVC haemodynamics and transplant-free survival during follow-up.

Assessment of inferior vena cava haemodynamics

Inferior vena cava haemodynamics was assessed using respirophasic changes in IVC diameter as stipulated in the American Society of Echocardiography guidelines for the assessment of right heart function.[12] Normal IVC haemodynamics was defined as IVC diameter $\leq$21 mm with $\geq$50% collapsibility during inspiration. Based on these criteria, we categorized all patients into three groups: (i) normal IVC haemodynamics; (ii) mild/moderately abnormal IVC haemodynamics defined as IVC size $>$21 mm or <50% collapsibility during inspiration; and (iii) severely abnormal IVC haemodynamics defined as IVC size $>$21 mm and <50% collapsibility during inspiration. Offline image analyses and measurements were performed by an experienced sonographer (R. P.). A random sample of 50 images for the derivation cohort and 100 images for the validation cohort was also reviewed by a second sonographer (J. W.) who was blinded to the assessment of the first sonographer.

Cardiac catheterization

All studies were performed on chronic medications in the fasting state and under mild sedation using 7 Fr fluid-filled catheters as previously described.[13] Pressure measurements were recorded at end expiration and represent an average

of 3 beats. Offline review of haemodynamic tracings, angiographic images, and cardiac catheterization reports was performed in all patients.

Outcomes assessment

We assessed disease severity using four indices as previously described[14]: (i) atrial arrhythmias were defined as atrial fibrillation, atrial tachycardia, or atrial flutter; (ii) ventricular arrhythmias were defined as sustained or non-sustained ventricular tachycardia; (iii) heart failure hospitalization was defined as hospitalization for volume overload requiring intravenous diuretics; and (iv) per cent predicted peak oxygen consumption (VO_2) was determined by cardiopulmonary exercise test. Heart transplant and death (all-cause mortality) were ascertained from the medical records and Accurint database in 100% of the patients as of 31 December 2018.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range), or count (%); χ^2 test, unpaired *t*-test, and analysis of variance test were used for between-group comparisons. The interobserver agreement between observer #1 (R. P.) and observer #2 (J. W.) was assessed using kappa coefficient (*k*). Multivariable linear regression analysis was used to assess the correlation between IVC haemodynamics and RAP. Logistic and linear regression analyses were used to assess the correlation between RAP and disease severity indices and between IVC haemodynamics and disease severity indices. Kaplan–Meier and Cox regression analyses were used for time-to-event analyses. In order to enable a direct comparison of the prognostic performance of RAP vs. IVC haemodynamics in the Cox model, we modelled RAP as categorical predictor variable using cut-off points that are known to be associated with clinical outcomes (RAP < 10, RAP 10–14, RAP > 14 mmHg).[11] Similar analyses were performed in the validation cohort. Model comparisons were performed using area under the curve (AUC) for logistic regression models, Meng test for linear regression models, and 95% confidence intervals (CIs) for Cox regression models.

All models were adjusted for age, age at TOF repair, sex, type of TOF repair (transannular patch repair vs. others), TOF–pulmonary atresia diagnosis, RV systolic dysfunction, tricuspid regurgitation velocity, tricuspid and pulmonary regurgitation severity, left ventricular ejection fraction, and QRS duration because of known association with clinical outcomes in this population.[1,14] We used manual backwards stepwise model selection based on likelihood ratio *P* value, with $P < 0.25$ required for entry and $P < 0.1$ required to remain in the model. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP software (version 14.1.0; SAS Institute Inc., Cary, NC).

Results

Derivation cohort

The derivation cohort was composed of 256 patients. The mean age at the time of baseline echocardiogram was 35 ± 11 years, age at the time of TOF repair was 5 (3–11) years, and 74 (29%) patients had transannular patch repair (*Table 1*). The indication for cardiac catheterization was for volume overload (*n* = 26), exercise intolerance (*n* = 72), atrial arrhythmias (*n* = 34), preoperative assessment (*n* = 104), and multiple indications (*n* = 20).

Inferior vena cava haemodynamics and right atrial pressure assessment

Of the 256 patients, 89 (35%) had normal IVC haemodynamics, 149 (58%) had mild/moderately abnormal IVC haemodynamics, and 18 (7%) had severely abnormal IVC haemodynamics. There was excellent interobserver agreement for IVC haemodynamic categories (*k* 0.93, 0.85–0.98). The median RAP was 10 (7–13) mmHg (*Table 1*). The median RAP was significantly different between the IVC haemodynamic categories, and the correlation coefficient between RAP and IVC haemodynamics was $r = 0.52$ ($P < 0.001$), suggesting a modest correlation between IVC haemodynamics assessed by echocardiography and invasively measured RAP (*Figure 1*).

Inferior vena cava haemodynamics and disease severity indices

Of the 256 patients, 84 (32%) had history of atrial arrhythmias, 51 (20%) had history of ventricular arrhythmias, and 31 (12%) had prior heart failure hospitalizations. Exercise test data were available in 112 (44%) patients, and the mean predicted peak VO_2 was 58 ± 15%. There was excellent correlation between invasively measured RAP and atrial arrhythmias (AUC 0.81) and modest correlations between RAP and ventricular arrhythmias (AUC 0.67), heart failure hospitalizations (AUC 0.78), and peak VO_2 ($r = 0.53$). We also observed an almost identical pattern of correlation between IVC haemodynamics and all domains of disease severity assessed, and there was no significant difference between invasive and non-invasively measured RAP and disease severity indices (*Table 2*). These correlation analyses suggest that IVC haemodynamics can be used as surrogate of invasive RAP, both for the estimation of right heart filling pressure and for risk stratification in this population.

Table 1 Baseline characteristics of derivation cohort (n = 256)

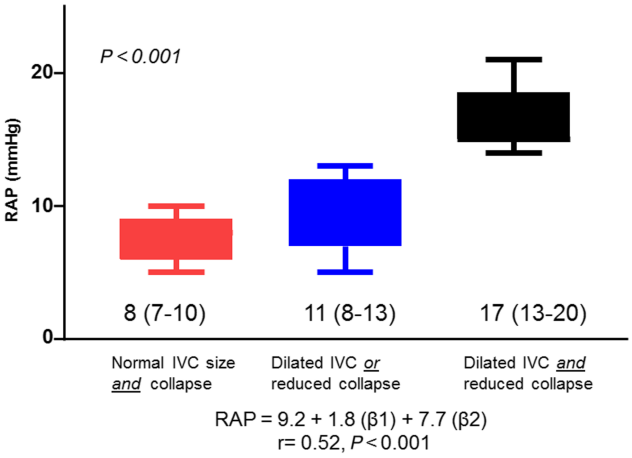
Age, years	35 ± 11
Male	138 (54%)
Body mass index, kg/m^2	25 ± 4
Body surface area, m^2	1.8 ± 0.3
Age at TOF repair, years	5 (3–11)
Prior pulmonary valve replacement	115 (45%)
Co-morbidities	
Atrial fibrillation	60 (23%)
Atrial flutter/tachycardia	56 (22%)
Diabetes mellitus	33 (13%)
Hypertension	62 (24%)
Coronary artery disease	19 (7%)
Chronic kidney disease	16 (6%)
Medications	
Loop diuretics	61 (24%)
RAAS antagonist	47 (18%)
Beta-blocker	41 (16%)
Echocardiography	
≥Moderate tricuspid regurgitation[a]	59 (23%)
≥Moderate pulmonary regurgitation[a]	146 (57%)
≥Moderate RV enlargement[a]	187 (73%)
≥Moderate RV systolic dysfunction[a]	80 (31%)
≥Moderate RA enlargement[a]	154 (60%)
RA volume index, mL/m^2	46 (29–78)
FAC, %	39 ± 11
RV s', cm/s	9 ± 2
TAPSE, mm	17 ± 4
RV systolic dysfunction[b] (n = 215)	161 (75%)
Tricuspid regurgitation velocity, m/s	3.6 ± 0.8
Pulmonary valve peak velocity, ms	2.8 ± 1.0
Left ventricular ejection fraction, %	57 ± 10
Cardiac catheterization	
RA pressure, mmHg	10 (7–13)
RV end-diastolic pressure, mmHg	14 (10–17)
RV systolic pressure, mmHg	62 (49–84)
PA systolic pressure, mmHg	39 (29–51)
PA diastolic pressure, mmHg	12 (8–16)
PA mean pressure, mmHg	23 (18–30)
PAWP, mmHg	13 (10–16)
Cardiac index, L/min/m^2	2.3 (1.9–2.8)

FAC, fractional area change; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; RA, right atrium; RAAS, renin angiotensin aldosterone system; RV, right ventricle; s', tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.
Chronic kidney disease was defined as stage ≥III (creatinine clearance <60 mL/min). Data were presented as mean ± standard deviation, median (interquartile range), or number (%).
[a]Qualitative echocardiographic assessment.
[b]RV systolic dysfunction based on quantitative assessment defined as FAC < 35% or s' < 10 cm/s or TAPSE < 16 mm.

Inferior vena cava haemodynamics and transplant-free survival

The median follow-up in the derivation cohort was 105 (33–189) months, and during this period, 36 (14%) patients died, and 5 (2%) patients underwent heart transplant. RAP was predictor of the endpoint of death/transplant (hazard ratio 1.38 per 5 mmHg increase in RAP, 95% CI 1.16–1.57, P = 0.014). Using RAP < 10 mmHg as the reference category, RAP 10–14 mmHg and RAP > 14 mmHg were associated with more than two-fold and three-fold increase in the risk of death/transplant, respectively. When we substituted IVC categories for RAP categories in the Cox model, severely abnormal IVC haemodynamics (but not mild/moderately abnormal IVC haemodynamics) was associated with risk of death/transplant (*Table* 3).

Figure 1 Box-and-whisker plot comparing right atrial pressure (RAP) between different inferior vena cava (IVC) categories in the derivation cohort. β1 represents mild/moderately abnormal IVC haemodynamics (dilated IVC or reduced collapse). β2 represents severely abnormal IVC haemodynamics (dilated IVC and reduced collapse).



Validation cohort

The validation cohort was composed of 492 patients. Supporting Information, *Table S1* shows a comparison of the clinical and echocardiographic characteristics of the derivation and validation cohorts. Compared with the derivation cohort, the patients in the validation cohort were younger, underwent TOF repair at an earlier age, had less co-morbidities, and had better right heart function.

Inferior vena cava haemodynamics and disease severity indices

Of the 492 patients in the validation cohort, 301 (58%) had normal IVC haemodynamics, 173 (35%) had mild/moderately abnormal IVC haemodynamics, and 18 (4%) had severely abnormal IVC haemodynamics. There was excellent interobserver agreement for IVC categories (k 0.94, 0.89–0.97). Compared with the derivation cohort, the validation cohort had less abnormal IVC haemodynamics and disease severity indices (Supporting Information, *Table S2*).

Mild/moderately abnormal IVC haemodynamics (dilated IVC or reduced inspiratory collapse) was associated with a higher risk of atrial arrhythmias and reduced exercise capacity. Severely abnormal IVC haemodynamics (dilated IVC and reduced inspiratory collapse) was associated with a higher risk of atrial arrhythmias, ventricular arrhythmias, and heart

Table 2 Comparison of robustness of disease severity models based on RAP vs. IVC in derivation cohort

	RAP	IVC	
	AUC (95% CI)	AUC (95% CI)	*P*
Atrial arrhythmia	0.81 (0.74–0.86)	0.80 (0.72–0.85)	0.6
Ventricular arrhythmia	0.67 (0.65–0.76)	0.68 (0.56–0.77)	0.8
Heart failure hospitalization	0.78 (0.67–0.86)	0.76 (0.66–0.84)	0.8
	r (*P* value)	*r* (*P* value)	Meng test *P*
Peak oxygen consumption	0.53 ($P < 0.001$)	0.51 ($P = 0.003$)	0.2

AUC, area under the curve; CI, confidence interval; IVC, inferior vena cava; *r*, correlation coefficient; RAP, right atrial pressure.

failure hospitalization (Supporting Information, *Table S3*). The strength of correlation between IVC haemodynamics and disease severity indices observed in the validation cohort was not significantly different from the correlation observed in the derivation cohorts (*Table 4*). Hence, IVC haemodynamics has a reproducible performance as a risk stratification metric in two different cohorts with significantly different clinical characteristics.

Inferior vena cava haemodynamics and transplant-free survival

The median follow-up in the validation cohort was 84 (19–136) months, and during this period, 40 (8%) patients died, and 1 (0.2%) patient underwent heart transplant. The 10-year survival was significantly different between the IVC haemodynamic categories (normal IVC haemodynamics 95%, mild/moderately abnormal IVC haemodynamics 83%, and severely abnormal IVC haemodynamics 49%, $P = 0.009$; *Figure 2*). Compared with patients with normal IVC haemodynamics, severely abnormal IVC haemodynamics was associated with more than three-fold increase in the risk of death/transplant (hazard ratio 3.84, 95% CI 1.08–28.6; *Table 4*).

Table 3 Multivariable Cox models for death/transplant in derivation cohort

	Death/transplant	
	HR (95% CI)	*P*
Model 1		
RAP 10–14 mmHg	2.89 (1.07–8.13)	0.037
RAP >14 mmHg	3.72 (1.31–10.8)	0.009
LV ejection fraction (per 5%)	0.78 (0.61–0.93)	0.018
≥Moderate RV systolic dysfunction	1.61 (1.00–2.85)	0.047
Age (per year)	1.05 (1.02–1.08)	<0.001
Age at TOF repair (per year)	1.04 (1.02–1.08)	0.001
Model 2		
Dilated IVC or reduced collapse	1.39 (0.67–4.16)	0.4
Dilated IVC and reduced collapse	3.22 (1.11–16.9)	0.002
LV ejection fraction (per 5%)	0.70 (0.55–0.89)	0.008
≥Moderate RV systolic dysfunction	1.65 (0.85–2.01)	0.093
Age (per year)	1.04 (1.01–1.09)	0.041
Age at TOF repair (per year)	1.02 (0.86–1.78)	0.086

CI, confidence interval; HR, hazard ratio; IVC, inferior vena cava; LV, left ventricle; RAP, right atrial pressure; RV, right ventricle; TOF, tetralogy of Fallot.
Model 1 is a multivariable model assessing the correlation between RAP categories and risk of death/transplant. Model 2 is a multivariable model assessing the risk of death/transplant using IVC categories instead of RAP categories.
Note: There was no significant difference in the models when substituting RV dysfunction based on quantitative echo assessment vs. using RV dysfunction based on qualitative assessment.

Discussion

Right heart failure due to RV systolic and diastolic dysfunction is the most common cause of cardiovascular mortality in patients with repaired TOF.[1,2] In contrast to the assessment of RV systolic function that is routinely performed in clinical practice, RV diastolic function assessment is challenging, because of the lack of validated diastolic function indices in patients with congenital heart disease. In this study, we showed that the assessment of IVC haemodynamics by echocardiography (size and collapsibility) is reproducible, correlates with invasively measured RAP, reflects current disease severity, and can predict transplant-free survival in two different TOF populations with significantly different clinical characteristics.

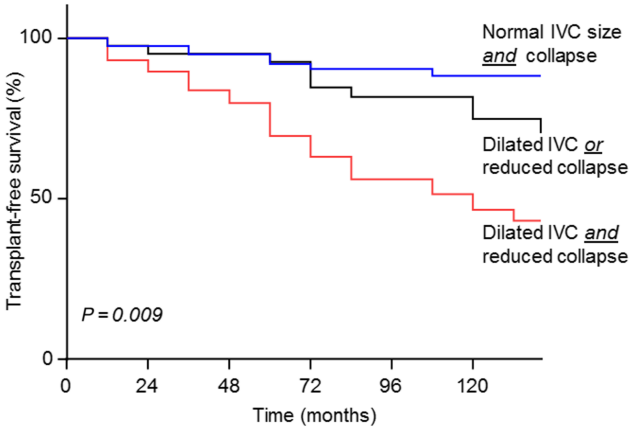
There are limited data about RV diastolic function assessment in the TOF population,[15–17] and the prevalence of RV diastolic dysfunction is estimated to be ~52% based on a

Table 4 Model comparison between derivation and validation cohorts

	Derivation	Validation	
	AUC (95% CI)	AUC (95% CI)	*P*
Atrial arrhythmia	0.80 (0.72–0.85)	0.79 (0.72–0.84)	0.8
Ventricular arrhythmia	0.68 (0.56–0.77)	0.67 (0.56–0.78)	0.9
Heart failure hospitalization	0.76 (0.66–0.84)	0.75 (0.64–0.84)	0.9
	r (*P* value)	*r* (*P* value)	Meng test *P*
Peak oxygen consumption	0.51 ($P = 0.003$)	0.48 ($P < 0.001$)	0.3
	Derivation HR (95% CI)	Validation HR (95% CI)	
Dilated IVC or reduced collapse	1.39 (0.67–4.16)	1.88 (0.72–5.47)	—
Dilated IVC and reduced collapse	3.22 (1.11–16.9)	3.84 (1.08–28.6)	—

AUC, area under the curve; CI, confidence interval; HR, hazard ratio; IVC, inferior vena cava; *r*, correlation coefficient

Figure 2 Kaplan–Meier curves comparing transplant-free survival between different inferior vena cava (IVC) categories in the validation cohort.



multicentre study of 556 TOF patients.[15] In that study, the diagnosis of RV diastolic dysfunction was based on tricuspid inflow and tricuspid annulus tissue Doppler indices, but these indices were not validated against invasive haemodynamic data.[15] Most of the literature about RV diastolic function assessment in the TOF population has centred on restrictive RV physiology, which is typically identified by the presence of diastolic forward flow in the pulmonary artery by Doppler assessment.[18–20] However, the relationship between restrictive RV physiology and disease severity indices such as arrhythmias, heart failure hospitalization, and exercise capacity reported in the literature is somewhat conflicting,[18–20] and this limits its clinical utility. In contrast to these previous studies, the current study took a different approach by evaluating right heart filling pressures (RAP), instead of RV diastolic function in isolation.

Right atrial pressure is determined by RV diastolic function, RA mechanical function, and volume status. TOF patients are likely to have abnormal RV and RA mechanics due to myocardial injury and remodelling because of prior surgical and ongoing haemodynamic insult and may also have abnormal volume status in the setting of chronic RV volume overload due to pulmonary regurgitation.[3] Therefore, RAP provides a composite metric of right heart function beyond what is measured by RV diastolic function indices alone. RAP is routinely used for prognostication in patients with heart failure due to acquired heart disease.[8–10] Concordant with the data from the acquired heart disease population, we observed a good correlation between RAP and all domains of disease severity evaluated in patients with repaired TOF. More importantly, we showed that the assessment of IVC size and collapsibility, which is part of routine echocardiographic assessment, provided a good estimate of RAP and also had comparable performance for risk stratification and prognostication as invasively measured RAP.

Clinical implications and future directions

Right ventricular volume overload due to chronic pulmonary regurgitation is the most common pathophysiologic pathway for RV systolic dysfunction, heart failure symptoms, and atrial/ventricular arrhythmias in patients with repaired TOF.[3] However, there is significant variation in how well patients tolerate RV volume overload, with some patient becoming very symptomatic (exertional symptoms and arrhythmias) even in the setting of relatively modest RV dilation and preserved RV systolic function.[21] We speculate that assessment of right heart filling pressure using IVC haemodynamics can help guide management in these patients because it provides complementary data beyond what is measured by cardiac magnetic resonance imaging (RV size and ejection fraction). In this subset of patients with symptoms out of proportion with the degree of RV dilation and systolic dysfunction, the presence of abnormal IVC haemodynamics should prompt referral for further and possible intervention if they have a target lesion or intensification of medical therapy in the absence of a target lesion.

Another important clinical implication of the current study has to do with the difference between the invasive correlate of normal IVC haemodynamics observed in TOF patients as compared with the thresholds recommended in the practice guideline.[12] In contrast to contemporary data showing that a normal IVC size with normal collapsibility typically corresponds to RAP of 5 (range 3–8), we observed that the median RAP in TOF patients with 'normal IVC haemodynamics' was 8 (range 7–10), which is above what is typically considered normal RAP. This suggests that any degree of IVC dilation or impaired collapsibility in a TOF patient should provoke concerns about abnormal right heart mechanics especially in a patient presenting with symptoms out of proportion to RV dilation, systolic dysfunction, or other associated lesions.

The results of the current study can also be used to improve the prognostic performance of the existing risk models. A recent multicentre study showed that the integration of cardiac magnetic resonance imaging-derived RV and left ventricular ejection fraction improved the predictive performance of the risk model that was originally proposed by Khairy *et al.*[22,23] While the current study did not assess the addictive benefit of integrating IVC haemodynamics into the existing clinical risk models, it sets the stage for further studies to bridge this knowledge gap. The assessment of IVC haemodynamics is already part of routine echocardiography and hence should be easy to integrate into clinical practice.

Limitations

This is a retrospective study. The current study was not based on simultaneously acquired echocardiographic and right heart catheterization data, and this may limit the internal

validity of the data because of potential differences in loading conditions at the time of both assessments. Because patients typically undergo cardiac catheterization in a fasting state, it is logical to speculate that the corresponding invasive RAP will even be higher for every IVC category if both assessments were performed simultaneously. Furthermore, the concordant data from the validation cohort of ambulatory patients, with significantly different clinical characteristics as compared with the derivation cohort, increase confidence about the external validity of the results of this study. Another limitation of the study was that cardiac magnetic resonance imaging data, which is the current gold standard for RV volumetric assessment, were not integrated in the risk models because they were not available in all patients.

Conclusions

The echocardiographic assessment of IVC haemodynamics is reproducible and correlates with invasively measured RAP in patients with repaired TOF. It also correlates with current disease severity across multiple domains and with the risk of mortality during follow-up. Putting all these together, the data suggest that IVC haemodynamics can potentially be used for risk stratification and prognostication in patients with repaired TOF because it provides complimentary haemodynamic data beyond what is measured during RV volumetric assessment. Further studies are required to determine if the integration of IVC haemodynamics as a complementary metric in the current clinical decision risk models will lead to improved outcomes.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of derivation and validation cohorts.
Table S2. IVC Hemodynamics and disease severity indices in derivation and validation cohorts.
Table S3. Multivariable models for the validation cohort.

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