IJC Heart & Vasculature 26 (2020) 100457

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Left ventricular filling pressure in Tetralogy of Fallot: Correlation between invasive and noninvasive indices

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ARTICLE INFO

Article history:
Received 6 September 2019
Received in revised form 16 November 2019
Accepted 16 December 2019

Keywords:
Tetralogy of Fallot
Left heart filling pressure
Pulmonary artery wedge pressure
Echocardiography

ABSTRACT

Background: Left heart filling pressures, as measured by pulmonary artery wedge pressure (PAWP), is associated with heart failure related mortality. Because of the prognostic importance of PAWP, several echocardiographic indices have been proposed for noninvasive assessment of PAWP. However, these indices have not been validated in the congenital heart disease population. The purpose of this study was to determine the correlation between echocardiographic indices of PAWP, and the effect of high PAWP on transplant-free survival in adults with tetralogy of Fallot (TOF).

Methods: Retrospective study of adult TOF patients that underwent cardiac catheterization at Mayo Clinic, 1990–2017. We selected these pre-defined set of echocardiographic indices of LV diastolic function: mitral valve early velocity (E), mitral valve early and late velocity ratio (E/A), mitral valve deceleration time (DT), mitral annular tissue Doppler early velocity (e′), and left atrial volume index (LAVI).

Results: Of the echocardiographic indices analyzed among 213 patients (age 37 ± 14 years), only E velocity ($\beta = 5.83$, standard error = 1.52, $p < 0.001$) and LAVI ($\beta = 0.14$, standard error = 0.05, $p = 0.007$) correlated with PAWP. LAVI > 28 ml/m^2 had sensitivity of 79% and specificity of 63% (AUC 0.712), and E velocity > 1.0 m/s had sensitivity of 66% and specificity of 89% (AUC 0.692), for detecting PAWP > 15 mmHg. LAVI > 28 ml/m^2 was associated with reduced 10-year transplant-free survival (49% vs 90%, $p < 0.001$).

Conclusion: This study supports the use of LAVI for noninvasive assessment of PAWP and for prognostication. Further studies are required to validate these results in a different population.

1. Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic heart disease, and it is one of the leading causes of heart failure in adults with congenital heart disease [1,2]. TOF is predominantly a right heart disease, and as a result most hemodynamic and outcomes studies have focused on the interaction between right heart hemodynamics and clinical outcomes [3–7]. Left heart filling pressure, as measured by pulmonary artery wedge pressure (PAWP) is a composite metric of left ventricular (LV) diastolic function, volume status, and left atrial compliance [8,9]. Elevated PAWP is a predictor of cardiovascular mortality in the acquired heart disease population [8,9]. A few studies that used LV end-diastolic pressure (LVEDP) as a measure of LV diastolic function have also shown that it is a predictor of outcomes in the TOF population [10].

The American Society of Echocardiography endorsed the use of echocardiographic indices such as mitral inflow early velocity and mitral annular tissues Doppler early velocity as noninvasive surrogates of PAWP [11]. However, the correlation between these echocardiographic indices and PAWP has not been studied in the TOF population. The purpose of this study was to determine the correlation between echocardiographic indices of left heart filling pressure and invasively measured PAWP.

2. Methods

2.1. Patient selection and study design

We identified patients (age ≥ 18 years) with repaired TOF that underwent right heart catheterization at Mayo Clinic Rochester,

Abbreviations: TOF, Tetralogy of Fallot; RV, Right ventricle; LV, Left ventricle; LVEDP, Left ventricular end-diastolic pressure; PAWP, Pulmonary artery wedge pressure; LAVI, Left atrial volume index; AUC, Area under the curve; E, mitral valve early velocity; DT, Deceleration time; e′, mitral annular tissue Doppler early velocity.

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https://doi.org/10.1016/j.ijcha.2019.100457
2352-9067/

Minnesota from January 1, 2004 through December 31, 2017. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization. We excluded patients with tricuspid and mitral valve prostheses, mitral valve stenosis, pulmonary vein stenosis and patients without assessment of PAWP.

The primary objective was to determine the echocardiographic predictors of PAWP, and the secondary objective was to determine the association between PAWP and transplant-free survival. For the purpose of this study, we assessed LV filling pressures using PAWP instead of LVEDP, because it has been shown to have better prognostic significance for heart failure related outcomes [8,12,13].

2.2. Echocardiographic assessment

Two-dimensional, M-mode and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines [11,14–16], and only echocardiograms performed within 7 days from the time of cardiac catheterization were analyzed for this study. The severity of tricuspid regurgitation, pulmonary regurgitation, right ventricular (RV) enlargement, and RV systolic dysfunction were graded as none/trivial, mild, mild-moderate, moderate, moderate-severe, and severe based on standard assessment by comprehensive echocardiogram [16].

We selected a pre-defined set of echocardiographic indices of LV filling pressure, based on the practice guidelines [11]. These variables were mitral valve early velocity (E), mitral valve early and late velocity ratio (E/A), mitral valve deceleration time (DT), mitral annular tissue Doppler early velocity (e'), and left atrial volume index (LAVI). LAVI was measured from 4- and 2-chamber views. Although the practice guidelines recommend the use of tricuspid regurgitation velocity as one the indices of LV filling pressures, we chose not to include it in our analysis because TOF is a predominantly right heart disease, and therefore tricuspid regurgitation velocity can therefore be affected by other factors such as RV outflow tract obstruction and pulmonary vascular disease.

2.3. Invasive hemodynamic assessment

All studies were performed 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 that 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 [17]. Cardiac output was determined by the Fick technique using assumed O_2 consumption and directly measured O_2 contents in the pulmonary and systemic circulations. 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.

2.4. Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range) or number (%). Linear regression was used to assess the correlation between PAWP and echocardiographic indices of left heart filling pressure. In order to account for the potential effect of LV systolic function on diastolic function assessment, separate linear regression analyses were performed for patients with normal LV systolic function defined as LV ejection fraction >50% [11].

We defined elevated left heart filling pressures as PAWP > 15 mmHg similar to the cut-off points used in the acquired heart disease population [9,18]. Receiver operator characteristic curves were used to determine the cut-off point for the echocardiographic indices to detect PAWP > 15 mmHg with the optimal balance between sensitivity and specificity. Transplant-free survival was assessed using the Kaplan Meier method, and log rank test was used for between-group comparison. A $p < 0.050$ was considered statistically significant. All statistical analyses were performed with JMP software (version 14.0; SAS Institute Inc, Cary NC).

3. Results

A total of 213 patients (males 105, 49%) met the inclusion criteria for the study, and the mean age at the time of cardiac catheterization was 37 ± 14 years, Table 1. The indicating for cardiac catheterization was because of heart failure with volume overload (n = 121, 57%), unexplained exertional dyspnea (n = 65, 31%), recurrent atrial arrhythmia (n = 6, 3%), and preoperative evaluation (n = 21, 10%). The mean PAWP was 14 ± 5 mmHg and LVEDP was 16 ± 5 mmHg. The echocardiographic indices for the cohort are shown in Table 2; mean E velocity was 1.03 ± 0.3 m/s, E/A was 0.6 ± 0.2 m/s, deceleration time was 178 ± 46 m/s, lateral e' velocity was 15 ± 4 m/s, and medial e' velocity was 12 ± 4 m/s. Although 60 (28%) patients had history of atrial fibrillation, only 12 patients were in atrial fibrillation at the time of echocardiography.

3.1. Determinants of LV filling pressures

Of the echocardiographic indices assess, only E velocity ($\beta = 5.83$, standard error = 1.52, $p < 0.001$) and LAVI ($\beta = 0.14$, standard error = 0.05, $p = 0.007$) were associated with PAWP, Table 3. A subgroup analysis performed in patients with preserved LV systolic function and in the 201 patients in sinus rhythm also showed that E velocity and LAVI were the only echocardiographic predictors of

Table 1
Baseline characteristics (n = 213).

Age, years	37 ± 14
Male	105 (49%)
Age at TOF repair, years	6 (3–14)
Prior palliative shunt	118 (55%)
TOF-pulmonary atresia	81 (38%)
Body mass index, kg/m^2	26 ± 7
Body surface area, m^2	1.9 ± 0.5
NT-Pro BNP	243 (95–806)
Creatinine, mg/dl	1.0 ± 0.2
Sodium, mg/dl	143 ± 9
Potassium, mg/dl	4.1 ± 0.2
Albumin, mg/dl	3.9 ± 0.1
Comorbidities	
Atrial fibrillation	60 (28%)
Atrial flutter/tachycardia	53 (25%)
Chronic kidney disease	16 (8%)
Hypertension	68 (32%)
Hyperlipidemia	91 (42%)
Coronary artery disease	24 (11%)
Current or prior smoker	40 (19%)
Diabetes mellitus	32 (15%)
Obesity	50 (23%)

TOF: Tetralogy of Fallot; Chronic kidney disease is defined as stage ≥ III (creatinine clearance < 60 ml/min).
.Data were presented as mean ± standard deviation, median (interquartile range) or number (%).

Table 2
Hemodynamic data.

Echocardiography	
Mitral E velocity, m/s	1.0 ± 0.3
Mitral A velocity, m/s	0.6 ± 0.2
Mitral deceleration time, ms	178 ± 46
Mitral E/A	1.7 ± 0.7
Medial e', cm/s	10 ± 3
Lateral e', cm/s	15 ± 4
Averaged e', cm/s	12 ± 4
Medial E/e'	11 ± 4
Lateral E/e'	7 ± 3
Averaged E/e'	8 ± 3
LA volume index, ml/m^2	32 ± 17
≥Moderate LA enlargement*	160 (21%)
≥Moderate aortic regurgitation*	11 (5%)
≥Moderate mitral regurgitation*	8 (4%)
Left ventricular ejection fraction, %	57 ± 9
≥Moderate tricuspid regurgitation*	8 (4%)
≥Moderate pulmonary regurgitation*	118 (58%)
≥Moderate RV enlargement*	154 (74%)
≥Moderate RV systolic dysfunction*	70 (33%)
RV systolic pressure, mmHg	63 ± 21
Pulmonary valve peak velocity, m/s	2.9 ± 1.0
Cardiac Catheterization	
RA pressure, mmHg	11 ± 5
RVEDP, mmHg	14 ± 6
RV systolic pressure, mmHg	62 ± 24
PA systolic pressure, mmHg	44 ± 19
PA diastolic pressure, mmHg	12 ± 7
PA mean pressure, mmHg	25 ± 11
PAWP, mmHg	14 ± 5
LVEDP, mmHg	16 ± 5
PVR index, WU*m^2	3.6 (2.4–6.6)
Cardiac index, L/min*m^2	2.3 ± 0.6
Mean arterial pressure, mmHg	87 ± 15
Mixed venous saturation, %	69 ± 7
Aortic saturation, %	96 ± 3

E: mitral inflow early velocity; A: mitral inflow late or atrial systolic velocity; e': tissue Doppler early velocity; LA: left atrium; RV: right ventricle; LV: left ventricle; RA: Right atrium; RVEDP: right ventricular end-diastolic pressure; LV: left ventricle; PA: pulmonary artery; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end-diastolic pressure; PVR: pulmonary vascular resistance.
*: qualitative echocardiographic assessment.
Data were presented as mean ± standard deviation, median (interquartile range) or number (%).

PAWP. LAVI > 28 ml/m2 had sensitivity of 79% and specificity of 63% (AUC 0.712), and E velocity > 1.0 m/s had sensitivity of 66% and specificity of 89% (AUC 0.692), for detecting PAWP > 15 mmHg.

3.2. LV filling pressures and prognosis

The mean follow-up from the time of cardiac catheterization was 7.1 ± 5.6 years, yielding a total follow-up of 1,591 patient-years. During this period, 4 patients underwent heart transplant and 32 patients died. The cause of death was end-stage heart failure (n = 18), arrhythmic death (n = 6), postoperative death after cardiac surgery (n = 3), bleeding/stroke related death (n = 1), malignancy (n = 1), sepsis (n = 1) and unknown (n = 2). The 10-year transplant-free survival was significantly lower in patients with PAWP > 15 mmHg (69% vs 86%, p = 0.005). Similarly the 10-year transplant free survival was significantly lower in patients with LAVI > 28 ml/m^2 (49% vs 90%, p < 0.001), Fig. 1. E velocity was not predictive of transplant-free survival.

4. Discussion

In this study, we demonstrated that of all the contemporary echocardiographic indices of LV diastolic function assessed, mitral E velocity and LAVI were the only indices that correlated with PAWP. E velocity > 1 m/s and LAVI > 28 ml/m^2 had a moderate discriminatory ability to detect PAWP > 15 mmHg. Similar to PAWP > 15 mmHg, LAVI > 28 ml/m^2 was associated with decrease transplant-free survival during follow-up. The results of the study showed that most of the echocardiographic indices endorsed by the practice guidelines [11] had very poor performance in the assessment of left heart filling pressures in the TOF population. This suggests that TOF patients may represent a unique population with different clinical and hemodynamic characteristics that deserves further exploration.

The American Society of echocardiography endorsed the use of echocardiography indices for noninvasive assessment of left heart filling pressures [11]. This is because elevated left heart filling pressure, which is one of the hallmarks of heart failure, is associated with heart failure related mortality [8]. The ratio of E and e' velocities >14 is associated with high PAWP [11]. Although there are robust data about noninvasive assessment of left heart filling pressures in the acquired heart disease population, there are limited data about invasive and noninvasive correlation of LV diastolic function in the congenital heart disease population [19]. In a study of 556 adults with repaired TOF, Aboulhosn et al. [19] defined LV diastolic dysfunction as mitral annular e′ < 10 cm/s and E/e′ > 9. Based on this defined, the prevalence of LV diastolic dysfunction was 14% in their study cohort. Although this robust multicenter study provided great insight about the prevalence of LV diastolic dysfunction in the TOF population, the definition of LV diastolic dysfunction in that study was based on arbitrary cut-off points, and these cut-off points were not validated against invasive hemodynamic data. In contrast, the current study was based on non-simultaneous correlation analysis of echocardiographic and cardiac catheterization data. Based on these correlation analyses, we observed that the contemporary indices such as E/e′ did not correlate with PAWP in the TOF population. In contrast, mitral E velocity and LAVI were the only non-invasive predictors of PAWP. More

Table 3
Univariate predictors of PAWP.

	All patients (n = 213)		Patients with LVEF ≥ 50% (n = 168)	
	β coefficient (SE)	p	β coefficient (SE)	p
Mitral E velocity, m/s	5.83 (1.52)	<0.001	6.22 (1.67)	<0.001
Mitral A velocity, m/s	1.70 (2.51)	0.499	1.44 (2.14)	0.243
Mitral deceleration time, ms	0.01 (0.01)	0.805	0.04 (0.06)	0.644
Mitral E/A	0.83 (0.57)	0.152	0.81 (0.44)	0.286
Medial e'	14.2 (18.6)	0.445	19.6 (18.9)	0.305
Lateral e'	−23.3 (16.4)	0.163	−16.2 (20.6)	0.437
Averaged e'	−6.34 (36.7)	0.813	1.94 (30.5)	0.945
Medial E/e'	0.21 (0.16)	0.191	0.07 (0.15)	0.628
Lateral E/e'	0.49 (0.24)	0.088	0.40 (0.31)	0.188
LA volume index, ml/m^2	0.14 (0.05)	0.007	0.09 (0.04)	0.033

PAWP: Pulmonary wedge pressure; RAP: Right atrial pressure; TOF: Tetralogy of Fallot; RV: Right ventricle; SE: standard error.

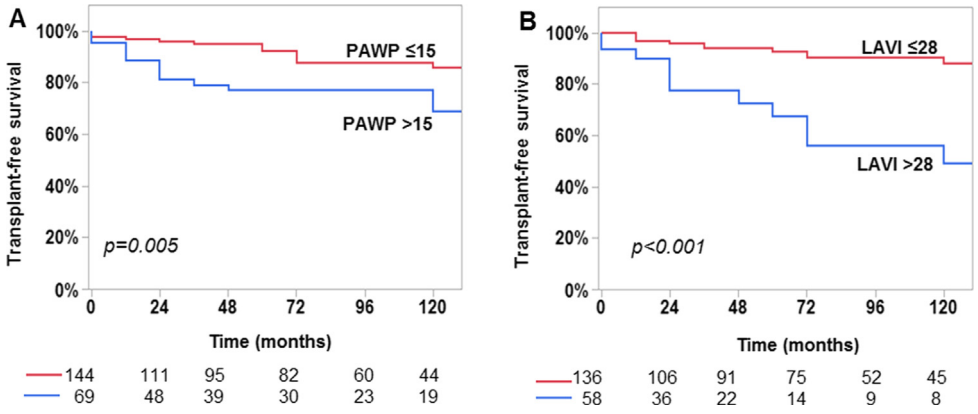

Fig. 1. Kaplan Meier curves comparing transplant-free survival. PAWP: Pulmonary artery wedge pressure; LAVI: Left atrial volume index.

importantly we observed that, LAVI, was also predictive of transplant-free survival similar to PAWP, suggesting that LAVI can potentially be used for prognostication. An interesting observation from this study was that the LAVI cut-off point that predicted increased filling pressure was 28 ml/m^2 which was still within limit of normal. We do not have a clear explanation for this but we speculate that this may be related to the young age of the cohort since older patients tended to have larger LAVI.

Although the current study does not provide explanation for the poor performance of the contemporary echocardiographic predictors of PAWP in the TOF population, we speculate that this may be related to differences in demographic characteristics. The data supporting the used of E/e' for noninvasive assessment of PAWP were derived for an older population with atherosclerotic cardiovascular disease risk factors [11]. In contrast, the mean age of the TOF patients in the current study was 37 years. Another potential explanation for the results of our study may related to the factors that TOF is right heart disease, and TOF patients sometimes have residual right heart hemodynamic lesions that may influence LV diastolic and systolic function. Right heart dysfunction can influence left heart diastolic and systolic function through ventricular-ventricular interaction.

4.1. Limitations

This study was conducted on a cohort of patients that had cardiac catheterization at a tertiary congenital heart disease center. As a result, the demographic, clinical, and hemodynamic characteristics of the study population may differ from that of the ambulatory TOF patients seen in other centers, hence limiting the generalizability of the results. Notwithstanding, the results of this study are still relevant in the management of symptomatic TOF patients. Another potential limitation of this study was the non-simultaneous acquisition of invasive and noninvasive hemodynamic indices. As a result, changes in loading conditions between echocardiogram and cardiac catheterization may introduce confounders.

5. Conclusions

Mitral E velocity and LAVI correlated with PAWP, and can be used to identify patients with high PAWP. Furthermore, LAVI was associated with transplant-free survival similar to invasively measured PAWP. The results of this study support the use of LAVI for noninvasive assessment of PAWP and perhaps for prognostication in patients with repaired TOF. Further studies are required to validate these results in a different population. Such studies should be based on simultaneous invasive and noninvasive hemodynamic assessment in order to minimize the confounding effect of changes in loading conditions.

Funding

Dr. Egbe is supported by National Heart, Lung, and Blood Institute (NHLBI) grant K23 HL141448-01.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100457.

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