Original Article

Prognostic Implications of Left Ventricular Cardiomyopathy in Adults With Tetralogy of Fallot

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ABSTRACT

Background: Despite the significant risk of cardiovascular mortality after tetralogy of Fallot (TOF) repair, there are limited data about left ventricular (LV) cardiomyopathy in this population, thus creating important knowledge gaps. This study aims to address some of these knowledge gaps by describing the risk and prognostic implications of LV systolic dysfunction (LVD) after TOF repair.

Methods: We performed a cohort study of adult patients after TOF repair with an echocardiographic assessment of LV ejection fraction (LVEF) to determine the association between LVD and cardiovascular events, defined as sustained ventricular tachycardia, aborted sudden death, heart transplantation, or death. Prevalent and incidence LVD were defined as LVEF < 50% at baseline or new decrease in LVEF to < 50% during follow-up, respectively.

RÉSUMÉ

Contexte : Malgré le risque important de mortalité cardiovasculaire après la réparation d'une tétralogie de Fallot, nous disposons de peu de données sur la cardiomyopathie ventriculaire gauche (VG) au sein de la population concernée, ce qui constitue une lacune importante dans nos connaissances. La présente étude vise à combler en partie cette lacune par une description du risque et des implications pronostiques de la dysfonction systolique VG (DSVG) après la réparation d'une tétralogie de Fallot.

Méthodologie : Nous avons réalisé une étude de cohorte chez des patients adultes ayant subi une réparation d'une tétralogie de Fallot et dont la fraction d'éjection ventriculaire gauche (FEVG) a été évaluée par échocardiographie, afin de déterminer le lien entre la DSVG et les événements cardiovasculaires, définis par une tachycardie ventricu-

Adults with repaired tetralogy of Fallot (TOF) have significantly lower long-term survival compared with the general population[1] because of premature cardiovascular deaths, and the median survival in the population with TOF is approximately 50 years.[2-4] End-stage heart failure and sudden cardiac deaths, which are the most common mechanisms of death after TOF repair, are postulated to result from ventricular cardiomyopathy.[2-4] Right ventricular (RV) cardiomyopathy is common in this population and results from a combination of factors such as cyanosis and RV pressure overload before surgical repair, intraoperative hypoxic injury, and ongoing hemodynamic stress from residual/recurrent hemodynamic lesions.[5-7] The same factors that cause RV cardiomyopathy can potentially lead to left ventricular (LV) cardiomyopathy as well,[8] but the prognostic implications of LV cardiomyopathy are understudied and underreported in this population.[4,9-14]

Considering the disappointing results of conventional heart failure therapy in the treatment of RV cardiomyopathy after TOF repair,[15,16] an in-depth understanding of the pathophysiologic mechanism and prognostic implication of LV cardiomyopathy is important because it may improve therapeutic options in this population. There are robust data on LV cardiomyopathy in patients with acquired heart disease,[17] but similar data on clinical outcomes are sparse in the TOF population, thus creating important knowledge gaps.[18,19] The current study aims to address some of these knowledge gaps by describing the prevalence and prognostic implications of LV cardiomyopathy after TOF repair. On the basis of the robust data from the acquired heart disease population and the limited data from the TOF population, we hypothesized that LV systolic dysfunction (LVD) was an independent risk factor for mortality and cardiovascular events in adults with TOF.

Methods

Patient selection

This is a retrospective cohort study, and the target population is adults with repaired TOF. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research

Results: Of 574 patients (age 38 ± 13 years), the baseline LVEF was 57% ± 9% and 68 (12%) had prevalent LVD. Cardiovascular events occurred in 126 patients (22%) during 10.5 ± 6.2 years of follow-up. LVEF was an independent predictor of mortality (hazard ratio, 1.16; 95% confidence interval, 1.16-1.24; P = 0.003) per 5%-point decrease in LVEF. Among the 357 patients with preserved LVEF and echocardiographic follow-up, incident LVD occurred in 23 (6%) during 3.8 ± 1.6 years of follow-up. Event-free survival was significantly lower in patients with incident LVD compared with patients without incident LVD (87% vs 71%, P = 0.021).

Conclusion: Prevalent and incident LVD occurred in 12% and 6% of this cohort, respectively, and were associated with lower event-free survival. Incident LVD suggests the presence of subclinical LV cardiomyopathy, and further studies are required to determine optimal strategies for diagnosing and treating subclinical LV cardiomyopathy to improve outcomes in the population with TOF.

laire soutenue, une mort subite avortée, une greffe cardiaque ou le décès. Les DSVG existantes et nouvelles étaient définies respectivement par une FEVG initiale < 50 % et par la diminution de la FEVG à une valeur < 50 % durant le suivi.

Résultats : Les 574 patients (âgés de 38 ± 13 ans) étudiés avaient une FEVG initiale de 57 ± 9 % et 68 (12 %) d'entre eux présentaient une DSVG existante au départ. Des événements cardiovasculaires sont survenus chez 126 patients (22 %) sur une période de suivi de 10,5 ± 6,2 ans. La FEVG était un facteur indépendant de prédiction de la mortalité (rapport des risques instantanés de 1,16; intervalle de confiance à 95 % : de 1,16 à 1,24; p = 0,003), par tranche de 5 points de pourcentage de diminution de la FEVG. Sur une période de suivi de 3,8 ± 1,6 ans, une DSVG est apparue chez 23 (6 %) des 357 patients présentant une FEVG préservée et ayant fait l'objet d'un suivi par échocardiographie. La survie sans événement était significativement plus courte chez les patients ayant présenté une DSVG nouvelle que chez les autres patients (87 % vs 71 %, p = 0,021).

Conclusion : Dans cette cohorte, 12 % des patients présentaient une DSVG existante et 6 % ont présenté une DSVG nouvelle, deux conditions qui ont été associées à une survie sans événement plus courte. La survenue d'une DSVG nouvelle semble indiquer la présence d'une cardiomyopathie VG subclinique; d'autres études sont nécessaires pour déterminer les stratégies optimales à employer pour diagnostiquer et traiter ces cardiomyopathies VG subcliniques afin d'améliorer les résultats chez les patients présentant une tétralogie de Fallot.

authorization. The **M**ayo **A**dult **C**ongenital **H**eart **D**isease (MACHD) Registry was reviewed for all adults (age ≥ 18 years) with repaired TOF who underwent transthoracic echocardiogram with the assessment of LV systolic function based on LV ejection fraction (LVEF) from January 1, 1990, to December 31, 2017. Only echocardiograms performed during ambulatory clinic visits were included in this study.

Study end points and definitions

The primary objective was to determine the association between prevalent LVD and cardiovascular events defined as a composite end point of sustained ventricular tachycardia, resuscitated/aborted sudden cardiac death, heart transplantation, or all-cause mortality. The secondary study objective was to determine the risk of incident LVD, the predictors of incident LVD, and the association between incident LVD and cardiovascular events. An exploratory analysis was performed to determine the number of patients with prevalent LVD who had subsequent recovery of LVEF and the predictors of recovery of LVD.

On the basis of the data from the first echocardiogram performed within the study period, LV systolic function was categorized as preserved LVEF (≥ 50%), midrange LVEF (40%-49%), and reduced LVEF (< 40%). Prevalent LVD was defined as LVEF < 50% at baseline echocardiogram (midrange LVEF and reduced LVEF). Among the patients with preserved LVEF, we reviewed subsequent echocardiograms performed during follow-up to determine the occurrence of incident LVD defined as a decrease by > 5% points from the baseline LVEF resulting in LVEF of < 50% on the follow-up echocardiogram. A patient has to meet both criteria (decrease in LVEF > 5% points and LVEF < 50%) to qualify for the definition of incident LVD. Among the patients with prevalent LVD, we also reviewed subsequent echocardiograms to determine recovery of LVEF defined as an increase in LVEF by > 5% points from the baseline LVEF resulting in LVEF of ≥ 50% on the follow-up echocardiogram. A patient has to meet both criteria (increase in LVEF > 5% points and LVEF ≥ 50%) to qualify for the definition of recovery of LVEF.

Echocardiography

Two-dimensional and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines.[20,21] Offline measurements of LV end-diastolic and end-systolic dimensions using 2-dimensional echocardiography were performed by an experienced sonographer (R.P.). LVEF was then calculated using the modified Quinones method as previously described.[20]

Outcomes assessment

Sustained ventricular tachycardia, aborted sudden cardiac death, and heart transplantation were ascertained by review of electronic health records in 100% of the cohort as of December 31, 2017, using the date of the last clinic visit. All-cause mortality was ascertained using Mayo Clinic registration database and Accurint, an institutionally approved location service, in 100% of the patients as of December 31, 2017.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range), or number (%). Between-group comparisons were performed using Fisher exact test, analysis of variance,

Table 1. Baseline clinical characteristics

	All (N = 574)	Preserved LVEF (N = 506)	Midrange LVEF (N = 46)	Reduced LVEF (N = 22)	P
Age at baseline, y	38 ± 13	37 ± 13	40 ± 10	44 ± 15	0.026
Male	263 (46%)	219 (43%)	26 (57%)	18 (82%)	0.001
Age at TOF repair, y	5 (3-10)	5 (3-10)	5 (4-10)	7 (4-14)	0.158
Prior palliative shunt	273 (48%)	242 (48%)	23 (50%)	8 (36%)	0.541
TOF pulmonary atresia	147 (26%)	128 (25%)	12 (26%)	7 (32%)	0.787
Comorbidities					
Atrial fibrillation	126 (22%)	104 (21%)	14 (30%)	8 (36%)	0.075
Atrial flutter/tachycardia	124 (22%)	107 (21%)	13 (28%)	4 (18%)	0.492
Chronic kidney disease	32 (6%)	25 (5%)	1 (2%)	6 (27%)	< 0.001
Hypertension	152 (26%)	126 (25%)	17 (37%)	9 (41%)	0.061
Coronary artery disease	66 (12%)	55 (11%)	7 (15%)	4 (18%)	0.409
Diabetes mellitus	79 (14%)	67 (13%)	6 (13%)	6 (27%)	0.174
Obesity*	148 (26%)	129 (26%)	12 (26%)	7 (32%)	0.801

LVEF, left ventricular ejection fraction; TOF, tetralogy of Fallot.

Chronic kidney disease defined as stage ≥ III (creatinine clearance < 60 mL/min).

*Obesity defined as body mass index > 30 kg/m^2. Data presented as mean ± standard deviation, median (interquartile range), or number (%).

or Kruskal−Wallis test as appropriate. Cox regression analyses were used to assess the relationship between LVEF and all-cause mortality, adjusting for age, TOF pulmonary atresia diagnosis, prior palliative shunt, atrial fibrillation, chronic kidney disease, sex, severity of RV systolic dysfunction, tricuspid regurgitation, and pulmonary regurgitation using manual backwards stepwise model selection based on the likelihood ratio P value. These variables were chosen a priori because of known association with clinical outcomes in patients with TOF.[7,9,22] We also adjusted for the effect of surgical technique of TOF repair and era of TOF repair. Surgical technique was modeled as a categorical variable with annular-sparing TOF repair as the reference group. The surgical era was divided into early and late eras using an arbitrary cutoff point of January 1, 1990. Surgical era was modeled as binary variable with the early era as the reference group. Kaplan−Meier analysis with log-rank test was used to compare between-group survival. The time of the first echocardiogram was used as the baseline for the time-to-event analyses, and the occurrence of cardiovascular adverse event was considered as the first event.

For the assessment of incident LVD, the risk of incident LVD was calculated as a quotient of the number of patients with incident LVD and the total interval between baseline and follow-up echocardiogram, and expressed as events per 100 patient-years. Univariate logistic regression analysis was used to determine the predictors of incident LVD. The associations between predictors and outcomes were expressed as hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI) as appropriate. A P value < 0.050 was considered statistically significant. All statistical analyses were performed with JMP software (version 14.0; SAS Institute Inc, Cary NC).

Results

Baseline characteristics

We studied 574 patients (263 men, 46%) who met the inclusion criteria, and the age at the time of baseline

Table 2. Echocardiographic data

	All (N = 574)	Preserved LVEF (N = 506)	Midrange LVEF (N = 46)	Reduced LVEF (N = 22)	P
LVEDD, mm	48 ± 12	47 ± 9	50 ± 6	57 ± 7	< 0.001
LVESD, mm	31 ± 8	30 ± 6	38 ± 5	43 ± 15	< 0.001
LVEF, %	57 ± 9	60 ± 6	45 ± 4	31 ± 5	< 0.001
LV stroke volume, mL/m^2	57 ± 25	52 ± 16	50 ± 21	42 ± 20	0.182
LV mass index, g/m^2	94 ± 38	92 ± 33	101 ± 34	127 ± 53	0.003
Relative wall thickness	0.41 ± 0.09	0.41 ± 0.05	0.38 ± 1.0	0.40 ± 0.03	0.141
Medial E/e'	10 ± 5	9 ± 3	10 ± 3	10 ± 2	0.727
Lateral E/e'	7 ± 3	7 ± 3	6 ± 3	7 ± 2	0.397
LA volume index, m:/m^2	29 ± 15	25 ± 12	23 ± 10	40 ± 17	0.038
Moderate or greater LA enlargement*	66 (11%)	53 (10%)	6 (13%)	7 (32%)	0.029
Moderate or greater TR*	116 (20%)	97 (19%)	11 (24%)	8 (36%)	0.117
Moderate or greater PR*	348 (61%)	309 (61%)	26 (57%)	13 (59%)	0.825
Moderate or greater RV enlargement*	379 (66%)	331 (65%)	30 (65%)	18 (82%)	0.244
Moderate or greater RV dysfunction*	162 (28%)	125 (25%)	21 (46%)	16 (73%)	< 0.001
TR velocity, m/s	3.2 ± 0.8	3.1 ± 0.7	3.3 ± 1.0	3.5 ± 0.8	0.016
RVSP, mmHg	50 ± 23	43 (32-57)	46 (37-63)	56 (48-72)	0.044
Pulmonary valve velocity, m/s	2.6 ± 1.0	2.6 ± 1.0	2.6 ± 1.0	2.8 ± 1.0	0.613

E, mitral inflow early velocity; e', tissue Doppler early velocity; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PR, pulmonary regurgitation; RV, right ventricle; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

Data presented as mean ± standard deviation, median (interquartile range), or number (%).

*Qualitative echocardiographic assessment.
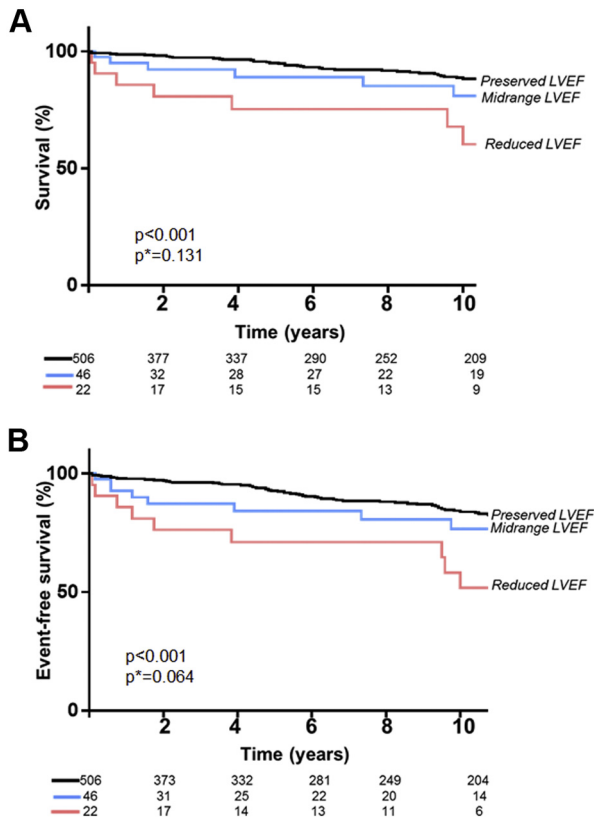
Figure 1. (A) Comparison of survival among preserved left ventricular ejection fraction (LVEF), midrange LVEF, and reduced LVEF. P < 0.001 represents a comparison between the preserved LVEF and reduced LVEF. *P = 0.131 represents a comparison between the preserved LVEF and midrange LVEF. (B) Comparison of event-free survival among preserved LVEF, midrange LVEF, and reduced LVEF. P < 0.001 represents a comparison between the preserved LVEF and reduced LVEF. *P = 0.064 represents a comparison between the preserved LVEF and midrange LVEF.

echocardiogram was 38 ± 13 years. The median age at the time of TOF repair was 5 years (3-10 years), and the surgical techniques used at the time of TOF repair were transannular patch repair (n = 123, 21%), annular-sparing repair (n = 292, 51%), and RV to pulmonary artery conduit repair (n = 159, 28%). A total of 273 patients (48%) underwent a palliative shunt before complete repair. The mean LVEF was 57% ± 9%, and 506 patients (88%) had preserved LVEF, 46 patients (8%) had midrange LVEF, and 22 patients (4%) had reduced LVEF. Compared with patients with normal LVEF, the midrange LVEF and reduced LVEF groups were older, were more likely to be male, and had a higher prevalence of chronic kidney disease (Table 1). As expected, the midrange LVEF and reduced LVEF groups had larger LV dimensions, left atrial size, RV systolic dysfunction, and RV hypertension (Table 2).

Prevalent LVD and outcomes

The mean follow-up was 10.5 ± 6.2 years, and during this period, 65 patients (11%) had sustained ventricular tachycardia, 15 patients (13%) had aborted sudden cardiac death, 4 patients (0.7%) underwent heart transplantation,

and 80 patients (14%) died. Altogether, the cardiovascular event end point occurred in 126 patients (22%). Among the 80 patients (14%) who died, the causes of death were end-stage heart failure (n = 47, 59%), arrhythmic/sudden cardiac death (n = 12, 15%), postoperatively after cardiac surgery (n = 5, 6%), sepsis (n = 5, 6%), malignancy (n = 5, 6%), gastrointestinal bleeding (n = 1, 1%), stroke/intracranial bleeding (n = 2, 3%), and mixed/unknown (n = 4, 5%).

The 10-year survival and event-free survival (freedom from cardiovascular events) were 86% and 82%, respectively. By using the normal LVEF group as reference, the 10-year survival and event-free survival were significantly lower in the reduced LVEF group (88% vs 60%, P < 0.001) and (84% vs 52%, P < 0.001), respectively (Fig. 1). However, there was no significant difference in the 10-year survival and event-free survival between the normal LVEF and midrange LVEF groups (88% vs 81%, P = 0.131) and (84% vs 77%, P = 0.064), respectively. LVEF was an independent predictor of mortality (HR, 1.16; 95% CI, 1.16-1.24; P = 0.003) per 5% points decrease in LVEF. In comparison with the normal LVEF group, the reduced LVEF group had a higher risk of mortality (HR, 2.86; 95% CI, 1.36-5.43; P = 0.007) (Table 3).

Incident LVD and outcomes

Of the 402 patients with echocardiographic follow-up, 357 (89%) had preserved LVEF and 45 (11%) had prevalent LVD at baseline. The interval between the baseline echocardiogram and the follow-up echocardiogram was 3.8 ± 1.6 years. Among the 357 patients with preserved LVEF at baseline, the median change in LVEF was 0 (−5 to 3) percentage points, and 23 patients (6%) met the prespecified criteria for incident LVD. The patients with incident LVD were older and more likely to have TOF pulmonary atresia diagnosis and atrial fibrillation (Table 4). The risk of incident LVD was 2.2 events per 100 patient-years, and the risk factors for incident LVD were older age (OR, 1.27; 95% CI, 1.02-1.22; P = 0.002) per 5-year increase in age and atrial fibrillation (OR, 3.87; 95% CI, 1.59-8.96; P = 0.003) (Supplementary Table S1). Event-free survival was significantly lower in the patients with incident LVD compared with the patients without incident LVD, (87% vs 71%, P = 0.021) (Fig. 2). Among the 45 patients with prevalent LVD at baseline, 15 (33%) had recovery of LVEF. Of the 15 patients who had recovery of LVEF, 2 (13%) had sustained ventricular tachycardia during follow-up, but no patient died or underwent heart transplant. The prevalence of a cardiovascular adverse event among these 15 patients was 13%. There was no significant difference in the baseline characteristics of the patients who had recovery of LVEF during follow-up compared with the patients with persistent LVD (Supplementary Table S2).

Discussion

In this study of 574 adult patients with TOF, we identified prevalent LVD (LVEF < 50%) in 12% of the cohort, and LVEF was an independent risk factor for mortality with a 16% increase in all-cause mortality for every 5% point decrease in LVEF. Among patients with preserved LVEF at baseline, 6% developed incident LVD during follow-up, and incident LVD

Table 3. Multivariate predictors of mortality

	Full model		Final model	
	HR (95% CI)	P	HR (95% CI)	P
LVEF (per 5% decrease)	1.16 (1.05-1.28)	0.014	1.16 (1.06-1.24)	0.003
Age at echocardiogram (per 1 y)	1.06 (1.04-1.08)	< 0.001	1.06 (1.04-1.08)	< 0.001
Prior palliative shunt	1.52 (0.95-2.46)	0.089		
TOF pulmonary atresia diagnosis	2.32 (1.28-4.11)	0.004	2.59 (1.49-4.38)	< 0.001
TOF repair in late era	1.21 (0.75-3.55)	0.214		
RV-PA conduit repair	1.08 (0.85-2.99)	0.137		
Transannular patch repair	1.12 (0.43-5.22)	0.675		
Atrial fibrillation	1.14 (0.69-1.90)	0.601		
Moderate or greater RV systolic dysfunction	1.44 (0.85-2.45)	0.178		
Moderate or greater tricuspid regurgitation*	1.07 (0.62-1.84)	0.813		
Moderate or greater pulmonary regurgitation*	0.93 (0.56-1.57)	0.761		
Male gender	1.42 (0.87-2.36)	0.164		
Chronic kidney disease	2.60 (1.43-4.58)	0.001	2.41 (1.35-4.16)	0.002
	Full model		Final model	
	HR (95% CI)	P	HR (95% CI)	P
Midrange LVEF (40%-49%)	1.27 (0.58-2.51)	0.518	1.32 (0.61-2.53)	0.447
Reduced LVEF (< 40%)	2.52 (1.48-5.08)	0.014	2.86 (1.36-5.43)	0.007
Age at echocardiogram (per 1 y)	1.06 (1.03-1.08)	< 0.001	1.06 (1.04-1.08)	< 0.001
Prior palliative shunt	1.50 (0.93-2.45)	0.096		
TOF pulmonary atresia diagnosis	2.32 (1.29-4.11)	0.004	2.68 (1.55-4.52)	0.001
TOF repair in late era	1.17 (0.72-3.34)	0.209		
RV-PA conduit repair	1.16 (0.89-2.45)	0.105		
Transannular patch repair	1.19 (0.66-4.87)	0.406		
Atrial fibrillation	1.15 (0.69-1.92)	0.560		
Moderate or greater RV systolic dysfunction	1.48 (0.86-2.50)	0.153		
Moderate or greater tricuspid regurgitation*	1.08 (0.61-1.84)	0.792		
Moderate or greater pulmonary regurgitation*	0.91 (0.55-1.50)	0.708		
Male gender	1.33 (0.81-2.48)	0.218		
Chronic kidney disease	2.64 (1.45-4.65)	0.001	2.46 (1.37-4.31)	0.002

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; PA, pulmonary artery; RV, right ventricle; TOF, tetralogy of Fallot.

Chronic kidney disease defined as stage ≥ III (creatinine clearance < 60 mL/min).

* Qualitative echocardiographic assessment.

was associated with cardiovascular events. Older age and atrial fibrillation were risk factors for incident LVD and thus may be prognostic markers of a high-risk group who may benefit from prophylactic interventions to prevent incident LVD.

The prevalence, risk factors, and clinical implications of RV cardiomyopathy are well described in the population with TOF, and as a result, RV systolic dysfunction is one of the indications for intervention in patients with hemodynamic or arrhythmic target lesions.[18,19,23] On the other hand, only a few observational studies have assessed the prognostic implications of LVD after TOF repair, and these studies reported that LVD was associated with clinical outcomes in this population.[4,9-14] In a study of 575 adult patients with TOF who underwent cardiac magnetic resonance imaging, Bokma et al.[4] reported that LVEF was an independent predictor of mortality. An interesting observation in that study was that the LVD threshold that predicted mortality was lower with an LVEF < 45% being the optimal cutoff point for prediction of mortality in contrast to RV dysfunction for which RVEF < 35% predicted mortality.[4] A similar observation was also reported in another study of 88 adult patients with TOF that showed that LVEF < 55% had a similar effect size (in terms of OR and CI) as RVEF <

45% in predicting cardiovascular events.[13] Concordant with our results, these prior studies demonstrated that LVD was at least as important as RV dysfunction in predicting mortality and cardiovascular events in the TOF population.

All the clinical outcomes studies[4,9-14] cited earlier have focused on the relationship between prevalence LVD and cardiovascular events after TOF repair, and the results show that patients with preserved LVEF have better event-free survival. A novel finding in our study was that among the patients with preserved LVEF, 6% develop incident LVD during short-term follow-up, and these patients with incident LVD had lower event-free survival. The occurrence of incident LVD suggests that some patients with preserved LVEF may have subclinical LV cardiomyopathy that subsequently led to progressive LVD overtime, and this has significant clinical implications that are highlighted next.

Clinical Implications and Future Directions

As mentioned earlier, the occurrence of incident LVD suggests subclinical LV cardiomyopathy in the setting of preserved LVEF. We postulated that subclinical LV cardiomyopathy may be a downstream effect of prior

Table 4. Baseline clinical characteristics

	Incident LVD (N = 23)	Others (N = 334)	P
Age at baseline, y	47 ± 12	37 ± 13	0.002
Male	14 (61%)	150 (45%)	0.141
Prior palliative shunt	13 (57%)	156 (47%)	0.369
TOF pulmonary atresia	11 (48%)	84 (25%)	0.024
Atrial fibrillation	11 (48%)	65 (29%)	0.003
Hypertension	5 (22%)	85 (25%)	0.687
Coronary artery disease	5 (22%)	40 (12%)	0.208
Medial E/e'	11 ± 6	10 ± 5	0.876
Lateral E/e'	8 ± 3	7 ± 3	0.149
Moderate or greater RV dysfunction*	8 (35%)	84 (25%)	0.333
RVSP, mm Hg	39 (32-84)	44 (33-57)	0.737
Beta-blocker therapy	6 (26%)	49 (15%)	0.173
ACEI/ARB	5 (22%)	45 (13%)	0.301

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; E, mitral inflow early velocity; e', tissue Doppler early velocity; RVSP, right ventricular systolic pressure; TOF, tetralogy of Fallot.

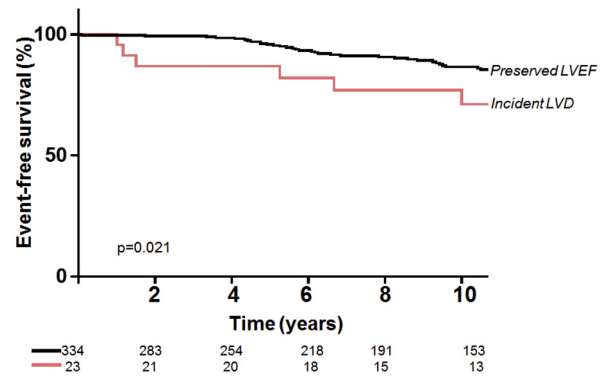Data presented as mean ± standard deviation, median (interquartile range), or number (%).

* Qualitative echocardiographic assessment.

Figure 2. Comparison of event-free survival between preserved LVEF and incident left ventricular dysfunction (LVD); P = 0.021.

myocardial injury from cyanosis, volume overload due to prior palliative shunt, and intraoperative hypoxic injury during surgical interventions. Another potential mechanism for incident LVD is the effect of RV dysfunction mediated through ventricular-ventricular interaction, and this can occur because both ventricles share myocardial fibers, ventricular septum, and pericardial space.[8] The LVD noted in this study may also be due to atherosclerotic cardiovascular disease considering the age of the patients and the presence of atherosclerotic cardiovascular disease risk factors. Because echocardiography with strain imaging can identify subclinical LV cardiomyopathy even in the setting of preserved LVEF,[12,24] strain imaging can potentially be used to identify patients with TOF at risk for incident LVD.

The goal of screening and diagnostic testing is to provide prophylactic and therapeutic interventions to improve outcomes. Conventional heart failure therapies such as renin-angiotensin-aldosterone system antagonists are ineffective in preventing or treating RV systolic dysfunction in patients with TOF.[15,16] However, these therapies are effective for LV cardiomyopathy due to acquired heart disease both in terms of improving LV remodeling and survival.[17,25,26] The risk of LV cardiomyopathy and the prognostic implications of LVD demonstrated in this study call for further study to determine the role of conventional heart failure therapy for the treatment and prevention of LV cardiomyopathy after TOF repair. Additionally, a proactive approach to the management of atrial fibrillations may decrease the risk of incident LVD because atrial fibrillation was one of the risk factors for incidence LVD. Although there have been no randomized studies of the comparative efficacy of rate control vs rhythm control therapies for atrial fibrillation in the TOF population, a recent observational study showed a reduction in mortality and heart failure hospitalizations in patients who received rhythm control therapy.[27]

Limitations

We used 2-dimensional linear measurements to derive LVEF because that was the method of LVEF assessment that was available in all patients. This method assumes normal LV geometry, which is not the case in most patients with TOF. This study was based on an older TOF cohort, and some of these patients underwent TOF repair in the early surgical era during which palliative shunts and inadequate (by current standard) myocardial protection during cardiopulmonary bypass were common. Not all the patients had follow-up at 10 years. Therefore, the prevalence of LVD reported in this cohort may overestimate the risk in more contemporary cohorts. However, the prognostic implications of LVD in this study should be generalizable because studies conducted in younger TOF cohorts have demonstrated similar effects.[10] Furthermore, we assessed LV systolic function using LVEF, which is a load-dependent measure of LV contractility; therefore, differences in loading conditions could have affected the LVEF assessments. We do not anticipate clinically significant differences in loading conditions because these echocardiograms were conducted in stable ambulatory patients. Finally, we were unable to account for the effect of temporal changes in the intensity of heart failure therapy used during the course of the study.

Conclusions

LVD was present in 12% of this ambulatory TOF cohort and was associated with mortality. Incident LVD occurred in 6% of patients and was associated with adverse outcomes. The risk and prognostic implications of subclinical LV cardiomyopathy reported in the current study highlight the need for further studies to explore alternate imaging modalities for early detection and perhaps treatment of subclinical LV cardiomyopathy. Considering the lack of viable medical therapies for RV cardiomyopathy, the results of this study add to the body of evidence supporting a paradigm shift to the LV as the target of medical interventions to improve long-term survival after TOF repair.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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