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Factors Associated With Impaired Clinical Status in Long-Term Survivors of Tetralogy of Fallot Repair Evaluated by Magnetic Resonance Imaging

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OBJECTIVES The purpose of this study was to identify independent factors associated with impaired clinical status in late survivors of tetralogy of Fallot (TOF) repair.

BACKGROUND Repair of TOF often results in chronic pulmonary regurgitation (PR) and right ventricular (RV) dilation, which have been linked to late morbidity and mortality. However, determinants of clinical status late after TOF repair have not been fully characterized.

METHODS The clinical and laboratory data of 100 consecutive patients with repaired TOF (median 21 years after repair) who completed a cardiac magnetic resonance imaging protocol were analyzed. Impaired clinical status was defined as New York Heart Association (NYHA) functional class ≥III.

RESULTS Of the patients, 88 were in NYHA functional class I or II and 12 were in NYHA functional class III. The degree of PR and indexed RV end-diastolic volume were not associated with impaired clinical status. By multivariate analysis, a lower left ventricular (LV) ejection fraction (EF) (odds ratio [OR] = 3.88 for 10% decrease, $p = 0.002$) and older age at TOF repair (OR = 1.70 for 5-year increase, $p = 0.013$) were the strongest independent factors associated with impaired clinical status. Among RV variables, a lower RV EF was the strongest independent factors associated with poor clinical status (OR = 2.41 for 10% decrease, $p = 0.01$). The LV EF correlated with RV EF ($r = 0.58$, $p < 0.001$).

CONCLUSIONS Moderate or severe LV or RV systolic dysfunction, but not PR fraction or RV diastolic dimensions, is independently associated with impaired clinical status in long-term survivors of TOF repair. The close relationship between LV EF and RV EF suggests unfavorable ventricular-ventricular interaction. (J Am Coll Cardiol 2004;43:1068–74) © 2004 by the American College of Cardiology Foundation

Survival of patients with tetralogy of Fallot (TOF), the most common cyanotic congenital heart disease, has steadily increased since the introduction of open-heart surgery, with early mortality currently <2% (1). Late survival has also improved, with recent reports showing a 20-year survival rate nearing 90% (2,3). The majority of these patients, however, have residual hemodynamic abnormalities, primarily due to a right ventricular (RV) volume load from chronic pulmonary regurgitation (PR). Recent studies on large cohorts of survivors of TOF repair who have been followed for >30 years demonstrated that during the third postoperative decade the risk of death more than tripled, increasing from 0.27% per year to 0.94% per year (2). This observation and other studies have suggested that chronic PR plays a major role in mortality related to right heart failure and ventricular arrhythmias (2–5).

However, demonstrating and quantifying the effects of chronic PR on RV dimension and function and on clinical outcome in patients with repaired TOF has been hampered by the lack of reliable tools to measure these variables. This deficiency also contributes to the uncertainty regarding the indications and timing for pulmonary valve replacement (6,7). The development of cardiac magnetic resonance imaging (MRI) techniques to noninvasively quantify ventricular volumes, mass, function and PR has provided insights regarding ventricular mechanics and risk of sudden death in this population (5,8–11). The available literature, however, has not addressed in detail the interactions between ventricular mechanics and clinical status in large cohorts of late survivors of TOF repair (8–15). The goals of the present study, therefore, were to identify independent factors associated with poor clinical status in 100 late survivors of TOF repair and to explore the relationships between clinical status and the degree of PR and RV dimensions and function measured by MRI.

METHODS

Subjects. This study was designed as a single-center cross-sectional investigation. Patients evaluated at Children's Hospital Boston between November 1, 1997, and August 31, 2001, who fulfilled the following criteria were included in this study: 1) repaired TOF with pulmonary stenosis or atresia, 2) ≥10 years after complete repair, 3) completed a cardiac MRI examination protocol as described later, and 4) underwent a concurrent clinical evaluation. The study cohort consisted of 100 patients with TOF (71 with pulmonary stenosis and 29 with pulmonary atresia) with a median

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Abbreviations and Acronyms

ECG = electrocardiogram
EF = ejection fraction
LV = left ventricle/ventricular
MRI = magnetic resonance imaging
NYHA = New York Heart Association
PA = pulmonary artery
PR = pulmonary regurgitation
ROC = receiver-operator characteristic
RV = right ventricle/ventricular
TOF = tetralogy of Fallot

age at MRI of 24 years (range 10 to 57 years) and with a median length of follow-up after TOF repair of 21 years (range 10 to 43 years). The Children's Hospital Committee on Clinical Investigations approved review of the medical records and computer databases.

Clinical data. The following demographic and clinical data were retrospectively abstracted from the patient's medical records: date of birth, gender, date and age at each surgical procedure, type of surgical procedures (categorized as shunt, transannular patch repair, non-transannular patch repair, and RV-to-pulmonary artery [PA] conduit repair), age at MRI, and length of postoperative follow-up. The following variables were recorded from the most recent clinical evaluation: height and weight, vital signs, symptoms (such as shortness of breath, exertional dyspnea, palpitations, syncope, chest pain), New York Heart Association (NYHA) functional class, findings on physical examination (such as tachypnea, gallop rhythm, jugular venous distention, hepatomegaly, pulsatile liver, peripheral edema), and medications (categorized as digoxin, diuretics, angiotensin-converting enzyme inhibitors, and antiarrhythmics).

MRI. Studies were performed with a commercially available 1.5-T scanner (either a Signa Horizon HighSpeed or Signa Horizon LX EchoSpeed, GE Medical Systems, Milwaukee, Wisconsin). Torso or cardiac-phased array coils were chosen according to body size. The technical details and imaging parameters of the MRI pulse sequences used in our laboratory were previously published (16). The following imaging protocol was employed: 1) three-plane localizing images; 2) breath-hold electrocardiogram (ECG)-triggered segmented k-space fast-spoiled gradient-recalled cine sequences in two- and four-chamber planes, followed by 12 contiguous short-axis slabs perpendicular to the long axis of left ventricle (LV) and RV (slice thickness 6 to 8 mm, interslice space 0 to 2 mm); 3) ECG-triggered cine phase-contrast blood flow measurements in the main PA and ascending aorta (17); and 4) contrast-enhanced (gadopentetate dimeglumine 0.2 mmol/kg) (Magnevist, Berlex Laboratories, New Jersey), three-dimensional magnetic resonance angiography sequence for anatomic evaluation of the PAs, aorto-pulmonary collaterals or other vascular abnormalities (18).

The MRI studies were reviewed on a commercially available computer workstation (Advantage Windows Version 2.0, GE Medical Systems, Milwaukee, Wisconsin). Left and right ventricular end-diastolic (maximal) and end-systolic (minimal) volumes, mass, stroke volumes, and ejection fraction (EF) were measured using commercially available software (MASS, Medis, Leiden, The Netherlands) as described by Lorenz et al. (19). Quantification of flow rates and calculation of PR were performed using customized software as previously described (17).

ECG. The most recent 15-lead ECG was reviewed for rhythm, conduction abnormalities, and duration of the QRS complex.

Statistical analysis. Patient characteristics, clinical history, and MRI data were compared for individuals with different anatomic diagnoses (TOF with pulmonary stenosis vs. TOF with pulmonary atresia) and different types of surgery (RV outflow tract patch and RV-PA conduit) using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Associations among clinical and MRI variables were explored using the Wilcoxon rank-sum test or Spearman rank correlation coefficient, as appropriate. Because most clinical and MRI variables were not normally distributed, nonparametric techniques were used. Multivariate logistic regression analysis was used to investigate the relationships between impaired clinical status (defined as NYHA functional class $\geq$III), patient characteristics and MRI variables. Receiver-operator characteristic (ROC) curves were used to identify cutoff points providing the best combinations of sensitivity and specificity for variables identified by multivariate analysis as being independently associated with impaired clinical status. A commercially available statistical software package was used for data analysis (STATA Version 7.0, College Station, Texas).

RESULTS

Subjects. The demographic and clinical data of the 100 patients included in the study are summarized in Table 1. Before TOF repair, 48 patients had at least one palliative shunt procedure. After TOF repair, 48 patients underwent 70 reoperations and 52 patients underwent 109 interventional cardiac catheterization procedures. Compared with the RV outflow patch group, patients who underwent RV-PA conduit were more likely to have undergone a reoperation (84% vs. 36%, $p < 0.001$) and an interventional catheterization procedure (80% vs. 43%, $p = 0.001$).

Clinical findings. Nearly one-half of the study patients (48%) were asymptomatic (NYHA functional class I) at the time of evaluation, an additional 40% had mild symptoms with exertion (NYHA functional class II), and 12% had symptoms with minimal exertion or at rest (NYHA class III) (Table 1). Of the 52 patients with at least one symptom or finding on physical examination related to the cardiovascular system, 32 (62%) had $\geq$2 symptoms or signs. Of the 44 patients who were on cardiac medications at the time of

Table 1. Patient Characteristics and Clinical Data

	All Patients (n = 100)	RVOT Patch (n = 75)	RV-PA Conduit (n = 25)	p* Value
Gender (M/F)	1.08	1.14	0.92	NS
Median BSA (m^2) (range)	1.73 (0.99–2.45)	1.73 (0.99–2.33)	1.74 (1.12–2.45)	NS
Median age at TOF repair (yrs)	3.0 (0–31.8)	3.0 (0–31.8)	4.9 (0–29.8)	NS
Median age at MRI (yrs)	24 (10–57)	27 (11–57)	20 (10–44)	NS
Median follow-up (yrs)	21 (10–43)	22 (10–43)	17 (10–30)	0.006
NYHA class				NS
I	48 (48%)	38 (51%)	10 (40%)	
II	40 (40%)	30 (40%)	10 (40%)	
III	12 (12%)	7 (9%)	5 (20%)	
Signs and symptoms	52 (52%)	37 (49%)	15 (60%)	NS
Fatigue	30 (30%)	20 (27%)	10 (40%)	NS
Dyspnea on exertion	28 (28%)	19 (25%)	9 (36%)	NS
Palpitations	26 (26%)	18 (24%)	8 (32%)	NS
Chest pain	10 (10%)	9 (12%)	1 (4%)	NS
Peripheral edema	4 (4%)	2 (3%)	2 (8%)	NS
Medications	44 (44%)	31 (41%)	13 (52%)	NS
Diuretics	17 (17%)	12 (16%)	5 (20%)	NS
Digoxin	16 (16%)	9 (12%)	7 (28%)	NS
ACE inhibitors	9 (9%)	5 (7%)	4 (16%)	NS
Antiarrhythmics	8 (8%)	7 (9%)	1 (4%)	NS

*Comparison between RVOT patch and RV-PA conduit.
ACE = angiotensin-converting enzyme; BSA = body surface area; NYHA = New York Heart Association; PA = pulmonary artery; RV = right ventricle; RVOT = right ventricular outflow tract.

evaluation, 26 (59%) received one class of medication and 18 (41%) received ≥2 classes of medications. Use of ≥1 class of cardiac medications was associated with decreased RV EF (median 44% vs. 50%, p = 0.005), increased RV end-systolic volume (median 120 ml vs. 91 ml, p = 0.05), lower LV EF (median 58% vs. 62%, p = 0.008), and higher LV mass-to-volume ratio (median 1.36 vs. 1.24, p = 0.02). There were no significant differences between patients who underwent a patch repair compared with the RV-PA conduit group in terms of NYHA functional class, signs on physical examination, or cardiac medications (Table 1).

MRI parameters. The distributions of PR, RV end-diastolic volume index, end-systolic volume index, and EF in patients with RV outflow patch and RV-to-PA conduit are shown in Figure 1. Compared to patients with conduit repair, those with a patch repair had a higher median PR fraction (36% vs. 18%, p = 0.001) and regurgitation volume (35 vs. 12 ml/beat, p = 0.001), RV end-diastolic volume index (122 vs. 106 ml/m^2, p = 0.03), and RV stroke volume (93.7 vs. 74.2 ml, p = 0.005). Although RV mass index did not differ significantly between groups, patients with a patch repair had a lower median RV mass-to-volume ratio compared to those with RV-to-PA conduit (0.47 vs. 0.67, p < 0.001). LV volume, mass, and EF did not differ significantly between groups.

Higher PR fraction was associated with increasing indexed RV dimensions (end-diastolic volume [r_s = 0.51, p < 0.001] and end-systolic volume [r_s = 0.38, p < 0.001]) as well as lower RV mass-to-volume index (r_s = −0.28, p = 0.01). However, PR fraction and volume were not associated with demographic data, clinical findings, RV EF, or LV dimensions and function.

Lower RV EF was not only associated with increasing RV dimensions (end-diastolic volume index [r_s = −0.44, p < 0.001], end-systolic volume index [r_s = −0.77, p < 0.001], and mass [r_s = −0.45, p < 0.001]) but also with a higher LV end-systolic volume (r_s = −0.46, p < 0.001) and a lower LV EF (r_s =0.58, p < 0.001) (Fig. 2). Lower RV EF also correlated with a longer postoperative follow-up period (r_s = −0.32, p = 0.001) and an older age at TOF repair (r_s = −0.25, p = 0.01).

ECG. All patients were in sinus rhythm during the evaluation. QRS duration ranged from 78 to 220 ms (mean ± SD 157 ± 30 ms). Longer QRS duration was associated with larger RV dimensions by MRI (end-diastolic volume, end-systolic volume, and mass) as well as with greater LV mass. Increasing QRS duration was significantly associated with decreasing RV EF (r_s = −0.69, p < 0.001).

Determinants of clinical status. Table 2 summarizes factors associated with poor clinical status (NYHA functional class ≥III) by univariate analysis. To identify independent factors associated with impaired clinical status, the variables shown in Table 2 (significant at the 0.15 level in univariate analysis) were entered into a logistic regression multivariate analysis. Of these variables, a lower LV EF and an older age at corrective surgery were independently associated with a NYHA functional class ≥III (Table 3). In patients with normal (>55%) or mildly depressed LV EF (40% to 55%), the probability of NYHA functional class ≥III was low at 0.09 (95% confidence interval 0.039 to 0.166). However, in patients with moderate or severe LV systolic dysfunction (EF <40%) the probability of NYHA functional class ≥III increased 8.3-fold to 0.75 (95% confidence interval 0.19 to 0.99, p = 0.004) (Fig. 3). The area under the ROC curve

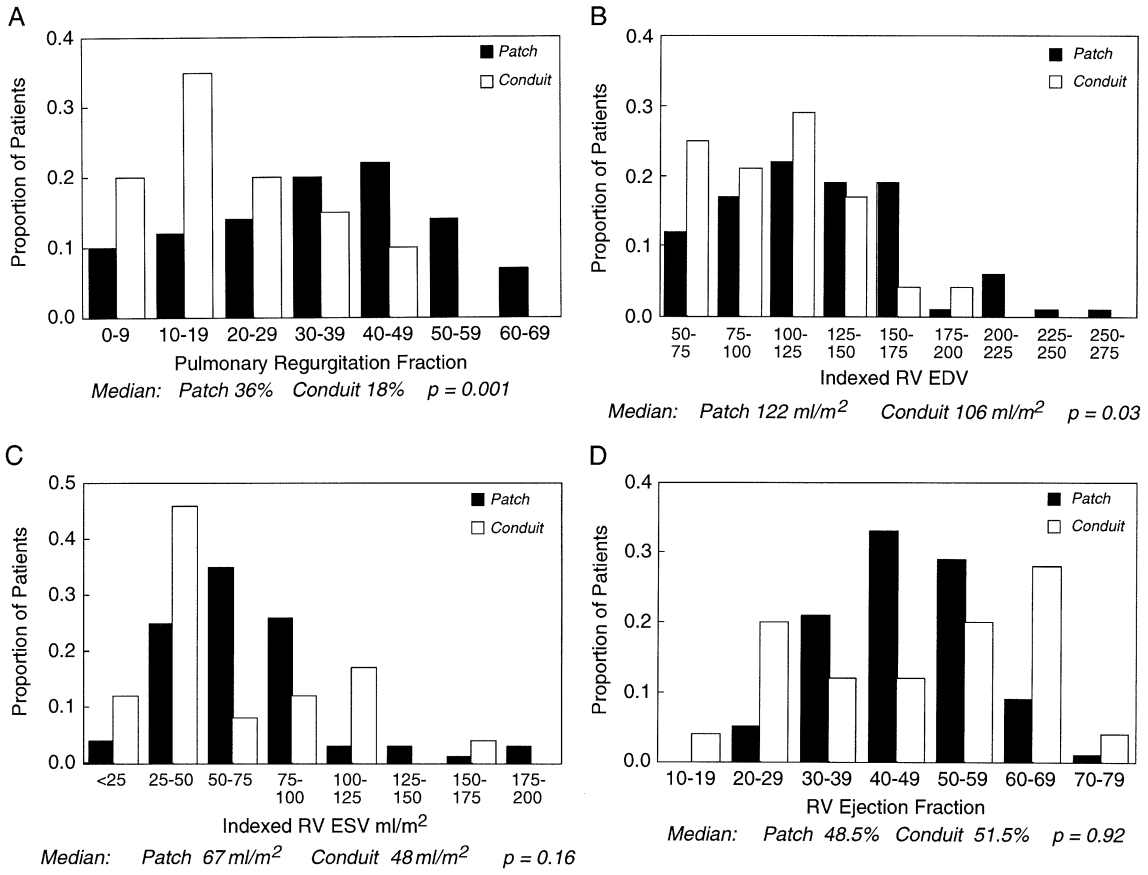

Figure 1. Histograms of magnetic resonance imaging variables in patients with right ventricular (RV) outflow tract patch repair (n = 75) and RV-to-pulmonary artery conduit (n = 25). **(A)** % pulmonary regurgitation; **(B)** indexed RV end-diastolic volume (EDV); **(C)** indexed RV end-systolic volume (ESV); **(D)** RV ejection fraction.

for the likelihood of NYHA functional class ≥III and LV EF was 0.812, and the area under the ROC curve for the combination of LV EF and an older age at TOF repair was 0.898 (Table 3).

To further investigate the potential effect of RV variables on clinical status, a second multivariate model that excluded LV variables was constructed. Of the variables examined, a lower RV EF, a higher RV mass-to-volume ratio, and an older age at corrective surgery were independently associated with a NYHA functional class ≥III with an area under the ROC curve for the model 0.884 (Table 3).

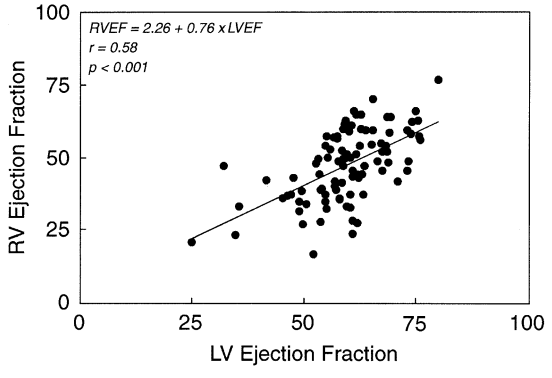

Figure 2. Association between right ventricular (RV) and left ventricular (LV) ejection fraction (EF).

DISCUSSION

The results of this study demonstrate that moderate or severe RV and LV systolic dysfunction is an important determinant of poor clinical status of long-term survivors of TOF repair. The combination of a lower LV EF and an older age at TOF had a high sensitivity and specificity for being in a NYHA functional class ≥III at a median follow-up period of 21 years after repair.

Ventricular dysfunction and clinical status. Previous investigations that used quantitative methods to assess ventricular function late after TOF repair have mainly focused on RV mechanics and its interaction with PR. These studies clearly demonstrated that the degree of PR is closely associated with the degree of RV dilation, but the data regarding the effect of PR on RV systolic function is inconsistent (9,10,13,15). More recently, Davlouros et al. (20) demonstrated that in addition to PR, the presence of an akinetic or aneurysmal RV outflow tract wall segment had a negative effect on RV EF late after TOF repair. These investigators also found a significant correlation between RV EF and LV EF and pointed out the importance of

Table 2. Univariate Analysis of Factors Associated With Poor Clinical Status (NYHA Class ≥III)

Variable	Odds Ratio	95% Confidence Interval	p Value
RV EF ≤35%*	5.00	(1.35, 18.5)	0.02
RV EF (for each 10% decrease)	2.18	(1.26, 3.75)	0.005
RV mass index (for each 20-g/m^2 increase)	1.78	(1.17, 2.71)	0.007
RV mass-to-volume ratio (for each 0.1-U increase)	1.55	(1.10, 2.19)	0.01
RV ESV index (for each 50 ml/m^2 increase)	1.89	(0.88, 4.07)	0.10
Age at MRI (for each 5-yr increase)	1.25	(1.00, 1.56)	0.05
Age at TOF repair (for each 5-yr increase)	1.63	(1.15, 2.31)	0.006
LV EF (for each 10% decrease)	3.65	(1.71, 7.80)	0.001
LV mass-to-volume ratio (for each 0.1-U increase)	1.37	(1.08, 1.74)	0.01
LV mass index (for each 20-g/m^2 increase)	1.71	(1.07, 2.74)	0.03

*Moderate-severe RV dysfunction.
EF = ejection fraction; ESV = end-systolic volume; LV = left ventricle; RV = right ventricle.

ventricular-ventricular interaction in patients with repaired TOF. Kondo et al. in a study of 29 patients who were studied with radionuclide first-pass ventriculography 16 ± 2 years after TOF repair demonstrated subclinical LV dysfunction during exercise (21). However, no studies systematically examined the relationship between ventricular mechanics and clinical status late after TOF repair.

The present study demonstrates that although moderate or severe RV systolic dysfunction is an important independent factor associated with poor clinical status, late after TOF repair, RV mechanics are only part of the problem. When all variables associated with poor clinical outcome in this cohort were included in a multivariate analysis model, moderate or severe LV dysfunction was the strongest independent variable (Table 3). Ghai et al. (22) recently demonstrated in a study of adults with repaired TOF that moderate or severe LV systolic dysfunction is an important risk factor for sudden cardiac death. Similar to our findings, the study of Ghai et al. (22) as well as the report of Hausdorf et al. (23) also demonstrated that an older age at TOF repair is a risk factor for depressed LV function. An older age at repair with its associated longer duration of LV volume overload and chronic hypoxemia may explain, in part, the degree of LV dysfunction seen in these patients. Other factors such as method of myocardial protection and surgical technique may also play a role. However, in our study an older age at repair was independently associated with poor clinical status, even after controlling for year of surgical repair and other variables such as LV and RV dimensions and function.

The close relationship between RV and LV EFs and the observation that each is closely and independently associated with clinical status provide strong evidence that RV-LV interaction is key to understanding the pathophysiology that ultimately leads to clinical deterioration late after TOF repair. Although such interaction has been previously demonstrated (20), the mechanism that links RV dysfunction to a decrease in LV function remains incompletely understood.

Role of PR. Unlike the previously reported data showing that the degree of PR is directly linked to exercise intolerance and symptoms (10,15), the findings in this cohort indicate that neither PR fraction nor PR volume measured at a single time point was independently associated with RV function or clinical status late after TOF repair. Instead, the degree of PR was mainly related to the degree of RV enlargement, a finding that concurs with other studies that utilized MRI to assess these variables (10,13). Rather than interpreting these results as indicating that the degree of PR is inconsequential for clinical outcome after TOF repair, our findings suggest a complex interplay between the volume load imposed by PR and the ultimate failure of compensatory mechanisms that lead to ventricular dysfunction. Although not directly documented by this study or previous investigators, it is conceivable that progressive RV dilation coupled with inadequate compensatory

Table 3. Multivariate Analysis of Variables Associated With a NYHA Class ≥3

Variables	Odds Ratio (95% Confidence Interval)	p Value
Model 1: Considering all variables (area under ROC curve = 0.898)*		
LV EF (10% decrease)	3.88 (1.65, 9.16)	0.002
Age at TOF repair (5-yr increase)	1.70 (1.12, 2.59)	0.013
Model 2: Considering RV variables only (area under ROC curve = 0.884)*		
RV EF (10% decrease)	2.41 (1.23, 4.70)	0.01
RV mass-to-volume ratio (0.1-U increase)	1.45 (1.01, 2.1)	0.046
Age at TOF repair (5-yr increase)	1.76 (1.15, 2.70)	0.01

*Area under the ROC curve refers to the combination of sensitivity and specificity of the model to predict NYHA class ≥III.
TOF = tetralogy of Fallot. Other abbreviations as in Table 2.

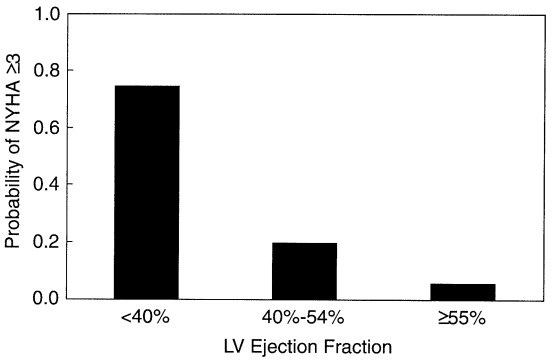

Figure 3. Estimated probability of New York Heart Association (NYHA) functional class ≥III in relation to left ventricular (LV) ejection fraction.

hypertrophy might lead to an increase in RV wall stress and systolic dysfunction. The inverse relationship between RV volume and RV mass-to-volume ratio found in this study ($r_s = -0.33$, $p = 0.002$) provides indirect evidence in support of such mechanism. Other mechanical factors such as dyskinesis of the RV outflow tract may also contribute to late RV dysfunction (20).

Clinical implications. Although several reports have demonstrated that pulmonary valve replacement can be achieved with low mortality and may lead to early clinical improvement, the indications, techniques, and long-term results of this intervention remain controversial (6,7,24). Although the present study was not designed to determine the optimal timing for pulmonary valve replacement, it provides some insights that can be used to rationalize the decision-making process. The following observations are worth noting when considering pulmonary valve replacement in an asymptomatic patient with repaired TOF: 1) all patients with RV end-systolic volume index ≥95 ml/m^2 exhibited RV dysfunction, and all patients with LV end-systolic volume index ≥50 ml/m^2 had LV systolic dysfunction; 2) LV or RV EF is a strong independent predictor of clinical status, with a threshold value of ≤35% for the RV and ≤50% for the LV having the highest sensitivity and specificity for predicting poor clinical status; and 3) patients who had their TOF repair at an older age are more susceptible for having cardiac-related symptoms.

Imaging strategy. The results of this study highlight the importance of quantitative evaluation of RV and LV dimensions and function during follow-up of patients with TOF. As previously shown, MRI is ideally suited for this purpose because it is noninvasive, unaffected by acoustic windows, and measures ventricular dimensions and function independent of geometrical assumptions (10–13). Echocardiography complements MRI by providing a noninvasive estimate of RV pressure and degree of RV outflow obstruction. Ideally, the strengths of MRI and Doppler echocardiography should be combined into a single comprehensive noninvasive evaluation (25). The potential role of tissue Doppler imaging evaluation of ventricular function in these patients deserves further investigation.

Study limitations. The cross-sectional design of this study precludes analysis of the time course of ventricular dysfunction or the optimal timing of pulmonary valve replacement. The influence of RV hypertension on clinical status cannot be assessed because of the lack of RV pressure data in many patients. The small number of patients with a nontransannular patch repair (n = 7) does not allow determination of whether this type of repair offers an advantage with regard to ventricular mechanics or symptoms. Similarly, analysis of other variations in surgical techniques was not practical because of small sample size of each variation.

Conclusions. The results of this study show that moderate or severe RV and LV systolic dysfunction, but not PR fraction or RV diastolic dimensions, is an important factor associated with poor clinical status of long-term survivors of TOF repair. The close relationship between LV EF and RV EF suggests unfavorable ventricular-ventricular interaction. Thus, evaluation of LV dimensions and function is as important in these patients as assessment of the right heart.

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