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Left Ventricular Dysfunction Is a Risk Factor for Sudden Cardiac Death in Adults Late After Repair of Tetralogy of Fallot

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OBJECTIVES The purpose of this study was to determine if left ventricular (LV) systolic dysfunction was also a predictor of sudden cardiac death (SCD) in adults late after repair of tetralogy of Fallot (TOF).

BACKGROUND Previous studies looking at risk factors for SCD in adults with repair of TOF have focused on the right ventricle (RV).

METHODS A retrospective chart review of patients assessed at the Toronto Congenital Cardiac Centre for Adults was performed. Twelve adult patients with repaired TOF and SCD were identified (SCD group). A total of 125 living adult patients with repaired TOF were randomly selected for comparison (control group).

RESULTS Patients with SCD were more likely to exhibit moderate or severe pulmonary regurgitation (92% vs. 51%, $p = 0.02$), have a history of sustained ventricular tachycardia (42% vs. 6%, $p < 0.01$), and have a QRS ≥180 ms (56% vs. 13%, $p = 0.02$). Moderate or severe LV systolic dysfunction was also significantly more common in patients with SCD than in the control group (42% vs. 9%, $p < 0.01$) with a positive predictive value of 29%. The combination of moderate or severe LV systolic dysfunction and QRS ≥180 ms had a positive and negative predictive value for SCD of 66% and 93%, respectively.

CONCLUSIONS Moderate or severe LV systolic dysfunction is significantly more common in adult patients with repaired TOF and SCD. The combination of QRS ≥180 ms and significant LV systolic dysfunction has high positive and negative predictive value for SCD. The implication of the role of prophylactic antiarrhythmic implantable cardiac defibrillator insertion in these patients needs further elucidating. (J Am Coll Cardiol 2002;40:1675–80) © 2002 by the American College of Cardiology Foundation

Intracardiac repair for tetralogy of Fallot (TOF), the most common cyanotic congenital heart defect, has been performed for over four decades with excellent long-term results (1,2). Risk for late sudden cardiac death (SCD), however, occurs in as many as 6% over 30 years of follow-up (3–15).

Several risk factors for the development of sudden death have been suggested including severe pulmonary regurgitation (PR), older age at repair, transient complete heart block postoperatively, increased right ventricular (RV) pressure after repair, ventricular premature contractions, late onset of complete heart block, and, more recently, QRS duration ≥180 ms (3–15). Indeed, increased QRS width has been shown to correlate with RV dilation and the propensity for sustained ventricular arrhythmia and SCD (4,15). Although some of these may be sensitive predictors, most of these risk factors have a rather low positive predictive value (3–15) and, as such, cannot be relied on to predict SCD. Further risk stratification is required in this patient population before intervention to prevent SCD can be recommended.

Left ventricular (LV) systolic dysfunction is an independent predictor for SCD in patients with ischemic and idiopathic dilated cardiomyopathy (16–19). We hypothesized that LV systolic dysfunction may play a role in SCD in adults patients with repaired TOF. The purpose of this study was to evaluate the prevalence of LV systolic dysfunction in these patients and assess its value in predicting SCD.

METHODS

Patient population. Adult patients (≥18 years old) with SCD were identified by a retrospective chart review performed on all patients with repaired TOF assessed at the Toronto Congenital Cardiac Centre for Adults (TCCCA). Sudden cardiac death was defined as a natural but unexpected death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms (20). As the purpose of this study was to examine for late events, patients who did not survive beyond 30 days after the initial TOF repair were excluded. Of the 602 living patients with repaired TOF listed in the TCCCA comput-

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Abbreviations and Acronyms

EF = ejection fraction
LV = left ventricle or left ventricular
NYHA = New York Heart Association
PR = pulmonary regurgitation
RV = right ventricle or right ventricular
SCD = sudden cardiac death
TCCCA = Toronto Congenital Cardiac Centre for Adults
TOF = tetralogy of Fallot
VT = ventricular tachycardia

erized database, 292 were excluded because they did not have complete follow-up data (i.e., echocardiogram or electrocardiogram) as they were not followed serially by the TCCCA. Of the remaining 310 living patients, every second patient from the alphabetized list was selected until it was judged that a large enough control group had been assembled (n = 125).

Baseline information including demographics and operative reports was obtained from the patient's medical records. New York Heart Association (NYHA) class, symptoms, clinical events, and medication intake were obtained from the latest clinical visit note in all patients. The research ethics board of the Toronto General Hospital approved this study.

Electrocardiographic measurements. QRS duration for all patients was analyzed manually from their latest standard (25 mm/s and 1 mV/cm) resting 12-lead electrocardiograms. QRS duration was defined as the maximal QRS length in any lead from the first inflection to the final sharp vector crossing the isoelectric line. Electrocardiographic data from patients who were paced were excluded from the QRS analysis (4).

Echocardiographic analysis. Data from the patient's most recent transthoracic echocardiogram before their SCD or latest clinical visit were reviewed by an experienced echocardiographer. The degree of pulmonary, tricuspid, mitral, and aortic regurgitation as well as RV dilation, RV and LV systolic function was recorded. The magnitude of valvular regurgitation was graded as none, mild, moderate, or severe using color and Doppler flow criteria (21,22). Right ventricular dilation was estimated from RV inlet measurements made at end-diastole from apical four-chamber view (23). Right ventricular enlargement was considered mild when the RV inlet measured between 40 and 50 mm, moderate when it was between 50 and 60 mm, and severe when it was >60 mm. Systolic function of the LV on echocardiography was visually assessed and recorded as normal (ejection fraction [EF] >60%), mildly reduced (EF = 40% to 59%), moderately reduced (EF = 20% to 39%), and severely reduced (EF <20%) (24).

Statistical analysis. Statistical calculations were performed using the SPSS package (SPSS for Windows, Base System User's Guide, Telease 10.0 Chicago: SPSS, 2000). Data were presented as mean ± 1 SD where appropriate. Patients were classified into two groups based according to the occurrence of SCD. Fisher exact or chi-square tests were used to compare categorical variables, as appropriate. Student *t* tests were used for comparisons of continuous variables. Kaplan-Meier survival curve was used to estimate survival of patients with and without moderate or severe LV systolic dysfunction, and a log-rank test was used to compare survival between these two groups. Significance was set at 0.05 (two-sided).

RESULTS

Patients. A total of 602 patients with repaired TOF were identified from the TCCCA database. Twenty-seven patients (4%) were known to have died. Of these, 15 patients were excluded from the study: four had died from postoperative complications within 30 days after their TOF repair, five died from noncardiac causes (two from motor vehicle accident, two from cancer, one from liver dysfunction), five died from nonsudden cardiac causes (four from progressive congestive heart failure and one from infective endocarditis), and one died from an SCD before any investigations

Table 1. Sudden Cardiac Death Group Characteristics

Patient	Age at SCD	Place of SCD	Outcome of SCD	History of Arrhythmia	Arrhythmia Medications	Autopsy Results
1	73	Out of Hospital	Death	None	None	NA
2	37	Out of Hospital	Death	Atrial flutter and VT	Amiodarone	? arrhythmia
3	24	Out of Hospital	Death	Atrial flutter	Digoxin	? arrhythmia
4	45	Out of Hospital	Death	None	None	NA
5	33	Out of Hospital	Death	None	None	? arrhythmia
6	57	Out of Hospital	Resuscitated*	VT	Amiodarone	NA
7	54	Out of Hospital	Death	None	Digoxin	NA
8	29	Out of Hospital	Death	WPW	Digoxin and Propatenone	? arrhythmia
9	24	Out of Hospital	Death	None	None	? arrhythmia
10	47	Out of Hospital	Resuscitated*	VT	Sotalol	NA
11	62	Hospital†	Death	Atrial flutter	Amiodarone	NA
12	70	Hospital†	Death	SVT and VT	Amiodarone	NA

*Patients subsequently had a pulmonary valve replacement with ventricular cryoablation and AICD insertion; †hospitalized for congestive heart failure but clinically stable at time of death.

AICD = antiarrhythmic implantable cardiac defibrillator; NA = not available; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VT = ventricular tachycardia; WPW = Wolff Parkinson White.

Table 2. Demographic and Surgical Data for the SCD and Control Groups

	SCD Group (n = 12)	Control Group (n = 125)	p Value
Male	9 (75%)	71 (57%)	0.36
Palliative surgery			
BT shunt	5 (42%)	63 (50%)	0.76
Mean age (yrs)*	5 ± 5	4 ± 7	0.10
Tetralogy repair			
Surgical era 1950s–1970s	7 (58%)	79 (63%)	0.76
Surgical era 1980s–2000s	5 (42%)	46 (37%)	0.76
Mean age at repair (yrs)	20 ± 21	13 ± 13	0.07
Transannular patch	7 (58%)	67 (54%)	1.00
Co-morbidities			
Coronary artery disease	2 (17%)	4 (3%)	0.09
Re-operations	6 (50%)	52 (42%)	0.76
Mean number per patient	0.62	0.50	0.53
Mean age (yrs) at last surgery†	43 ± 19	29 ± 17	0.15
Surgery type			
Resection of aneurysm	1 (8%)	1 (1%)	0.17
Pulmonary valve replacement	4 (33%)	27 (22%)	0.47
Relief of RVOTO	0 (0%)	22 (18%)	0.21
Closure of residual shunts	3 (25%)	10 (8%)	0.11
Mitral valve replacement	2 (17%)	0 (0%)	0.09
Aortic valve replacement	0 (0%)	3 (2%)	1.00
Tricuspid valve surgery	2 (17%)	7 (6%)	0.18
Atrial cryoablation	0 (0%)	6 (5%)	1.00
Ventricular cryoablation	0 (0%)	1 (1%)	1.00
Maze procedure	0 (0%)	2 (2%)	1.00
CABG	1 (8%)	1 (1%)	1.00
Last follow-up			
Mean age (yrs)	45 ± 18	38 ± 14	0.10
Mean time (yrs) from repair	21 ± 9	25 ± 9	0.13

*Data available for 68 patients; †Data available for 58 patients.
BT = Blalock-Taussig; CABG = coronary artery bypass surgery; RVOTO = right ventricular outflow tract obstruction; SCD = sudden cardiac death.

could be performed. The study group thus comprised 12 patients (2%) with SCD (two resuscitated from SCD and alive, 10 deceased) (Table 1) and a control group of 125 living patients. Forty-seven (34%) of these patients (eight from the SCD group and 39 from the control group) were previously reported in other studies (15,25).

Demographic and surgical data are presented in Table 2. There was no significant difference between the two groups in terms of the era of surgical repair and age at last follow-up, although a trend towards older age at repair was noted in the SCD group (20 ± 21 years vs. 13 ± 13, p = 0.07).

Clinical outcome. Clinical data are presented in Table 3. The SCD group was more symptomatic with a significantly higher incidence of dyspnea, orthopnea, palpitations, edema, pre-syncope/syncope, and sustained ventricular tachycardia (VT) compared with the living control group. Diuretics, angiotensin-converting enzyme inhibitors, antiarrhythmics, and anticoagulants/antiplatelets were also prescribed more commonly in the SCD group. Eight patients (67%) in the SCD group were prescribed antiarrhythmics. The majority were receiving amiodarone alone (4 patients) or digoxin alone (2 patients), one patient used sotalol (1 patient), and one patient was prescribed propafenone and digoxin (1 patient).

Electrocardiographic data. Electrocardiographic data were recorded in 132 of 137 patients (three patients in the SCD group and two in the control group were excluded due to paced rhythms). Mean QRS duration was significantly greater in the SCD group compared with controls (170 ± 14 vs. 153 ± 21 ms, p = 0.02), and a QRS duration ≥180 ms was significantly more common in the SCD group compared with the control group (56% vs. 13%, p = 0.02).

Echocardiographic features. Echocardiographic data are presented in Table 3. Patients with SCD had a greater incidence of moderate-to-severe PR as well as a trend toward moderate-to-severe RV dilation (92% vs. 51%, p = 0.02 and 54% vs. 32%, p= 0.09, respectively). Furthermore, patients with SCD had a significantly higher incidence of moderate or severe LV systolic dysfunction when compared with the control group (42% vs. 9%, p < 0.01). When patients who had paced rhythms at their latest echocardiogram were excluded, the aforementioned statistically significant difference in the incidence of moderate or severe LV systolic dysfunction between the SCD and control group was still present (33% vs. 7%, p < 0.01). In addition, there was no significant difference in the incidence of moderate or severe LV systolic dysfunction in patients with normal-to-mild RV dilation or moderate-to-severe RV dilation (10% vs. 15%, p = 0.40). The positive and negative predictive value of moderate or severe LV systolic dysfunction for SCD was 29% and 94%, respectively. When combined with QRS ≥180 ms, the positive and negative predictive value for SCD was 66% and 93%, respectively.

Survival analysis. In a Kaplan-Meier analysis, moderate or severely impaired LV systolic function was associated with a greater mortality (p < 0.01) (Fig. 1).

DISCUSSION

The present study provides, for the first time, evidence that moderate or severe LV systolic dysfunction is an important predictor of SCD in adult patients late after TOF repair. The combination of moderate or severe LV systolic dysfunction and QRS ≥180 ms had a high positive and negative predictive value for SCD.

RV. Previous studies of risk factors for SCD in adults with repaired TOF have focused on RV hemodynamics. Significant PR has been associated with RV dilation, and, more recently, a mechanoelectric relationship between increased QRS duration and RV dilation has been demonstrated. In fact, in adult patients with repaired TOF, a QRS duration ≥180 ms has been found to be predictive of sustained VT and SCD (4,15). It is believed that RV myocardial stretch engenders areas of inhomogeneous electrical activity (25,26), predisposing to the development of ventricular arrhythmia (4,26–28). In our study we corroborated the association of SCD with significant PR, sustained VT, and QRS width ≥180 ms. A trend toward moderate-to-severe RV dilation in the SCD group was shown but did not reach statistical significance. The qualitative nature of two-

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Table 3. Clinical Outcomes, Electrocardiographic and Hemodynamic Data for the SCD and Control Groups

	SCD Group (n = 12)	Control Group (n = 125)	p Value
Symptoms			
Dyspnea	7 (58%)	31 (25%)	0.03
Orthopnea	5 (42%)	15 (12%)	0.01
Palpitations	10 (83%)	41 (33%)	0.01
Presyncope or syncope	7 (58%)	14 (11%)	< 0.01
Edema	5 (42%)	16 (13%)	0.01
NYHA class ≥ 2	4 (33%)	18 (14%)	0.12
Atrial fibrillation or atrial flutter	3 (25%)	23 (19%)	0.74
Ventricular tachycardia	5 (42%)	7 (6%)	< 0.01
Medications			
Anticoagulation/antiplatelets	7 (58%)	29 (23%)	0.05
Antiarrhythmic drugs	8 (67%)	18 (14%)	< 0.01
ACE inhibitors	5 (42%)	16 (13%)	0.02
Diuretics	6 (50%)	13 (10%)	< 0.01
Beta-blockers	2 (17%)	5 (4%)	0.05
ECG data			
Number of patients with data	9	123	—
Mean (ms) QRS duration	170 ± 14	153 ± 21	0.02
QRS ≥ 180 ms	5 (56%)	16 (13%)	0.02
Echocardiographic data			
Mean age (yrs) of last echocardiogram	43 ± 18	38 ± 14	0.58
Moderate or severe LV dysfunction	5 (42%)	11 (9%)	< 0.01
RV > mild dilation	7 (54%)	40 (32%)	0.09
Mean RVSP (mm Hg)*	46 ± 19	44 ± 13	0.54
PR ≥ moderate	11 (92%)	64 (51%)	0.02
TR ≥ moderate	6 (50%)	38 (30%)	0.38
MR ≥ moderate	2 (17%)	7 (6%)	0.06
AR ≥ moderate	0 (0%)	1 (1%)	0.87

*Data available for 90 patients only.

ACE = angiotensin-converting enzyme; AR = aortic regurgitation; ECG = electrocardiogram; LV = left ventricular; MR = mitral regurgitation; NYHA = New York Heart Association; PR = pulmonary regurgitation; RV = right ventricle; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation.

dimensional transthoracic echocardiography and its lack of precision in assessing RV size is well known and probably accounts for our findings. QRS duration, a more quantifiable and reproducible measure of RV size (29), was indeed significantly prolonged in our SCD group. It is clear that RV hemodynamics in adult patients with repaired TOF play a major role in the pathophysiology of SCD, but we think that RV hemodynamics may constitute only part of the problem.

LV. In our study moderate or severe LV systolic dysfunction was demonstrated to be a strong predictor in SCD. The etiology of LV systolic dysfunction in our cohort of patients, however, remains unclear. The era of intracardiac repair did not differ between the two groups, making poor myocardial protection at the time of repair an unlikely culprit. A trend toward older age at intracardiac repair in our SCD group, however, was observed. Older age at repair, with longer periods of volume overload and chronic hypoxemia, may, in part, explain the degree of LV dysfunction seen in these patients (26). Of note, older age at repair was previously found to be a predictor of LV systolic dysfunction in a study reported by Hausdorf et al. (30), but data on the incidence of SCD in these patients was not provided.

Patients in our SCD group had clearly been more symptomatic over the duration of follow-up, with an increased incidence of dyspnea, arrhythmias, and syncope (evidence supportive of our findings of LV systolic dysfunction on echocardiography), but were all clinically stable with appropriate medical therapy, with no difference in NYHA class at the time of their sudden death.

In our study amiodarone was the single most prescribed antiarrhythmic medication in the SCD group, a medication that is known to protect from, and not to provoke, SCD (31,32). Digoxin was also commonly prescribed as a standalone medication (except in one case with propafenone), and, while it is known to lower the ventricular fibrillation threshold, it should not have caused an increased incidence in SCD in our population as was shown with the Digoxin Investigation Group (DIG) study (33).

Our hypothesis is that, while abnormal RV hemodynamics with its associated RV stretch and scarring provide the substrate for VT, it is the LV hemodynamics that ultimately dictate the clinical outcome of such arrhythmias.

Given the high positive and negative predictive value of moderate or severe LV systolic dysfunction and QRS >180 ms to predict SCD in adult patients with repaired TOF, the role of prophylactic antiarrhythmic implantable cardiac defibrillator insertion in these patients warrants further elucidating.

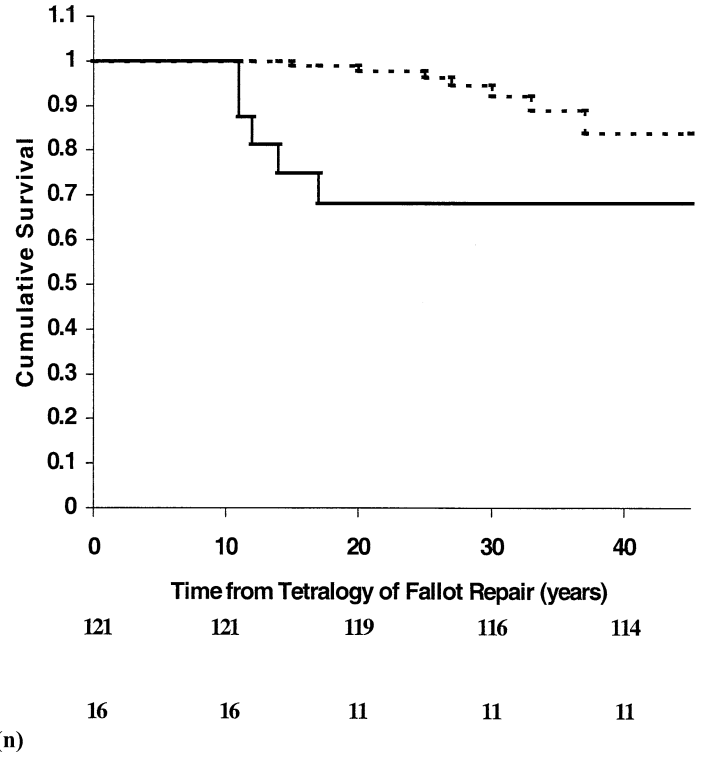

Figure 1. Kaplan-Meier survival curve beyond the age of 18. **Solid line** = patients with moderate or severe left ventricular (LV) systolic dysfunction; **dotted line** = patients with normal or mild reduction in LV systolic function. The difference between the two groups reached significance ($p < 0.01$). n = number of patients remaining in follow-up at the corresponding time after the tetralogy of Fallot repair.

Study limitations. This was a retrospective study and includes only adult survivors who successfully made the transition from a pediatric to an adult institution. The size of the SCD group is small, and the study may lack the power to determine a significant difference in ages of palliation and surgical repair between the two populations in the study. In addition, autopsy reports were not available for all of the patients in the SCD group, and, thus, it is not possible to ascertain that their deaths were solely arrhythmic in nature. There are also limitations with echocardiographic assessment of LV systolic function in this study, which was determined by visual assessment by an experienced echocardiographer rather than by quantitative methods. However, this limitation is minimized by the fact that visual assessment of LV EF has been shown to be at least equal, if not superior to, quantitative measurements of LV systolic function when performed by an experienced echocardiographer (34). Symptoms of left-sided heart failure were also more common in our SCD, which would support our echocardiographic assessment of LV systolic function. Of note, much of the data reflect outcomes of operations that were done in an earlier surgical era, and newer current surgical strategies may diminish the incidence of LV systolic dysfunction and SCD in the future. This study, however, is representative of the adult population with repaired TOF that is being cared for at the present time, and our results do apply to the current patient population.

Conclusions. Moderate or severe LV systolic dysfunction is a risk factor for SCD and predicts survival in adult patients with repaired TOF. The combination of moderate or severe LV systolic dysfunction and QRS ≥180 ms had a positive and negative predictive value for SCD of 66% and 93%, respectively. The implications of the role of prophylactic antiarrhythmic implantable cardiac defibrillator insertion in these patients need further elucidating.

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