Ventricular Arrhythmia and Life-Threatening Events in Patients With Repaired Tetralogy of Fallot

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Risk stratification for malignant arrhythmias and risk of sudden cardiac death in tetralogy of Fallot (TOF) remains challenging. We aimed to ascertain factors associated with life-threatening arrhythmic events. A multicenter retrospective case-control study including 72 TOF patients with documented cardiac arrest and/or sustained ventricular tachycardia, compared with 216 controls matched for era of surgery. The mean age at event in the cases was 27.3 ± 12.5 years. The majority (57%) presented with sustained ventricular tachycardia. Fatal events occurred in 9. Random forest analysis and a decision tree demonstrated surgical era specific risk factors (< vs ≥ 1980). For both eras, arrhythmic symptoms and left ventricular dysfunction were strongly associated with malignant arrhythmias. In addition, right ventricular dysfunction and age at repair ≥ 6.5 years preceded by a shunt were associated with a higher risk group in the early era, whereas a trans-annular patch type repair was associated with a lower risk group in the recent era. For the moderate and high-risk groups, the decision tree showed a sensitivity of 88.4% and specificity of 68.1%. An "importance factor" was calculated for each predictor, creating a risk score and 4 risk categories. In conclusions, this risk stratification scheme, based on clinical history and noninvasive testing, allows categorization of TOF patients at high risk of malignant arrhythmia. A multicenter prospective evaluation of the accuracy of this scoring system is now being planned. **(Am J Cardiol 2020;132:126−132)**

There continues to be a significant incidence of late morbidity and mortality related to ventricular tachycardia (VT) in patients with repaired tetralogy of Fallot (TOF) and its variants.[1−3] Since the seminal report by Wolff in 1972,[4] multiple studies have analyzed clinical and laboratory risk factors, but this task remains difficult.[5−11] Previous studies were limited by small cohorts with the primary outcome of arrhythmic sudden death or documented VT, or by imperfect surrogate outcomes such as ventricular ectopy and implantable cardioverter defibrillator (ICD) shocks.[6−11] Koyak et al attempted to validate a risk score based on appropriate ICD shocks and showed that, of the 6 variables identified, only NSVT was associated with the outcome.[12] Other studies were also limited by inclusion criteria restricted to subjects who underwent cardiac magnetic resonance imaging (cMRI) or preselected for electrophysiologic testing.[3,13,14] This multicenter case-control study aimed to collect a relatively large number of cases having firmly documented malignant rhythm events (sudden cardiac death or sustained VT), with a goal of identifying a practical predictive tool applicable to the general TOF population.

Methods

This was a multicenter case-control study, with 3 controls for each case matched for surgical era. The project was undertaken under the auspices of the Pediatric and Congenital Electrophysiology Society, and ethics board approval was obtained from each participating institution. Inclusion criteria comprised patients with TOF (with or without pulmonary atresia), double outlet right ventricle with a sub-aortic ventricular septal defect (VSD) having undergone TOF-like repair, and transposition of the great arteries (d-TGA) with a VSD who had undergone a Rastelli type of repair. Subjects must have undergone at least 1 attempt at complete intracardiac repair involving VSD closure and relief of right ventricular (RV) outflow tract obstruction by either patch, conduit, or muscle resection. Patients with sub-aortic stenosis or those simply palliated by shunts were excluded. Inclusion criteria for cases included: (1) sudden death without identifiable non-cardiac cause that was suspected or documented to be due to any arrhythmia, whether or not the patient was successfully resuscitated, (2) documented spontaneous sustained VT, even if hemodynamically tolerated, and (3) documented appropriate ICD discharge for VT/VF. Controls had to have undergone surgery within a 5-year window of the case to minimize the influence of shifting surgical techniques.

A total of 13 institutions participated in the study, and the reported events occurred between 1980 and 2010. Collected information included demographics, medical and surgical history, electrocardiograms (ECGs), chest X-ray,

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See page 132 for disclosure information.

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ambulatory monitoring or exercise stress test (EST) data, and cardiac imaging by echocardiogram or cMRI. Invasive hemodynamic data and results of an electrophysiology study were included when available. Data chosen for analysis had to satisfy a specific timeline as follows: 12-lead ECGs had to be within 2 years of the event or last follow-up, whereas Holter recording, exercise test, cardiac catheterization or chest x-ray data had to be within 5 years of the event or last follow-up. Data were coordinated at Children's Hospital Boston. Complete surgical repair was categorized into 5 types based on the RV outflow tract surgical intervention and the complexity of the repair. The 5 categories included: (1) pulmonary valve trans-annular patch (TAP), (2) non trans-annular pulmonary outflow tract patch (Non-TAP), (3) use of a right ventricle to pulmonary artery conduit (Conduit), (4) Rastelli procedure, and (5) a staged repair. For staged repairs, the date of the last operation was used for the age at complete repair. Surgical repair was compared between 'TAP', 'Non-TAP', and 'Complex Repair' (combined categories 3 to 5). Imaging data included chest x-ray, echocardiogram or cMRI. When quantitative data were available, RV outflow tract obstruction (RVOTO) was graded as mild, moderate and severe based on a peak gradient of <35, 35 to 65, and >65 mm Hg, respectively. Otherwise, a reported qualitative descriptive category was used. The same applied for the RV percent-systemic pressure estimate. Left ventricular systolic dysfunction was defined as mild (Ejection Fraction 45% to 54%), moderate (Ejection Fraction 35% to 44%) and severe Ejection Fraction < 35%). Imaging data was dichotomized during analysis, with 'moderate-severe' compared with 'normal-mild'.

For statistical analysis, continuous variables were graphically analyzed for the normality of their distribution. They were transformed if necessary and presented as means with standard deviation and were analyzed using *t* tests. Categorical variables are presented as counts with percentages and were analyzed using the Fisher Exact test or the Chi-square test where appropriate. The primary analysis was to compare cases and controls. Missing baseline variables were imputed using a regression model. Variables with a priori determined clinical significance and a statistically significant difference between the 2 study groups were compared using marginal event rate plots with adjusted relative event values. A random forest model was used to develop a decision tree analysis and identify variables associated with the cases. The 500 random forest models were created requiring a minimum node size of 5. The variable importance was determined by a Gini plot of the forest models, indicating the loss of information if the variable is not included. From these, conventional classification trees were developed which identified groups of similar outcomes based on optimal splits in the selected covariates. The strength of each variable is proportionally represented by the length of the vertical arm in the tree. Adjusted relative risk values in the decision tree were used to define low, moderate, and high-risk groups. Sensitivity and specificity were calculated for a composite of the moderate and high-risk groups. Using the variable importance score from the random forest analysis results, as well as the variable ranking in the decision tree, an 'Importance Factor' was assigned to each variable, per surgical era. Further, 4 risk groups were defined based on specific score ranges. Statistically significant data was defined as a p-value of < 0.05. Data analysis was performed using SAS version 9.3 and R version 3.0.

Results

The study group consisted of 288 patients (72 cases and 216 controls). Clinical characteristics are presented in Table 1. TOF was the most common cardiac diagnoses (96%) and a single stage approach with a TAP was the most common surgical repair (76%). An aorto-pulmonary shunt before complete repair was more commonly performed in the cases (63% vs 45%, $p = 0.014$), but the mean age at shunt placement was comparable between cases and controls (1.6 ± 2.3 vs 2.3 ± 3.2 years, $p = 0.17$), as was the age at complete repair after a shunt (8.6 ± 8.5 vs 9.7 ± 7.4, $p = 0.43$), respectively. Early post-op arrhythmias were rare: atrial flutter (1 case), VT or VF (3 cases), and permanent heart block (9 cases and 16 controls). On long-term follow-up, right-sided cardiac failure (31% vs 16%, $p = 0.01$) and arrhythmia-like symptoms of syncope, palpitation or pre-syncope (64% vs 21%, $p < 0.001$) were more common in the cases (Table 1). The arrhythmia-like symptoms occurred before the primary outcome event in the cases. There was no history of appropriate shock for the 8 controls with a primary prevention ICD.

The mean age at event for the cases was 27.3 ± 12.5 years and the event categories are presented in Table 2. The majority (57%) were patients with sustained VT without cardiac arrest. Ultimately, a total of 16 of the 72 cases (22%) were reported deceased upon completion of the study, all in the non-ICD group. A secondary prevention ICD was implanted in 22 survivors and 6 are known to have received an appropriate shock.

ECG, Holter, and EST data are presented in Table 3. QRS duration on ECG was slightly longer in cases versus controls (162 ± 26 ms vs 152 ± 30 ms, $p = 0.01$); however, there was no statistically significant difference when categorized as a QRS $\geq$ 140, 160, or 180 ms. Imaging data is presented in Table 4, with cases having a higher proportion of patients with moderate to severe RVOTO, PR, TR, RV dilation, and moderate-severe RV and LV dysfunction. Hemodynamic data is presented in Supplemental Table 1. There was no significant difference in the RV or LV end-diastolic pressure between the 2 groups. Data from electrophysiology (EP) studies were available for 55 cases and 43 controls and were all performed after the index arrhythmic event in the cases (Supplemental Table 1). Overall, there were a total of 180 EP studies. The mean age at the first EP study was not statistically different between the 2 groups. Sustained VT was induced in 55% of cases and only 12% of controls ($p < 0.001$). Ablation for a ventricular or atrial substrate was attempted in 22 patients (23%) and was successful in 19, 12 of whom were in the control group. The decision to proceed with an ICD implantation based on the results of the EP study was made in 15 patients (15%) including 7 cases (13%). When all EP studies were reviewed, including multiple studies in 48 patients,

Table 1
Clinical and Surgical patient characteristics for the entire cohort, comparing cases and controls: mean±SD, n (%)

Variables	Total cohort (n = 288)	Cases (n = 72)	Controls (n = 216)	p
Age at last follow-up (years)	33.3 ± 14.5	31.7 ± 12.9	33.8 ± 15.0	0.287
Diagnosis				
TOF	275 (96%)	67 (93%)	208 (96%)	
DORV	5 (2%)	2 (3%)	3 (1%)	0.515
d-TGA	8 (3%)	3 (4%)	5 (2%)	
Genetic Diagnosis	21 (7%)	7 (10%)	14 (7%)	0.432
Age at complete surgical repair (years)	6.5 ± 6.9	7.2 ± 7.5	6.2 ± 6.7	0.273
Era of repair (< 1980)	163 (57%)	43 (60%)	120 (56%)	0.584
Type of repair				0.004
TAP	218 (76%)	47 (65%)	171 (79%)	
Non-TAP	13 (5%)	3 (4%)	10 (5%)	
Conduit	37 (13%)	10 (14%)	27 (13%)	
Rastelli	16 (6%)	9 (13%)	7 (3%)	
Staged	4 (1%)	3 (4%)	1 (1%)	
Shunt before repair	143 (50%)	45 (63%)	98 (45%)	0.014
Type of shunt				0.099
Blalock-Tausig	104 (73%)	30 (67%)	74 (76%)	
Central	2 (1%)	2 (4%)	0	
Pott's	13 (9%)	3 (7%)	10 (10%)	
Waterston	24 (17%)	10 (22%)	14 (14%)	
Symptoms				
Exercise intolerance	111 (39%)	32 (44%)	79 (37%)	0.264
Palpitations	74 (26%)	38 (53%)	36 (17%)	<0.001
Dizziness	36 (13%)	21 (29%)	15 (7%)	<0.001
Syncope	22 (8%)	16 (22%)	6 (3%)	<0.001
NYHA 3-4	30 (11%)	14 (20%)	16 (7%)	0.006
Medications				
None	101 (35%)	28 (39%)	73 (34%)	0.477
Digoxin	57 (20%)	21 (29%)	36 (17%)	0.026
Diuretics	66 (23%)	18 (25%)	48 (22%)	0.630
Angiotensin converting enzyme inhibitor	38 (13%)	10 (14%)	28 (13%)	0.842
Coumadin	35 (12%)	9 (13%)	26 (12%)	0.999
Other Meds	117 (41%)	16 (22%)	101 (47%)	<0.001
Class 1A: quinidine	1 (1%)	1 (2%)	0	0.250
Class 1B: mexiletine, dilantin or tocainide	10 (4%)	10 (14%)	0	<0.001
Class 1C: encainide, flecainide or propafenone	5 (2%)	3 (4%)	2 (1%)	0.102
β-Blockers	64 (22%)	13 (18%)	51 (24%)	0.413
Sotalol	8 (3%)	2 (3%)	6 (3%)	0.999
Amiodarone	12 (4%)	7 (10%)	5 (3%)	0.013
Calcium channel blocker	3 (1%)	2 (3%)	1 (1%)	0.155
Any anti-arrhythmic drug	94 (33%)	33 (46%)	61 (28%)	0.009
Atrial pacemaker	1 (1%)	0	1 (1%)	0.999
Ventricular pacemaker	2 (1%)	1 (1%)	1 (1%)	0.438
Dual chamber pacemaker	15 (5%)	2 (3%)	13 (6%)	0.371
ICD	20 (7%)	12 (17%)	8 (4%)	<0.001

p values are for comparisons between study and control group.

sustained VT was induced in 38 cases (69%) and 9 controls (21%) ($p < 0.001$).

Random forest analysis was used to explore for variables associated with the outcome of life-threatening arrhythmic events. Surgical era was determined to be important for categorization of risk predictors based on a priori clinical perspective and univariate analysis using marginal event rate plots. Early versus recent surgical era was defined as surgical repair completed before versus starting in 1980. The random forest model included the following variables: (1) surgical era, (2) arrhythmic symptoms (palpitations and/or arrhythmic syncope), (3) LV or RV moderate-severe dysfunction, (4) RV pressure load (moderate-severe RVOTO and/or >1/2 systemic RV pressure), (5) RV volume load (moderate-severe PR and/or TR), (6) age at complete repair, (7) shunt pre-repair, (8) complex surgical repair, (9) QRS duration ≥ 180 ms, and (10) sustained or non-sustained VT on Holter or EST. The random forest model analysis yielded the decision tree presented in Figure 1. Low,

Table 2
Cardiac events for the cases (n = 72): n (%)

Event	Cases
Sudden arrhythmic cardiac death	9 (13%)
Resuscitated arrhythmic cardiac arrest	15 (21%)
Sustained ventricular arrhythmia without arrest	41 (57%)
Appropriate ICD shock (primary prevention ICD)	7 (9%)

Table 3
Non-invasive electrophysiological investigations, comparing cases and controls: mean±SD, n (%)

ECG	Total cohort (n = 286)	Cases (n = 70)	Controls (n = 216)	p
Age (years)	32.2 ± 14.7	27.6 ± 12.6	33.7 ± 15.1	0.003
Heart rate (beats/min)	74 ± 16	76 ± 19	74 ± 15	0.442
Sinus rhythm	243 (85%)	56 (80%)	187 (87%)	0.183
PR interval (ms)	172 ± 38	181 ± 32	169 ± 40	0.024
QRS interval (ms)	155 ± 30	162 ± 26	152 ± 30	0.010
QRS ≥ 180	53 (19%)	19 (27%)	34 (16%)	0.052
QRS axis (degree)	59 ± 81	61 ± 90	59 ± 79	0.869
QT interval (ms)	435 ± 49	434 ± 55	436 ± 47	0.766
QTc interval	477 ± 42	477 ± 43	476 ± 42	0.856
Right bundle branch block	253 (91%)	64 (90%)	189 (91%)	0.817
Left anterior hemiblock	50 (18%)	19 (27%)	31 (15%)	0.031
Holter Monitoring	(n = 200)	(n = 48)	(n = 152)	
Age (years)	31.3 ± 15.4	25.3 ± 11.9	33.2 ± 15.9	<0.001
Sinus node dysfunction	9 (5%)	5 (10%)	4 (3%)	0.038
Atrioventricular block	34 (17%)	10 (21%)	24 (16%)	0.508
Atrial flutter or fibrillation	3 (2%)	3 (6%)	0	0.013
Other supraventricular tachycardia	47 (24%)	7 (15%)	40 (26%)	0.119
Any sustained or non-sustained ventricular tachycardia	21 (11%)	9 (19%)	12 (8%)	0.055
Exercise Test	(n = 175)	(n = 38)	(n = 137)	
Age (years)	32.2 ± 14.7	26.9 ± 12.1	33.6 ± 15.1	0.013
Sinus node dysfunction	52 (30%)	12 (32%)	40 (30%)	0.845
Atrioventricular block	20 (11%)	2 (5%)	18 (13%)	0.252
Atrial flutter or fibrillation	6 (3%)	0	6 (4%)	0.340
Other supraventricular tachycardia	6 (3%)	2 (5%)	4 (3%)	0.614
Any sustained or non-sustained ventricular tachycardia	8 (5%)	1 (3%)	7 (5%)	0.999

p values are for comparison between study and control group.

moderate, and high-risk groups were defined based on an adjusted relative risk of <1, 1 to 2, and >2, respectively.

The decision tree demonstrated 2 main variables strongly associated with life threatening arrhythmic events in the cases: a history of arrhythmic symptoms (preceding the arrhythmic event in the cases) and LV dysfunction. In addition, the tree showed era specific associations. RV dysfunction and age at repair ≥ 6.5 years preceded by the use of a shunt were associated with a higher risk group in the early era, whereas a TAP type repair was associated with a lower risk group in the recent era. When the moderate and high-risk groups were combined, the decision tree showed a sensitivity of 88% (95% CI: 79% to 94%) and specificity of 68% (95% CI: 65% to 70%). The decision

Table 4
Imaging data, comparing cases and controls: mean±SD, n (%)

	Total cohort	Cases	Controls	p
Chest X-ray	(n = 221)	(n = 62)	(n = 159)	
Age (years)	29.3 ± 14.0	26.4 ± 12.1	30.5 ± 14.6	0.053
Cardiomegaly: moderate-severe	150 (68%)	44 (71%)	106 (66%)	0.527
Pulmonary venous markings: congested-increased	53 (24%)	25 (41%)	28 (18%)	<0.001
Pulmonary arterial flow: congested-increased	32 (15%)	4 (7%)	28 (18%)	0.052
Flow asymmetry	29 (13%)	17 (28%)	12 (8%)	<0.001
Echo or cMRI imaging	(n = 286)	(n = 70)	(n = 216)	p
Age (years)	31.9 ± 14.4	27.6 ± 12.0	33.3 ± 14.8	0.002
Right ventricular outflow tract obstruction: moderate-severe	27 (9%)	12 (17%)	15 (7%)	0.020
Right ventricular pressure > half systemic	42 (17%)	17 (28%)	25 (13%)	0.010
Pulmonary regurgitation: moderate-severe	123 (45%)	38 (61%)	85 (40%)	0.004
Tricuspid regurgitation: moderate-severe	32 (11%)	18 (27%)	14 (7%)	<0.001
Right ventricular size/dilation:				
Normal or mild	81 (29%)	6 (9%)	75 (35%)	
Mild to moderate	103 (37%)	30 (46%)	73 (34%)	<0.001
Moderate or severe	95 (34%)	29 (45%)	66 (31%)	
Right ventricular dysfunction: moderate-severe	31 (11%)	15 (23%)	16 (7%)	0.001
Left ventricular dysfunction: moderate-severe	14 (5%)	10 (15%)	4 (2%)	<0.001
Residual ventricular septal defect: moderate-large	3 (1%)	3 (5%)	0	0.013
Residual atrial septal defect: moderate-large	1 (1%)	0	1 (1%)	0.999

p values are for comparison between study and control group.

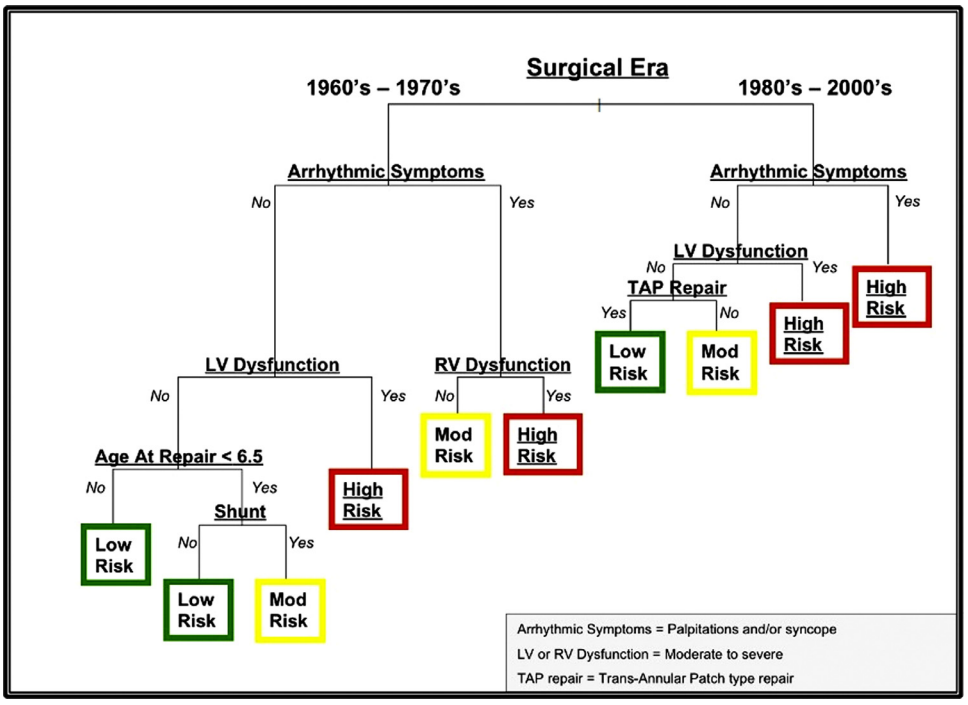

Figure 1. Classification tree based on random forest model. The strength of each variable is proprotionally represented by the length of the vertical arm in the tree.

tree analysis was repeated using 2 different nested groups: one included only TOF patients, the other excluded cases with a primary prevention ICD. Both nested group trees showed no significant difference when compared with the main tree in Figure 1.

Using the variable-importance score in the random forest model and the ranking of the variables in the decision tree, a proportional 'Importance Factor' based on the Gini index was applied to each variable and is presented in Table 5, by era. The potential total score for the early era is 17 and for the recent era 14. Consequently, categories for low, medium, high and very high-risk groups for sudden death or life-threatening arrhythmic events are presented in Table 5. Using the 'Importance Factor', total scores were calculated for all patients. The median score was 5 (range 0 to 14) in the early era and 3 (range 0 to 9) in the recent era. A score ≥ 7, defining the high and very high-risk groups, showed a sensitivity of 54% (95% CI: 44% to 63%) and specificity of 86% (95% CI: 83% to 89%). The 4 risk groups and the relative proportion of events for all patients is presented in Figure 2 as a Kaplan-Meier distribution (Log-rank $p < 0.001$).

Table 5
Variable "Importance Factor" derived using the variable-importance score in the random forest model and the ranking of the variables in the decision tree

Variables	Importance factor	
Surgical era	1960−1970s	1980−2000s
Symptoms (arrhythmic syncope, palpitations)	3	3
Left ventricular dysfunction (moderate-severe)	3	3
Right ventricular dysfunction (moderate-severe)	2	1
Right ventricular pressure load (moderate-severe)	1	1
Right ventricular volume load (moderate-severe)	1	1
Age at repair < 6.5 years	2	0
Shunt pre-repair	2	1
Complex type of repair	1	2
QRSd ≥ 180 ms	1	1
Sustained or non-sustained ventricular tachycardia	1	1
Total Score	17	14
Risk Group	Score	
Low	<3	
Moderate	3-6	
High	7-9	
Very High	>9	

Risk groups are categorized based on a stratified risk of life-threatening arrhythmic events.

Discussion

This study describes an era-specific risk stratification scheme for malignant arrhythmias in patients with repaired TOF. The main strength of this study is the relatively large number of cases with firmly confirmed malignant arrhythmic events. To cast perspective, there was a total of only 4 SCD and 4 patients with VT among the 873 patients enrolled in a recent international multicenter TOF registry (INDICATOR).[9] Furthermore, in another publication including 3 registries with a total of 25790 ACHD patients, there was a total of 26 TOF patients with confirmed or presumed arrhythmic SCD.[15]

The classification tree presented in this study identified incremental risk groups, allowing characterization of patients

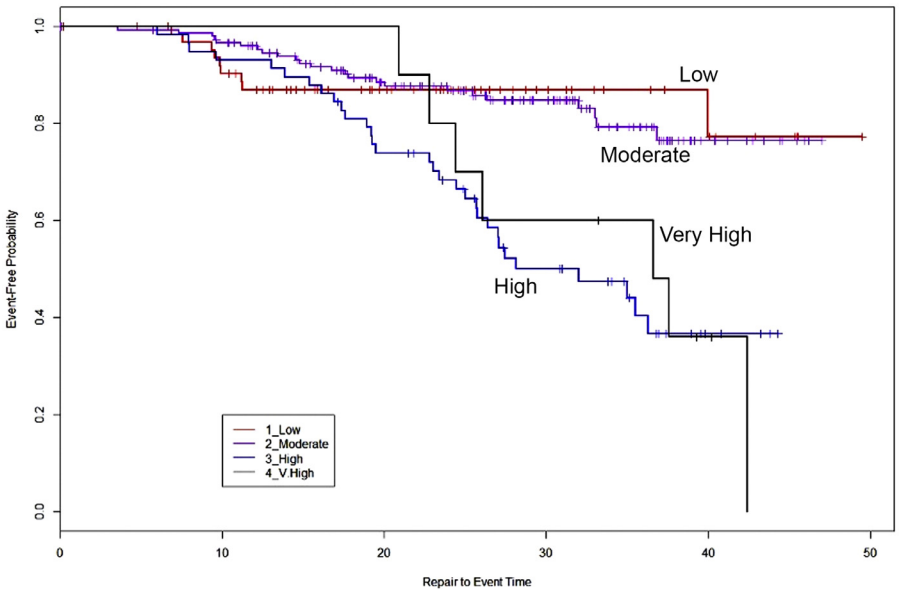

Figure 2. Kaplan-Meier actuarial analysis of events by risk group category, showing the actuarial rate of life-threatening arrhythmic events (note that the curves do not represent accurate event rates due to the study design, rather only represent a comparative relative proportion).

in need of further evaluation. The sensitivity for the high-moderate group was favorable at 88%, potentially useful in the clinical setting. Using the risk factors identified in the Forest Model and the classification Tree, we devised a risk scoring system and 4 subgroup categories. This scoring system incorporates complimentary patient characteristics such as symptoms, myocardial function, hemodynamics, surgical factors and electrophysiologic parameters.

Identifying the effect of surgical era was instrumental in developing an accurate risk classification tree in this study. Others have recognized the importance of stratification by era.[2,16] We also identified arrhythmic symptoms and moderate-severe LV dysfunction as predominant independent risk factors for life threatening arrhythmias in both eras. Other studies have shown an association between moderate-severe LV dysfunction and life threatening arrhythmias, but were limited by a small number of 8 to 14 cases (SCD and VT) per study.[6,9,13,17] In a larger study of 551 TOF patients, a high prevalence of LV dysfunction was identified albeit not associated with VT on multivariable analysis.[18] In the multi-database cohort of 25790 ACHD patients, moderate-severe systemic and sub-pulmonary ventricular dysfunction were predictors of sudden cardiac death for the overall cohort on multivariable analysis, but only on univariate analysis for the TOF subgroup.[15] In contrast, our data, based on a relatively large cohort, highlights the hierarchy of LV dysfunction in a multivariable risk stratification scheme for patients with repaired TOF and malignant arrhythmic events.

For the contemporary surgical era of 1980 to 2000's in our cohort, complex or staged surgery was associated with additional risk when compared with the TAP technique performed in the majority of subjects. In the landmark study by Gatzoulis et al, although TAP was associated with an increased risk of SCD, it was in fact associated with a decreased risk of VT.[5] Although Nollert et al initially showed an association between TAP and late mortality,[19] their subsequent study, along with other recent studies, failed to show the same.[10,11,20 11] They observed that of the studies showing TAP as a risk factor, the average age at repair was > 10 years.

For the early era of 1960 to 1970's in our cohort, RV dysfunction and a palliative aorto-pulmonary shunt identified higher risk groups. However, the shunt was in the context of age at repair < 6.5 years, whereas older age at repair was not a risk factor. A history of shunt surgery has been previously shown to be independently associated with all-cause mortality in repaired TOF from the same early era (1968 to 1980).[10] Patients not requiring a shunt and undergoingt repair at an older age may represent a subgroup with less severe RVOTO and cyanosis, and potentially at less risk for pro-arrhythmic myocardial injury. In a histopathology study of RV muscle tissue obtained at the time of TOF repair, risk factors for hypertrophy and fibrosis were hypoxia, polycythemia and elevated RV end-diastolic pressure.[21]

QRS duration and LV end-diastolic pressure (LVEDP) were not identified as independent predictors in this study, nor in several other recent studies.[7,8,10–12] In a validation study, LVEDP could not be assessed as this invasive measurement was not available for most patients; rather, only NSVT correlated with appropriate shocks in TOF patients with a primary prevention ICD.[12]

The inherent limitations of this study are its retrospective design, limited patient material and possible recall bias. In addition, although all outcomes were adjudicated, sudden cardiac arrests with no documented rhythm can only be presumed secondary to a ventricular arrhythmia. A rapidly conducted atrial tachycardia or non-arrhythmic etiology cannot be confidently excluded. Although the majority of patients presented with monomorphic ventricular tachycardia, the relatively small numbers did not allow for a subgroup analysis or identification of risk factors specific to this group. Lastly, appropriate ICD shock is an imperfect surrogate for sustained VT, although these were fortunately a small portion of the

cases, and a subgroup analysis excluding these patients showed the same results for the decision tree.

In conclusion, the genesis of life-threatening arrhythmias in patients with TOF is a time-dependent phenomenon that is the culmination of several inter-dependent variables. Identifying the most reliable predictors will continue to be a quest. This case-control study has shed light on the importance of surgical era in the evaluation of risk factors and has placed certain variables such as symptoms and systemic ventricular dysfunction at the forefront of risk stratification. The proposed risk score could potentially serve as a risk stratification tool for primary prevention therapy. Further studies will need to validate and further refine this new risk stratification scoring system. A multicenter prospective evaluation is now being planned.

Disclosures

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

Author contributions

Joseph Atallah: Methodology, Formal analysis, Writing - Original Draft. Maria Cecilia Gonzalez Corcia: Data Curation, Writing - Review & Editing. Edward P Walsh: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.012.

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