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JACC REVIEW TOPIC OF THE WEEK

Preventing Arrhythmic Death in Patients With Tetralogy of Fallot

JACC Review Topic of the Week

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ABSTRACT

Patients with tetralogy of Fallot are at risk for ventricular arrhythmias and sudden cardiac death. These abnormalities are associated with pulmonary regurgitation, right ventricular enlargement, and a substrate of discrete, slowly-conducting isthmuses. Although these arrhythmic events are rare, their prediction is challenging. This review will address contemporary risk assessment and prevention strategies. Numerous variables have been proposed to predict who would benefit from an implantable cardioverter-defibrillator. Current risk stratification models combine independently associated factors into risk scores. Cardiac magnetic resonance imaging, QRS fragmentation assessment, and electrophysiology testing in selected patients may refine some of these models. Interaction between right and left ventricular function is emerging as a critical factor in our understanding of disease progression and risk assessment. Multicenter studies evaluating risk factors and risk mitigating strategies such as pulmonary valve replacement, ablative strategies, and use of implantable cardiac-defibrillators are needed moving forward. (J Am Coll Cardiol 2021;77:761–71) © 2021 by the American College of Cardiology Foundation.

Although the overall survival of tetralogy of Fallot (TOF) has significantly improved since initial palliative efforts using the Blalock-Taussig-Thomas shunt, peri-procedural and longer-term risk of arrhythmias and sudden cardiac death (SCD) persist. For electrophysiologists, TOF poses important and challenging questions. First, can one accurately predict risk of cardiac arrhythmia and sudden death in both symptomatic and asymptomatic TOF patients? Second, what are effective strategies to control symptoms and reduce SCD risk?

TOF is a heterogeneous condition consisting of a nonrestrictive subaortic ventricular septal defect (VSD) and varying degrees of right ventricle (RV) outflow obstruction caused by anterior deviation of the conal septum. Related conditions with similar anatomy, hemodynamics, and surgical approaches include: double outlet right ventricle, absent pulmonary valve syndrome, and truncus arteriosus and much of what has been learned in the management of TOF can be cautiously applied to these rarer defects.

Unrepaired patients with TOF often have chronic cyanosis. A systemic-to-pulmonary artery shunt as a palliative procedure improves oxygenation but causes some degree of left ventricular (LV) volume overload. In the 1960s, complete repair of TOF (VSD

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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

EPS = electrophysiology studies

ICD = implantable cardioverter-defibrillator

LV = left ventricle/ventricular

PR = pulmonary regurgitation

PVR = pulmonary valve replacement

RV = right ventricle/ventricular

RVEDVi = right ventricular end-diastolic volume indexed

RVESVi = right ventricular end-systolic volume indexed

RVOTO = right ventricular outflow tract obstruction

SCD = sudden cardiac death

TOF = tetralogy of Fallot

VSD = ventricular septal defect

VT = ventricular tachycardia

closure and relief of right ventricular outflow tract obstruction [RVOTO], often with a ventriculotomy), became common in older patients. By the 1970s, corrective neonatal surgery could be safely performed with low mortality, albeit often using a transannular patch (1). By the 1990s, efforts to reduce the need for a ventriculotomy and preserve pulmonary valve competence were revisited with transatrial and transatrial-transpulmonary approaches (2). However, in patients with small pulmonary annulus, a transannular patch remains necessary, often resulting in chronic pulmonic regurgitation (PR).

Among the most feared sequelae of complete surgical repair of TOF are ventricular tachycardia (VT) and SCD (3) (**Figure 1**). They can occur decades following surgical repair. The pathogenesis of VT and SCD is multifactorial (**Central Illustration**). Patient age, age at repair, and method of repair interact to increase the risk of arrhythmias. Early clinical experience noted the frequent occurrence of premature ventricular contractions in patients who had previously undergone TOF repair. High prevalence of simple and complex ventricular ectopy was observed on ambulatory electrocardiography, often in asymptomatic patients (4). An association between ventricular arrhythmias and RV hemodynamics was reported in a series of nearly 500 patients with repaired TOF (5). The incidence of ventricular ectopy was higher in those with RV systolic pressure >60 mm Hg, and in those with a RV end-diastolic pressure >8 mm Hg, suggesting that both residual RVOTO and PR are important predictors of ventricular ectopy.

Co-occurrence of SCD and a high prevalence of spontaneously occurring simple and complex ventricular arrhythmias led to the hypothesis that SCD in such patients was due to VT. Early efforts to prevent the occurrence of SCD were directed at suppression of spontaneous and induced ventricular arrhythmias in patients who had undergone TOF repair. Results of electrophysiological testing in patients with repaired TOF were disturbing in that VT could be induced in a large proportion, most of whom had never had clinical VT. These reports, coupled with the data suggesting a direct link between ventricular arrhythmias and SCD, led to the widespread use of invasive electrophysiology studies (EPS) to guide antiarrhythmic drug therapy. However, in subsequent multicenter reviews in TOF patients without clinical VT, invasive EPS was not supported (6). Although the positive predictive value of inducible VT in predicting clinical VT or SCD was 55% in patients with clinical indications for programmed ventricular stimulation, it dropped to 25% in those routinely screened. Most studies have therefore called into question the rationale behind aggressive invasive diagnostic investigation in asymptomatic patients.

HIGHLIGHTS

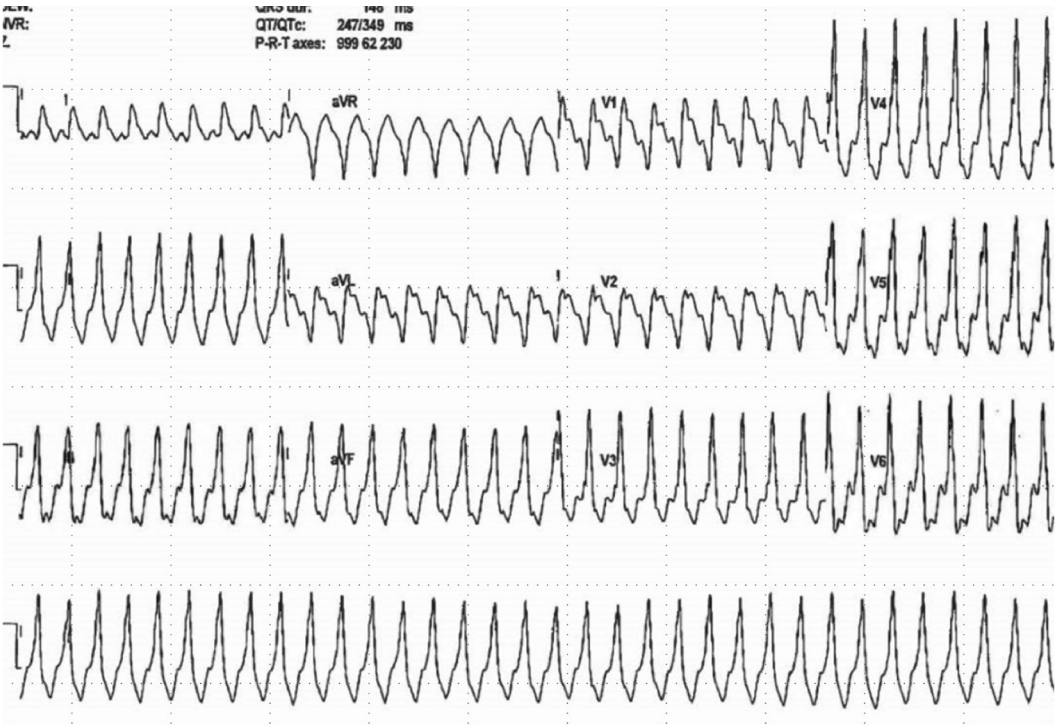
- Patients with TOF remain at risk of lethal cardiac arrhythmias decades after initial surgical repair.
- Risk stratification should be based on noninvasive markers and judicious use of programmed ventricular stimulation in selected patients.
- Most ventricular arrhythmias after TOF repair involve monomorphic re-entrant ventricular tachycardia, although some involve slow-conducting pathways in the right ventricle amenable to catheter-based ablation.
- LV dysfunction is a powerful predictor of outcomes after TOF repair with or without pulmonary valve replacement.

COMPLEXITIES OF RISK STRATIFICATION

The goal of risk stratification is to accurately quantify an individual's risk status to prescribe an appropriate care plan. The accuracy of predictive models is dependent on whether the modeled event is predominantly deterministic or stochastic. Outcomes such as sudden death in TOF patients, binary and occurring over time, are stochastic events and are difficult to predict in any given individual with respect to occurrence and timing. The objective of risk stratification in such situations should be to calculate a probability estimate for each individual. Another important consideration with predictive models involving stochastic elements is that the longer the time horizon for predictions, the more random effects and competing outcomes will gain in importance and degrade the accuracy of prediction. Therefore, risk stratification for SCD should be updated over time to maximize accuracy.

While predicted risk is a continuous variable, decisions made in response to risk are typically binary (e.g., implantation of a defibrillator) (7). This is also true of many individual predictive factors. For example, a QRS width of 170 ms could be associated with higher risk than lower values, but its predictive

FIGURE 1 **Monomorphic Right Ventricular Outflow Tract Ventricular Tachycardia**



Electrocardiogram demonstrating monomorphic ventricular tachycardia with left bundle branch block and inferior axis; the qR pattern in V_1 is consistent with a right ventricular outflow tract focus.

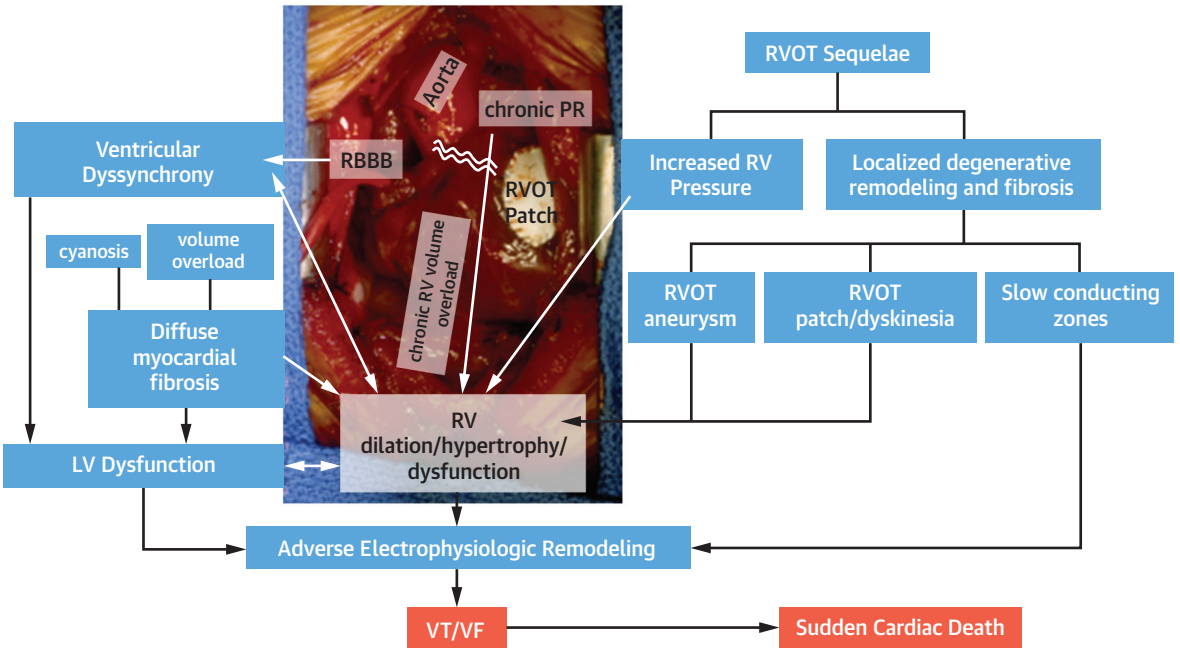
value would be overlooked if the risk factor were defined by a dichotomous 180-ms cutoff value. In addition, qualitative elements not captured by risk stratification schemes may convey meaningful information. The significance of syncope, for example, may be nuanced by the clinical scenario. Importantly, surgical techniques and interventions evolve and some risk factors identified in earlier cohorts may become less relevant to younger patients.

EVOLVING LITERATURE ON RISK STRATIFICATION

Although TOF is among the congenital heart defects at highest risk of SCD, the estimated annual incidence of 0.2% is an order of magnitude lower than adults with primary prevention implantable cardioverter-defibrillator (ICD) indications for ischemic or dilated cardiomyopathy (7,8). However, the SCD event rate is not linear, with most deaths occurring decades after surgery (9). Several observational studies have assessed predisposing factors. Collectively, they portray a reasonably consistent pattern associated with higher risk, and typically have considered combinations of factors. In a meta-analysis of over 7,000 TOF patients, mortality and VT was associated with older age at repair, prior palliative shunt, longer QRS duration, and at least moderate RV dysfunction (10). Additional risk factors for cardiac death/VT were previous ventriculotomy, lower LV ejection fraction (EF), and higher RV end-diastolic volume (10). However, with the exception of moderate-severe LV systolic dysfunction, no single variable studied appears to have sufficient discriminative ability to reliably guide decisions to implant primary prevention ICDs.

Multivariable approaches to risk stratification must factor in correlations between individual factors. Branding a variable as an "independent predictor" is contingent on the list of variables considered in the models. As an example, transannular outflow tract patches lead to severe PR, which in turn are associated with RV dilation, tricuspid regurgitation, myocardial scarring, and a wide QRS complex. In models that have considered these variables together, transannular patch and QRS ≥180 ms emerged as independent predictors (9). If programmed ventricular

CENTRAL ILLUSTRATION **Midline Sternotomy View of a Patient With Repaired Tetralogy of Fallot**



Cohen, M.I. et al. J Am Coll Cardiol. 2021;77(6):761–71.

The potential contributory mechanisms leading to sudden cardiac death are shown. LV = left ventricular; RV = right ventricular; RVOT = right ventricular outflow tract; VF = ventricular fibrillation; VT = ventricular tachycardia.

stimulation is added to these candidate variables, inducible sustained VT carries additional prognostic value independent of the noninvasive markers (6). **Table 1** summarizes a risk score derived in a population with TOF and primary prevention ICDs. Risk categories could be generated from these types of risk scores, along with quantified probabilities of events (11).

Although the importance of a QRS duration ≥180 ms has widely been accepted as a risk marker for more than 2 decades (12), the sensitivity is <50% and its predicative value may be superior in older cohorts who underwent a transventricular repair (10,13,14). More contemporary evaluative risk factors have emerged. QRS fragmentation (**Figure 2**), a marker of myocardial fibrosis, is superior to QRS duration alone in predicting all-cause mortality (14). In the recent long-term French Registry of TOF patients with ICDs, QRS fragmentation was the only independent predictor of appropriate ICD therapies (15). Myocardial fibrosis results in decreased myocardial contractility and relaxation, and serves as a potential substrate for scar-induced VT (16). The burden of scar on magnetic resonance imaging was recently shown to be predictive of inducible VT (RV late gadolinium enhancement volume of 25 cm^3 had a 72% sensitivity and 81% specificity for predicting inducible VT) (17). Similarly, other measures such as myocardial strain and rotation patterns (18), QRS vector magnitude (19), location and extent of myocardial fibrosis (13), LV systolic circumferential strain rate (20), and other parameters derived from magnetic resonance imaging (13,21) all contribute to our understanding of higher-risk substrates. Additionally, exercise stress testing has been used to assist in the evaluation of TOF patients (22).

Surgical era is associated with risk. In a recent multicenter case-control study of TOF patients with documented cardiac arrest and/or sustained VT, in the surgical era between 1960 and 1979, RV dysfunction and age at repair ≥6.5 years preceded by a shunt were associated with a moderately increased risk of a life-threatening event (23). In contrast, in repairs performed after 1980, the transannular patch was associated with lower risk (23). Regardless of the surgical era, metrics of LV dysfunction outperform RV size and function in predicting events (11,23). A low RVEF has been shown to predict a low LVEF (24). The

mechanism of RV-LV interaction in TOF is incompletely understood, but likely relates to shared myocardial fibers and the impact of septal shift on LV function as well as the effects of PR on RV volume overload coupled with electrical dyssynchrony from an underlying bundle branch block (25). It remains to be determined how all of these various risk factors can be combined in the future to generate a risk score with the greatest discriminative ability.

BAYESIAN APPROACH TO PROGRAMMED VENTRICULAR STIMULATION

In considering probabilistic risk prediction models, some factors such as demographic variables, surgical history, hemodynamic parameters derived from standard imaging, and ECG metrics are readily available and are, therefore, easy to integrate in risk calculations. In contrast, other variables, such as inducible VT, require invasive testing that is not indicated in a substantial proportion of patients nor is it feasible to repeat annually. A Bayesian approach could be helpful in sorting out who may benefit from further risk stratification with programmed ventricular stimulation.

If test characteristics are known and a post-test probability of sudden death could be defined as a reasonable cut-off for ICD implantation, then a pre-test probability range could be calculated to identify suitable candidates for the test. If, for example, we were to accept a 3.5% annual risk of SCD as a reasonable cut-off value (based on ICD primary prevention trials), programmed ventricular stimulation would be most helpful in further stratifying patients with a pre-test probability of SCD ranging between 1.0% and 11.5%/year (26). In those with a pre-test probability below 1%/year, a positive test would result in a post-test probability of SCD <3.5%/year, such that the test would not alter the decision for ICD therapy. At the other end of the spectrum, patients with a >11.5%/year probability of SCD would likewise not benefit from programmed ventricular stimulation, because the post-test probability would remain >3.5%/year with a negative test result. Patients most likely to benefit from programmed ventricular stimulation for risk stratification are those at intermediate risk, whereby a positive study would shift a given individual into a high-risk category or a negative test into a low-risk category (**Figure 3**).

RESIDUAL PROBLEMS, REINTERVENTION, AND THE EFFECT ON VT AND SCD

Arrhythmias in repaired TOF patients are influenced by the confluence of surgical scarring, native anatomical borders, hemodynamic perturbations, and neurohumoral input. As such it is critical that any new or worsening arrhythmia include assessment for potential hemodynamic contributions, such as RVOTO, valvar regurgitation, and ventricular dysfunction. Residual RVOTO is common after TOF repair and results in concentric hypertrophy. In the INDICATOR study, RV mass/volume ratio ≥0.45 g/ml was a more important long-term risk predictor for death or VT than right ventricular end-diastolic indexed volume (RVEDVi) (27). Moderate to severe pulmonary valve regurgitation occurs in 40% to 85% of patients within the first 5 to 10 years after surgical repair of TOF (28,29). There is generally a long latency period whereby compensatory mechanisms maintain RV function. However, over decades, this chronic load leads to progressive RV dilation and dysfunction and, in some patients, exceeds the capacity for compensatory RV remodeling (30). Patients with repaired TOF with progressive RV dilation and dysfunction are at risk for exercise intolerance, atrial and ventricular arrhythmias, and SCD (31,32). Additionally, RV dilation through septal shift and ventricular-ventricular interactions may impart deleterious effects on LV filling and performance (33). Restoring pulmonary valve competence is critical to curtailing the maladaptive RV response of hypertrophy, dyssynchrony, and circumferential strain, and improving clinical symptoms and exercise capacity (34,35).

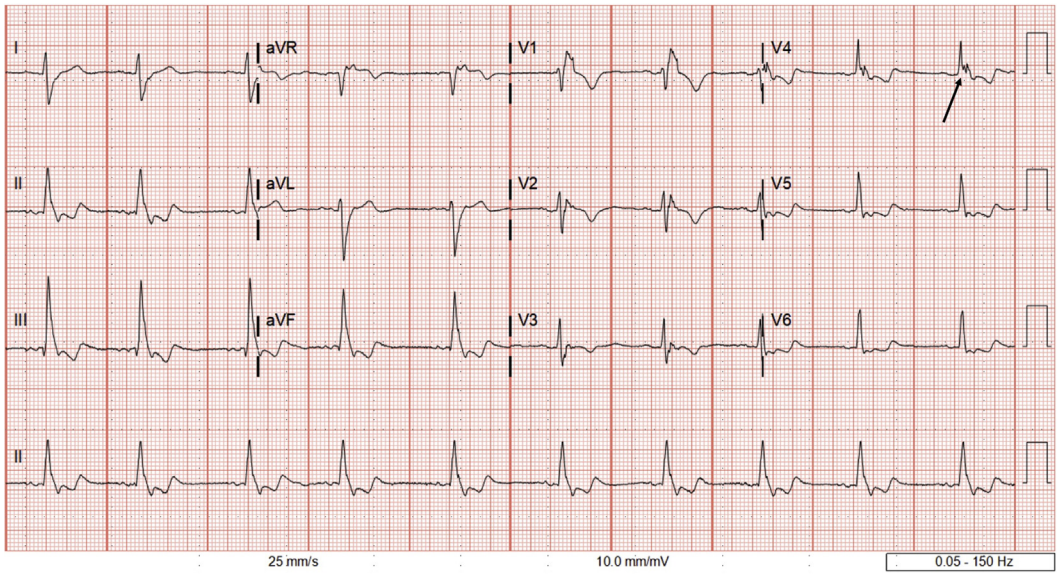
In the absence of cardiovascular symptoms, current guidelines recommend pulmonary valve replacement (PVR) when individuals have at least 2 criteria including mild/moderate RV or LV dysfunction, RVEDVi ≥160 ml/m^2, right ventricular end-systolic indexed volume (RVESVi) ≥80 ml/m^2, RV systolic pressure ≥2/3 systemic, or progressive deterioration in exercise performance (36). In a meta-analysis of nearly 3,200 patients, restoration of pulmonary valve competence significantly decreased

TABLE 1 Risk Score for Appropriate ICD Shocks in Patients With Tetralogy of Fallot

	Exp (B)	Point Attributed
Prior palliative shunt	3.2	2
Inducible sustained ventricular tachycardia	2.6	2
QRS >180 ms	1.4	1
Ventriculotomy incision	3.4	2
Nonsustained ventricular tachycardia	3.7	2
Left ventricular end-diastolic pressure ≥12 mm Hg	4.9	3
TOTAL POINTS		0–12

Adapted with permission from Wolters Kluwer Health Inc Khairy et al. (11).
Exp(β) = exponential of the beta-coefficient; ICD = implantable cardioverter-defibrillator.

FIGURE 2 Repaired Tetralogy of Fallot With Right Bundle Branch Block and QRS Fragmentation



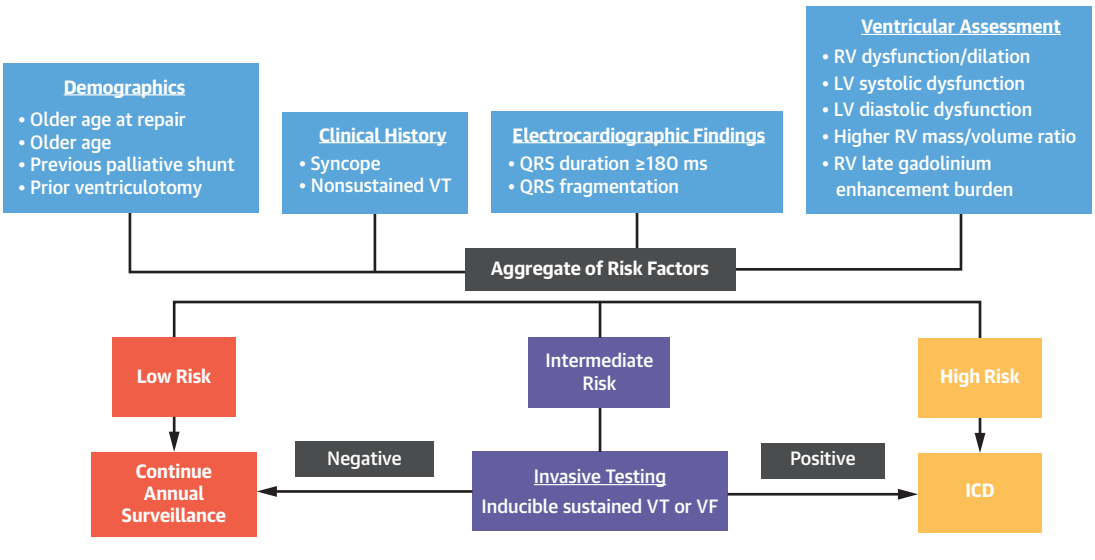
Electrocardiogram demonstrating sinus rhythm with right bundle branch block. QRS fragmentation in V_4 with multiple notched R waves **(arrow)**.

RVEDVi, RVESVi, pulmonary regurgitant fraction, and increased LV end-diastolic indexed volume and improved LVEF (37). However, by 7 to 10 years after PVR, late adverse RV remodeling occurs with a significant increase in RVEDVi and RVESVi and decline in RVEF (35). It has yet to be shown that PVR improves long-term survival.

The presence of pulmonic insufficiency as a potential risk factor for ventricular arrhythmias and SCD has sparked interest in a more aggressive strategy for reoperation in TOF patients with chronic pulmonic insufficiency (38). Although it was initially suggested that PVR is protective against the development of ventricular arrhythmias (39), recent data has not supported such a claim (27,40), even though there is some evidence of a small but statistically significant decrease in QRS duration (37). In a study of 98 patients with TOF and late PVR for RV dilation with matched control subjects having RV dilation but not undergoing PVR, there was no difference in the incidence of death or VT (40). In a follow-up to the INIDICATOR study, PVR was found not to be associated with a reduced rate for death or sustained VT during 5 years of follow-up (41). Although restoration of RV dimensions through a remodeling process post PVR has been well documented, persistent LV systolic or diastolic dysfunction may be a more important predictor of late VT and SCD (42). Depressed RV systolic function has been shown both pre- and post-operatively after PVR to be strongly associated with death and sustained VT (42). As such, simply unloading the RV with PVR may not adequately address the life-threatening arrhythmic risk. Longer-term prospective studies assessing PVR timing strategies are needed to identify the ideal time for the RV to best remodel and reduce late VT and SCD. Older age at the time of PVR (≥28 years) has been associated with worse outcomes (27).

VT ABLATION. The majority of ventricular arrhythmias documented in repaired TOF patients are monomorphic re-entrant VTs located within an anatomical critical isthmus, whereas 19% are polymorphic VT or VF (11,43,44). Areas of dense fibrosis owing to surgical incisions, patch material, and the valve annuli, form regions of conduction block that define re-entry circuit borders and create anatomically defined isthmuses with slow conduction. In total, 4 anatomic isthmuses related to VT in repaired TOF have been identified: isthmus 1 bordered by the tricuspid annulus and the scar or patch in the anterior RVOT; isthmus 2 between the pulmonary annulus and the RV free wall incision or RVOT patch sparing the pulmonary valve annulus; isthmus 3 between the pulmonary annulus and the upper margin of the VSD patch; and isthmus 4 between the VSD patch and the

FIGURE 3 Risk Stratification Approach in TOF



The assessment of risk factors for ventricular tachycardia (VT)/sudden cardiac death should include an aggregate of patient-specific demographics, clinical history, electrocardiographic findings, and noninvasive assessment of the right ventricle (RV) and left ventricle (LV). Low-risk patients should continue annual surveillance. Tetralogy of Fallot (TOF) patients at high risk for VT/sudden cardiac death should undergo implantable cardioverter-defibrillator (ICD) implantation. TOF patients whose aggregate risk factor profile falls in the intermediate zone may be considered for invasive electrophysiology testing to facilitate decision making with regards to ICD implantation.

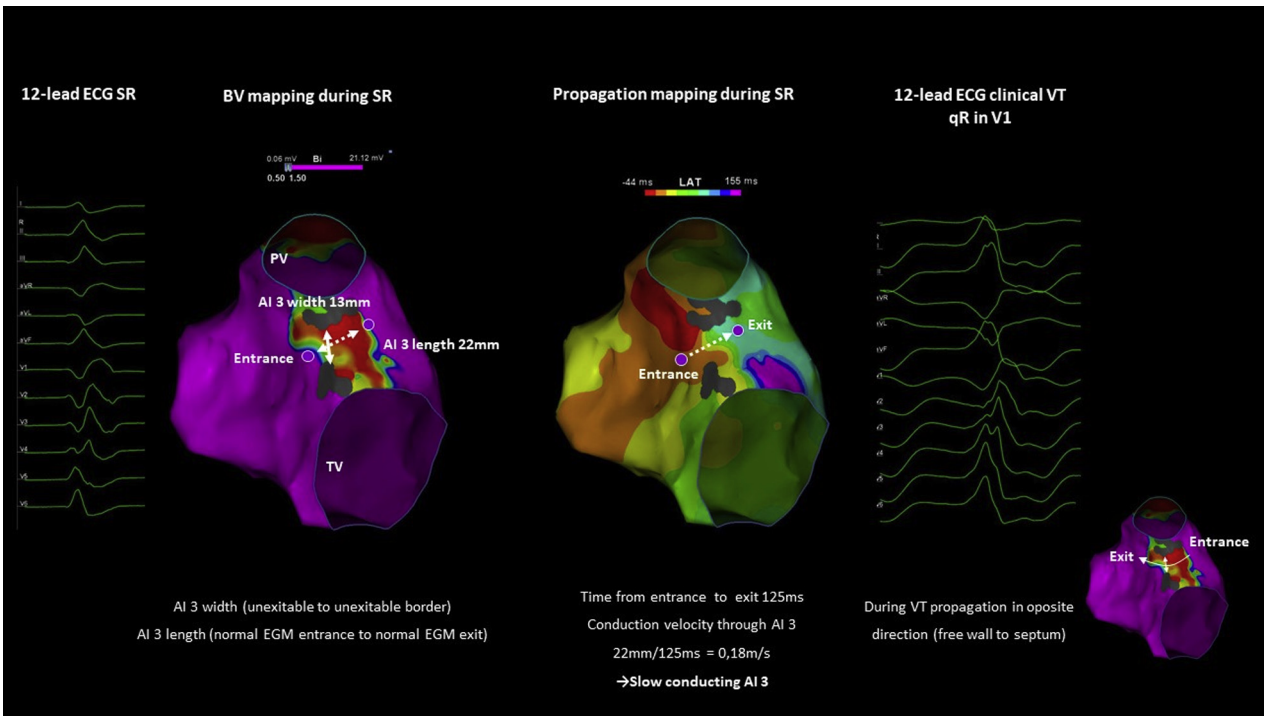
tricuspid annulus in the small subset of TOF patients with muscular VSDs (43).

These isthmuses can be identified by catheter mapping during stable sinus rhythm using 3-dimensional electroanatomic voltage mapping. Healthy ventricular myocardium generally has electrograms >1.5 mV, whereas sites with amplitudes <0.5 mV that are unexcitable with high-output pacing indicate either patch material or scars and serve as the boundaries of these critical isthmuses. Mapping of induced VT circuits is ideal, but hemodynamic instability commonly necessitates pace mapping within the anatomic isthmus and transection using linear RF lesions. Transection of the critical isthmus with RF energy (**Figure 4**) has been shown to result in low rates of VT recurrence if conduction block across the isthmus can be achieved (45). In 1 series on VT ablation in 34 adults with CHD, the majority having TOF, complete procedural success was defined as noninducibility of any VT and transection of the critical anatomic isthmus, an endpoint achieved in 75% of patients. None of the patients in whom complete procedural success was achieved had recurrence of a monomorphic VT at follow-up (45).

Not all anatomic isthmuses are related to VT, with properties of width and conduction velocity determining potential for supporting re-entry (46). Detailed electroanatomical mapping during sinus rhythm demonstrated that only narrow and slow conducting anatomic isthmuses (conduction velocity <0.5 m/s) were the substrate for all documented and induced VT in TOF patients with preserved cardiac function (46).

Variation of the malformation and the type of repair are important determinants for the presence of arrhythmogenic isthmuses (47). In a postmortem series of repaired TOF, isthmuses 1 and 3 were present in almost all specimens, whereas isthmus 2 and 4 were observed in only 25% to 42% and 6% to 13%, respectively (47,48). Of importance, the current routine use of transatrial-transpulmonary correction below the age of 1 year prevents isthmus 2 and is associated with thicker myocardium and a broader isthmus 1, which may be less likely to develop slow conduction as a result of degenerative remodeling from hemodynamic stress over time. Accordingly, in contemporary TOF, isthmus 3 may be the most important remaining arrhythmogenic isthmus. Unfortunately, catheter ablation fails to achieve complete conduction block of this isthmus in a significant number of patients. Ablation failure is likely due to a combination of hypertrophied myocardium and overlying prosthetic material after PVR, preventing effective radiofrequency energy delivery (49). The

FIGURE 4 Conduction Velocity and Measurements Across Isthmus 3



(A) Baseline electrocardiogram (ECG) with RBBB. **(B)** Bipolar voltage (BV) map (color coded). Area with abnormal BV <1.5 mV between 2 unexcitable areas **(gray tags)** is consistent with the pulmonary annulus and the ventricular septal defect (VSD) patch, which are the borders of anatomical isthmus 3 (AI3) (width of 13 mm). The lengths of AI3 = distance between normal BV sites **(purple)** at entrance and exit is 22 mm. **(C)** Propagation mapping during sinus rhythm (local activation time color-coded). Time from entrance to exit is 125 ms; thus, conduction velocity is 0.18 m/s, consistent with a slow-conducting AI3. **(D)** Ventricular tachycardia (VT) ECG: inferior axis, qR in V_1, positive concordance in precordial leads, consistent with a high septal VT exit, suggesting that during VT, AI3 was activated in the opposite direction (free wall to the septum) **(E)**, confirmed by activation mapping (not shown). Connecting the unexcitable borders by a linear RF lesion until bidirectional block across the line resulted in noninducibility of VT and no clinical VT recurrence.

potential loss of target accessibility by catheter ablation after placement of a valved conduit attached to the conal septum is of concern. Accordingly, in patients with sustained VT who are undergoing surgical PVR or, rarely, primary transcutaneous valve insertion, pre-operative catheter mapping and transection of VT related anatomical isthmuses before or during the intervention should be considered.

INTRAOPERATIVE ABLATION. Pre-operative electrophysiology studies have been implemented in the evaluation of Fallot patients who underwent PVR to allow ablative interventions at the time of valve replacement (50,51). After empirical surgical cryoablation at several anatomical isthmuses or empirical surgical unipolar radiofrequency catheter ablation at anatomical isthmuses 1 and 3 in 20 patients, 16% to 48% of pre-operatively inducible patients remained inducible and 10% to 21% had spontaneous VT (51). In both series, conduction block across the isthmuses could not be proven, which leaves the possibility of incomplete ablation and possible pro-arrhythmia if empirical ablation results in slowing of conduction in previously normal tissue. Recently, the feasibility of intraoperative cryoablation and verification of bidirectional conduction block as a desired procedural endpoint has been demonstrated in consecutive patients with a slow-conducting isthmus 3 identified at pre-operative EPS (52).

Whether patients without documented, spontaneous VT benefit from pre-operative mapping and preventive ablation before or during PVR has not been proven. Doing so would require a large number of patients with long-term follow-up due to the overall low event rate of late VTs and the required long-term follow-up. However, considering the low risk of the intervention and the availability of a well-defined procedural endpoint, the benefit for patients with a proven substrate for monomorphic sustained

VT, who may develop late spontaneous VT from a then potentially inaccessible substrate, may outweigh risks and costs of mapping and intraoperative cryoablation.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS. Patients with TOF constitute the largest subgroup of ICD recipients in adults with CHD (11,53). Although the decision for *secondary* prevention ICD implant is often clear-cut in survivors of cardiac arrest or spontaneous sustained VT, current guidelines and consensus statements recommend *primary* prevention ICD implantation in adults with TOF and multiple risk factors for SCD including LV dysfunction, nonsustained VT, QRS duration ≥180 ms, inducible sustained VT on programmed stimulation, extensive RV scarring, or diastolic dysfunction (27,36,54). ICD implantation should also be considered in patients with syncope of unknown etiology with inducible ventricular arrhythmia at EPS or in those in whom there is a high clinical suspicion of VT (54). A risk score distinguished between low risk, intermediate, and high-risk patients with ICDs with an annualized rate of appropriate ICD shocks of 0%, 3.8%, and 17.5%, respectively (11) (**Figure 5**). Other studies using a similar score adjusted model have been able to distinguish between low- and intermediate-/high-risk, but not between intermediate- and high-risk subgroups (53). Monomorphic VT comprises nearly 80% of all appropriate ICD therapies in patients with TOF with only 18% having polymorphic VT or ventricular fibrillation (11). Although ICDs have proven to be quite reliable in sensing and terminating VT they are not without complications. Inappropriate ICD shocks, most often related to SVT, have been observed in 20% to 42% of adult TOF ICD recipients (11,53).

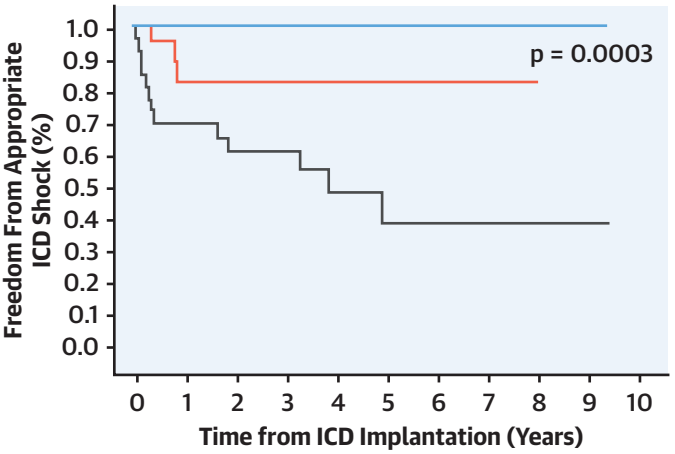
Acute procedural complication rates for ICD implantation in patients with repaired CHD approximate 2% and are predominantly lead-related (55). Given the high incidence of adverse events associated with endocardial ICD lead systems, the subcutaneous ICD has emerged as an alternative option for selected patients who do not require antibradycardia or antitachycardia pacing (56). However, as a result of RBBB with a wide QRS, many TOF patients fail ECG screening for the subcutaneous ICD, although the proportion of eligible candidates increases with right-sided screening (57).

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Much has been learned regarding associated risk factors for VT and their interaction in TOF patients, as well as the anatomical basis for macro-re-entrant VT. These advances have led to sophisticated models of risk to inform decision making, as well as mechanistically sound ablation strategies to reduce the risk of VT. Whether they will also lead to reduction of morbidity and mortality over the long-term remains to be studied.

We understand the cause of SCD to be VT for the majority of cases, and that the anatomical and physiological myocardial substrates are variable and evolve over time. RV adaptation and remodeling in response to chronic volume overload from PR remains poorly understood. Although much has been learned regarding RV-LV interaction and the important deleterious effect on LV function, its arrhythmogenic potential remains unknown. Not surprisingly, LV dysfunction has repeatedly been validated to be a strong predictor of SCD. However, our limited understanding of RV adaptation has challenged our ability to identify for whom and when PVR is indicated, and whether that may curtail

FIGURE 5 Freedom From Appropriate ICD Shocks in Primary Prevention Patients With TOF According to Their Risk Category



Risk Score	Risk Category	N	Annualized Rate of Appropriate Shocks
0-2	Low	18	0.0%
3-5	Intermediate	24	3.8%
6-12	High	26	17.5%

Low Intermediate High

In patients with TOF and primary prevention ICDs, Kaplan-Meier survival curves for freedom from first appropriate ICD shock are plotted and compared according to risk score classification. Risk score, corresponding risk category, number of patients, and annualized rate of appropriate shocks are summarized at the **bottom**. Reproduced with permission from Wolters Kluwer Health Inc. Khairy et al. (11). Abbreviations as in **Figure 3**.

further maladaptive RV and LV behaviors that could potentially impact late VT.

Although the anatomy of repaired TOF is generally favorable for implantable devices, significant opportunities exist for refinement of ICD and lead design, algorithms, and indications to tailor this therapy most effectively. Clinicians need to be mindful of these risks when weighing the pros and cons of primary prevention ICDs in young adults with Class II indications. Additionally, while the mechanisms of scar-mediated re-entrant VT along slowly conducting critical isthmuses have been uncovered and can be successfully ablated, it remains unknown if proactive ablation lines can prevent VT and SCD or simply serve to decrease arrhythmia symptom burden.

Finally, effective clinical research to firmly ground future risk stratification and therapies in TOF will depend on multicenter collaboration. There are many patients with TOF and other related forms of repaired CHD who can benefit from such research, but local populations are typically too small to allow for meaningful incremental advancement. Thus, teamwork will be required to continue to advance this field.

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