

Review

Late arrhythmia in patients with repaired tetralogy of Fallot: who is at risk?

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Summary

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart defect. Over the last century, the life expectancy of TOF patients has significantly improved. This, however, has brought new challenges both to patients and their health-care providers, the main of them being late arrhythmia. Ironically, late arrhythmia is predominantly generated due to the fibrotic scars caused by the life-saving surgical repair. Once the first two mainly arrhythmia-free decades after the repair pass, the risk of developing late arrhythmia and, therefore, SCD becomes substantial. Consequently, young adults with repaired Tetralogy of Fallot (rTOF) require careful outpatient monitoring.

There have been many attempts to predict the risk of life-threatening arrhythmia in rTOF patients. This has led to the defining of various risk factors, ranging from the widely used QRS prolongation to novel predictors, derived from cardiac magnetic resonance (CMR) based anatomical findings (left ventricular dyssynchrony indexes, right ventricular output tract akinetic length, right ventricular mass-to-volume ratio). The latter predictors have recently established CMR as a tool of high significance in evaluation of rTOF patients.

Although the role of Holter monitoring findings in rTOF patient-assessment remains unclear, it may be useful in those who are 25 years and older. Implantable cardioverter-defibrillator (ICD) implantation is the first-line treatment for secondary prevention of sudden cardiac death (SCD). rTOF patients suffer from the highest rate of inappropriate and the lowest rate of appropriate ICD shocks, when compared to other congenital heart diseases. As a consequence, ICD implantation for primary SCD prevention should be carefully weighed. Catheter-based ablation therapy leads to high rate of initial success when abolishing monomorphic ventricular tachycardia and intra-atrial reentrant tachycardia, however recurrence rates remain high.

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Introduction

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease (CHD) [1]. Since Lillehei succeeded complete intracardiac repair in 1954, tremendous advances in cardiac surgery have significantly lowered peri-

operative mortality rates dropping from 50% to 2% [2,3].

However, long-term survival of TOF patients still does not allow reaching the life expectancy of the general population. Patients who undergo repair of TOF present with a survival rate of approximately 90% after 30 years postoperatively [4,5]. Late mortality rate varies with age, however, it significantly rises at 25 years after the operation from 0.24%/y to 0.94%/y [6]. More than half of late mortality is related to CHD, namely sudden cardiac death (SCD) (~30%) and heart failure (HF) (> 20%) [7].

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Ventricular arrhythmias were linked to SCD several decades ago [8]. Regardless of knowledge of various identified risk factors for late arrhythmia, it is still insufficient to predict and therefore prevent related adverse future events.

Our aim was to review the existing evidence concerning arrhythmia-related morbidity and mortality in patients with repaired TOF (rTOF). Specifically, we present the following topics: (1) prevalence of types of arrhythmia and their individual properties, (2) risk factors for development of late arrhythmia and optimal diagnostic techniques for their detection, (3) treatment (catheter ablation and drug therapy) and (4) preventive approaches (implantable cardioverter-defibrillator (ICD) for primary and secondary prevention, pulmonary valve replacement, operative timing and type).

Methods

The search for suitable articles was conducted by using “Fallot tetralogy” as the main along with “arrhythmia”, “ventricular tachycardia”, “risk”, “stratification”, “sudden cardiac death”, “prevention”, “treatment” as additional keywords. The search was carried using MEDLINE database. We selected relevant articles published within the last 7 years, but did not exclude highly referenced older publications that were out of our target-time period. We also checked the lists of references of found articles and used significant publications for our work. Only articles written in English were reviewed. The search was carried out in May, 2014.

Late arrhythmia in rTOF patients

Late arrhythmias remain a major worry in the population of rTOF, due to the fact that a larger proportion of patients develop symptomatic arrhythmia compared with other CHDs [9]. Patients are predominantly arrhythmia-free for the first two decades subsequent to the corrective surgery [9–11]. During the first 35 years postoperatively, ventricular tachycardia (VT) with the prevalence of ~15% of rTOF patients is most common. However, at 45 years after the repair atrial fibrillation/intraatrial reentrant tachycardia (AF/IART) overreach the rate of VT and can be found in more than 50% of rTOF population using 12-lead ECG, ambulatory 24 h ECG or implantable cardiac device [9].

It is believed that a fraction of late arrhythmias in rTOF patients are acquired due to the

formation of myocardial substrate caused by fibrotic scars after the repairing surgery [12,13]. Other long-standing risk factors are chronic pulmonary regurgitation (PR) and right ventricular outflow tract (RVOT) aneurysm which commonly coexist and have a proarrhythmic role [11]. According to Therrien et al., 39% of the rTOF patients with PR experience episodes of sustained VT or non-sustained VT. Once rTOF patients with PR undergo pulmonary valve replacement surgery, this rate decreases down to 21% ($p = 0.005$) [14]. As for supraventricular arrhythmias, they are present in 70% of rTOF patients with tricuspid regurgitation, which leads to the right atrial dilation, therefore provoking rhythm disturbances [10].

Sudden cardiac death

Sudden cardiac death (SCD) is reported to account for 30% of late deaths in patients with rTOF [15]. It was proved 40 years ago that SCD is attributed to ventricular tachyarrhythmias [16]. Since then, several studies have found SCD as the most prominent element leading to late patient mortality [6,17].

Many studies have been run in order to develop a reliable tool for risk stratification in patients with rTOF, who are vulnerable to main adverse cardiac outcomes, mainly SCD (Table 1). Despite the researchers' endeavour to improve early risk stratification, it is yet unknown whether it leads to improved outcomes in the targeted patient population. Several clinical values associated with SCD in rTOF patients are similar to the risk factors for SCD in patients with ischemic and dilated cardiomyopathy: supraventricular tachycar-

Table 1. Risk factors for ventricular tachycardia and sudden cardiac death in patients with repaired tetralogy of Fallot

Older age at the time of repair
Older age after repair (chronological)
Palliative shunting prior to the radical repair
Moderate or severe PR
RV size enlargement, increased RV volume
RV hypertrophy (increased mass ratio > 0.3)
Documented history of AT
RV dysfunction
LV dysfunction
Prolonged QRS duration on ECG (≥ 180 ms)
Positive programmed ventricular stimulation
LV dyssynchrony indexes
RVOT akinetic length (CMR)

PR – pulmonary regurgitation; LV – left ventricular; RV – right ventricular; AT – atrial tachyarrhythmias; RVOT – right ventricular outflow tract.

dia (SVT), increased QRS (≥ 180 ms) duration, prolonged QT dispersion, left ventricular systolic dysfunction [18].

Ventricular arrhythmias

Occurrence of sustained VTs in rTOF patients can be explained by macro-reentrant mechanism which causes this kind of dysrhythmia as was found during electrophysiological studies [19–22]. Ventricular rhythm disturbances often co-exist alongside lesions of the right heart pulmonary and tricuspid regurgitation, RVOT aneurysm, which appear due to cardiac surgical manipulations, creating these macro-reentrant circuits [11].

Induced sustained VTs by programmed ventricular stimulation in patients with rTOF were previously found as diagnostic predictors for clinical VT or SCD [23]. However, it was later described as a screening tool lacking in predictive value [24].

Supraventricular arrhythmias

During a long-term follow-up 20–30% of rTOF patients develop atrial reentrant arrhythmias (intra-atrial reentrant tachycardia (IART), atrial fibrillation (AF)) [9,25]. Within the group of 556 patients with rTOF, atrial tachyarrhythmias had the rate of 20.1 (95% CI 17.0–23.6) with intra-atrial reentrant tachycardia (IART) being the most common of them (11.5%) [9]. Right atrial dilation, linked to TOF, contributes to IART being mainly a right-sided arrhythmia.

Hesselink et al. found that supraventricular arrhythmias were present in the recordings (monitor strip, routine ECG, or Holter recording) of 34% of rTOF patients (mean follow-up of 17.5 years after surgery).

Presence of documented atrial arrhythmias (described as atrial flutter, AF or SVT) in rTOF patients plays a predictive role in risk stratification for VT and SCD (HR 3.65 (95% CI 1.75–7.62, $p = 0.001$)) [26]. Echocardiography-based study found that most of undocumented arrhythmias were likely to be supraventricular and linked to increased right atrial (RA) size [27].

Risk factors

Role of timing and techniques of surgical repair

Definite repair of TOF is a cardiac correction relieving RVOT obstruction and closing ventricular septal defect. The early outcomes of total repair of TOF have significantly improved since the radical

procedure was first introduced and now operative mortality in young infants and even neonates does not exceed 2% [28–32].

Questions related to optimal timing, appropriate techniques for the repair and the use of palliative operation beforehand remain unclear. Harmful effects have been observed to the conduction system of the heart leading to life threatening arrhythmias and SCD after TOF repair by ventriculotomy. Despite transatrial and transatrial-transpulmonary techniques showing survival rate of >99% (including infants) and low risk of need for early re-intervention, ventriculotomy is still widely performed [28,29,33,34]. A retrospective study published by Niu et al. suggests right ventricular infundibulum sparing (ventriculotomy of 5 mm or less), which could lead to extremely low incidence of perioperative and mid-term arrhythmias [35].

Considering optimal time, the vast majority of centres tend to choose early primary elective repair in infancy, as no benefit in delay until the end of the first year of life was observed [29,36]. As for repair in the neonatal age, there are controversial opinions [37]. Patients under 3 months of age are linked to longer hospitalization and ventilation with the increased need of inotropic agents compared to the population over 6 months of age [38]. Modified palliative Blalock–Taussig shunting is still agreed on as useful for complex cases of patients with anomalous coronary arteries or multiple ventricular septal defects [39].

Residual pulmonary regurgitation and right ventricular dilation

A study of 793 patients by Gatzoulis et al. found at least moderate pulmonary regurgitation to be the most common haemodynamic abnormality in patients with SCD (100%) and VT (94%) [10]. Continuous exposure to pulmonary regurgitation leads to progressive RV dilation and dysfunction, therefore initiating adverse clinical outcomes (arrhythmias, heart failure, sudden cardiac death) [7,40,41]. PR is consistent with transannular patch use in TOF patients, a technique predominantly applied in the 20th century to relieve RVOT obstruction [42]. Optimal timing for late pulmonary valve replacement (PVR) after surgical TOF is crucial and needs to be chosen wisely. A recent study suggests that patients with PR gain 4.3 ml/m^2 in indexed RV end diastolic volume (RVEDVI) annually [43]. It was thought, that PVR should be considered once RVEDVI reaches 170 ml/m^2 or RV end-systolic volume index (RVESVI) reaches 85 ml/m^2 [44], however RVEDVI threshold was later lowered to 160 ml/m^2 [40] and finally to 150 ml/m^2 based on preoperative cardiac magnetic resonance (CMR)

findings [45]. A decade ago, echocardiographic measurements were widely used to measure the severity of PR. Now CMR is accepted as the “gold standard” technique to measure PR and assess RV volume [46–48].

Indications for PVR include a combination of PR and clinical symptoms or severe PR and moderate to severe RV enlargement [47–49]. It is presumed that PVR lowers RV volume that leads to decrease in QRS duration, which works as a preventable mechanism for VT and SCD [14, 50–52]. Geva et al. carried out a randomized trial, which compared outcomes of two rTOF patient groups with pulmonary regurgitation. Those who undergone RV surgical remodeling in addition to PVR did not show any benefits within a 6 month-period after the intervention in comparison to PVR only group [53]. In patients with dilated RV (RVEDVI = 196 ± 76 ml/m²), PVR did not play a protective role for ventricular arrhythmias and sudden cardiac death, therefore “window of opportunity” for this intervention exists and should not be missed [54].

QRS prolongation

Right bundle branch block is a common finding on ECG in TOF patients after the surgical repair (90%) [55,56]. Gatzoulis et al. demonstrated that prolonged (≥ 180 ms) QRS duration on resting ECG is a strong predictor for late ventricular arrhythmias and SCD with the negative predictive value of 100% [57]. QRS with a duration of ≥ 180 ms is often present along with an enlarged heart (cardiothoracic ratio > 0.5), $r = 0.44$, $p < 0.001$ [10]. Another study suggests moderate correlation between QRS duration and end-diastolic volume ($r = 0.6$ ($p < 0.01$)) [41]. Association between prolonged QRS and asynchronous contraction of RVOT in patients with rTOF has been reported [58]. 99% of 92 patients with previously repaired TOF from the study conducted by Babu-Narayan et al. presented with fibrotic tissue in the free wall of RVOT detected by late gadolinium enhancement CMR [59]. Asynchronous contraction in the areas of fibrotic tissue acts as a substrate for late arrhythmias through QRS prolongation, as stated previously. Cardiac resynchronization therapy could serve as a treatment strategy for regional asynchronous RV contraction [60].

Left ventricular dysfunction and dyssynchrony

A cross-sectional study of 88 rTOF patients proved LV systolic dysfunction (ejection fraction $< 55\%$) to be an independent predictor in sudden cardiac death and sustained VTs (OR = 8.05, 95% CI 2.14–30.2, $p = 0.002$) [49]. Moderate or severe systolic left ventricular dysfunction (LVD),

when combined with QRS duration ≥ 180 ms, had even stronger positive predictive value (with an increase from 29% to 66%) for SCD [61].

Although there is no definite explanation for the mechanism of LVD in rTOF patients, a probable interrelation between interventricular dyssynchrony and prolonged QRS duration is suggested [54]. Fibrotic lesions of LV, mostly found in the apex (using LGE CMR), are related with LVD as potential cause for SCD [59].

Growing evidence suggest LV dyssynchrony indexes to be the new promising measurements assessed by tissue tracking of CMR images [62]. In the patient group with history of VT or SCD, LV dyssynchrony indexes, especially maximum segmental time difference to peak circumferential strain were associated with adverse events.

Right ventricular hypertrophy

RV hypertrophy (increased myocardial mass assessed by CMR) is a significant independent predictor for SCD and sustained VT in patients with repaired TOF as found by large International Multicenter TOF Registry (INdiCaTOR) cohort study. Ratio ≥ 0.3 of RV mass-to-volume for rTOF patients was sufficient to reach high risk regarding adverse outcomes (HR 5.04, 95% CI 2.3–11.0, $p < 0.001$) [26]. Additionally, LV and/or RV dysfunction and documented atrial tachyarrhythmia may independently increase the probability of life-threatening outcomes. These newly proposed risk factors should be taken into account and reassessed in the future studies.

Right ventricular outflow tract akinetic region length

Akinetic RVOT regions combined with chronic PR, emerge as the main underlying causes for late RV dysfunction in rTOF patients [63]. A prospective longitudinal study found RVOT akinetic length measured by CMR as a predictor for ventricular arrhythmias ($p = 0.003$) [64]. Those with RVOT akinetic length > 30 mm had worse ventricular arrhythmia-free survival (log rank $p = 0.02$).

Treatment and prevention

Risk assessment by Holter monitoring

24-h Holter monitoring is a noninvasive ambulatory method used to detect cardiac rhythm abnormalities among children and adult patients after radical repair of tetralogy of Fallot. A recent study revealed that 43% of these patients had arrhythmias on Holter monitoring, 90% of them being asymptomatic [65]. In another study with similar rate of asymptomatic rTOF patients (83%) most frequently recorded cumulative lifetime

Holter findings were atrial (28%) and ventricular (44%) couplets/triplets, frequent premature ventricular contractions (25%) and non-sustained VT (10%) [66]. Early detection of arrhythmias by routine screening could lead to initial intervention by catheter ablation or ICD implantation. Findings on Holter monitoring changed the course of management for only two percent of study population with rTOF. The analysis on cost effectiveness of Holter monitoring concluded, that the method has a minor role for assessment in patients with CHD due to its low sensitivity (0.40) for future clinically significant arrhythmias [66]. However, the effectiveness differs by CHD type and age of the patient, with Holter monitoring being markedly useful in clinical management and risk assessment for rTOF patients over 25 years of age [66]. PACES/HRS Expert Consensus Statement on Arrhythmias in Adult Congenital Heart Disease recommends periodic Holter monitoring for those TOF patients who are over 35 years of age (class I, level of evidence: B) [67].

Implantable cardioverter–defibrillator

ICD therapy is aimed at preventing life-threatening arrhythmias, which could potentially lead to SCD. TOF patients constitute the largest group receiving ICD therapy when compared with patients suffering from other CHDs [68–70].

Due to the lack of randomized clinical trials and meta-analyses investigating the use of cardiac devices in CHD, indications for ICD implantation differ between different guidelines. Therefore, the recent PACES/HRS Expert Consensus Statement on Arrhythmias in Adult CHD (2014) is based on B and C levels of evidence only. ICD therapy is agreed to be indicated in the presence of: previously occurred cardiac arrest (due to ventricular fibrillation or haemodynamically unstable VT) with the exclusion of reversible causes, impaired left ventricular function (ejection fraction $\leq 35\%$) or spontaneous sustained ventricular tachycardia followed by haemodynamic and electrophysiologic evaluation [67].

Importantly, patients with rTOF experience higher incidence of receiving inappropriate ICD shocks compared to patients with other CHDs (HR 3.6, 95% CI 1.0–12.4, $p < 0.048$) [71]. This often has negative impact on the mental state of these patients [69]. This should not be dismissed when treatment strategies are considered, as the population of younger patients is more prone to mental depression and poor quality of life when ICD is applied [72].

The majority of inappropriate ICD shocks were seen in patients who suffered from supraventricular tachycardia with the rate of overall unnecessary shocks of 20% [73]. In addition, rTOF

patients were associated with lower appropriate shock rate when compared with other CHD (HR 0.29, $p = 0.02$) [69]. Lead failure was responsible for the largest part of complications (early and late, combined) related to ICD implantation [69].

Multi-central retrospective study by Koyak et al. described non-sustained VTs as significant predictor for appropriate ICD shocks (HR 9.1, 95% CI 2.8–29.2, $p < 0.001$) [71]. Indication for secondary prevention was also associated with higher risk of appropriate shocks (HR 3.6, 95% CI 1.3–9.5, $p = 0.009$). Importantly, larger number of first appropriate ICD shocks occurred in the first 2 years of follow-up.

Catheter-based ablation therapy

Catheter ablation is often used for patients with rTOF and other CHDs in order to abolish monomorphic VT and, therefore, reduce the need for ICD use. As for today, it stands as one of the most active fields of research over TOF, focusing on refinement of the treatment for late life-threatening rhythm disturbances.

In rTOF patients, the macro-reentry type circuits situate mainly in the anatomic isthmuses, namely between RVOT/adjacent RV scar and tricuspid annulus or between PV and septal scar, surrounded by unexcitable tissue [74]. The success rate for treating VTs in rTOF patients by ablation varies from 50% to 91% according to the studies using electroanatomic substrate-based mapping approach [74,75]. Described VT recurrence rates remain high (up to 20%) in turn hindering wider use of this treatment strategy in patients with rTOF [76,77]. Effective ablation is even more complicated to achieve in patients who are haemodynamically unstable during VT. However, there is evidence implying, that non-contact mapping system could be applied for effective treatment of haemodynamically unstable VTs in patients with rTOF [76].

Cavotricuspid isthmus (CTI) and lateral right atrium (RA) wall served as conduction pathways of intraatrial macro-reentrant tachycardia (IART) circuits in 85% of rTOF and double outlet right ventricle patients [77]. Though initial success rate for AT ablations was high, 19% of the patients experienced recurrent sustained AT within 6.5 months of follow-up [78]. Recurrence rate may decrease if both the CTI and lateral RA wall are ablated, even if single substrate region is detected by mapping [77].

Atrial pacing and medical therapy

In contrast to the general population, atrial pacing did not prove to be effective in prevention of atrial arrhythmias in patients with CHD [79].

Medical therapy (beta-blockers and amiodarone) is only advised as a supplementary treatment option along with ICD implantation or catheter ablation in high-risk patients with life-threatening arrhythmias [80].

Conclusions

Despite the breakthroughs in treatment of TOF patients over the last century, several challenges remain unresolved. Late arrhythmia followed by SCD is the main contributor to premature death of those with rTOF. The development of accurate risk-stratification for SCD would assist in selecting rTOF patients most in need of active prevention. Hopefully, near future will bring discoveries aimed at improving life quality and lifespan of rTOF patients.

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