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Maury, P.; Sacher, F.; Rollin, A.; Mondoly, P.; Duparc, A.; Zeppenfeld, K.; ... ; Reseau Francophone Rythmolo

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REVIEW

Ventricular arrhythmias and sudden death in tetralogy of Fallot



Arrhythmies ventriculaires et mort subite dans la tétralogie de Fallot

Philippe Maury^{a,b,*}, Frederic Sacher^c, Anne Rollin^a,
Pierre Mondoly^a, Alexandre Duparc^a,
Katja Zeppenfeld^d, Sebastien Hascoet^{e,f}, on behalf of
the Réseau francophone de rythmologie pédiatrique
et congénitale

^a University Hospital Rangueil, 31059 Toulouse cedex 09, France

^b Unité Inserm U1048, Toulouse, France

^c Inserm 1045, LIRYC Institute, Bordeaux University Hospital, Bordeaux, France

^d Department of Cardiology, C5-P, Leiden University Medical Centre, Leiden, The Netherlands

^e University Children Hospital, Toulouse, France

^f Marie-Lannelongue Hospital, Department of Congenital Heart Diseases, Le Plessis-Robinson, France

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Summary Malignant ventricular arrhythmias and sudden cardiac death may late happen in repaired tetralogy of Fallot, although probably less frequently than previously thought, especially with the advent of new surgical techniques/management. Ventricular tachycardias are caused by reentry around the surgical scars/patches and valves. Many predictive factors have been proposed, which suffer from poor accuracy. There is currently no recommended indication for prophylactic implantable cardioverter defibrillator implantation—except maybe in the case of multiple risk factors—while radiofrequency ablation may be proposed in secondary prevention with or even without a back-up implantable cardioverter defibrillator in selected cases.

Abbreviations: ACHD, adult congenital heart disease; GUCH, grown-up congenital heart disease; ICD, implantable cardioverter defibrillator; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; TOF, tetralogy of Fallot; VT, ventricular tachycardia.

* Corresponding author. Department of Cardiology, University Hospital Rangueil, 31059 Toulouse cedex 09, France.

E-mail address: mauryphil@hotmail.com (P. Maury).

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Repeated cardiological investigations and monitoring should be proposed for every operated patient.

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MOTS CLÉS

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Ablation

Résumé Des arythmies ventriculaires malignes ou une mort subite peuvent survenir tardivement après correction chirurgicale de tétralogie de Fallot, quoique probablement moins fréquemment que précédemment supposé, surtout avec l'avènement de nouvelles techniques chirurgicales ou de prise en charge. Les tachycardies ventriculaires sont dues à des réentrées autour/entre les cicatrices de ventriculotomie ou patchs et les anneaux valvulaires. Un certain nombre de facteurs favorisants ont été proposés qui souffrent cependant de valeurs prédictives insuffisantes pour être utilisés seuls en pratique clinique. Il n'y a actuellement pas de recommandation pour l'implantation prophylactique de défibrillateur en prévention primaire – sauf peut-être en cas d'association de facteurs prédictifs multiples – alors que l'ablation percutanée par radiofréquence peut être proposée en prévention secondaire avec ou même sans défibrillateur dans certains cas sélectionnés. Des investigations cardiaques répétées et une surveillance au long cours doivent être effectués chez chaque patient opéré.

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Background

Congenital heart disease is present in 0.9% of living births; currently, 90% of those affected will reach adulthood because of recent progress made in paediatrics, cardiology, surgery and resuscitation [1,2]. Among what are commonly called “grown-up congenital heart diseases” (GUCHs) or, more recently, “adult congenital heart diseases” (ACHDs), tetralogy of Fallot (TOF) has a preponderant place, because of its relatively high prevalence (7–10% of all congenital heart diseases; 1/3500 to 1/4300 in the adult population) [3,4], and because it is possible to have corrective surgery, leading to almost normal anatomy and physiology in adulthood. Indeed, very long-term follow-up has demonstrated that health status is excellent, with a mortality rate that is considered to be low (14% mortality for hospital survivors at 40-year follow-up, after surgery performed in the 1970s), even if it is still higher than in the general population, mainly because of heart failure and ventricular arrhythmias [5]. Thus, the third reason for making TOF one of the main GUCHs of concern is the late risk of malignant ventricular arrhythmias and sudden cardiac death (SCD).

The aim of this review is to highlight the mechanisms of ventricular arrhythmias in TOF, and to present current knowledge of secondary and primary prevention of SCD in this setting.

SCD in GUCH patients

The occurrence of SCD in patients with previous surgical repair of congenital heart defects is a tragic event, as many are usually considered to be “cured” of their congenital heart disease (even if this terminology may be a bit too optimistic), with rather low mortality rates and usually

excellent quality of survival. Some of these SCDs are probably linked to paroxysmal high-degree atrioventricular block (e.g. in repaired TOF with relevant intraventricular conduction disturbances, but also in ventricular septal defect, cushion defect or congenitally corrected transposition of the great arteries). Some other SCDs are caused by ventricular fibrillation induced by fast ventricular rates during supraventricular tachycardia (e.g. atrial tachycardia with 1/1 atrioventricular conduction after atrial switch for transposition of the great arteries, or after Fontan procedures for single ventricle). Other causes probably include haemodynamic compromise, embolism, myocardial infarction or aneurism rupture, but it is now clear that most SCDs (a proportion estimated at around 75% [6]) are secondary to arrhythmias, and among these, malignant ventricular arrhythmias have been documented in 85% of cases at the time of the cardiac arrest [6].

Even if the culprit GUCH for SCD has changed in recent decades, TOF remains one of the main GUCHs carrying the risk of late SCD. In 1974, congenital aortic stenosis, Eisenmenger's syndrome, TOF and hypertrophic obstructive cardiomyopathy were responsible for more than half of SCDs in children (non-operated defects in most) [2]; whereas TOF, systemic to pulmonary anastomosis, pulmonary hypertension caused by left to right shunt and dilated cardiomyopathy were present in half of the SCDs in a report published 10 years later (postoperative in a significant number of cases) [7]. In 1998, Silka et al. found that in 3600 patients with GUCH, most late SCDs were linked to aortic stenosis, aortic coarctation, transposition of the great arteries and TOF, leading to a yearly SCD rate of 0.22% (50 to 200 times higher than in the general population); most were suspected to have an arrhythmic cause [6]. Similar causes of SCD have been found in more recent studies [8]. However, even if it is always a clinically relevant issue, SCD is not the major cause

of death in GUCH, representing only one-quarter of all-cause mortalities in adults with GUCH in many series [6,9,10], or even fewer, according to more recent data [11], while it is known to account for half of cardiac deaths among those with acquired heart disease.

Prospective trials regarding SCD in GUCH are lacking for many reasons:

- first, these are very heterogeneous defects;
- second, the number of cases needed to reach statistical power makes any trial almost unachievable (e.g. TOF would require 1700 patients to be followed for 10 years) [12];
- third, earlier conclusions may not be relevant to newer generations of patients with GUCH (complete repairs during the neonatal period, improved physiological outcomes, extended survival of patients with more complex forms) [13].

SCD and ventricular arrhythmias in TOF

The modern management of TOF began before the 1960s, after the first surgical complete repair performed by Dr D. C. Lillehei in 1954. As early as 1975 – around 15 to 20 years later – the first cases of unexpected cardiac arrest in repaired TOF were noticed, and were already suspected to be caused by malignant ventricular arrhythmias [14–16].

Since then, SCD has been identified repeatedly as the major cause of mortality in repaired TOF, representing, however, only one-third to half of all-cause mortalities in different series [14,17–19]. Over the past 30 years, many studies have evaluated the risk of SCD in TOF to be between 0 and 0.8% yearly [6,14,16–23]. In a meta-analysis including 39 studies and 4583 patients, the late rate of SCD in TOF was evaluated to be 1.8% over more than 8 years of follow-up, i.e. an annual SCD rate of only 0.15% [21], which is, of course, higher than in the general population, but does not constitute an objectively “high” risk sufficient to warrant systematic prevention. For comparison, a yearly risk of SCD of up to 0.8% in hypertrophic cardiomyopathy does not constitute an indication for an implantable cardioverter defibrillator (ICD) [24]. Interestingly, the risk of late SCD in TOF is not linear but increases over time, especially 20–25 years after the surgery [6,19]. However, it is still unclear if this increase is simply caused by ageing or is dependent on ongoing progress in surgical techniques.

For the occurrence of sustained ventricular tachycardia (VT), the risk has been evaluated as 4% at 21-year follow-up (i.e. 0.2% yearly) [17], and as 14% in 556 adults operated on for TOF after a follow-up of around 30 years [25]. The risk also changes with age, with an increase at around 40 years of age [25]. Thus, it is tempting and logical to mainly link SCD in TOF to the occurrence of sustained VT.

Mechanisms of VT and SCD in TOF

Data on unrepaired TOF are scarce, as these usually have a very poor prognosis [26]; what we know comes from ancient studies, where ventricular arrhythmias were commonly found in older TOF patients before repair [27,28].

For repaired TOF, conduction disturbances are probably not a common cause of SCD because long-term evolution from right bundle branch block to bi-/tri-fascicular block is uncommon [22], and because postoperative bi-fascicular block (without transient high-degree atrioventricular block) has never been shown to lead to late SCD [18,22,29,30]. Only transient complete heart block that persisted beyond the third postoperative day has been correlated with the risk of late SCD [31]. Even if prolonged QRS duration has been correlated with SCD [17,32], QRS prolongation relates rather to right ventricular size, and predicts malignant ventricular arrhythmias [32]. Moreover, autopsies in patients with TOF who died from SCD revealed that the conduction tissues were undamaged, but found extensive fibrosis of the right ventricular myocardium at both the ventriculotomy site and the septum [33]. Ventricular arrhythmias such as premature beats [22,30] and documented ventricular fibrillation [30] were soon suspected to be involved in SCD mechanisms and, finally, repeated documentation of sustained VT during aborted SCD in repaired TOF patients [32] sealed the causal relationship between ventricular arrhythmias and SCD.

After the first cases of surgical or intracardiac mapping and ablation, reentry circuits around the surgical ventriculotomy scars, using fibrotic areas of slow conduction, have been shown to be the cause of sustained VT in repaired TOF [34–37]. It is not known, however, if ventricular fibrillation is always caused by degenerating monomorphic sustained VT.

Factors associated with SCD in TOF

Many factors have been proposed to try to better define the risk of SCD in repaired TOF (Table 1). These factors are based on history, clinical features, surface electrocardiogram or signal-averaged electrocardiogram, and the presence of spontaneous or inducible arrhythmias or surgical characteristics, but also on echocardiographic or haemodynamic variables thought to be associated with a poorer prognosis. A review of all these variables can be found elsewhere [12]. However, if the holy grail of TOF risk stratification lies in any of these variables, it would surely have been found already. Apart from the combination of QRS prolongation and increased JT dispersion, which has been associated with good positive and negative predictive values [38], none of these factors has sufficient accuracy, at least individually, to allow their use alone for risk stratification in primary prevention. Moreover, most of these variables are probably not independent of each other [12] and would be better used in combination (see later).

When trying to explore risk stratification further, it seemed to make sense to first consider the presence of complex asymptomatic ventricular arrhythmias as one of the major variables linked to SCD; these were found in 13% of patients when looking at routine electrocardiograms, and in around half of patients when looking at ambulatory recordings [15,20]. The dramatically lower rate of premature beats on routine electrocardiograms in uneventful compared with sudden-death patients, together with the lower SCD rate in patients with frequent ventricular premature beats successfully versus unsuccessfully/not treated with antiarrhythmic drugs [15], supported this hypothesis. However,

Table 1 Factors proposed to be related to the risk of sudden cardiac death in repaired tetralogy of Fallot (modified from [12]).

Atrioventricular conduction block
Right bundle branch block with left axis deviation
Atrial arrhythmias
Sustained ventricular tachycardia
Non-sustained ventricular arrhythmias on 24-hour ambulatory monitoring
Ventricular arrhythmias on exercise testing
Right ventricular hypertension
Residual ventricular septal defect
Right ventricular dilation
Residual right ventricular outflow tract obstruction
Ventricular hypertrophy
Size of ventriculotomy scar
Diminished right ventricular myocardial blood flow reserve
Restrictive right ventricular physiology
Size of ventriculotomy scar
Diminished right ventricular myocardial blood flow reserve
Left ventricular end-diastolic pressure
Left ventricular involvement
Abnormal signal-averaged electrocardiogram
Complex or multiple operations
Transventricular as opposed to transatrial approach to repair
QRS duration on electrocardiogram
Older age at operation
Early surgical era
Coronary artery disease

conflicting data exist on that point [17], while symptomatic non-sustained VT has been associated with a poorer outcome [39].

The logical next step was to consider the role of inducible ventricular arrhythmias in selecting patients prone to SCD, despite the fact that inducible patients may have excellent outcome [20] and that SCD may occur in non-inducible patients with TOF [40]. Khairy et al. reported the prognostic value of programmed ventricular stimulation after TOF repair, as determined in a multicentre cohort study including 252 patients investigated from 1985 to 2002 (mean age 16 ± 12 years) [41]. Of note, two-thirds of these patients had already presented with syncope, palpitations, sustained VT or even cardiac arrest. Sustained monomorphic VT was inducible during standard programmed ventricular stimulation in 30% of cases, and polymorphic VT in 5% of cases (under isoproterenol in a quarter of cases). After multivariable analysis, inducible patients were older, and presented with palpitations, high-grade ventricular premature beats, previous palliative surgery and a large cardiothoracic ratio. A quarter of inducible patients were implanted with an ICD (and only a very few non-inducible patients). Overall, 17% of patients experienced SCD or sustained VT during the 6-year follow-up. Inducibility of any VT was significantly linked to arrhythmia-free survival in a multivariable analysis [41]. Analyses performed in patients without ICDs or in asymptomatic patients yielded similar results; however, even if

negative and positive predictive values of inducibility of any VT were considered interesting (98% and 25% respectively), with a relative risk of 10.4 in asymptomatic patients, the 95% confidence intervals were very large, and the statistical analysis could be considered to be of borderline significance ($P = 0.0425$). Moreover, a subsequent publication by the same group did not confirm these results in patients with ICD [42] (see later).

According to the 2014 guidelines for management of arrhythmias in GUCH [1] and the 2015 European guidelines for SCD [24], programmed ventricular stimulation can be useful in risk stratification in adults with repaired TOF who have more than one risk factor for SCD (including left ventricular systolic or diastolic dysfunction, non-sustained VT, QRS duration > 180 ms or extensive right ventricular scarring; class IIa indication). According to the same guidelines, an ICD may be proposed for primary prevention in selected patients with TOF in case of multiple risk factors (i.e. those mentioned above, inducible sustained VT; class IIa indication). In our opinion and experience, however, prophylactic ICD implantation is rare, and should be reserved mainly for left ventricular alteration and/or very broad QRS and impaired right ventricular function.

Medications for ventricular arrhythmias in TOF

There has been no dedicated study of antiarrhythmic drugs in TOF or, more generally, in GUCH. Drug management in GUCH is adapted from what has been largely demonstrated in acquired heart disease. Beta-blockers are probably useful, while sotalol and amiodarone should be avoided – at least as first-intention treatment – because of the risk of proarrhythmia and relevant non-cardiological side effects during long-term therapy [1]. Class I antiarrhythmic drugs may be harmful in case of diseased ventricle [1], as is present in TOF.

ICDs in TOF

GUCH and children represent fewer than 1% of all ICD implantations. Series are few, and are usually limited to tens of patients, and, of course, there have been no randomized trials. ICDs in GUCH are hampered by an important rate of inappropriate therapy, late technical or psychological issues or complications with residual significant mortality rates and even relevant SCD rates [43].

Patients with TOF form by far the largest subgroup of ICD recipients with congenital heart disease [44–46]. In secondary prevention, an older report on 25 operated patients with TOF revealed 45% oversensing, 20% appropriate antitachycardia pacing, 5% appropriate ICD shock, 20% inappropriate antitachycardia pacing, 20% inappropriate ICD shock and 5% mortality over 2 years [47].

In 2008, Khairy et al. reported their experience of ICDs in 121 implanted patients with TOF, half of whom were implanted for primary prevention (although a large number had symptoms compatible with ventricular arrhythmia) [42]. Thirty per cent of patients experienced appropriate therapy over 3.5 years (81% VT, 19% ventricular fibrillation). The only

independent predictor was previous ventriculotomy incision. One-quarter of patients presented with inappropriate therapy – either in primary or secondary prevention – and ICD-related complications occurred in 30%. Interestingly, the all-cause mortality rate was high (2% yearly, rather higher than for unselected TOF), and half of the deaths were sudden, despite the ICD [42]. In the subgroup of patients implanted for primary prevention, appropriate shocks happened in 23%, and independent predictors were elevated left ventricular end-diastolic pressure and the presence of non-sustained VT. Interestingly, inducibility was not significantly linked to the occurrence of appropriate shock. The authors built a risk score for predicting appropriate ICD shock in primary prevention, but other authors failed to validate it in a subsequent series of 36 patients with TOF also implanted for primary prevention [39]. In this work, only symptomatic non-sustained VT was associated with future appropriate therapy in a univariate analysis (which, in fact, challenges the notion that these were really “primary prevention” TOF patients). In this report, there was 19% appropriate therapy, 42% inappropriate therapy and 5% mortality over the 5-year follow-up [39]. However, it is not clear if fast VT prompting ICD therapy was non-sustained when different ICD settings were programmed.

In a recent French retrospective registry of 62 implanted patients with TOF (18% in primary prevention), 9% received appropriate therapy in primary prevention compared with 50% in secondary prevention, while 34% experienced major ICD-related complications, and 10% died over a follow-up of 3.5 years (Bouzeman, unpublished data). Thus, inappropriate therapies equal or exceed appropriate therapies in patients with TOF implanted in primary prevention.

No relevant data are available today on the use of subcutaneous ICDs in GUCH and hence in TOF. What is known from very limited early experience is a high rate of inappropriate shocks (issues in tachycardia discrimination because of intraventricular conduction disturbances or T-wave abnormalities) and the drawback of the impossibility

of anti-brady/tachy pacing, which may be relevant in TOF [48,49]. An increased risk of device exteriorization and the use of right parasternal screening have also been evoked in GUCH or children implanted with a subcutaneous ICD [48,50].

Finally, recent new modalities of surgical epicardial ICD implantation in congenital heart disease have been proposed, but with limited experience to date [51].

VT ablation in TOF

Successful catheter ablation using conventional mapping techniques, with or without drugs, has been reported in short series of patients with TOF [52,53], although only limited success rates have been reported in other series [54] because of complex anatomy, hypertrophied myocardium, dense fibrosis, broad isthmuses, haemodynamic instability or non-inducibility.

Zeppenfeld et al. were the first to investigate in depth the details of various VT reentry circuits in repaired TOF using three-dimensional mapping [55]. Four potential slow-conducting VT isthmuses were present in most patients with TOF referred for sustained VT, and were also found in autopsied hearts from patients with TOF who died shortly after surgery: two isthmuses were bordered by the anterior/lateral right ventricular outflow tract (RVOT) scar/patch and the tricuspid (the main one) or pulmonary annulus (absent if transannular patch); while the other two were delineated by the ventricular septal defect scar/patch and the tricuspid (absent after closure of perimembranous septal defect) or pulmonary annulus (Fig. 1) [55]. Transecting anatomic isthmuses by linear radiofrequency lesions during sinus rhythm (Fig. 2) abolished all inducible VT, and led to a lack of VT recurrence in 90% of cases at 30-month follow-up [55]. Of note, only half of the patients were finally implanted with an ICD during follow-up.

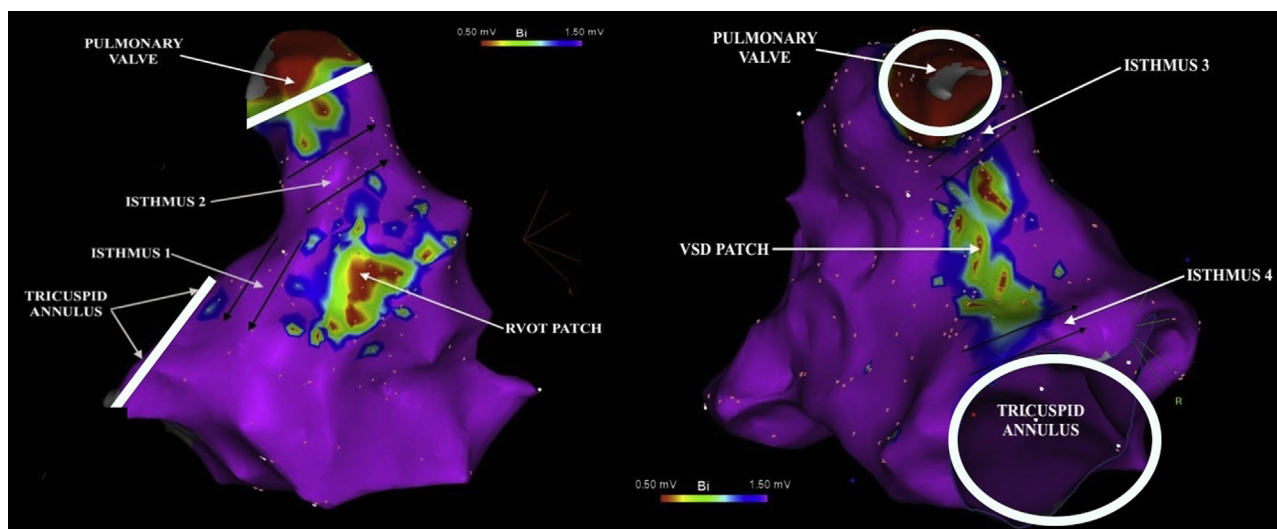


Figure 1. Anterior (left) and posterior (right) views of repaired tetralogy of Fallot right ventricular voltage map, showing scars at the sites of the ventriculotomy/patch at the outflow tract (left) and the ventricular septal defect (VSD) patch (right), together with the four potential isthmuses described by Zeppenfeld et al. [55] (see text). RVOT: right ventricular outflow tract.

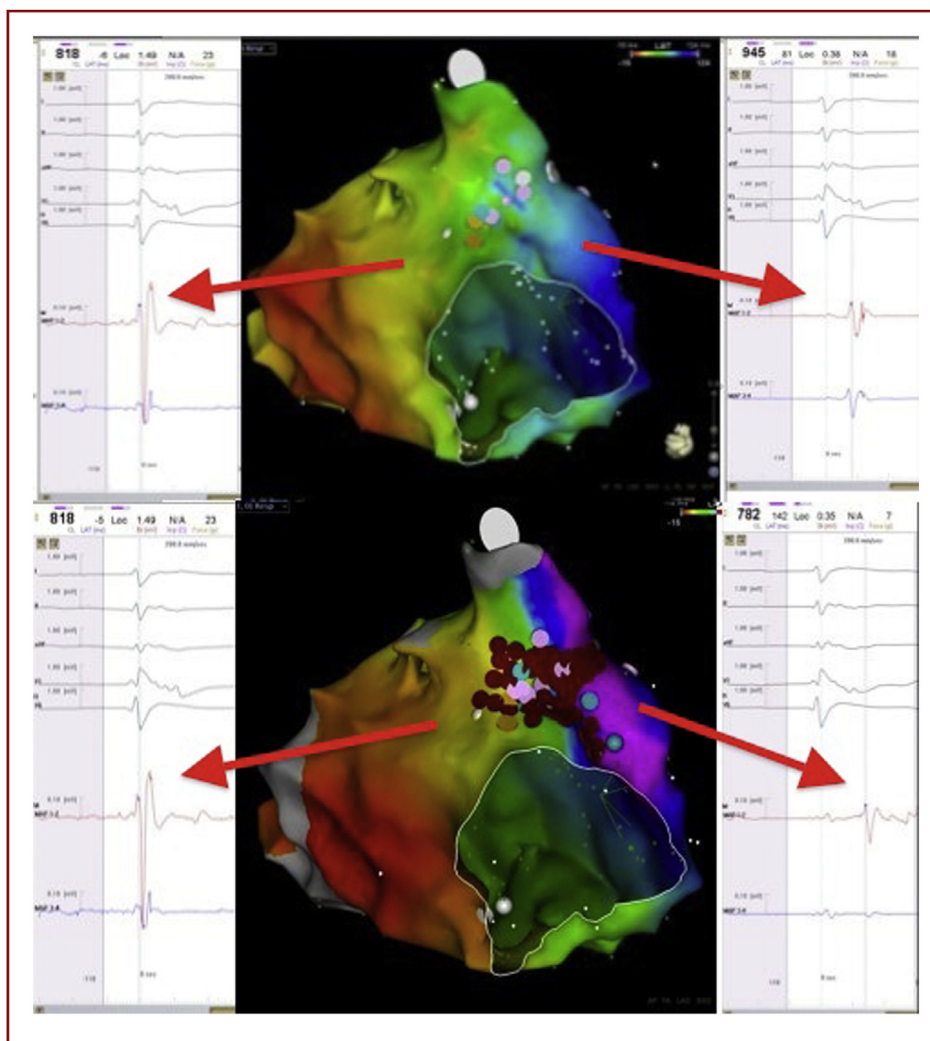


Figure 2. Activation during sinus rhythm before (above) and after (below) radiofrequency-induced block of the isthmus located between tricuspid and pulmonary annulus, with the respective electrograms from both sides of the isthmus. Activation is coded by rainbow colours (from red to purple), showing progressive activation from left to right through the isthmus (above) and inversion of the activation once the block is achieved (below).

All operated patients with TOF have at least one potential anatomical VT isthmus, but isthmuses were narrower, longer and had slower conduction in patients with inducible VT, according to recent work from the same group [56]. Patients without a slow-conducting isthmus did not present with VT during follow-up [56]. This factor may be proposed in the future for stratifying the risk of late SCD. The same group also demonstrated that right-sided ablation may fail because of septal hypertrophy, overlying pulmonary homograft or overlying ventricular septal defect patch. In these cases, representing 15% of the patients, VT had to be ablated from the left ventricle (septum or aortic root) [57].

Current guidelines recommend a role for ablation only as an alternative to ICD therapy in carefully selected patients with TOF (class I indication) [1]. Otherwise, ablation is indicated as adjunctive therapy to ICD in adults with TOF and recurrent monomorphic VT, with or without failed drug therapy [1].

Towards better prevention of ventricular arrhythmia

Some surgical procedures may decrease late VT occurrence. For example, better cardioprotection during extracorporeal circulation, shorter transannular incisions or lack of transection of the annulus, less aggressive muscle resection and less generous RVOT patching [58,59] should be preferred when possible. Earlier correction is probably worthwhile because of less prolonged cyanosis, less pressure overload of the right ventricle, and avoidance of aortopulmonary bypass and subsequent less left ventricular volume overload [17]. Earlier correction of pulmonary valve stenosis or regurgitation by surgical or even percutaneous intervention [60] is probably also beneficial, even if still unproved. Subpulmonary resection and ventricular septal defect closure can be accomplished transatrially, while pulmonary valve/artery surgery can be achieved through a pulmonary arteriotomy (“RV infundibulum sparing repair”) [61,62],

which will probably carry a reduced arrhythmia risk in the long term [63], despite experience still being lacking.

Finally, surgical ablation guided by electrophysiological mapping performed during or before surgery may be considered in TOF with inducible sustained monomorphic VT with an identified critical isthmus (class IIb indication) [24]. Studies are still pending, however, for the evaluation of the clinical role of this dual strategy in decreasing late SCD occurrence.

Conclusions

Malignant ventricular arrhythmias and SCD probably occur less frequently than previously thought in repaired TOF, and will possibly become even less common with the advent of new surgical techniques/management. There are currently no recommended indications for prophylactic ICDs (except perhaps in very selected cases based on multiple risk factors), while radiofrequency ablation may be proposed in secondary prevention, with or even without a back-up ICD in selected cases. Repeated cardiological investigations and monitoring should be proposed for every operated patient.

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Disclosure of interest

The authors declare that they have no competing interest.

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