Selecting the Right Patient with Tetralogy of Fallot for an Implantable Cardiac Defibrillator

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Introduction

Significant improvements in the management of patients with congenital heart disease have occurred over the last half century. Evolution of surgical technique, intensive care, nursing and medical management has led to a marked increase in the number of such patients who are surviving into adulthood (1). The electrophysiologist has a number of key roles for enhancing the care of patients with adult congenital heart disease (ACHD). In general, patients with ACHD are at greater risk of ventricular arrhythmias and sudden cardiac death (SCD) than the general population (2). Close collaboration between the specialist in ACHD and the electrophysiologist is essential.

Patients with tetralogy of Fallot.

In this editorial we have focussed discussion on patients with tetralogy of Fallot (TOF). Such patients usually survive long into adulthood without limiting symptoms. However, patients with TOF have a high ‘arrhythmic burden’ with over 10% developing ventricular arrhythmias during their lifetime and the first occurrence is at a young age – approximately 30 years old (3, 4). Of all the ACHD patients who are followed up in the outpatient setting, patients with TOF are proportionally the largest group at risk of SCD – although SCD may occur in a small number, it is a tragic occurrence in a young patient who is otherwise well (5, 6). The risk of SCD in patients with TOF is 25-100 times greater than age matched subjects (7). Risk stratification and selection of patients for a primary preventive implantable cardiac defibrillator (ICD) is a commonly discussed issue (8). In most cases, the physician’s estimate of the risk of demise often far exceeds the actual risk.

What is tetralogy of Fallot?

Tetralogy of Fallot is the commonest form of cyanotic congenital heart disease (9). TOF comprises a non restrictive (i.e. large) ventricular septal defect, right ventricular outflow tract obstruction (RVOT), right ventricular (RV) hypertrophy and an aorta which overrides the ventricular septal defect (VSD). Almost all patients who are reviewed in the ACHD clinic have undergone complete surgical repair. This entails closing the VSD with a patch and, trying to eliminate as much obstruction as possible which may be at the level of the RVOT,
pulmonary valve or pulmonary artery alone or, at multiple levels. Nowadays, surgery is usually performed before the age of 1 year since children who undergo reparative surgery at an older age usually have higher operative mortality (10).

**Arrhythmia Substrate**

Akin to patients with acquired cardiac disease, the substrate for atrial and ventricular arrhythmias in patients with ACHD is usually scar related around regions of surgical repair (11). Surgical techniques to treat patients with TOF have evolved substantially since the pioneering (palliative) surgical interventions of the 1940s and the first complete repair in 1954 (12). Where possible, a transatrial-transpulmonary surgical approach is now used rather than the historic approach via a right ventriculotomy. Earlier surgical approaches were associated with more extensive resection and transannular patching of the RVOT and possibly pulmonary valvectomy. Surgical procedures in the past tended to cause greater scar formation and a more pulmonary incompetence (PI) compared those which are performed today (9, 13). Over time, PI can lead to excessive volume loading of the RV which may cause adverse remodelling, RV dysfunction and ultimately RV failure. RV dilation is associated with a broadening of the QRS width and QT dispersion – the phenomenon of electromechanical interaction (14, 15). Compared to healthy subjects, patients with TOF have derangements in autonomic function - lower baroreflex sensitivity and heart rate variability – both are associated with a higher incidence of SCD in patients with acquired cardiovascular disease (16). Using SPECT imaging, MIBG radionucleotide uptake is attenuated in patients with TOF indicating that sympathetic nervous innervation of the heart is impaired. As a result of these electromechanical alterations, myocardial electrical stability is lower and ventricular arrhythmias can be more easily induced (17). The incidence of sudden cardiac death for patients with TOF is approximately 2.5% per decade with the commonest cause being ventricular tachycardia (VT).

**Do current guidelines make decision making any easier?**

One often hopes that consensus guidelines will make decision making easier. In comparison to patients who have left ventricular systolic dysfunction due to ischaemic heart disease or dilated cardiomyopathy, there have been no randomised controlled trials examining the use of ICDs in patients with TOF. This means that there is no evidence based guideline which can be used. The most current guideline (TA95) from the National Institute for Health and Clinical Excellence (NICE) published in 2006 for *Implantable cardioverter defibrillators for arrhythmias*, recommended that a primary prevention ICD could be recommended for ACHD patients who “have undergone surgical repair of congenital heart disease”. Naturally, such guidance is impractical since almost all patients with TOF have undergone surgical repair and such a strategy would evidently do more harm than good.

**Risk Stratification**

Accurate risk stratification and prediction of death in all walks of cardiology is an imperfect science, none more so than for patients with ACHD. With reference to primary prevention, in ‘real world’ practice, the patient who is symptomatic with palpitations, pre-syncope or syncope will be subjected to greater investigative scrutiny and possibly a lower threshold to intervention than the patient who is asymptomatic. The asymptomatic patient almost always poses the greatest challenge to risk stratify. It has been estimated that only a longitudinal
cohort study of at least 1700 patients with TOF, followed up over a decade, would be sufficiently powered to identify significant risk indicators to allow prediction of survival (18). An ever increasing number of risk indicators are reported to help predict survival in patients with TOF; some are statistically significant but have lesser clinical importance and have been identified from small observational studies. Other risk indicators may be sensitive but lack specificity. Rather than using risk indicators in isolation, incorporating a number into a scoring system may be more helpful for decision making (4, 19). For patients with TOF, the frequently used risk indicators associated with life threatening ventricular arrhythmias or SCD are listed in Table 1.

Table 1. Risk Factors Associated with Ventricular Arrhythmia/Sudden Cardiac Death in Patients with Tetralogy of Fallot

<table>
<thead>
<tr>
<th><strong>Demographic factors</strong></th>
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<tr>
<td>Older age at surgical repair (6)</td>
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<th><strong>Surgical factors</strong></th>
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<td>Palliative shunt rather than definitive repair (20)</td>
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<th><strong>Electrical factors</strong></th>
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<tr>
<td>QRS duration ≥ 180ms (6)</td>
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<tr>
<td>QRS duration increasing &gt;3ms per year (6)</td>
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<tr>
<td>Inducible VT on electrophysiology study (20)</td>
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<tr>
<td>‘High grade’ VT on Holter monitoring (21)</td>
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<td>Atrial tachyarrhythmia (4)</td>
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<tr>
<th><strong>Structural factors</strong></th>
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<tr>
<td>Severe RV dilation (end diastolic Z score (end diastolic Z score ≥ 7)) and/or RV impairment (RV ejection fraction &lt;45%) (4, 22)</td>
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<tr>
<td>Left ventricular systolic dysfunction (4, 22)</td>
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<tr>
<td>RV/LV fibrosis (23)</td>
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<tr>
<td>RV mass to volume ratio ≥ 0.3 g/ml (4)</td>
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<th><strong>Catheter based factors</strong></th>
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<tr>
<td>Elevated end LV diastolic pressure &gt;12 mmHg (19)</td>
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Risk Assessment Tools

Holter

The 24 hour Holter monitor, a favourite test for cardiologists, is a blunt instrument for predicting survival (24). Ventricular ectopics and non sustained ventricular arrhythmias are common in patients with TOF and increase in frequency as patients get older (21). Such findings are not strong indicators to predict SCD (6) (24). In patients with TOF and ICDs implanted for primary prevention (a longer term, more elaborate method of Holter monitoring), symptomatic episodes of non sustained ventricular tachycardia (VT) are associated with appropriate shocks whereas asymptomatic episodes are not. Patients experiencing the latter had no appropriate shocks during a mean follow up of over five years (25).

Echo and MRI

Right ventricular dilation, RV impairment and LV impairment are significantly associated with worse survival in patients with TOF. Subclinical impairment of LV function may be also important. Independent of QRS duration, Diller et al. showed that mitral annular plane systolic excursion (<12mm) and LV two dimensional strain (<15%) are predictors of mortality in patients with TOF but unusually, LV ejection fraction was not a significant predictor of survival (26).

Electrophysiology Study

A popular method thought to be helpful for predicting SCD is the electrophysiology study, a.k.a. the ‘VT stim’. Kairy et al. investigated the discriminatory benefit of performing an electrophysiology procedure in 252 patients who had previously undergone repair for TOF (20). Over half were men; the median age which EPS was performed was 16 ± 12.3 years; a fifth had a QRS duration ≥ 180ms and; three quarters had at ≥ moderate pulmonary incompetence. Sustained (i.e. ≥30 seconds) monomorphic/polymorphic VT was induced in a third. Inducible sustained VT was an independent risk marker for VT/SCD (hazard ratio 4.7, 95% CI 1.2 - 18.5, p=0.027). The negative predictive value of the EPS was better than the positive predictive value. Event free survival for patients who had no inducible VT at one year was 98% compared to 79% in patients with inducible VT. After a decade of follow up, 11% of patients who had a negative ‘VT stim’ and 41% with a positive ‘VT stim’ experienced sustained VT or SCD. Overall, the positive predictive value of inducing VT during EPS was only 55% but the negative predictive value was 92%. During follow up, 87 patients experienced VT or SCD. This was not a study to assess the efficacy of ICD implantation and of the 87 patients with inducible ventricular arrhythmias, only 17% had ICDs implanted. One should note that this was a non randomised, observation study comprising a ‘high risk’ group of patients - 63% had symptoms which led to referral. In another retrospective study by the same group, 86 patients underwent EPS and of these 62 had inducible VT. During follow up, of the patients who were non-inducible, 12.5% had appropriate ICD shocks. Of the patients with inducible VT, 37.1% had appropriate shocks. The EP study may be better than nothing but it is not the definitive test that one often assumes it is. No randomised study to date has been designed to assess the prognostic utility of an EPS in asymptomatic patients to decide whether an ICD should be implanted or not.
Treatment Options

No single treatment algorithm can decide which TOF patients should receive a primary prevention ICD. Naturally, the decision to offer an ICD implant is easier to make if the patient has symptoms e.g. palpitations, pre-syncope or syncope together with a combination of risk factors listed in Table 1, but in patients who are entirely asymptomatic, “therapy is largely on institutional experience and philosophy” and very individualised (27).

The Implantable Defibrillator

ICDs are often viewed as a ‘cure all’ anti-arrhythmic strategy. One often breathes a sigh of relief once the device is fitted. From then on, the patient is finally ‘protected’. However, we should all be more aware of the potential hazards posed by ICDs, particularly in the setting of primary prevention (28, 29). Everyone will remember the patient who experienced the appropriate shock but some individuals derive no long term benefit or at worst, come to greater harm. This is not due to poor decision making. Predicting death is difficult and the clinician is under considerable pressure (either overt or covert), to offer what may be the best possible strategy to avoid a disastrous life threatening event in a young person. It is all too easy to get on with the implant and gloss over the potential hazards. Patients with TOF undergoing ICD implant will be relatively young compared to patients with acquired cardiac disease. The longer duration of implant means that there will be a more box changes and higher risk of infection plus greater risk of inappropriate shocks or other device complications (30). Uncomfortable as it may be to accept, in the longer term, complications due to the device are probably more likely to occur than appropriate device therapy (30). Risk prediction is a high stakes game. Most clinicians and their patients are more at ease accepting the relatively frequent chance of complication as opposed to the much less probable but more disastrous outcome of SCD.

In multicentre study of 121 patients with TOF who had an ICD (68 for primary prevention and 53 for secondary prevention), 31% of patients had at least one appropriate discharge (i.e. anti-tachy pacing or shock) (19). The annual appropriate shock incidence was 8% in the primary prevention group and 10% in the secondary prevention group. Of the appropriately treated arrhythmias, monomorphic VT was the commonest (81.5%). Worryingly, inappropriate shocks were delivered in 6% of patients yearly and almost 30% (n=36) had complications ensuing from device therapy. In this selective, high risk cohort, nine patients died in total but only one was definitely due to ventricular tachyarrhythmia. Clinicians often prescribe beta blockers and amiodarone as they believe that they reduce the incidence of ventricular arrhythmias. In this analysis, use of beta blockers or amiodarone had little effect on reducing the risk of ICD shock.

Pulmonary Valve Replacement

Pulmonary incompetence is a common occurrence in patients with TOF who have undergone corrective surgery. Approximately 15% of patients who have undergone TOF repair develop significant PI and require pulmonary valve replacement (31). RV dilation resulting from PI can cause electrical instability and ventricular arrhythmias, therefore replacing a dysfunctional pulmonary valve means less PI, a reduction in RV volume loading and reverse remodelling of the RV. The threshold value for severity of RV dilation (either
measured by systolic or diastolic volume indices) to recommend PVR is debated. Most recommend PVR before the corrected diastolic RV volume exceeds ≥ 150-170ml/m² or if the corrected systolic volume is ≥80-90 ml/m² (32). A lack of large randomised trials, reliance on observational data and difficulties in standardising the patient dataset, mean that it is difficult to decide about how effective PVR is at modulating arrhythmias (33). It is hypothesised that a PVR plus cryoablation may be better than a PVR alone for reducing the burden of arrhythmia (34).

**VT ablation**

Patients may be suitable for VT ablation if their ventricular arrhythmia can be induced during the EPS and they remain haemodynamically stable. VT ablation is usually reserved for patients who already have an ICD in situ and experience VT despite optimised medical treatment. It is debatable whether VT ablation could be used as an alternative to ICD implantation, particularly for primary prevention or, for patients who are haemodynamically stable during their episodes of VT. To most, this proposition would be a little ambitious. From the limited evidence available (five studies, n=56), the ‘success’ of VT ablation of patients with TOF is almost 90% but nearly a fifth have recurrent VT during follow up (< 5 years). Given the high recurrence rate and possibility of SCD due to ventricular fibrillation or other haemodynamically unstable ventricular arrhythmias which develop at a later time, for now, VT ablation is an adjunct rather than an alternative to ICD implant (35).

**Conclusions**

The decision to offer ICD implantation for primary prevention in patients with TOF requires careful consideration. Prediction of arrhythmias and sudden cardiac death is an inexact science and often one must accept a significant degree of uncertainty. Randomised controlled clinical trials are needed to identify significant clinical risk factors in patients with TOF and to help identify who would benefit most from primary preventive ICD therapy.

**References**


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