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Review

Use of Cardiovascular Magnetic Resonance for Risk Stratification in Repaired Tetralogy of Fallot

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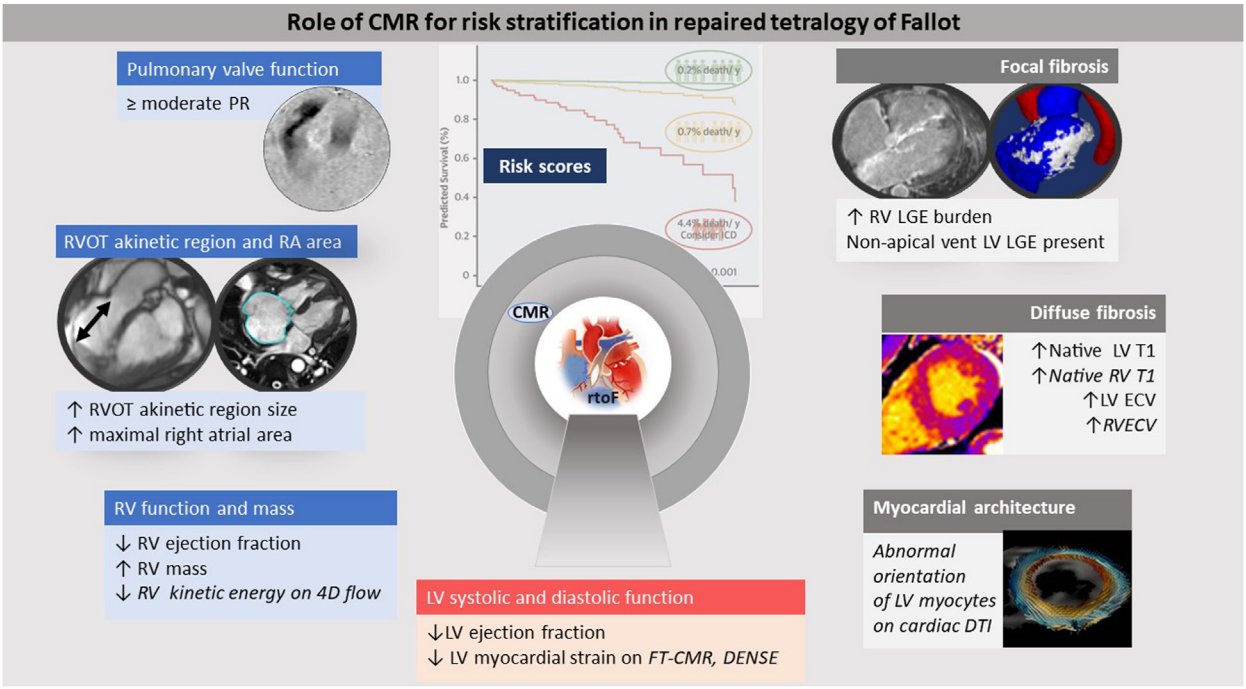

ABSTRACT

The risk of premature death in adult patients with repaired tetralogy of Fallot is real and not inconsiderable. From the third decade of life, the incidence of malignant ventricular arrhythmia (VA) is known to exponentially rise. Progressive adverse mechanoelectrical modelling because of years of volume and/or pressure overload from residual pulmonary valve dysfunction and ventricular scar creates the perfect catalyst for VA. Although potentially lifesaving, implantable cardiac defibrillators are associated with substantial psychological and physical morbidity. Better selection of patients most at risk of VA, so that

RÉSUMÉ

Le risque de décès prématuré chez les patients adultes présentant une tétralogie de Fallot réparée (TFr) est bien réel et doit être pris en considération. À partir de la trentaine, l'incidence de l'arythmie ventriculaire (AV) maligne augmente exponentiellement chez ces patients. Le remodelage mécanoélectrique défavorable causé sur de nombreuses années par une surcharge de volume ou de pression liée à la dysfonction de la valve pulmonaire et à la cicatrice ventriculaire constitue un catalyseur de l'AV. Les défibrillateurs implantables peuvent sauver la vie des patients, mais ils sont également associés à des taux

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implantable cardiac defibrillators are not inflicted on patients who will never need them, is therefore crucial and has inspired research on this topic for several decades. Cardiovascular magnetic resonance (CMR) enables noninvasive, radiation-free clinical assessment of anatomy and function, making it ideal for the lifelong surveillance of patients with congenital heart disease. Gold standard measurements of ventricular volumes and systolic function can be derived from CMR. Tissue characterization using CMR can identify a VA substrate and provides insight into myocardial disease. We detail risk factors for VA identified using currently available CMR techniques. We also discuss emerging and advanced CMR techniques that have not all yet translated into routine clinical practice. We review how CMR-defined predictors of VA in repaired tetralogy of Fallot can be incorporated into risk scores with other clinical factors to improve the accuracy of risk prediction and to allow for pragmatic clinical application. Finally, we discuss what the future may hold.

de morbidité psychologique et physique importants. Il est donc crucial de mieux cerner les patients les plus susceptibles de présenter une AV pour éviter d'implanter un défibrillateur à ceux qui n'en auront jamais besoin. Plusieurs études ont d'ailleurs porté sur cette question au cours des dernières décennies. La résonance magnétique cardiovasculaire (RMC) permet une évaluation clinique non invasive et sans radiation de l'anatomie et la physiologie, ce qui en fait une technique idéale pour la surveillance à vie des patients atteints de cardiopathies congénitales. Des mesures de référence du volume ventriculaire et de la fonction systolique peuvent être obtenues par RMC. La caractérisation des tissus par RMC peut permettre de repérer le substrat de l'AV et de renseigner sur la maladie myocardique. Nous décrivons les facteurs de risque de l'AV pouvant être repérés par les techniques de RMC actuelles, et nous présentons des techniques de pointe et en émergence qui n'ont pas encore trouvé leur place dans la pratique clinique courante. Nous examinons la façon dont les facteurs de prédiction de l'AV définis par RMC chez les patients atteints de TFr peuvent être intégrés aux indices de risque et conjugués à d'autres facteurs cliniques pour améliorer l'exactitude des prédictions et connaître une application clinique pratique. Nous évoquons enfin les possibilités futures.

Haemodynamic and Structural Risk Factors Defined by Cardiovascular Magnetic Resonance

Pulmonary regurgitation as a haemodynamic substrate for ventricular tachycardia

The relief of right ventricular outflow tract (RVOT) obstruction during tetralogy of Fallot (TOF) repair commonly results in chronic pulmonary regurgitation (PR). This can cause adverse effects in the long run as it results in dilatation and in turn dysfunction of the right ventricle (RV), symptomatic decline, ventricular arrhythmia, and sudden cardiac death (SCD). The presence of at least moderate PR was found to be the main haemodynamic lesion that predicted SCD in a landmark study.[1]

Patients who have advanced RV remodelling where the indexed RV end-systolic volume and indexed RV end-diastolic volume exceed 80 mL/m^2 and 160 mL/m^2, respectively, are most unlikely to undergo complete reverse remodelling after a pulmonary valve replacement (PVR).[2] Many centres have therefore adopted a proactive approach to intervening on significant PR for prognostic reasons before the onset of symptoms and irreversible RV cardiomyopathy.[2,3] Clinical guidelines support PVR in asymptomatic patients with at least moderate PR who have reached RV volumes at the surgical thresholds identified by cardiovascular magnetic resonance (CMR).[3] Recently, in the largest cohort of adult patients with repaired TOF (rTOF) reported to date, PVR was associated with a reduction in the risk of sustained ventricular tachycardia (VT) and death.[4] In the current era, there is consensus that it is no longer the goal to completely abolish RVOT obstruction at all costs. Instead, where there is a choice, it is better to leave a small degree of RVOT obstruction if it avoids free PR as a result of transannular patch surgery or overgenerous RVOT resection by using more conservative surgical techniques.[5] Because the long-term detrimental effects of RV pressure load are also well recognized,[6] a residual RVOT gradient over 25 mm Hg is to be avoided.[5,7] With the advent of transcatheter PVR, the question has been raised as to whether suitability for this approach should be considered at earlier RV volume thresholds or whether indications remain the same regardless of the mode of implantation.

Pulmonary regurgitation and RV flow

Given that PR is not a benign bystander in rTOF, it is important to know when it has become significant and CMR is the gold standard with which to quantify it. This is widely performed by measuring PR regurgitant fraction (the percentage of retrograde blood flow to total antegrade flow) using 2-dimensional (2D) phase contrast flow imaging acquired in a through-plane orientation perpendicular to the main pulmonary artery in a single breath-hold. 4D phase contrast flow imaging is acquired in free breathing using the velocity measured in 3 spatial dimensions (x, y, z) for each pixel. This enables the assessment of further flow characteristics including intracardiac kinetic energy, visualization of vortices, and areas of turbulent flow.[8] But prospective studies showing how these features may predict clinical heart failure or arrhythmia substrates are lacking, so these measures are not used in clinical practice for risk stratification.

RVOT akinetic region

Patients with rTOF have previously undergone resection of RV muscle bundles that cause subpulmonary obstruction and may have also had an RV ventriculotomy incision and/or

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patch augmentation for RVOT reconstruction leaving an akinetic region in the RVOT. A large RVOT akinetic region is associated with delayed electrical conduction within the RV (intra-RV), dyssynchrony,[9] increased RV volumes, and impaired RV systolic function.[9,10] On CMR, the pragmatically chosen and simple linear measure of the maximum 2D length of the akinetic RVOT predicted first onset sustained ventricular arrhythmia during follow-up.[11] Again, in a more recent study, an akinetic region ≥55 mm on CMR was an independent predictor of life-threatening ventricular arrhythmia and SCD.[12] Large akinetic RVOT regions may have lower prevalence among future adult populations given the more RV-conserving current era surgical approach and access via a transatrial/transpulmonary approach.[12]

Right atrial size and function

In rTOF, right atrial dilatation and dysfunction, secondary to years of RV volume and/or pressure overload and surgical atriotomy scars,[13] reflects RV diastolic dysfunction.[14] Right atrial area is associated with restrictive RV physiology in rTOF.[13] A maximum right atrial area indexed to body surface area ≥16 cm^2 was found to independently predict clinically important atrial and ventricular arrhythmia.[11] Sustained atrial arrhythmia, in itself, was found to be a predictor of mortality in a prospective study.[12] Reduced right atrial reservoir function as a marker of impaired right atrial emptying has been shown to be associated with the elevated brain natriuretic peptide (BNP) level and reduced exercise capacity.[14,15]

Restrictive RV physiology

Restrictive RV physiology is a phenomenon recognized in a proportion of patients with rTOF (28%-68% at different life stages or around 50% by the age of 23 years).[13,16] It occurs when the RV reaches the limits of its compliance, thus acting as a conduit that transmits atrial contraction directly to the pulmonary artery. The hallmark of restrictive RV physiology is laminar antegrade flow in the pulmonary artery in late diastole and throughout the respiratory cycle, detected as an "a" wave on Doppler echocardiography.[16] It is not possible to reliably diagnose restrictive RV physiology as originally defined and validated based on 2D phase-contrast flows as these are typically acquired with a breath-hold or free breathing. Real-time phase-contrast flow with respiratory bellows may help to allow assessment throughout the respiratory cycle to enable the same diagnosis as validated with echo but with the advantage of reliable characterization of the percentage of atrial forward flow but is not routinely performed in routine clinical CMR practice. 4D flow may also enable precise measures of RV diastolic function including from *post hoc* analysis of the caval vein, tricuspid valve, and pulmonary blood flow profiles.

RV restrictive physiology was initially noted to be associated with a small ventricle that was considered "stiff" with fibrosis. This could be regarded as "primary RV restrictive physiology," which is present in early life and associated with a turbulent clinical course in paediatric intensive care[13] but also a smaller cardiothoracic ratio, reduced PR, and better maximal oxygen uptake in adolescence.[17] It became increasingly recognized that RV restrictive physiology may also be associated with a large RV, often full at end diastole due to the burden of longstanding PR that might be considered "secondary RV restrictive physiology." We found that RV restrictive physiology measured on echo in the presence of larger RV volumes (≥170 mL/m^2) was associated with ventricular arrhythmia in our prospective study.[12] These data suggest that RV restrictive physiology may not comprise a single phenotype nor be universally protective in the long term.[18] RV restrictive physiology has been demonstrated in patients with severe degrees of myocardial fibrosis in keeping with myocardial fibrosis as culprit for this physiology.[19]

RV systolic dysfunction and RV hypertrophy

Several thresholds for RV ejection fraction (EF) have been reported to predict death and sustained VT in rTOF including RV EF <30%,[20] RV EF <48%,[6] RV EF <35%,[12] and RV EF <47%.[12] There have been different reported EF cutoffs for predicting risk, but the over-riding message is clear—impaired RV EF is an important predictor of risk. RV hypertrophy (RV mass indexed to RV end-diastolic ratio) independently predicted death and sustained VT in one large study.[6] When comparing local RV mass measures with study cutoffs, it is useful to consider that CMR analysis choices as to whether trabeculations are included in the blood pool or in the RV mass vary by congenital heart institution.

Left ventricular systolic and diastolic dysfunction and left ventricular-RV interaction in rTOF

Although rTOF has been traditionally regarded as primarily a disease of the right heart, evaluation of the left ventricle (LV) is equally important as it also relates to important clinical outcomes. CMR is the gold standard for evaluating LV systolic dysfunction in rTOF, and guideline-based clinical practice includes quantification of not only RV EF but also LV EF. CMR is less commonly used than echo to assess diastolic function. Primarily in research centres, CMR has been applied to evaluate diastolic dysfunction by measuring directly myocardial strain with displacement encoding using stimulated echoes (DENSE) or using 4D flow CMR.

LV ejection fraction

It is well known that LV and RV EF are closely related to each other. In rTOF, RV volume overload secondary to significant PR was associated with increased QRS duration, reduced RV EF, and reduced LV EF.[21] After PVR, LV EF was found to improve as well as RV EF demonstrating ventricular interaction effects.[2] In one of few randomized controlled trials available in congenital heart disease, the angiotensin-converting enzyme inhibitor ramipril was found to improve LV EF in the subgroup of patients who had restrictive RV physiology, further demonstrating ventricular-ventricular interdependence.[22] CMR-derived LV EF thresholds of ≤35% and ≤55% were found to be predictors of death and life-threatening ventricular arrhythmia.[12,20]

LV long axis function

A reduction in the LV longitudinal function is known to be an early marker of myocardial dysfunction that occurs before the decline in EF. This is thought to be due to the location of longitudinal fibres in the subendocardial layer

making them most susceptible to myocardial ischaemia.[23] A reduced mitral annular plane systolic excursion measured on echo was found to be associated with ventricular arrhythmia and SCD.[23] In the APPROPRIATE study, ramipril was found to improve biventricular long axis function after 6 months of treatment when compared with placebo.[22,24] This suggests more favourable ventricular-ventricular interaction with ramipril, which may have potential to reverse subclinical myocardial disease. Although the trial was negative for its primary end point, CMR-derived RV EF (as was with the REDEFINE trial of losartan[25]), the findings remain intriguing with regard to not only considering the RV but also targeting the LV. To date, however, using CMR vs M-Mode Echo to derive mitral annular plane systolic excursion has no proven role for predicting survival in rTOF albeit it has been associated with adverse cardiac events in patients with acquired heart disease.[26]

LV myocardial strain

Myocardial strain, a measure of how much the myocardium deforms in systole relative to its resting state in diastole, is like end-systolic volume, a marker of intrinsic myocardial contractility and speculated to be also an early, sensitive identifier of "preclinical" LV dysfunction. Reduced global longitudinal strain measured with echocardiography has been shown to be associated with an adverse outcome in rTOF.[23] In a case control study of adult patients with rTOF, both reduced LV strain and CMR-derived diffuse fibrosis were associated with adverse outcomes, but were not related to each other; hence the authors suggested that they contribute by different mechanisms.[27] Although feature tracking CMR is deployed more commonly to infer strain as it can be added to routinely acquired cine data, several CMR techniques have been developed to measure directly myocardial strain. DENSE CMR enables direct measure of strain at high spatial and temporal resolution that makes it particularly advantageous for quantifying strain in the thin and hypermobile RV wall as well as in the LV.[28] Regional abnormalities in LV dyssynchrony and radial strain measured with DENSE CMR were associated with diffuse fibrosis[29] detected with T1 mapping, suggesting that these may be markers of earlier disease. There is no evidence to date that either feature tracking CMR or the more accurate DENSE CMR to define myocardial strain predicts survival and with incremental value to other measures.

LV diastolic dysfunction in rTOF

In keeping with ventricular-ventricular dependence, restrictive RV physiology has been linked to impaired LV diastolic filling. Patients with prolonged RV systole secondary to RVOT obstruction also have impaired LV diastolic filling due to septal shift in early diastole.[30,31] In a subset of rTOF patients with implantable cardiac defibrillators (ICDs) *in situ*, raised LV end-diastolic pressure (LV EDP)[32] was found to be a strong predictor of appropriate ICD shock. This invasively obtained measure is pragmatically challenging to apply in unselected cases for risk stratification. It remains unclear whether increased LV EDP in rTOF could be secondary to diffuse fibrosis, which in itself is a predictor of an adverse outcome as discussed below. This also creates interest into whether this reversible form of fibrosis could be targeted with antifibrotic heart failure therapies in order to restore diastolic function in patients with rTOF. Ramipril was found to improve LV diastolic function in rTOF patients with stable significant PR after 6 months of treatment in a small hypothesis generating randomized control trial, which requires further investigation[24] that could add the CMR measurement of diffuse LV fibrosis.

Tissue Microstructure and Ventricular Arrhythmia Substrate

Myocardial fibrosis is the final common pathophysiological process that links a wide spectrum of cardiovascular disease and is a known nidus for ventricular arrhythmia. Myocardial fibrosis can be regarded as a continuous spectrum that includes diffuse (interstitial) fibrosis, a known precursor for the patchy focal fibrosis visible with late gadolinium enhancement (LGE) CMR. More recently, it has also become possible to quantify diffuse LV fibrosis with CMR. Focal fibrosis may be the tip of the iceberg[33,34] when considering the global burden of macroscopic and microscopic fibrosis.

Focal Fibrosis

Direct insult to myocytes can cause dense scar (focal fibrosis), which is irreversible. This type of focal fibrosis seen in adult patients with rTOF and preserved EF is associated with fast monomorphic VT, whereas polymorphic VT is more common in patients with poor ventricular function.[32,35] Noninvasive assessment of ventricular arrhythmia scar substrate is possible with LGE CMR. In rTOF, regions of LGE are detected at sites of previous surgery: the RVOT where muscle bundles were resected with or without further reconstruction including surgical patches, the ventricular septal defect repair site as well as locations appearing remote to direct incisions and reconstructions during cardiac surgery such as within RV and LV trabeculations.[36] In addition, fibrosis that does not discriminate future clinical events was seen in both the LV (at the site of surgical LV apical venting) and the RV (in the RV LV septal insertion point regions), also demonstrating the sensitivity of the technique. Focal fibrosis in patients with rTOF studied with LGE CMR was also confirmed histologically.[12,36] Focal fibrosis was first reported to be related to reduced exercise capacity, elevated neurohormonal markers, and arrhythmia in a cross-sectional study in 2006.[36] In a more recent prospective study, the burden of scar in the RV defined by LGE CMR (excluding the ubiquitous presence of RV LV insertion point enhancement) was found to independently predict death and life-threatening ventricular arrhythmia.[12] As for the LV, the mere presence of LV LGE (ie, excluding the finding of apical vent LGE reflecting de-airing of the heart perioperatively) also predicted this adverse outcome.[12]

2D late gadolinium enhancement CMR

Typically, LGE CMR images are acquired using a phase-sensitive inversion-recovery gradient-echo sequence starting from 8 to 10 minutes after the intravenous administration of a 0.1 mmol/kg gadolinium-diethylenetriamine penta-acetic acid contrast agent. In our experience, acquisition needs to be performed up until at least 25 minutes duration following gadolinium based contrast administration so that high-quality

diagnostic RV LGE images can be obtained and false-negative LGE results are avoided. However, as some patients do have a faster washout, it is not feasible to simply wait this long in all as there will be patients in whom the window of best possible RV LGE imaging would then be missed. Meticulous visual inspection of each acquired breath-hold is required to select the subsequent inversion time (Ti) that would most optimally null the myocardium particularly for detecting small areas of focal fibrosis in the RV. Imaging of the RV is susceptible to false-positive LGE, not only due to abandoning acquisitions too early after contrast but also due to partial-volume effects where one pixel can contain both myocardium and surrounding tissue such as pericardium, fat, or sternal wires. False-positive LGE interpretation should be avoided and can be reduced by cross-cutting suspicious areas, phase swapping, and comparing with cine images.

Motion-corrected, free-breathing phase-sensitive inversion recovery LGE can be useful in patients who have poor breath-holding or have arrhythmia. This sequence is also more tolerant to imperfect Ti selection where nulling of the myocardium can be maintained over a range of values due to its method of reconstruction, thereby enabling it to be more operator independent. We believe that this may be especially relevant for centres less experienced in RV LGE acquisition.

Quantification of LGE in the RV

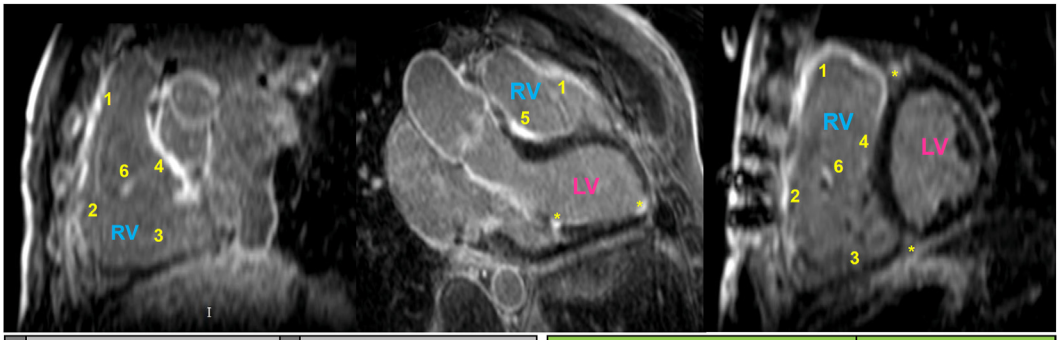
Assessing the burden of RV LGE in adult patients with rTOF is important as it has been shown that large amounts of RV LGE predict death and clinically important ventricular arrhythmia.[12] Unlike for the LV, the quantification of LGE in the RV is challenging due to its thin wall and complex geometry. Simply saying scar is present would not help to differentiate between patients as LGE is present at surgical sites in the ventricle in rTOF.[36] A semiautomated full-width half-maximum technique that is usually employed for the LV[37] is susceptible to significant partial volume effects due to difficulties with performing endocardial and epicardial contours around a thin-walled RV. 2D RV LGE is therefore semiquantitatively measured using a visual segmental scoring system in patients with rTOF designed to take into consideration the unique geometry of the RV (see Fig. 1).[36] This was shown to be a highly reproducible method of analysis. The presence of LGE at the RV/LV septal insertion points is a usual and nonspecific finding that should be visible in all patient studies with optimal-quality LGE CMR and is not included in the quantification of 2D LGE.[36]

Three-dimensional LGE CMR

An inversion prepared gradient echo, 3D respiratory-navigated, LGE CMR acquisition can image the whole heart with contiguous slices at a higher resolution when compared with 2D LGE (1.5 × 1.5 × 4 mm reconstructed in any plane to 0.7 × 0.7 × 2 mm voxel size vs 7 mm slice thickness, respectively).[38,39] We have optimized this sequence to ensure high spatial resolution, maximal efficiency through respiratory gating[39] and have incorporated beat-to-beat dynamic Ti to help it withstand arrhythmia.[38] The enhanced spatial resolution is particularly appealing for studying the thin-walled RV. Using 3D LGE CMR, personalized virtual whole heart models that include visualization of ventricular scar can be created and the volume of LGE can be quantified (see Fig. 2).[35,40,41]

Role of 3D LGE CMR in electrophysiology procedures

Inducible VT during programmed electrical stimulation (PES) was found to predict sustained VT and SCD in a multicentre study.[42] A negative PES had a high negative predictive value and therefore is considered to be a useful rule-out test to reassure patients that a primary prevention ICD is not required.[42] Conversely, a positive PES had low specificity, therefore, suggesting that it is best avoided in rTOF patients with low pretest probability.[42] This important outcome study



1	Anterior wall of RVOT (0-3)	4	RV surface of septum (0-3)
2	Anterior wall of RV (0-3)	5	VSD patch region (0-3)
3	Inferior wall of RV (0-3)	6	Trabecular bands (0-3)

Minimal RV LGE	≤ 2
Mild RV LGE	3 or 4
Moderate RV LGE	5-7
Severe RV LGE	≥ 8

Figure 1. Visual segmental scoring system to semiquantify RV LGE in patients with repaired tetralogy of Fallot. Segmental system for scoring the RV as published previuously.[36] The RV is divided into 6 segments (yellow numbers 1-6). Regions of RV LGE were scored according to linear extent (0 = no enhancement, 1 = up to 2 cm, 2 = up to 3 cm, and 3 = 3 or more cm in length) and number of trabeculations enhanced including the moderator band (0 = no enhancement, 1 = 1 trabeculation, and 2 = 2-4). Scoring of LV LGE was performed using the universally accepted 17-segment LV model. Figure from Ghonim et al.[16] LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

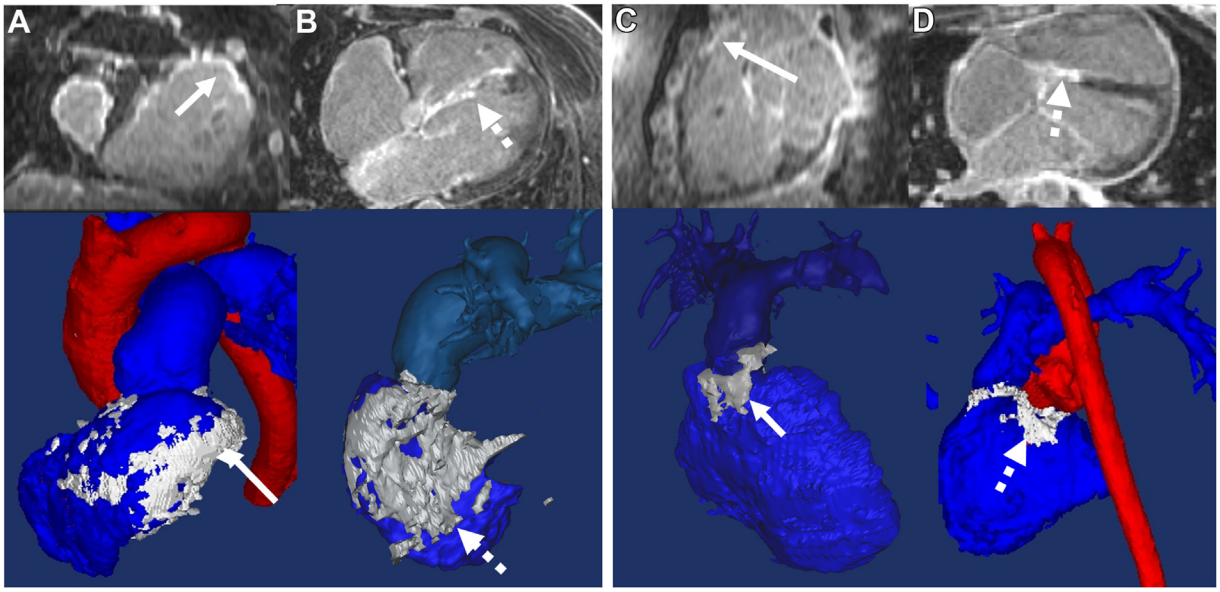


Figure 2. Examples of the RV LGE burden defined by 3D LGE cardiovascular magnetic resonance in patients with repaired tetralogy of Fallot (rTOF). Left panel: 60-year-old patient with TOF (repaired late aged 17 years with transannular patch) who had extensive RV scar. (**A, B**) 3D LGE from coronal and transaxial multiplaner reconstructions with corresponding RV scar and chamber segmentation below. (**A**) Large area of LGE in the RVOT extending on to the anterior RV wall (**white arrow**). (**B**) LGE in the VSD repair site extending to involve the entire septum (**dotted arrow**). Right panel: 21-year-old patient with TOF (repaired at age 4 years with RVOT patch) who had a minimal amount of RV scar. (**C, D**) 3D LGE from sagittal and transaxial multiplaner reconstructions with corresponding RV scar and chamber segmentation below. (**C**) Very small area of subendocardial LGE in the RVOT (**white arrow**) (**D**) Small region of LGE in the VSD repair site (**dotted arrow**). 3D, 3-dimensional; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; RV, right ventricular; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

has informed clinical guidelines that recommend PES to be performed in rTOF cases clinically deemed to be of intermediate risk of VT/SCD. Such patients typically represented those with 2 or more of the following concerning features: cardiac syncope, QRS duration >180 ms, mild LV impairment, or moderate RV impairment.[3,43,44] Recently, increased RV LGE volume measured by 3D LGE CMR was found to predict inducible VT, over and above established risk factors for mortality such as age and QRS duration >180 ms.[35] RV LGE volume also had a high negative predictive value with patients with minimal RV LGE being very unlikely to have inducible VT.[35] This suggests a role for 3D LGE CMR in the selection of patients for PES and can help to identify those patients with the lowest risk who could avoid this invasive procedure.[35]

Ventricular scar identified by 3D LGE CMR was found to closely correlate with low-voltage areas on electrical anatomic maps.[35,45] This supports a role for the integration of 3D LGE CMR with electrophysiology in order to help plan a substrate-guided approach for VT ablations as opposed to an anatomically guided approach. An anatomically guided approach whereby VT is induced can cause haemodynamic instability, particularly in patients who have LV dysfunction.[46] This patient group may be helped by a substrate-guided approach enhanced by high-resolution scar imaging acquired with preceding CMR, and integrating it into the invasive procedure. It will require a learning curve and expertise to achieve high-quality RV 3D LGE imaging on each attendance, which is the main hurdle for its translation into clinical practice.

Virtual native enhancement

Virtual native enhancement is a novel technique that uses artificial intelligence to analyse cine images and native T1 maps to create images that resemble LGE without contrast.[47] For the LV of patients with hypertrophic cardiomyopathy, it has been reported to closely correlate with LGE images and also have superior image quality.[47] This contrast-free technique will have major appeal to patients with congenital heart disease who require lifelong imaging, but its application to the RV is untested and will most likely be limited by the same challenges that face T1 mapping of the RV (discussed below).

LGE dispersion mapping

It has been recognized that it is not just the amount of scar present but also the heterogeneity of scar that can be a risk factor for ventricular arrhythmia. Scar heterogeneity has been quantified using LGE-dispersion mapping.[48] In this technique, parametric maps are created from LGE images and each pixel is allocated a score representing the signal intensity of its surrounding pixels relative to the central core pixel. A global dispersion score as a marker of scar heterogeneity is calculated as the average score of LGE pixels.[48] For patients with hypertrophic cardiomyopathy who are low and intermediate risk of SCD, global dispersion score has identified patients at the highest risk of SCD beyond the LGE presence and amount.[48] If this technique can be further developed for application in the RV, it could further refine risk stratification for patients with rTOF beyond the RV LGE burden.

Identifying scar core, border zones, conducting channels, and isthmuses

Regions of RV scar or patch material and valve annuli form areas of "electrically dead" nonconducting tissue. Between these nonconducting tissues is healthy myocardium (anatomic isthmuses) from which monomorphic re-entrant tachycardias can arise. Detailed electroanatomic mapping has identified the anatomic isthmuses, typically II and III (between the RVOT patch and pulmonary annulus and between the ventricular septal defect patch and pulmonary annulus, respectively).[49] Electrophysiology studies have identified that ventricular arrhythmia is most likely with narrower anatomic isthmuses. In future, 3D LGE CMR may be able to noninvasively detect anatomic isthmuses and aid with planning for VT ablation.[50] A novel postprocessing analysis method for LV LGE in patients with hypertrophic cardiomyopathy was able to differentiate between scar core, border zones, and conducting channels,[51] and it would be of interest if postprocessing could also reveal more about rTOF scars

Diffuse Fibrosis

Diffuse (interstitial) fibrosis is secondary to increased collagen deposition that expands the extracellular matrix as a response to abnormal loading conditions on the myocardium. This pathologic change in the extracellular matrix can be noninvasively detected by measuring extracellular volume (ECV) and T1 mapping.[52] Its presence defined by CMR is associated with ventricular arrhythmia and SCD in acquired heart disease. In patients with rTOF, diffuse fibrosis in the RV and LV was linked to adverse markers of outcome and events.[53,54] Enthusiasm for its noninvasive detection using CMR is further driven by the concept that diffuse fibrosis is a reversible process, making it also a potential therapeutic target.

Extracellular volume measurement and native T1

The calculation of ECV can be cumbersome, as it requires the administration of a contrast agent as well as a blood sample taken to measure the haematocrit at the same time of the scan. Potential advantages of native T1 measurements include the lack of requirement for contrast administration or haematocrit and a minimal increase in the scan duration.

Challenges of T1 mapping in the RV

Like all parametric mapping of the RV, T1 mapping is susceptible to partial volume effects due to the highly mobile and thin RV wall, which may be only 1-2 pixels thick, and the close proximity of pericardium, blood pool, and sternal wires. Due to these challenges that are specific to the RV, it is unclear whether standard T1 mapping techniques applied to the LV will be as accurate if extrapolated to the RV without making bespoke modifications. Studies so far have examined RV diffuse fibrosis without a dedicated RV T1 sequence. Elevated RV native T1 was found to correlate with dilated RV and greater severity of PR.[40] Although it is plausible that diffuse fibrosis is associated with and proportional to the amount of adverse remodelling, it is also difficult to be sure that these effects seen are not secondary to partial volume effects that might be more commonly encountered when measuring T1 in a more dilated RV with a lower RV mass-volume ratio.

Clinical applicability in rTOF

In a prospective study of adult patients with rTOF in whom RV ECV was measured using meticulous care, increased RV ECV was associated with death and life-threatening ventricular arrhythmia.[53] These findings are encouraging for a further study of RV T1 in larger prospective studies. However, it is worth noting that in this study, it was only possible to measure RV T1 in 50% of patients due to partial volume effects.[53] Future development of a T1 mapping sequence tailored to the RV may help to mitigate this and will be required for its translation into routine clinical practice.

An LV ECV $\geq$30% was associated with death and sustained atrial arrhythmia in an older population of patients with rTOF (mean age 40 years).[54] A higher proportion of patients (29%) were found to have LV ECV above the abnormal cutoff (defined as more than 2 standard deviations above the mean)[54] when compared with other studies suggesting increased LV diffuse fibrosis with age. In this study by Broberg et al.,[54] LV ECV was found to correlate with older age, late repair, exercise capacity, BNP, and atrial dimensions. Other studies have demonstrated the association of arrhythmia with increased LV ECV but with softer end points studied such as ventricular ectopy.[40] Increased LV native T1 and LV ECV were linked to longer cardiopulmonary bypass and aortic cross-clamp times, suggesting early onset for diffuse fibrosis secondary to postoperative ischaemia.[55] In these patients, elevated LV T1 was found despite preserved LV systolic function suggesting that diffuse fibrosis precedes LV systolic dysfunction and its identification with LV T1 mapping may be an early warning of further clinical manifestations to come.

The correlation between diffuse fibrosis in the LV and RV with T1 mapping is reflective of ventricular-ventricular interdependence.[40,56] Given the technical challenges faced with measure T1 in the RV reliably, one might argue that LV T1 assessment alone could be a sufficient first step in informing us about RV diffuse fibrosis.

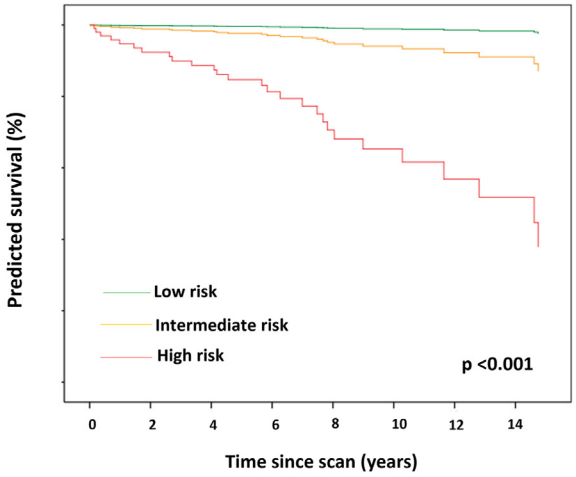
3D T1 and achieving a global fibrosis measure

Further down in the pipeline may be 3D T1 mapping that can enable comprehensive LV T1 estimates with coverage of the entire LV in free-breathing using a respiratory navigator. It has been reported to show good accuracy, precision, and potentially improved spatial resolution (1.5 mm^3).[57] Current 2D T1 maps involving sampling selected slices (typically mid-ventricle) with a single breath-hold of typically 8 mm slice thickness. Potentially, we may be able to quantify the global fibrosis burden (focal and interstitial) in a patient using 3D T1 when combined with 3D LGE.

Diffusion Tensor Imaging CMR

Besides myocardial fibrosis, it is known that other pathologic changes in myoarchitecture such as myocardial disarray can also be a focus for ventricular arrhythmia. Diffusion tensor (DT)-CMR is a noninvasive technique that can study the orientation of myocytes by interrogating the diffusion of water within the myocardial matrix. It uses a mathematical tensor that conveys information in 3 perpendicular dimensions known as eigenvectors that are found to correspond with the arrangement of myocytes in the LV and has been validated

Mortality Risk	Points
RVLGE extent	
Minimal/mild extent	0
Moderate extent	24
Severe extent	40
LVLGE present	
No	0
Yes	6
RV ejection fraction	
>47%	0
36-47%	4
≤35%	10
LV ejection fraction	
>55%	0
36-55%	4
≤35%	12
Peak Oxygen Uptake	
>17ml/kg/m²	0
≤17ml/kg/m²	6
B-type Natruretic Peptide	
<127ng/l	0
≥127ng/l	12
Sustained atrial arrhythmia	
No	0
Yes	8
Age over 50 years	
No	0
Yes	6
Total	/100



Risk score	Mortality/year
0-20	0.2%
21-50	0.7%
≥51	4.4%

Figure 3. Annualised risk of mortality according to the risk category. The weighted risk score of independent predictors of mortality derived from a prospective study of 550 adult patients with repaired tetralogy of Fallot . The Cox proportional hazard survival graph showing freedom from mortality with each risk category. Corresponding risk categories with annualized mortality rate. Figure adapted from Ghonim et al.[16] LV, left ventricular; LGE, late gadolinium enhancement; RV, right ventricular.

with histology.[52] Certain DT-CMR parameters have been shown to correspond with regions of myocardial disarray and fibrosis.[58] Recent sequence developments to overcome motion artefact have enabled its application *in vivo*. However, DT-CMR is currently confined to research with further development still required to reduce scan duration and resilience to arrhythmia. Like T1 mapping, investigation of myoarchitecture in the thin-walled RV with DT-CMR will require improvement in spatial resolution.

Putting It All Into Perspective

The annual incidence of SCD in unselected adult patients with rTOF is estimated to be around 0.15%.[59] Bricker[60] in 1995 calculated that a large study that includes at least 1700 patients followed up for 10 years will be required to be able to predict SCD. Prospective studies of this scale in congenital heart disease as a rare condition are challenging to perform and are almost unheard of. It has become apparent that no single variable on its own will be robust enough to predict VT and SCD.

Risk scores

Several risk scores suggesting how we use risk factors such as the ones discussed in this article to predict ventricular arrhythmia have been proposed. A study by Khairy et al.[32] in 2008 was pioneering as the first to attempt to address this problem with a risk score but with all the limitations inherent in a retrospective analysis of data from different centres. The study end point was the appropriate ICD shock as opposed to mortality and included patients who were sicker and had already secondary prevention ICDs limiting its clinical applicability.[32] It also proposed a strong role for data that were obtained invasively such as inducible VT and LV EDP, making it inappropriate to apply in unselective cases. Modifications of the score by the replacement of the invasive measures with noninvasive CMR-derived RV EF ≤30% and LV EF ≤45% were a step forward in making the score user friendly for the prediction of a composite end point of death and life-threatening ventricular arrhythmia.[20] Although it may not have been the authors' intention to turn in to a score, RV mass/volume ratio ≥0.3 g/m^2, history of atrial arrhythmia and RV or LV EF <2 standard deviations derived from the largest observational study of patients with rTOF was also found to predict a combined end point of death and VT.[6] In 2022, we proposed a weighted multifactorial risk factor that incorporated all noninvasive independent predictors of mortality and life-threatening ventricular arrhythmia.[12] This score included the BNP level,[61] peak oxygen consumption (PVO_2),[62] and age[12] as other predictors of outcome. RV LGE burden was a strong predictor of mortality and ventricular arrhythmia in this study with appropriate weighting to reflect that in the score. Using this, we were able to identify the highest risk patients (approximately 10%) of the cohort that could be targeted for further monitoring and consideration for therapy such as with primary prevention ICD or VT ablation. This score was not externally validated at the time of publication. Subsequently, it has been tested in a different large tertiary centre cohort but without LGE CMR, the most weighted contributor to the score as this was unavailable—even without the LGE data the score performed well.[63] This score is yet to be externally validated. The score included cutoff thresholds

for the strongest independent measures for purposes of making it simple to apply in day-to-day clinical practice (see Fig. 3).[12] However, a risk calculator with all relevant continuous variables could help to overcome the fact that risk is a continuum with no hard cutoff points and allow the sum of smaller effect variables to be incorporated to give the more specific estimation of risk.

Recently, a score to risk stratify for life-threatening VT and SCD in rTOF using machine learning that included routinely available clinical and CMR data performed well against other published scores.[63] This score included variables that were consistent with other risk factors reported. A significant advantage of this score due to its generation from machine learning is that it is not limited to a certain number of variables, thereby strengthening its predictive power. It does not include LGE data, which is currently not part of routine world-wide clinical practice and still requires a learning curve to acquire and analyse robustly at every attendance. It also does not include BNP that has become standard of care in many tertiary centres.

With future changes in the profile of the adult population with rTOF reflecting early diagnosis and more recent era surgery and medical care, it is expected that risk profiles will change; for example, we may see smaller amounts of focal fibrosis. Conversely, age and risk factors such as obesity, hypertension, lipid dysregulation, diabetes, and sleep apnoea are increasingly well represented as the population ages.

Advanced Analytics and Computer Simulation

Looking to the horizon, we anticipate that artificial intelligence will have an increasing role in determining prognosis and risk stratification. It is capable of identifying numerous risk factors without being limited by collinearity or model overfitting using standard regression analysis.[63,64] Using deep neural networks, risk stratification models can be built that are inclusive of all risk factors and, in the future, there may include genomics, proteomics, and metabolomic biomarkers for arrhythmia preponderance. Artificial intelligence may play a larger role in not only the acquisition of CMR images to make the sequences faster and less operator dependent but also the analysis of images such as automated 3D LGE segmentation. This could be pivotal in rolling out these novel and advanced CMR techniques to routine clinical practice. Recently, personalized image-based virtual heat modelling using 3D LGE segmentation and simulations of rapid ventricular pacing determined VT inducibility.[65] Although this was demonstrated in a small group of patients with rTOF, this innovative work paves the way for further large studies and potentially could have an important role in the selection of patients for PES and preprocedural planning for VT ablation.

Conclusion

The accurate and robust prediction of life-threatening VT and SCD in patients with rTOF is considered to be a holy grail of arrhythmia care in adult congenital heart disease. Decades of research have identified multiple clinical, electrical, haemodynamic, and structural risk factors. CMR has a fundamental role in evaluating cardiac anatomy and function in the lifelong surveillance of patients with rTOF. It is capable of interrogating tissue microstructure for a deeper assessment of a ventricular arrhythmia substrate. Newer CMR approaches show promise but are not yet ready for prime-time clinical use.

Ethics Statement

Research reported has adhered to relevant ethical clinical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article.

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Disclosures

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