3D late gadolinium enhancement cardiovascular magnetic resonance predicts inducibility of ventricular tachycardia in adults with repaired tetralogy of Fallot

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Running title 3D CMR scar and VT inducibility in Fallot

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Abstract

Background: Adults with repaired tetralogy of Fallot (rTOF) die prematurely from ventricular tachycardia (VT) and sudden cardiac death. Inducible VT predicts mortality. Ventricular scar, the key substrate for VT, can be non-invasively defined with late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) but whether this relates to inducible VT is unknown.

Methods: Sixty-nine consecutive rTOF patients (43 male, mean 40±15 years) clinically scheduled for invasive programmed VT-stimulation were prospectively recruited for prior 3D LGE CMR. Ventricular LGE was segmented and merged with reconstructed cardiac chambers and LGE volume measured.

Results: VT was induced in 22(31%) patients. Univariable predictors of inducible VT included increased RV LGE (OR 1.15;p=0.001 per cm^3), increased non-apical vent LV LGE (OR 1.09;p=0.008 per cm^3), older age (OR 1.6;p=0.01 per decile), QRS duration ≥180ms (OR 3.5;p=0.02), history of non-sustained VT (OR 3.5; p=0.02) and previous clinical sustained VT (OR 12.8;p=0.003); only prior sustained VT (OR 8.02;p=0.02) remained independent in bivariable analyses after controlling for RV LGE volume (OR 1.14;p=0.003). An RV LGE volume of 25cm^3 had 72% sensitivity and 81% specificity for predicting inducible VT (AUC 0.81;p<0.001). At the extreme cutoffs for 'ruling-out' and 'ruling-in' inducible VT, RV LGE >10cm^3 was 100% sensitive and >36cm^3 was 100% specific for predicting inducible VT.

Conclusion: 3D LGE CMR-defined scar burden is independently associated with inducible VT and may help refine patient selection for programmed VT-stimulation when applied to an at least intermediate clinical risk cohort.

Key words

tetralogy of Fallot, ventricular tachycardia, fibrosis, magnetic resonance imaging, late gadolinium enhancement

Non-standard Abbreviations and Acronyms

rTOF repaired tetralogy of Fallot

PR pulmonary regurgitation

PVR pulmonary valve replacement

SCD sudden cardiac death

VT ventricular tachycardia

PES programmed electrical stimulation

LGE late gadolinium enhancement

CMR cardiovascular magnetic resonance

bSSFP balance steady state free precession

CLAWS continuously adaptive windowing strategy

ECG electrocardiogram

BNP B-type natriuretic peptide

CPEX cardiopulmonary exercise testing

RV right ventricle

PA pulmonary artery

LV left ventricle

LVEDP left ventricular end-diastolic pressure

EAM electro-anatomical mapping

ICD implantable cardiac defibrillator

Introduction

Survival of patients with repaired tetralogy of Fallot (rTOF) has greatly improved over the past 60 years. With success comes new challenge. Pulmonary regurgitation (PR) is a common haemodynamic lesion associated with ventricular tachycardia (VT)[1]. Despite proactive and timely pulmonary valve replacement (PVR), the risk of VT and sudden cardiac death (SCD) is not abolished[2,3]. Arrhythmia sequelae have become a major issue for the growing number of adults with rTOF. Contemporary clinical concerns have moved on from who should a receive a new pulmonary valve and when towards addressing the increasing burden of arrhythmia related morbidity and mortality. The combination of previous surgical scar with years of volume and or pressure chamber overload and consequent progressive adverse mechano-electrical remodelling, can be catastrophic. The risks of VT and SCD rise exponentially in rTOF from the 4th decade of life[1].

Invasive programmed electrical stimulation (PES) was an independent predictor of mortality during follow-up of rTOF patients, associated with an approximate 5-fold increased risk of subsequent VT/SCD [4]. Thus, PES is selectively recommended in current guidelines [5-8] albeit there is uncertainty about application, timing, interpretation and frequency of use.

Three-dimensional (3D) late gadolinium enhanced (LGE) cardiovascular magnetic resonance (CMR) enables both high-spatial resolution non-invasive scar definition (more appropriate to the thin-walled RV than 2D LGE) and entire contiguous coverage of the heart enabling precise volumetric quantification of total LGE burden [9-12]. We sought to prospectively examine whether 3D LGE extent predicts inducible VT at PES.

Methods

Patients and study design

Consecutive adult (>16 years old) rTOF patients were prospectively recruited and gave their informed consent for 3D LGE CMR preceding clinically scheduled PES from 2008 to 2018 unless LGE CMR contraindicated. The study was approved by the local research ethics committee and conducted according to the Declaration of Helsinki. Inducible sustained VT was defined as >30 seconds or causing haemodynamic compromise requiring cardioversion. The data that support the findings of this study are available from the corresponding author upon reasonable request.

CMR acquisition, analysis and reconstruction

CMR was acquired using a standardised protocol as previously described [13,14.] whereby RV trabeculations and LV papillary muscles were excluded from the blood pool for the purposes of ventricular volume analysis. A free-breathing whole-heart 3D balanced Steady State Free Precession (bSSFP) 'roadmap' was acquired[9].Approximately 20 minutes after gadolinium (0.15mmol/kg) was administered, when the myocardial wash-in and wash-out reached a steady state, a free-breathing inversion prepared gradient echo 3D LGE acquisition was performed, the inversion time being set to null normal myocardium by meticulous visual inspection of the preceding long and short axis 2D LGE images[9]. Sequence sensitivity to heart rate variations during the acquisition were minimised by making real-time changes to the inversion time as the acquisition proceeded [10]. The 3D LGE images covered the entire heart, typically requiring 64 slices at 1.5x1.5x4mm^3 voxel resolution which were post processed to 0.75x0.75x2mm^3 voxel resolution [9,10]. For both roadmap and 3D LGE acquisitions, the continuously adaptive windowing strategy (CLAWS) was used for efficient respiratory gating [9,15]. Manual 3D segmentation and fusion of cardiac chambers, vessels and ventricular LGE was carried out using dedicated segmentation software (Mimics, Materialise, Le). LGE volume (cm^3) in each ventricle was recorded. LGE

segmentation was performed by 2 experienced operators co-reviewing for consensus and blind to the PES. To test intra-observer and inter-observer reproducibility 20 cases were re-segmented by the same operators blinded to their previous segmentation as well as each other.

Routinely acquired clinical data

Patients routinely underwent 12-lead electrocardiogram (ECG), blood sampling for B-type natriuretic peptide (BNP), echocardiography, cardiopulmonary exercise testing (CPEX), and CMR as part of their standardised adult congenital heart disease care[7]. Ambulatory ECG Holter monitoring was performed when clinically indicated by symptoms volunteered or for risk stratification. Non-sustained VT defined as ≥3 consecutive ventricular beats ≥100 bpm for ≤30 seconds duration and sustained atrial arrhythmia defined as ≥30 seconds that occurred prior to index CMR were recorded. RV restrictive physiology was assessed on echocardiography using diastolic forward flow through the pulmonary artery, PA ('a wave') throughout the respiratory cycle by a single operator. LV restriction as a non-invasive surrogate for a raised LVEDP was assessed using standard echographic criteria. CPEX was assumed valid within 1 year from the CMR study.

PES was performed using a standardised protocol under assisted sedation. No patients were taking amiodarone prior to the procedure. Electroanatomical mapping (EAM) was performed with CARTO (Biosense Webster Inc., CA, CARTO XP RMT, CARTO 3 RMT up to version 7). PES was achieved at 2 RV sites (RV apex and outflow tract) at twice the diastolic threshold with ≥2 eight-beat drive trains (cycle lengths between 440 - 510ms) and with up to 3 extra-stimuli with coupling intervals ≥180 ms. If VT was non-inducible, this protocol was repeated with isoprenaline (200mcg in 500ml normal saline via a peripheral line) until heart rate increased by 20%-50%. RV mapping was performed both in sinus rhythm using an endocardial bipolar voltage map or atrial pacing for intrinsic ventricular activation mapping.

LGE correlation with electroanatomical mapping (EAM) sub-study

In a sub-study of 22 rTOF patients in whom mapping points were available, correspondence of LGE CMR with EAM was investigated. Registration of 3D LGE CMR segmentation with CARTO bipolar voltage maps for each patient was undertaken using MeshLab software. A 2-stage registration process was applied to minimise misalignment: first with landmark registration of the ascending aorta and second with surface registration of the iterative closest point [16]. The surface registration error, defined as the distance between points matched on the 3D LGE segmentations and EAM was measured. EAM regions with a pre-specified bipolar signal amplitude of <1.5mV were identified as scar tissue, as previously reported in several histological validation studies. To quantify the correspondence between LGE CMR and low-voltage bipolar signal, we defined LGE CMR sensitivity as the proportion of low voltage mapping points within 5mm of LGE-defined scar against total mapping points, where 5mm was the allowance made for LGE to mapping point registration error. Similarly, we defined LGE CMR specificity as the proportion of normal voltage points ≥25mm away from LGE-defined scar against total mapping points.

Statistical methods

Continuous data are summarized as mean (±SD) or median (interquartile range) as appropriate. Comparisons between groups were made using a Mann-Whitney test, chi-squared test or Fishers exact test as appropriate. Correlation between continuous data was assessed using Spearman's test (ρ). Receiver-operating characteristics (ROC) analysis was used to determine the discriminative power of RV LGE. The optimum cutoff value with the highest sensitivity and specificity in predicting inducible VT was determined using the optimum Youden index (J). In addition, RV LGE volume cutoff values achieving 100% sensitivity and 100% specificity were measured. The association between RV LGE and other variables with inducible VT was tested using logistic regression analysis. Given the relatively small number of patients with inducible VT, it was

not appropriate to perform full multi-variable analysis. Instead, following univariable analysis, RV LGE volume (cm^3) was combined with other predictive variables in a series of bivariable analyses. All tests were 2-sided and a P value of <0.05 was considered significant. Intraobserver and interobserver variability was expressed as the coefficient of variation (percent), derived from the within-subject SD divided by the mean, multiplied by 100. Intra-class correlation coefficients were calculated using absolute agreement, 2-way mixed model. Statistical analysis was performed with SPSS (IBM Statistics V.22).

Results

Study Patients

A total of 69 consecutive adult rTOF patients (mean age 40±15 years; male 43, 62%) fulfilled inclusion criteria and underwent 3D LGE CMR prior to invasive programmed VT-stimulation. Baseline patient demographics and characteristics are summarised in **Table 1**.

Of the 69 patients, 22 (31.8%) had inducible VT. All 10 patients who had sustained VT prior to PES had VT induced. For those with inducible VT, 18 underwent ablation for sustained monomorphic VT (mean total cycle length 259±29ms) and of the remaining 4 severe haemodynamically unstable VT was monomorphic in 2 and polymorphic in the remaining 2. Haemodynamically unstable VT PES patients had significantly worse LV ejection fraction [median 51% (42-56) versus 63% (48-67);p=0.03] compared to the remaining VT ablation patients.
In most patients 14(78%), a linear ablation connecting the pulmonary valve towards the tricuspid annulus (**Figure 1**) was performed towards the RV free wall reflecting the operator's preferred approach to avoid ablating close to the conal septum in order to both minimise complications with the conduction system and make VT non-inducible. In 4 patients (22%) however, an ablation very towards the VSD patch was required. All 18 patients were offered an implantable cardiac

defibrillator (ICD) following VT ablation (2 have received an appropriate VT shock and 2 an inappropriate shock for atrial tachyarrhythmia at median 6.7years follow-up). There were 4 patients (22%) who declined ICD, one died suddenly (presumed arrhythmic).

LGE-defined scar and clinical correlates

All patients had RV LGE at the surgical sites (both RVOT patch site and VSD patch site in 69, 100%). RV LGE was observed in areas apparently remote to surgery (n=32, 45%): RV trabeculations in 31 and/or moderator band in 14(**Table 2**). Patients with this remote type of LGE were older (46±14 versus 35±14 years; p<0.001) and had later repairs [repair at 8(4-11.4) versus 3.4(0.5-6.9) years;p<0.001]. RV/LV insertion point LGE (typically subtle) was observed in all cases. Given that we know this is a non-specific finding in normal hearts and that it is routinely observed in our practice, and consistent with our previous study it was excluded from quantification[13].

Apical LV LGE corresponding with site of previous surgical vent insertion was found in 36 (52%) patients and was not considered relevant for further analyses. Non-apical vent LV LGE occurred in 20 (29%) cases. This was inferolateral and transmural in 3 (15%) and in 13(65%) discrete foci of LGE occurred in other locations. Four patients (20%) had non-apical vent LV LGE confined to papillary muscles only.

As shown in **Table 1,** supramedian RV LGE volume (>20 cm^3) was associated with older age (p<0.001), late repair (p=0.001), increased RVESVi (p=0.04), reduced RV EF (p=0.004), increased indexed right atrial area, RAAi (p<0.001), NYHA≥II (p=0.04) and restrictive LV filling pressure (p=0.02).

LGE-defined scar, histological and electroanatomical correlates

In the substudy of 22 rTOF patients (mean age 44 ±15 years, male 12) in which LGE-defined scar was compared with clinically available bipolar voltage mapping points, the mean surface

registration error was 5.0mm±1.4mm. In these patients a total of 369 low voltage points (<1.5mV) occurred within a 5mm vicinity of the LGE tissue perimeter versus 151 normal voltage points found in this area. Conversely, there were 35 low voltage points that were more than 25mm away from the LGE tissue perimeter and 141 normal voltage points in that area. LGE CMR was therefore, 71% sensitive and 80% specific for its correspondence with low-voltage areas (<1.5mV) on EAM **(Figure S1)**.

In one patient we were able to correlate 3D LGE findings with subsequent surgical excision of the same region (**Figure 2**) and the LGE-defined RV scar was confirmed as fibrosis histologically.

Predictors *of VT inducibility*

Significant univariable predictors of VT inducibility were RV LGE volume (OR 1.15, CI 1.06-1.25:p=0.001 per cm^3), non-apical vent LV LGE volume (OR 1.09, CI 1.02-1.17:p=0.008 per cm^3), QRS duration ≥180 ms (OR 3.5, CI 1.2-10.7:p=0.02), age (OR 1.6; CI 1.1-2.3:p=0.01 per decile), previous non-sustained VT (OR 3.5, CI 1.2-10.1:p=0.01) and clinical sustained VT (OR 12.8, CI 2.4-67:p=0.003). Non-apical vent LV LGE was also predictive of VT inducibility (OR 1.09, CI 1.02-1.17:p=0.008) and remained predictive even when the 4 patients with only LV papillary muscle LGE were excluded (OR 1.1, CI 1.03-1.17:p=007, see **Table 2) .** In bivariable analysis, RV LGE volume (OR 1.14, CI 1.04-1.24:p=0.003) and clinical sustained VT (OR 8.02, CI 1.26-51.2:p=0.02) were the independent predictors of inducible VT (**Table 2**), whereas QRS duration, age, non-sustained VT and non-apical vent LV LGE volume did not stay significant when tested against RV LGE.

On ROC analysis, RV LGE had a good discriminative power in predicting inducible VT (area under the curve, AUC, 0.81, 95% CI 0.7-0.9:p<0.001, see **Figure S2**). A cutoff volume of 24.7cm^3 RV LGE had a 72% sensitivity and 81% specificity for predicting inducible VT. This cutoff value had the highest Youden index (J=0.53) by ROC analysis. A 100% sensitivity was achieved at a RV LGE volume ≥10.2cm^3 and 100% specificity was reached at a RV LGE volume ≥36.0cm^3 (**Figure S2)**. A RV LGE

volume of 10.2cm^3 had a negative predictive value of 100% for predicting inducible VT and positive predictive value of 37%.

LGE segmentation reproducibility

Quantification of LGE volume by manual segmentation was highly reproducible. Intra-observer and interobserver coefficients of variability were 2.9% and 2.8% respectively. For interobserver variability, the interclass correlation coefficient for LGE volume measurements was 0.985 (95% CI 0.98-0.99:p<0.001).

Discussion

This is the first prospective study to date that examines the association between ventricular myocardial scar burden defined by state-of-the-art 3D LGE CMR and VT inducibility in a well-phenotyped cohort of high-risk adult rTOF patients.

Our major and unique finding is that RV LGE burden independently predicts inducible VT over and above well-established risk factors, namely, older age and prolonged QRS duration. RV LGE also remained independently associated with inducible VT even when tested against sustained VT that occurred pre-PES. A small increase in LGE volume is associated with a large increase in risk of inducible VT whereby for every 1cm^3 of LGE there is a 15% increased risk of inducible VT. We found thresholds for RV LGE volume that discriminated between patients with inducible and non-inducible VT (see **Figure 3**). These findings may help improve the selection of patients for PES and identify those who potentially can avoid needless invasive studies.

Inducible VT in repaired tetralogy of Fallot

Inducible VT was a strong independent predictor of clinical sustained VT and SCD during follow-up in a multicentre study[4], one of very few studies on outcome in adult congenital heart disease. This study with its clinically important follow-up endpoints has influenced clinical practice and contributed to guidelines [5-8]. Therefore, we chose inducible VT as a justifiable endpoint

acknowledging it is a surrogate endpoint for sudden death or life-threatening VT. There are notable differences between this previous study and our own. Their patients were younger (mean age 16 years versus 40 years), more had at least moderate PR (74% versus 20%), more had history of clinical sustained VT or syncope (17% versus 14%, 24% versus 16%, respectively) and they included patients who already had ICDs at baseline, implying in combination, that PES was being performed in an even higher risk rTOF population in this older study than the one we describe here. Since then, the approach to managing significant pulmonary regurgitation has also evolved with efforts concentrated on proactive pulmonary valve implantation before symptom onset. Our study cohort reflects this more contemporary practice.

In our centre, patients who were deemed clinically to be of at least 'intermediate-risk' were individually selected for PES after multidisciplinary input. Albeit clinical judgement may be more nuanced than a sum of factors[17], typically, selected patients would have 2 or more of the following: QRS duration ≥180ms, mild LV impairment, moderate RV impairment or cardiac syncope. Given the high negative predictive value of inducible VT in rTOF patients[4], it is often speculated that a negative PES given its negative predictive value is more useful as a 'rule-out' test to reassure patients that a primary prevention ICD is not required. Conversely, an inducible VT compared with a sustained clinical VT is not highly specific and hence testing is avoided in those with low pretest probability.

3D LGE predicts inducible VT

We found that 3D LGE extent was strongly associated with inducible VT and was stronger than established predictors, including age, QRS duration>180ms [1,18]and non-sustained VT[19] which did not remain significant when tested in combination with RV LGE in bivariable analyses. Even when combined with clinical sustained VT which, as expected, was independently predictive of VT inducibility in univariable analysis, RV LGE burden remained still an independent predictor in

bivariable analysis. In recent large cohort studies other non-invasive risk factors of adverse outcome have been reported in rTOF including sustained atrial arrhythmia, RV ejection fraction, LV ejection fraction[2], maximal right atrial area, RV outflow tract akinetic region length[14], BNP[20] and peak VO_2 [21]. These were not found to be predictors of inducible VT outcome in this smaller cohort. RV LGE volume had a high negative predictive value of 100% vs lower positive predictive value of 37% (at RV LGE 10cm^3 cutoff). This suggests that RV LGE volume may have a role as a 'rule out' test to reassure patients, potentially sparing lower risk patients from having an invasive test in future or perhaps be a "rule in" test for those in whom VT ablation is considered an option. In our study, 10 of the 49 patients (20%) with non-inducible VT had an RV LGE volume below the 'rule-out' cutoff of 10cm^3. LGE volume is a continuous variable hence the cutoffs we show are illustrative rather than highly specific thresholds prescribed for local clinical practice. These first study results beg the question as to whether 3D LGE to guide management can allow avoidance of invasive PES in selected patients.

3D LGE-defined anatomical substrates of arrhythmia

We previously reported the association of 2D LGE-defined scar with adverse clinical features most importantly history of arrhythmia, in a cross-sectional study[13]. Whilst 2D LGE CMR application in the RV is feasible it requires expertise as it is susceptible to false positive results secondary to partial volume effects from sternal wires, pericardial fat and the thin RV wall of only a few millimetres. It is also susceptible to false negative results due to, for example, inexperience in setting acquisition parameters and/or suboptimal timing of the acquisition following contrast agent administration including finishing inversion recovery acquisitions too early after contrast given. Furthermore, 2D RV LGE quantification remains challenging to translate from highly expert research settings to the real world. Personalised virtual whole heart models that include myocardial scar can now allow better clinical visualisation and robust quantification of the arrhythmia substrate in the

RV (**Figures 1-3**) with the potential for deeper mechanistic insight and integration into invasive procedures.

Differences between electrically and anatomically defined scars are well described[6,22]. These may be due to inherent limitations with endocardial EAM not being able to assess intramural and epicardial scar and its dependence on good catheter contact whereas 3D LGE may be more comprehensive. Though it was not the primary intention of our study we demonstrated RV LGE-defined scar corresponded to histological RV fibrosis (**Figure 2**) and show a good albeit imperfect geographical match between LGE and low-voltage mapping points. Integration of LGE and EAM is challenging due to differences in (1) the co-ordinate systems, (2) spatial resolutions, (3) timings of the acquisitions within the cardiac and respiratory cycles and (4) the patient condition. These are the most likely reasons why a more exact match was not seen. It is also possible and remains unclear if the small area of disagreement may be attributed to the heterogeneity within the scar regions and at the perimeter of the scar or 'gray' zone. High resolution mapping studies with smaller electrodes will most likely give better insight into this problem.

Agreement between 3D LGE CMR and EAM paves the way for the use of 3D LGE CMR in planning anatomical substrate guided electrophysiology procedures, in rTOF patients likely to require VT ablation. A substrate-based approach facilitated by whole heart 3D LGE CMR can be particularly advantageous for patients who cannot haemodynamically tolerate VT, for those with biventricular systolic dysfunction (all 4 haemodynamically unstable inducible VT patients in our study), for patients with complex scar substrate and for those with atypical substrates that are unexpectedly remote from usual surgical scar sites but may cause VT.

Future directions

Machine learning and computational modelling based on 3D RV scar features may further help differentiate patients for example targeting the large overlap in scar extent in patients

inducible and non-inducible for VT. T1 mapping which is a CMR technique to document interstitial fibrosis, an entity which is also associated with arrhythmia may also have a future role in further differentiation[23,24]. To date, concerns remain as to its robustness for addressing the thinner RV.

Others have used very detailed EAMs to define the anatomical isthmuses (typically "isthmus 2" and "3") known to underlie the mechanism of macro re-entry VT in rTOF [25,26] to individually risk stratify and treat culprit VT substrates. In future, LGE-augmented electrophysiology study could be used to facilitate mapping approaches as it is done in the left heart [27,28] by incorporating rTOF patient specific 3D LGE CMR reconstructions of scar in to the invasive procedure. Given atrial arrhythmia is more prevalent in adults with rTOF the opportunity to extend image integration and ablation guidance to right atrial scar substrate is the next frontier. Experience from adult congenital heart disease with diverse and extensive scar substrates and most challenging arrhythmia to treat may in turn help to manage more common, acquired heart diseases.

Limitations

We recognise that VT inducibility as a primary outcome in this study is not a direct indicator of mortality but rather a surrogate marker for it. Equally, we considered this to be the most robust secondary marker of mortality available as we wanted to avoid using soft endpoints, like frequent ectopy, which may have driven the arrhythmic endpoint in other fibrosis rTOF studies[12]. We studied only patients at intermediate or more risk as clinically judged, so we cannot comment on the relationship of 3D LGE CMR and inducible VT in larger low risk cohorts. A large prospective and inclusive follow-up rTOF cohort may inform us of the prognostic value of 3D LGE CMR with respect to mortality. We did not perform multivariable analysis to avoid over fitting of the model. 3D LGE acquisition requires a learning curve to achieve robust high-quality 3D RV LGE reliably at every attendance. The quantity of ventricular fibrosis may be underestimated in several patients in whom there is absence of signal in the region of sternal wire artefact for example as shown in **Figure 1**.

Conclusion

RV LGE-defined scar burden is a strong and independent predictor of inducible VT in adult patients with rTOF and may help to refine patient selection for PES when applied to an at least intermediate clinical risk rTOF cohort. Not only can 3D LGE help predict which of these patients are most likely to need to proceed to VT ablation and or ICD but it can also help avoid needless invasive procedures.

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Table 1 Patient characteristics

Variable	All patients (n=69)	Inframedian RV LGE <20cm^3 (n=35)	Supramedian RV LGE ≥20cm^3 (n=34)	P Value	Correlation with LGE (cm^3) r coefficient (p) **
Age at scan, y	40 ±15	32 ± 13	48±13	**<0.001**	**0.57 (P<0.001)**
Age at surgery, y	5.8 (1.4-9.3)	2.7 (0.7-5.9)	7.5 (5.6-13)	**0.002**	**0.5 (P<0.001)**
Male sex, n	43	23	20	0.6	
Palliative shunt*, n	29	14	15	0.8	
Transannular patch, n	23	9	14	0.3	
RVOT patch, n	17	9	8	0.7	
RV-PA conduit, n	11	7	4	0.4	
Redo-PVR†, n	41	18	23	0.5	
NYHA class ≥ II, n	26	11	15	0.3	
Syncope, n	11	4	7	0.5	
Sustained atrial arrhythmia‡, n	23	9	14	0.2	
Non-sustained VT‡, n	24	12	12	0.5	
Sustained VT, n	10	3	7	0.2	
BNP§, ng/L	59 (28-106)	51 (17-100)	69 (8-130)	0.3	**0.3 (P=0.02)**
QRS duration‖, ms	162 (145-178)	162 (151-177)	180(161-185)	**0.01**	**0.29 (P=0.01)**
QRS duration ≥ 180 ms	19	7	12	0.1	
Peak $V0_2$, # mL/kg/min	24.7 (20.6-30)	25.1 (20-31.6)	22.1 (20-30)	0.5	-0.2 (P=0.3)
% predicted $V0_2$	71 (45 -85)	80.3 (61-95)	75 (57-85)	0.3	-0.2 (P=0.3)
VE/VCO_2 slope	30 (26-34)	28 (24-31.4)	32 (28.5-36)	0.1	**0.47 (P=0.02)**
RV LGE volume, cm^3	20 (12.6-27)				
LV LGE volume (non-apical vent), cm^3	3.7 (0.5-9.7)	2.8 (0.1-14)	4.4 (1.5-8.5)	0.4	**0.45 (P<0.001)**
Akinetic length of RVOT, mm	38 (28-50)	30(22-42)	43 (35-57)	**0.003**	**0.4 (P=0.001)**
RVEDVi, mL/m^2	125 (99-147)	113 (97-147)	133(105-155)	0.2	0.1 (P=0.35)
RVESVi, mL/m^2	65 (47-89)	62 (44-75)	76 (53-92)	**0.04**	**0.29 (P=0.01)**
RVEF, %	47 (42-55)	52 (44-59)	43(40-51)	**0.004**	**-0.46 (P=<0.001)**
RV:LV volume ratio	1.4 (1.1-1.8)	1.4 (1.1-1.9)	1.4 (1.2-1.9)	0.3	0.05 (P=0.7)
RV mass/volume, g/m^2	0.4(0.32-0.47)	0.39 (0.31-0.47)	0.42(0.32-0.49)	0.4	0.07 (P=0.56)
RAAi, cm^2/m^2	15 (12-17)	13 (12-15)	17 (13-19)	**0.005**	**0.3 (P=0.008)**
LVEDVi, mL/m^2	85 (73-101)	84 (75-99)	84 (69-110)	0.9	0.04 (P=0.8)
LVESVi, mL/m^2	33 (28043)	33(27-43)	34 (28-48)	0.6	0.1 (P=0.4)
LVEF, %	60 (50-66)	58 (54-67)	55 (49-65)	0.3	-0.2 (P=0.08)
LAAi, cm^2/m^2	10 (9-12)	10 (9-11)	11 (9-13)	0.7	0.07 (P=0.5)

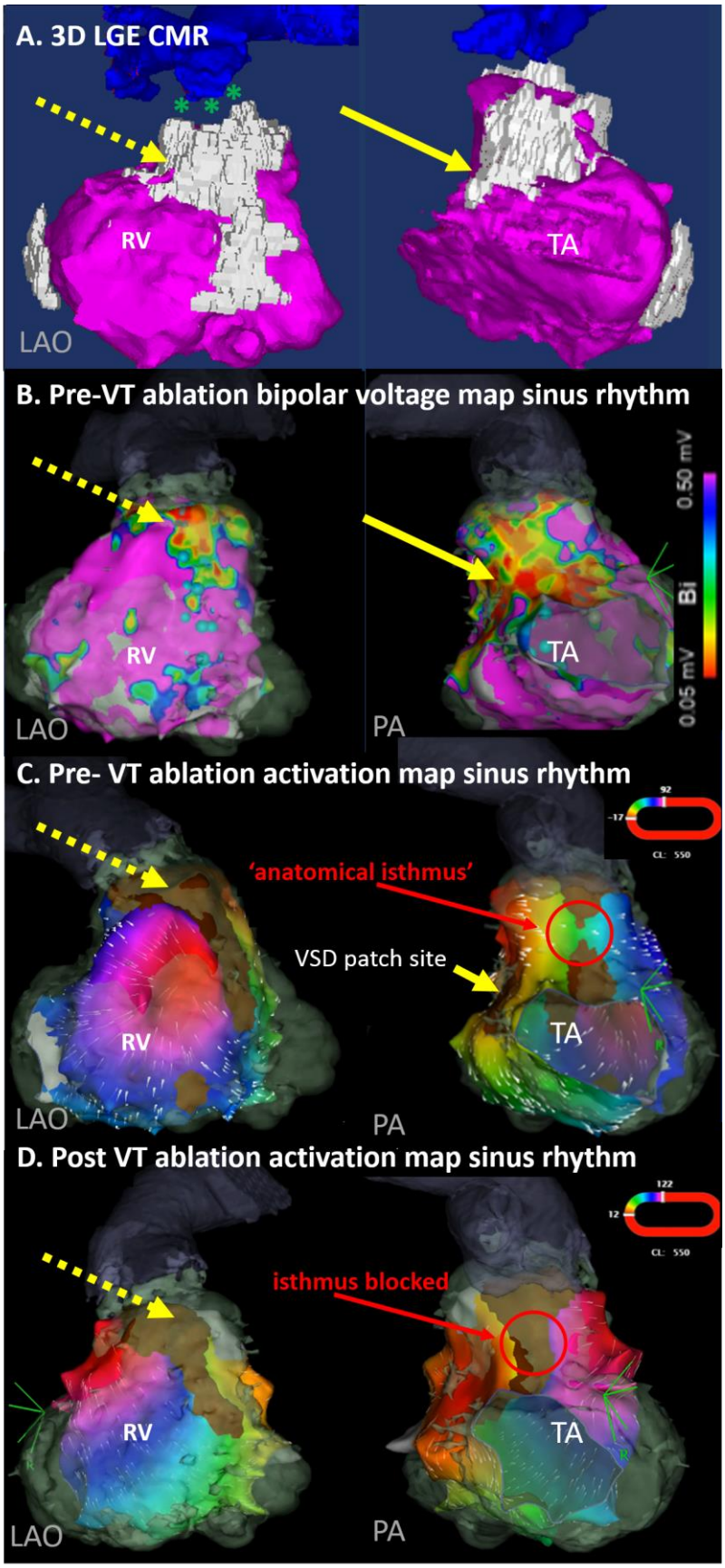
Pulmonary regurgitation, %	14 (2-32)	21 (4-48)	13 (1-45)	0.3	-0.2 (P=0.2)
Restrictive LV filling, n**	12	2	10	**0.01**	
Restrictive RV physiology, n**	11	7	4	0.7	

* A total of 29 palliative shunts where used: Blalock-Taussig shunt n=19, central shunt n=7, Brock procedure n=3 † 5 cases had percutaneous pulmonary valve implantation with Melody valve. ‡ Holter monitors were available in 54 (78%), §BNP was available in 55 (80%). ‖ 12-lead ECG was available in 69 (100%), # CPEX was available in 50 (72%), ** echo data on LV and RV restriction was available in 66 (96%) and 55(80%) respectively Spearman's coefficient of correlation.

Table 2 Univariable and bivariable predictors of inducible VT

Univariable predictors inducible VT	OR (95% CI)	P value
Age at CMR, per decile	**1.6 (1.1-2.3)**	**0.01**
Age of repair, y	1.03 (0.97-1.01)	0.2
Palliative shunt	0.9 (0.3-2.6)	0.9
NYHA>II	1.6(0.57-4.5)	0.4
Syncope	0.78(0.18-3.2)	0.7
Clinical sustained atrial arrhythmia ≥30s	0.48 (1.15-1.56)	0.2
Non-sustained VT	**3.5 (1.2-10.1)**	**0.02**
Clinical sustained VT ≥30s	**12.8 (2.4-67)**	**0.003**
BNP, per 10ng/L	1.02(0.96-1.08)	0.59
QRS> 180ms	**3.5 (1.16-10.7)**	**0.02**
Peak VO_2, mL/kg/min	1.05 (0.9-1.1)	0.55
VE/VCO_2 slope	1.1 (0.97-1.2)	0.14
RV LGE volume, cm^3	**1.15 (1.06-1.25)**	**0.001**
Supramedian RV LGE volume, cm^3	**3.4 (1.2-9.7)**	**0.02**
LV LGE volume (non-apical vent), cm^3	**1.09(1.02-1.17)**	**0.008**
Remote to surgical sites RV LGE volume, cm^3	1.62 (0.58-4.5)	0.35
Akinetic length of RVOT, mm	1.03(0.99-1.06)	0.07
RVEDVi, mL/m^2	1 (0.99-1.01)	0.6
RVESVi, mL/m^2	1 (0.98-1.02)	0.4
RVEF, %	0.98(0.92-1.04)	0.1
RAAi, cm^2/m^2	1.02 (0.9-1.13)	0.6
RAAi ≥ $16cm^2/m^2$	1.81 (0.63-5.2)	0.27
LVEDVi, mL/m^2	1.02 (0.98-1.05)	0.1
LVESVi, mL/m^2	1.02 (0.97-1.05)	0.2
LVEF, %	0.99 (0.94-1.05)	0.6
LAAi, cm^2/m^2	1.06 (0.89-1.3)	0.5
Pulmonary regurgitation %	1 (0.97-1.03)	0.8
Restrictive LV filling pressure	2 (0.5-7.4)	0.3
Restrictive RV physiology	0.4 (0.1-2.03)	0.3
Bivariable predictors inducible VT		
RV LGE volume cm^3	1.12 (1.03-1.23)	**0.007**
Age at scan (per decile)	1.4 (0.85-2.3)	0.2
RV LGE volume cm^3	1.14 (1.05-1.24)	**0.002**
QRS duration >180ms	1.9 (0.48-7.8)	0.35
RV LGE volume cm^3	1.14 (1.1-1.24)	**0.001**
Non-sustained VT	3.2 (0.8-12.3)	0.1
RV LGE volume cm^3	1.14(1.04-1.24)	**0.003**
Clinical sustained VT ≥30s	8.02(1.26-51.2)	**0.02**
RV LGE volume cm^3	1.14(1.04-1.24)	**0.004**
LV LGE volume cm^3	1.1(0.9701.23)	0.12

Figure 1: 3D LGE-defined scar correlation with invasive bipolar voltage mapping and activation mapping preceding induction of VT

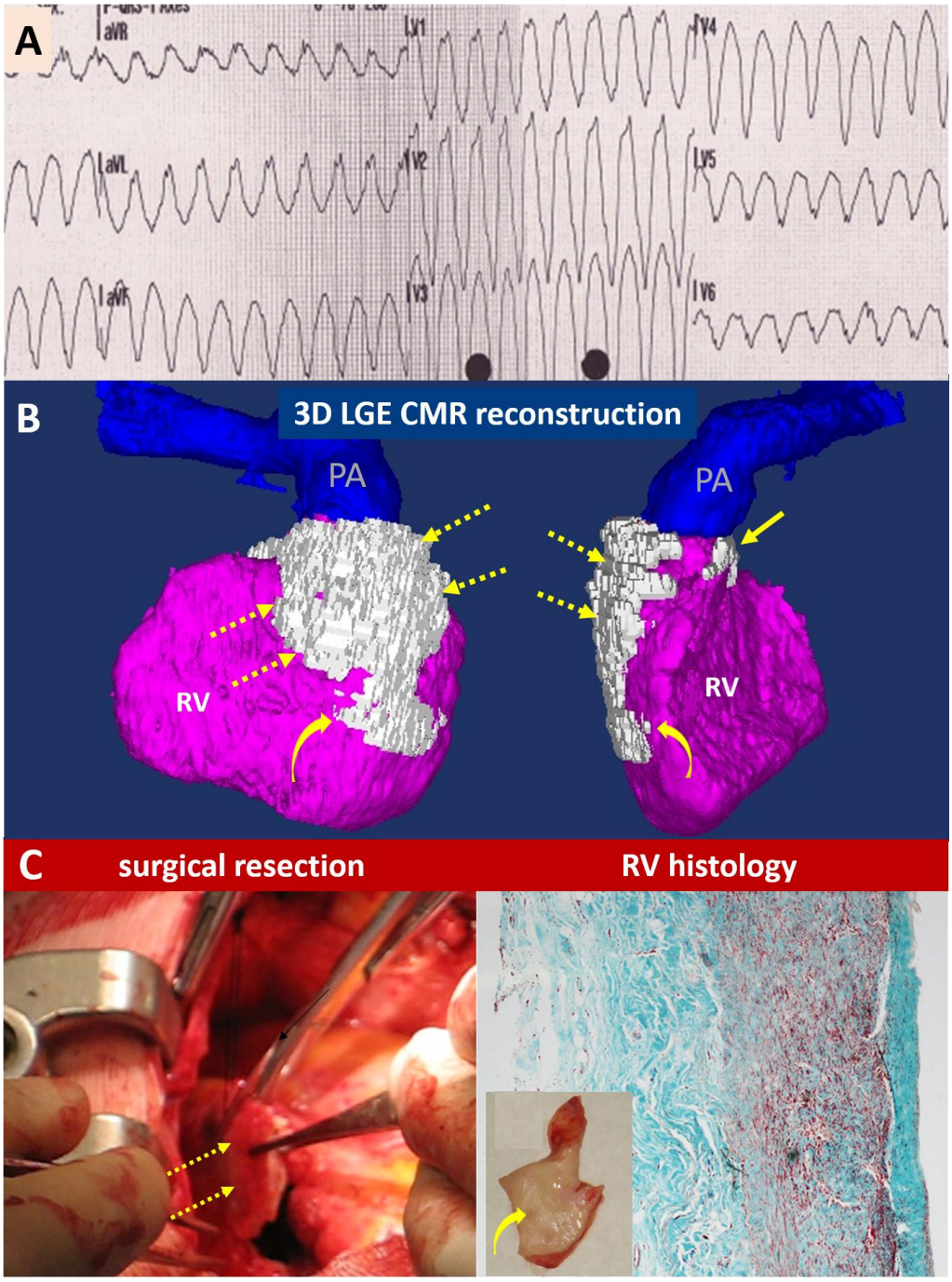


Personalised virtual model of the RV and pulmonary artery (PA) segmented from 3D LGE and 3D bSSFP CMR (**A**) with scar (grey) and healthy tissue (purple). There is CMR drop out of signal related to metallic artefact from a previous Mosaic pulmonary valve in the region marked with green asterisks.

LGE scar compares well with bipolar voltage mapping using CARTO 3 version 7 (**B**) in which low-voltage scar in the RVOT (yellow dotted arrow) and RV septum (yellow arrow) is colour coded as red/yellow/green (0.5mv- 1.5mv) and healthy myocardium as purple.
A good match with LGE-defined scar was similarly seen with activation mapping where brown areas showed slow or no conduction (SNO zone) in the RVOT free wall and septal surface (**C**) A re-entry mechanism was induced through an 'anatomical isthmus' between two RV scars; one in continuity with the tricuspid annulus and one in continuity with the pulmonary valve, with clockwise activation seen. Critical activation across the isthmus (red circle) induced a well-tolerated monomorphic VT (TCL 280ms) at this site.

This patient proceeded to VT ablation and repeat mapping post-ablation showed complete block (D; red circle) through the isthmus with the course of activation changed to going inferiorly around the tricuspid annulus (TA) and anterior RV wall. Subsequently the latest activation occurred adjacent to the applied ablation line at study end.

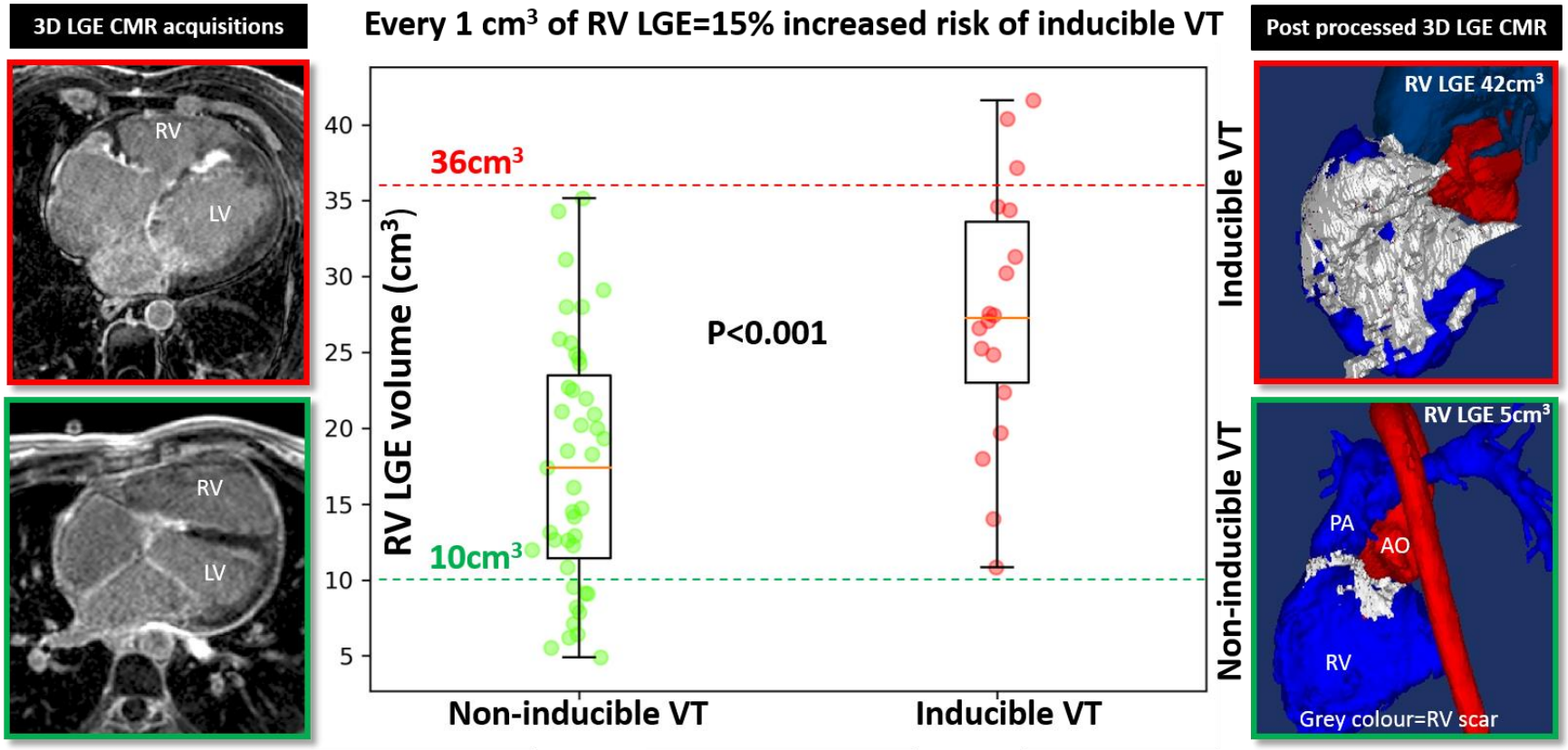
Figure 2



3D LGE-defined scar in VT patient correlated with surgical specimen and fibrosis histology

ECG from a thirty-year-old patient with repair including RVOT patch and subsequent significant pulmonary regurgitation who presented with sustained RVOT morphology VT (**A**)**.** 3D LGE CMR **(B)** demonstrated scar (grey) in the VSD surgical site (yellow arrow), RVOT patch site (dotted yellow arrows) with endocardial native RVOT scar (curved yellow arrow). The patient underwent ablation of VT that originated from the RVOT scar prior to surgical pulmonary valve replacement where scarred RVOT patch (dotted yellow arrows) and native RVOT were confirmed (**C**) and these regions excised as part of the procedure; surgical images courtesy of Professor Darryl Shore. The native RVOT tissue (inset; curved yellow arrow) was histologically assessed with Masson's Trichrome stain (magnification x20) where fibrosis appears blue and myocytes red. The endocardium is to the left of the stained tissue and it is the RVOT endocardial surface that is arrowed.

Figure 3



Clinical application of 3D RV LGE cutoffs

Dot graph (centre) illustrating that all rTOF patients with RV LGE volumes ≤10cm^3 (n=10; below the green line) were non-inducible for VT and all patients who had ≥36cm^3 of RV LGE (n=3; above the red line) were inducible for VT. A CMR 3D LGE slice (left panel) and 3D reconstruction (right panel) including scar volume is shown for the patient with the most scar volume (red boxes) and the patient with the least scar volume (green boxes) to show example images.