Universitat Autònoma de Barcelona

TESI DOCTORAL

RESTORATION OF PULMONARY VALVE COMPETENCE IN PATIENTS WITH REPAIRED TETRALOGY OF FALLOT, SHORT AND LONG-TERM EXPERIENCE

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Directors de Tesi:

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CONTENTS

ABBREVIATIONS

BMI, body mass index

BP, blood pressure

CI, confidence interval

ECG, electrocardiogram

EF, ejection fraction

EPS, electrophysiological study

HR, hazard ratio

ICD, implantable cardioverter-defibrillator

LV, left ventricle

MRI, magnetic resonance imaging

NYHA, New York Heart Association

PVR, pulmonary valve replacement

RER, respiratory ex-change ratio

RV, right ventricle

RVOT, right ventricular outflow tract

SCD, sudden cardiac death

SD, standard deviation

SMD, standardized mean difference

TOF, tetralogy of Fallot

VE, ventilation

VE/VCO_2, ventilatory response to carbon dioxide production

VO_2, oxygen consumption

VPB, ventricular premature beats

VT, ventricular tachycardia

INTRODUCTION

I. DESCRIPTION OF THE DISEASE

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, with an incidence of 356 per million live births[1]. It is characterized by an anterior and cephalad displacement of the infundibular septum, which creates right ventricular outflow tract (RVOT) obstruction leaving underneath a ventricular septal defect and an overriding aorta, with a secondary right ventricular (RV) hypertrophy (**Figure 1**).

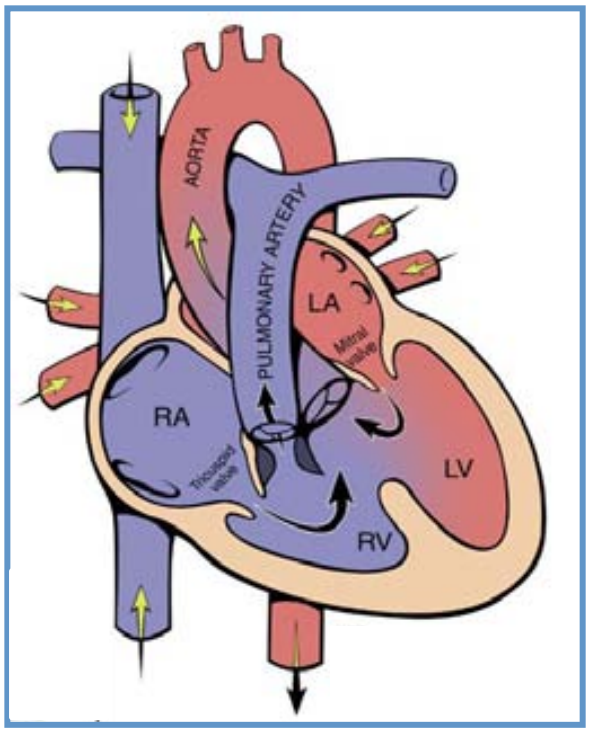


Figure 1: Characteristics of a heart with tetralogy of Fallot

Varying levels of severity and a morphological spectrum exist. The most extreme form is pulmonary atresia with ventricular septal defect, which will not be discussed in this Thesis. Associated lesions include atrial septal defect (35%)[2], right aortic arch with mirror image branching (20-25%)[2], anomalous coronary artery (5-7%)[3], and complete atrioventricular septal defect (rare, usually in association with Down

syndrome). Approximately 20% of patients with TOF have a deletion of chromosome 22q11[4].

A Danish anatomist and Bishop Niels Stenson first described this congenital cardiac anomaly in 1671. He reported his pathologic findings in a fetus with multiple abnormalities, including cardiac features we would now recognize as TOF. One hundred years later, Eduard Sandifort, an anatomist at the University of Leiden, published the first clinical–anatomical correlate of this condition when he described the life and subsequent autopsy findings of a 12-year-old boy. In 1846 a British physician Thomas Peacock reported several cases; but it was not until 1888 that the French physician Etienne-Louis Fallot diagnosed it in patients and coined the term tetralogy[4, 5].

II. SURGICAL REPAIR

Since the first successful repair using a heart and lung machine was performed by Kirklin at the Mayo Clinic in 1955 numerous contributions have been made, leading to excellent early survival and an increasing population of TOF repair survivors[6]. The complete repair involves: closure of the VSD with a patch and relieve of the RVOT obstruction with or without a transannular patch, see **Figure 2**. Currently, it is typically repaired in infancy with low risk and outstanding long-term results[7-9].

Severe pulmonary regurgitation is common in patients with repaired TOF, especially in those repaired with transannular patch. The resultant chronic RV volume overload leads to RV dilatation, biventricular dysfunction, heart failure symptoms,

arrhythmias and ultimately death[10-12]. It has been suggested that pulmonary regurgitation also plays a role in the development of left ventricular (LV) dysfunction due to adverse ventricular-ventricular interactions[13-17].

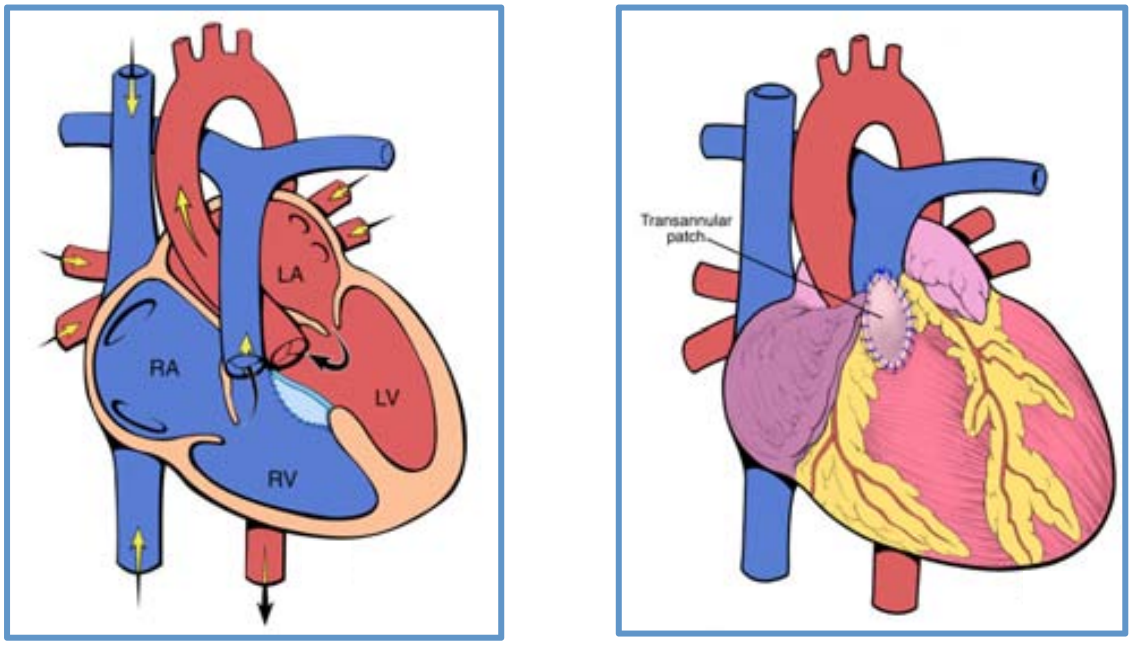


Figure 2: Complete repair of a heart with tetralogy of Fallot. On the left, patch closure of the VSD. On the right, transannular patch to relieve RVOT obstruction

Even though valve-sparing procedures are being used more frequently in the last few years[18-20], long-term outcomes with this procedure are far to be known. Regardless, the number of patients with repaired TOF requiring intervention due to pulmonary valve regurgitation remains high nowadays. These are usually young patients, on their 20s or 30s, with a normal full life despite moderate or severe pulmonary regurgitation and a chronic decreased exercise capacity. Decision making at this point in life is difficult, especially as long-term outcomes including recovery of ventricular function and functional class, risk of arrhythmias, need of reintervention and survival after pulmonary valve replacement (PVR) are unknown.

RATIONALE FOR THIS RESEARCH, HYPOTHESIS AND AIMS

I. RATIONALE FOR THIS RESEARCH

Unfortunately, most patients with repaired tetralogy of Fallot do require pulmonary valve replacement (PVR), and usually occurs at a pivotal stage in their disease process. Timing for surgical referral continues to be challenging in clinical practice as excessive delay (watchful waiting) may impact recovery of aerobic capacity and ventricular function and may increase the risk of ventricular arrhythmia and death; and excessive expedition may precipitate the need of re-intervention in this young population.

1.- Indications for Pulmonary Valve Replacement

Current indications for cardiac surgery in patients with repaired TOF were published in the ACC/AHA Guidelines for adults with congenital heart diseases (2008)[21] and the ESC Guidelines for the management of grown-up congenital heart disease (2010)[22]. In essence, both documents support the following recommendations:

Class I

- PVR is indicated for severe pulmonary valve regurgitation and presence of symptoms or decreased exercise tolerance

Class IIa

- PVR is reasonable for asymptomatic patients with severe pulmonary valve regurgitation and any of the following:

  - Moderate to severe RV dysfunction
  - Moderate to severe RV enlargement
  - Symptomatic or sustained atrial and/or ventricular arrhythmias
  - Moderate or severe tricuspid regurgitation

- Surgery is reasonable for residual RVOT obstruction (valvular or subvalvular) and any of the following:
  - Peak instantaneous echocardiography gradient greater than 50 mmHg
  - RV/LV pressure ratio greater than 0.7
  - Progressive and/or severe dilatation of the RV with dysfunction
  - Residual ventricular septal defect with a left-to-right shunt greater than 1.5:1
  - Severe aortic regurgitation with associated symptoms or more than mild LV dysfunction
  - A combination of multiple residual lesions leading to RV enlargement or dysfunction

Other aspects not included in these guidelines have been mentioned by some groups as potential indications for intervention. QRS length (≥ 180 ms)[23-25] and/or progressive prolongation of the QRS (≥ 3.5 ms/year)[26-28] have been linked to long-term high risk of adverse event, including death due to any cause, reoperation for recurrent pulmonary regurgitation, symptomatic heart failure and ventricular arrhythmias[25].

The above mentioned indications are based on clinical features, electrocardiographic and echocardiographic characteristics. Most recently, cardiac

magnetic resonance imaging (MRI) has emerged as the promising gold standard technique to measure biventricular dimensions and function[27, 29]. Specifically, an RV end-diastolic volume index ≥ 160 mL/m2, RV end-systolic volume index ≥ 70 mL/m2, LV end-diastolic volume index ≤ 65 mL/m2 and RVEF ≤ 45% have been proposed by Geva et al[30] as thresholds leading to surgery in patients with repaired TOF and moderate or severe pulmonary regurgitation, although the same group in later publications[27] and other groups[28, 31-34] have differed slightly.

Currently, the advent and utilization of new echocardiographic techniques based on myocardial deformation (strain and strain rate) may facilitate decision-making process in these patients. These would be of special value as a bedside diagnostic tool and particularly for patients with devices implanted precluding magnetic resonance imaging (MRI). These novel echocardiographic techniques have been used to assess ventricular dysfunction and biventricular interaction late after TOF repair[15, 17, 35, 36]. If found to provide an accurate measurement of ventricular function, deformation imaging could be used as an alternative diagnostic tool in patients with repaired TOF both before and after PVR. This would offer a quantitative ventricular function assessment to all patients irrespective of their clinical status or presence of implanted devices. However, there are scanty data and no consensus on the role of these new echocardiographic techniques to guide surgical referral in TOF patients. In addition, biventricular response after PVR has not been extensively evaluated using these new techniques.

Indications will continue to evolve as new information and diagnostic techniques become available and as valve technology and percutaneous valve implantation methods continue to improve. With currently available technology, catheter-delivered stent-mounted valves are limited by the size and geometry of the RVOT to mostly patients

with failing bioprosthetic valves or RV-to-pulmonary artery conduits[37-39]. Future development of this technology may reduce the need for reoperation after PVR or even be available for patients with previous RVOT patch[40]. Improvements in new technology will likely lower the threshold for referral to pulmonary competence restoration in patients in whom perceived risk of multiple open reoperations bias clinicians despite clear cut indications to intervene.

2.- Surgical approach

The optimal surgical approach to PVR is controversial. Homograft and syntectic conduits, tissue and mechanical valves have been used for this purpose[32, 41-46]. Many patients with chronic pulmonary valve regurgitation have concomitant tricuspid valve regurgitation. The main physiopathologic mechanism is thought to be RV dilatation that leads to lack of leaflet coaptation[46]. Therefore, tricuspid valve intervention at the time of PVR is controversial as RV remodeling may potentially mitigate tricuspid regurgitation by improving leaflet coaptation[46, 47].

3.- Arrhythmia management

There is no consistent approach in the stratification and management of sudden cardiac death (SCD) risk at the time of PVR. The utility of preoperative electrophysiological study (EPS) to indicate ablative procedures at the time of surgery is controversial[48-50]. Despite programmed ventricular stimulation being of diagnostic and prognostic value[51], the appropriate timing of EPS has not been studied. Prior to PVR,

and in the context of severe pulmonary regurgitation, the failing RV is more vulnerable to ventricular arrhythmia[52], and conceptually replacement of the pulmonary valve can reverse the volume overload and potentially mitigate the risk of ventricular arrhythmia. Intracardiac mapping and ablation, however, have shown that ventricular tachycardia (VT) is typically macroreentrant in nature using cardiac valves and scars as boundaries[50, 51]. Therefore, surgical ablation of the RVOT appears to be a logical approach to isolate diseased substrate[25, 49, 53].

4.- Clinical implications

PVR restores pulmonary valve function, but the beneficial impact on RV and LV size and function, aerobic capacity, QRS duration, ventricular arrhythmias and survival rates have been inconsistent[25, 31-34, 54-56]. A recent meta-analysis focusing on postoperative outcomes in patients with repaired TOF undergoing PVR summarized the international experience, although lacks information on aerobic capacity measured on exercise testing[57]. Yet, comparisons among studies reporting outcomes after PVR are challenging, as many series include different types of congenital heart disease and have limited sample sizes.

In summary, even though there are guidelines and plenty of publications trying to address the best timing and approach to PVR in patients with repaired TOF, there is still insufficient evidence to support a single strategy. Uncertainty remains on defining appropriate intervention referral and the optimal surgical approach aiming to preserve ventricular function and improve functional and vital outcomes in these patients.

Careful analysis of the past experience will provide guidance on how to proceed in order to optimize outcomes of this challenging population.

II. HYPOTHESIS

When and how restoration of pulmonary valve competence is accomplished impacts left and right ventricular function, functional class, risk of arrhythmias and long-term survival in patients with repaired TOF.

III. OVERALL AIM

Define the appropriate timing and the best surgical approach for restoring pulmonary valve function in patients with repaired TOF.

IV. SPECIFIC AIMS

1. Establish predictors of mortality in patients with repaired TOF undergoing PVR.
2. Establish predictors of pulmonary valve reintervention in patients with repaired TOF undergoing PVR.
3. Evaluate the effect of PVR on aerobic capacity in patients with repaired TOF.
4. Establish predictors of significant arrhythmia in patients with repaired TOF undergoing PVR.
5. Establish the role of novel deformational echocardiographic techniques on predicting postoperative RV and LV function and functional class in patients with repaired TOF undergoing PVR.

METHODS

I. STUDIES INCLUDED

This Thesis includes data and results from 4 different projects involving patients with TOF undergoing PVR. Each of these studies was designed to respond one or more of the specific questions mentioned above.

1) Survival study: includes overall survival and freedom from reintervention after PVR as the primary endpoints. Special attention on the need of concomitant tricuspid valve repair for significant regurgitation was considered.
2) Exercise testing study: includes a description and analysis of the experience in exercise testing for patients with repaired TOF before and after PVR. In addition, it includes a comparison between our results and those previously published in the literature using a meta-analysis.
3) Ventricular arrhythmia study: includes ventricular arrhythmias, SCD and appropriate implantable cardioverter-defibrillator (ICD) discharges after PVR as the primary combined endpoint. The role of RVOT cryoablation and EPS at the time of PVR was evaluated.
4) Echocardiography study: includes RV and LV function assessment measured by novel deformational echocardiographic techniques before and after PVR in patients with repaired TOF. Comparison of these novel techniques with MRI measurements was performed.

These studies were conducted within the Mayo Clinic (Rochester, MN), reviewing 40 years of surgical experience. All the studies were approved by the Mayo Clinic Institutional Review Board, and all patients provided consent for participation in clinical research.

II. OVERALL INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: patients with TOF of all ages who had undergone previous complete repair in their infancy and had reintervention to restore pulmonary valve function for the first time at Mayo Clinic.

Exclusion criteria: patients with ventricle to pulmonary artery conduit or pulmonary valve replaced in a previous operation, as well as patients with concomitant atrioventricular septal defect, pulmonary atresia or absent pulmonary valve. Patients that refused research authorization were also excluded.

SURVIVAL STUDY

This study will be found at:

- Sabate Rotes A, Burkhart HM, Eidem BW, Rosedahl JK, Bonnichsen CR, Connolly HM, Schaff HV, Dearani JA. Long-term Follow-up after Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. Am J Cardiol. 2014 Jul 2. pii: S0002-9149(14)01370-8. doi: 10.1016/j.amjcard.2014.06.023.

EXERCISE TESTING STUDY

This study will be found at:

- Sabate Rotes A, Johnson JN, Burkhart HM, Eidem BW, Allison TG, Driscoll DJ. Cardiorespiratory Response to Exercise Before and After Pulmonary Valve Replacement in Patients with Repaired Tetralogy of Fallot. Congenit Heart Dis. 2014 Aug 4. doi: 10.1111/chd.12207.

VENTRICULAR ARRHYTHMIAS STUDY

I. METHODOLOGY

A total of 537 consecutive patients with the diagnosis of TOF had 641 surgeries between October 1988 and December 2010 in Mayo Clinic, Rochester, MN. The initial date was chosen based on the first patient with electrocardiogram (ECG) available for review. Before 1988 ECG strips were not archived in our institution. The last date was chosen to allow at least 2 years of follow-up. From those, 205 patients with TOF who had undergone previous complete repair and had reoperation to restore pulmonary valve function were selected.

Descriptive and Baseline Data

Medical history, perioperative and follow-up data were collected using all available records. Every effort was made to identify the patients who had had a ventriculotomy done at some point during their multiple previous surgeries, and differentiate them from the patients who had had a transannular incision. Of note, is that some patients had undergone both at different stages.

An ECG at the time of PVR was available for all patients. The QRS duration was provided by the automated analysis performed by *the General Electric Marquette Electronics (Fairfield, Conn)* and confirmed by manual inspection.

Holter monitoring before the PVR was available in 46 patients (22%). The degree of ectopy was graded following the Lown criteria[82], although modified as described:

0 - No ventricular ectopic beats

1 - Occasional, isolated ventricular premature beats (VPB)

2 - Frequent VPB (>1/min or 30/hr)

3 - Multiform VPB

4 - Repetitive VPB

(a) Couplets

(b) Salvos: 3 or more VPBs

5 - VT (>30sec)

Nonsustained VT was defined as 4 or more consecutive ventricular beats documented on a 12 lead-ECG, Holter recording, or ECG strips; lasting ≤ 30 seconds. An independent observer who was blinded to the clinical outcome of each patient analyzed electrocardiograms.

The criteria utilized for QRS fragmentation are well validated for other forms of cardiac disease[83], and the ECG phenotype was broken into:

(i) Notched QRS: defined by the presence of an additional R wave (various RSRprime patterns), or the presence of notching in nadir of the S wave or notching of the R wave

(ii) Fragmented QRS: defined by the presence of more than one R prime, or more than two notches or R primes in wide QRS complexes.

(iii) Normal ECG

High risk for arrhythmia was considered when patients had documented sustained VT, unexplained syncope, QRS duration ≥180 ms, prior ventriculotomy,

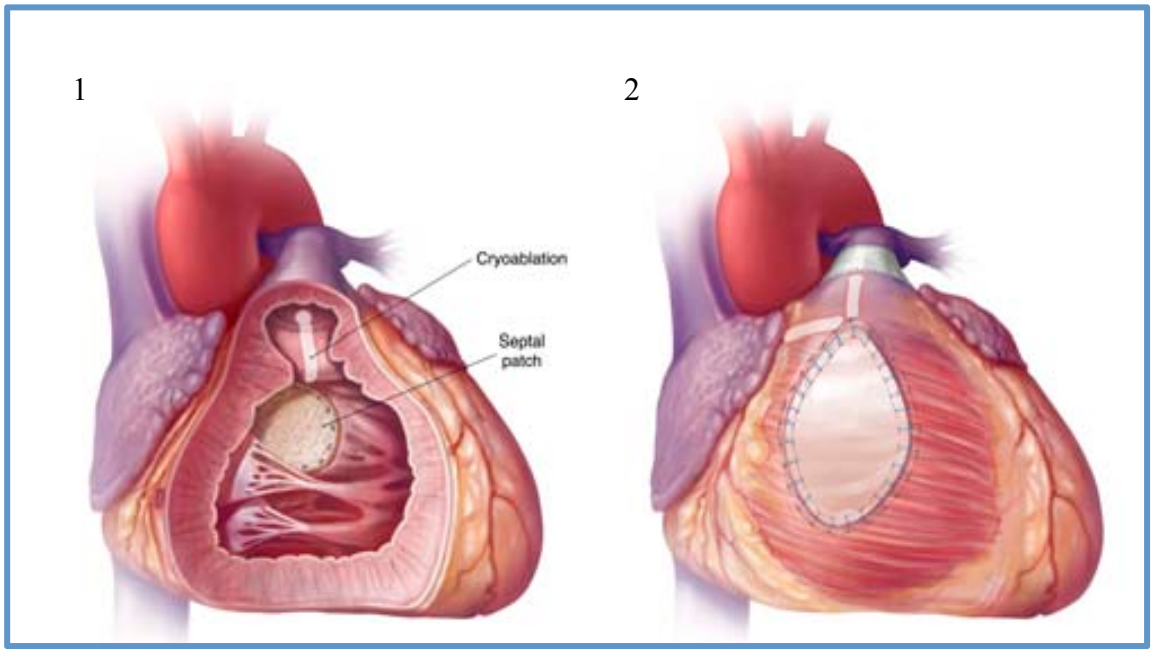
documented nonsustained VT or LV dysfunction. Indications for performing an EPS before surgery included: unexplained syncope or near syncope and non-sustained VT on Holter. Indications for ICD implant after surgery included VT or out-of-hospital cardiac arrest, inducible VT at post-operative EPS, LVEF < 35% and unexplained syncope.

Baseline echocardiographic data included qualitative assessments of RV size and function and quantitative LVEF (%) on the latest evaluation before PVR (at most 3 years removed). Dysfunction or dilatation of the RV was recognized when more than moderate.

Surgical Cryoablation

Surgical RVOT ablation was started in our practice in 2000 as VT treatment or prophylaxis based on preoperative conditions. During this procedure, a cryoablation lesion is placed to connect the superior aspect of the ventricular septal defect patch to the pulmonary annulus. Next, a lesion grounding the ventriculotomy to the pulmonary or tricuspid annulus is performed (see **Figure 8**). The freezes are made for 90 to 120 seconds with a 15 mm probe each. Indications for surgical cryoablation of the RVOT include history of non-sustained VT or VT, inducible VT at EPS that was not ablated and history of unexplained syncope or near-syncope.

Figure 8: Drawing showing surgical cryoablation lesions: 1, from ventricular septal defect patch, across the pulmonary annulus and up to the pulmonary artery; and 2, from the right ventriculotomy/transannular or ventricular patch up to the pulmonary annulus and/or proximally towards the tricuspid valve annulus level.



Outcome Data

Test results and operation notes were reviewed according to the patient outcome. The primary outcome was defined as combined event at follow-up, including VT, out of hospital cardiac arrest, appropriate therapy in those with ICD and SCD:

- VT was defined as sustained monomorphic VT documented on a 12 lead-ECG, Holter recording, or ECG strips. Sustained tachycardia defined as arrhythmia lasting > 30 seconds or of any length of time if associated with hemodynamic compromise, requiring cardioversion or admission[49, 51].
- Out-of-hospital cardiac arrest was considered when the patient had a documented cardiac arrest that needed resuscitation.
- Defibrillator discharges or anti-tachycardia overdrive pacing was considered appropriate if the device was triggered by VT or fibrillation, and which was

documented by stored intracardiac electrogram or cycle-length data in conjunction with patient's symptoms immediately before and after device discharge. Inappropriate discharges were defined as those triggered by a rapid ventricular rate exceeding the programmed threshold rate as a consequence of supraventricular tachycardia, exercise-related sinus tachycardia, or a malfunction of the device. Each discharge and ATP therapy for ventricular arrhythmias was classified as either appropriate or inappropriate by experienced electrophysiologists.

- SCD was established based on autopsy reports. Two patients died suddenly and were considered to succumb to SCD although no autopsy was performed.

Statistical analysis

Descriptive statistics are reported as proportions for discrete data and means and standard deviations for continuous data, except for variables that are not normally distributed in which case median and range are used. Survival and free-event times were estimated using Kaplan-Meier method with 95% confidence intervals. Survival curves were compared by the log-rank test. Cox proportional hazards models were used for the univariate and multivariate analysis.

II. RESULTS

1.- Characteristics of the Study Population

A summary of the clinical characteristics is shown in **Table 13**. All patients had at least one previous operation accounting for the TOF repair and 126 of them (62%) had a transannular patch placed on the RVOT at that time. In addition, 95 patients (46%) had two and 35 (17%) had three or more previous operations including palliative surgery, closure of persistent VSD and other residual lesions. Fifteen patients had a permanent pacemaker placed after the repair and before the PVR, 12 (80%) due to high degree atrioventricular block and 3 (20%) due to sinus node dysfunction. Preoperative mean indexed RV end-systolic volume was 102 ± 32 mL/m2, RV end-diastolic volume 175 ± 45 mL/m2, and RVEF 42 ± 8 %. Their indexed LV end-systolic volume was 31 ± 13 mL/m2, LV end-diastolic volume 72 ± 20 mL/m2, and LVEF 56 ± 8 %.

Holter monitoring was abnormal for the majority of patients in whom it was available, with repetitive VPBs in form of couplets or salvos occurring in 31 patients (67%, Lown criteria 4a and 4b)[82]; no VT was detected on Holter monitoring. Exercise testing before the PVR revealed non-sustained VT in 1 of the 92 patients for whom it was available; and 21 patients had repetitive VPBs in form of couplets or salvos. A clinically identified VT event occurred in 16 patients prior to PVR (7.8%) and one patient had an out-of-hospital cardiac arrest (0.5%) prior to the PVR.

An EPS was conducted in 40 patients (20%) at a median time of 5 days before PVR, and pre-PVR ablation of VT was performed in 5 patients (1.3%). At the time of

surgery, 45 patients (22%) had a QRS duration ≥ 180 ms and 37 (16%) had a LVEF < 50%. Surgical RVOT cryoablation at the time of PVR was performed in 22 patients (11%).

Table 13: Summary of the past medical history for the whole group and comparing patients that had an event at follow-up and those who did not

Past medical history	Combined event*		Total
	Yes N=19	No N=186	N=205
Age at initial repair, mean ± SD	9.9 ± 9.9	7.3 ± 8.8	7.5 ± 8.9
History of palliative surgery, N (%)	6 (32)	85 (46)	91 (44)
Number of previous interventions, mean ± SD	3.0 ± 1.0	2.8 ± 0.8	2.8 ± 0.8
History of prior ventriculotomy, N (%)	10 (59)	54 (33)	64 (36)
History of syncope, N (%)	3 (16)	16 (9)	19 (9)
Lown criteria 4a or 4b, N (%)	3 (100)	28 (65)	31 (67)
Documented spontaneous NSVT, N (%)	0 (0)	21 (11)	21 (10)
NSVT inducible at EPS, N (%)	1 (13)	3 (9)	4 (10)
History of VT, N (%)	5 (26)	11 (6)	16 (8)
VT inducible at EPS, N (%)	6 (75)	15 (47)	21 (53)
History of ICD implantation, N (%)	4 (21)	11 (6)	15 (7)
Age at PVR surgery, mean ± SD	41 ± 15	32 ± 16	33 ± 16
Fragmented QRS at PVR, N (%)	14 (82)	121 (69)	135 (66)
QRS duration (ms) at PVR, mean ± SD	173 ± 29	156 ± 32	158 ± 32
LV function (%), mean ± SD	51 ± 9	56 ± 9	56 ± 9
RV dysfunction, N (%)	5 (31)	19 (12)	24 (13)
RV dilatation, N (%)	13 (68)	107 (61)	120 (62)
RVOT ablation at PVR, N (%)	1 (5)	21 (11)	22 (11)

* Combined event includes: ventricular tachycardia, out of hospital cardiac arrest, appropriate therapy in those with ICD and sudden cardiac death

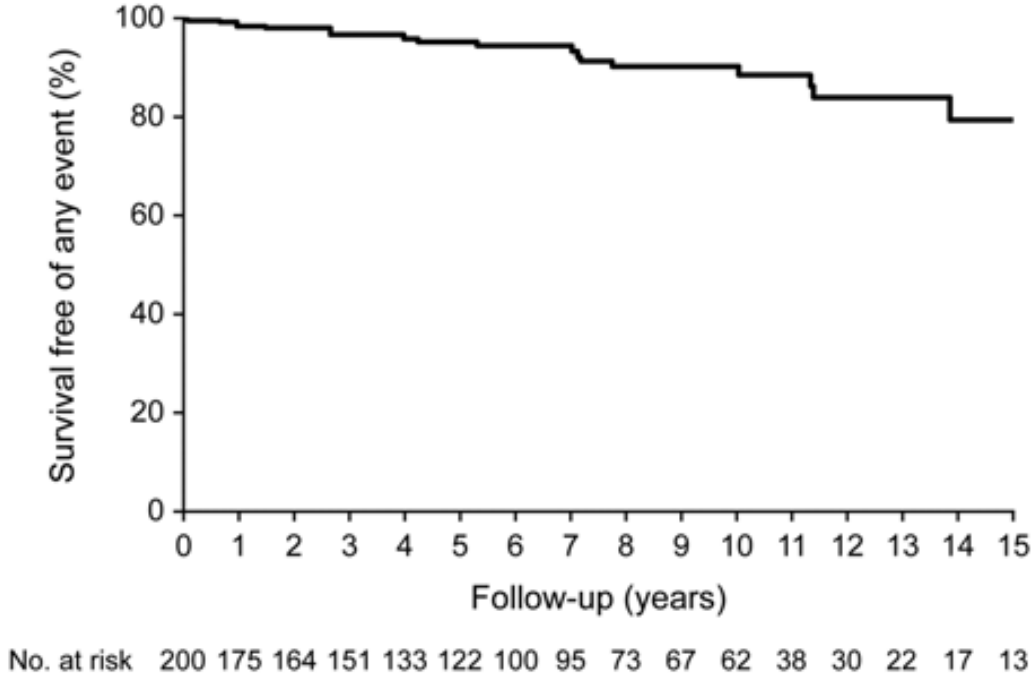
Abbreviations: EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia; PVR, pulmonary valve replacement; LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; VT, ventricular tachycardia

2.- Follow-up

Complete follow-up was available for 200 patients (98%) during a mean time of 7.2 ± 5.2 years, maximum of 24 years. A total of 22 patients had one or more EPS done at follow-up, 3/22 were done 7 days after operation (none had inducible VT), 4/22 between 1 month and 6 months after operation (2 had inducible VT, one was percutaneously ablated and the other one had an ICD placed) and 15/22 were performed more than one year after operation (7 had inducible VT, 5 were percutaneously ablated and 2 had an ICD placed).

The combined event occurred in 19 patients, including SCD in 5 patients, appropriate ICD therapy in 7 patients, out-of-hospital cardiac arrest in 3 patients, and clinically identified sustained VT in 4. Differences in the clinical history of this group compared with the non-event group are detailed in **Table 13**. Freedom from the combined event is shown in **Figure 9**. Freedom from the combined event was 95.1% (95% CI 91.8 – 98.5) at 5 years, 90.1% (95% CI 84.9 – 95.6) at 10 years and 79.1% (95% CI 67.9 – 92.1) at 15 years.

Figure 9: Freedom from the combined event (including ventricular tachycardia, out of hospital cardiac arrest, appropriate therapy in those with ICD and sudden cardiac death)



3.- ICD therapies

ICD placement occurred in 23 patients at a median time of 1 month after the PVR (range 3 days to 23.5 years). A total of 7 patients had 18 appropriate discharges and 6 patients had 14 inappropriate discharges during follow-up. Two patients had only inappropriate discharges. Inappropriate discharges were due to oversensing in 43% and supraventricular tachyarrhythmia in 57%.

4.- Risk factors

Univariate and multivariate risk factors for the combined event are detailed in **Table 14**. Lown criteria on Holter monitoring prior to PVR did not predict the combined event at follow-up. This is potentially limited by the small number of Holter studies available (n = 46, 22.4%). Similarly, inducible VT at EPS did not predict the combined event at follow-up. History of preoperative VT and reduced LVEF were independent predictors for the combined event in the multivariable analysis. **Figure 10** shows the survival curves for freedom from any event by history of VT, LVEF and QRS duration. Importantly, patients with LVEF < 50% were over 3 times more likely to have RV dysfunction > moderate, 95% CI 1.4 - 6.8, p = 0.01.

Table 14: Risk factors for the combined event, univariate and multivariate analysis

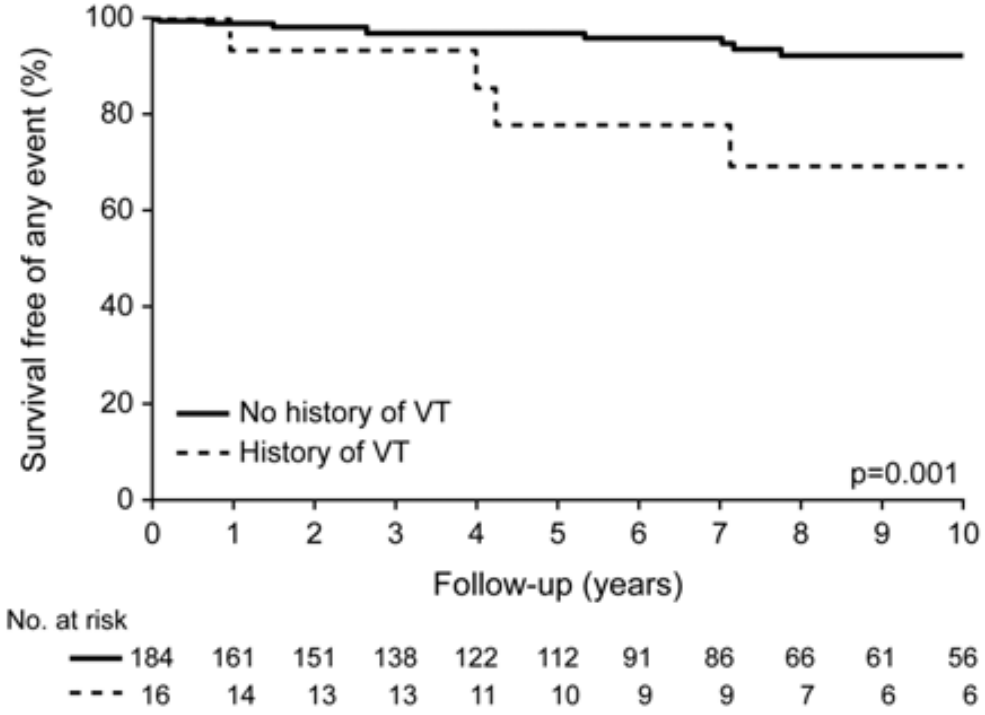
Risk factors	HR	95% CI		p value
Univariate analysis				
Previous palliation procedure	0.59	0.2	1.6	0.29
History of ventriculotomy	2.32	0.9	6.1	0.09
Transannular patch	0.56	0.2	1.4	0.22
Age at initial Repair*	1.04	0.9	1.1	0.12
Number of previous interventions	1.04	0.6	1.8	0.89
History of VT	**4.68**	**1.6**	**13.4**	**0.004**
History of syncope	2.05	0.6	7.1	0.26
History of pacemaker implantation	2.38	0.7	8.2	0.17
History of ICD implantation	**4.13**	**1.3**	**12.8**	**0.01**
History of VT Cath ablation	2.77	0.4	21.2	0.33
Longer QRS duration at PVR (Δ 10ms)[†]	**1.16**	**1.0**	**1.3**	**0.02**
QRS ≥ 180ms at PVR	**2.89**	**1.1**	**7.5**	**0.03**
Fragmented QRS at PVR	1.55	0.4	5.5	0.50
Higher LVEF (Δ 5%)[‡]	**0.73**	**0.6**	**0.9**	**0.008**
LVEF < 50%	**3.62**	**1.4**	**9.4**	**0.008**
RV dilatation	1.62	0.6	4.4	0.34
RV dysfunction	2.02	0.6	6.5	0.24
Older age at PVR (Δ 5years)[§]	**1.26**	**1.1**	**1.5**	**0.006**
RVOT ablation at surgery	0.85	0.1	6.4	0.87
Multivariate analysis				
History of VT	**3.8**	**1.3**	**11.1**	**0.02**
Higher LVEF (Δ 5%)[‡]	**0.75**	**0.6**	**0.9**	**0.02**

*For every 1 year increase in age; [†]For every 10ms increase in QRS length; [‡]For every 5% increase in LVEF; [§]For every 5 years increase in age.

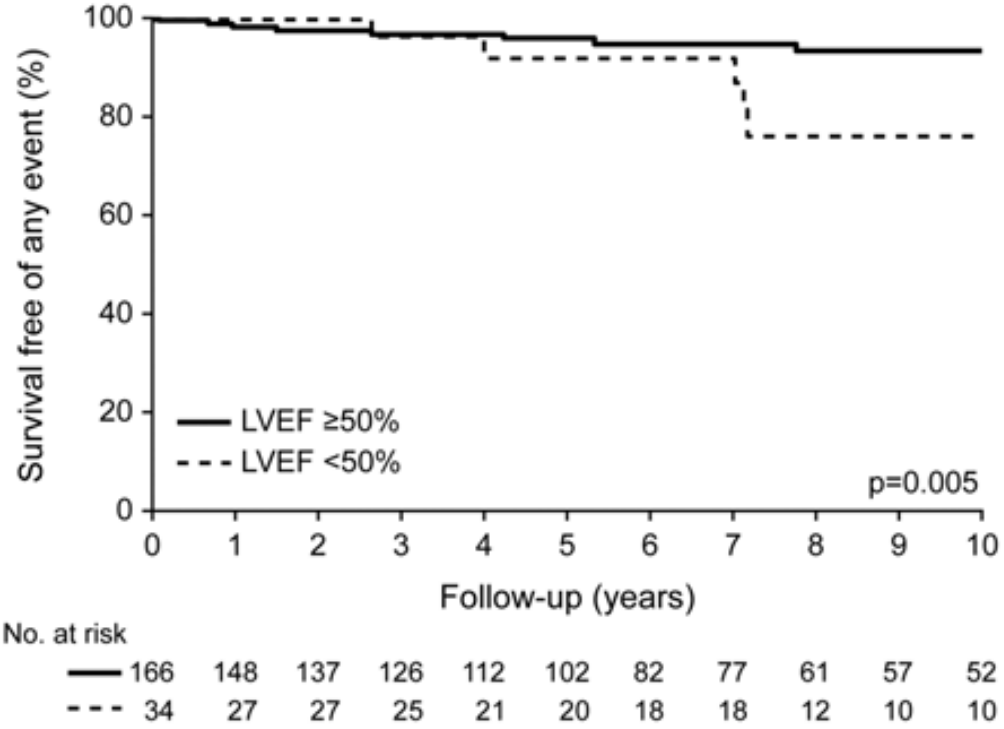
Abbreviations: CI, confidence interval; EP, electrophysiologic; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; VT, ventricular tachycardia

Figure 10: Survival curves by risk factors

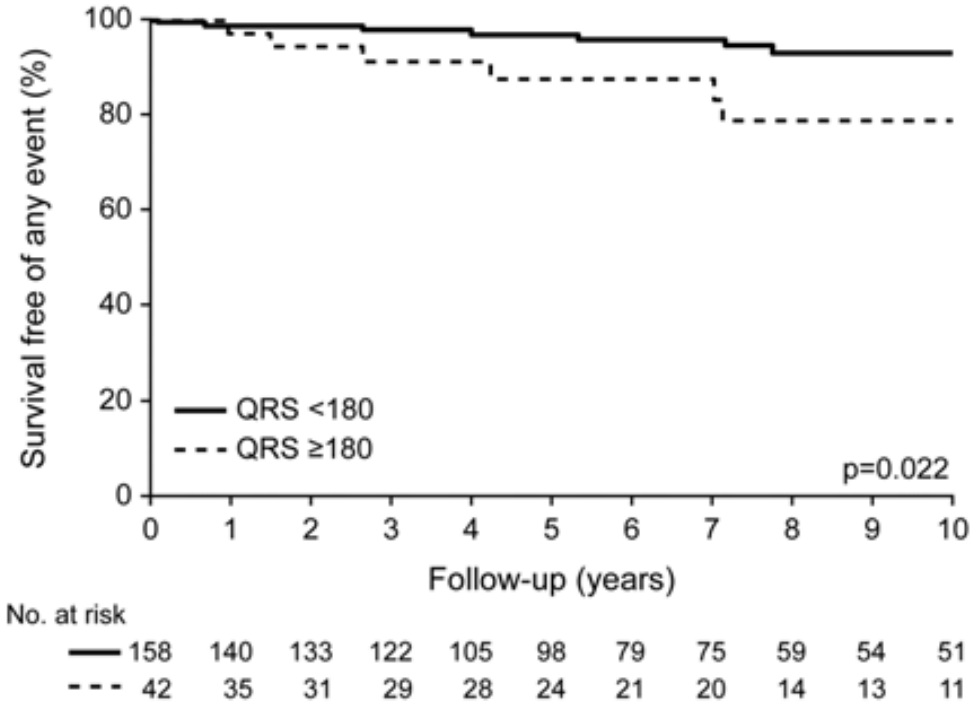
a) Freedom from the combined event by history of ventricular tachycardia, dashed line; no history of ventricular tachycardia, solid line



b) Freedom from the combined event by LVEF < 50%, dashed line; ≥ 50%, solid line.



c) Freedom from the combined event by QRS ≥ 180, dashed line: < 180, solid line.



5.- Surgical cryoablation

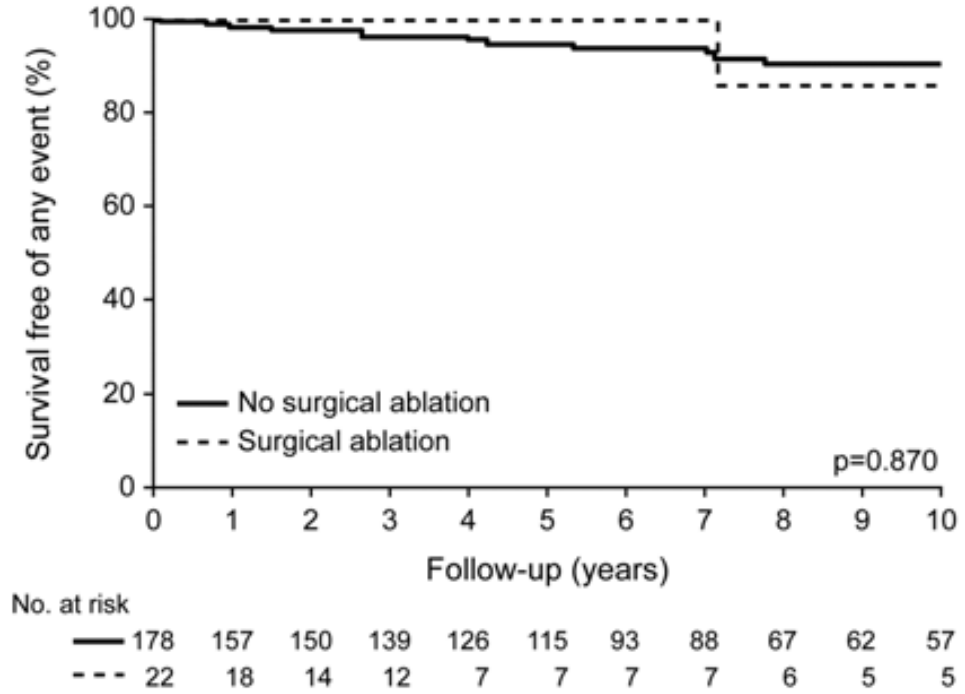
None of the 22 patients who underwent open surgical RVOT ablation died suddenly, sustained an out-of-hospital cardiac arrest or VT episode during follow-up. Only one of the 22 had an appropriate ICD discharge 7 years after surgery. In contrast, 18 of the 183 patients without surgical cryoablation sustained events: SCD (n=5), appropriate ICD therapy (n=6), out-of-hospital cardiac arrest (n=3) or VT (n=4) at follow-up. For the majority, pre-operative baseline risk factors were not significantly different between these groups, although patients in the cryoablation group were older at PVR and were more likely to have inducible VT at EPS. ICD implantation was more common in this group (see **Table 15**). **Figure 11** shows the survival curve for freedom from any event by surgical cryoablation.

Table 15: Summary of pre-operative risk factors comparing patients that did undergo cryoablation at surgery and those who did not

	Cryoablation at surgery		
	yes (22)	**no (183)**	**p value**
History of VT, N (%)	4 (18)	12 (7)	0.08
History of syncope, N (%)	3 (14)	16 (9)	0.87
History of ICD implantation, N (%)	**5 (23)**	**10 (5)**	**0.01**
Inducible VT at EPS, N (%)	**12 (55)**	**28 (15)**	**0.02**
QRS duration (ms) at PVR, mean ± SD	158±2	156±7	0.82
Age at PVR (y), mean ± SD	**41±10**	**32±16**	**0.02**
LVEF (%), mean ± SD	55±2	56±1	0.82

Abbreviations: EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; VT, ventricular tachycardia

Figure 11: Freedom from the combined event by surgical cryoablation, dashed line: patients that had ablation at surgery; solid line: patients that did not.



6.- QRS duration and morphology

QRS duration was found to be longer in patients with an LVEF <50%; QRS 172 ± 41 ms vs 155 ± 29 ms, p = 0.02. However, no association between QRS duration and RV function was found. All patients with prolonged QRS duration had a right bundle block pattern; therefore no conclusion could be inferred about LV dyssynchrony and ventricular function.

QRS fragmentation was identified in 135 patients, while 13 patients were found to have notched QRS morphologies. Twelve patients had paced QRS morphologies and were excluded. QRS fragmentation was not predictive of the combined event. An entirely normal ECG without PR, QRS or ST abnormality was noted in 10 patients and none of this group sustained any event at follow-up.

7.- Events within one year of pulmonary valve replacement

The first year after PVR was analyzed for evidence of any combined endpoint events (SCD, appropriate ICD, out-of-hospital cardiac arrest or VT). None of the patients that had surgical cryoablation had any event the first year after PVR. An appropriate ICD therapy was delivered at one year after PVR for monomorphic VT in one patient. In a different patient, an appropriate ICD therapy was delivered in the early postoperative period after the patient underwent coronary bypass grafting and valve replacement in the context of severe biventricular failure. A single SCD event was identified, occurring eight months after PVR in a patient whose initial presentation was near-syncope and preoperative characteristics included QRS duration of 136 ms, LVEF

67%, RVEDVi by MRI measured 235ml/m2, RVESVi 130ml/m2, RVEF 45%. The patient did not undergo Holter, EPS, open surgical cryoablation, or ICD implantation. Open cryoablation could not be performed because of inadequate exposure at the time of surgery.

8.- Survival

Twenty-one patients died at follow-up. Three of them died in the perioperative period accounting for an operative mortality of 1.5%. Cause of death was myocardial infarction, postoperative bleeding and RV failure respectively. Survival at 5, 10 and 15 years was 94.6% (95% CI 91.4 – 97.9), 84.6% (95% CI 78.3 – 91.5) and 81.7% (95% 73.6 – 90.7), respectively.

9.- EP studies and ablation

Although the numbers are too small to draw firm conclusions, there are several salient findings from EPS prior to PVR:

1. In those patients who had inducible VT at the EPS (n = 21/40, 52.5%), 3 underwent catheter ablation preoperatively, 10 underwent surgical ablation and 2 patients underwent catheter ablation postoperatively. Nine patients had pre-existing ICD's, and almost half of the remaining patients (5 patients) received an ICD after PVR based on the inducibility of VT at EPS. These data suggest that, on our hands, if patients had inducible VT on pre-PVR EPS, they were treated with ablation

(surgical or catheter) or underwent prophylactic primary prevention ICD implantation.

2. In the group where VT was not inducible at the EPS (n = 19/40, 47.5%) a total of 2 patients underwent surgical ablation. One patient did receive an ICD at the time of PVR hospitalization based on LV dysfunction (LVEF < 30%), and 3 others at a later date.
3. In patients who did not undergo an EPS before surgery (n = 165/205, 80.5%), 6% underwent surgical ablation, 2.4% catheter ablation at a later date, and 8.5% ultimately required ICD implantation.

III. DISCUSSION

PVR occurs at a critical stage in the natural history of patients with repaired TOF. The pulmonary valve is typically severely regurgitant and the RV is volume overloaded. This combination of ventricular scar, hemodynamic stress and myocardial stretch provides a potential arrhythmogenic environment for the development of life threatening VT[52]. Despite the increased risk of ventricular arrhythmias and SCD, to-date there is no consistent approach to the risk stratification and management of repaired TOF patients.

The results of this study highlight that any degree of LV dysfunction (LVEF < 50%) confers an increased risk for ventricular arrhythmia/SCD in the TOF patient undergoing PVR. LV systolic dysfunction with LVEF <50% is present in around a fifth of adults with repaired TOF[84], and in multi-center analyses, LV systolic and diastolic function both appear to be associated with VT in this population[85, 86]. The data have

suggested that moderate to severe LV systolic dysfunction is predictive of arrhythmic events[86]. Results from our investigation propose that even a mild reduction in LVEF prior to PVR is associated with increased risk – and raises the question of whether these patients should be treated differently. It is also remarkable that in the repaired TOF patients with PR and associated right-sided cardiac enlargement and dysfunction, right ventricular features were not associated with arrhythmic events after PVR. However, patients with reduced LVEF were more likely to have right ventricular dysfunction. In addition, this study highlights that patients with a history of clinical VT at the time of PVR have an increased risk of ventricular arrhythmia/SCD at follow-up. This important and intuitive finding has not been previously reported in the literature. Nonsustained VT had been associated with appropriate ICD shocks in patients with TOF undergoing primary prevention ICD implantation[87]. We found no association between nonsustained VT and events at follow-up in our patient group.

This investigation confirms that a prolonged QRS duration is predictive of ventricular arrhythmic events in patients with repaired TOF prior to PVR, yet interestingly, ECG criteria such as QRS fragmentation or an entirely normal ECG is not positively or negatively predictive. QRS fragmentation represents cardiac conduction delay and is thought to be a marker of fibrosis and scar within the myocardium. It is a marker of increased mortality and ventricular arrhythmia in patients with coronary disease[88] and also portends a poor prognosis in those with arrhythmogenic right ventricular dysplasia[83, 89, 90]. Although, less well-studied, data suggest that this electrocardiographic signature is predictive of SCD in other groups such as cardiac sarcoid and Brugada syndrome[90, 91]. It remains speculative as to why this feature is not predictive of arrhythmic events in TOF – yet this morphology is especially common –

occurring in 70% of repaired TOF patients. Since no TOF patient with PR and a QRS duration of < 180 ms suffered from sustained VT or SCD in the original investigation on mechanoelectrical interaction[61], we hypothesized that an entirely normal ECG represents a less malignant phenotype. This appears to be the case, in other forms of congenital heart disease[92], and it is interesting to note that patients in our study group with a normal ECG did not sustain any arrhythmic event.

Surgical cryoablation

A central message from this study despite the small numbers is that surgical cryoablation in the RVOT is safe and potentially reduces the risk of arrhythmic events after PVR. Importantly, surgical cryoablation does not appear to be pro-arrhythmic. A major concern with any ablation procedure (done percutaneously or via an open approach) centers on whether bidirectional block can be achieved across a corridor of electrical conduction. If lesion depth is not transmural – damaged myocardium can serve as substrate providing slow cardiac conduction and thereby providing one of the key ingredients for reentrant arrhythmia. Intraoperative open EPS mapping is typically no longer performed, and therefore lesion depth/discrete linear block cannot be confirmed during open cryoablation cases. Although underpowered because of small numbers and low event rates these data do suggest a trend towards surgical cryoablation of the RVOT being associated with less post-PVR ventricular arrhythmic events. Only one patient sustained an appropriate ICD discharge 7 years after the PVR/cryoablation procedure. This is especially important information given that the literature is currently limited to only 9 patients from a small series and follow-up limited to 5 years[49].

EP studies

A remaining question therefore in managing the risk of malignant arrhythmia in TOF patients with pulmonary regurgitation revolves around the need for an EPS and its optimal timing. The highest risk group in the study is TOF/PVR with prior documentation of VT; we suggest these patients undergo preoperative EPS to more carefully assess risk of malignant events. Ventricular stimulation protocols have demonstrated risk-stratification potential with differences in freedom from VT and SCD between patients with inducible VT versus those without[51]. It is a concern, however, that ventricular arrhythmia prior to PVR is in part related to the volume overloaded RV, and improvement in the hemodynamic milieu with PVR offloads the RV, reduces myocardial stretch and thereby allows for geometric and electrical remodeling. A significant reduction in the incidence of monomorphic VT after PVR has been previously recognized[49, 93]. In these analyses, appropriate ICD therapy was not included as an endpoint. Even though data from this current study does reflect a similar trend, with the prevalence of VT decreasing after PVR, patients with history of VT have a higher risk of ventricular arrhythmia/SCD at follow-up. Only two events occurred in the first year after PVR – 8 and 12 months after the operation. The majority of events occurred in patients who did not undergo pre- or postoperative EPS. These findings suggest that all patients with risk factors for VT undergoing PVR should have an EPS pre- or postoperatively. Patients with high risk for arrhythmia include patients with documented sustained VT, unexplained syncope, QRS duration ≥ 180 ms, prior ventriculotomy, documented nonsustained VT and LV dysfunction at the time of PVR. Additional study is required to determine whether this study can potentially be delayed until RV remodelling has taken place.

Holter monitoring was performed in only 22% of our patients prior to PVR and failed to detect sustained VT but interestingly VPBs and non-sustained VT using Lown-grade criteria were not associated with arrhythmic events after PVR. Prior studies evaluating ambulatory monitoring are heterogeneous[23, 94], yet all patients in this report underwent PVR which can improve arrhythmogenic substrate.

Patients with syncope do appear to be a high-risk group with the vast majority in this cohort undergoing EPS, surgical cryoablation or ICD implantation.

Limitations

The combination of endpoints (including VT and appropriate ICD therapies as a surrogate for life-threatening events) provides greater statistical power to discern between risk factors – an approach not undertaken in other investigations of this type. Yet it must be acknowledged that these events are surrogates and not all ICD or VT events go on to result in SCD. The retrospective historical nature of the study is inherently limited, but given the small population with congenital heart disease, this is unfortunately integral to current investigation in this setting. Recommendations for monitoring patients with pulmonary valve regurgitation after TOF repair and determining optimal timing of PVR changed over the course of the study period and thus testing and referral patterns varied during the study. Given the small number of preoperative MRIs performed preoperatively, qualitative right ventricular dimensions and function were measured by echocardiography before PVR and failed to predict the combined event after surgery. A small study found right ventricular end-systolic volume index to be predictive of death or VT in a cohort of patients with repaired TOF[95]. The

measurements in this particular study were done by MRI, which could be more accurate than the qualitative echocardiographic measures we have reported.

IV. CONCLUSION

Patients with repaired TOF undergoing PVR with a history of VT, QRS ≥ 180ms and/or LVEF < 50%, are at high risk of arrhythmic events after operation. Surgical cryoablation at the time of PVR does not appear to be pro-arrhythmic, and may be beneficial.

ECHOCARDIOGRAPHY STUDY

I. METHODOLOGY

We performed a retrospective review of all patients with repaired TOF who underwent first time PVR at our institution between 2003 and 2012 (n = 146). To be included in this study, patients were required to have at least one preoperative echocardiographic examination at our institution. Overall, 133/146 (91%) patients met the inclusion criteria to be analyzed.

Descriptive and Baseline Data

Medical history, as well as perioperative and follow-up data was collected using all available records and surveys that are sent on a routine scheduled basis. In addition, the Social Security Death Index was reviewed.

Echocardiography

We selected the last echo prior to surgery and the echo closest to 1 year after surgery (range 3.6 months to 2.7 years) for each patient.

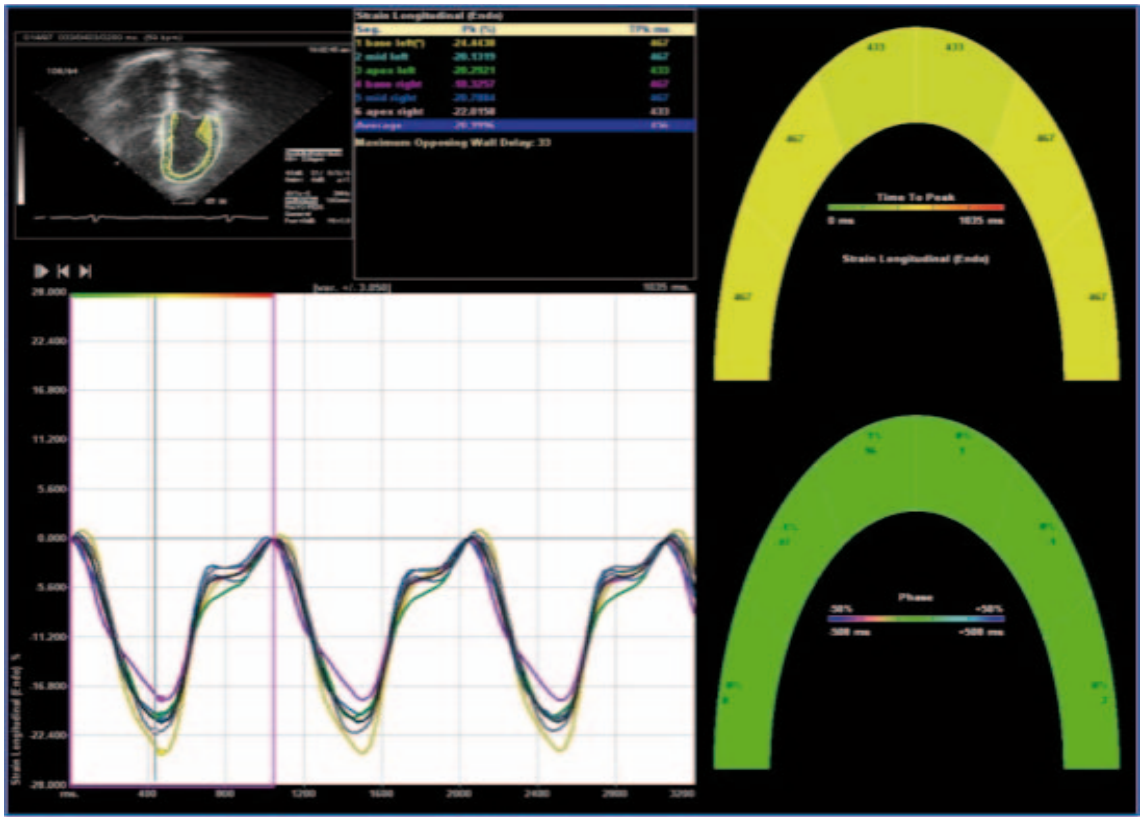
1) Strain analysis

Digital echocardiographic images were transferred to a dedicated workstation for offline analysis. Images were analyzed with Velocity Vector Imaging software (VVI Siemens Medical Systems, Mountain View, California). A single observer blinded to the clinical data performed strain analysis. The endocardium was manually traced, and the region of interest was manually adjusted to the wall thickness. Adequate tracking was visually assessed, and strain curves were accepted only if tracking appeared

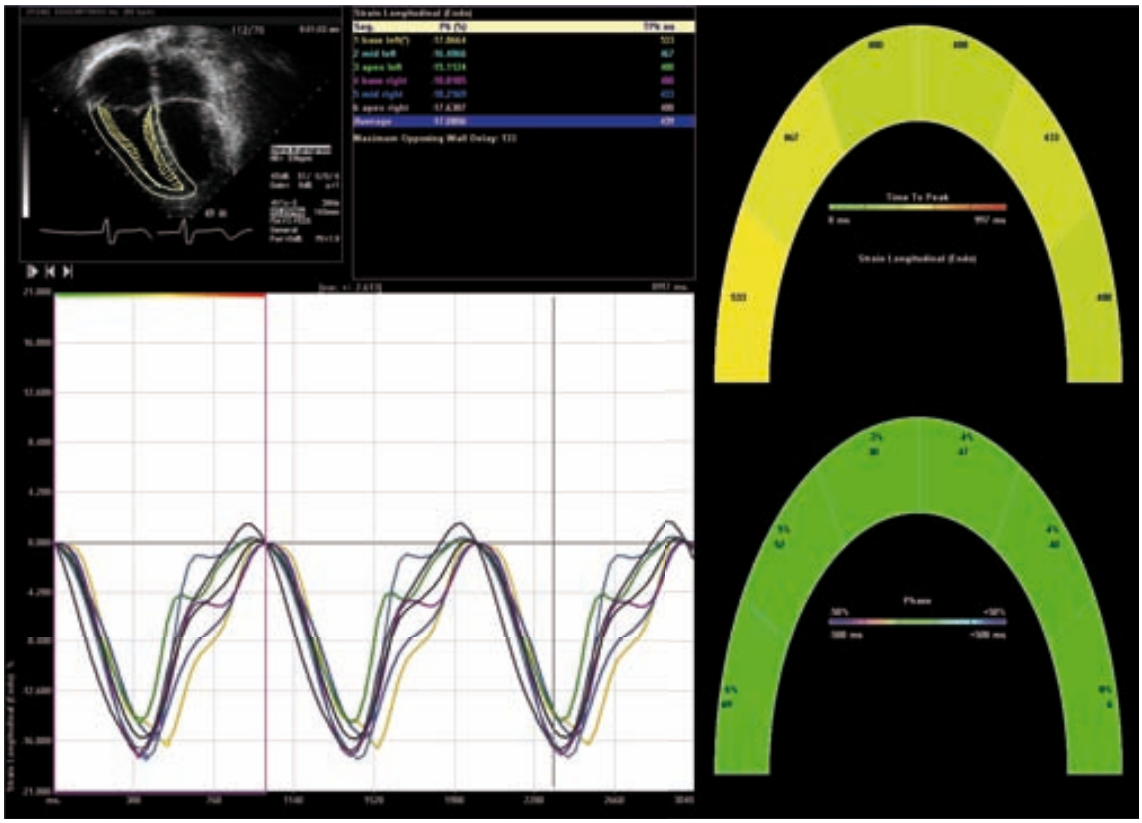
appropriate. The apical four-chamber view was used for the LV analysis (septum and free wall), and the RV free wall was used for the RV analysis. See **Figure 12**.

Figure 12: Snapshot of the VVI program showing: adequate tracing on the upper left hand corner, peak systolic strain values on the upper center, longitudinal strain curves on the bottom and time-to-peak values on the left side.

(a) Left ventricle



(b) Right ventricle. Only the free wall curves and values were used for the right ventricle.



2) Echo 2D and Doppler analysis

Categorical variables such as chamber size, ventricular function and valve regurgitation were codified using a numeric scale for analysis purposes: -1, small; 0, normal or none; 1, borderline or trivial; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; and 6, severe. These were qualitatively assessed by experts according with American and European guidelines[58, 59] (see description on page 25).

3) Intraobserver and interobserver reliability analysis

Intraobserver and interobserver reliability analysis of both LV and RV peak systolic longitudinal strain, strain rate and diastolic strain rate was performed in 10 randomly chosen patients. Curves were traced anew, and strain curves generated anew,

on the same cardiac cycle by the same observer and independently by a second observer for intraobserver and interobserver reliability, respectively. Bland-Altman limits of agreement analysis were used.

4) Measurements of dyssynchrony

Both LV and RV longitudinal mechanical dyssynchrony was measured as the maximum absolute difference in time to peak systolic longitudinal strain, strain rate and diastolic strain rate between the earliest and latest activated myocardial segments of the septal and lateral walls (maximum opposite wall delay, expressed in milliseconds).

QRS duration for all patients before and after surgery was analyzed manually from standard (25mm/s and 1mV/cm) 12-lead electrocardiograms at rest.

Outcome Data

Three different outcomes were chosen: (1) LV and RV peak systolic longitudinal strain at follow-up; (2) functional class at follow-up, defined in terms of the New York Heart Association (NYHA) classification; and (3) death of any cause. Independent variables evaluated for their association with the outcome variables included past medical history, clinical, electrocardiographic and echocardiographic variables. Specifically, age at initial repair, history of previous palliations and number of cardiac surgeries; age, functional class (NYHA) and QRS at PVR; and LV and RV peak systolic strain and RV size before PVR were studied.

MRI

Cardiac MRI was available for 49 patients before PVR. Correlations comparing MRI to strain imaging and to the traditional 2D echo were performed. All studies were performed on a 1.5-T system (Signa, GE Healthcare, Waukesha, Wisconsin) utilizing an 8-element phased array cardiac coil. After initial scout images, short-axis cine balanced steady state free precession (SSFP) images were obtained from the atrioventricular ring to the apex and axial SSFP images were obtained. The RV and LV volumes and ejection fraction were obtained by manual tracing of endocardial borders from the short axis images at end diastole and end systole. In 2008 RV volumes and ejection fraction from the axial images were also routinely obtained. The following measurements were included: RV and LV end diastolic volume index, RV and LV end systolic volume index, and RV and LV ejection fraction. The RVOT was not included in the measurements for the RV. Diastolic function, regurgitation fractions and measurements of the atrium are not routinely performed in our lab. Therefore, were not available for all patients and were not included in the analysis.

Statistical analysis

Descriptive statistics are reported as proportions for discrete data and means and standard deviations for continuous data, except for variables that are not normally distributed in which case median and interquartile range were used, unless specified differently. T-test was used to compare continuous variables. Chi-square test of independence was used to compare categorical variables, unless for cells with % predicted < 5% where Fisher's exact test was used. Comparisons of patient and echo data before and after surgery were performed using t-test pairs or Wilcoxon test

accordingly. For quantifying correlations between two variables, the Spearman correlation test was applied. Stepwise multivariate analysis included only variables that had a low number of missing data and $p \leq 0.2$ in the univariate analysis. P-values < 0.05 were considered statistically significant.

II. RESULTS

1.- Characteristics of the Study Population

A total of 133 patients with TOF had a PVR at a mean age of 35.5 ± 16.2 years, 29.4 ± 12.4 years after the initial repair. Characteristics of the population are summarized in **Table 16**. Almost half of the cohort had 3 or more previous interventions, including palliation procedures in half of them. The majority was symptomatic at the time of surgery. In the 49 patients with MRI available, mean indexed RV end-systolic volume was 100 ± 30 mL/m^2, RV end-diastolic volume 172 ± 44 mL/m^2, and RVEF 42 ± 8 %. Their indexed LV end-systolic volume was 28 ± 12 mL/m^2, LV end-diastolic volume 69 ± 19 mL/m^2, and LVEF 58 ± 9 %.

Table 16: Patient characteristics

Variable	N = 133
Female, N (%)	72 (54.1)
BSA, mean ± SD	1.8 ± 0.4
BMI, mean ± SD	25.7 ± 6.4
Age at initial repair, y, median (range)	3.3 (0.2 – 47.2)
Previous palliation procedure, N (%)	47 (35.6)
Previous surgery ≥ 3, N (%)	59 (44.7)
Age at PVR, y, median (range)	35.0 (3.6 - 64.9)
QRS at PVR, ms, mean ± SD	154 ± 29
QRS post, ms, mean ± SD	148 ± 30
NYHA class pre ≥ II, N (%)	103 (77.4)
NYHA class post ≥ II, N (%)	12 (12.4)
Follow-up time, y, mean ± SD	3.0 ± 2.7
Death, N (%)	5 (3.9)

Abbreviations: BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; PVR, pulmonary valve replacement.

2.- Echocardiography before and after pulmonary valve replacement

The preoperative echo was performed 56 ± 87 days before the PVR, with a median of 37 days. The postoperative echo was performed 390 ± 181 days after the PVR, with a median of 1 year.

Strain imaging

Table 17 shows LV and RV peak systolic and diastolic deformation parameters both before and after PVR. Peak systolic deformation parameters were decreased for both the LV and RV preoperatively, and did not change significantly after surgery. RV diastolic strain rate worsened slightly after surgery.

Bland-Altman analysis of intraobserver and interobserver variability for LV and RV peak systolic and diastolic deformation parameters and maximal opposite wall delay is presented in **Table 18** and **Figure 13**. Intraobserver and interobserver reliability was very good for LV and RV systolic and diastolic deformation parameters, but not as good for maximal opposite wall delay.

Table 17: LV and RV peak systolic and diastolic deformation, 2D echo and Doppler parameters both before and after PVR

Variable	Echo pre	Echo post	Matched difference	p value
LV				
Strain (%)	-14.8 ± 3.5	-14.5 ± 3.3	0.6 ± 0.5	0.3
Strain rate (s^{-1})	-0.8 ± 0.2	-0.8 ± 0.2	0.02 ± 0.03	0.5
Diastolic SR (s^{-1})	0.9 ± 0.3	0.9 ± 0.3	-0.04 ± 0.4	0.4
RV free wall				
Strain (%)	-16.2 ± 4.1	-15.8 ± 4.4	0.2 ± 0.7	0.8
Strain rate (s^{-1})	-0.9 ± 0.3	-0.9 ± 0.3	0.007 ± 0.05	0.9
Diastolic SR (s^{-1})	1.0 ± 0.3	0.9 ± 0.5	-0.2 ± 0.06	**0.02**
2D echo and Doppler				
LVEF (%)	57 ± 8	59 ± 6	2.8 ± 1.0	**0.006**
RV pressure (mmHg)	47 ± 17	40 ± 13	-7.2 ± 2.4	**0.004**
LA size*	0 (0, 2)	0 (0, 2)	0 (0, 0)	0.08
LV size*	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.5
LV function*	0 (0, 0)	0 (0, 0)	0 (0, 0)	**0.048**
PR*	6 (6, 6)	1 (0, 1)	-5 (-6, -4)	**<0.001**
RV size*	5 (4, 6)	3 (2, 4)	-2 (-3, -1)	**<0.001**
RV function*	2 (1, 4)	2 (0, 3)	-0.5 (-2, 0)	**<0.001**
TR	2 (2, 3)	2 (1, 2)	-1 (-2, 0)	**<0.001**

Data are shown as mean ± SD or median (interquartile range) as appropriate.
(*) Categorical variables are codified using a numeric scale: -1, small; 0, normal or none; 1, borderline or trivial; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; and 6, severe.
Abbreviations: EF, ejection fraction; LA, left atrium; LV, left ventricle; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation

2D and Doppler imaging

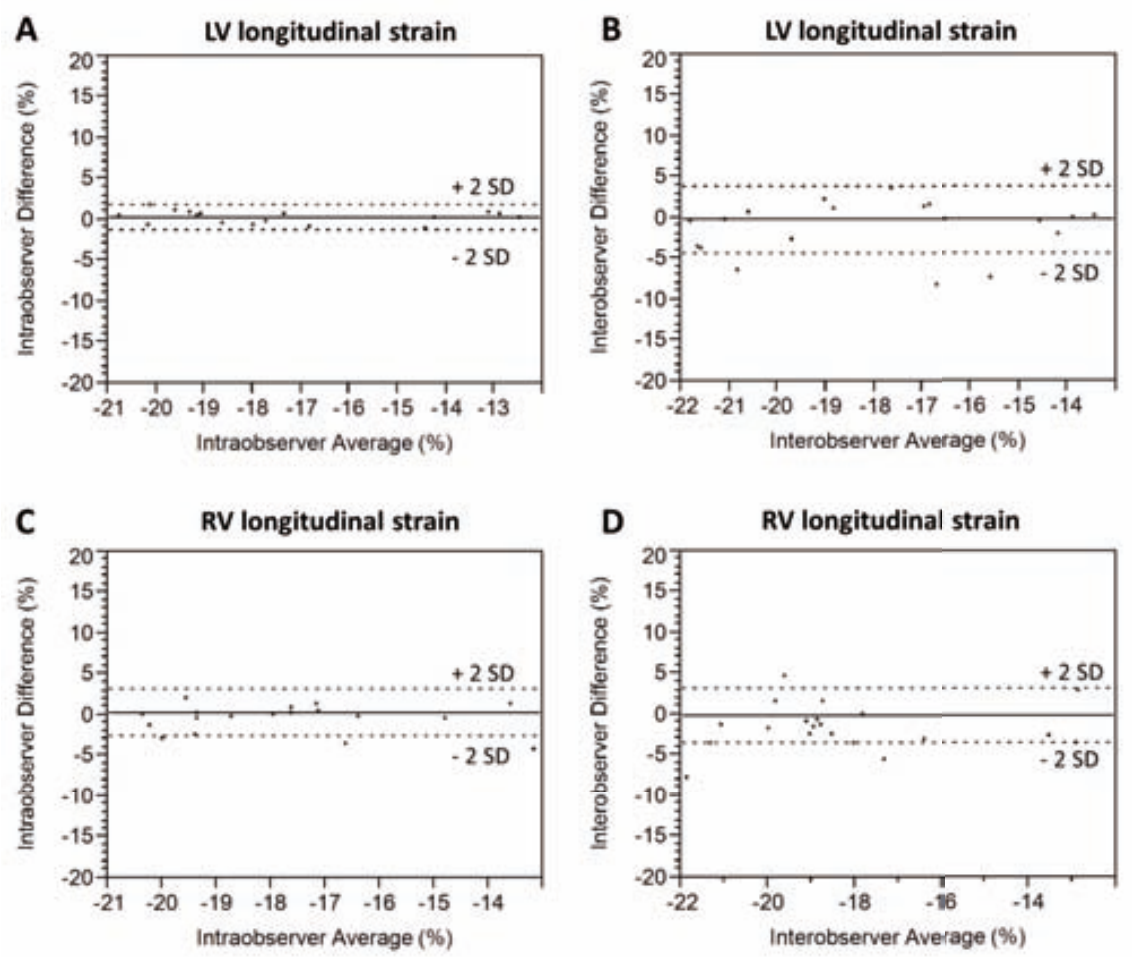
Table 17 shows detailed information on 2D and Doppler parameters before and after surgery. Both LVEF and qualitative LV function improved after surgery, although the change was not clinically relevant. As expected, pulmonary regurgitation decreased significantly and thus right-sided chambers remodeled and RV systolic function

Table 18: Bland-Altman analysis of intraobserver and interobserver variability for LV and RV peak systolic and diastolic deformation parameters and dyssynchrony

	Intraobserver variability		Interobserver variability	
		Difference		Difference
Variable	mean ± SD	mean ± SD	mean ± SD	mean ± SD
LV strain	-17.7 ± 2.8	0.2 ± 0.8	-18.2 ± 3.2	-0.3 ± 2.1
LV systolic SR	-0.9 ± 0.1	-0.03 ± 0.2	-1.0 ± 0.2	-0.007 ± 0.3
LV diastolic SR	1.1 ± 0.3	-0.07 ± 0.2	1.2 ± 0.4	-0.1 ± 0.3
RV strain	-18.3 ± 2.0	0.2 ± 1.5	-18.5 ± 2.2	-0.2 ± 1.7
RV systolic SR	-0.9 ± 0.1	-0.01 ± 0.2	-1.0 ± 0.1	-0.1 ± 0.2
RV diastolic SR	1.0 ± 0.3	0.1 ± 0.3	1.1 ± 0.2	0.1 ± 0.4
LV strain MOWD	108.7 ± 42.3	25.7 ± 56.2	86.7 ± 32.6	-24.8 ± 44.9
LV systolic SR MOWD	139.8 ± 49.2	28.1 ± 74.6	126.4 ± 42.9	-11.8 ± 75.5
LV diastolic SR MOWD	99.0 ± 58.5	19.3 ± 58.9	78.4 ± 38.4	-28.4 ± 38.3
RV strain MOWD	95.2 ± 43.6	1.4 ± 32.9	75.0 ± 31.4	-25.9 ± 31.7
RV systolic SR MOWD	190.4 ± 66.2	5.7 ± 86.1	161.1 ± 55.8	-52.8 ± 51.7
RV diastolic SR MOWD	110.9 ± 48.7	-2.9 ± 32.9	101.1 ± 33.9	-15.8 ± 50.7

Abbreviations: LV, left ventricle; MOWD, maximum opposite wall delay; PR, pulmonary regurgitation; RV, right ventricle; SR, strain rate; TR, tricuspid regurgitation

Figure 13: Bland-Altman plots depicting intraobserver and interobserver reliability for measurement of LV longitudinal strain (A, B) and RV longitudinal strain (C, D)



3.- Ventricular-ventricular interactions before and after pulmonary valve replacement

Correlations between LV and RV peak systolic and diastolic parameters both before and after PVR are shown in **Table 19**. A close correlation between LV and RV peak systolic strain, strain rate and diastolic strain rate was found before PVR and was maintained after surgery. However, no correlation was found between chamber size and contralateral function either before or after surgery. Patients with higher degrees of pulmonary regurgitation had a larger RV both before and after surgery ($r = 0.3$, $p = 0.003$, and $r = 0.2$, $p = 0.06$), although this was not correlated with LV size or function.

Table 19: Ventricular-ventricular interactions before and after PVR

Variable	by Variable	Before		After	
		Spearman correlation	pvalue	Spearman correlation	pvalue
LV size	RV size	-0.16	0.07	0.18	0.14
LV strain	RV strain	0.4	**0.002**	0.5	**0.001**
LV SR	RV SR	0.4	**0.002**	0.3	**0.03**
LV diastolic SR	RV diastolic SR	0.4	**0.002**	0.4	**0.01**
LV function	RV function	0.4	**<0.0001**	0.3	**0.009**
LV strain	RV size	-0.06	0.6	0.2	0.1
LV size	RV strain	0.06	0.6	0.2	0.1
LV size	PR	-0.09	0.3	-0.08	0.5

Abbreviations: LV, left ventricle; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation; SR, strain rate

RV and LV maximum opposite wall delay did not correlate with QRS duration either before or after surgery. Even though an improvement in QRS duration was noted after surgery (154 ± 29 ms vs 148 ± 30 ms, $p = 0.002$), there was no change in maximum opposite wall delay after surgery.

4.- Outcomes

Patients were followed for a mean time of 3.0 ± 2.7 years; six patients were lost at follow-up (4.5%).

Predictors of LV and RV peak systolic strain at follow-up

Univariate and multivariate analyses for LV and RV peak systolic strain after surgery are depicted in **Table 20**. In the multivariate analysis, patients with better LV peak systolic strain preoperatively predicted better LV peak systolic strain after surgery. Similarly, patients with better RV peak systolic strain preoperatively independently predicted better RV peak systolic strain after surgery, although the patients that had the most improvement were those with worse RV peak systolic strain preoperatively (0.5 ± 0.2%, p = 0.002), as shown in **Figure 14**.

Figure 14: Scatterplots depicting the association between RV peak systolic strain before pulmonary valve replacement and (A) RV peak systolic strain after surgery; and (B) change of RV peak systolic strain after surgery (pre – post RV peak systolic strain)

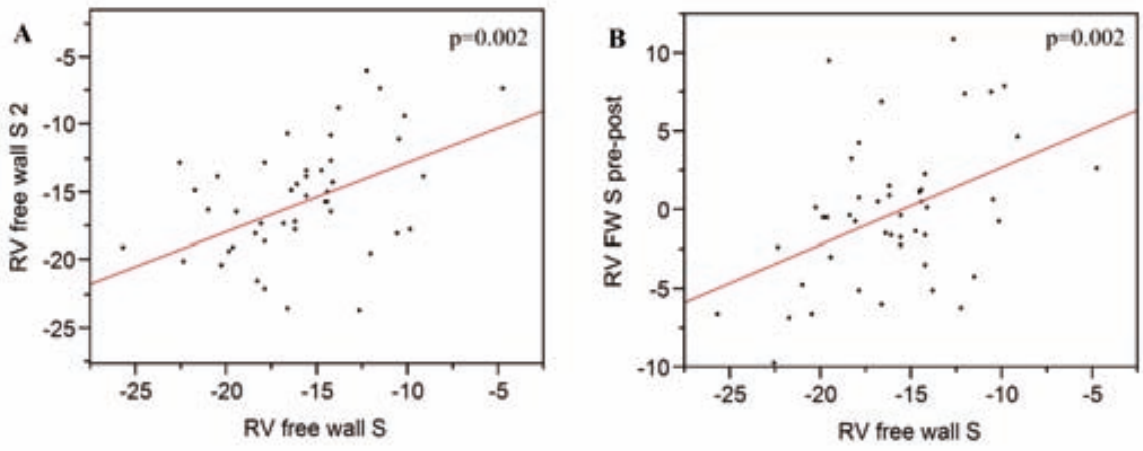


Table 20: Univariate and multivariate analyses for LV and RV peak systolic strain after surgery

	LV peak systolic strain after PVR			
	Univariate		Multivariate	
	estimate ± SE	p value	estimate ± SE	p value
LV strain	0.8 ± 0.2	**0.0004**	0.68 ± 0.2	**0.004**
RV strain	0.2 ± 0.1	0.2	-0.02 ± 0.1	0.9
Age at initial repair	0.02 ± 0.04	0.7		
Previous palliation	1.6 ± 1	0.1	1.6 ± 2.2	0.5
≥ 3 surgeries	1.4 ± 0.9	0.1	0.008 ± 2.1	1
Age at PVR	0.02 ± 0.03	0.5		
NYHA pre ≥ II	0.9 ± 1	0.4		
QRS pre	0.008 ± 0.02	0.6		
RV pre > moderate	1.4 ± 0.9	0.1	0.9 ± 1.1	0.4

	RV peak systolic strain after PVR			
	Univariate		Multivariate	
	estimate ± SE	p value	estimate ± SE	p value
LV strain	0.9 ± 0.2	**0.001***		
RV strain	0.5 ± 0.2	**0.002**	0.5 ± 0.2	**0.006**
Age at initial repair	0.03 ± 0.06	0.6		
Previous palliation	0.7 ± 1.3	0.6		
≥ 3 surgeries	-0.3 ± 1.2	0.8		
Age at PVR	0.06 ± 0.04	0.09	0.04 ± 0.04	0.3
NYHA pre ≥ II	-0.4 ± 1.4	0.8		
QRS pre	0.03 ± 0.02	0.2	0.009 ± 0.03	0.7
RV pre > moderate	1.7 ± 1.2	0.2	0.9 ± 1.4	0.5

Abbreviations: LV, left ventricle; NYHA, New York Heart Association; PVR, pulmonary valve replacement; RV, right ventricle

*Variable not included in the multivariate model due to the number of missing

Predictors of functional class at follow-up

NYHA class at a median follow-up of 8 months (interquartile range 4.5 to 12.5 months) improved from 2.2 ± 0.8 to 1.2 ± 0.6, p<0.0001. In the univariate analysis, RV peak systolic strain predicted NYHA ≥ II early after surgery (OR 1.3, p = 0.02). All

other variables including LV peak systolic strain, age at initial repair, previous palliation procedures, 3 or more previous cardiac surgeries, QRS duration, RV size and age at the time of PVR were not predictive of NYHA class at follow-up. There were insufficient numbers to proceed with a multivariate analysis in this cohort.

Mortality

There were 5 deaths (3.9 %) at a median follow-up of 6 months (range 17 days to 2.6 years) after PVR. The early death was due to sepsis. The 4 late deaths were cardiac related in 3 (one was a SCD) and the other one was infection related. Patients who died had worse preoperative systolic deformation parameters for both the LV and RV: LV strain -7.9 ± 2.2 % vs -15.2 ± 3.2 %, p = 0.002; LV strain rate -0.6 ± 0.05 s^{-1} vs -0.8 ± 0.2 s^{-1}, p = 0.04; RV strain -10.6 ± 7.2 % vs -16.4 ± 4.1 %, p = 0.008; and RV strain rate -0.6 ± 0.4 s^{-1} vs -0.9 ± 0.3 s^{-1}, p = 0.04. Patients who died also had worse preoperative diastolic deformation parameters for both the LV and RV, although the difference did not reach statistical significance: LV diastolic SR 0.6 ± 0.1 s^{-1} vs 1 ± 0.3 s^{-1}, p = 0.09; and RV diastolic SR 0.7 ± 0.2 s^{-1} vs 1 ± 0.3 s^{-1}, p = 0.06. Of note, only 2 of 5 patients had LV analysis preoperatively while 4 of 5 patients had RV analysis preoperatively.

5.- MRI analysis

Correlations between MRI and echocardiographic measurements are shown in **Table 21**. RVEF and LVEF on MRI did not correlate with the corresponding strain parameters. Interestingly, there was an association between RV volume and RV strain,

where larger ventricles had better function. RV dimensions on MRI correlated closely to RV dimensions on 2D echo. Therefore, we used 2D echo assessment for all other analyses since that information was available for all patients.

RVEF and RV volumes did correlate well with the corresponding qualitatively functional assessment on 2D echo. Patients with larger RV size on 2D echo had worse LVEF measured on MRI.

Table 21: Correlations between MRI and echocardiography (2D echo and strain imaging)

MRI Variable	by Echo Variable	Spearman correlation	p value
RVEF	RV strain	-0.08	0.6
RVEF	RV strain rate	0.06	0.7
RVEF	RV diastolic strain rate	0.07	0.7
RVEDVi	RV strain	-0.3	0.07
RVESVi	RV strain	-0.2	0.1
RVEDVi	RV strain rate	-0.3	**0.049**
RVESVi	RV strain rate	-0.3	**0.04**
RVEDVi	RV size	0.5	**0.001**
RVESVi	RV size	0.4	**0.004**
LVEF	LV strain	-0.2	0.3
LVEF	LV strain rate	-0.1	0.6
LVEF	LV diastolic strain rate	-0.003	1
LVEDVi	LV size	0.2	0.2
LVESVi	LV size	0.3	0.07
LVEF	EF	0.5	**0.0001**
LVEF	RV size	-0.3	**0.046**

Abbreviations: EDVi, end diastolic volume indexed (mm/m^2); ESVi, end systolic volume indexed (mm/m^2); EF, ejection fraction (%); LV, left ventricle; RV, right ventricle

III. DISCUSSION

Our data support the conclusion that systolic and diastolic deformational parameters for both the LV and RV are decreased in patients with TOF long after initial repair. We found that there is no significant change in these parameters after PVR and that these biventricular interactions do not seem to be affected by surgery. We also found that pre-operative LV and RV peak systolic strain are predictive of LV and RV peak systolic strain after PVR, and that RV peak systolic strain is predictive of NYHA class at early follow-up. In addition, the few patients who died at follow-up had worse LV and RV function before surgery compared to those that survived. These results suggest a potential role for these novel quantitative deformational parameters to determine optimal timing of PVR in this cohort.

Biventricular response after pulmonary valve replacement

Patients with TOF undergoing first time PVR after initial complete repair have decreased LV and RV systolic and diastolic deformational parameters. This was previously highlighted in some studies reviewing patients with TOF long after initial repair compared with healthy controls[15, 36], although our numbers are lower, likely because the majority of our patients were symptomatic. A decreased LV systolic strain and strain rate contrasts with a normal LVEF assessed by 2D echo in the majority of our patients. This discrepancy supports the theory that reduced longitudinal function (assessed by longitudinal strain) may be present in TOF patients before circumferential function (assessed by LVEF) is affected[15].

To our knowledge, the biventricular response after PVR has not been extensively studied using these novel techniques. In our cohort, there was no significant

change in biventricular function after intervention when measured with strain, although RV function improved qualitatively after surgery. The lack of strain improvement after surgery could be due to the late surgery in our cohort or due to too early assessment of the strain imaging after surgery, as cardiopulmonary bypass time would likely play a role in decreasing myocardial function immediately after PVR. However, there was an improvement in qualitative RV functional assessment. This discrepancy could be due to different mechanisms that are being assessed with each of these techniques. Strain imaging evaluates active contraction whereas 2D echocardiography may be influenced by passive motion secondary to volume loading.

Unfavorable ventricular-ventricular interactions were found in our study. An association between LV and RV systolic and diastolic dysfunction was found using strain imaging, similar to previous studies[15]. We found a close correlation between PR and RV size, but in contrast to other studies we did not find a relation between PR or RV size and LV strain[35].

Biventricular maximum opposite wall delay did not correlate with QRS duration or LV strain either before or after surgery in our cohort, similar to one other study[35]. However, this result contrasts with other previously published data that shows a close correlation between QRS duration, LV maximum opposite wall delay and LV peak systolic longitudinal strain[17].

Clinical implications

Functional class measured with the subjective method of NYHA classification detects a statistically significant improvement early after PVR. RV systolic strain

predicted NYHA class at early follow-up; patients with worse RV systolic strain had an increased risk of NYHA class ≥ II at early follow-up. The fact that there was an association between biventricular function before surgery and biventricular function and functional class after surgery is consistent with early PVR being beneficial. The limited number of events precluded a receiver operating characteristic type of analysis to find a cutoff for RV strain and/or LV strain.

LV dysfunction measured on 2D echocardiography[62] and MRI[96] has been linked to adverse clinical outcomes in adults after TOF repair. In our cohort, LV function on 2D echo was normal in the majority of patients whereas LV deformational parameters were all abnormal and patients who died were those with lower values. This suggests that deformational parameters may be more sensitive to evaluate ventricular function and may add value during follow-up in this cohort. Other studies have shown the prognostic value of LV global longitudinal strain in patients with TOF[97] and in non-selected populations[98]. In our study, even though the mortality was low, those few patients who died at follow-up had worse LV and RV function before surgery compared to those that survived.

MRI

Systolic and diastolic deformational parameters did not correlate well with ventricular function measured on MRI. This may possibly be due to differential regional RV function in these patients. This discrepancy has been reported[99, 100]. Bonnemains et al found a lack of correlation between RVEF on MRI and longitudinal RV free wall strain and strain rate in a cohort of patients with repaired TOF[100]. Kutty et al attributed this discrepancy to the infundibular dysfunction that existed in the majority of these

patients[99]. They showed that in patients with good infundibular function, RV systolic strain correlated well with RVEF on MRI whereas in patients with poor infundibular function this correlation was weak.

Limitations

Velocity vector imaging has some limitations, especially in retrospective studies where low frame rates and poor image resolution are frequent and may prevent the precise characterization of regional myocardial motion impacting the overall temporal resolution of the regional strain map. Qualitative 2-dimensional echocardiography measurements were subjective and limits external validity. Patient numbers were low in our study and precluded a multivariate analysis for the NYHA predictive model. Mortality was also low and precluded a more accurate predictive model.

IV. CONCLUSION

LV and RV peak systolic strain, SR and diastolic SR are all decreased in patients with repaired TOF undergoing PVR, and there is no significant change after surgery. Biventricular interactions are not affected by the surgery. However, patients with better preoperative LV and RV peak systolic strain have better LV and RV peak systolic strain after surgery, respectively. Patients with worse peak systolic strain have worse functional class at early follow-up. Therefore, these novel quantitative functional parameters are potentially helpful to determine optimal timing of PVR and can be valuable to ongoing serial evaluation.

CONCLUSIONS

I. SPECIFIC CONCLUSIONS

Each of the specific conclusions below refers to one of the specific aims on page 17, and on the same order:

1. The most important predictors of mortality in patients with repaired TOF undergoing PVR were: older age at initial repair, three or more previous cardiac operations, advanced functional class prior to PVR and large body surface area at the time of PVR.
2. Regarding the predictors of pulmonary valve reintervention, age was the most important factor. Younger patients were at higher risk of reintervention, especially those younger than 18 years old.
3. The effect of PVR on aerobic capacity in patients with repaired TOF was the third specific aim of this Thesis. Patients with repaired TOF have an abnormally low aerobic capacity at the time of PVR. Even though there is subjective improvement in functional class after PVR, we appreciated a modest improvement in exercise capacity in our cohort and did not demonstrate a statistically appreciable difference in the meta-analysis.
4. Predictors of significant arrhythmia after PVR in patients with repaired TOF were: history of VT and LV dysfunction (LVEF <50%).
5. The fifth and last of the specific aims was regarding the role of novel deformational echocardiographic techniques on predicting postoperative RV and LV function and functional class in this population. Patients with repaired TOF undergoing PVR have an abnormally low RV and LV systolic and diastolic function measured by

novel quantitative echocardiographic techniques (strain and strain rate). Ventricular function measured with these new techniques is not equivalent to ventricular function measured by MRI. However, pre-operative systolic and diastolic deformational parameters are predictive of early ventricular function and functional class after PVR in patients with repaired TOF.

II. OVERALL CONCLUSION

The results of this Thesis show that patients with repaired TOF undergoing PVR have been operated late in their disease process to achieve ideal postoperative outcomes. Even though subjective functional class and qualitative echocardiography show improvement after PVR, objectively measured exercise capacity and novel quantitative functional echocardiographic techniques show no clinically or statistically relevant improvement. In addition, freedom from life-threatening events and overall survival are poor at 15 year follow-up, being below 80% in a young population with a mean age at PVR around 30 years old.

However, the appropriate moment for PVR needs to be balanced with the risk of pulmonary valve reintervention. Operating sooner may lead to earlier need of reintervention, especially in patients younger than 18 years old. Currently, the advent of percutaneously implantable valves may have the potential to reduce the number of sternotomies at follow-up, and should be considered in the decision making.

Careful preoperative assessment including coronary anatomy, risk of arrhythmia and degree of tricuspid regurgitation is important to decide the optimal surgical approach at the time of PVR. Exercise testing may be convenient preoperatively as an objective measurement of functional class. Besides, novel deformational echocardiographic techniques may be helpful to determine optimal timing of PVR and can be valuable to ongoing serial evaluation, adding to the current imaging strategy.

Importantly, the appropriate moment and the best surgical approach for restoring pulmonary valve function in patients with repaired TOF are still not clear. Several aspects highlighted in this Thesis should be considered and evaluated by a comprehensive multidisciplinary team, involving a congenital cardiologist, electrophysiologist with expertise in congenital heart disease and a congenital cardiac surgeon.

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