European Journal of Cardio-Thoracic Surgery 59 (2021) 1329–1336
doi:10.1093/ejcts/ezab026 Advance Access publication 6 February 2021

ORIGINAL ARTICLE

Cite this article as: Rozzi G, Lo Muzio FP, Fassina L, Rossi S, Statello R, Sandrini C *et al.* Right ventricular functional recovery depends on timing of pulmonary valve replacement in tetralogy of Fallot: a video kinematic study. Eur J Cardiothorac Surg 2021;59:1329–36.

Right ventricular functional recovery depends on timing of pulmonary valve replacement in tetralogy of Fallot: a video kinematic study

Giacomo Rozzi[a,b,c,†], Francesco Paolo Lo Muzio [a,b,†], Lorenzo Fassina[d], Stefano Rossi [b], Rosario Statello[b,e], Camilla Sandrini [f], Maira Laricchiuta[a], Giuseppe Faggian [a], Michele Miragoli[b,c,‡] and Giovanni Battista Luciani [a,*]

[a] Department of Surgery, Dentistry, Pediatrics and Gynecology, University of Verona, Verona, Italy
[b] Department of Medicine and Surgery, University of Parma, Parma, Italy
[c] Departement of Molecular Cardiology, Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy
[d] Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy
[e] Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[f] Department of Medicine, University of Verona, Verona, Italy

* Corresponding author. Section of Cardiac Surgery, Department of Surgery, Dentistry, Pediatrics and Gynecology, University of Verona, O.C.M. Piazzale Stefani 1, 37126 Verona, Italy. Tel: +39-045-8123303; e-mail: giovanni.luciani@univr.it (G.B. Luciani).

Received 31 August 2020; received in revised form 19 November 2020; accepted 7 December 2020

Key question

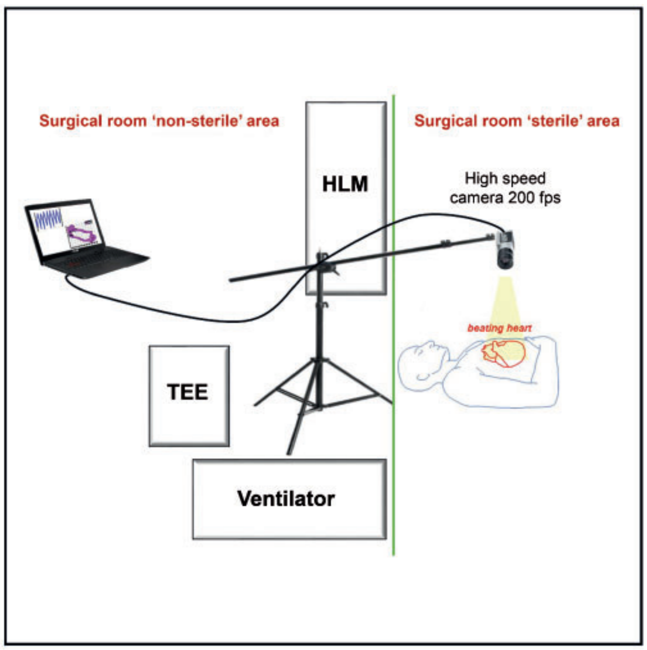
Can video kinematic evaluation (Vi.Ki.E.) identify a relationship between timing of PVR and right ventricular recovery in tetralogy of Fallot?

Key finding(s)

Patients with RVEVDi <147 ml/m^2, thus shorter interval to PVR, have predictable recovery of right ventricle kinematics.

Take-home message

Real time Vi.Ki.E. may predict extent of intraoperative right ventricular functional recovery after PVR in tetralogy of Fallot.



†The first two authors contributed equally to this work.
‡Co-last senior author.
Presented at the 34th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 8–10 October 2020.

CONGENITAL

Abstract

OBJECTIVES: Indications for and timing of pulmonary valve replacement (PVR) after tetralogy of Fallot repair are controversial. Among magnetic resonance imaging indices proposed to time valve replacement, a right ventricular (RV) end-diastolic volume index greater than 160 ml/m^2 is often used. Recent evidence suggests that this value may still identify patients with irreversible RV dysfunction, thus hindering recovery. Our goal was to define, using intraoperative video kinematic evaluation, whether a relationship exists between timing of PVR and early functional recovery after surgery.

METHODS: Between November 2016 and November 2018, a total of 12 consecutive patients aged 27.1 ± 19.1 years underwent PVR on average 22.2 ± 13.3 years after tetralogy of Fallot repair. Mean RV end-diastolic volume evident on the magnetic resonance images was 136.9 ± 35.7 ml/m^2. Intraoperative cardiac kinematics were assessed by video kinematic evaluation via a high-speed camera acquiring videos at 200 fps before and after valve replacement.

RESULTS: Patients presenting with RV end-diastolic volume <147 ml/m^2 were significantly younger (11.2 ± 5.0 vs 38.4 ± 17.0; P = 0.005) and had a shorter time interval to valve replacement (11.0 ± 5.2 vs 30.1 ± 11.3; P = 0.03). The entire population showed a moderate correlation among energy expenditure, cardiac fatigue, perimeter of contraction and preoperative RV end-diastolic volume index. Both groups showed a reduction in all kinematic parameters after PVR, but those with end-diastolic volume >147 ml/m^2 showed an unpredictable outcome.

CONCLUSIONS: Video kinematic evaluation provides insight into intraoperative RV recovery in patients with tetralogy of Fallot undergoing PVR. Accordingly, functional recovery can be expected in patients with preoperative end-diastolic volume <147 ml/m^2.

Keywords: Tetralogy of Fallot • Pulmonary valve replacement • Video kinematic evaluation • Magnetic resonance imaging

ABBREVIATIONS

ANOVA	Analysis of variance
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PR	Pulmonary regurgitation
PVR	Pulmonary valve replacement
RV	Right ventricular
RVEDVi	RV end-diastolic volume index
RVEF	RV ejection fraction
RVESVi	RV end-systolic volume index
ToF	Tetralogy of Fallot
Vi.Ki.E	Video kinematic evaluation

INTRODUCTION

Indications for and timing of pulmonary valve replacement (PVR) in repaired tetralogy of Fallot (ToF) are debated due to limitations in estimating right ventricular (RV) dysfunction and predicting its recovery [1, 2]. Moreover, clinical outcomes assessed both subjectively and objectively by cardiopulmonary exercise testing have not been uniformly consistent concerning a beneficial effect of PVR [2]. Whereas consensus exists on indications for PVR in symptomatic patients with severe pulmonary regurgitation (PR), the debate continues on predictive diastolic and systolic indices of RV functional recovery [1–3]. Among the parameters proposed in the current guidelines to define the timing of PVR are the RV end-diastolic volume index (RVEDVi) and the RV end-systolic volume index (RVESVi) determined from magnetic resonance imaging (MRI). Accordingly, values above 160 ml/m^2 or 80 ml/m^2, respectively, would lead us to recommend PVR in patients with ToF with at least moderate PR [3]. However, recent studies suggest that these cut-off values may still preclude a significant portion of patients from recovering RV function [4–6], suggesting that the thresholds for PVR should be lowered even further. The debate stems from the paucity of prospective studies [5] and from the limitations inherent in retrospective analyses, in which patients surviving from the pioneering era of ToF repair are mixed with those from the current era. This situation has stimulated the quest for alternative methods, including experimental ones, to investigate RV function during PVR [7–9].

Previous pilot work from our group assessed the safety and efficacy of video kinematic evaluation (Vi.Ki.E.), an original contactless experimental technology [10], to define RV functional changes in patients with ToF before and after PVR [11].

The goal of the present study was to establish whether Vi.Ki.E. can be used to assess intraoperative RV functional recovery after surgery, possibly offering prognostic insight into the timing of PVR in patients with ToF.

PATIENTS AND METHODS

Patients

The study was approved by our institutional review board (#847CESC Protocol # 13371), and all patients signed an informed consent form. Between November 2016 and November 2018, a total of 12 consecutive patients aged 27.1 ± 19.1 years undergoing PVR 22.1 ± 13.2 years after ToF repair were enrolled. Per institutional protocol, all patients undergoing surgical PVR, including the 12 herein, were initially assessed for transcatheter pulmonary valve implants. When deemed not suitable for catheter-based intervention, patients were referred for surgical PVR. The first 6 patients in this series were the object of a previous pilot study designed to assess the safety and efficacy of the Vi.Ki.E. technique [11].

The inclusion criteria for the current study were (i) isolated PR after transannular patch repair of ToF with pulmonary stenosis; (ii) symptomatic patients with severe PR or asymptomatic patients with evidence of progressive severe RV dilatation or dysfunction; and (iii) feasibility of PVR normothermic cardiopulmonary bypass on the beating heart. Patients with associated septal defects, aortic valve or root disease, pulmonary artery branch stenosis or acquired coronary artery disease were excluded from this study. The entire population underwent preoperative MRI

Table 1: Demographic and magnetic resonance imaging variables of patients with tetralogy of Fallot

	N = 12	Mean ± SD	Median	Range
Gender (male/female)	7/5			
BSA (m^2)		1.6 ± 0.41	1.7	0.73–1.97
Age at PVR (years)		27.1 ± 19.1	20	6–64
ToF to PVR (years)		22.2 ± 13.3	19.5	6–48
RVEDVi (ml/m^2)		136.9 ± 35.7	147.5	62.5–183
RVESVi (ml/m^2)		74.0 ± 30.1	81	12.5–104
RVEF (%)		50.1 ± 12.0	51	37–79
LVEF (%)		54.3 ± 5.9	54	42–62

BSA: body surface area; LVEF: left ventricular ejection fraction; PVR: pulmonary valve replacement; RVEDVi: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; RVESVi: right ventricular end-systolic volume index; ToF: tetralogy of Fallot.

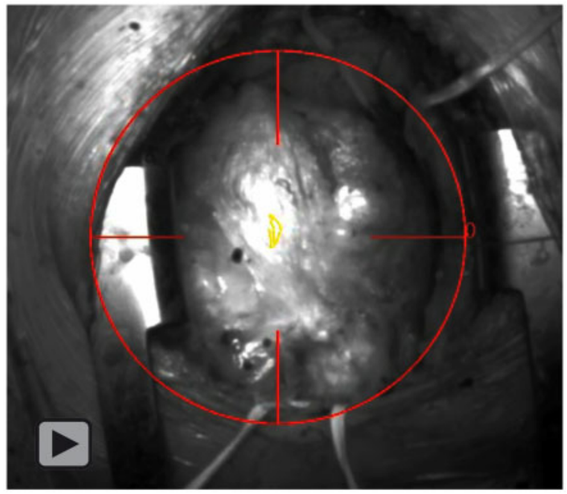
and transthoracic echocardiographic evaluation. The demographic and MRI variables of the patient population are shown in Table 1.

Surgical methods

All surgical procedures were performed by 1 surgeon (G.B.L.) via repeat median sternotomy, using aortic and bicaval cannulation, under normothermic (36°C) cardiopulmonary bypass on the beating heart. Video kinematic recordings were focused on the apical trabecular component of the right ventricle, in line with previous evidence showing this portion as the one taking most of the chronic volume overload [12]. The camera and the tripod were sterilized before being brought into the operating room and between every recording.

Intraoperative video kinematic evaluation

The video recordings were performed as previously described by our group [10]. Briefly, Vi.Ki.E. comprises placing a high-speed camera (Basler acA1300-200um USB 3.0 with the ON Semiconductor PYTHON 1300 CMOS sensor, Ahrensburg, Germany, equipped with Edmund Optics 6-mm compact fixed focal length lens, Barrington, NJ, USA) approximately 0.45 m above the patient during open-heart surgery to acquire videos of the beating heart at high temporal and spatial resolution. Four videos of 5 s each were recorded before and after PVR for each patient. The pre-PVR time point was at chest opening after freeing pericardial adhesions, whereas the post-PVR recording was performed 30 min after protamine sulfate was administered. In the post-PVR recording, care was taken to re-establish the same haemodynamic conditions observed in the pre-PVR recording, including central venous pressure, systolic arterial blood pressure, heart rate and ventilator settings. Right after completing the recordings, the tracking software Video Spot Tracker (Computer Integrated Systems for Microscopy and Manipulation, UNC, Chapel Hill, NC, USA) was used to process the videos because it placed a virtual marker on the epicardium on the first frame of the video. The virtual marker was positioned and optimized on the light spots present on the epicardial surface through a kernel (mathematical function). The frame-by-frame movement of the marker was recorded as a list of coordinates in *x* and *y* (Video 1).



Video 1: Video reproduces the tracking function in a patient with tetralogy of Fallot, head down. Red circle: virtual marker attached to the light on the epicardium; yellow line: the epicardial trajectory obtained by the marker movement.

Then, a custom-made algorithm, implemented in MATLAB® and based on Hamiltonian mechanics, elaborated those coordinates and provided the following cardiac kinematic parameters:

- Displacement: frame-by-frame estimate of the virtual marker movement. It is used to calculate the instantaneous movement of the epicardial tissue.
- Perimeter: the sum of all the virtual marker displacements during the cardiac cycles. It represents the entire movement of the epicardial tissue during the video recording and is used as an index of the ventricular compliance.
- Contraction velocity: the frame-by-frame estimation of the virtual marker velocity during the contraction phase. It estimates the instantaneous velocity of the epicardial tissue during the contraction phase.
- Cardiac fatigue: the mean acceleration of the virtual marker (of unitary mass) over all the cardiac cycles following the Hamiltonian mechanics. It calculates the epicardial tissue acceleration during the cardiac cycles.
- Energy: the mean kinetic energy of the virtual marker over all the cardiac cycles following the Hamiltonian mechanics. It estimates the heart energy expenditure during the video recording.

In this work, the perimeter of contraction was used instead of the displacement [10], because it estimates the ventricular compliance, which is clinically more relevant. As in the previous work [10], these parameters were converted from the pixel unit, the raw unit derived from the algorithm, to the SI-accepted unit (m).

Statistical analyses

The Pearson correlation was performed to evaluate the correlation between kinematic parameters and RVEDVi at MRI. After observation of a relationship between preoperative RVEDVi and intraoperative kinematic parameters recorded prior to PVR, the population was divided into 2 groups based on the RVEDVi

CONGENITAL

threshold of 147 ml/m^2, the median value of the parameter (<147 ml/m^2 for group 1 vs >147 ml/m^2 for group 2). Therefore, after checking the normality of the data for each parameter with the Kolmogorov–Smirnov test, the Wilcoxon matched pairs signed rank test or a two-way analysis of variance (ANOVA) for repeated measures with 'time' as the within-subject factor (2 levels: pre-PVR and post-PVR) and 'group' as the between-subject factor (2 levels: group 1 and group 2) was performed. A *post hoc* analysis was conducted using the Student's *t*-test with a Bonferroni correction for multiple comparisons where necessary. The Wilcoxon matched pairs signed-rank test or the paired *t*-test was used only for the parameters for which the two-way ANOVA for repeated measures could not be performed. A value of $P < 0.05$ was considered significant. The programme SPSS version 26 (IBM, Armonk, NY, USA) was used for the statistical analyses and GraphPad v.6 (GraphPad Software, Inc., La Jolla, CA, USA) was used to display the results.

RESULTS

Clinical outcome

All patients underwent surgical PVR on the beating heart: 5 patients received 23-mm stented bioprostheses; 2 patients, 25 mm; 2 patients, 21 mm; and 3 patients received a pulmonary homograft (size 27 mm in 2, and 25 mm in 1), respectively. A brief period of cardioplegic cardiac arrest was necessary to complete a right-sided Maze procedure using cryoablation catheters in 3 patients with a history of paroxysmal atrial fibrillation. There were no perioperative complications, except for 1 patient who experienced reversible subclinical hepatic dysfunction and 1 patient who required 2 days of inotropic support in the intensive care unit. Patients were discharged after a mean of 7.2 ± 2.4 days (5–12 days) of hospitalization, all in regular sinus rhythm. Transthoracic echocardiography prior to discharge documented the recovery of normal RV dimensions in 8 patients (67%) and moderate dilation in 4 (33%). Preserved (>50%) RV ejection fraction (RVEF) was found in 7 (58%) patients, mildly reduced (>40%) in 4 and severely reduced in 1 patient, who was 64 years old at PVR and the oldest in this series. Doppler studies showed the absence of PR in all patients and a mean peak trans-prosthetic pulmonary valve gradient of 16.5 ± 7.1 mmHg. During a mean follow-up of 24.6 ± 12.5 months (13–39 months), all patients were in New York Heart Association (NYHA) functional class I, except for 1 patient who was in NYHA functional class II. No patient experienced adverse cardiovascular events, and all were in regular sinus rhythm, free from oral anticoagulation, except for 1, who developed complete atrioventricular block 6 months after PVR and the Maze procedure, requiring a permanent pacemaker implant. The information from the follow-up echocardiogram was similar to that from the evaluation prior to discharge, with a mean peak trans-prosthetic pulmonary valve gradient of 18.5 ± 7.9 mmHg, preserved RVEF in 8 (67%) patients and mildly reduced RVEF in 3. RV dilation was absent or mild in 11 (92%) patients, whereas 1 patient in NYHA functional class II maintained moderate RV dilation and reduced RVEF.

Intraoperative cardiac kinematics

As previously observed [11], the pre-PVR Vi.Ki.E. parameters that yield the strongest clinical implications, namely energy and cardiac fatigue, along with the perimeter, were plotted against preoperative RVEDVi to investigate the degree of correlation. Figure 1 shows the correlation coefficient *r* for energy expenditure ($r = 0.59$), cardiac fatigue ($r = 0.62$) and the perimeter of contraction ($r = 0.64$) in the whole population. For the 3 kinematic parameters, a cut-off value of 147 ml/m^2 emerged, whereafter the curve describes an exponential relationship. Plotting of pre-PVR kinematic parameters against preoperative RVESVi, an index also recently proposed to guide PVR timing, did not depict a moderate-to-good correlation (data not shown).

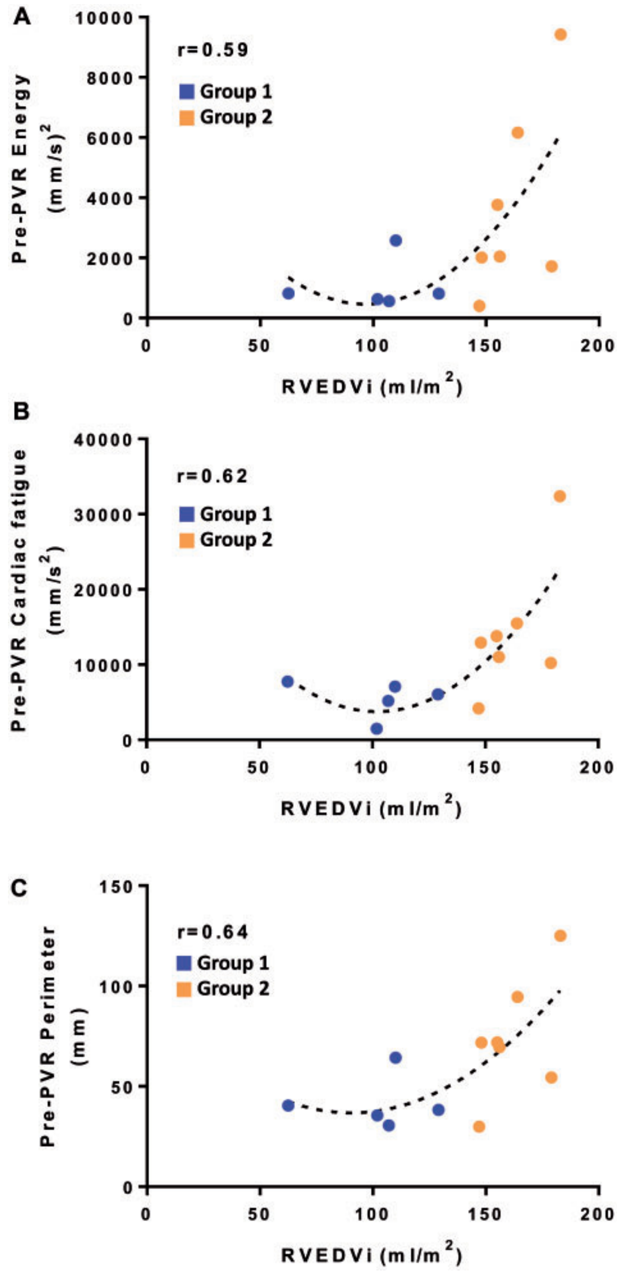


Figure 1: Correlation between video kinematic evaluation parameters and RVEDVi during pre-PVR in patients with tetralogy of Fallot. (**A**) Correlation between the average energy expenditure parameter against RVEDVi at pre-PVR. (**B** and **C**) Same as **A** but for cardiac fatigue and perimeter of contraction, respectively. Blue: patients with RVEDVi <147 ml/m^2; orange: patients with RVEDVi >147 ml/m^2. The dashed line represents the best fitting curve, which is an exponential with the correlation coefficient (*r*) displayed. PVR: pulmonary valve replacement; RVEDVi: right ventricular end-diastolic volume index.

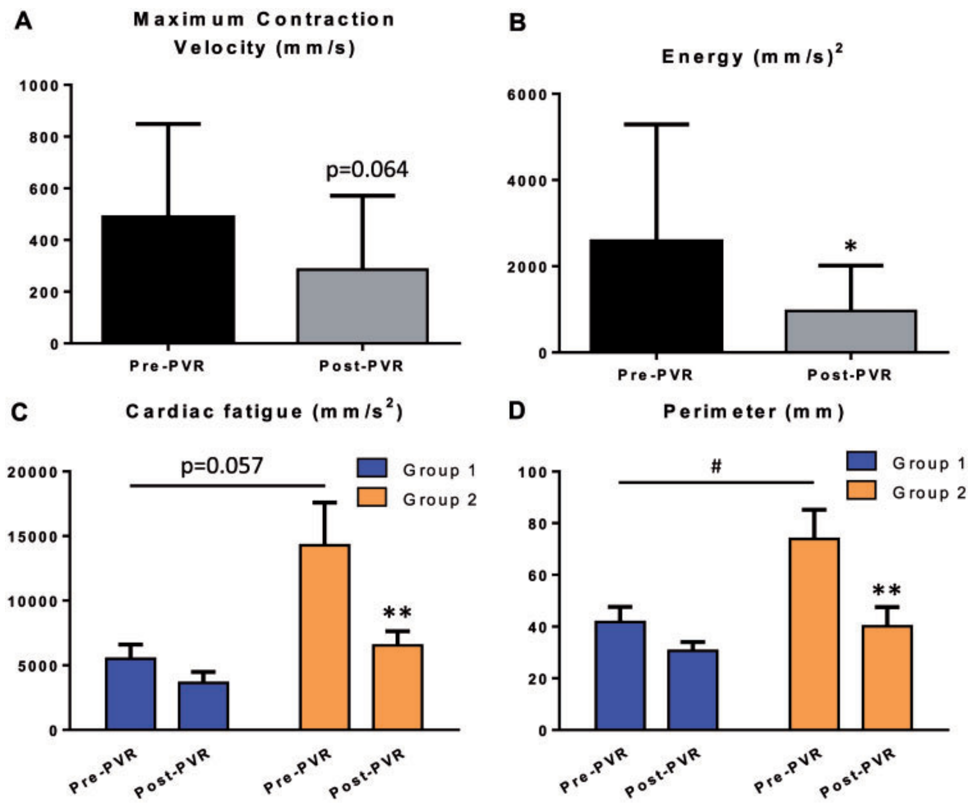


Figure 2: Kinematic parameters in patients with tetralogy of Fallot before and after PVR. (**A**) Maximum contraction velocity in patients with tetralogy of Fallot ($N = 12$) at both pre-PVR (black) and post-PVR (grey) time points. (**B**) Same as **A** but for the energy parameter. (**C**) Cardiac fatigue for group 1 (blue, $N = 5$) and group 2 (orange, $N = 7$). (**D**) Same as **C** but for the perimeter. Data are shown as mean ± SEM. *$P < 0.05$; **$P < 0.01$ versus pre-PVR. $^{\#}P < 0.05$ versus group 1. PVR: pulmonary valve replacement.

In Fig. 2A–D, the kinematic parameters of the 12 patients are displayed. All parameters examined decreased significantly after PVR. In detail, the maximum contraction velocity (Fig. 2A) decreased from 486.8 ± 104.2 to 285.4 ± 82.4 mm/s ($P = 0.064$) and the energy expenditure (Fig. 2B), from 2.55×10^3 ± 7.84×10^2 to 9.65×10^2 ± 3.03×10^2 mm^2/s^2 ($P = 0.016$). The two-way ANOVA for repeated measures yielded a main effect of both 'time' ($F[1,10] = 6.810$; $P = 0.026$) and 'group' ($F[1,10] = 5.635$; $P = 0.039$) on cardiac fatigue, reflecting a significant difference between pre-PVR and post-PVR (9900.86 ± 2039.27 vs 5090.30 ± 748.87) and between group 1 and group 2 (4578.30 ± 1877.18 vs 10412.86 ± 1586.51). Similarly, the two-way ANOVA revealed a main effect of 'time' ($F[1,10] = 13.13$; $P = 0.005$) on the perimeter, reflecting a significant difference between pre-PVR and post-PVR (57.84 ± 7.21 vs 35.40 ± 4.64). *Post hoc* analysis also revealed that group 2 showed almost significantly higher pre- ($P = 0.057$) and post-PVR ($P = 0.082$) cardiac fatigue compared to group 1. In addition, the average pre-PVR value of perimeter was higher ($P = 0.05$) in group 2 than in group 1. Finally, within group 2, we observed a significant decrease between pre- and post-PVR values of both cardiac fatigue ($P = 0.009$) and perimeter ($P = 0.002$). Therefore, all patients showed prompt recovery, whether partial or complete, of RV functional parameters.

Cardiac kinematics and right ventricular end-diastolic volume index

The patient population was thus stratified based on the relationship between pre-PVR kinematic parameters and preoperative RVEDVi, around a threshold value of 147 ml/m^2 (Fig. 1). Thereafter, significant differences emerged, showing that patients in group 1 were younger ($P = 0.005$), had a shorter time interval from ToF repair to PVR ($P = 0.03$), presented with greater RVESVi ($P = 0.054$) and had greater RVEF and left ventricular ejection fraction, albeit the difference was not significant (Table 2). To investigate possible differences in intraoperative experimental results based on timing of PVR (i.e. age at PVR, time interval of ToF repair and PVR), the kinematic parameters were also compared within the 2 groups for maximum contraction velocity and energy expenditure because they were not suitable for a two-way ANOVA comparison (see Statistical analyses). In group 1, a counterintuitive increasing trend for the maximum contraction velocity (from 3.20×10^2 ± 77.4 to 3.44×10^2 ± 189 mm/s) (Fig. 3A) and a decreasing trend for the energy expenditure (from 1.08×10^3 ± 3.78×10^2 to 9.65×10^2 ± 5.97×10^2) (Fig. 3C) emerged. The maximum contraction velocity result was probably influenced by 1 patient experiencing reversible atrial tachycardia after PVR. In group 2, the maximum contraction velocity significantly decreased from 6.07×10^2 ± 159.8 to 2.43×10^2 ± 60.18 mm/s ($P = 0.037$) (Fig. 3B) and the energy expenditure from 3.65×10^3 ± 1.19×10^3 to 9.65×10^2 ± 3.47×10^2 mm^2/s^2 ($P = 0.024$) (Fig. 3D).

When comparing the post-PVR kinematics between the 2 groups, we found that only cardiac fatigue was significantly higher in group 2 ($P = 0.001$) (data not shown).

Finally, in order to offer prognostic insight about the timing for PVR, the difference of the recovery between pre- and post-PVR for the parameters that yield the strongest clinical implication

Table 2: Demographic and magnetic resonance imaging variables stratified by right ventricular end-diastolic volume index at pre-operative assessment

	RVEDVi < 145 ml/m^2			RVEDVi > 145 ml/m^2			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	*P*-value
BSA (m^2)	1.2 ± 0.4	1.3	0.73–1.61	1.8 ± 0.1	1.86	1.64–1.97	0.025
Age at PVR (years)	11.2 ± 5.0	10	6.0–19.0	38.4 ± 17.0	39	20.0–64.0	0.005
ToF to PVR (years)	11.0 ± 5.2	10	6.0–19.0	30.1 ± 11.3	25	18.0–48.0	0.03
RVESVi (ml/m^2)	53.0 ± 32.4	48	12.5–102.0	91.5 ± 12.7	94.5	72–104	0.054
RVEF (%)	57.5 ± 13.6	55	42–79	44.0 ± 6.3	43	37–52	0.1
LVEF (%)	56.4 ± 4.5	55	51–62	52.5 ± 6.8	54	42–62	0.18

BSA: body surface area; LVEF: left ventricular ejection fraction; PVR: pulmonary valve replacement; RVEDVi: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; RVESVi: right ventricular end-systolic volume index; ToF: tetralogy of Fallot.

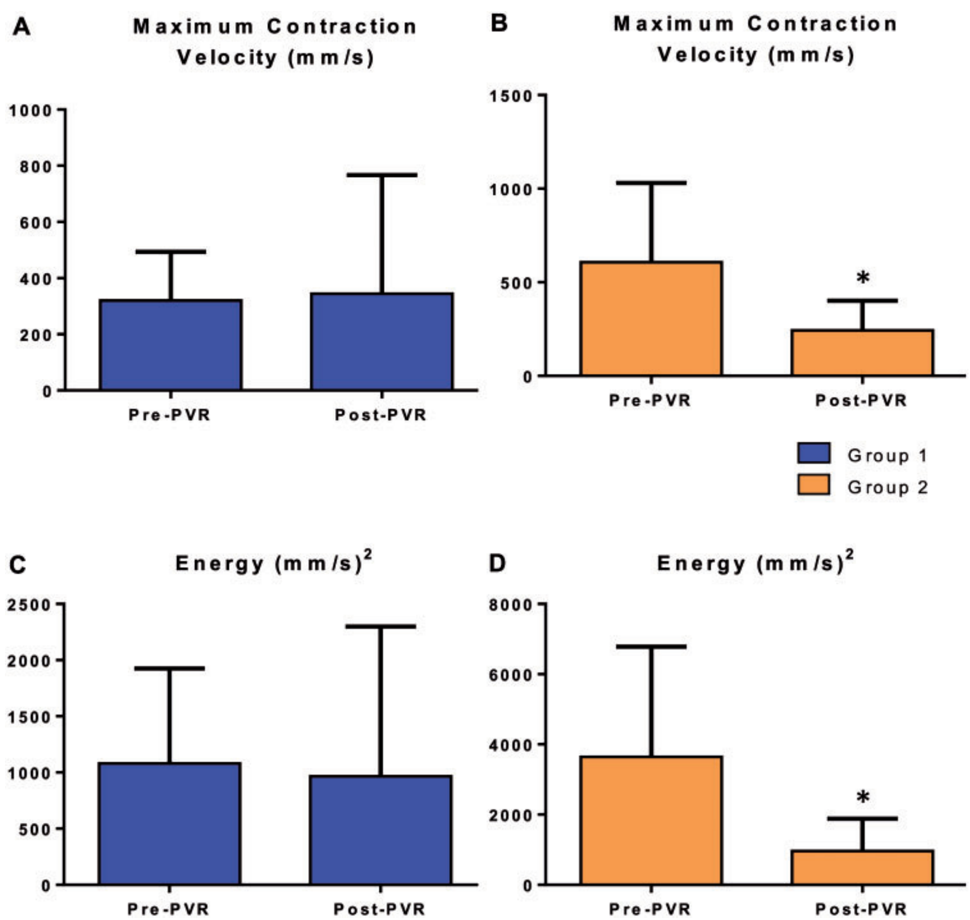


Figure 3: Maximum contraction velocity and energy in groups 1 and 2 before and after PVR. (**A**) Maximum contraction velocity in group 1 (blue, $N = 5$) before and after PVR (pre- and post-PVR time points, respectively). (**B**) Same as **A** but for group 2 (orange, $N = 7$) at pre- and post-PVR. (**C** and **D**) Same as **A** and **B** but for the energy parameter. Data are shown as mean ± SEM. *$P < 0.05$ versus pre-PVR. PVR: pulmonary valve replacement.

was compared in the 2 groups (Fig. 4A–C). Patients in group 2 showed greater relative recovery compared to those in group 1. In detail, the energy expenditure decreased by 58% vs 31%, cardiac fatigue by 45% vs 35% and perimeter of contraction by 41% vs 25%. However, patients referred later for PVR (group 2) showed greater variability in postoperative outcomes (Fig. 4).

DISCUSSION

This experimental study shows that intraoperative video kinematics can describe early RV functional recovery after PVR in patients with ToF. Furthermore, the current results provide insight into factors influencing prompt ventricular recovery. Accordingly,

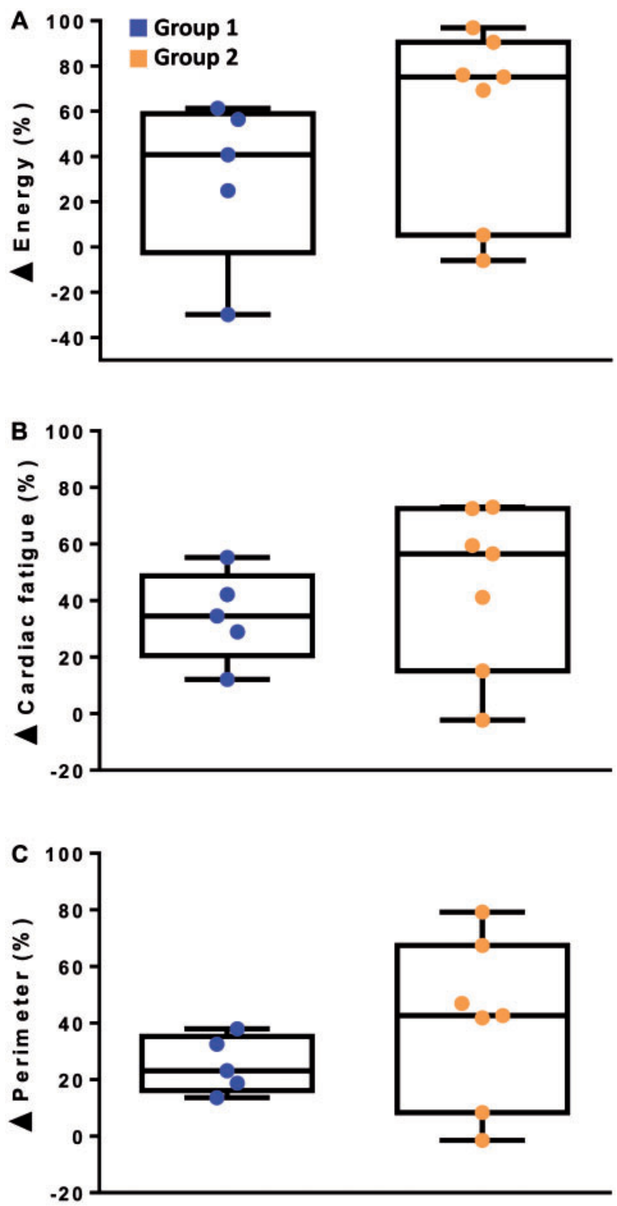


Figure 4: Distribution of percentage changes (Δ%) in energy, cardiac fatigue and perimeter for both group 1 and group 2. (**A**) The percentage changes (Δ%) were calculated as the difference between the values of energy at pre-PVR and post-PVR for both group 1 and group 2. (**B** and **C**) same as **A** but for cardiac fatigue and perimeter. PVR: pulmonary valve replacement.

RVEDVi lower than 147 ml/m^2 at preoperative MRI, a surrogate for earlier timing of PVR in the present work, is associated with intraoperative RV functional recovery.

Our experience allowed us to corroborate the preliminary observation from a safety and efficacy study, whereby a correlation was suggested between preoperative RVEDVi at MRI and the kinematic parameters of cardiac fatigue and energy expenditure in patients with preoperative RV volumes lower than those that are the current 'proactive' recommendations for surgery [11]. It is evident that long-standing RV volume overload due to PR is directly correlated with preoperative RV dysfunction, as assessed by intraoperative video kinematic analysis (Fig. 1). Interestingly, the correlation with cardiac fatigue, energy expenditure and ventricular compliance presents with a dichotomous behaviour with a watershed around an RVEDVi of 150 ml/m^2.

Our entire patient population showed prompt improvement in all kinematic parameters after PVR with a significant decrease in maximum contraction velocity, cardiac fatigue, energy consumption and, indirectly, increase in ventricular compliance (reduction of perimeter of contraction). These changes may be explained by the Frank-Starling law, which asserts that a decrease in ventricular preload is followed by a reduction of the force generated [13], in line with the reduction of cardiac fatigue and of energy consumption. The acute preload reduction right after PVR leads to a less stretched ventricle and indirectly improves ventricular compliance, herein measured using the perimeter of contraction. Finally, the maximum contraction velocity is reduced because of the force–velocity relationship of the Frank-Starling law, which states that, after a decrease in preload, cardiac muscle fibres will have a lower velocity of shortening. The decrease in preload after PVR not only affects the right ventricle but, indirectly, also the left ventricle [14]. The interventricular interactions are regulated by the changes in chamber pressure and volume and anatomically by the pericardium, interventricular septum and myocardial tracts linking the ventricles [15]. In the open-chest setting, the interaction between ventricles is important in determining the position of the interventricular septum during diastole. Physiologically, the position of the septum is determined by the difference in the pressures on both sides. Hence, pathological conditions like ToF characterized by increased RV end-diastolic pressure and chamber enlargement determine a septal shift towards the left ventricle, thereby hampering its mechanical performance. Therefore, any decrease in RV end-diastolic pressure after PVR may also lead to an improvement in the mechanics of the left ventricle.

However, patients presenting with RVEDVi greater than 147 ml/m^2 undoubtedly had a distinct behaviour compared with those with lower RV volume overload. This situation was evidenced not only by the worse kinematic performance prior to PVR, but also by the observation that recovery of baseline kinematic functional parameters was not always complete and was, most notably, less predictable. Considering that the RVEDVi threshold value clearly separated younger patients with a shorter time interval between ToF repair and PVR, from our experimental study, we infer that recovery of the RV functional parameter directly depends on the timing of the PVR. The present results agree with prior experimental findings using cardiac catheterization and MRI, where rapid decline in RV power and efficiency were shown at cut-off values of 139 ml/m^2 RVEDV and 75 ml/m^2 RVESVi [8].

Retrospective studies and meta-analyses have been unable to unravel the issue of benefits and timing of PVR after ToF repair, possibly due to limitations inherent with study design such as the heterogeneity of the patient population, overlap of historical and current patients, variability in operative techniques and outcome [1, 2, 16]. Although the issue of PVR timing in current clinical practice depends on a variety of parameters, including symptoms, exercise testing, RV and left ventricular function and RV volumes at MRI, previous clinical studies support the present experimental analysis. One prospective study has identified thresholds for complete RV remodelling at MRI (RVEDVi < 158 ml/m^2; RVESVi < 82 ml/m^2), which closely mirror our findings [5]. Furthermore, a previous observational study reporting on a patient population comparable to the one herein (relative to age at PVR, time of original repair and preoperative MRI profile) has shown how more proactive indications (RVEDVi < 150 ml/m^2) may afford negligible early and late mortality, recovery of RV volumes, improvement in biventricular function and normalization of V_E/V_{CO2} [4]. Finally, there is more recent evidence supporting

CONGENITAL

the inference that earlier timing of PVR may reduce the risk of malignant arrhythmias and death after PVR [17, 18].

Limitations

This study has some limitations. The patient cohort size is partly due to the stringent selection criteria. In addition, 3 patients in group 2 required a brief period of myocardial ischaemia so we could perform a right-sided Maze procedure. Although the kinematic results in the latter patients did not diverge significantly from those in patients having a completely beating heart operation (data not shown), an influence on the experimental results cannot be ruled out. Furthermore, a limitation of the Vi.Ki.E. evaluation is the use of a single 2-dimensional camera to record the 3-dimensional movement of the heart. Therefore, the present results may represent a simplification of kinematics analysis, albeit necessary to derive translational inferences on the impact of surgery on RV functional properties.

Conversely, the present technique may offer some advantages over echocardiography and MRI when assessing patients undergoing PVR. Compared with MRI, PVR allows real-time, cost-effective patient evaluation during the acute phase. Compared with transoesophageal echocardiography, it is non-invasive, contactless and less operator-dependent due to the algorithm-driven evaluation. Other advantages compared to both techniques are the higher spatial and temporal resolutions, the image quality and the RV mechanical quantitative assessment. Future developments related to the current observations include follow-up MRI and exercise testing to assess late clinical implications of intraoperative findings.

CONCLUSIONS

Vi.Ki.E. is an experimental technique able to describe intraoperative RV functional changes in patients with ToF undergoing PVR. The results herein offer further insight into the extent of RV recovery. Accordingly, prompt recovery can be expected in patients with preoperative end-diastolic volume less than 147 ml/m^2, suggesting earlier timing of PVR.

Funding

The current study was supported by institutional funds from the University of Verona and the University of Parma FFBR-MIUR-2017, FIL-2018 to M.M.

Conflict of interest: none declared.

Author contributions

Giacomo Rozzi: Data curation; Formal analysis; Investigation; Writing—original draft. **Francesco Paolo Lo Muzio:** Data curation; Formal analysis; Investigation; Writing—original draft. **Lorenzo Fassina:** Methodology; Validation. **Stefano Rossi:** Validation; Visualization. **Rosario Statello:** Data curation; Formal analysis. **Camilla Sandrini:** Data curation; Formal analysis. **Maira Laricchiuta:** Data curation; Formal analysis. **Giuseppe Faggian:** Funding acquisition; Project administration. **Michele Miragoli:** Funding acquisition; Supervision; Writing—review & editing. **Giovanni Battista Luciani:** Conceptualization; Investigation; Supervision; Writing—original draft; Writing—review & editing.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Hitendu Hasmukhlal Dave, Martin M. Kostolny, James A. Quintessenza and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Bokma JP, Geva T, Sleeper LA, Babu Narayan SV, Wald R, Hickey K *et al.* A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart 2018;104:738–44.

[2] Ferraz Cavalcanti PE, Sá MP, Santos CA, Esmeraldo IM, de Escobar RR, de Menezes AM *et al.* Pulmonary valve replacement after operative repair of tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol 2013;62:2227–43.

[3] Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM *et al.* 2018 AHA/ACC Guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e81–192.

[4] Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G *et al.* Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182–90.

[5] Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC *et al.* Immediate and midterm cardiac remodeling after surgical pulmonary valve replacement in adults with repaired tetralogy of fallot: a prospective cardiovascular magnetic resonance and clinical study. Circulation 2017;136:1703–13.

[6] Lee C, Choi ES, Lee CH. Long-term outcomes of pulmonary valve replacement in patients with repaired tetralogy of Fallot. Eur J Cardiothorac Surg 2020;58:246–52.

[7] Tang D, Del Nido PJ, Yang C, Zuo H, Huang X, Rathod RH *et al.* Patient-specific MRI-based right ventricle models using different zero-load diastole and systole geometries for better cardiac stress and strain calculations and pulmonary valve replacement surgical outcome predictions. PLoS One 2016;11:e0162986.

[8] Fogel MA, Sundareswaran KS, de Zelicourt D, Dasi LP, Pawlowski T, Rome J *et al.* Power loss and right ventricular efficiency in patients after tetralogy of Fallot repair with pulmonary insufficiency: clinical implications. J Thorac Cardiovasc Surg 2012;143:1279–85.

[9] Kopic S, Stephensen SS, Heiberg E, Arheden H, Bonhoeffer P, Ersbøll M *et al.* Isolated pulmonary regurgitation causes decreased right ventricular longitudinal function and compensatory increased septal pumping in a porcine model. Acta Physiol (Oxf) 2017;221:163–73.

[10] Fassina L, Rozzi G, Rossi S, Scacchi S, Galetti M, Lo Muzio FP *et al.* Cardiac kinematic parameters computed from video of *in situ* beating heart. Sci Rep 2017;7:46143.

[11] Rozzi G, Lo Muzio FP, Sandrini C, Rossi S, Fassina L, Faggian G *et al.* Real-time video kinematic evaluation of the in situ beating right ventricle after pulmonary valve replacement in patients with tetralogy of Fallot: a pilot study. Interact CardioVasc Thorac Surg 2019;29:625–31.

[12] Bodhey NK, Beerbaum P, Sarikouch S, Kropf S, Lange P, Berger F *et al.* Functional analysis of the components of the right ventricle in the setting of tetralogy of Fallot. Circ Cardiovasc Imaging 2008;1:141–7.

[13] Amiad Pavlov D, Landesberg A. The cross-bridge dynamics is determined by two length-independent kinetics: implications on muscle economy and Frank-Starling Law. J Mol Cell Cardiol 2016;90:94–101.

[14] Belenkie I, Smith ER, Tyberg JV. Ventricular interaction: from bench to bedside. Ann Med 2001;33:236–41.

[15] Friedberg MK. Imaging right-left ventricular interactions. JACC Cardiovasc Imaging 2018;11:755–71.

[16] Geva T, Mulder B, Gauvreau K, Babu-Narayan SV, Wald RM, Hickey K *et al.* Preoperative predictors of death and sustained ventricular tachycardia after pulmonary valve replacement in patients with repaired tetralogy of fallot enrolled in the INDICATOR cohort. Circulation 2018;138:2106–15.

[17] Romeo JLR, Takkenberg JJM, Cuypers JAAE, de Groot NMS, van de Woestijne P, Bruining N *et al.* Timing of pulmonary valve replacement in patients with corrected Fallot to prevent QRS prolongation. Eur J Cardiothorac Surg 2020;58:559–66.

[18] Dorobantu DM, Sharabiani MTA, Taliotis D, Parry AJ, Tulloh RMR, Bentham JR *et al.* Age over 35 years is associated with increased mortality after pulmonary valve replacement in repaired tetralogy of Fallot: results from the UK National Congenital Heart Disease Audit database. Eur J Cardiothorac Surg 2020;58:825–31.