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### Authors

Kohi, Maureen P  
Ordovas, Karen G  
Naeger, David M  
et al.

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# CMR assessment of right ventricular function in patients with combined pulmonary stenosis and insufficiency after correction of tetralogy of Fallot

Maureen P Kohi<sup>1</sup>, Karen G Ordovas<sup>1</sup>, David M Naeger<sup>1</sup>,  
Alison Knauth Meadows<sup>2</sup>, Ellyse Foster<sup>2</sup> and Charles B Higgins<sup>1</sup>

## Abstract

**Background:** Tetralogy of Fallot (TOF) is one of the most common types of congenital heart disease and requires prompt surgical correction. Post-correction pulmonary insufficiency (PI) often ensues in adulthood. At times, the PI is accompanied by residual pulmonary stenosis (PS). Little is known regarding right ventricular (RV) function in the setting of combined PS and PI.

**Purpose:** To compare cardiac magnetic resonance (CMR) parameters for the assessment of RV function between patients with combined pulmonary stenosis and pulmonary insufficiency (PSPI) and isolated PI following surgical repair of TOF.

**Material and Methods:** Retrospective review of patients with comparable corrected TOF and similar PI was performed. Seventeen patients (median age, 24 years; range, 10–52 years) had combined PSPI and 30 patients (median age, 30 years; range, 6–70 years) had isolated PI. Cine magnetic resonance (MR) images (Philips Medical Systems, Best, The Netherlands) in the short-axis plane were used to calculate end-systolic, end-diastolic, and stroke volumes (RVESV, RVEDV, RVSV) and to measure RV wall thickness. Velocity-encoded cine MR images were used to measure pulmonary regurgitation fraction (PRF) by calculating the ratio of backward flow and total forward flow, obtained from the main pulmonary flow analysis. Peak pressure gradient across the pulmonary valve was obtained from spectral Doppler echocardiography.

**Results:** RVEF was  $51 \pm 8\%$  in the PSPI patients and  $39 \pm 11\%$ , in the patients with isolated PI ( $P = 0.001$ ). Additionally, RV wall thickness was  $5.2 \pm 0.8$  mm in the PSPI patients compared to  $2.6 \pm 0.9$  mm in the isolated PI patients ( $P = 0.001$ ). RVESVi and RVEDVi were significantly lower ( $P < 0.05$ ) in patients with combined PSPI ( $60 \pm 21$  mL/m<sup>2</sup>,  $121 \pm 35$  mL/m<sup>2</sup>, respectively) compared to the patients with isolated PI ( $95 \pm 48$  mL/m<sup>2</sup>,  $152 \pm 61$  mL/m<sup>2</sup>, respectively).

**Conclusion:** RV function is preserved in patients with PSPI when compared to patients with PI following surgical repair of TOF.

## Keywords

Cardiac, magnetic resonance imaging (MRI), heart, pediatrics, congenital, anatomy

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## Introduction

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease (1). Following surgical correction, many patients have moderate to severe pulmonary insufficiency (PI) with minimal or no residual pulmonary stenosis (PS). Chronic PI plays a pivotal role in right ventricular (RV) dilatation and dysfunction, following surgical repair of RV outflow

<sup>1</sup>Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

<sup>2</sup>Department of Medicine, University of California, San Francisco, CA, USA

### Corresponding author:

Maureen P Kohi, Department of Radiology and Biomedical Imaging, University of California, 505 Parnassus Ave, San Francisco, CA 94143, USA.

Email: Maureen.kohi@ucsf.edu

tract (RVOT) obstruction (2–8). Most patients following surgical correction of TOF experience a prolonged asymptomatic phase. However, in older childhood and adulthood, morbidity and mortality occurs secondary to RV dysfunction, arrhythmias, and sudden death (9). Without pulmonary valve (PV) replacement, irreversible RV dysfunction may occur (10).

Using magnetic resonance imaging (MRI) and conductance catheter techniques, a study using a growing pig model demonstrated that chronic PI impairs biventricular systolic function, RV myocardial contractility, and left ventricular (LV) diastolic performance (11). Another study by the same group using the same techniques demonstrated that combined pulmonary stenosis and pulmonary insufficiency (PSPI) results in sparing of RV myocardial contractility when compared to isolated PI (12).

Little is known regarding the combined effect of PSPI on RV function in humans. In the case of combined PSPI, the expected PI seen in the setting of TOF correction is accompanied by residual stenosis of the RVOT. This is in contrast to the majority of patients following TOF correction who do not have residual RVOT stenosis and only have isolated PI. We hypothesize that patients with combined PSPI will have better RV function when compared to patients with isolated PI. If combined PSPI is proved to be protective of RV function, the current surgical approach for the correction of RVOT obstruction may need to be reassessed.

## Material and Methods

### Patients

Our study was approved by our Institutional Review Board. Informed consent requirement was waived. Through our cardiac MRI database, we retrospectively identified 54 consecutive patients with history of surgical correction of TOF without PV replacement. We excluded patients whose heights and weights were not available and a body surface area calculation could not be performed. A total of 47 patients were included in the study. Of those 47 patients, 17 patients had combined PSPI defined by anatomic stenosis of the RVOT identified on cardiac magnetic resonance imaging (CMR) and any degree of PI. The remaining 30 patients had isolated PI. All patients had Doppler echocardiograms performed within 6 months of the CMR.

### MRI

For all CMR studies, a 1.5-Tesla Intera CV MRI scanner (Philips Medical Systems, Best, The Netherlands) with a phased-array cardiac coil was used. Steady-state free precession (SSFP) cine images were obtained in the

short-axis plane encompassing the entire heart with a slice thickness of 8 mm and no gap. Sixteen phases in the cardiac cycle were obtained (TR, 1.4–3.0 ms; TE, 1.4–3.2 ms; FA, 450°).

Velocity-encoded cine MR images were obtained perpendicular to the direction of blood flow in the main pulmonary artery, just above the expected location of the PV, with a slice thickness of 8 mm. Sixteen frames were acquired per average cardiac cycle (TR, 15–30 ms; TE, 5.3–7.5 ms; FA, 150°; FOV, 140–300 mm). Velocity encoding gradients were set to acquire a dynamic range from –400 to 400 cm/s, with sequential increase in maximum range if aliasing artifact was encountered.

### MR analysis

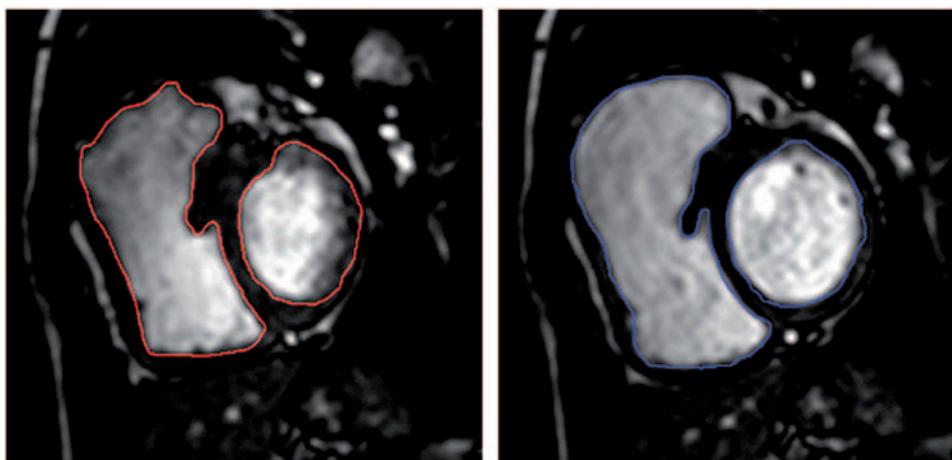
Volumetric analysis was performed on a separate workstation (View Forum, Philips Medical Systems), using the cine MR images in the short-axis plane and manually outlining the endocardial contour of the RV and LV on the end-diastolic and end-systolic frames (Fig. 1). This was done in all slices encompassing the volume of both ventricular chambers in order to calculate the end-diastolic volume (EDV) and end-systolic volume (ESV). Care was taken to separate the RVOT from the right atrium by toggling back and forth on the cine images. Measurements were performed by a single fellowship-trained cardiac and pulmonary attending radiologist who had been in training for >5 years.

For flow analysis, a region of interest was manually delineated around the main pulmonary artery in the 16 phase-images. This region of interest provides a cross-sectional area and average velocity. The product of these two measurements represents instantaneous blood flow. Integration of the flow *versus* time curve yields volume flow for an average cardiac cycle. Short-axis cine images were also used to identify anatomic RVOT stenosis.

Short-axis cine images were used to manually measure the thickness of the diaphragmatic portion of the RV wall on a mid-ventricular frame at end diastole. The diaphragmatic portion of the RV was chosen as its thickness is least likely affected by the different corrective surgeries and it is less influenced by thickened trabecula compared to the anterior and lateral walls.

### MR parameters

Pulmonary regurgitation fraction (PRF) was calculated as the ratio of backward flow and total forward flow, obtained from the main pulmonary flow analysis. The difference of EDV less ESV yielded stroke volume (SV) for both ventricular chambers. RV and LV EFs were calculated by dividing SV by EDV. Volumes were



**Fig. 1.** Volumetric analysis. The short-axis cine MR images were used to perform volumetric analysis through manual outlining of the endocardial contour of the right and left ventricles in end-diastolic (left) and end-systolic (right) frames.

adjusted for body surface area providing end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and stroke volume index (SVi).

### Echocardiogram

Peak transpulmonary valve velocity was measured by continuous wave Doppler echocardiography in the parasternal short-axis plane. The probe size was chosen based on patient size. The net peak instantaneous pressure gradient across the PV was calculated using the modified Bernoulli equation. The degree of PS was classified as mild if the transpulmonary valve gradient was  $\leq 40$  mmHg and moderate if the gradient was  $>40$  mmHg and  $\leq 60$  mmHg (13).

### Statistical analysis

Patient age and years since TOF repair at the time of the CMR were compared between the PSPI and isolated PI using the Wilcoxon rank sum test. Gender distribution and surgical techniques of TOF correction for the patients in each group were compared with the chi square test. CMR parameters are reported as a mean  $\pm$  SD and were compared with the Student's t-test. A  $P$  value of  $<0.05$  was considered statistically significant.

### Results

The study groups were similar in age range, gender distribution, time since surgical correction, and surgical techniques for TOF repair. There were no significant differences for these characteristics between the two groups. The mean PRF for the combined PSPI group was  $34 \pm 14\%$  compared to  $41 \pm 17\%$  for the isolated PI group ( $P=0.16$ ). The mean peak transpulmonary

valve gradient in the combined PSPI group was  $36 \pm 10$  mmHg compared to  $17 \pm 6$  mmHg in the isolated PI group ( $P<0.001$ ). All patients in the PSPI group had mild or moderate PS. None of the patients in the PSPI group had a transpulmonary valve gradient  $>60$  mmHg to qualify for a severe degree of PS. None of the patients in the isolated PI group had evidence of a hemodynamically significant transpulmonary valve gradient. In the isolated PI group, two patients had a small residual ventricular septal defect (VSD) located at the superior aspect of the VSD repair patch. Neither patient demonstrated hemodynamically significant left-to-right shunting based on CMR flow calculations. Seven patients in the isolated PSPI group and four patients in the combined PSPI group demonstrated mild narrowing of a branch pulmonary artery. None of these patients demonstrated a  $>10\%$  difference in blood flow to the left or right pulmonary artery based on cine phase-contrast CMR. In both groups, when present, tricuspid regurgitation was trivial. Patients' characteristics are shown in Table 1.

Table 2 shows the comparison of CMR parameters between the two study groups. RVEF was significantly higher ( $P<0.05$ ) in patients with combined PSPI ( $51 \pm 8\%$ ) when compared to patients with isolated PI ( $39 \pm 11\%$ ). In addition, RVESVi and RVEDVi were significantly lower ( $P<0.05$ ) in patients with combined PSPI ( $60 \pm 21$  mL/m<sup>2</sup>,  $121 \pm 35$  mL/m<sup>2</sup>, respectively) compared to the patients with isolated PI ( $95 \pm 48$  mL/m<sup>2</sup>,  $152 \pm 61$  mL/m<sup>2</sup>, respectively). There was no statistically significant difference in RVSVi, LVEF, LVESVi, LVEDVi, or LVSVi between the two groups. RV wall thickness measured at the diaphragmatic portion was significantly increased ( $P<0.05$ ) in patients with combined PSPI ( $5.2 \pm 0.8$  mm) when compared to patients with isolated PI ( $2.6 \pm 0.9$  mm) (Figs. 2 and 3).

**Table 1.** Patient characteristics.

Variables	PSPI (n = 17)	PI (n = 30)	P value
Age at CMR (years), median (range)	24 (10–52)	30 (0.25–70)	0.28
Male gender, n (%)	7 (41)	16 (53)	0.70
Median time from TOF repair to CMR (years), (range)	21 (8–47)	22 (6–53)	0.63
Type of TOF repair, n (%)			0.11
Transannular patch	9 (52)	22 (73)	
RV-PA conduit	4 (24)	1 (3)	
Non-transannular patch	4 (24)	7 (24)	
Pulmonary regurgitant fraction, mean $\pm$ sd (%)	34 (14)	41 (17)	0.16
Transpulmonary valve gradient, mean $\pm$ sd (mmHg)	36 (10)	17 (6)	<0.001

PI, pulmonary insufficiency; PSPI, pulmonary stenosis and pulmonary insufficiency; RV-PA conduit, right ventricle to pulmonary artery conduit; sd, standard deviation; TOF, tetralogy of Fallot.

**Table 2.** MRI parameters.

Variables	PSPI (n = 17) Mean $\pm$ sd	PI (n = 30) Mean $\pm$ sd	P value
Global right ventricular variables			
RVEF (%)	51 (8)	39 (11)	<0.001
RVESVi (mL/m <sup>2</sup> )	60 (21)	95 (48)	<0.01
RVEDVi (mL/m <sup>2</sup> )	121 (35)	152 (61)	0.03
RVSVi (mL/m <sup>2</sup> )	61 (21)	57 (23)	0.54
RVWT (mm)	5.2 (0.8)	2.6 (0.9)	<0.001
Global left ventricular variables			
LVEF (%)	61 (6)	56 (12)	0.11
LVESVi (mL/m <sup>2</sup> )	31 (7)	37 (43)	0.47
LVEDVi (mL/m <sup>2</sup> )	79 (18)	79 (41)	0.98
LVSVi (mL/m <sup>2</sup> )	48 (11)	42 (11)	30.11

LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; PI, pulmonary insufficiency; PSPI, pulmonary stenosis and pulmonary insufficiency; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; RVSVi, right ventricular stroke volume index; RVWT, right ventricular wall thickness; sd, standard deviation.

## Discussion

Survival after total correction of TOF has been excellent during the past three decades and there is now a large population of older children and adults with corrected TOF. Most reported causes of long-term patient morbidity and mortality following surgical correction of TOF has resulted from RV dysfunction (14). The current study demonstrates that RV function, as measured by RVEF, RVESVi, and RVEDVi, following surgical correction of TOF with similar degree of PI, is better in patients with combined PSPI when compared to patients with isolated PI. This finding is in accordance with a previous study using a growing pig

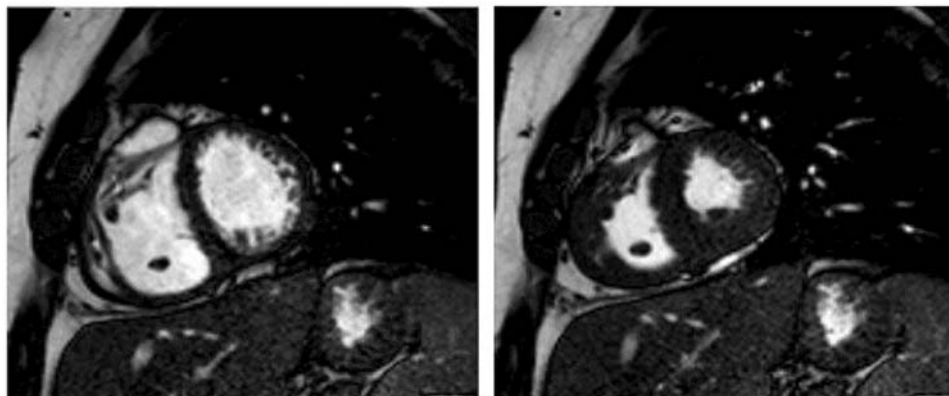
model which demonstrated better RV myocardial contractility in the setting of combined PSPI when compared to isolated PI (12).

In our study, all patients with combined PSPI had mild to moderate PS. While transpulmonary pressure gradient across the PV was reported for the two groups, the small gradient generated in the isolated PI group was likely attributed to the large RV stroke volume during the ejection period accompanying moderate to severe PI. While RVSVi appears greater in the isolated PI group, this difference was not statistically significant. None of the patients in the isolated PI group demonstrated anatomic stenosis of the RVOT on MRI. Therefore, the presence of morphologic RVOT stenosis and a significant difference in transpulmonary pressure gradient across the PV distinguishes the patients in the combined PSPI group from the patients in the isolated PI group.

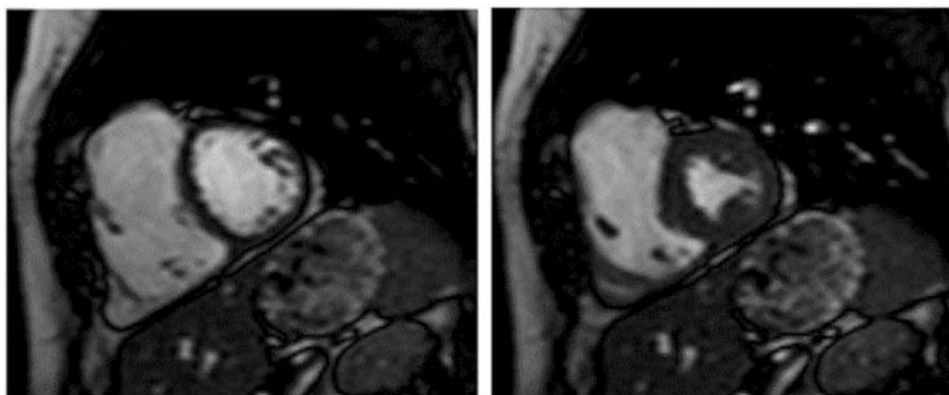
Preserved RV function in the setting of combined PSPI suggests that stenosis, in addition to insufficiency, promotes compensatory RV myocardial hypertrophy, limiting RV dilatation and enhancing myocardial contractility. In the current study, RV wall thickness measured at the diaphragmatic portion of the RV was increased in patients with combined PSPI when compared to patients with isolated PI suggesting the presence of RV hypertrophy in this group. RV myocardial hypertrophy in patients with moderate to severe PI seems to limit RV enlargement and results in preserved RVEF. This finding brings into question the accepted belief that surgical correction of TOF should completely relieve RVOT obstruction.

The limitations of this study included the retrospective nature of the investigation. While chart review was undertaken to acquire data regarding patient characteristics, necessary data were not available in all cases to characterize patients' clinical status or exercise tolerance. It should be noted that the different surgical techniques for TOF correction can be a confounder on the





**Fig. 2.** Right ventricular wall thickness in combined pulmonary stenosis and pulmonary insufficiency (PSPI). Short-axis cine images in end-diastolic (left) and end-systolic (right) frames demonstrate the increased thickness of the diaphragmatic portion of the right ventricular wall in a patient combined PSPI. Note the greater reduction in right ventricular volume during the cardiac cycle compared to the patient with isolated pulmonary insufficiency (Figure 3).



**Fig. 3.** Right ventricular wall thickness in isolated pulmonary insufficiency (PI). Short-axis cine images in end-diastolic (left) and end-systolic (right) frames demonstrate the thickness of the diaphragmatic portion of the right ventricular wall in a patient with isolated PI.

RV function reported, particularly in the setting of a transannular patch. However, the retrospective nature of the study and the small number of patients limit subgroup analysis. Since the CMR studies were performed over several years, different techniques were used to acquire the MR images. In addition, only 16 phases in the cardiac cycle were obtained for the cine images. This was the standard protocol at the institution at that time. However, in all cases a full set of short-axis cine MR images were available which could be used to quantify RV volumes and function. Moreover, phase-contrast cine images perpendicular to the long axis of the main pulmonary artery were available to quantify PI. The moderate size of the patient population in each group warrants further studies to substantiate the conclusions of the current study. Due to the small number of patients in the PI group, those patients with mild VSD or branch

pulmonary artery narrowing were not excluded. It was deemed that the VSD or the branch pulmonary artery narrowing was not hemodynamically significant in those cases. Further studies are needed to compare the exercise capacity in the two groups as well as long-term morbidity and survival.

The current approach for the treatment of TOF is complete surgical repair early in life (15). Different surgical maneuvers are performed to relieve the varying sites and severity of PS. It should be noted that studies which report good long-term outcome for patients following such corrective surgeries focus on the adaptive quality of the RV, in light of the impending PI (16,17). However, this is in direct contraindication to other studies which have demonstrated the deleterious effect of chronic PI on RV function (3–6). While most patients do well soon after surgical correction, in the setting of hemodynamically significant PI, some will develop RV

dysfunction in adulthood which increases late mortality primarily through an increased risk for sudden death and or RV failure. Such patients will subsequently need PV replacement in order to prevent RV failure. After PV replacement, RV function improves if the RVEDV and RVESV have not exceeded a critical value (18).

In conclusion, by demonstrating that patients with combined PSPI have better RV systolic function, it is suggested that PS may have a protective role in the setting of moderate to severe PI by promoting RV myocardial hypertrophy. As such, surgical approaches that aim to completely relieve the RVOT obstruction at the expense of substantial PI should be re-evaluated. Perhaps a mild degree of PS can be allowed at the initial surgical correction, knowing that RV function can be preserved in light of impending PI. Additionally, in the setting of preserved RV function such patients may benefit from delayed timing of PV replacement, which will lead to fewer surgical interventions in their lifetime. Further follow-up studies are required to substantiate the protective role of PS in the setting of PI.

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