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Improvement in left ventricular filling properties after relief of right ventricle to pulmonary artery conduit obstruction: contribution of septal motion and interventricular mechanical delay

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Aims To investigate the impact of relief of right ventricle (RV) to pulmonary artery (PA) conduit obstruction on septal motion and ventricular interaction and its functional implications for left ventricular (LV) filling properties.

Methods and results In 20 consecutive patients with congenital heart disease and RV to PA conduit obstruction, the following were prospectively assessed before and after percutaneous pulmonary valve implantation (PPVI): the septal curvature and LV volumes throughout the cardiac cycle by magnetic resonance imaging; RV to LV mechanical delay by 2D-echocardiographic strain imaging; and objective exercise capacity. Percutaneous pulmonary valve implantation led to a reduction in RV to LV mechanical delay (127.9 $\pm$ 50.9 vs. 37.7 $\pm$ 35.6 ms; $P < 0.001$) and less LV septal bowing in early LV diastole (septal curvature: -0.11 ± 0.11 vs. 0.07 ± 0.13 cm^{-1}; $P < 0.001$). Early LV diastolic filling (first one-third of diastole) increased significantly (17.5 $\pm$ 9.4 to 30.4 $\pm$ 9.4 mL/m^2; $P < 0.001$). The increase in early LV diastolic filling correlated with the reduction in RV to LV mechanical delay ($r = -0.68$; $P = 0.001$) and change in septal curvature ($r = 0.71$; $P < 0.001$). In addition, the improvement in peak oxygen uptake (56.0 $\pm$ 16.0 vs. 64.1 $\pm$ 13.7% of predicted; $P < 0.001$) was associated with the increase in early LV diastolic filling ($r = 0.69$; $P = 0.001$).

Conclusion Relief of RV to PA conduit obstruction significantly improves early LV filling properties. This is attributed to more favourable septal motion and reduction in interventricular mechanical delay.

Keywords Ventricular interaction • Interventricular mechanical delay • Right ventricle to pulmonary artery conduit • Septal motion • Congenital heart disease

Introduction

Right ventricle (RV) to pulmonary artery (PA) conduit obstruction is a common and clinically challenging problem in patients with congenital heart disease (CHD).[1,2] Conduit degeneration late after surgical repair adds to the cumulative haemodynamic burden on the RV with its well-recognized detrimental effects on RV function. However, the impact of unfavourable RV loading on left ventricular (LV) function in children and young adults with CHD is often not assessed and poorly understood.

We have previously shown that relief of conduit obstruction increases LV end-diastolic volume (EDV), suggesting improved LV filling.[3] Better LV filling can be partially attributed to better left atrial filling as a consequence of increased effective RV stroke volume (SV). However, the impact of altered ventricular interaction after conduit obstruction relief remains unknown.

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Previous studies in patients with RV pressure overload secondary to pulmonary hypertension have reported significant leftward ventricular septal bowing (LVSB) and impairment of LV filling characteristics.[4–7] This was thought to be due to interventricular dyssynchrony with RV to LV mechanical delay.[8,9]

The availability of a transcatheter technique [percutaneous pulmonary valve implantation (PPVI)] to relieve RV pressure overload[3,10] provides an elegant model to test whether some of the postulated causes of septal bowing can be reversed following relief of conduit obstruction, without the confounding effects of surgery.

The aim of this study was to investigate the potential impact of PPVI on septal motion and interventricular mechanical delay and its functional implications for early LV filling and exercise performance in patients with RV to PA conduit obstruction and CHD.

Methods

Patients and study protocol

In this prospective study, 20 consecutive patients were recruited. Inclusion criteria were the presence of pulmonary stenosis in the absence of significant pulmonary regurgitation. This was defined by a gradient across the RV to PA conduit >50 mmHg on echocardiography and <20% pulmonary regurgitation fraction [as assessed on magnetic resonance (MR) imaging]. Patients also had to fulfil clinical and morphological criteria for PPVI, as published previously.[10]

Valve implantation (Melody™, Medtronic Inc., Minneapolis, MN, USA) was performed under general anaesthesia. Pressure measurements were carried out before and immediately after PPVI as reported previously.[3,10] The following investigations were performed before and within 1 month after PPVI: MR imaging, echocardiographic studies, and cardiopulmonary exercise testing. The protocol for cardiopulmonary exercise testing has been described previously.[3] Written informed consent was obtained from patients and parents as appropriate. The Ethics Committees at the two contributing institutions approved the study protocol.

Magnetic resonance imaging

Magnetic resonance imaging was performed at 1.5 T (Avanto; Siemens Medical Systems, Erlangen, Germany) before PPVI and at a median of 4 days (range 1–34 days) after PPVI. Imaging protocols for assessment of bi-ventricular function and great vessel blood flow were described previously.[3]

Where pulmonary regurgitation was present, an effective RVSV was calculated to reflect the net forward blood flow into the PAs as follows: effective RVSV = RVSV − pulmonary regurgitant volume.

The amount of maximal LVSB was evaluated and quantified throughout the cardiac cycle for each phase (*Figure 1*). The septal curvature was measured at the level of the papillary muscles. This position was chosen in order to avoid confounding results caused by the presence of ventricular septal defect patches. Quantification of the septal curvature has been described previously by others.[6] The most extreme septal curvature was used for analysis, where a negative value represents leftward bowing of the septum into the LV cavity and a positive value indicates rightward bowing or a more physiological septal contour. Assessment of septal curvature was performed by one of the investigators (R.P.). In order to assess LV filling properties, LV volumes throughout the cardiac cycle were calculated. Early LV filling, defined as the increase in LV volume during the first one-third of diastole, and late diastolic filling (last two-thirds of diastolic filling) were calculated. Left ventricular volumes throughout the cardiac cycle were calculated by three of the investigators (P.L., R.P., and A.M.T.). Magnetic resonance measurements of LV volumes and septal curvatures were performed in a random and blinded fashion in all but two subjects, due to visible metal artefacts on MR short-axis views caused by the valved stent post-PPVI.

Echocardiography assessment

All patients had a transthoracic echocardiographic study (Vivid 7 GE Vingmed, Milwaukee, WI, USA) at the same time as the MR scan pre- and post-PPVI. This scan included assessment of trans-mitral flow patterns and early and late diastolic mitral annular velocities on spectral colour tissue Doppler echocardiography as described previously.[3] Colour tissue Doppler echocardiography was obtained from the apical four-chamber view. Regional longitudinal strain was determined placing the region of interest in the mid-segments of the RV free wall, septum, and the LV free wall. The time to peak strain (T_{peak}) from the onset of QRS was measured for the RV and LV free wall. Interventricular mechanical delay was defined as the difference in T_{peak} between the RV and the LV free wall as described previously.[11–13]

Timing parameters for mitral valve opening and for pulmonary and aortic valve opening and closure were obtained from pulsed-wave Doppler images of the LV inflow and RV and LV outflow, respectively. The time to peak septal bowing was assessed on echocardiographic mid-ventricular short-axis views on anatomical m-mode images. All timing and strain parameters were normalized for heart rate. All echocardiographic measurements were performed by one of the investigators (P.L.) in a random and blinded fashion. All echocardiographic recordings were stored on digital versatile discs for off-line analyses with Echopac software (GE Vingmed). Measurements were made in three cardiac cycles, and the average was used for statistical analysis.

Estimation of right ventricular wall stress

Right ventricular wall stress can be estimated according to the Laplace's law following the equation:[14]

$$\text{Wall stress} = \frac{\text{RV systolic pressure} \times \text{RV end-systolic radius} \times 0.5}{\text{RV end-systolic wall thickness}}$$

The RV systolic pressure was measured invasively before and after PPVI. The RV end-systolic radius can be estimated under the simplified assumption that the RV end-systolic volume (RVESV) (as derived from MR images) is similar to a sphere. Therefore, the radius is determined by:[8]

$$\text{End-systolic radius} = (0.620 \times \text{RVESV})^{1/3}$$

Finally, RV wall thickness was measured from the four-chamber view obtained from MR images. Wall thickness was measured at the midpoint of the RV free wall according to the sample position for strain analysis on echocardiography. The wall thickness was averaged over three measurements.

Statistical analysis

Data are expressed as mean ± SD. Paired samples were analysed with paired Student's *t*-test. Different timing parameters at the same point in time were compared with unpaired Student's *t*-test. Correlation between variables was assessed with Pearson's test.

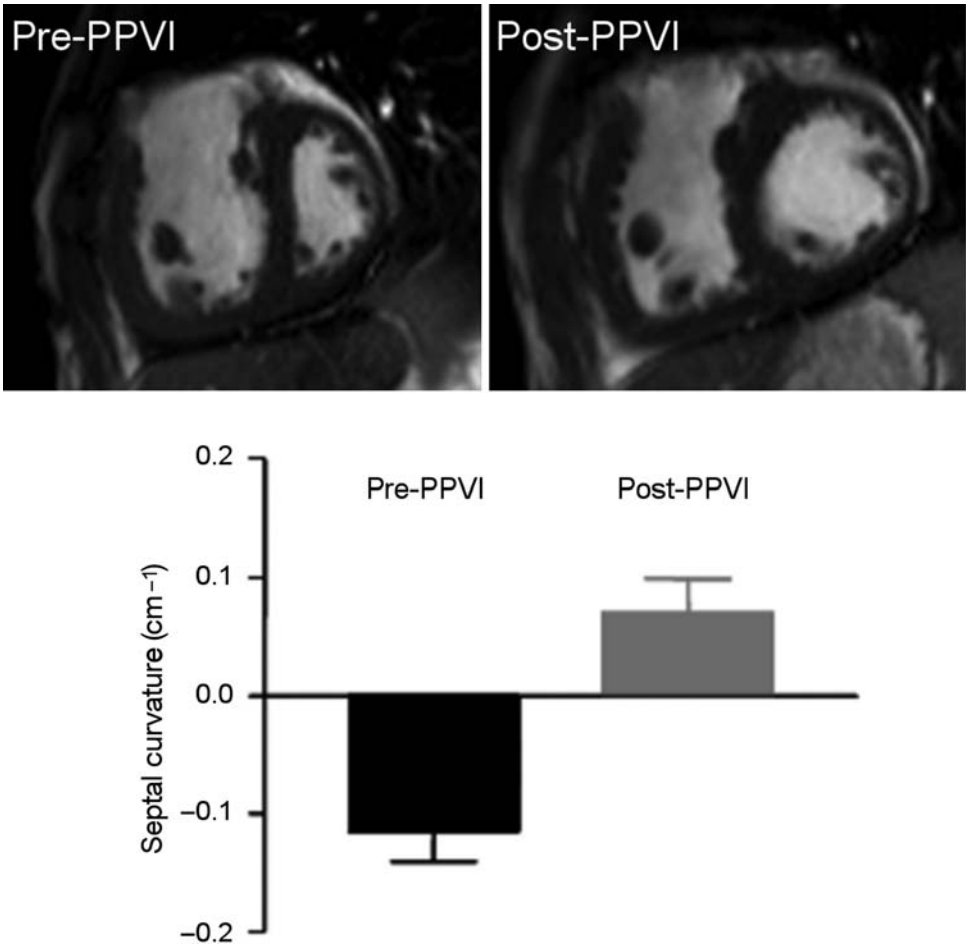

Figure 1 Leftward ventricular septal bowing and septal curvature before and after percutaneous pulmonary valve implantation. Magnetic resonance short-axis images (top panel) at mid-ventricular level showing leftward ventricular septal bowing at the time of early left ventricular diastole before percutaneous pulmonary valve implantation (left). After percutaneous pulmonary valve implantation, the septal curvature is positive with no leftward bowing (right). The graph shows the mean septal curvature before and after relief of conduit obstruction (-0.11 ± 0.11 vs. 0.07 ± 0.13 cm^{-1}; $P < 0.001$).

Multivariate linear modelling was performed to compare the contribution of the assessed parameters of ventricular interaction (altered septal motion, reduction in RV to LV mechanical delay, and reduction in RV wall stress) and the contribution of increased effective RVSV on improved early LV filling (change in early LV filling expressed as the percentage of LVSV).

In order to avoid possible multicollinearity between parameters of ventricular interaction, three different multivariate regression models were performed: (i) increase in effective RVSV and change in septal curvature as predictors for the dependent outcome measure (change in early LV filling). (ii) Increase in effective RVSV and change in RV to LV delay as predictors for the dependent outcome measure. (iii) Increase in effective RVSV and change RV wall stress estimation as predictors for the dependent outcome measure. Part (also known as semi-partial) correlation coefficients (r_{part}) were used to describe the actual association.

In order to account for the multiple tests performed, a *P*-value of <0.01 was considered statistically significant. Statistical analysis was performed with SPSS version 11 (SPSS Inc., Chicago, IL, USA) and GraphPad InStat 3 Demo (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Patient characteristics are shown in *Table 1*. The median age of the patient population was 20.8 years (range 9–37) and 40% were female. Most patients (60%) had Tetralogy of Fallot or a variant morphology; all patients had had an RV to PA conduit placed at previous surgery, of which all but one were homografts. Prior to the procedure, an RV to systemic pressure ratio >3/4 was present in 75%. All patients were symptomatic (see *Table 1* for details). A ventricular septal defect patch was placed in 80% of the patients at the time of surgical correction. On electrocardiogram, right bundle branch block was present in 16 patients. The QRS duration before PPVI was 147.1 ± 30.4 ms.

Haemodynamic and functional results

Percutaneous pulmonary valve implantation was successful in all patients, resulting in a significant reduction in RV systolic pressure

Table 1 Baseline characteristics

Patients	Sex	Age	Diagnosis	Outflow tract	Previous operations	NYHA	RV to sys pressure (%)
1	M	19.6	PA/VSD	Homograft	2	3	92.8
2	F	19.2	ToF	Homograft	2	3	76.9
3	M	33.8	PA/VSD	Homograft	1	2	62.4
4	F	20.5	PA/VSD	Homograft	2	2	94.0
5	M	18	Truncus	Homograft	2	2	65.6
6	M	31.6	ToF	Homograft	2	2	80.2
7	F	20.2	APV	Homograft	1	2	90.4
8	M	22	ToF	Hancock	3	2	77.3
9	F	25.5	CAS/Ross	Homograft	3	4	89.3
10	M	10	Truncus	Homograft	2	2	76.6
11	M	11.6	PA/VSD	Homograft	3	2	55.3
12	M	14.1	PA/VSD	Homograft	4	3	86.9
13	F	29.8	PA/VSD	Homograft	1	2	77.1
14	M	27.7	CPS	Homograft	2	3	74.4
15	M	11.5	PA/VSD	Homograft	2	2	86.7
16	M	37.6	CPS	Homograft	3	3	85.5
17	M	28.3	CAS/Ross	Homograft	2	3	71.8
18	F	9.6	TGA/CPS/VSD	Homograft	1	2	102.2
19	F	14.1	TGA	Homograft	2	2	71.7
20	F	11.7	ToF	Homograft	2	2	77.0

PA, pulmonary atresia; VSD, ventricular septal defect; ToF, Tetralogy of Fallot; Truncus, truncus arteriosus; APV, absent pulmonary valve syndrome; CAS, congenital aortic stenosis; Ross, Ross operation; CPS, congenital pulmonary stenosis; TGA, transposition of the great arteries; RV to sys pressure, RV to systemic systolic pressure ratio.

Table 2 Invasive pressure measurements

	Pre-PPVI	Post-PPVI	*P*-value
RV systolic pressure (mmHg)	71.4 ± 14.8	41.4 ± 9.8	<0.001
RV end-diastolic pressure (mmHg)	11.7 ± 4.8	9.15 ± 3.8	<0.001
PA systolic pressure (mmHg)	24.4 ± 8.6	26.95 ± 7.1	0.370
PA diastolic pressure (mmHg)	10.2 ± 4.5	12.15 ± 5.9	0.070
Systemic systolic pressure (mmHg)	89.5 ± 11.3	103.6 ± 15.1	0.003
Systemic diastolic pressure (mmHg)	54.1 ± 11.5	61.9 ± 10.6	0.025
PA to RV pullback gradient (mmHg)	47.0 ± 17.5	14.5 ± 6.2	<0.001
RV to systemic pressure ratio (%)	79.7 ± 11.5	40.4 ± 10.4	<0.001

RV, right ventricle; PA, pulmonary artery.

(71.4 ± 14.8 vs. 41.4 ± 9.8 mmHg; $P < 0.001$) and PA to RV pullback gradient (47.0 ± 17.5 vs. 14.5 ± 6.2 mmHg; $P < 0.001$). Invasive pressure measurements are summarized in *Table 2*.

On cardiopulmonary exercise testing, peak oxygen uptake (peak VO_2) increased from 22.5 ± 7.9 to 25.8 ± 7.1 mL/min/kg ($P = 0.002$). Peak VO_2 expressed as the percentage of predicted peak VO_2 also improved significantly (56.0 ± 16.0 vs. 64.1 ± 13.7%; $P = 0.001$).

Magnetic resonance volumes and ventricular function

The pulmonary regurgitation fraction before PPVI was small and decreased further after valve implantation (11.0 ± 9.4 vs. 2.2 ± 4.1%; $P = 0.003$). Following the procedure, there was a significant reduction in RVEDV (113.6 ± 51.6 vs. 106.5 ± 49.3 mL/m^2; $P < 0.001$) and RVESV (67.0 ± 44.5 vs. 56.0 ± 45.7 mL/m^2; $P < 0.001$). Consequently, effective RVSV (41.8 ± 12.8 vs. 49.4 ± 7.8 mL/m^2; $P < 0.001$) and RV ejection fraction (44.9 ± 15.2 vs. 53.7 ± 16.9 mL/m^2; $P < 0.001$) increased. Left ventricular end-diastolic volume increased significantly (72.2 ± 22.3 vs. 86.1 ± 20.7 mL/m^2; $P < 0.001$) with a stable LVESV (29.9 ± 12.8 vs. 31.8 ± 11.3 mL/m^2; $P = 0.08$). Therefore, effective LVSV (40.1 ± 11.1 vs. 51.7 ± 10.5 mL/m^2; $P < 0.001$) and LV ejection fraction (58.4 ± 9.0 vs. 63.7 ± 7.7%; $P < 0.001$) improved significantly (*Table 3A*).

Septal curvature and left ventricular filling properties

Assessment of the septal curvature showed negative values (representing LVSB into the LV cavity in early LV diastole) in all but two patients, in whom the septum was flattened in diastole. After reduction in RV pressures by PPVI, there was significantly less

Table 3 Results of magnetic resonance, echocardiographic, and timing parameters before and after percutaneous pulmonary valve implantation

	Pre-PPVI	Post-PPVI	*P*-value
(A) Magnetic resonance results			
RVEDV (mL/m^2)	113.6 ± 51.6	106.5 ± 49.3	<0.001
RVESV (mL/m^2)	67.0 ± 44.5	56.0 ± 45.7	<0.001
RV stroke volume (mL/m^2)	46.6 ± 13.4	50.5 ± 7.0	0.04
RV effective stroke volume (mL/m^2)	41.8 ± 12.8	49.4 ± 7.8	<0.001
RV ejection fraction (%)	44.9 ± 15.2	53.7 ± 16.9	<0.001
Pulmonary regurgitation fraction (%)	11.0 ± 9.4	2.2 ± 4.1	0.003
LVEDV (mL/m^2)	72.2 ± 22.3	86.1 ± 20.7	<0.001
LVESV (mL/m^2)	29.9 ± 12.8	31.8 ± 11.3	0.08
LV effective stroke volume (mL/m^2)	40.1 ± 11.1	51.7 ± 10.5	<0.001
LV ejection fraction (%)	58.4 ± 9.0	63.7 ± 7.7	<0.001
Septal curvature (cm^{-1})	−0.11 ± 0.11	+0.07 ± 0.13	<0.001
Volume of early LV filling (mL/m^2)	17.5 ± 9.4	30.4 ± 9.4	<0.001
Early LV filling as % of LVSV (%)	39.5 ± 13.2	56.6 ± 9.8	<0.001
Volume of late LV filling (mL/m^2)	24.9 ± 7.6	22.8 ± 5.9	0.08
Late LV filling as % of LVSV (%)	60.5 ± 13.2	43.4 ± 9.8	<0.001
(B) Echocardiographic results			
Mitral valve *E* velocity (m/s)	0.88 ± 0.23	1.04 ± 0.24	0.001
Mitral valve *A* velocity (m/s)	0.57 ± 0.22	0.44 ± 0.13	0.021
E/*A* ratio	1.76 ± 0.77	2.57 ± 1.11	0.01
LV lateral E_m velocity (cm/s)	8.75 ± 3.26	9.98 ± 3.1	0.04
MV lateral A_m velocity (cm/s)	4.10 ± 2.37	3.66 ± 2.42	0.08
E/E_m ratio	11.16 ± 4.23	10.93 ± 2.52	0.76
(C) Timing parameter			
Time to opening of PV (ms)	112.2 ± 37.5	115.7 ± 32.6	0.67
Time to opening of AV (ms)	88.1 ± 32.0	88.5 ± 29.2	0.96
RV to LV pre-ejection delay (ms)	24.0 ± 30.2	27.2 ± 25.9	0.74
Time to closure of PV (ms)	554.9 ± 68.34	481.2 ± 47.6	<0.001
Time to closure of AV (ms)	426.7 ± 42.9	409.5 ± 48.6	0.12
Time to opening of MV (ms)	504.3 ± 57.4	473.1 ± 47.7	0.028
Time to peak RV strain (ms)	534.5 ± 71.9	457.9 ± 56.1	<0.001
Time to peak SP strain (ms)	422.9 ± 70.0	410.5 ± 59.8	0.42
Time to peak LV strain (ms)	406.7 ± 53.1	424.52 ± 53.7	0.19
Time to LV septal bowing (ms)[a]	552.8 ± 80.9	n.a.	n.a.
RV to LV peak strain delay (ms)	127.9 ± 50.9	37.7 ± 35.6	<0.001
RV to SP peak strain delay (ms)[b]	107.5 ± 53.6	47.8 ± 36.3	<0.001
QRS duration (ms)	147.1 ± 30.4	149.4 ± 30.2	0.11

EDV, end-diastolic volume; ESV, end-systolic volume; E_m/A_m, early/late diastolic mitral annular velocity; PV, pulmonary valve; AV, aortic valve; MV, mitral valve; n.a., not applicable.
[a]Time to LV septal bowing in 18/20 patients. In two patients with septal flattening but no leftward bowing, this parameter could not be assessed.
[b]Time to peak septal strain in 19 patients pre- and post-PPVI; in 1 patient with an extensive ventricular septal defect, strain assessment of the septum was not possible.

LVSB, with a shift to a positive or more physiological septal curvature (−0.11 ± 0.11 to +0.07 ± 0.13 cm^{-1}; $P < 0.001$; *Figure 1* and *Table 3A*).

Analysis of LV volume–time curves showed an increase in early LV filling (one-third of diastole) from 17.5 ± 9.4 to 30.4 ± 9.4 mL/m^2 ($P < 0.001$). The contribution of early LV filling to total LV filling increased from 39.5 ± 13.2 to 56.6 ± 9.8% ($P < 0.001$). Whereas the LV filling in late diastole remained unchanged (24.9 ± 7.6 vs. 22.8 ± 5.9 mL/m^2; $P = 0.08$), there was a significant reduction in contribution of late LV filling to total amount of filling (60.5 ± 13.2 vs. 43.4 ± 9.8%; $P < 0.001$). The changes in septal motion and LV filling properties are demonstrated in *Figure 2*.

On echocardiography, mitral inflow *E*-wave velocity increased significantly (0.88 ± 0.23 vs. 1.04 ± 0.24 m/s; $P < 0.001$), whereas *A*-wave velocity decreased (0.57 ± 0.22 vs. 0.44 ± 0.13; $P = 0.021$). This led to an increase in *E*/*A* ratio (1.76 ± 0.77 vs. 2.57 ± 1.11; $P = 0.01$). Lateral mitral annular velocity (E_m), as assessed with tissue Doppler, increased from 8.75 ± 3.26 to 9.98 ± 3.1 cm/s ($P = 0.04$); E/E_m ratio did not change after PPVI (11.16 ± 4.23 vs. 10.9 ± 2.52; $P = 0.76$). Magnetic resonance and echocardiographic LV filling parameters are summarized in *Table 3B*.

Strain and timing

The results of strain analyses and timing parameters are shown in *Table 3C*. Before PPVI, there was a significant pre-ejection delay with opening of the aortic valve occurring earlier than opening of the pulmonary valve. The time to peak RV strain (T_{peak}RV) was significantly longer compared with T_{peak}LV, resulting in a peak RV to LV strain delay. Leftward ventricular septal bowing occurred shortly after peak RV strain, but significantly later than peak LV strain ($P < 0.001$) and time to mitral valve opening.

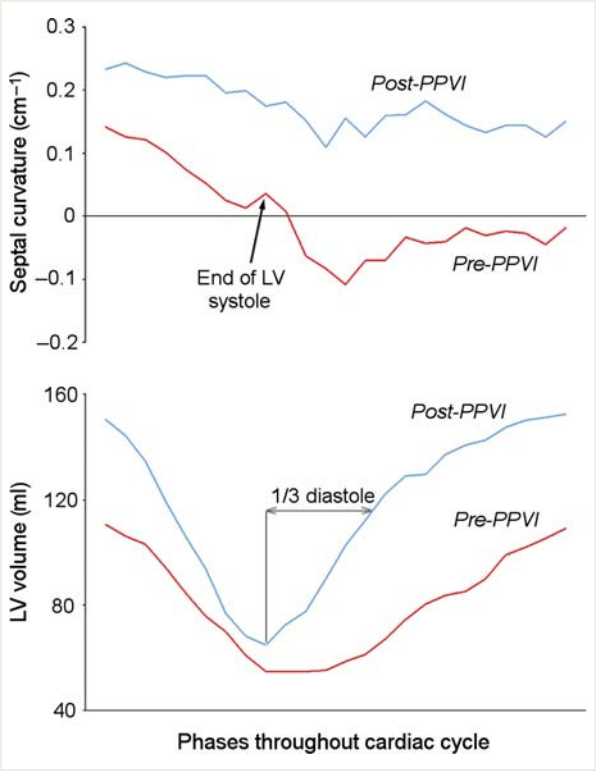

Figure 2 Septal curvature and left ventricular volume over time before and after percutaneous pulmonary valve implantation. This is a representative example demonstrating the change in septal curvature throughout the cardiac cycle before and after percutaneous pulmonary valve implantation (top panel) and the change in left ventricular volume in the same patient (bottom panel). As demonstrated, the most severe leftward ventricular septal bowing occurs after the end of left ventricular systole in early left ventricular diastole. This corresponds to a delayed filling of the left ventricular during early diastole. After percutaneous pulmonary valve implantation, the septal curvature is positive throughout the cardiac cycle (top panel) with improved left ventricular filling in early diastole (during the first one-third of diastole) (bottom panel).

Post-procedure, there was no change in RV to LV pre-ejection delay or QRS duration. T_{peak}RV was substantially reduced, whereas time to peak strain in the LV free wall and septum did not change significantly (*Figure 3*). Hence, there was significantly less RV to LV mechanical delay post-procedure. Percutaneous pulmonary valve implantation led to a shorter RV ejection period (earlier closure of the pulmonary valve). Opening of the mitral valve occurred earlier after PPVI.

Results of right ventricular wall stress estimation

There was a significant reduction in the estimated RV wall stress after PPVI, which decreased from 13.75 ± 5.47 to 7.61 ± 4.05 kPa ($P < 0.001$). This is attributed to a reduction in estimated RV radius (2.98 ± 0.69 vs. 2.67 ± 0.76 cm; $P < 0.001$) and RV systolic pressure (*Table 2*). Right ventricular free wall thickness remained unchanged acutely after PPVI (1.09 ± 0.28 vs. 1.06 ± 0.29 cm; $P = 0.12$). Due to heavy trabeculations of the RV free wall, wall thickness and therefore RV wall stress estimation could not be determined in one subject.

Correlation and linear regression analyses

Results of correlation and linear regression analyses are shown in *Tables 4* and *5* and *Figure 4*. Improvement in early LV filling, expressed as the percentage of total filling, correlated significantly with the change in septal curvature ($r = 0.71$, $P < 0.001$) (*Figure 4A*). The improvement in septal curvature was associated with the reduction in LV to RV delay ($r = -0.65$, $P = 0.001$) (*Figure 4B*). The change in RV to LV delay correlated significantly with the reduction in RV wall stress ($r = 0.63$, $P = 0.002$) (*Figure 4C*). As demonstrated, there was a significant association between improvement in early LV filling and change in peak oxygen uptake during exercise ($r = 0.69$, $P = 0.001$) (*Figure 4D*). On multivariate regression analyses, the change in septal curvature was the best predictor for improved early LV filling ($r_{part} = 0.69$, $P = 0.001$ vs. $r_{part} = -0.64$, $P = 0.002$ for RV to LV mechanical delay vs. $r_{part} = -0.34$, $P = 0.16$ for reduction in RV wall stress). The increase in effective RVSV was not a significant predictor in either of the regression models ($r_{part} = 0.16$, $P = 0.35$; $r_{part} = 0.11$, $P = 0.55$; and $r_{part} = 0.16$, $P = 0.49$; *Table 5*).

Discussion

Previously, we have demonstrated that relief of RV to PA conduit obstruction using PPVI increases LV end-diastolic volumes.[3] Here, we show that this increase is due to an improvement in early diastolic filling and that this correlates best with more favourable septal motion. We show that this is secondary to less interventricular mechanical delay, as a consequence of reduced RV wall stress following relief of conduit obstruction. Importantly, these alterations in ventricular interaction after PPVI are associated with better exercise capacity.

Studies to date have shown that pathological RV loading can impact on LV function and shape,[15–17] and that by treating pulmonary vascular disease (pulmonary hypertension and pulmonary thrombo-embolic disease[4,18]), LV filling can be improved. However, to our knowledge, there has been no in-depth study that describes how relief of conduit obstruction in patients with CHD can lead to changes in LV function and the potential mechanisms that might underlie these changes.

By applying MR imaging, we aimed to determine the contribution of ventricular interaction and septal motion to the improvement in LV filling after relief of conduit obstruction. Better LV filling after relief of conduit obstruction could be explained by two main mechanisms:[5] Improved pulmonary venous return as a consequence of increased effective RVSV volume, and/or less LV septal bowing as a consequence of more favourable direct ventricular interaction.

The increase in total LV filling must equal the increase in effective RVSV. However, when we assessed the change in early diastolic filling on multivariate regression analysis, effective RVSV did not correlate significantly with the improvement in early diastolic filling, whereas the change in septal curvature (positive, rightward

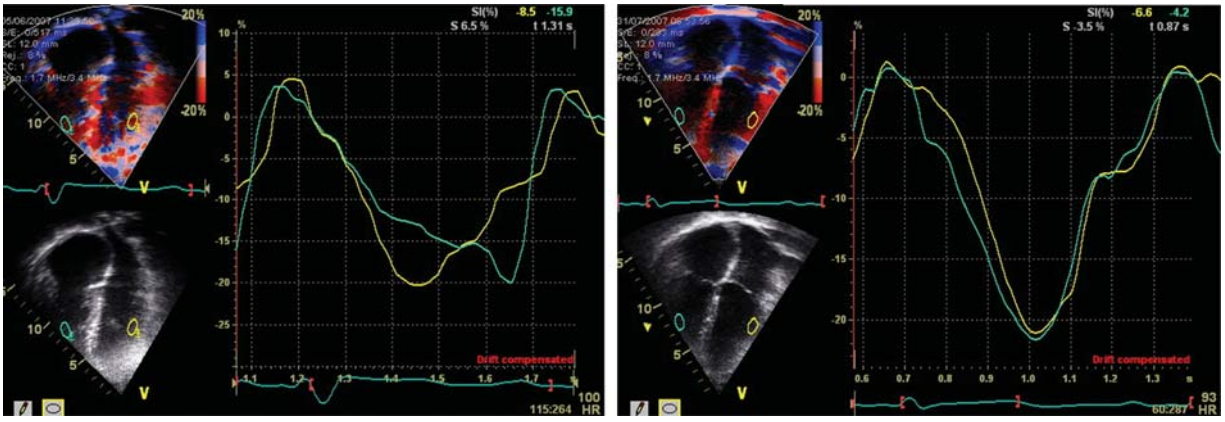

Figure 3 Longitudinal strain analyses on echocardiography. (Left panel) Longitudinal strain curves over time for the right ventricular free wall (green) and left ventricular free wall (yellow). Time to peak right ventricular strain, as calculated from the beginning of the QRS complex, is significantly longer compared with the time to peak left ventricular strain. (Right panel) Longitudinal strain curves in the same patient after percutaneous pulmonary valve implantation; the time to peak right ventricular strain (green) is significantly reduced compared with pre-procedure and coincides with peak left ventricular strain (yellow).

Table 4 Results of correlation analyses

Dependent value	Independent value	*r*-value	*P*-value
Δ RV to LV delay (ms)	Δ RV wall stress (kPa)	0.63	0.002
Δ septal curvature (cm^{-1})	Δ RV to LV delay (ms)	−0.65	0.001
Δ early LV filling as % of LVSV (%)	Δ Septal curvature (cm^{-1})	0.71	<0.001
Δ early LV filling as % of LVSV (%)	Δ RV to LV delay (ms)	−0.68	0.001
Δ early LV filling as % of LVSV (%)	Δ RV effective stroke volume (mL/m^2)	0.363	0.139
Δ peak VO_2 of predicted (%)	Δ RV pressures (ms)	−0.21	0.188
Δ peak VO_2 of predicted (%)	Δ RV to LV delay (ms)	−0.73	<0.001
Δ peak VO_2 of predicted (%)	Δ early LV filling as % of LVSV (%)	0.69	0.001

Δ, change in parameter pre-PPVI vs. post-PPVI.

Table 5 Results of multivariate regression analyses

Dependent value	Predictors	r_{part} value	*P*-value
Δ early LV filling as % of LVSV (%)	Δ septal curvature (cm^{-1})	0.69	0.001
	Δ RV effective stroke volume (mL/m^2)	0.16	0.35
Δ early LV filling as % of LVSV (%)	Δ RV to LV delay (ms)	−0.64	0.002
	Δ RV effective stroke volume (mL/m^2)	0.11	0.55
Δ early LV filling as % of LVSV (%)	Δ RV wall stress (kPa)	−0.34	0.16
	Δ RV effective stroke volume (mL/m^2)	0.16	0.49

Δ, change in parameter pre-PPVI vs. post-PPVI.

bowing of the septum post-PPVI) was the best predictor for improvement. Therefore, we suggest that altered direct ventricular interaction (as judged by septal motion) contributes significantly to the improvement in early LV filling.

What are the potential mechanisms of improved ventricular interaction?

Left ventricular septal bowing in early diastole has been shown to be related to a time-dependent pressure gradient across the septum.[6,19] This is thought to be caused by the presence of significant RV to LV mechanical delay, as demonstrated previously in different models of RV pressure overload.[8,9,13] In this study, we show that there is marked RV to LV mechanical delay in patients with RV pressure overload secondary to conduit obstruction, prior to PPVI. In early diastole, the LV is beginning to relax whereas the RV continues to contract. This interventricular mechanical delay is caused by both pre-ejection delay and prolongation of the RV free wall shortening duration, secondary to RV pressure overload. Leftward bowing of the ventricular septum occurs at the time of peak RV shortening, after opening of the mitral valve in early LV diastole.

Acutely, post-PPVI, RV to LV mechanical delay significantly improved. This reduction in RV to LV mechanical delay may be due to either altered electrical activation (onset of RV shortening) and/or altered RV shortening duration. Although there was a high incidence of right bundle branch block in our patients, there was no significant change in QRS duration after PPVI. Also, the RV to LV pre-ejection delay did not change after relief of conduit obstruction. Both of these observations suggest that electrical

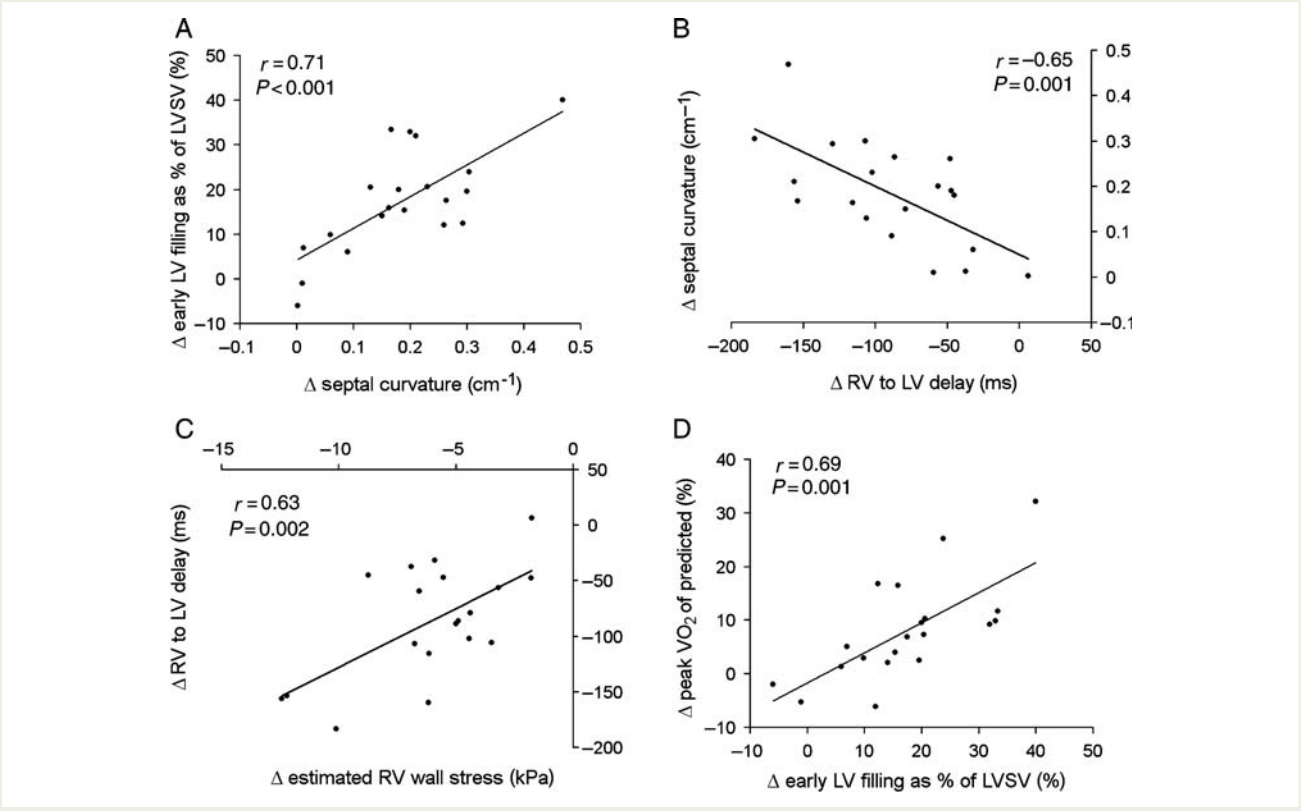

Figure 4 Correlation analyses of parameters measured before and after percutaneous pulmonary valve implantation. Δ, change in parameter pre-percutaneous pulmonary valve implantation vs. post-percutaneous pulmonary valve implantation; (*A*) Δ septal curvature vs. Δ left ventricular early filling expressed as the percentage of left ventricular stroke volume; (*B*) Δ right ventricular to left ventricular delay vs. Δ septal curvature; (*C*) Δ estimated right ventricular wall stress vs. Δ right ventricular to left ventricular delay; (*D*) Δ early left ventricular filling expressed as the percentage of total left ventricular stroke volume vs. Δ peak VO_2 expressed as the percentage of predicted.

activation was not altered post-PPVI. Hence, we postulate that the improvement in RV to LV delay following relief of RV to PA conduit obstruction relates to the duration of RV shortening rather than the onset of RV shortening. Furthermore, in our patients, reduction in our estimated measure of RV wall stress was associated with reduction in RV to LV mechanical delay. We know from previous studies in pulmonary hypertension patients that increased wall tension and high RV pressures are related to prolonged RV shortening.[8] Taken in conjunction, these two observations also support the idea that reduction in the duration of RV shortening is the main mechanism for the improved interventricular mechanical synchrony.

Based on the data of this study, we propose the following underlying mechanisms for the improvement in ventricular interaction:

- Relief of RV to PA conduit obstruction leads to reduction in RV wall stress.
- The reduction in RV wall stress improves RV to LV mechanical delay by reducing RV shortening duration.
- The improvement in RV to LV mechanical delay reduces the time-dependent pressure gradient across the septum and therefore diminishes septal bowing during early LV diastole.
- Establishment of a more favourable ventricular interaction optimizes LV early diastolic filling conditions.

Clinical implications

Although the clinical importance of LV function in patients with pulmonary hypertension has been shown, this is often neglected in patients with pathological RV loading conditions in the context of CHD. The presence of LV dysfunction is commonly underestimated in clinical practice, despite the fact that LV function is a powerful predictor for sudden death and prognosis in this patient population.[20] In our study, relief of conduit obstruction improved LV systolic function. This is explained by the Frank–Starling mechanism: Increase in LV preload leads to more favourable muscle fibre stretch, resulting in higher LV ejection fraction.

The improvement in early diastolic filling of the LV at rest was strongly associated with an increase in peak VO_2 on cardiopulmonary exercise testing. We would expect the RV systolic pressure and, in particular, RV wall stress to increase during exercise. This would mean that septal bowing to the left, restricting LV filling, is more prominent during exercise in RV to PA conduit obstruction. During exercise, rapid LV filling is crucial in order to increase cardiac output. Hence, enhanced ventricular interaction after PPVI with less leftward bowing of the septum should improve early LV filling to an even greater extent at exercise than at rest, and this should contribute to the improvement in exercise performance of our patients.

Overall, these results emphasize the importance of LV functional assessment in these patients and suggest better methods for predicting and monitoring successful outcome of the treatment of right heart conditions. In addition, better understanding of the described mechanisms of improvement after PPVI might improve patient selection for this intervention.

Study limitations

Although the estimation of wall stress was performed under the simplified assumption that the RVESV is spherical, this is an established method in the literature.[8] The impact of electrical conduction delay was indirectly assessed by QRS duration and RV to LV pre-ejection delay. The true impact of reduction in RV pressures on intraventricular electrical conduction and activation remains unknown and is subject to ongoing research.

Conclusions

Our observations stress the importance of the interaction between the two ventricles when physiological conditions are changed by disease. Furthermore, by using a minimally invasive method to alter afterload (PPVI), without the confounding effects of surgery, we have been able to accurately describe the changes that occur when afterload is reduced. Relief of conduit obstruction significantly improves early LV filling properties. This improvement is not only related to the increase in RV forward flow, but is also secondary to more favourable ventricular interaction. The presence of RV to LV delay—the cause of LVSB—is reversible after PPVI, which we postulate to be related to a reduction in RV wall stress. These findings shed light on effects that were previously observed clinically and can now be studied in more detail and followed up in the individual patient with conduit obstruction. Prospectively, the results of this study may guide clinical decisions.

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