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ORIGINAL ARTICLE

Real-Time Biventricular Pressure-Volume Loops During Percutaneous Pulmonary Valve Implantation in Patients With RVOT Dysfunction

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BACKGROUND: In patients with right ventricular (RV) outflow tract stenosis and pulmonary regurgitation (PR), percutaneous pulmonary valve implantation (PPVI) aims to preserve RV and left ventricular (LV) integrity and function. Our study aimed to assess acute changes in biventricular intrinsic myocardial function occurring with PPVI.

METHODS: Twenty patients with RV outflow tract dysfunction (mean±1 SD; age, 23.0±10.9 years; mean peak echocardiographic RV outflow tract gradient, 64±25 mm Hg) underwent PPVI with biventricular assessment of pressure-volume loops using the conductance catheter technique during the same cardiac catheterization. Load-independent parameters of ventricular contractility (ventricular elastance) and ventricular compliance function, as well as pulmonary/systemic arterial elastance and ventriculoarterial coupling, were assessed before and directly after PPVI. Cardiac magnetic resonance for quantification of biventricular volumes, function, and PR was also performed.

RESULTS: After PPVI, both RV ventricular elastance (median [interquartile range], 0.26 [0.16–0.83]–0.19 [0.13–0.42] mm Hg/mL per m^2; P=0.029) and pulmonary systemic arterial elastance (0.32±0.20–0.25±0.19 mm Hg/mL per m^2; P<0.001) decreased significantly, while right ventriculoarterial coupling (1.14±0.61–1.10±0.59; P=0.76) did not change statistically significant. LV ventricular elastance (1.31±0.93–1.23±0.72 mm Hg/mL per m^2; P=0.68) and left ventriculoarterial coupling (0.75 [0.51–1.23]–0.82 [0.53–1.10]; P=0.98) were not affected by PPVI although systemic arterial elastance increased significantly (0.83±0.26–0.90±0.34 mm Hg/mL per m^2; P=0.032). Both RV (P=0.37) and LV (P=0.20) compliance showed no significant change after PPVI. Patients with relevant PR (≥25%; n=10) had lower RV ventricular elastance (P=0.043) before and higher LV compliance (P=0.010) after PPVI compared with patients with minor PR (<25%; n=10), whereas ventriculoarterial coupling was similar between the 2 groups.

CONCLUSIONS: Acute reduction of RV overload by PPVI is accompanied by an instantaneous decline in RV contractility with persistent and inefficient ventriculoarterial coupling. The LV adequately adapts to an increase in pre- and post-load with nonsignificant changes in LV intrinsic function and ventriculoarterial coupling. The relevance of these response patterns on long-term biventricular remodeling requires further investigation.

Key Words: constriction, pathologic ■ exercise tolerance ■ pulmonary valve ■ stroke volume ■ ventricular dysfunction

Both stenosis and pulmonary regurgitation (PR) frequently evolve following right ventricular outflow tract (RVOT) surgery in patients with congenital heart disease. Long-term pressure and volume overload of the right ventricle (RV) may result in RV dysfunction, exercise intolerance, arrhythmias, and sudden cardiac death.[1,2] Pulmonary valve replacement (PVR), either performed surgically or by a percutaneous approach (percutaneous pulmonary valve implantation [PPVI]), restores pulmonary valve function with the potential to induce a

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WHAT IS NEW?

- By using the conductance catheter technique, our study quantified load-independent parameters of both left ventricular and right ventricular (RV) functions in patients with RV outflow tract dysfunction and assessed acute hemodynamic changes that occurred with percutaneous pulmonary valve implantation.
- Treatment of RV outflow tract dysfunction by percutaneous pulmonary valve implantation was not able to restore RV cardiovascular efficiency, while left ventricular performance appeared to be preserved.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The results of our study elucidate different hemodynamic effects of combined RV volume and pressure overload that may add to the understanding of the mechanisms that promote biventricular dysfunction in this patient population.
- Given the uncertainty surrounding the optimal time point for RV outflow tract reintervention in patients with RV outflow tract dysfunction, our findings could serve as a groundwork for future trials that should aim to predict clinical improvement and favorable outcomes by pulmonary valve replacement procedures.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
Ea	systemic arterial elastance
EDV	end-diastolic volume
Eed	ventricular compliance
Ees	ventricular elastance
LV	left ventricle
PR	pulmonary regurgitation
PRSW	preload recruitable stroke work
P-V	pressure-volume
PVR	pulmonary valve replacement
RV	right ventricle
RVOT	right ventricular outflow tract
TOF	tetralogy of Fallot

favorable biventricular remodeling process that translates into improved outcomes.[3] However, uncertainties still exist regarding the indication and optimal time point for the PVR as not all patients show a clinical benefit post-PVR with improvement in functional class, exercise capacity, and RV function. Furthermore, in one of the first studies addressing functional remodeling post-PPVI, no further improvement in biventricular function and exercise performance was observed beyond 1 year after the intervention, thus raising the question whether the favorable effect of PPVI is limited to acute altered RV loading.[4] The authors hypothesized whether treatment of RVOT dysfunction simply breaks the unfavorable course of declining cardiac function (therefore leading to a stabilization of cardiac performance) or whether it can induce a real recovery process that leads to an improvement in cardiac performance and exercise tolerance in the mid- to long-term.

Noninvasive imaging using cardiac magnetic resonance (CMR) plays a major role in the decision-making for PVR/PPVI as it enables accurate quantification of biventricular volumes, ejection fraction (EF), and PR. However, EF as a parameter of the global pump function has some inherent limitations due to its dependency on both pre- and post-load. Analysis of ventricular pressure-volume (P-V) loops by conductance catheter technique is still considered the gold standard for in vivo assessment of intrinsic myocardial function (ie, myocardial contractility and ventricular compliance) and enables real-time assessment of acute hemodynamic changes.[5] Accordingly, variations in ventricular load, as caused by PVR, can substantially change EF, while intrinsic myocardial function (ie, ventricular contractility) remains rather unaffected. Conversely, contractile performance of the ventricle may be impaired although EF is still preserved.[6] Load-independent parameters of RV performance have already been investigated in patients late after repair of tetralogy of Fallot (TOF) and provided insights into RV adaptation to chronic volume overload.[7–10] This is of equal importance as current concepts of the RV response to both chronic pressure and volume overload include reversible impairment of ventricular contractility as a critical stage before transmission to irreversible myocardial injury with fibrotic remodeling and onset of circulatory failure occurs.[11–14] Considering the mentioned questions that arise around the evolution of cardiac dysfunction and its modulation by restoration of RVOT function, the mechanisms by which PPVI may influence RV and left ventricle (LV) pre- and post-load, contractility, and efficiency are still to be determined.

Thus, the purpose of our study was (1) to quantify the acute effects of PPVI on load-independent parameters of RV/LV function and RV/LV interactions, (2) to investigate the role of the type of RVOT lesion on acute RV/LV response to PPVI, and (3) to study the role of patients' age on measures of biventricular function post-PPVI.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The participation in this study was offered to patients with RVOT dysfunction who were scheduled for PPVI with a Melody valve in the catheterization laboratory. Indications for PPVI at

our center included RVOT obstruction with or without PR and (1) tricuspid regurgitation jet velocity >3.5 m/s in the presence of symptoms or decreased physical capacity (<65% of the norm), (2) tricuspid regurgitation jet velocity >4.3 m/s or more than two-third systemic RV pressure without symptoms, or (3) severe PR with progressive RV dilatation with indexed RV end-diastolic volume (EDV) >150 mL/m^2 and declining RV function.

Patients were excluded if PPVI was performed with a transcatheter pulmonary valve other than the Melody valve; the patient's body weight was <20 kg if anatomic or hemodynamic difficulty existed to place the conductance catheter in the RV/LV or if any other disorders disabled the patient from taking part in the study. Demographic and clinical data were obtained from hospital medical records. The New York Heart Association classification was used to grade the severity of functional limitations. All patients or parents of the patients gave written informed consent to a protocol approved by the local ethics committee.

Echocardiography

Transthoracic echocardiography was performed to determine the maximal velocity across the RVOT using continuous wave Doppler. RVOT gradients were calculated according to the Bernoulli equation. The severity of tricuspid valve regurgitation was graded according to current guidelines and was quantified as no/mild, moderate, and severe.

Cardiac Magnetic Resonance

For a detailed description of the CMR protocol, as well as further image analysis, please see the Supplemental Methods. In brief, ventricular volumes were assessed in axial orientation and were calculated after the endocardial borders were traced manually.[15]

P-V Loop Analysis Using Conductance Catheter Technique

To assess the intrinsic myocardial function of the RV and LV, we used P-V loop analysis by the conductance catheter technique. Measurements were performed at baseline level (before PPVI) and directly after PPVI (Figure 1). For a detailed description of the cardiac catheterization protocol, see the Supplemental Methods.

Assessment of Ventricular-Arterial Coupling

Effective pulmonary and systemic arterial elastance (Ea) was calculated as the ratio of end-systolic pressure to stroke volume (indexed for body surface area). The ratio Ea/ventricular elastance (Ees) was used as an index for ventriculoarterial coupling. The framework of ventriculoarterial coupling quantifies the interplay between the heart and the great vessels by relating arterial to ventricular elastance, allowing to evaluate the energetic efficiency of cardiac output. For a more detailed description of the framework of ventriculoarterial coupling and published normal values in adults, please see the Supplemental Methods.

Statistical Analysis

All continuous variables were tested for normality using the D'Agostino-Pearson test. Results are presented as mean with 1 SD or median and interquartile range. Comparisons of pre- and post-PPVI data were performed using the *t* test for paired data or the nonparametric Wilcoxon matched-pairs signed-rank test. An unpaired, nonparametric Mann-Whitney *U* test was used to compare patients with relevant PR (≥25%) to those patients with less PR (<25%), as well as the subgroups according to the median age of 18.5 years of the study population. Categorical variables were analyzed with the Fisher exact test. The Pearson correlation coefficient was used to analyze simple linear relationships between different variables. Analysis was performed using GraphPad Prism, version 6.0.0, for Mac (GraphPad Software, Boston, MA; www.graphpad.com) and SPSS statistical software package (version 25.0; IBM, Inc, Armonk, NY). $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics and Clinical Findings

A total of 20 patients (mean age, 23.0±10.9 [range, 11.3–53.2] years; mean BSA, 1.68±0.25 m^2; 9 females) were enrolled in the study. Five patients had to be excluded from the final analysis due to various reasons (Figure 2), and 16 of the 20 patients (80%) had already undergone a previous PVR procedure, while the remaining 4 patients had a native RVOT. For detailed information on demographic and clinical data, see Table 1.

Echocardiography and CMR Findings

The echocardiographic peak gradient across the RVOT was 64±25 mm Hg, and the tricuspid valve regurgitation was none/mild in the majority of patients (n=14), moderate in n=4 patients, and severe in n=2 patients. Results of the CMR studies (mean time interval between CMR and cardiac catheterization with PPVI, 7±3 months) are displayed in Table 1.

Conductance Catheter Measurements

P-V loop analysis of both the RV and the LV with hemodynamic data measured before and after PPVI is presented in Tables 2 and 3. After PPVI, heart rate dropped from 71±12 to 65±19/min ($P=0.01$).

Indexed RVEDV ($P=0.77$) and indexed RV end-systolic volume ($P=0.71$) did not change significantly, which resulted in no statistically significant change in RVEF ($P=0.22$) and indexed RV stroke volume ($P=0.80$). RV end-systolic pressures decreased (from 40±16 to 27±12 mm Hg; $P<0.0001$), while end-diastolic pressures did not change significantly (6±4 to 5±3 mm Hg; $P=0.19$). Preload recruitable stroke work (PRSW), maximum and minimum rate of pressure change in the ventricle, and minimum rate of pressure change in the ventricle decreased, while early RV relaxation parameter τ did not change significantly. With PPVI, both RV Ees (0.26 [0.16–0.83]–0.19 [0.13–0.42] mm Hg/mL per m^2; $P=0.036$; RV *x* axis intercept of the slope of

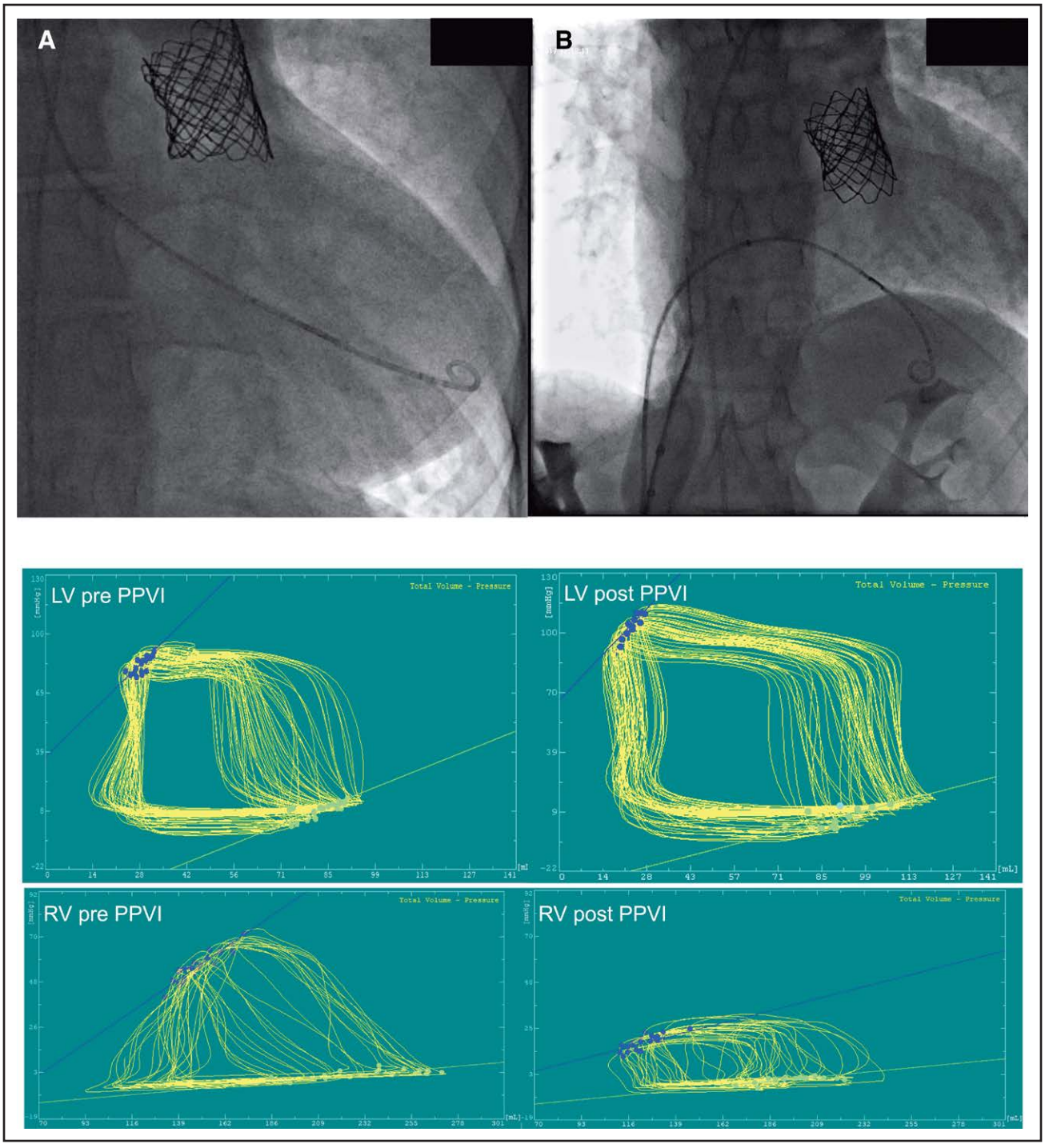

Figure 1. XXX.

Top, Placement of the conductance catheter in the apex of the left ventricle (LV; **A**) and the right ventricle (RV; **B**). **Bottom**, Group of pressure-volume loops during preload reduction maneuvers before and directly after percutaneous pulmonary valve implantation (PPVI). Changes in load-independent parameters of LV function: note the increase in ventricular elastance (Ees; blue line) from 1.62 to 1.83 mm Hg/mL and the increase in ventricular compliance expressed by a drop in ventricular compliance (Eed) from 0.53 to 0.45 mm Hg/mL (green line). *x* axis from 0 to 141 mL; *y* axis from −22 to 130 mm Hg. Changes in load-independent parameters of RV function before and after PPVI: a decrease in ventricular elastance Ees (blue line; from 0.63 to 0.44 mm Hg/mL) and an increase in Eed (green line; from 0.09 to 0.12 mm Hg/mL) as a sign of reduced compliance were observed. *x* axis from 70 to 301 mL; *y* axis from −19 to 92 mm Hg.

the end-systolic P-V relationship, 18 [5–35]–12 [−3 to 31] mL; *P*=0.01) and pulmonary Ea (0.32±0.20–0.25±0.19 mm Hg/mL per m^2; *P*=0.0002) decreased. Right ventriculoarterial coupling appeared to be impaired with ratios of ≥0.66 in the majority of patients (n=14) and showed no statistically significant change post-PPVI

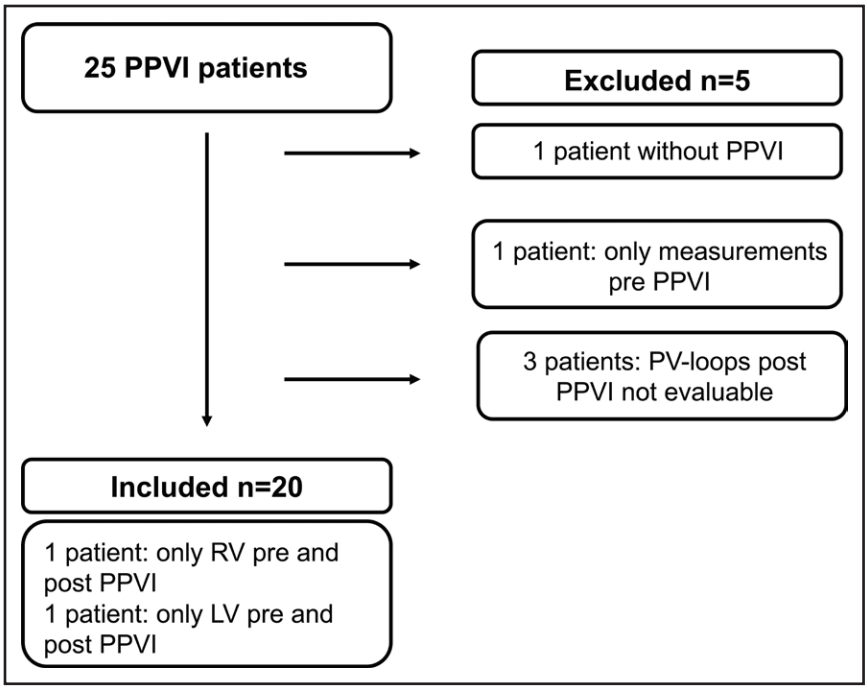

Figure 2. Graph displaying the study flow with the total number of 20 patients who were included in the final analysis.
LV indicates left ventricle; PPVI, percutaneous pulmonary valve implantation; P-V, pressure-volume; and RV, right ventricle.

(1.14±0.61–1.10±0.59; *P*=0.76). In the 5 patients with compensated ventriculoarterial coupling before PPVI (ratios <0.66), ventriculoarterial coupling increased in 3 and did not change significantly in 2 patients after PPVI. RV compliance (Eed) showed no significant change with PPVI (from 0.03 [0.01–0.07] to 0.03 [0.01–0.07] mm Hg/mL per m^2; *P*=0.37).

On the left-hand side, indexed LVEDV (*P*=0.038) and indexed LV stroke volume (*P*=0.028) increased, while LVEF did not change (*P*=0.10). LV end-systolic (91±15–106±12 mm Hg; *P*<0.001) and end-diastolic pressures (8±3–10±4 mm Hg; *P*=0.005) both showed an increase with PPVI. PRSW and maximum and minimum rate of pressure change in the ventricle showed no statistically significant change, while the minimum rate of pressure change in the ventricle increased (*P*=0.011).

LV Ees (1.31±0.93–1.23±0.72 mm Hg/mL per m^2; *P*=0.68), LV *x* axis intercept of the slope of the end-systolic P-V relationship (−21 [−36 to −17] to −20 [−32 to −15] mL; *P*=0.96), and left ventriculoarterial coupling (0.75 [0.51–1.23]–0.82 [0.53–1.10]; *P*=0.98) did not change significantly with PPVI although systemic Ea increased (0.83±0.26–0.90±0.34 mm Hg/mL per m^2; *P*=0.032). LV stiffness (Eed) was not affected significantly by PPVI (0.05 [0.03–0.13]–0.07 [0.03–0.22] mm Hg/mL per m^2; *P*=0.20), while LV relaxation (τ) increased from 32±5 to 37±8 ms (*P*<0.001).

Correlations

RV Ees showed a significant relationship with pulmonary elastance Ea (r=0.59; *P*=0.008) and an inverse relationship with indexed RVEDV (r=−0.61; *P*=0.005) before PPVI. LV and RV Ees before PPVI were not significantly associated (r=0.22; *P*=0.37), while LV and RV Eed showed a strong relation (r=0.95; *P*<0.001; Figure 3).

Relevance of RV Volume Overload

To assess the effect of RV loading conditions on acute changes in biventricular function, the study population was divided into 2 subgroups according to the severity of PR: patients with moderate/severe (PR fraction ≥25%; group 1) and patients with mild/moderate PR with a regurgitant fraction <25% (group 2; Figure 4; Table S1). No differences were observed between the 2 groups regarding age (*P*=0.78), New York Heart Association class (*P*=0.59), and peak echocardiographic RVOT gradient (*P*=0.86).

Indexed RVEDV was (*P*=0.034) higher in group 1 pre-PPVI but did not change after PPVI in both groups. RVEF was not different between the 2 groups. Both RV Ees (*P*=0.043) and pulmonary Ea (*P*=0.003) were lower in group 1 before PPVI. After PPVI, RV Ees did not change within both groups and was not different post-PPVI (*P*=0.11), while Ea remained elevated in group 2 (*P*=0.034). Right ventriculoarterial coupling was not different before PPVI in both groups (*P*=0.86) and did not change after PPVI (*P*=0.87). No difference in RV Eed response to PPVI was observed between the 2 groups (*P*=0.92).

Indexed LVEDV and LVEF were not different between the 2 groups both before and after PPVI. Systemic Ea increased only in group 1 after PPVI (*P*=0.021) but was not different between the 2 groups (*P*=0.56). LV Ees did not differ between group 1 and group 2, both before (*P*=0.27) and after PPVI (*P*=0.78), while left ventriculoarterial coupling did not change statistically

Table 1. Demographic Data of the Study Population Including Results of the CMR Study Including the Subgroups of Patients With Relevant PR Fraction (≥25% Estimated by CMR) and Those With Minor PR (PR Fraction <25%)

Variable	Total group (N=20)	PR≥25% (n=10)	PR<25% (n=10)	*P* value
Male/female	11/9	7/3	4/6	0.37
Diagnosis, n (%)				
Tetralogy of Fallot, n (%)	10 (50)	6 (60)	4 (40)	
Common arterial trunk, n (%)	4 (20)	0 (0)	4 (40)	
Double outlet right ventricle, n (%)	2 (10)	2 (20)	0 (0)	
Ross (pulmonary autograft) procedure, n (%)	1 (5)	1 (10)	0 (0)	
Pulmonary atresia/ventricular septal defect, n (%)	1 (5)	0 (0)	1 (10)	
Rastelli procedure, n (%)	1 (5)	0 (0)	1 (10)	
Pulmonary artery ectasia, n (%)	1 (5)	1 (10)	0 (0)	
Previous PVR, n (%)	16 (80)	6 (60)	10 (100)	0.08
Age at PPVI, y	23.0±10.9	25.7±13.4	20.8±7.5	0.78
Weight, kg	61±15	64±18	58±12	0.43
Height, cm	168±10	169±11	166±8	0.55
BSA, m^2	1.68±0.25	1.72±0.29	1.65±0.22	0.58
NYHA class I/II/III/IV	7/10/3	4/4/2	3/6/1	0.59
Echocardiography				
Peak RVOT gradient, mm Hg	64±25	63±27	65±24	0.86
TR grade, none or mild/moderate/severe	14/4/2	9/0/1	5/4/1	0.10
CMR				
Heart rate/min	72±16	68±12	76±19	0.29
LVEDVi, mL/m^2	73±16	70±15	77±16	0.54
LVESVi, mL/m^2	31±10	70±15	35±9	0.10
LVSVi, mL/m^2	42±9	43±10	42±10	0.89
LVEF, %	58±8	62±8	55±7	0.06
RVEDVi, mL/m^2	94±20	102±20	85±18	0.07
RVESVi, mL/m^2	44±14	45±16	43±13	0.86
RVSVi, mL/m^2	50±14	57±14	42±10	0.01*
RVEF, %	53±11	57±11	50±10	0.15
PR, %	23±15	36±7	11±8	<0.0001*

Data are presented as mean and SD. BSA indicates body surface area; CMR, cardiac magnetic resonance; EDV, end-systolic volume; ESV, end-diastolic volume; i, indexed to BSA; LV, left ventricle; NYHA, New York Heart Association; PPVI, percutaneous pulmonary valve implantation; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; SV, stroke volume; and TR, tricuspid valve regurgitation.

*XXX.

and significantly and was not different between the groups (*P*=0.77). A nonsignificant rise in LV Eed post-PPVI was observed in group 1 (*P*=0.20), which resulted in a higher (*P*=0.009) LV Eed after PPVI compared with group 2.

Impact of Age

To study the impact of age on the response to PPVI, the study population was divided into 2 groups according to the median age of the group of 18.5 years: the younger group (n=10; mean age, 15.4±2.6 years) and the older group (n=10; mean age, 31.2±10.2 years). No significant differences existed regarding demographic, clinical, and echocardiographic data (Table S2). Besides a higher heart rate in the younger group and minor differences in systemic Ea, PRSW, and LV relaxation (τ), no significant differences were observed between RV and LV hemodynamic parameters, both before and after PPVI, in particular, RV and LV contractility (Ees), compliance (Eed), and ventriculoarterial coupling.

DISCUSSION

Our study reveals novel and unique insights into biventricular performance in patients with RVOT dysfunction and its immediate response to PPVI. Despite an effective reduction in various degrees of RV pressure and volume

Table 2. Hemodynamic Parameters of the RV Derived From Conductance Catheter Measurements (Study Population n=19)

RV	Pre-PPVI	Post-PPVI	Δ Pre-/post-PPVI	*P* value
Pes, mm Hg	40±16	27±12	−11 (−19 to −5)	<0.001*
Ped, mm Hg	6±4	5±3	−1 (−3 to 1)	0.19
RVEDVi, mL/m²	92±21	91±27	−1 (−11 to 2)	0.77
RVESVi, mL/m²	43±14	42±17	−1 (−4 to 3)	0.71
RVSVi, mL/m²	49±14	49±19	1 (−9 to 3)	0.80
RVEF, %	54±11	56±15	1 (−1 to 9)	0.22
dp/dt max, mm Hg/s	336±94	266±88	−66 (−101 to −21)	<0.001*
dp/dt min, mm Hg/s	−357±135	−254±110	75 (13to 198)	<0.001*
PRSW, mm Hg	19 (14to 27)	13 (10to 18)	−4 (−9 to 0)	0.029*
Eed, mm Hg/mL per m²	0.03 (0.01 to 0.07)	0.03 (0.01 to 0.07)	0.0 (−0.01 to 0.01)	0.37
τ, ms	33±10	33±10	2 (−11 to 6)	0.73
Ea, mm Hg/mL per m²	0.32±0.20	0.25±0.19	−0.07 (−0.16 to −0.02)	<0.001*
Ees, mm Hg/mL per m²	0.26 (0.16 to 0.83)	0.19 (0.13 to 0.42)	−0.07 (−0.20 to 0.02)	0.029*
RV V0, mL	18 (5to 35)	12 (−3 to 31)	−5 (−9 to 1)	0.012*
Ea/Ees	1.14±0.61	1.10±0.59	0.02 (−0.31 to 0.29)	0.76

Data are presented as mean and 1 SD or median with interquartile range. dp/dt max indicates maximum and minimum rate of pressure change in the ventricle; dp/dt min, minimum rate of pressure change in the ventricle; Ea, systemic arterial elastance; Ea/Ees, ventriculoarterial coupling; EDV, end-diastolic volume; Eed, ventricular compliance; Ees, ventricular elastance; EF, ejection fraction; ESV, end-systolic volume; i, indexed; Ped, end-diastolic pressure; Pes, end-systolic pressure; PPVI, percutaneous pulmonary valve implantation; PRSW, preload recruitable stroke work; RV, right ventricle; SV, stroke volume; SW, stroke work; τ, time constant of isovolumic relaxation; V0, *x* axis intercept of the slope of the end-systolic pressure-volume relationship; and Δ pre-/post-PPVI, the changes from pre- to post-PPVI.

*XXX.

overload, an instantaneous decline in RV contractility occurred with PPVI that resulted in persistent and inefficient right ventriculoarterial coupling in the majority of patients. The LV adequately adapted to an increase in pre- and post-load with constant LV intrinsic function and preserved ventriculoarterial coupling. Importantly, compared with patients with minor PR, those with relevant RV volume overload showed reduced RV contractility before and decreased LV compliance after PPVI. Furthermore, the patients' age at PPVI did not emerge as a factor associated with parameters of intrinsic RV and LV function.

RV Performance in RVOT Dysfunction and Response to PPVI

Preservation of biventricular function represents a primary objective in the long-term surveillance of patients with dysfunctional RVOTs. Pathophysiologic adaptation of the RV in response to pressure and volume overload has primarily been derived from invasive hemodynamic studies in animals, which provided detailed information on intrinsic biventricular function.[16–18] By assessing real-time P-V loops during PPVI procedures in patients with significant RVOT dysfunction, our study adds important findings to this topic: an immediate decline in RV contractility (both RV Ees and PRSW) occurred with PPVI despite a significant reduction in pulmonary elastance Ea, a composite parameter of all elements of RV afterload. As a result, RV-PA coupling persisted at abnormal levels with coupling ratios >0.66 in the majority of patients who must, therefore, be interpreted as a sign of limited cardiovascular mechanical efficiency. A wide variation in our ventriculoarterial coupling ratio measurements was noted, while its clinical significance remains difficult to define. In fact, a cutoff value for ventriculoarterial coupling that would indicate ventriculoarterial uncoupling in this population is not yet available, and the level of ventriculoarterial uncoupling at which right or LV failure occurs is not exactly known.[9,19,20] Importantly, Tello et al[19] observed a considerable reserve in the RV-PA coupling ratio up to >1.25 in patients with pulmonary hypertension that was associated with other parameters of RV maladaptation. Whether RV-PA coupling will normalize during later follow-up remains yet uncertain and highlights that the long-term process of RV recovery after relief of RV overload is still not sufficiently characterized.

Our finding of decreasing RV contractility post-PPVI is in accordance with a biomechanical model from Gusseva et al,[21] which combined input data from CMR and invasive catheterization to quantify RV performance before and after PVR in 20 patients with repaired TOF. Importantly, RV contractility appeared significantly higher in TOF patients compared with healthy controls and showed the greatest reduction after PVR in patients with predominant pressure overload. Another study used noninvasive P-V loop analysis and found improved hemodynamics with reduced RV stroke work after PVR.[22] A

Table 3. Hemodynamic Parameters of the LV Derived From Conductance Catheter Measurements (Study Population n=19)

LV	Pre-PPVI	Post-PPVI	Δ Pre-/post-PPVI	*P* value
Heart rate/min	71±12	65±19	−7 (−13 to −2)	0.010*
CI, L/min per m²	3.0±1.0	3.1±1.2	−0.1 (− 0.4 to 0.5)	0.98
Pes, mm Hg	91±15	106±12	14 (5to 22)	<0.001*
Ped, mm Hg	8±3	10±4	3 (1to 7)	0.005*
LVEDVi, mL/m²	73±16	79±23	5 (−1 to 11)	0.038*
LVESVi, mL/m²	30±10	31±12	1 (−1 to 3)	0.59
LVSVi, mL/m²	43±10	48±16	4 (1to 8)	0.028*
LVEF, %	59±9	61±9	1 (−1 to 5)	0.10
dp/dt max, mm Hg/s	894±173	905±177	14 (−101 to 36)	0.71
dp/dt min, mm Hg/s	−981±157	−1064±138	−118 (−135 to 30)	0.011*
PRSW, mm Hg	54±26	61±24	10 (−4 to 13)	0.09
Eed, mm Hg/mL per m²	0.05 (0.03 to 0.13)	0.07 (0.03 to 0.22)	0.02 (−0.01 to 0.04)	0.20
τ, ms	32±5	37±8	5 (2to 7)	<0.001*
Ea, mm Hg/mL per m²	0.83±0.26	0.90±0.34	0.05 (−0.02 to 0.16)	0.032*
Ees, mm Hg/mL per m²	1.31±0.93	1.23±0.72	0.11 (−0.32 to 0.48)	0.68
LV V0, mL	−21 (−36 to −17)	−20 (−32 to −15)	1 (−4 to 7)	0.96
Ea/Ees	0.75 (0.51 to 1.23)	0.82 (0.53 to 1.10)	−0.02 (−0.22 to 0.20)	0.98

Data are presented as mean and 1 SD or median with interquartile range. dp/dt max indicates maximum rate of pressure change in the ventricle; dp/dt min, minimum rate of pressure change in the ventricle; Ea, systemic arterial elastance; Ea/Ees, ventriculoarterial coupling; EDV, end-diastolic volume; Eed, ventricular compliance; Ees, ventricular elastance; EF, ejection fraction; ESV, end-systolic volume; i, indexed; LV, left ventricle; Ped, end-diastolic pressure; Pes, end-systolic pressure; PPVI, percutaneous pulmonary valve implantation; PRSW, preload recruitable stroke work; SV, stroke volume; SW, stroke work; V0, *x* axis intercept of the slope of the end-systolic pressure-volume relationship; Δ pre-/post-PPVI, the changes from pre- to post-PPVI; and τ, time constant of isovolumic relaxation.

*XXX.

different response of the LV to acute unloading was reported in a study that performed P-V loop measurements during transcatheter aortic valve implantation and revealed no statistically significant change in LV contractility but improved ventriculoarterial coupling and cardiac output due to a reduction in pre- and post-load.[23]

In addition, our study also noted a significant inverse relationship between RV Ees and Ea before PPVI, suggesting that the RV may adjust its mechanical work by reducing contractility when afterload acutely decreases. Data from animal studies seem to support this finding by showing that the RV adaptation to pressure load is characterized by increased contractility to restore ventriculoarterial coupling.[17,18] However, it must also be considered that extrinsic factors such as repeated RVOT balloon occlusions during the PPVI procedures might have a negative impact on RV contractility and may also account for the acute decline in RV Ees.[24]

Restrictive RV filling has been described as an important hemodynamic burden among patients with dysfunctional RVOT, but the effect of PPVI on RV filling characteristics and its clinical implications are not yet clarified. It should be noted that RV diastolic performance was not directly influenced by PPVI: both τ, a parameter of early ventricular relaxation, and RV compliance Eed did not change significantly. This finding supports the study from Romeih et al[25] that reported a delayed improvement in RV diastolic function compared with early recovery of systolic RV performance. The authors attributed this finding to a reduction in RV mass, a process that may last for several months and might explain why diastolic function did not improve immediately after PPVI in our study. Contrary results exist from other studies that assessed the impact of PPVI on RV diastolic function using different imaging modalities and reported either improved or nonsignificant changes in RV filling.[26,27] Our group recently published CMR data on atrial emptying function in a larger group of patients undergoing PPVI and found an improvement in early RV filling.[15] Consequently, uncertainties regarding the effect of PPVI on intrinsic RV diastolic function still remain and need to be addressed in future studies.

Interventricular Interactions and LV Performance

LV dysfunction represents an important risk factor for adverse clinical outcomes in patients after repair of TOF burdened by various degrees of volume and pressure overload.[2,28–30] In addition to impaired systolic LV function, diastolic impairment and adverse interventricular interactions are well described in patients with RVOT dysfunction.[31–34] Although the underlying mechanisms for these altered ventricular mechanics are not yet understood

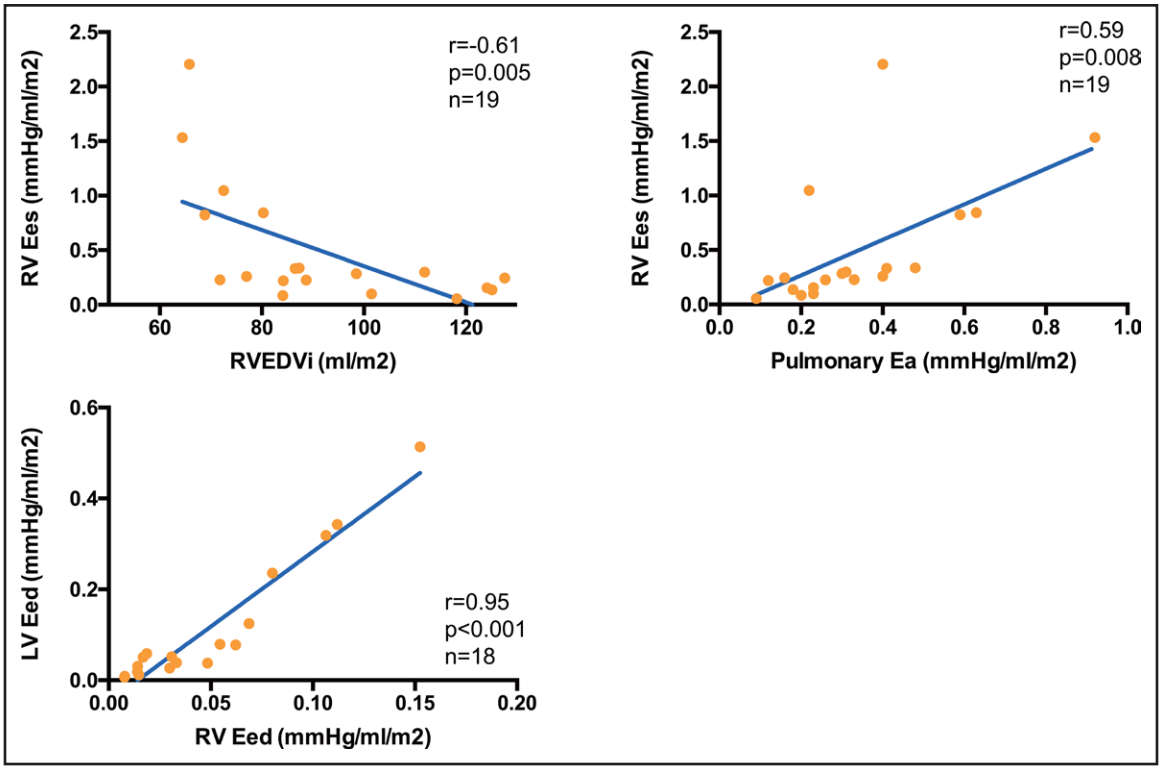

Figure 3. Graph displaying several significant linear associations between important hemodynamic parameters before percutaneous pulmonary valve implantation (PPVI) assessed by pressure-volume loop analysis.
With increasing right ventricular (RV) dimensions (RV end-diastolic volumes, RVEDVi), a decrease in RV contractility (RV ventricular elastance [Ees]) was noted, which illustrates that, in the remodeling process with (even mild) dilatation of the RV, a reduction in contractility is already occurring. A significant association was also noted between RV Ees and RV (pulmonary) elastance (systemic arterial elastance [Ea]) as a measure of total RV afterload. This finding might be interpreted as the aim of the RV to increase its contractility to compensate for higher afterload to maintain adequate ventriculoarterial (V-A) coupling. A strong and significant relationship was also detected between diastolic ventricular compliance Eed, suggesting that adverse interventricular interactions may promote diastolic dysfunction in this patient population.

in detail, fibrotic myocardial remodeling and chronically reduced LV preload seem to have a major impact.[35–37] Our findings support the existence of interventricular cross-talk with a strong association between RV and LV diastolic compliance Eed. On the contrary, such a significant relationship was not present between RV and LV elastance Ees. Whether this is a sign of early systolic impairment with a loss of beneficial ventricular-ventricular interaction remains speculative. In this context, it must be considered that quantification of ventricular elastance was solely determined at the resting state, whereas inotropic stimulation with assessment of a contractile reserve was not part of the study protocol.[7]

Our study further showed an immediate increase in LV end-diastolic volume, indicating an increment in preload, while the rise in end-systolic LV pressure and systemic Ea indicates an increment in systemic arterial afterload. LV load-independent parameters, namely, Ees, Eed, and PRSW, were not affected, and ventriculoarterial coupling remained constant within the reported normal limits in the majority of patients (only 2 patients showed an abnormal left ventriculoarterial coupling ratio). Accordingly, PPVI acutely altered the filling of the LV, whereas the LV was capable of adapting to these rapid volume and pressure loads without signs of pulmonary edema or LV diastolic failure.

Impact of RV Volume Overload

We were able to demonstrate that patients with relevant PR showed reduced RV contractility before PPVI and decreased LV compliance after PPVI. Furthermore, a significant association was found between larger RV dimensions and lower Ees before PPVI. Accordingly, biventricular performance and RV-LV interactions seem to be distinctly different between primarily pressure and volume-loaded RVs. Several previous studies suggested that response patterns to PPVI differ between pressure and volume-loaded RVs.[4,15,38] In an early pilot study by Lurz et al[4] who investigated the effect of PPVI, RVEF recovered only in patients with primary stenosis, whereas it did not change statistically and significantly in patients with primary PR. Another study found a significant increase in RV strain after PPVI solely in the group with predominant stenosis and a significant improvement in LV strain in both groups.[38]

Our findings in a human population match with a recent animal study by Jani et al,[39] who used invasive P-V

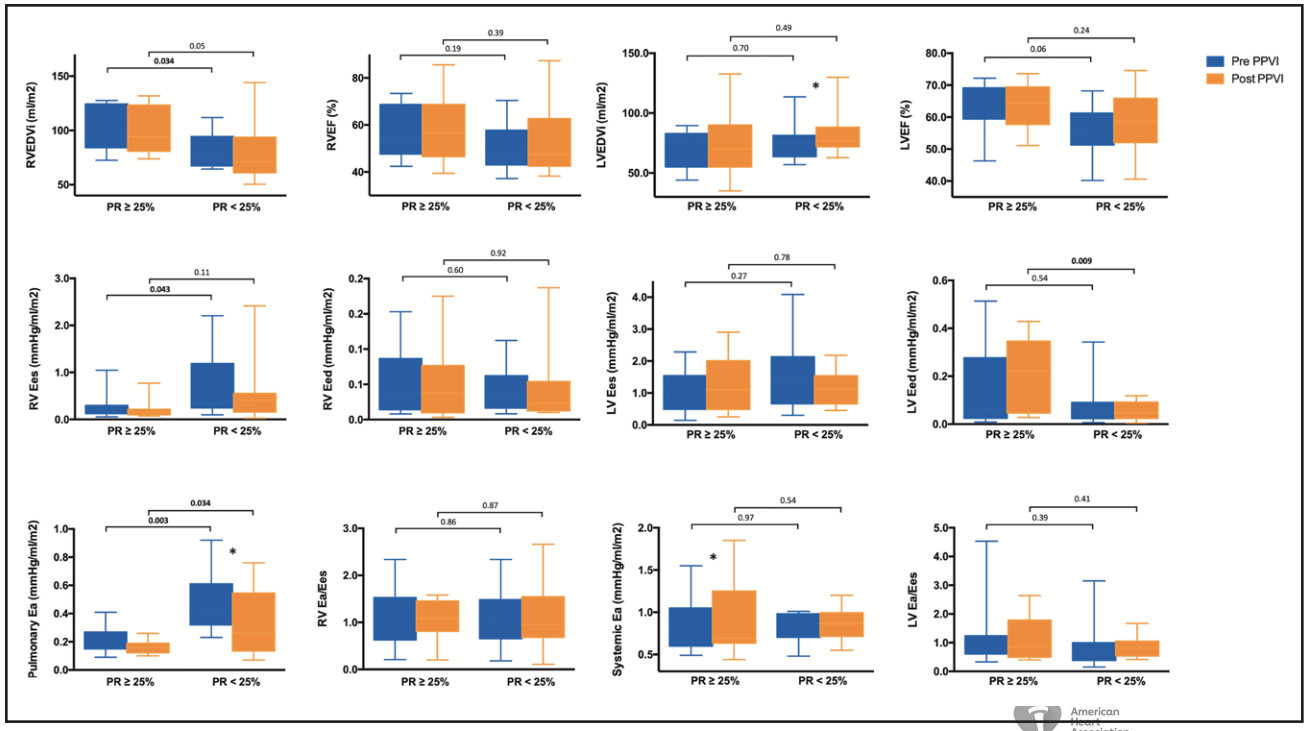

Figure 4. Comparison of the subgroup of patients with relevant pulmonary regurgitation (PR fraction ≥25% estimated by cardiac magnetic resonance (n=10) and those with minor PR (PR fraction <25%; n=10) for both the right ventricle (RV) and left ventricle (LV).

Patients with relevant PR showed lower RV contractility, ventricular elastance (Ees; *P*=0.043), and RV pulmonary elastance (systemic arterial elastance [Ea]; an estimate of pulsatile RV afterload; *P*=0.003) before and reduced LV compliance (Eed; *P*=0.010) after percutaneous pulmonary valve implantation (PPVI) compared with patients with minor PR. Both right and left ventricular-arterial coupling (Ea/Ees) were similar between the 2 groups before and after PPVI. Box-and-whiskers plots for the key variables. The central line represents the median with the boxes representing minimum and maximum values. EDVi indicates end-diastolic volume; and EF, ejection fraction. * indicates a significant within change pre- vs post-PPVI in the corresponding subgroup.

loop assessment in a porcine model of pulmonary stenosis and insufficiency. Importantly, as seen in our analysis, the authors found LV noncompliance and reduced RV contractility in the subgroup with PR.[39] However, other than reported in their study, RV compliance and LV contractility did not seem to be different in our subgroups both before and after PPVI. It is important to emphasize that both our subgroups included patients with relevant RVOT stenosis, and a subgroup with pure PR (as frequently present in patients after TOF repair with native RVOT) was not available.

Does Age Impact Response to PPVI?

Defining the best individual time point for PPVI needs to consider the patients' age as a potential factor, which may affect the biventricular response to PPVI.[40] Our analysis of 2 subgroups (cutoff, 18.5 years of age) demonstrated significant differences only in a minor number of hemodynamic parameters that may reflect physiological changes with increasing age such as LV relaxation and systemic afterload. The study by Borik et al[41] reported that PPVI at a younger age is associated with better RV function, reduction in RV size, and improvement in exercise capacity. In another study investigating patients with severe PR undergoing surgical PVR, Frigiola et al[40] observed a normalization of exercise performance in patients aged <17.5 years with the younger subgroup showing a greater benefit to PVR with better LV filling and cardiac output. Accordingly, as the results of our study show no evidence for an age-dependency of functional indices, future studies might focus on determining the relevance of the exact onset and duration of relevant RVOT dysfunction in this population.

Study Limitations

The limited number of patients included in our study and various congenital heart diagnoses may not allow us to detect any causal relationships between hemodynamic parameters and patients' demographic characteristics. This is particularly relevant for the subgroup analysis of patients with major versus those with minor PR. The fact that only patients with implantation of a Melody valve were included may result in a selection bias toward smaller outflow tracts. Nevertheless, the assessed parameters provide unique insights into cardiovascular interactions and mechanical efficiency that occur with PPVI.

Invasive measurement of P-V loops using the conductance catheter technique is a demanding and complex diagnostic procedure. It is invasive, needs volume calibration, and may substantially prolong a cardiac catheterization examination. To minimize variance in hemodynamics that occur throughout the respiratory cycle, P-V loop measurements should ideally be performed in intubated patients during a breath-hold maneuver.[42]

Although we used the gold standard for assessment of load-independent functional parameters during preload reduction, the reported Ea, Ees, and ventriculoarterial coupling values in our study differ from those in other studies. Importantly, normal values for load-independent parameters of LV and RV function (Ees and Eed) and ventriculoarterial coupling of an age- and gender-matched healthy control group are not available but would enable a more comprehensive interpretation of our findings. Furthermore, differences in heart rate before and after PPVI, as well as between the subgroups studied, may affect ventricular volumes and diastolic parameters (by modulating the duration of diastole), while Ea is known to be influenced by heart rate.[43] Furthermore, objective data on exercise performance other than New York Heart Association functional class (such as cardiopulmonary exercise testing or 6-minute walk distance) were not assessed in the entire patient population before and after PPVI. Finally, how these acute hemodynamic changes relate to midterm clinical outcomes could not be adequately assessed with the chosen study.

Conclusions

The results of our study suggest that parameters of biventricular intrinsic myocardial function are directly modulated by PPVI. Acute relief of pressure and volume overload of the RV is accompanied by an instantaneous decline in RV contractility, resulting in persistent and inefficient ventriculoarterial coupling. The LV adequately adapts to an increase in pre- and post-load with nonsignificant changes in LV intrinsic function and ventriculoarterial coupling. The ventricular response patterns further vary dependent on the type of RVOT lesion with primary volume-loaded RVs displaying reduced RV contractility before and decreased LV compliance after PPVI.

It remains unclear whether these acute changes may help to predict clinical improvement and translate into a favorable outcome post-RVOT intervention.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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