

Mechanism of the right ventricular reverse remodeling after balloon pulmonary valvuloplasty in patients with congenital pulmonary stenosis: A three-dimensional echocardiographic study

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ABSTRACT

- Background and Objectives** : The main effect of pulmonary stenosis is a rise in right ventricular pressure. This pressure overload leads to multiple changes in the shape, dimensions, and volumes of the right ventricle (RV) that are reversed after the relieve of the valve obstruction. We thought to study the changes in the RV in patients undergoing balloon pulmonary valvuloplasty (BPV) using three-dimensional (3D) echocardiography.
- Subjects and Methods** : The study included 50 patients with isolated valvular pulmonary stenosis who underwent BPV at our hospital from December 2016 to August 2017; echocardiography was recorded preprocedural and 3 months after the procedural.
- Results** : The median age of the study group at the time of the procedure was 2.7 years. The indexed RV wall thickness, basal, and mid-right ventricular dimensions decreased significantly after the procedure ($P < 0.005$), and the longitudinal dimension increased significantly after the procedure ($P < 0.005$). The end-systolic and the end-diastolic volumes (EDVs) by 3D echocardiography increased insignificantly ($P > 0.05$), and the right ventricular function increased significantly ($P < 0.05$), indicating that the changes in the EDVs were more than the changes in the end-systolic volumes.
- Conclusions** : There are several factors that interplay together and result in reverse remodeling of the RV after BPV including regression in the RV hypertrophy; changes in the interventricular septal morphology, bowing, and mobility; and changes in the ventricular geometry and dimensions, rather than changes in the ventricular volumes.
- Keywords** : Balloon pulmonary valvuloplasty, balloon pulmonary valvuloplasty, pulmonary stenosis, right ventricular reverse remodeling, three-dimensional echocardiography

INTRODUCTION

Pulmonary stenosis is the second most common congenital cardiac malformation which comprises 7.5%–9% of all congenital heart defects.^[1]

Secondary changes in the right ventricle (RV) and pulmonary arteries occur as a result of pulmonary valve obstruction.^[2]

The main physiologic effect of valvular pulmonary stenosis (PS) is a rise in RV pressure proportional to the severity of obstruction. This elevation of RV pressure is accompanied by an increase in muscle mass where hyperplasia of the muscle cells with a concomitant

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increase in the number of capillaries occurs. In contrast, the adult myocardium responds with hypertrophy of the existing fibers, with no change in the capillary network.^[2]

This is associated with changes in the morphology and the mobility of the interventricular septum, as well as the dimensions, volumes, and morphology of the right ventricular cavity.^[2]

After successful balloon pulmonary valvuloplasty (BPV), these changes are reversed, so we thought to study and evaluate these changes by three-dimensional (3D) echocardiography.

Aim

The aim was to study the changes in the function, dimensions, and volumes of the RV using 3D echocardiography before and 3 months after percutaneous BPV in patients with congenital pulmonary stenosis.

SUBJECTS AND METHODS

Methods

This study was approved by our institutional review board and informed consent was obtained from the parents of all the children enrolled in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

The study included 50 patients with isolated valvular pulmonary stenosis who underwent BPV at our hospital from December 2016 to August 2017; echocardiography was recorded preprocedural and 3 months after the procedural.

Data collection

Patient demographic data included age at the time of the procedure, gender, body weight, and body surface area.

Pre-BPV-echocardiographic data included pulmonary valve annulus, peak pressure gradient across the pulmonary valve, valve morphology, degree of tricuspid regurgitation (TR), degree of pulmonary regurgitation, and right ventricular dimensions, volumes, and functions by 2D and 3D echocardiography.

Right ventricle assessment

Imaging views

Apical four-chamber (RV focused), modified apical four-chamber, left parasternal long axis and parasternal short axis, left parasternal RV Inflow, and subcostal views were used for the comprehensive assessment of the RV. Right ventricular hypertrophy and contractility were observed. The RV dimensions were measured at end-diastole from a RV-focused apical four-chamber view without foreshortening.^[3]

Right ventricle dimensions and free wall thickness

RV dimensions were measured by 3D echocardiography in the apical four chamber view at the end diastole. The

basal diameter was defined as the maximal short axis dimension in the basal one third of the RV cavity, the mid RV diameter was measured in the middle third of the RV at the level of the left ventricular (LV) papillary muscles, while the longitudinal dimension was drawn from the RV apex to the mid point of the TV annulus. RV wall thickness was measured in diastole, from the parasternal long axis view [Figure 1].^[3]

Right ventricle volumes

At the apical four-chamber view, a 2DQ software automatically traced the end-diastole and end-systole frames and consequently detected the end-diastolic volume (EDV) and the end-systolic volume (ESV) using the area length method. Manual adjustment was done when needed to include the myocardial trabeculae and papillary muscles and to optimize the RV border tracing. The software generates volume/time curves through which the EDV and ESV were measured.^[3]

Right ventricle function

Fractional area change

The fractional area change was estimated by tracing the RV in the apical four-chamber view to obtain the end-diastolic and the end-systolic areas, and then, the percentage change between them was calculated according to the following equation:^[3]

$$\text{Fractional Area Change} = \frac{(\text{End - Diastolic area}) - (\text{End - Systolic area})}{(\text{End - Diastolic area})}$$

Tricuspid annular peak systolic excursion

M-mode was used to estimate the RV function by applying M-mode to the lateral TV annulus in the apical four-chamber view and then measuring the peak distance of annular motion [Figure 1].^[3]

Doppler evaluation

The severity of pulmonary valve stenosis was assessed by applying continuous-wave Doppler across the PV flow to estimate the pressure drop across the pulmonary valve using the simplified Bernoulli equation which states that $P = 4 (V_2)^2$, where P is the peak instantaneous pressure gradient, in millimeters of mercury (mmHg), across the pulmonary valve, and V_2 is the peak flow velocity, in meters per second, distal to the orifice. The degree of stenosis was classified into: Moderate PS (peak pressure gradient [PPG] of 30–64 mmHg) and severe PS (PPG >64 mmHg).^[4]

Three-dimensional echocardiography

After completing the two-dimensional echocardiography, all the cases were subjected to electrocardiogram gated 3D echocardiography using the same Phillips iE33 echocardiography machine. RV data sets were recorded during a four-beat acquisition (obtaining one subvolume during each heartbeat). The subvolumes were

then electronically merged into one dataset from the four-chamber apical view ensuring that the entire RV was viewed simultaneously in both orthogonal planes with minimal spatial and temporal artifacts. Both the patient and the transducer positions were modified for optimal simultaneous visualization, and then, a full-volume loop was acquired. The data sets were then stored for further analysis.^[5]

QLAB 10 quantification software was used to assess the image quality including analyzable RV apex, lateral wall, and tricuspid valve. Manual tracing of the endocardial border was done during the end-diastolic phase and the end-systolic phase. The software then automatically delineated the RV endocardial border. By sequential analysis, the software created an RV mathematic dynamic 3D endocardial surface that represents changes in the RV cavity over the cardiac cycle. From this 3D endocardial surface, global RV volumes and ejection fraction (EF) were automatically calculated [Figure 2].^[6]

Procedural data included pre- and postprocedure pressure gradient, pulmonary valve annulus, balloon type and balloon size used, balloon-to-annulus ratio, and any intra or immediate postprocedure complications.

Follow-up echocardiogram

All patients underwent follow-up echocardiographic study 3 months after the procedure using a Philips IE33 machine with emphasis on the evaluation of the RV.

The degree of residual pulmonary stenosis as well as the degree of pulmonary regurgitation and TR was recorded.

RESULTS

The study included 20 males (40%) and 30 females (60%) with a mean age of 2.7 years (ranged from 6 months to 21 years). The patient's body surface area ranged from 0.2 to 1.92 m², with a mean of 0.5 m²; their height ranged from 50 to 172 cm, with a mean of 79.7 cm;

and their weight ranged from 3 to 85 kg, with a mean of 14.1 kg [Table 1].

There was a highly significant drop in pressure gradient cardiac catheterization from a mean of 67.84 ± 13.47 mmHg before BPV to a mean of 27.56 ± 3.80 mmHg immediately after BPV and that concurred with the drop of the pressure gradient measured by echocardiography that dropped from a mean of 80.4 ± 28.8 mmHg before BPV to a mean of 17.1 ± 8.4 mmHg immediately after successful BPV; this drop in the PG was maintained during the follow-up.

The change in the RV end-diastolic pressure and the pulmonary artery diastolic pressure showed a nonsignificant change before and after BPV as measured by cardiac catheterization with values of 6.40 ± 1.44 mmHg and 6.38 ± 1.32 mmHg before and after BPV for the end-diastolic pressure and 10.68 ± 2.11 mmHg and 10.50 ± 2.05 mmHg for the pulmonary artery diastolic pressures.

The change in the pulmonary artery systolic pressure increased significantly before and immediately after BPV as measured by catheterization from 20.34 ± 2.43 mmHg to 19.58 ± 2.15 mmHg with $P = 0.015$.

Early restenosis was detected in three cases (6%) as they reported a PPG across PV >36 mmHg, while 47 cases (94%) reported a PPG across PV <36 mmHg recorded by Doppler echocardiography at the 3-month follow-up after BPV.

Table 1: Demographic characteristics of the study groups

Characteristic	Value
Gender (male/female), mean±SD	20/30
Age (months), mean±SD	32.571±56.971
Weight (kg), mean±SD	14.198±16.720
Height (cm), mean±SD	79.780±30.865
BSA (m ²), mean±SD	0.530±0.397
PV annulus indexed to BSA (mm/m ²), mean±SD	25.582±8.516

SD: Standard deviation, BSA: Body surface area, PV: Pulmonary valve

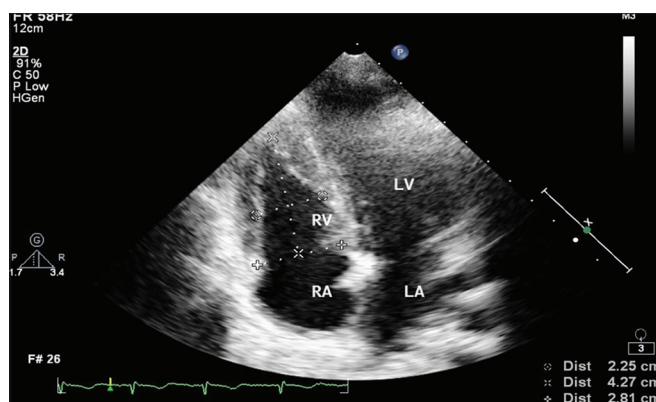


Figure 1: Showing the apical four-chamber view right ventricle focused measuring dimensions in patient number 16

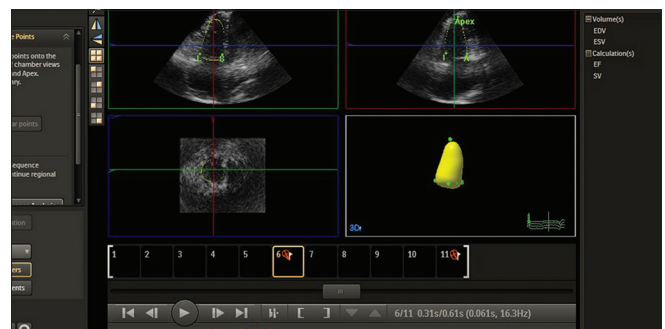


Figure 2: Apical four-chamber view showing the end-diastolic volume, end systolic volume and right ventricle function automatically calculated by the software after manual tracing of the right ventricle endocardial borders in both end-diastolic and end-systolic phases and a three-dimensional image of the right ventricle at the end-systolic phase in patient number 1

At follow-up, there was no significant increase in patients with pulmonary regurgitation (PR) and TR compared to baseline before BPV; 82% had mild PR, 18% had trivial PR, 54% had mild TR, and 46% had trivial TR.

The right ventricle free wall thickness indexed to body surface area

It decreased from a mean of 13.2 ± 4.84 mm/m² before BPV to a mean of 10.01 ± 3.11 mm/m², and this decrease was statistically highly significant with $P < 0.001$ [Figure 3].

The basal right ventricle dimension (V1) indexed to body surface area

It decreased from a mean of 6.74 ± 3.68 cm/sqm before BPV to a mean of 5.90 ± 2.87 cm/sqm after successful BPV, and the decrease was statistically highly significant with $P = 0.001$ [Figure 4].

The mid-right ventricle dimension (V2) indexed to body surface area

It decreased from a mean of 5.44 ± 3.14 cm/m² before BPV to a mean of 4.87 ± 2.38 cm/m², and the decrease was statistically significant with $P = 0.018$.

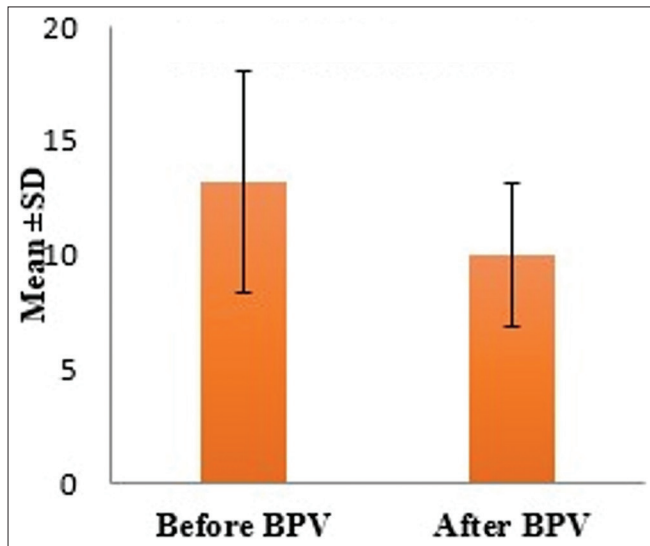


Figure 3: Right ventricle wall thickness before and after balloon pulmonary valvuloplasty

Before BPV, the transverse dimensions of 32 patients were above the normal values. After BPV, the transverse dimensions of those patients decreased; 22 of them restored their normal values, while the transverse dimensions of the other ten patients were still above the normal values.

The longitudinal right ventricle dimension (V3) indexed to body surface area

It increased from a mean of 10.48 ± 5.46 cm/m² before BPV to a mean of 11.36 ± 5.69 cm/sqm after successful BPV, and the increase was statistically highly significant with $P = 0.003$.

Before BPV, the longitudinal dimensions of 26 patients were below the normal values. After BPV, three of them showed a slight increase in the longitudinal dimension yet remained below normal values, while the other 23 patients regained their normal values. It was noted that six patients of those who denoted longitudinal dimensions within normal values before BPV showed an increase in their longitudinal dimension after BPV yet remained within the normal values.

Regarding the Z-score values for the RV dimensions, there was statistically highly significant changes in these parameters before and after BPV with median value and interquartile range of 1.10 (0.7-1.4) before BPV and 1.20 (0.9-1.4) after BPV.

The end-diastolic right ventricle volume indexed to body surface area measured by two-dimensional echocardiography

It increased from a mean of 28.71 ± 13.49 ml/m² before BPV to a mean of 28.95 ± 13.43 ml/m² after successful BPV, but this increase was statistically insignificant with $P = 0.086$.

The end-systolic right ventricle volume indexed to body surface area measured by two-dimensional echocardiography

It increased from a mean of 14.31 ± 8.69 ml/m² before BPV to a mean of 14.77 ± 8.96 ml/sqm after successful BPV, but this increase was statistically insignificant with a $P = 0.053$.

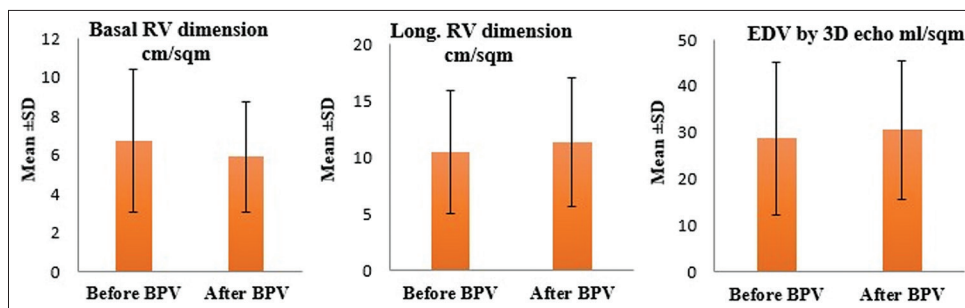


Figure 4: Right ventricle dimensions before and after balloon pulmonary valvuloplasty

The fractional area change

It increased from a mean of 51.99% \pm 9.57% before BPV to a mean of 55.41% \pm 10.02% after successful BPV, and this increase was statistically significant with $P = 0.021$.

Tricuspid annular peak systolic excursion

It increased from a mean of 21.58 \pm 3.22 mm before BPV to a mean of 22.5 \pm 3.41 mm after successful BPV, and the increase was statistically highly significant with $P = 0.005$ [Table 2].

Regarding the RV diastolic parameters, there were no significant changes in the tricuspid valve E velocity, A velocity, and E/A ratio before and after BPV [Figure 5].

The E/E' of the TV lateral annulus showed statistically highly significant changes after BPV with a value

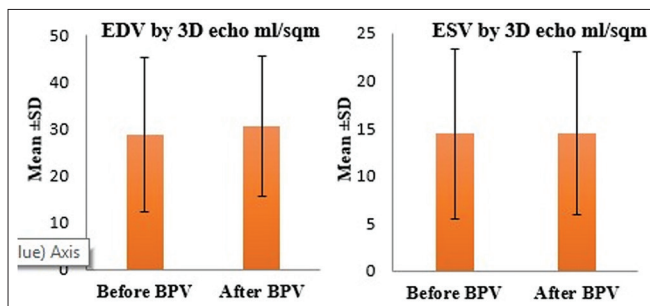


Figure 5: Changes in the right ventricle indexed volumes by three-dimensional echocardiography before and after balloon pulmonary valvuloplasty

of 6.90 \pm 1.02 before BPV and value of 6.10 \pm 0.85 after BPV, although the changes in the RV diastolic dysfunction grade did not show statistically significant changes before and after BPV; this may suggest that it may take a longer time until the RV diastolic dysfunction grade improves.

Three-dimensional echocardiography assessment before and three months after balloon pulmonary valvuloplasty

The end-diastolic right ventricle volume indexed to body surface area

It increased from a mean of 28.77 \pm 16.45 ml/sqm before BPV to a mean of 30.51 \pm 15.03 ml/m² 3 months after successful BPV, and this increase was statistically insignificant with a $P = 0.085$.

End-systolic right ventricle volume indexed to body surface area

It increased from a mean of 14.39 \pm 8.85 ml/m² to a mean of 14.45 \pm 8.52 ml/m² 3 months after successful BPV, and this increase was statistically insignificant with $P = 0.94$ [Figure 5].

Right ventricle function by three-dimensional echocardiography

It increased from a mean of 50.72% \pm 8.074% before BPV to a mean of 53.74% \pm 9.56% 3 months after successful BPV, and this increase was statistically significant with $P = 0.043$, which indicates that the increase in the right ventricular EDV index (RVEDVI) was larger than the increase in the right ventricular ESV index (RVESVI).

Table 2: Two-dimensional echocardiographic measurement before and three months after balloon pulmonary valvuloplasty

	Time		Paired differences (SD)	Paired samples test (P)
	Before BPV	3 months after BPV		
PPG (mmHg), mean \pm SD (range)	80.440 \pm 28.820 (40-166)	17.120 \pm 8.441 (6-40)	28.922	<0.001*
Basal RV dimension indexed (cm/m ²), mean \pm SD (range)	6.746 \pm 3.681 (2.2-22.8)	5.900 \pm 2.876 (1.8-13.8)	1.622	0.001*
Mid-RV dimension indexed (cm/m ²), mean \pm SD (range)	5.444 \pm 3.141 (1.4-18.5)	4.874 \pm 2.382 (1.1-12.5)	1.647	0.018*
Long. RV dimension indexed (cm/m ²), mean \pm SD (range)	10.488 \pm 5.462 (1.7-31)	11.362 \pm 5.694 (3.6-30.9)	1.948	0.003*
EDV indexed (ml/m ² 2D), mean \pm SD (range)	28.710 \pm 13.495 (6.1-88)	28.952 \pm 13.434 (8.1-88)	0.975	0.086
ESV indexed (ml/m ² 2D), mean \pm SD (range)	14.316 \pm 8.697 (2.1-54)	14.778 \pm 8.965 (2.7-55)	5.241	0.536
FAC (%), mean \pm SD (range)	51.996 \pm 9.579 (32.4-77)	55.410 \pm 10.024 (38-75)	10.106	0.021*
TAPSE (mm), mean \pm SD (range)	21.580 \pm 3.220 (14-27)	22.500 \pm 3.412 (16-28)	2.202	0.005*
RV wall thickness indexed (ml/m ²), mean \pm SD (range)	13.207 \pm 4.849 (3.54-25)	10.011 \pm 3.118 (35-16.6)	2.934	<0.001*

SD: Standard deviation, RV: Right ventricle, EDV: End-diastolic volume, ESV: End-systolic volume, FAC: Fractional area change, TAPSE: Tricuspid annular peak systolic excursion, BPV: Balloon pulmonary valvuloplasty, PPG: Peak pressure gradient, 2D: Two-dimensional, *Values are statistically significant

Table 3: Three-dimensional echocardiographic measurement before and three months after balloon pulmonary valvuloplasty

	Time		Paired differences (SD)	Paired samples test (P)
	Before BPV	3 months after BPV		
EDV indexed (ml/m ² by 3D), mean \pm SD (range)	28.772 \pm 16.456 (6.2-111)	30.518 \pm 15.031 (7.5-97)	7.015	0.085
ESV indexed (ml/m ² by 3D), mean \pm SD (range)	14.396 \pm 8.857 (2.1-56.6)	14.454 \pm 8.523 (2.5-50)	5.719	0.943
3D-RV (function percentage), mean \pm SD (range)	50.722 \pm 8.074 (34-70)	53.740 \pm 9.568 (17.9-73)	10.261	0.043*

3D: Three-dimensional, BPV: Balloon pulmonary valvuloplasty, EDV: End-diastolic volume, SD: Standard deviation, ESV: End-systolic volume, RV: Right ventricle. *Values are statistically significant

Only nine cases (18%) had trivial PR recorded by Doppler echocardiography at the 3-month follow-up after BPV, while 82% of the patients had mild PR.

Early restenosis was detected in three cases (6%) as they reported a PPG across PV >36 mmHg, while 47 cases (94%) reported a PPG across PV <36 mmHg recorded by Doppler echocardiography at the 3-month follow-up after BPV [Table 3].

DISCUSSION

The main effect of pulmonary stenosis is a rise in right ventricular pressure. This elevation is accompanied by multiple changes in the RV muscle and geometry, including changes in the morphology, movement of the interventricular septum, as well as changes in the shape of the RV cavity, and an increase in the RV muscle mass.^[2]

Since the first description of BPV in 1982 by Kan, the procedure became the treatment of choice. Immediate reduction of gradient and increase in jet width and free motion of the pulmonary valve leaflets with less doming have been observed following balloon dilatation. Improvement of right ventricular function has also occurred.^[1] There are insufficient data about the effects of BPV on RV geometry, volumes, and function in patients with congenital pulmonary stenosis mainly because the quantification of RV size and function with conventional echocardiography is challenging because of the anterior position of the RV in the chest, its complex asymmetrical geometry, complex crescentic shape, highly trabeculated endocardial border, impossibility to simultaneously visualize both inflow and outflow tracts, and the lack of realistic geometric models for volume calculation.

Indeed cardiac magnetic resonance (CMR) is the current gold standard for the quantification of RV geometry and function, but its widespread use is limited by costs, time consumption, and contraindications, making it unsuitable for patients screening or monitoring on large scale.^[7]

As right ventricular size and function have been found to be important predictors of cardiovascular morbidity and mortality, the development of novel echocardiographic techniques including 3D became a must and opened new exciting opportunities in right ventricular imaging.

3D echocardiography has proven accuracy in measuring RV volumes and function when compared with CMR.^[8]

Echocardiography is a widely available imaging technique particularly suitable for follow-up studies because of its noninvasive nature, low cost, and lack of ionizing radiation or radioactive agent. Real-time 3D echocardiography has been shown to be accurate in assessing RV and LV volumes, stroke volumes, and EFs in comparison with CMR imaging.^[8]

Where several studies in the past decades have focused on the intermediate and long-term follow-up after BPV,^[9-11] independent predictors of long-term results, causes of restenosis,^[12] balloon annulus ratio, and predictors of pulmonary regurgitation,^[13] we did not find much data on the reverse remodeling of the RV after BPV.

In the current study, there was an interaction of several factors in the RV after BPV.

Three months after BPV, the transverse dimensions of the RV were significantly reduced in comparison to the preprocedural dimensions; this may be due to changes in the RV lateral wall and the interventricular septum morphology after reduction of the RV pressure with decreased interventricular flattening and bowing.

The changes in the transverse dimensions of the RV seem to be also as a result of regression in the RV wall thickness that decreased significantly after BPV.

The longitudinal dimension of the RV was significantly increased after BPV, suggesting that after relieve of the RV pressure, the dilated RV regains its normal elongated geometry rather than globular shape.

The data of our study concur with the results published by Broch *et al.* in 2016; when they studied the effect of pressure overload reduction on the RV in 26 patients with chronic thromboembolic pulmonary hypertension (CTEPH), they found that the reduction in the RV pressure leads to a significant decrease in the RV end-diastolic diameter, area, and free wall thickness.^[14]

Fukui *et al.* have also demonstrated that in 20 patients with CTEPH, the RV reverse remodeling by magnetic resonance imaging was due to the regression in the RV thickness and marked improvement in the RV mass and interventricular septal bowing.^[15]

In our current study, although the RVESVI and RVEDVI volumes by 3D echocardiography increased after BPV, none of these changes were statistically significant, indicating that the immediate and short-term changes after BPV are more related to the changes in the geometry and regression of hypertrophy rather than significant changes in the volumes.

Fukui *et al.* have demonstrated in their study that the RV end-diastolic and ESV index markedly improved, with concomitant improvements in RV EF.^[15]

These results concur with the study of Tsugu *et al.*, which showed a significant improvement in the RV volumes and EF in patient with CTEPH after balloon pulmonary angioplasty.^[16]

These results suggest that the mechanism of RV reverse remodeling in patients with CTEPH after balloon pulmonary angioplasty shares partially some features with the changes that occur in patients with congenital PS after BPV.

In the current study, only patients with trivial and mild TR and PR were included because we intended to study the changes in RV that result from the relieve of the elevated RV pressure without the development of other significant valvular lesion that may lead to the affection of the results.

Study limitations

We used a non-RV dedicated echocardiography software in this current study, although RV dedicated software is now becoming available in many echo laboratories, they are still expensive and there are no available data comparing those softwares with the old ones.

Further studies on the RV with the new software are needed, and it will give us more insight on the reverse changes that occur to the RV after relieve of the pressure overload in patients with congenital pulmonary stenosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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