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ORIGINAL ARTICLE

Supravalvular and Valvular Pulmonary Stenosis: Predictive Features and Responsiveness to Percutaneous Dilation

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Abstract
Supravalvular pulmonary stenosis (SVPS) is considered a rare form of pulmonary stenosis (PS) and represents both a diagnostic and therapeutic challenge. There currently exist no reliable echocardiographic criteria to accurately predict the supravalvular form. The aims of the study were to describe the response to treatment of the different PS presentations and to outline the diagnostic capacity of echocardiogram to differentiate the SVPS from valvular PS (VPS). This retrospective study included 106 patients who underwent percutaneous angioplasty between 2006 and 2017. Interventional outcomes of patients with SVPS were compared to those of patients with VPS. Diagnosis of VPS *vs*. SVPS by echocardiogram was compared to diagnosis obtained by angiogram. Echocardiogram yielded a sensitivity of 56%, a specificity of 82.5%, a positive predictive value of 50%, and a negative predictive value of 85.7%. Patients with SVPS had a significantly smaller pulmonary artery to pulmonary valve (PA:PV) ratio. At 6–12 months of follow-up, the VPS group had a mean right ventricular to pulmonary artery (RV-PA) gradient of 21.68 ± 19.85 mmHg compared to 45.27 ± 24.58 mmHg in the SVPS group. Patients with SVPS had a higher rate of reintervention than patients with VPS (32% *vs.* 6.2%, $p < 0.001$). There was no difference in major complications between groups, whereas VPS patients had a higher proportion of pulmonary insufficiency. Percutaneous angioplasty for PS is less effective in patients with a supravalvular component. A better understanding of the underlying histopathology of different PS subtypes could lead to development of different techniques to improve outcomes, with fewer reinterventions, in this population.

Keywords Supravalvular pulmonary stenosis · Valvular pulmonary stenosis · Percutaneous · Balloon valvuloplasty · Congenital heart disease

Introduction

Pulmonary stenosis (PS) represents between 8 and 14% of congenital cardiac defects, making it one of the most common congenital heart malformations [1–3]. This entity has many presentations: purely valvular stenosis, i.e., valvular PS (VPS), supravalvular PS (SVPS), subvalvular PS or stenosis or the right ventricular (RV) outflow tract or a combination of these [2]. VPS is the most common, easiest to diagnose, and has the best response to treatment. SVPS, either alone or in combination with VPS, is considered a rare form of PS that has been described as a narrowing of the pulmonary artery (PA) and represents both a diagnostic and therapeutic challenge [4, 5].

Regardless of its subtype, the initial step in evaluating PS is the echocardiogram. Nevertheless, there currently exist no reliable echocardiogram-based criteria to accurately predict a supravalvular component and, hence, its response to treatment. Availability of this type of marker could allow for better planning of therapeutic options and provide earlier prognostic information [3, 4, 6].

Percutaneous balloon dilation of the valve, as a minimally invasive technique, is the preferred treatment approach for severe VPS instead of surgery [2, 5]. However, little is known about the outcomes of this procedure for SVPS;

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current literature suggests results are inferior to those seen in patients with VPS [2, 5, 7].

Given the limited data on SVPS outcomes, the first aim of our study was to outline the results of percutaneous dilation in SVPS compared to VPS. The second goal was to evaluate the diagnostic accuracy of SVPS by echocardiogram and to determine echocardiogram-based criteria to help distinguish between VPS and SVPS. These would help predict the response to percutaneous balloon dilation of PS.

Methods

Study Population and Outcome

This retrospective study included 106 patients who underwent percutaneous angioplasty for congenital PS between 2006 and 2017 at *CHU Sainte-Justine* (*Université de Montréal, Montreal, Quebec)*. The study was approved by the institutional scientific and ethics committees. Parental consent was waived by applicable laws pertaining to retrospective clinical research studies. Patients with multiple significant peripheral pulmonary artery stenosis, iatrogenic pulmonary stenosis, or other complex cardiac malformations (tricuspid atresia or stenosis, Ebstein anomaly, transposition of great arteries, tetralogy of Fallot (TOF), hemodynamically significant ventricular septal defect, etc.) or other cardiac malformations that required primary repair other than atrial septal defect or patent ductus arteriosus were excluded.

Two main outcomes were monitored: the response to percutaneous balloon dilation, measured by residual RV to pulmonary artery (RV-PA) gradient, and the need for reintervention on the pulmonary valve (PV) or the PA. Secondary outcomes included the development of pulmonary valvular insufficiency and potential interventional complications.

Data Collection and Definitions

In this study, SVPS is defined as PS with a supravalvular component regardless of the presence of a valvular component and VPS is valvular PS without a supravalvular component. The infundibular component secondary to reactive hypertrophy was not taken into account in this study. Patients were categorized in the SVPS or VPS group based on the angiogram findings. The last echocardiogram before intervention was used to determine baseline hemodynamic status of the PS.

Studied parameters included RV-PA gradient, PV and PA diameters, pulmonary and tricuspid valve function, balloon size, and type and incidence of peri-interventional complications. Available echocardiogram recordings were reviewed to retrieve missing PA and PV measurements. Pulmonary and tricuspid valve insufficiency (PI and TI) were classified according to severity: 0 absence/trace, 1 mild, 2 moderate, 3 severe, and significant PI was defined as moderate or severe regurgitation [8]. Data from echocardiogram reports, catheterization reports, and operative protocols were compiled from clinical charts. RV-PA pressure gradients were retrieved from echocardiogram reports at baseline (pre-intervention), post-intervention, 1–2 weeks, 1–2 months, and 6–12 months of follow-ups. Invasive RV-PA gradients were obtained from catheterization reports. Follow-up data after a second intervention on the pulmonary valve, either surgical or percutaneous, were not included in the calculated statistics.

Identification of the supravalvular component by echocardiogram was based on the interpretation of anatomic and Color Doppler flow location by the operator, which includes description of supravalvular narrowing, acceleration of flow distal to the PV, and valve description (mobility, shape, etc.). Diagnosis of SVPS during catheterization was determined by anatomical narrowing of the PA, as seen during the angiogram and balloon dilation. The PA-to-PV (PA:PV) ratio is defined as the narrowest point of the PA above the PV divided by the diameter of the PV as measured during the echocardiogram.

Accuracy of echocardiogram in distinguishing SVPS from VPS was assessed by comparing catheterization classification to pre-intervention (baseline) echocardiogram classification.

Clinical relevance of PA:PV ratio was assessed by comparing the ratio between patients who were responsive *vs*. those refractory to percutaneous angioplasty. Resistance to treatment was defined by a RV-PA gradient ≥ 30 mmHg at the 6–12 month s of follow-up or by having undergone a second intervention on the PA or PV at any time.

Presence of Noonan, Williams–Beuren, or Alagille syndromes were confirmed by genetic testing performed based on clinical suspicion.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM, USA), $p < 0.05$ was considered significant. Continuous data are expressed as mean $\pm$ standard deviation, and compared by the Student T-test when normally distributed; otherwise non-parametric tests were used for comparison. Categorical data are expressed as ratios and/or percentage or median [range], and compared using the χ^2 or the Fisher exact test as appropriate. One-way ANOVA on rank analysis was introduced to validate significant change of RV-PA gradient upon follow-up stages compared to baseline.

The Receiver Operator Characteristics (ROC) curve and the Area Under the Curve (AUC) statistics were performed to determine a cut-off value, by the Youden J statistics, of the echocardiographic PA:PV ratio that best predicted the

presence of SVPS, using angiogram diagnosis as reference, and another that predicted response to the first balloon dilation.

Results

A total of 163 patients underwent percutaneous angioplasty for PS between 2006 and 2017, 106 of which were included in the study (50 males, 56 females); 57 were not eligible due to associated complex heart defects or pulmonary stenosis following a surgical intervention (i.e., not congenital), most exclusions being related to presence of TOF. The mean age at intervention was 1.96 ± 4.28 years old with a mean Doppler RV-PA gradient of 67.07 ± 20.11 mmHg, which was comparable between the study groups (SVPS: 68.04 ± 21.65 *vs.* VPS: 64.10 ± 14.37; $p = 0.312$) (Table 1).

The comparison between echocardiographic and angiographic identification of a supravalvular component yielded a significant discordance of 23.8% (Table 2). Accordingly, using angiogram conclusions as the gold standard, echocardiogram had a diagnostic sensitivity of 56%, a specificity of 82.5%, with a positive predictive value of 50% and a negative predictive value of 85.7%. Baseline echocardiographic PA:PV ratio was significantly smaller in patients with SVPS determined by angiogram compared to VPS (1.06 ± 0.45 *vs.* 1.47 ± 0.44, respectively; $p < 0.001$). ROC analysis of the echocardiographic PA:PV ratio with regard to SVPS or VPS status yielded an area under the curve (AUC) of 0.764 (CI 95% [0.642–0.884]; $p \leq 0.001$), and a cut-off ratio of 1.16 with the Youden's index (Fig. 1). Applying this cut-off value to discriminate between SVPS and VPS (patients with a ratio ≤ 1.16 were considered positive) increased echocardiogram sensitivity from 56 to 64.7%, while maintaining a high specificity of 80.3%. The positive predictive value remained at 47.8% and the negative predictive value at 89.1%.

Similar to the results obtained when comparing SVPS to VPS, children with PS refractory to balloon dilation also had a significantly smaller PA:PV ratio compared to patients with stenosis responsive to dilation (1.09 ± 0.50 *vs.* 1.43 ± 0.40, $p = 0.003$). ROC analysis based on balloon angioplasty failure yielded a cut-off value of 1.20, below which the PS would likely be resistant to percutaneous angioplasty (AUC = 0.730, CI 95% [0.600–0.8360], $p = 0.002$) (Fig. 1). High-pressure balloons were used in 3 patients with SVPS during the first intervention and two patients with VPS had radiofrequency perforation of their PV during the first intervention.

Invasive pressure gradients were comparable between SVPS and VPS (40.9 ± 20.12 *vs.* 38.5 ± 20.22; $p = 0.644$). The residual invasive pressure gradient at the end of the procedure was however higher in SVPS (26.8 ± 12.6 mmHg *vs.* 11.5 ± 8.5 mmHg; $p \leq 0.001$). The Doppler echocardiographic gradient estimates after the procedure were also different, despite gradients being significantly lower than at baseline within respective groups (Fig. 2).

Of patients with SVPS, 71.4% ($n = 15$) were considered resistant to treatment compared to 25.9% ($n = 14$) in the VPS group ($p = 0.001$) (Table 3). There was no significant difference in balloon-to-valve ratio between patients who were responsive to dilation and those who were not (1.31 ± 0.12 *vs.* 1.33 ± 0.25, $p = 0.560$). The rate of reintervention in patients with SVPS was 32% ($n = 8$) compared

Table 1 Patient characteristics at intervention classified based on the presence (SVPS) *vs.* the absence (VPS) of a supravalvular component to the stenosis as identified by angiogram

	SVPS ($N = 25$)	VPS ($N = 81$)	p value
Age (years)	1.66 ± 2.97	2.06 ± 4.62	0.687
Male gender (%)	14 (56%)	35 (43%)	0.186
Weight (kg)	9.72 ± 7.62	11.98 ± 21.17	0.422
Height (cm)	73.64 ± 23.59	69.56 ± 35.88	0.511
BSA (m^2)	0.43 ± 0.24	0.43 ± 0.47	0.969
PA:PV ratio at echo	1.06 ± 0.45	1.47 ± 0.45	≤ 0.001

Table 2 Diagnostic classification and response to treatment

	SVPS	VPS	p value
Echocardiogram-based SVPS:VPS	14:11	14:66	≤ 0.001
Echo PA:PV below SVPS cut-off * (%)	11 (64.7%)	12 (19.7%)	≤ 0.001
Balloon Refractoriness (%)	15 (71.4%)	14 (26%)	≤ 0.001
Echo PA:PV below refractoriness cut-off** (%)	16 (64%)	14 (17.2%)	≤ 0.001
Reintervention rate (%)	8 (32%)	5 (6.2%)	≤ 0.001
Interval to reintervention (years)	1.75 ± 1.85	0.70 ± 0.66	0.252

Provisional echocardiographic diagnosis of valvular or supravalvular pulmonary stenosis (VPS and SVPS, respectively) showed discordance in 23.6% when compared to angiography diagnosis

*Upper limit of PA:PV ratio of 1.16 according to ROC analysis based on angiographic characterization of the pulmonary stenosis components for classification as SVPS

**Upper limit of PA:PV ratio of 1.20 according to ROC analysis based on refractoriness to balloon dilation for classification as at risk of treatment failure

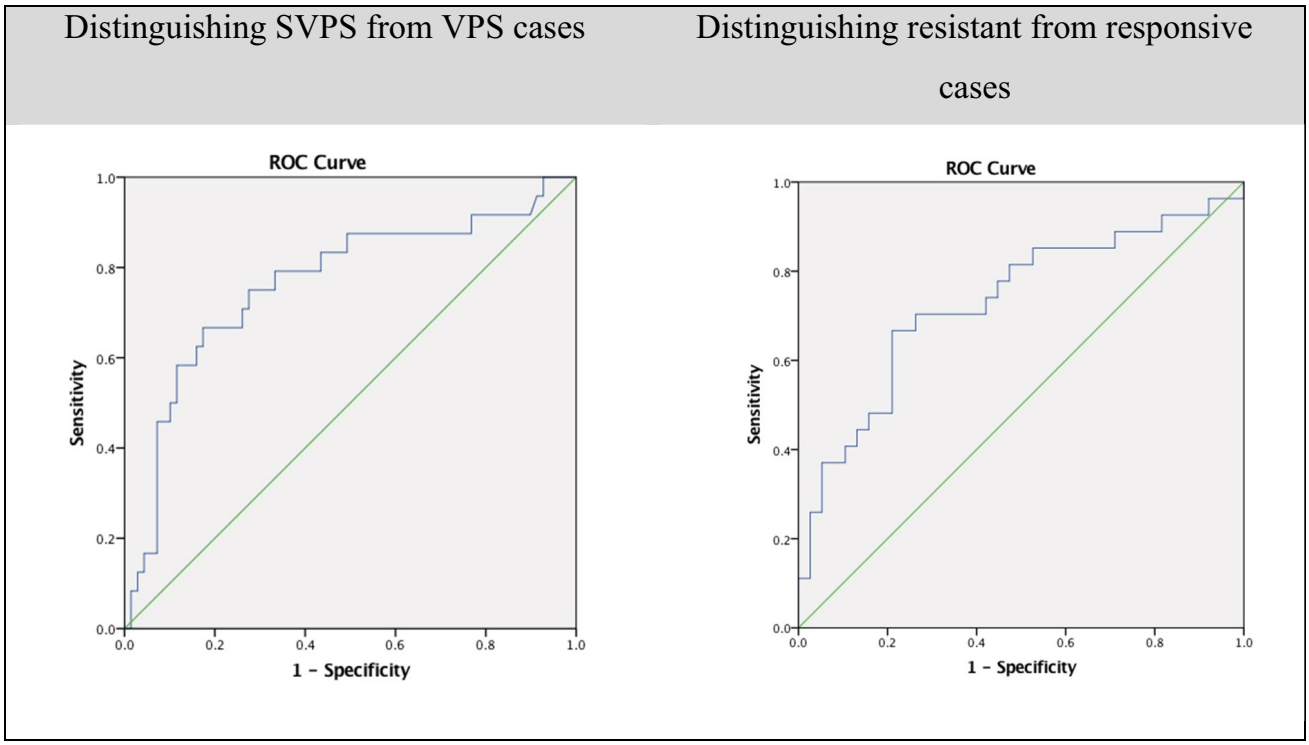

Fig. 1 Receiver Operator Characteristic analysis of the PA:PV ratio in distinguishing SVPS from VPS (left) and resistant from responsive PS (right). Left panel: Receiver Operator Characteristic (ROC) analysis of the PA:PV ratio for the cut-off value distinguishing cases with supravalvular component (SVPS) from cases without (VPS) demonstrates an area under the curve (AUC) of 0.764 (CI 95% [0.642–0.884]) ($p \leq 0.001$). Right panel: ROC analysis of the PA:PV ratio for the cut-off value distinguishing cases that were resistant from those responsive to balloon dilation demonstrates an area under the curve (AUC) of 0.730 (CI 95% [0.600–0.860]) ($p = 0.002$)

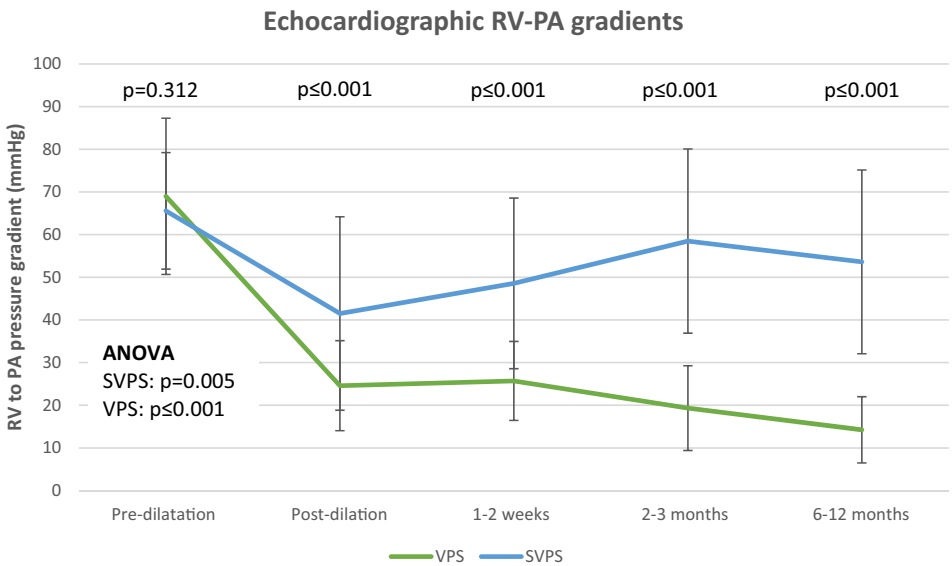

Fig. 2 Echocardiographic follow-up of RV-PA gradients. Follow-up excludes all data measured after a second intervention, of any kind, on the PV or PA. There was significant decrease in RV-PA gradients in both groups; however, gradients in patients with SVPS were significantly higher than patients with VPS

to 6.2% ($n = 5$) in those with VPS ($p \leq 0.001$). Time to reintervention was comparable between groups (1.75 ± 1.85 *vs.* 0.70 ± 0.66 years, respectively; $p = 0.252$). In the SVPS group, the second intervention consisted of a dilation with a standard balloon in 5 patients (one of which had their initial intervention with a high-pressure balloon) and with a high-pressure balloon for one patient. One patient with SVPS who had two dilation procedures with a standard balloon eventually underwent dilation with a cutting balloon and did not require subsequent intervention. In the SVPS group,

Table 3 Comparative data between cases responsive or refractory to primary balloon angioplasty

	Responsive	Refractory	*p* value
SVPS:VPS	6:40	15:14	≤0.001
Echocardiographic PA:PV ratio	1.43 ± 0.40	1.09 ± 0.40	0.003
RV:PA gradient at pre-intervention echocardiogram	68.93 ± 18.31	65.57 ± 13.65	0.312
RV:PA gradient post-intervention echocardiogram	24.59 ± 10.54	41.51 ± 22.68	≤0.001
Invasive baseline pressure gradient	38.60 ± 19.30	42.18 ± 18.81	0.500
Invasive post dilation pressure gradient	11.86 ± 7.66	25.00 ± 15.37	≤0.001

Pressures and pressure gradients are in mmHg

two patients required surgical repair after their first dilation (one had initial dilation with a standard balloon and the other with a high-pressure balloon). Among the VPS patients, 4 had a repeat balloon dilation procedure, after initial radiofrequency perforation in one, while the other required dilation with a cutting balloon. The latter two patients later required surgical repair, as did another patient who had undergone a single dilation with a standard balloon.

One child with VPS had a confirmed Williams–Beuren syndrome, and the diagnosis of Noonan syndrome was confirmed by genetic testing in 8 (32%) SVPS patients compared to 2 (2.5%) among the VPS patients ($p \leq 0.001$). Of the 10 patients with Noonan syndrome, 7 with SVPS had at least a second intervention compared to one patient with VPS and Noonan syndrome. All patients who required surgical repair (SVPS and VPS) had Noonan syndrome.

The prevalence of PI at baseline was comparable between groups, where 16% of children with SVPS had mild PI vs 25.5% in the VPS group ($p = 0.862$). Despite comparable ratio of balloon size to PV diameter (1.31 ± 0.15 vs 1.34 ± 0.21, respectively; $p = 0.637$), VPS patients had a higher prevalence of high-grade PI following initial balloon intervention; there was no significant difference in TI (Fig. 3). There was no statistically significant difference in balloon-to-valve ratio between patients who developed significant PI and those who did not (1.42 ± 0.30 vs 1.31 ± 0.14; $p = 0.155$; ROC analysis: AUC = 0.615 CI95% [0.433–0.797]; $p = 0.186$).

There was one major adverse event in each group. One patient with SVPS sustained a PA rupture during angioplasty with a high-pressure balloon. Immediate surgical rescue was undertaken and the patient was placed on ECMO, but subsequent anoxic encephalopathy ensued. One VPS patient with septal valve atresia developed cardiac tamponade when radiofrequency valve perforation was attempted. The hemopericardium was evacuated transthoracically with retransfusion of the evacuated volume and surgical repair of the main PA with repair of the valve was performed with no subsequent cardiac or general sequelae. Other transitory complications include one patient in the VPS group who required a temporary pacemaker for bradycardia and another for third-degree AV block during catheterization. Four others had transient high-grade AV block (3 among the VPS and 1 among the SVPS cases). One VPS patient had transient hypotension requiring inotropic support.

Discussion

In this series, patients with SVPS diagnosed by angiogram had a smaller echocardiographic PA:PV ratio, as did those who were refractory to angioplasty. Although the PA:PV ratio is significantly lower compared to patients with VPS, our ROC analysis failed to yield a highly reliable cut-off point. This is possibly due to the retrospective nature of our study. Whereas angiogram measurements could be done retrospectively, these could not be extrapolated to echocardiographic recordings. The identification of the optimal echocardiographic measurement location would need to be studied prospectively with considerations of various projections and locations. In 1988, an "hour-glass deformity of the pulmonary valve" was seemingly first described, with a narrowing noted in the plane of the commissures and orifice [9]. This site, for instance, could be a target measurement site in a prospective design, but other features, such as the angle forming the pulmonary artery wall, could be taken into account.

The SVPS is a predictor of percutaneous dilation failure (defined by gradient reduction of less than 50% in most studies) and restenosis [2, 5, 7]. Other predictors for recurrence included a balloon-to-valve diameter ratio < 1.2 and an immediate post-intervention gradient ≥ 30 mmHg [2]. Current literature recommends surgical intervention for patients with SVPS, hypoplastic valve annulus, or dysplastic PV leaflets [1]. This preference, compared to repeat percutaneous dilation, is based on the higher rate of reintervention and of significant residual RV-PA gradient at one-year follow-up compared to VPS [1]. Predictive features based on echocardiogram alone are yet to be determined; nevertheless, magnetic resonance (MR) angiogram and computed tomography (CT) scan showed more precise findings to detect supravalvular lesions; however, they are not indicated unless a supravalvular component is already suspected [10, 11].

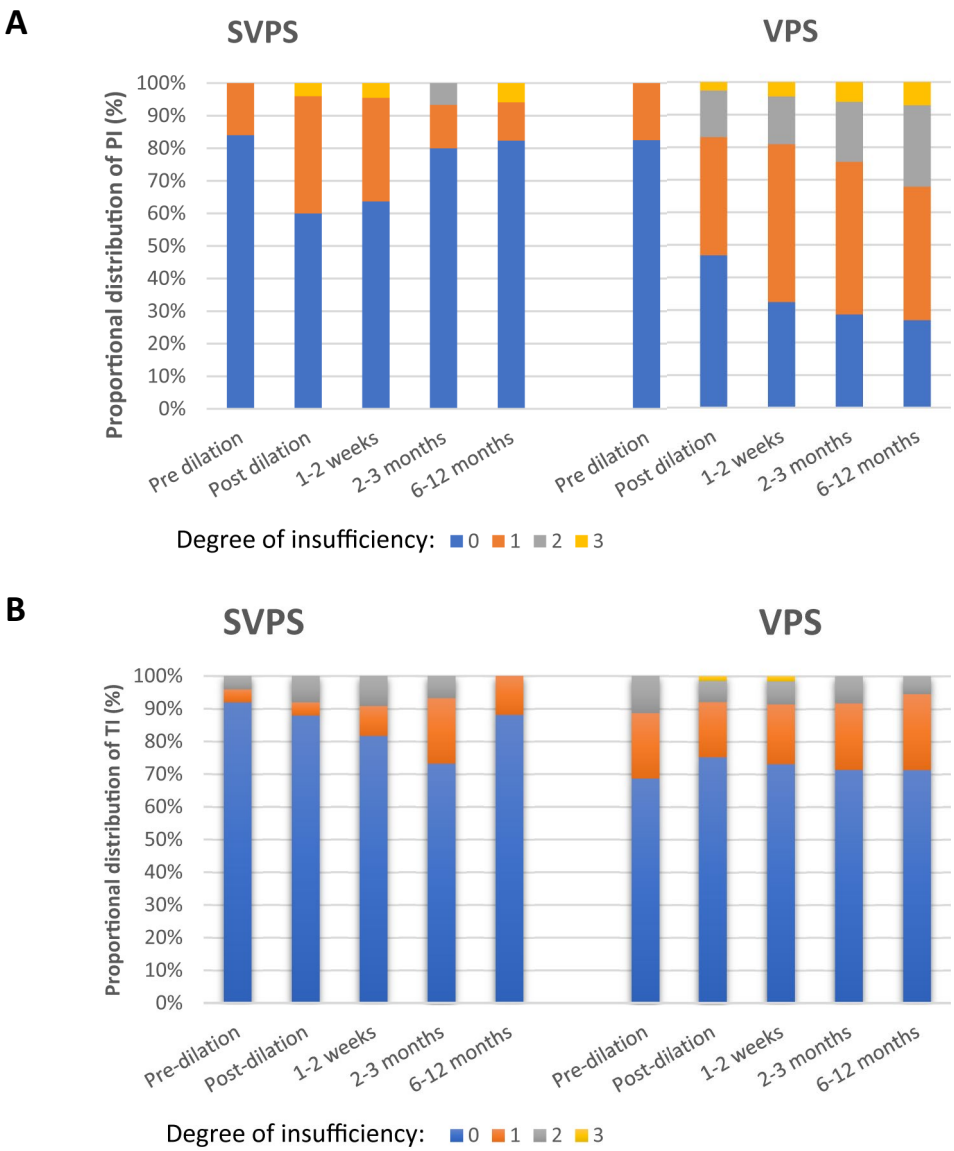

Fig. 3 Pulmonary and tricuspid insufficiency in SVPS *vs.* VPS. The prevalence of pulmonary insufficiency (PI) **a** was similar between groups before intervention ($p = 0.862$). A progressive increase of the prevalence and the degree of PI occurred in VPS when compared to SVPS ($p = 0.862$ pre dilation, 0.225 immediately post dilation, then 0.039, 0.005, and ≤ 0.001, subsequently). There was no statistically significant difference at the tricuspid valve level; **b** the prevalence of tricuspid insufficiency (TI) before and following intervention was the same between groups ($p = 0.066$, 0.383, 0.610, 0.980, and 0.328, respectively). Insufficiency grading: 0 to 3 are absent, mild, moderate, severe. Statistical test for proportion dichotomously: grades 3 and 4 *vs.* 0 and 1

There is little information on the histopathology of congenital supravalvular pulmonary stenosis in non-syndromic patients, but there is evidence suggesting that failure of the percutaneous approach is related to elastic recoil properties of the supravalvular ridge [3, 12]. Our series suggests that SVPS and VPS are not inherently similar entities, as evidenced by a lower success rate of angioplasty in the SVPS group (28.6% vs 74.1%). Similar to supravalvular aortic stenosis and branch PA stenosis, SVPS is considered secondary to an elastin arteriopathy, such as observed in clinical entities consistent with Williams' syndrome [13]. Hallbergson et al. suggest that the underlying pathology for the PS plays an important role in predicting success of balloon dilation and stenting [14]. An altered endothelial response to vascular injury in patients with Tetralogy of Fallot, for instance, indicates that major aortopulmonary collateral arteries are at increased risk of intrastent stenosis compared to those with normal vasculature [14]. These findings suggest that the current approach, shown successful for VPS, may be inadequate for some cases of SVPS.

PI may result from VPS balloon dilation. Current literature estimates the prevalence of severe PI after angioplasty to be 6%, with little RV overload, which is consistent with our results (4.7% of all patients had PI = 3 at 6–12-month follow-up) [2]. The balloon-to-valve ratio in our series was in accordance with current guidelines in order to predict intervention success (> 1.2) and did not differ between patients who developed significant PI and those who did not [2]. Although similar balloon-to-valve ratio was used in both SVPS and VPS groups, the rate of significant PI was lower in the SVPS group. This could hypothetically be explained by the supravalvular narrowing of the PA limiting

the expansion of the balloon as well as by the abnormal recoil properties of the valve itself.

Study limitations included the relatively small sample size of SVPS. It has been described that the SVPS in patients with Williams–Beuren syndrome tends to regress over time [13]. This means the syndromic PS could behave differently than non-syndromic PS. Unfortunately, our study sample and design could not describe the natural evolution of SVPS as there was no control group of patients with SVPS who did no undergo angioplasty. Nevertheless, comparing SVPS patients who have undergone percutaneous dilation to those who have not could be biased by the degree of stenosis, potentially milder in observational cases. This brings up another limitation relative to a shorter follow-up relative to previous observational studies of up to 10 years demonstrating the tendency of all SVPS to regress [5, 7]. However, as our study's aim was to compare interventional results rather than natural evolution, a shorter follow-up was deemed sufficient to evaluate outcomes. Our series also included very little cardiac CT scan and MRI data, which both seem to be interesting diagnostic modalities for SVPS [10, 11]. Finally, the follow-up length of our series showed adequately higher residual gradient leading to a higher reintervention rate compared to VPS, but did not (by design) study the efficacy of dilation in patients with associated cardiac malformations.

Conclusion

Percutaneous angioplasty is less effective for patients with PS that have a supravalvular component and its diagnosis remains challenging. There is a need for better understanding of the underlying histopathology in order to offer different, more tailored, therapeutic techniques to improve prognosis and reduce the rate of reintervention in this population. The PA:PV ratio should be part of the echocardiographic diagnostic study protocol in order to more efficiently classify patients with possible SVPS. This could allow teams to complete the evaluation with CT scan or MRI and improve decision making with regard to prognosis and treatment options. Further description of SVPS is required: natural evolution, different imaging modalities, and histopathologic differences between different subtypes.

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Compliance with Ethical Standards

Conflict of interest No conflicts of interest to declare.

Ethical Approval This work was approved by the Institutional Research Ethics Board.

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