ORIGINAL ARTICLE

Left ventricle dysfunction in patients with critical neonatal pulmonary stenosis: echocardiographic predictors.

A single-center retrospective study

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Introduction

Pulmonary stenosis (PS) is a congenital heart disease characterized by narrowing of the right ventricle outflow tract (RVOT) and, in most severe forms, complete pulmonary atresia. **[1]** In the latter form, pulmonary blood flow depends completely on patent ductus arteriosus. Pulmonary stenosis (PS) and pulmonary atresia with an intact ventricular septum (PAIVS) represent 25-30% of all cyanotic congenital heart diseases and approximately 3% of all congenital heart diseases. While pulmonary stenosis is relatively common, pulmonary atresia with an intact ventricular septum is a complex and uncommon congenital heart defect, associated with a relatively high morbidity and mortality, despite (surgical or catheter) treatment. Deaths occurs within the first postoperative year, and 15-years survival rates of all subtypes of PA-IVS patients being reported to be anywhere from 58% to 87%. **[2]**

The main treatment goal is to achieve anterograde flow across the RVOT, in the neonatal period, in order to improve the systemic arterial oxygenation. Trans-catheter intervention with pulmonary valve balloon dilatation (PVBD), represents the primary therapy for infant with critical PS and PAIVS. Right ventricular features deemed necessary to perform PVBD include large, tripartite right ventricle without coronary artery connections and coronary dependent circulation or with interrupted coronary arteries. **[3]**

It is widely demonstrated that PV perforation and /or BD is characterized by a high rate of initial success with acute gradient reduction, ducuts independence and low rate of re-intervention.

Nonetheless, significant left ventricle dysfunction has been described in PV/PAIVS after PVBD. Ronai et al. **[4]** described significant transient left ventricular dysfunction after PVBD, as the possible consequence of three hemodynamic effects including the impact of change in size of right ventricle, the loading effect for closure of ductus arteriosus or the acute change in coronary perfusion.

In previous studies, pre-existing left ventricular dysfunction has been suggested as a risk factor for left ventricle dysfunction after PV perforation and/or BD. **[5-7]**

The aim of the present study, is to describe the risk factors and hemodynamics mechanisms in

patients with PS and/or PAIVS, with normal left ventricle and without coronary anomalies, for the development of left ventricle dysfunction after PVBD.

Methods

Study population

We retrospectively enrolled patients admitted in the Bambino Gesù Children Hospital for neonatal PS and/or PAIVS from January 2012 to January 2017, with available complete echocardiographic examination, angiograms and operative reports.

Data were retrieved from the clinical records and a dedicate database was collected, after local ethical committee approval (prot 2387_OBPG_2021).

Management of patients

All patients received intravenous prostaglandin E1 at an initial dose that ranged between 0.005 and 0.1 ng/kg/min. After clinical stabilization, patients were transferred to the catheterization laboratory. The radiofrequency perforation, when necessary, was performed with 2 F cable with 5 W of energy administered for 1-2 sec under fluoroscopic guidance. Pulmonary valve was dilated with a balloon measuring 1.2-1.4 times the pulmonary annulus. The procedure was considered effective if the RVOT final gradient was less than 30 mmHg.

Prostaglandin infusion was discontinued 2-5 days after reaching the goal of adequate anterograde pulmonary blood flow (defined as oxygen saturation > 92%).In contrast, ductal stent placement or a systemic-to-pulmonary shunt were the treatment options if an additional shunt was required for impossibility to wean patients off from prostaglandin.

Imaging methods

Imaging data were collected as described in our previous study. **[8]**

Specifically all patients underwent two-dimensional complete echocardiographic examination, using a Philips iE33 (Philips Medical System, Bothell, WA, USA) with 8- and/or 12-MHz transducers

before and after pulmonary valve balloon dilatation. Images were analyzed with a dedicated offline review software (Philips Xcelera 4.1 System).

The echocardiographic views considered were the subcostal right and left oblique axis, parasternal long axis, parasternal short axis at the level of ventricle and great arteries, left parasternal (with specific focus on the right ventricle inflow), apical 4- and 5-chambers and suprasternal views. End-diastolic and end-systolic LV volume and RV area and tricuspid Z –score and regurgitation degree were measured in apical 4-chamber view.

Functional parameters included: manually traced right ventricular fractional area change (e-RVFAC), speckle tracking automatically derived (STAD) RVFAC by 2D (a-RVFAC), Tricuspid Annular Plane Systolic excursion (TAPSE), the systolic wave of the tricuspid valve on the Tissue Doppler Imaging (TDI) and Right and Left Ventricle 2D Systolic Global Longitudinal Strain (RVGLS and LVGLS). According to the American Society Echocardiography guidelines, all right and left ventricular dimensions were evaluated in end-diastolic phase in both apical and parasternal views.

The Echocardiographic FAC (e-RVFAC) was estimated with the following calculation: [(RVEDA-RVESA/RVEDA) x 100] and the automatic FAC (a-RVFAC) was measured with a speckle tracking automatically derived RVFAC by 2D-STAD using a standard 4-chamber apical view. The Ejection Fraction (LVEF) was estimated with the following calculation: [(LVEDV-LVESV/LVEDV) x 100]

Normal RVFAC value was greater than 35%**[9]**.

TAPSE identified the longitudinal right ventricle function obtained positioning the M-mode cursor on the lateral portion of the tricuspid annulus. Normal value was considered above 16 mm**[9]**

Tissue Doppler analysis was used to measure systolic tricuspid annulus velocity (Ts'). A velocity below 10 cm/sec was considered as a sign of systolic dysfunction.

For strain analysis, cine-loops recordings were reviewed off-line and analyzed by one single expert operator blinded to diagnosis. Analyses were performed using Philips QLAB software version 10.3 (Philips Andoven, MA, USA). 2D strain was calculated using apical four-chamber view, focused on the right ventricle with a modified apical view, obtaining a complete image of the right ventricle, particularly the free wall. The speckle tracking strain software developed for the left ventricle was applied also to the right one. RVGLS measure derived by averaging only strain curves from the RV free wall (4 RV segment model: basal, median, apical free wall and apex). The normal mean values of RVGLS in children were considered from -20.80% to -34.10 (mean -30.06, 95% CI -32.91 to -27.21) and for LVGLS from -16.7% to -23.6% (mean -20.2%, 95% CI -19.5% to -20.8%). **[10]**

Statistical analysis

Data are expressed as percentages for categorical data and mean ± standard deviation for normally distributed continuous variables.

Comparison between groups (group 1: patients with left ventricle dysfunction; group 2: patients with normal left ventricle function after PVBD) was carried out by Student's t-test for continuous normally distributed variables and the χ^2 test was used to compare categorical variables.

A p value less than 0.05 was considered statistically significant.

Statistical analysis was performed by SPSS Statistics for Windows software, version 21.0 (released 2012; IBM Corp., Armonk, NY, USA).

Results

We retrospectively enrolled twenty-nine patients in the study (21 male and 8 female). The median age was 5.8±7.1 days. Twenty-five infants with critical pulmonary valve stenosis (PVS) and four with pulmonary atresia with intact ventricular septum (PAIVS) were included.

The pulmonary valve balloon dilation was performed between one and fourteen days of age.

The indications for PVBD were standard for neonates with critical PVS and PAIVS. **[11]**

All patients before the procedure had a normal left ventricle ejection fraction (EF) > 57%. After the PVBD, eight patients developed a transient left ventricle dysfunction (5 PVS and 3 PAIVS) with EF < 50% calculated by the Simpson biplane method.

Comparing the demographics and echocardiographic data before the procedure in patients with transient left ventricle dysfunction, there was no difference in the demographics data except the timing of PVBD. In fact, in patients who developed LV dysfunction, an earlier PVBD was associated with greater reduction in LV EF (2.0±1.2 vs 8.7±5.2, p=0.04). **Table 1**However, pulmonary valve regurgitation at more than a mild degree after PVBD was statistically significant, associated with the left ventricle dysfunction (p<0.0001). **Figure 1**

Patients with a greater change in right ventricle area after PVBD (1.2±0.8 vs 0.3±0.9, p=0.042) and left ventricle volume (-1.1±0.9 vs -0.1±21, p=0.001) developed left ventricle dysfunction. **Table 3**

Ultimately, there was not difference between patients with and without the transient left ventricle dysfunction in right and left pressure ratios (RV/LV ratio pre: 1.7±0.4 vs 1.5±0.5, p=0.122 and RV/LV ratio post: 0.88±0.18 vs 0.80±0.14, p=0.350). **Table 4**

Discussion

The aim of the study was to investigate incidence and risk factors for the development of left ventricle dysfunction in neonates with PS or PAIVS undergoing PVBD.

Several studies suggest that abnormal intraventricular interaction may be the reason of left ventricle dysfunction with an important prognostic effect on mortality. **[12-14]**

Since the right ventricle shares myocardial fibers, interventricular septum and pericardium with the left ventricle, it is intuitive that significant changes in geometry and function of one ventricle involves the contralateral one, independently of neural, humoral or circulatory effect**[15-16-17]**

Burkett et al. have shown the role of ventricular interdependence in influencing the left ventricle function in patients with pulmonary hypertension. A reduced left ventricle longitudinal and circumferential strain and strain rate, primarily at the basal septum, as a consequence of the leftward septal shift of the right ventricle, has been demonstrated in children and young adult with pulmonary hypertension, suggesting direct pressure-loading effects on right and left ventricle performance and hemodynamics. **[18]**

The theory of interventricular interaction and its effect on left ventricle function has been demonstrated also in patients with Tetralogy of Fallot both for volume and pressure overload **[19]**. Patients with repaired Tetralogy of Fallot (rToF) and pulmonary regurgitation (PR) have a different pathophysiological response to RV chronic volume overload but share with PS and PAIVS the indirect effect worsening of left ventricle function. It has also been shown, that patients with rToF and PR have altered RV longitudinal mechanical performance and a tendency to right systolic dysfunction, as shown in a previous study from our institution **[8]**, and that the pulmonary valve replacement in these patients improves global LV strain. **[20-21]**

Moreover, in patients with rToF, residual RV outflow tract obstruction induces an early protective effect on RV modeling and RV strain, but a negative impact on LV strain. **[22]**

As compared to patients with repaired Tetralogy of FallotrToF and PR, patients with PVS/PAIVS, show a more severe RV diastolic dysfunction with a restrictive physiology, mainly due to RV ventricular hypertrophy, myocardial disarray and fibrosis. **[23]**

Ronai et colleagues have suggested that, in patients with pulmonary stenosis/atresia after PVBD, worsening of LV longitudinal and circumferential global and segmental strain, is a predictor of left ventricle dysfunction, while longitudinal RV strain remains unchanged pre- and post-PVBD. The authors also suggested that right ventricle volume overload was responsible for subsequent left ventricle dysfunction.

The mechanism involved in altering myocardial performance in the ventricular septum is a consequence of the change in RV volume loading conditions, following right ventricular outflow obstruction relief. Patients who developed LV dysfunction after PVBD had larger right ventricles but not significantly larger left ventricles. **[24]**

In our study, left and right ventricular strains before PVBD are reduced, even if although not statistically significantly, in patients who develop left ventricle dysfunction, and. In agreement with Ronai's study, the greatest increase of right ventricle area after PVBD is statistically significantly in patients with left ventricle dysfunction. This evidence has confirmed that the right ventricle volume overload (RVVO) after PVBD, due to the iatrogenic development of pulmonary regurgitation, is a predisposing risk factor for transient left ventricle dysfunction. The underlying mechanism depends on the resultant acute right volume overload, regardless of the reduction of pressure load, which can alter right chambers geometry. This then causes left ventricle dysfunction due to the known physiological processes of ventricular interdependence and also the decreased relative contribution of left atrial systole to the left ventricular filling.

Acute right volume overload induces flattening of the ventricular septum resulting from leftward displacement of the septum toward the center of the left ventricle, opposing the normal forces of left ventricle distension. Normal ventricular septal curvature ~~restores at end~~ recovers by the end of systole, which opposes the inward motion of the ventricular septum toward the center of the left ventricle during systole contraction. As a result, the net shortening along the ventricular septum-to-posterolateral free wall short axis in RVVO is reduced.

The regional nature of LV impairment depends on ventricular septal flattening, strongly refutes a systemic mechanism explanation (loading alteration, neurohumoral interaction, autonomic influence), and shows that transient left ventricle dysfunction is a consequence of acute RVVO. **[25-26]**

In our study, in all patients the greater impairment of longitudinal regional strain more in the septum than in the lateral free wall ~~proves that~~ supports the most accredited theory for transient left ventricle dysfunction and demonstrates that it depends on volume overload and interventricular dependence. **Table 5-6**

We have also considered that the creation of a 'detrimental shunt' could have played a role in the etiology of the LV dysfunction. In presence of a severe pulmonary regurgitation, a detrimental shunt due to the wide patent ductus arteriosus can be present. Because of the significant pulmonary regurgitation, blood coming into the pulmonary artery by the wide ductus arteriosus is "drawn" to the right ventricle, leading to systemic and coronary stealing. The establishment of this detrimental shunt is sometimes terms as "circular shunt" in the setting of congenital heart disease. **[27]** However, the theory of the detrimental circular shunt does not match significantly with is unsupported by our data. In fact, we found no relation between ductus closure and left ventricle dysfunction improvement. Furthermore, our data show that LV dysfunction is mainly related to a segmental motion abnormality rather that a than global dysfunction (as shouldwould be expected in reduced coronary flow) and to the degree of pulmonary regurgitation. **Table 7**

Limitations

This is a single-center retrospective study with a small sample size, even for the low percentage of cases due to the rarity of the this congenital heart disease. Potential selection biases include the influence of multiple factors such as heart rate, preload and afterload in the echocardiographic evaluation of functional and morphological indices. Studies with a larger sample size and future collaborations with other centers are therefore needed to demonstrate the universality of these observations.

Conclusion

Moderate-severe degree pulmonary valve regurgitation predisposes to transient left ventricle dysfunction in patients with PVS and PAIVS after PVBD. Probably tThe acute

right ventricle volume overload, which also influences the left ventricle through the known pathophysiological mechanisms of ventricular interdependence, is the implied mechanism. This hypothesis could be a starting point for defining features of patients at higher risk to develop ventricular dysfunction and to draw up a protocol for greater surveillance for improving clinical management to ensure a better outcome for these patients.

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