Is There Any Relationship Between Biomarkers and Echocardiographic Markers in Patients With Pulmonary Stenosis Underwent Balloon Valvuloplasty?

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Abstract :

Background:

Congenital pulmonary stenosis (PS) is a progressive disease. Balloon pulmonary valvuloplasty (BPV) is the treatment of choice in valvular PS.

Aim:

We aim to study the relationship between biomarkers and echocardiographic markers in valvular PS and to assess the impact of BPV on these markers.

Patients & Methods

Patients with moderate and severe valvular PS amenable for BPV were recruited. Serum troponin I was measured. Echocardiographic assessment of PS and right ventricular (RV)function were done. All patients underwent BPV. Troponin level and echocardiographic data were re-assessed two weeks & six months after BPV.

Results:

Fifty patients with valvular PS were recruited. There was significant correlation between peak SPG and troponin ($p < 0.001$). Troponin was significantly decreased 2 weeks after BPV. Similarly, there was an initial improvement in RV function.

After 6 months of follow up, we divided patients into 2 groups:

Group-A: 36 patients with no restenosis.

Group-B: 14 patients with restenosis.

There were high significant differences between both groups regarding troponin level and RV functions with re-elevated troponin in group-B that correlated with peak PG ($r= 0.9$, $p < 0.001$). RV

function parameters in group-B became significantly worse 6 months after BPV than those after the initial 2 weeks.

Conclusion

Troponin correlates with the severity of PS and associates with RV dysfunction. Both troponin & RV functions improved with BPV. Recurrent elevation of troponin and impairment of RV function are associated with PV restenosis and could be set as an indication for repeated balloon dilatation of PV.

Introduction

Pulmonic stenosis (PS) is mostly always congenital in origin. Acquired stenosis of the pulmonary valve (PV) is uncommon. Carcinoid disease is the commonest cause of acquired pulmonic valve disease. Rheumatic PS is rare even when the valve is affected by the rheumatic process **(1)**.

Congenital PS is a progressive disease, which requires appropriate management in different periods of life. The decision about the method of management is determined according to the degree of hemodynamic changes. Besides, very early detection of changes is very important to follow them. Even in mild or moderate disease, rapid progression in infancy or early childhood was documented **(2)**.

Balloon pulmonary valvuloplasty (BPV) was found to be the treatment of choice in cases of significant valvular PS. This technique was widely adopted, and it showed good long-term outcomes regarding successful relief of right ventricular outflow tract (RVOT) obstruction since it was first reported by **Kan et al. (3)**.

We aim to study the relationship between biomarkers and echocardiographic markers in valvular PS and to assess the impact of BPV on these markers as well.

Patients and Methods

Study design and population:

This study was conducted in the Congenital Unit, Cardiology Department, Zagazig University Hospital. We included fifty patients with congenital moderate and severe valvular pulmonary stenosis scheduled for BPV in Congenital Unit, Cardiology Department, Zagazig University Hospital in the period between March 2018 and September 2019.

Inclusion criteria:

Patients with moderate and severe valvular PS amenable for BPV were included. The indication of BPV depends on 2D echocardiography according to guidelines as follows.

- Asymptomatic patients with a doomed pulmonary valve& peak systolic pressure gradient (SPG)>60mmHg or mean systolic pressure gradient (MSPG)> 40mmHg (with less than moderate PR).
- Symptomatic patients with a doomed pulmonary valve& SPG>50mmHg or MSPG>30mmHg (less than moderate PR) **(4).**

Exclusion criteria:

We excluded the patients with:

1- RVOT obstruction associated with complex congenital heart disease e.g. Fallot tetralogy (F4).

2- Subvalvular & supravalvular PS.

3- Moderate & severe Pulmonary regurge.

4- Other causes of troponin elevation: e.g.

- Chronic or acute renal dysfunction.
- Severe congestive heart failure.
- Hypertensive crisis.
- Pulmonary embolism.

Ethical consideration:

Written informed consent was obtained from every patient or his parents after the explanation of the procedure. The medical research and ethics committee (IRB) of Zagazig University approved the study.

Data collection:

Data were collected for all patients once moderate or severe valvular pulmonary stenosis was proved.

The following data were collected:

1- **Demographic characteristics and risk factors**: age, gender, any other congenital or valvular heart disease, and family history of congenital heart diseases.

2- **Full history taking involving**:

- Risk factors: age, sex, any other congenital, or valvular heart disease.
- Onset, course, duration of the presenting complain (cyanosis, exertional dyspnea, fatigue, low cardiac output symptoms, chest pain, syncope ..etc)
- Family history of any congenital heart diseases

3- **Physical examination**:

* General examination including:

- Pulse and blood pressure.
- Neck veins.
- Edema of lower limbs.
- Abdominal and chest examination.

*Cardiac examination Including:

- Inspection, palpation and auscultation

5- **Laboratory investigations including**:

- Serum troponin I level before BPV then two weeks & six months later.

6- **Twelve lead electrocardiography** with special emphasis on QRS duration. It was recorded in each patient immediately after hospital admission. ECG was done on admission at a paper speed of 25mm/s and amplification of 10mm/mv.

7- **Echocardiography:**

A standard transthoracic echocardiogram (TTE) was performed using Vivid E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA). Echocardiography was done on admission, 2 weeks and 6 months after BPV.

Images were obtained using a 2-5 MHz transducer. Cardiac champers and pulmonary artery and their valvular structures were assessed in detail using the standard left lateral decubitus position.

The PV was structurally assessed in the parasternal short-axis image. Then, peak SPG over the PV was obtained using CW Doppler.

- We considered the following according to 2018 AHA/ACC guidelines **(5) :**

- Moderate PS is diagnosed if the valve area is 0.5-1.0 cm^2, with a transvalvular pressure Peak PG 36–64 mm Hg (peak velocity 3–4 m/s)

- Severe PS is defined as a valve area smaller than 0.5 cm^2 and a transvalvular Peak PG 64 mm Hg (peak velocity >4 m/s

- The PV annulus was measured**.**

- Color & continuous-wave Doppler across PV to assess the degree of pulmonary regurge.

- For assessment of RV function the following parameters were used:

a) RV fractional area change (RVFAC):

RVFAC was defined as (RV end-diastolic area − RV end-systolic area)/end diastolic area × 100. RV area in both systolic and diastolic frames was obtained by tracing the RV endocardium from the annulus along the free wall to apex and then back to the annulus along the interventricular septum in apical 4 chamber view.

b) Tricuspid annular plane systolic excursion (TAPSE):

In apical 4-chamber view, M-mode cursor was placed through the tricuspid annulus at the lateral RV free wall in such a way that the annulus moved along M-mode cursor.

From M-mode tracing the amount of longitudinal motion of annulus at peak systole was measured. Total displacement was measured by leading edge of echoes and expressed in millimeter.

c) Myocardial performance index (MPI) by pulsed-wave tissue Doppler imaging.

d) Pulsed wave tissue Doppler imaging:

A major positive velocity (S′) was recorded with the movement of annulus towards apex during systole. With the movement of annulus towards base during diastole, two major negative waves were recorded, one during early diastole (E′) and one during late diastole (A′). S′ duration from its beginning was measured as ejection time (ET), the time between the end of S′ and the beginning of E′ as isovolumic relaxation time (IRT), the time between the end of A′ and beginning of S′ as isovolumic contraction time (ICT). Right ventricular MPI was calculated as (IRT + ICT)/ ET.

e) RV diastolic dysfunction :

Trans-tricuspid E/A ratio, E/E′ ratio, E deceleration time were measured for grading RV diastolic dysfunction. Impaired relaxation was defined as E/A ratio <0.8, pseudo normalization as E/A ratio 0.8 to 2.1 with E/E′ ratio >6, and restrictive filling as E/A ratio >2.1 with deceleration time <120 ms.

8- Catheterization and balloon valvuloplasty:

Single balloon technique BPV was done with a target balloon: annulus diameter ratio (BAR) about 1.2:1.4 **(6)**. Data recorded included: age at catheterization, initial RV pressure, the ratio of RV pressure to systemic arterial or ventricular pressure, the diameter of the largest balloon used for valve dilatation at maximum inflation, & the PV annulus diameter measured during systole & the balloon annulus ratio (BAR) was estimated as the ratio of these two diameters.

After 6 months of follow-up, patients were classified according to the presence of restenosis of PV. Restenosis was diagnosed if SPG has been re-elevated to the level of moderate or severe PS. In this situation, balloon diameters larger than the initial valvuloplasty were used**.**

Statistical analysis

SPSS 15.0 (SPSS Science, Chicago, IL, USA) for Windows was used for statistical analysis. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as percentages. A comparison of categorical and continuous variables between the two groups was performed using chi-square test and independent-sample t-test, respectively. continuous variables were compared before and after intervention using paired-sample t-test, Linear correlation analysis was done using person correlation test. A P value <0.05 was considered statistically significant.

Results

Fifty patients with valvular PS were recruited. Their mean age was 4.35 ± 2.7 years old. They included 29 males and 21 females.

The balloons used had a diameter range between (8-14 mm). No major complications of the technique have been encountered in our series. In all cases, the RV pressure has fallen sufficiently (>50% drop) after the procedure to preclude the need for further treatment. There is no clinical evidence that pulmonary regurgitation is caused by the procedure in any of the patients.

There was a significant correlation between peak SPG and troponin before BPV ($p < 0.001$) ($r = 0.797$) (figure 1).

There was an initial significant decrease in troponin level 2 weeks after BPV ($p<0.001$).

Similarly, there was an initial improvement in RV function after 2 weeks. There were significant differences in all echocardiographic parameters in the whole studied populations before and two weeks after BPV regarding PPG, TAPSE, MPI, FAC, and E/e' ($p < 0.001$) for each. However, there was a non-significant difference in LVEF (68.9 ± 4.3 vs 68.9 ± 4.2, $p > 0.05$) (table 1).

After 6 months of follow up, we divided patients into 2 groups:

Group A: 36 patients with no restenosis. (Figure 2 shows an example of group A).

Group B: 14 patients with restenosis. (Figure 3 shows an example of group B).

Echocardiographic data in group A and group B revealed high significant differences between both groups 6 months after BPV regarding cardiac functions: TAPSE, MPI, FAC, E/e' and PPG ($p < 0.001$) for each (Table 2).

Group A included one patient (2.8%) with positive troponin and group B comprised 13 patients (92.9%) with positive troponin. There was a highly significant difference between both groups regarding the positivity of troponin test ($p < 0.001$).

Echocardiographic data in patients of group A without restenosis revealed no significant differences between that of 2 weeks and 6 months after valvuloplasty regarding cardiac functions: LVEF, TAPSE, MPI, FAC, E/e' and PPG ($p > 0.05$) for each **(Table 3)**.

In patients with restenosis (group B), there were highly significant differences between echocardiographic data after 2 weeks and 6 months of valvuloplasty regarding cardiac functions: TAPSE, MPI, FAC, E/e' and PPG ($p < 0.001$) for each, but there was a non-significant difference in LVEF ($p > 0.05$) (table 4).

There was a positive significant correlation between peak PG and troponin in group B ($r= 0.9$, $p < 0.001$).

Discussion

To our knowledge, there are no published data about the impacts of PS & BPV on the troponin level. In the present study, patients with PS showed significant increase in troponin level, which was reduced after BPV. The troponin level was significantly correlated to the severity of PS & the degree of RV dysfunction.

The main effect of PS is the rise in RV pressure. This elevation is accompanied by multiple changes in the RV muscle morphology, function, and geometry **(7)**.

Pressure overload inducing RV dysfunction usually causes elevation of cardiac markers. Troponin is one of the cardiac biomarkers that increase in some settings of RV dysfunction due to RV dilation and strain as in case of pulmonary embolism (PE) with sudden increase in pulmonary arterial resistance **(8)**. On the other hand, Troponin-T-positive patients are more likely to have some cardiac disorders like RV dysfunction **(9)**.

BPV is the treatment of choice for valvular PS, whereas some authors prefer surgery in case of dysplastic PV **(10),(11)**. Other modalities such as radiofrequency **m**ay be used for recanalization of pulmonary valve or occluded pulmonary branches **(12).**

The recurrence of PS or residual RVOT obstruction in infants and children who had undergone BPV is rare (4.8%) and occurs mainly in patients with PV dysplasia **(13).**

The current study was conducted on 50 patients with congenital moderate & severe valvular pulmonary stenosis scheduled for BPV after ruling out the exclusion criteria. The diagnosis of PS depends on 2D echocardiography & peak-to-peak pressure gradient difference between the pulmonic artery and RV.

The current study also revealed that the troponin level was significantly high in PS and correlated significantly with the severity of stenosis. Troponin was significantly reduced after BPV.

In our study, echocardiography was performed before BPV, then two weeks and six months later. Echocardiographic data in patients with PS revealed that RV functions in those patients were significantly impaired regarding TAPSE, FAC, MPI, and E/e'. All these parameters were significantly improved after BPV, however there were no significant changes in LV cardiac functions after BPV.

After 6 months of follow-up, patients with restenosis showed more troponin elevation which was correlated significantly with SPG.

Follow-up data in patients with restenosis, there was marked disturbance of RV functions and elevation of troponin level after 6 months of follow-up than those obtained 2 weeks after BPV.

However in patients without restenosis, there were no significant differences after 2 weeks and 6 months of BPV regarding cardiac functions and troponin level.

Recurrent elevation of troponin level associated with RV dysfunction in patients with restenosis and its correlation with peak pressure gradient gives the impression that troponin could be used as an indicator of restenosis and predictor of RV dysfunction that might necessitate repeating BPV. This is because elevated troponin carries evidence of myonecrosis and RV dysfunction.

Cardiac troponins are very sensitive and specific biochemical markers of cardiac muscle injury **(14)**

Myocardial injury may occur due to increased pressure and/or volume load. Cardiac troponins may be helpful in the evaluation of myocardial injury in children with congenital heart diseases **(15); (16),(17)**.

The thin flexible RV walls can resist the afterload mismatch resulted from the increased pulmonary flow and pulmonary resistance. Increased pulmonary flow leads to RV dilatation and consequently increased RV wall thickness according to Laplace's law. Previous studies reported that increased ventricular wall thickness and tension due to some congenital heart diseases could impede the myocardial perfusion **(18),(19)**. In addition, increased intra-myocardial tension also disrupts the coronary blood flow **(20)**. The resulting relative ischemia may cause elevated troponin levels.

In a previous study **(21)** performed on children with congenital heart diseases, patients with pressure overload lesion, such as aortic coarctation, aortic or pulmonary valve stenosis had higher troponin I

level than those with volume overload such as atrial septal defect and patent ductus arteriosus.

Kyali et al demonstrated that both troponin I and T levels increased significantly in pulmonary hypertension patients (due to pressure overload) compared with healthy control populations **(22).**

The Tei index (RT ventricular MPI) is a good, non-invasive and reproducible echocardiographic marker of RV dysfunction in pediatric patients with congenital heart disease especially if other expensive or invasive tools, like MRI and cardiac catheterization, are not available **(23)**.

Tei index could be a sensitive indicator of RV dysfunction in the setting of elevation of RV pressure overload as in case of pulmonary hypertension **(24)**. It could also predict the severity of such pressure overload and the resulting hemodynamic changes **(25)**.

Moreover, RV MPI decreased significantly in responders versus non-responders among patients with idiopathic pulmonary hypertension **(26)**.

Evaldsson et al cleared that RVFAC was significantly lower in patients with RV pressure overload than those with volume overload ($P<0{\cdot}001$) **(27).**

Menzel et al (28) stated that in CTEPH, the reduction of RV pressure overload through pulmonary thromboendarterectomy (PTE), resulted in a marked decrease of RV size and an improvement in RVFAC as an indicator of systolic function recovery.

In another study of the mechanism of RV reverse remodeling after BPV in patients with congenital PS, **Mansour et al (29)** found that the E/E' of the TV lateral annulus improved significantly after BPV. This agrees with our results.

The evaluation of RV function has a great importance during the assessment of congenital heart disease involving the pulmonary valve either stenosis or regurge **(30)**. The Tricuspid annular motion could be used for the evaluation of RV function. However, the descent of the RV base can detect patients with hemodynamically significant RV dysfunction with high sensitivity and specificity **(31)**. This importance of tricuspid annular motion may be because longitudinal shortening has an important role in RV function **(32), (33).**

Mahfouz et al found that diastolic parameters with TDI were significantly altered in PS but showed significant improvement after BPV. These findings support our results in the current study **(34)**.

The troponin biomarker and the parameters of RV function could present objective evidence of RV myonecrosis and dysfunction necessitating balloon dilatation even in moderate PS. Some children with moderate valvular PS may not be able to express symptoms, and therefore the decision for BPV is postponed. In such cases, biomarkers and echocardiographic markers can help in determining the correct time for intervention. Moreover, these parameters can be used to justify the need for re-dilatation of PV in case of moderate re-elevation of PG associated with high troponin and/or RV dysfunction.

Finally, we demonstrated our experience with the percutaneous BPV with immediate relief of stenosis of the pulmonic valve in all patients with moderate to severe valvular PS. The procedure not only improved the hemodynamics but also improved the clinical status of the patients.

Conclusion:

Troponin is a good biomarker correlated with the severity of PS and associated with RV dysfunction. RV function improved significantly with BPV. Recurrent elevation of troponin and impairment of RV function after BPV are associated with PV restenosis and could be set as an indication for repeated balloon dilatation of PV.

Conflict of Interest: There is no conflict of interest concerning this manuscript.

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Legends:

Tables:

Figures:

(b) TAPSE measurement before valvuloplasty (14 mm)

(c) RV myocardial performance index (RV MPI) before valvuloplasty (0.61)

(e) Rt ventricular myocardial performance index (RV MPI) two weeks after valvuloplasty (0.51)

(f) Pulmonary PPG six months after valvuloplasty, restenosis occurd, serum troponin I=3ngm/ml

(g) TAPSE measurement six months after valvuloplasty

(h) Rt ventricular myocardial performance index (RV MPI) six months after valvuloplasty (0.65)

Table (1): Comparison between echocardiographic parameters before and 2 weeks after balloon valvuloplasty

	Before balloon valvuloplasty	**After 2 weeks**	**t test**	**p value**
LVEF	68.9 ± 4.3	68.9 ± 4.2	0.7	0.47 (NS)
PPG	91.8 ± 11.4	31.02 ±9.75	41.27	< 0.001 (HS)
TAPSE	12.1 ± 1.8	20.7 ± 2.1	-20.8	< 0.001 (HS)
MPI	0.65 ± 0.043	0.51 ±0.026	24.7	< 0.001 (HS)
FAC	30.6 ± 1.6	37.6 ± 1.45	-24.7	< 0.001 (HS)
E/e'	8.8 ± 1.07	4.57 ± 0.59	24.1	< 0.001 (HS)
Troponin	7.62 ± 2.2	0.24 ± 0.15	23.7	< 0.001 (HS)

Table (2): Comparison between both groups regarding echocardiographic parameters 6 months after balloon valvuloplasty

	Group A (n = 36)	**Group B (n = 14)**	**t**	**p**
LVEF	68.9 ± 3.35	69.9 ± 4.5	-0.82	0.416 (NS)
TAPSE	20.52 ± 2.29	13.85 ± 1.09	10.4	< 0.001 (HS)
MPI	0.516±0.032	0.6 ± 0.027	-0.05	< 0.001 (HS)
FAC	37.9 ± 2.06	32.1 ± 1.2	9.9	< 0.001 (HS)
E/e'	4.5 ± 0.72	7.6 ± 0.44	-14.82	< 0.001 (HS)
PPG	28.3 ± 5.2	61.7 ± 11.2	-10.7	< 0.001 (HS)

Table (3): Comparison between echocardiographic parameters after 2 weeks and 6 months of BPV in Group A (patients without restenosis (n = 36))

Echocardiographic parameters	After 2 weeks	After 6 months	t	p
LVEF	68.7 ± 4.3	68.9 ± 3.3	-0.481	0.633 (NS)
TAPSE	20.5 ± 1.9	20.5 ± 2.28	0.04	1 (NS)
MPI	0.51±0.0288	0.51± 0.032	-1	0.32 (NS)
FAC	37.8 ± 1.45	37.97±2.06	-0.712	0.481 (NS)
E/e'	4.53 ± 0.54	4.52 ± 0.72	0.043	0.966 (NS)
PPG	30.69 ± 4.97	29.66 ±5.27	.42	0.16 (NS)

Table (4): Comparison between echocardiographic parameters after 2 weeks and 6 months of BPV in patients with restenosis (n = 14)

Echocardiographic parameters	After 2 weeks	After 6 months	t	p
LVEF	69.28 ± 3.4	69.9 ± 4.5	-1.26	0.224 (NS)
TAPSE	21.4 ± 2.4	13.8 ± 1.04	10.14	< 0.001 (HS)
MPI	0.51±0.018	0.6 ± 0.027	-16.9	< 0.001 (HS)
FAC	37.2 ± 1.4	32.1 ± 1.24	11.16	< 0.001 (HS)
E/e'	4.6 ± 0.71	7.6 ± 0.44	-10.8	< 0.001 (HS)
PPG	31.47 ± 4.5	61.71±11.16	-9.92	< 0.001 (HS)