Sympathetic Overactivity in Patients with Pulmonary Stenosis and Improvement after Percutaneous Balloon Valvuloplasty

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Objective: Percutaneous balloon valvulotomy (PBV) is the procedure of choice for the treatment of valvular pulmonary stenosis (PS) with similar results comparable to surgical valvotomy but less invasive. .

Methods and Results: Twenty-seven consecutive patients with PS being evaluated for PBV were enrolled in the study. Peak instantaneous transvalvular gradient, right ventricle (RV) diameter, mean atrial pressures, RV systolic pressure (RVSP), pro-brain natriuretic peptide (proBNP) levels significantly decreased immediately after PBV. Regarding heart rate variability (HRV) parameters, mean HR (heart rate), LF (low frequency) day and night, LF/HF day and night significantly decreased and standard deviation of all NN intervals (SDNN), root mean square of successive differences (RMSSD), P number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals (PNN50), HF (High frequency) day and night significantly increased 1 day after PBV and these changes were shown to be preserved at the first month. The increase in SDNN was correlated with the decrease in right atrial pressure (RAP) ($r = -0.5$, $P = 0.04$); the increase in standard deviation of the 5-minute mean RR intervals (SDANN) was correlated with the decrease in proBNP ($r = -0.4$, $P = 0.03$).

Conclusions: Sympathetic overactivity and increased proBNP levels were associated with the symptomatic status of patients with PS. Associated with a decrease in atrial pressures and proBNP levels, PBV yielded a decrease in adrenergic overactivity in the patients with PS.

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pulmonary stenosis; percutaneous balloon valvulotomy; heart rate variability

INTRODUCTION

Balloon dilatation is the procedure of choice for the treatment of valvular pulmonary stenosis (PS).^{1–3} Besides the short-term⁴ results, intermediate- and long-term^{5–8} successful results have been well documented. Follow-up of up to 10 years appears to demonstrate similar results comparable to surgical valvotomy⁹ but it is less invasive, less expensive, and requires a shorter hospital stay.¹⁰

The existence of sensory nerve endings in the pulmonary trunk and proximal parts of the left and right pulmonary arteries has been demon-

strated.¹¹ These endings were described at the media-adventitial junction and were similar to those seen in the carotid sinuses and aortic arch. Previous studies demonstrated the pulsatile discharge in these myelinated vagal afferent nerves synchronized to pulmonary arterial pressure.^{12,13} Moreover, sympathetic nerve activation is shown to cause vasoconstriction in pulmonary vessels via $\alpha 1$ and $\alpha 2$ receptors whereas vasodilation via $\beta 2$ adrenoreceptors.^{13,14} However, autonomic nervous system activity in the patients with PS and the influence of balloon dilatation of stenotic pulmonary valve on the sympathetic nervous system and heart

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rate variability (HRV) are not clear. The aim of this study was to assess the effect of pulmonary balloon valvuloplasty (PBV) on autonomic nerve activity by HRV analysis and plasma NT-proBNP levels and also we aimed to show the changes in hemodynamic factors on autonomic nervous system functions in patients with PS.

MATERIAL AND METHODS

Patients

Twenty-seven consecutive patients with pulmonary valve stenosis and sinus rhythm being evaluated for PBV between January 2002 and August 2006 were enrolled in the study. All data were collected prospectively. Patients who fulfilled the following criteria were selected for balloon dilatation of the PV: a peak-to-peak systolic pressure gradient across the PV of ≥ 50 mmHg with a normal cardiac index irrespective of symptoms.¹⁵ Patients with moderate-to-severe valvular disease other than pulmonary stenosis, mitral valve prolapse, coronary heart disease, diabetes mellitus, hypertension, or thyroid disorders were excluded from the study. Thirty-two healthy subjects (14 male, 18 female with an average age of 20 ± 7 years; ranged between 8 and 41 years) were evaluated for controls among outpatients in our institute. Dyspnea was the major complaint in the patients and was classified according to American Thoracic Society Scale of Dyspnea.¹⁶

Electrocardiography

A high-quality 12-lead ECG recorded at 25 mm/s speed and 10 mm/mV gain 2 days before and after PBV and 1 month after the procedure. ECGs were analyzed by two observers blind to outcome manually using caliper and magnifying lens. R wave amplitude in lead V_1 , S wave amplitude in lead I, T wave amplitude in lead III were measured and R/S wave ratio in lead V_1 was calculated. A minimum of eight leads, out of which at least four were precordial, were required for QT dispersion to be calculated. QT and RR intervals were measured of which at least two consecutive cycles and the mean value for each lead was considered for further calculations. QT interval was measured from the onset of the QRS complex to the end of the T wave, defined visually as the point of return of the T wave to baseline. The nadir of the T and U waves did not involve extrapolation of the T downslope to the iso-

electric baseline. Results are given as rate-corrected QT dispersion (the difference between the maximum and minimum QT across the 12-lead ECG) using Bazett's formula.

Transthoracic Echocardiography

The transthoracic studies were done by a standard technique using Vingmed System Five machine with a 2.5-MHz probe (General Electric Medical Systems, Horten, Norway). M-mode measurements were taken according to the recommendations of the American Society of Echocardiography.¹⁷ Right ventricular diameter (RVD) represents the distance between the trailing echoes of the anterior right ventricular wall and the leading echo of the right side of the interventricular septum at the R wave of the ECG in the parasternal long-axis. RVD was divided by body surface area (meter square) for each patient. Medially angulated parasternal long-axis is used to measure right ventricular free wall thickness.¹⁸ The PV annulus was measured in the parasternal short-axis view as the maximal distance between the hinge points of the valve leaflets in systole. The maximal instantaneous gradient across the PV was calculated from the peak spectral Doppler velocity using the modified Bernoulli equation.¹⁹ The measurements were made in three beats. Pulmonary valve regurgitation was semiquantified by the criteria described previously^{8,20} as none, grade I, II, III, and IV.

Percutaneous Pulmonary Balloon Valvulotomy

After local anesthesia or sometimes sedation if necessary, right femoral vein and artery were cannulated. Also, after hemodynamic studies, right ventriculogram was performed in the anteroposterior and lateral projections to evaluate the size of the right ventricle (RV) and the morphology of the PV. The technique of PBV was similar to that reported previously.²¹⁻²³ The size of the balloon was generally 1.2 to 1.3 times that of the pulmonary valve annulus. Progressively larger size balloon catheters were used if the initially selected balloon catheters failed to cross the valve. Following valvuloplasty, hemodynamic studies and right ventriculogram were repeated. If the pressure gradient did not decline below 40 mmHg in the absence of infundibular spasm, a larger size balloon was used for repeated valvuloplasty.

Heart Rate Variability Analysis

All patients underwent a three-channel 24-hour Holter ambulatory ECG monitoring (Biomedical System Century 2000/3000 Holter System, Version 1.32) on three occasions: 1 day before PBV, in the first day, and 1 month after PBV. Recordings were analyzed by Biomedical Systems Century 2000/3000 HRV Package System (Biomedical Systems, St. Louis, MO, USA), following manual adjustment of RR intervals. Patients were instructed to behave in a normal manner with a usual daily physical activity. Analog data were digitized at 200 Hz and edited by a cardiologist. The validation procedure consisted of beat labeling and tagging of noisy regions. The continuous series of RR intervals (tachogram) was obtained and all 5-minute segments with at most five isolated ectopic beats were retained for spectral analysis. Recordings with <18 hours of data or <85% of qualified sinus beats were excluded. Seven recordings were excluded during study period. The time and frequency-domain analysis of HRV were performed according to the recommendation of the task force.²⁴ The mean heart rate, standard deviation of all NN intervals (SDNN), root mean square of successive differences (RMSSD), number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals (PNN50) were measured in the time domain analysis of HRV. A reduced SDNN has been considered to reflect a diminished vagal and an increased sympathetic modulation of sinus node.²⁴ The power spectrum of HRV was measured using fast-Fourier transform analysis in four frequency bands: <0.0033 Hz (ultra low frequency, ULF), 0.0033 to 0.04 (very low frequency, VLF), 0.04 to 0.15 (low frequency, LF), and 0.15 to 0.40 (high frequency, HF). HF was used as a marker of parasympathetic nervous system and LF was used as a marker of both sympathetic and parasympathetic modulation.²⁴ The power of these components was stated as normalized units (nu). The use of the nu is recommended for interpretation of data.²⁵ We also measured the ratio of low-to-high frequency power (LF/HF) reflecting the sympathovagal balance. High values (>2) considered to reflect a shift of sympathovagal balance toward a sympathetic predominance.^{24,25} For frequency domain parameters three circadian periods were considered: the complete 24 hour, the diurnal, and the nocturnal periods defined on the basis of patient diaries. Diurnal periods covered lengths

of at least 6 hours to maximum of 10 hours; nocturnal periods covered a minimum of 4 hours to a maximum of 6 hours. Normalized LF and HF components were defined dividing the corresponding raw power by total power minus the power in the VLF band [$LF_{nu} = LF / (TP - VLF)$]. All drugs that may affect HRV analysis were withheld for at least 5 half-times. The investigators that performed HRV analysis were blinded to the hemodynamic and proBNP results.

Measurement of proBNP Plasma Levels

Blood samples were collected in ethylenediamine-tetraacetic acid containing tubes for each patient three times during holter monitoring. The samples were spun at 3000 rpm for 10 minutes at 0°C. The plasma was then extracted and frozen in aliquots at -70°C until analysis. ProBNP was measured using a chemiluminescent kit (Roche Diagnostics). The results were given in pg/mL (N: <100 pg/mL for male and <150 for female). The clinicians involved in the study were blinded to the proBNP values obtained.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD and discrete variables are expressed as frequencies and percentages. For continuous variables, differences between patients and the control group were tested using Student's *t*-test (normal parameters) or with a Mann-Whitney U test (nonnormal parameters), the differences before and after PBV in the patients were tested using paired *t*-test and for categorical variables chi-square (or Fisher's exact test) was used. Pearson's correlation analysis was performed to define the correlation between echocardiographic, clinic, hemodynamic parameters, and HRV. Linear logistic regression analysis was performed to define the changes between the echocardiographic, hemodynamic parameters, symptomatic class and heart rate variability after PBV. A P-value <0.05 was considered statistically significant.

RESULTS

Study Population

Twenty-seven patients (11 male, 16 female with an average age of 21 ± 9 years; ranged between 6 and 42 years) were enrolled in the study. None

of the subjects was taking any medication nor had more than one intervention. Fifteen of those patients (56%) had class III symptoms, 9 (33%) had class II, and 3 (7%) had class I symptoms. The variables affecting the symptomatic status of the patients were right atrial pressure (RAP) ($R = 0.4$, $t = 2.1$, $P = 0.04$), plasma proBNP levels ($R = 0.6$, $t = 3.4$, $P = 0.001$), and LF/HFday ratio ($R = 0.6$, $t = 3.6$, $P = 0.001$). Seven patients (26%) had had syncopal attacks, mainly on effort before admission. These patients had higher peak instantaneous pressure gradient (132.7 ± 20.8 vs 94.8 ± 25.9 , $P = 0.002$), greater right axis deviation on ECG (144.3 ± 17.9 vs 118.3 ± 28.2 , $P = 0.007$), higher LF/HF day ratio (4.7 ± 0.8 vs 3.6 ± 0.6 , $P = 0.007$), and higher proBNP levels (89.71 ± 11.73 vs 76.55 ± 10.42 , $P = 0.009$) compared to those without syncope. Linear regression analysis revealed that the independent variables affecting syncope were RV-PA pressure gradient (odds ratio [OR] = 1.1, $P = 0.02$, 95% confidence interval [CI] :1.01–1.21), mean QRS axis (OR = 1.1, $P = 0.02$, 95%CI: 1.01–1.14), LF/HF (OR

= 12.3, $P = 0.01$, 95%CI:1.8–84.5), and proBNP levels (OR = 1.1, $P = 0.03$, 95%CI: 1.01–1.2).

Baseline Characteristics

When compared to the age and genderly matched control group the patients with PS had higher proBNP, mean HR, LF, LF/HF ratio, QTc dispersion, mean QRS axis, R amplitude in V_1 , S amplitude in V_6 , R/S ratio in V_1 , and lower SDNN, SDANN, RMSSD, PNN50, HF (Table 1). Echocardiographic, hemodynamic variables, electrocardiographic, and HRV parameters before and after percutaneous PBV are shown in Tables 2 and 3. Echocardiographic examination showed a thickened RV wall and dome-like appearance of the PV with a peak instantaneous transvalvular pressure gradient of 113.6 ± 31.9 mmHg. Mean PV annulus was 1.5 ± 0.2 cm. Infundibular pressure gradient was 13.4 ± 6.3 mmHg before PBV, 11.4 ± 4.3 just after the procedure and 7.8 ± 9.9 mmHg 1 month later. Five patients had no pulmonary regurgitation

Table 1. Comparison of Clinical Characteristics and Heart Rate Variability Parameters of Patients with Pulmonary Stenosis and Control Group at Baseline

Variables	Control (n = 32)	Pulmonary Stenosis (n = 27)
Age (years)	20 $\pm$ 7	21 $\pm$ 9
Male/Female	14/18	11/16
ProBNP (pg/mL)	51.74 $\pm$ 15.92	100.72 $\pm$ 34.03*
QTc dispersion	30.8 $\pm$ 12.6	44.9 $\pm$ 7.8*
Mean QRS axis ($^{\circ}$)	45.8 $\pm$ 25.6	125 $\pm$ 21.2*
R Amplitude in lead V_1 (mm)	5.5 $\pm$ 3.2	13.6 $\pm$ 5.8*
R/S ratio in lead V_1	0.8 $\pm$ 0.2	4.5 $\pm$ 1.2*
S wave amplitude in lead V_6 (mm)	4.5 $\pm$ 2.5	10.3 $\pm$ 4.5*
Mean heart rate (beats/min)	71.2 $\pm$ 9.0	90.8 $\pm$ 13.1*
SDNN (ms)	128.2 $\pm$ 18.2	54.6 $\pm$ 15.8*
SDANN (ms)	102.2 $\pm$ 22.6	49.2 $\pm$ 17.8*
RMSSD (ms)	56.6 $\pm$ 19.8	52.7 $\pm$ 11.9*
PNN50 (%)	23.8 $\pm$ 10.6	13.7 $\pm$ 5.9*
Day		
LFnu	63.4 $\pm$ 12.8	78.9 $\pm$ 13.5*
LF (ms ²)	688.2 $\pm$ 144.9	985.1 $\pm$ 208.1*
HFnu	34.2 $\pm$ 10.6	21.1 $\pm$ 12.6*
HF (ms ²)	349.8 $\pm$ 46.9	262.3 $\pm$ 68.1*
LF/HF	2.1 $\pm$ 0.8	3.9 $\pm$ 0.8*
Night		
LFnu	54.6 $\pm$ 12.1	70.6 $\pm$ 13.8*
LF (ms ²)	685.4 $\pm$ 45.3	928.1 $\pm$ 208.4*
HFnu	42.8 $\pm$ 10.7	30.4 $\pm$ 13.7*
HF (ms ²)	362.1 $\pm$ 29.8	249.7 $\pm$ 56.9*
LF/HF	1.3 $\pm$ 0.5	3.7 $\pm$ 0.8*

* $P < 0.05$.

SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the 5-minute mean RR intervals; RMSSD = root mean square of successive differences; PNN50 = number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals; LF = low frequency; HF = high frequency; QTc: corrected QT, BNP = brain natriuretic peptide.

(PR), 20 (74%) had grade I, 2 (7.5%) had grade II PR before PBV. After PBV, one patient had grade III, 12 (44%) patients had grade II, and 14 (52%) had grade I PR. However, no patient required surgical treatment.

Regarding the parameters before PBV, the mean HR was found to be correlated with right atrial pressure (RAP), right atrial diameter (RAD), peak systolic and mean valvular gradients. SDNN was correlated with RAD and right ventricle wall thickness (RVWT). LF day was correlated with, LF/HF night was correlated with right ventricle diameter (RVD). ProBNP levels were correlated with RAP, peak systolic gradients, mean valvular gradients, and RVWT (Table 4). Linear regression analysis revealed that left atrial pressure ($\beta = 0.3$, $t = 2.8$, $P = 0.01$), and transvalvular gradient ($\beta = 0.9$, $t = 6.0$, $P = 0.001$) were independent factors affecting proBNP levels in the patients with PS.

Effect of Pulmonary Balloon Valvuloplasty on Hemodynamic and Echocardiographic Parameters

Peak instantaneous transvalvular gradient, mean pressure gradient, RAD, RVD, mean atrial pres-

ures, RV systolic pressure (RVSP), RV-PA systolic gradient, proBNP levels significantly decreased and left ventricle EF (LVEF) significantly increased immediately after PBV (Table 2). At first month control visit, the increase in LVEF, the decrease in peak and mean pressure gradients, RA and RV diameters, and proBNP levels were seen to persist. Moreover, it was also found that the left atrial diameter and RVWT significantly reduced (Table 2). Among the ECG parameters, although only S wave amplitude in lead V₆ and QTc dispersion decreased significantly 1 day after PBV, all the measured parameters were found to be decreased 1 month later (Table 2) when compared to those before PBV.

Effect of Pulmonary Balloon Valvuloplasty on Heart Rate Variability

Regarding HRV parameters, mean HR, LF day, LF night, LF/HF day and night significantly decreased and SDNN, RMSSD, PNN50, HF day and night significantly increased 1 day after PBV and these changes were shown to be preserved at the first month (Table 3). All the patients were totally asymptomatic at the first month follow-up visit.

Table 2. Echocardiographic, Hemodynamic Variables and Electrocardiographic Parameters before and after Percutaneous Pulmonary Balloon Valvulotomy

		After PBV	
	Before PBV	1st Day	1st Month
Echocardiographic variables			
Systolic transpulmonary pressure gradient (mmHg)	113.6 ± 31.9	32.7 ± 8.6*	31.8 ± 8.6*
Mean pressure gradient (mmHg)	50.4 ± 19.4	17.4 ± 5.6*	16.4 ± 7.4*
Right atrial diameter (cm)	3.8 ± 0.3	3.6 ± 0.2*	3.3 ± 0.2*
Left atrial diameter (cm)	3.4 ± 0.4	3.4 ± 0.3	3.3 ± 0.4*
Left ventricle EF (%)	67.9 ± 2.7	70.5 ± 2.9*	71.3 ± 3.1*
Right ventricle anterior wall thickness (cm)	8.8 ± 1.8	8.5 ± 1.6	6.7 ± 0.2*
Right ventricle end-diastolic diameter (cm/m ²)	1.26 ± 0.24	1.19 ± 0.2*	1.16 ± 0.19*
Hemodynamic variables			
Mean left atrial pressure (mmHg)	12.2 ± 1.9	8.9 ± 1.9*	
Mean right atrial pressure (mmHg)	12.6 ± 1.6	7.2 ± 1.5*	
Right ventricular systolic pressure (mmHg)	125.9 ± 30.7	54.2 ± 13.9*	
RV-PA gradient (mmHg)	104.6 ± 29.7	30.6 ± 10.4*	
Systolic pulmonary arterial pressure (mmHg)	21.3 ± 6.5	23.5 ± 8.7	
ProBNP levels (pg/mL)	100.72 ± 34.03	91.43 ± 29.06*	84.33 ± 22.32*
Electrocardiographic parameters			
Mean QRS axis (°)	125 ± 21.2	124.3 ± 20.9	116.7 ± 27.9*
R amplitude in lead V ₁ (mm)	13.6 ± 5.8	13.6 ± 5.7	10.3 ± 4.9*
R/S ratio in lead V ₁	4.5 ± 1.2	4.4 ± 1.2	3.9 ± 1.1*
S wave amplitude in lead V ₆ (mm)	10.3 ± 4.5	9.5 ± 4.2*	7.5 ± 3.6*
QTc dispersion (ms)	44.9 ± 7.8	42.4 ± 8.1*	40.0 ± 6.4*

EF = ejection fraction; RV = right ventricle; PA = pulmonary artery; PBV = pulmonary balloon valvuloplasty; HRV = heart rate variability; QTc = corrected QT; *P < 0.05 compared to before PBV.

Table 3. Heart Rate Variability Parameters before and after Percutaneous Pulmonary Balloon Valvulotomy

HRV Parameters		Before PBV	After PBV	
			1st Day	1st Month
Day	Mean heart rate (beats/min)	90.8 ± 13.1	70.7 ± 9.1*	69.9 ± 7.8*
	SDNN (ms)	54.6 ± 15.8	102.8 ± 23.1*	112.9 ± 24.2*
	SDANN (ms)	49.2 ± 17.8	85.9 ± 21.9*	93.7 ± 24.1*
	RMSSD (ms)	52.7 ± 11.9	60.5 ± 9.5*	60.3 ± 8.9*
	PNN50 (%)	13.7 ± 5.9	17.1 ± 5.9*	33.6 ± 7.2*
	LF (nu)	78.9 ± 13.5	51.6 ± 13.8*	49.5 ± 14.1*
	LF (ms ²)	985.1 ± 208.1	448.4 ± 91.7*	428.1 ± 96.2*
	HF (nu)	21.1 ± 12.6	48.4 ± 13.6*	50.5 ± 14.4*
	HF (ms ²)	262.3 ± 68.1	419.2 ± 83.4*	432.7 ± 84.5*
	LF/HF	3.9 ± 0.8	1.1 ± 0.2*	1.1 ± 0.1*
Night	LF (nu)	70.6 ± 13.8	50.2 ± 13.6*	47.9 ± 13.9*
	LF (ms ²)	928.1 ± 208.4	417.3 ± 82.7*	393.6 ± 81.6*
	HF (nu)	30.4 ± 13.7	50.1 ± 13.9*	53.1 ± 14.6*
	HF (ms ²)	249.7 ± 56.9	412.7 ± 68.5*	425.7 ± 72.8*
	LF/HF	3.7 ± 0.8	1.0 ± 0.2*	0.9 ± 0.2*

PBV = pulmonary balloon valvuloplasty; HRV = heart rate variability, SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the 5-minute mean RR intervals; RMSSD = root mean square of successive differences; PNN50 = number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals; LF = low frequency; HF = high frequency.

*P < 0.05 compared to before PBV.

The correlation between pre- and post-valvuloplasty parameters are shown in Table 5. The decrease in proBNP after PBV was correlated with the decrease in RVSP ($r = 0.7$, $P = 0.001$), RV-PA pressure gradient ($r = 0.8$, $P = 0.001$). The change in SDNN after PBV was affected only by the change in RAP ($\beta = -0.5$, $t = -2.3$, $P = 0.003$). The independent factors affecting the decrease in LF/HF after PBV were the decreases in atrial pressures, RVD and proBNP. The only independent parameter affecting the decrease in proBNP was the decrease in RVSP ($\beta = 0.7$, $t = 4.7$, $P = 0.001$).

DISCUSSION

In this study, we found that (1) Plasma proBNP levels are increased and HRV is decreased in older children, adolescents, and young adults with severe PS compared to healthy individuals, (2) increased proBNP levels and HRV were associated with symptoms of heart failure (3) ProBNP levels, RV-PA pressure gradient and LF/HF daytime ratio were associated with syncopal attacks in the patients with PS, and (4) HRV and autonomic function returned toward normal after PBV and this improvement was correlated with the changes in some hemodynamic factors and proBNP levels.

There are several possible mechanisms for this improvement in HRV and autonomic nervous system activity in the patients with PS after PBV. Firstly, sympathetic activity may be increased in association with a reduction in cardiac index as in the patients with mitral stenosis²⁶ and congestive heart failure.²⁷ The sympathetic overactivity in the patients with PS may also be related to decrease in pulmonary flow due to the obstruction. Sustained pulmonary hypoperfusion is shown to be associated with the increase in heart rate and pulmonary arterial resistance due to sympathetic stimulation.²⁸

Previously, Galal et al.²⁹ studied the influence of balloon dilatation on the sympathetic nervous system in PS. They found that the lymphocyte β -adrenoreceptor density is reduced and the α -adrenoreceptor density is significantly increased. The combination of an elevation in α -adrenoreceptors and attenuation of the β -adrenoreceptors may explain how the sympathetic nervous system adapts to hemodynamic changes in PS. Similar elevations in α -adrenoreceptors were observed in patients with other congenital diseases³⁰ and rheumatic heart valvular diseases.³¹ Galal et al.²⁹ demonstrated that both the elevation in the α -adrenoreceptors and the decrease in β -adrenoreceptors are reversed within 10 minutes

Table 4. Association between Autonomic Nervous System Function/ProBNP and Echocardiographic/Hemodynamic Parameters in Patients with Pulmonary Artery Stenosis before Valvuloplasty

	RAP	RAD	Peak Systolic Gradient	Mean Valvular Gradient	RVWT	RVD
Heart rate	$r = 0.4, P = 0.03$	$r = 0.6, P = 0.001$	$r = 0.6, P = 0.003$	$r = 0.6, P = 0.002$		
SDNN		$r = -0.6, P = 0.03$			$r = -0.4, P = 0.003$	
LF		$r = 0.5, P = 0.001$				
LF/HF						$r = 0.4, P = 0.03$
ProBNP	$r = 0.6, P = 0.001$		$(r = 0.9, P = 0.001)$	$r = 0.7, P = 0.001$	$r = 0.6, P = 0.001$	

RAP = right atrial pressure; RAD = right atrial diameter; RVWT = right ventricle wall thickness; RVD = right ventricle diameter; SDNN = standard deviation of all NN intervals; LF = low frequency; BNP = brain natriuretic peptide.

from PBV. They suggested that the sympathetic system may be chronically hyperstimulated in PS to counteract the right ventricular systolic pressure resulting from the pulmonary obstruction and sudden relief is likely to trigger vagal stimulation in conformation with the new hemodynamic conditions. Similarly, Moore et al.³² demonstrated that an increase in pulmonary arterial pressure causes a significant elevation in vagal afferent nerve activity. McMahon et al.³³ also found that the stimulation of pulmonary arterial receptors due to pressor reflex evoked by increased arterial pressure.

We previously demonstrated that the increase in LF/HF and decrease in SDNN in patients with mitral stenosis are correlated with left atrial dimensions and left ventricular ejection fraction.³⁴ However, the decrease in LF/HF and increase in SDNN after percutaneous mitral balloon commissurotomy were correlated with the changes in atrial pressures rather than the changes in ejection fraction.³⁵ Similarly, in this study we found that the mean HR, SDNN, LF day were correlated with right atrial pressure, RAD, and the changes in LF, LF/HF, and SDNN after PBV are correlated mostly with the changes in the atrial pressures. We know that stretching the RA produces an increase in sympathetic activity and left atrial stretch causes biphasic response as an initial sympathetic nerve inhibition followed by excitation.³⁶ Therefore, increased atrial pressures and chronic atrial stretch may be probable explanation for the sympathovagal imbalance in these patients and the relief of atrial stretch by PBV decreases the sympathetic activity.

The effects of hormonal factors on autonomic nervous system functions are under debate. Atrial natriuretic peptide (ANP) exerts a sympathoinhibitory action in heart failure and in normal men.^{37,38} Brunner et al.³⁹ demonstrated a sympathoinhibitory effect of brain natriuretic peptide (BNP), at BNP concentrations within the physiologic range but systemic and cardiac sympathetic nervous activity returned to baseline levels with high-dose BNP. In our study, we found that proBNP levels were higher in the patients with PS than normal individuals but not as high as reported previously in those with acute RV failure.^{40,41} N-terminal proBNP decreased significantly in the early period after PBV associated with the decrease in RVSP and this decrease was correlated with the decrease in LF/HF ratio (reflecting the decrease in sympathetic activity) and with the increase in SDANN (reflecting the increase in heart rate variability) suggesting the sympathoinhibitory effect of BNP.

Table 5. The Correlation between Hemodynamic and Heart Rate Variability Parameters

	Δ RAP	Δ LAP	Δ SPAP	Δ GRAD	Δ EF	Δ RVWT	Δ RVD	Δ RAD
Δ HR	$r = 0.07$ $P = 0.7$	$r = -0.04$ $P = 0.8$	$r = -0.3$ $P = 0.2$	$r = 0.4$ $P = 0.03^*$	$r = -0.2$ $P = 0.3$	$r = 0.1$ $P = 0.6$	$r = 0.3$ $P = 0.1$	$r = 0.2$ $P = 0.3$
Δ SDNN	$r = -0.5$ $P = 0.04^*$	$r = 0.05$ $P = 0.8$	$r = -0.08$ $P = 0.7$	$r = -0.1$ $P = 0.7$	$r = -0.3$ $P = 0.1$	$r = 0.2$ $P = 0.3$	$r = -0.3$ $P = 0.2$	$r = -0.1$ $P = 0.3$
Δ SDANN	$r = -0.1$ $P = 0.7$	$r = -0.1$ $P = 0.8$	$r = 0.1$ $P = 0.6$	$r = -0.1$ $P = 0.7$	$r = -0.1$ $P = 0.6$	$r = 0.3$ $P = 0.1$	$r = -0.2$ $P = 0.3$	$r = -0.1$ $P = 0.4$
Δ RMSSD	$r = -0.1$ $P = 0.6$	$r = 0.1$ $P = 0.5$	$r = -0.01$ $P = 0.9$	$r = -0.1$ $P = 0.5$	$r = 0.1$ $P = 0.7$	$r = -0.3$ $P = 0.04^*$	$r = 0.03$ $P = 0.9$	$r = 0.1$ $P = 0.7$
Δ PNN50	$r = 0.2$ $P = 0.5$	$r = 0.2$ $P = 0.4$	$r = -0.2$ $P = 0.4$	$r = -0.02$ $P = 0.9$	$r = 0.1$ $P = 0.7$	$r = -0.4$ $P = 0.04^*$	$r = -0.3$ $P = 0.2$	$r = 0.2$ $P = 0.3$
Day	Δ LF	$r = -0.2$ $P = 0.4$	$r = 0.2$ $P = 0.4$	$r = -0.2$ $P = 0.3$	$r = 0.3$ $P = 0.2$	$r = -0.1$ $P = 0.6$	$r = 0.01$ $P = 0.9$	$r = 0.3$ $P = 0.2$
	Δ HF	$r = -0.1$ $P = 0.4$	$r = -0.2$ $P = 0.3$	$r = 0.04$ $P = 0.9$	$r = 0.1$ $P = 0.6$	$r = 0.3$ $P = 0.08$	$r = 0.2$ $P = 0.4$	$r = -0.02$ $P = 0.9$
	Δ LF/HF	$r = 0.4$ $P = 0.04^*$	$r = 0.3$ $P = 0.08$	$r = -0.2$ $P = 0.2$	$r = 0.3$ $P = 0.2$	$r = -0.1$ $P = 0.3$	$r = -0.1$ $P = 0.6$	$r = 0.2$ $P = 0.3$
	Δ LF	$r = 0.3$ $P = 0.1$	$r = 0.2$ $P = 0.3$	$r = 0.1$ $P = 0.6$	$r = -0.1$ $P = 0.6$	$r = 0.1$ $P = 0.5$	$r = -0.3$ $P = 0.2$	$r = 0.2$ $P = 0.3$
Night	Δ HF	$r = -0.05$ $P = 0.8$	$r = 0.2$ $P = 0.4$	$r = 0.4$ $P = 0.04^*$	$r = -0.2$ $P = 0.4$	$r = 0.1$ $P = 0.8$	$r = -0.02$ $P = 0.9$	$r = -0.1$ $P = 0.6$
	Δ LF/HF	$r = 0.2$ $P = 0.4$	$r = 0.01$ $P = 0.9$	$r = -0.2$ $P = 0.4$	$r = 0.1$ $P = 0.6$	$r = -0.3$ $P = 0.08$	$r = -0.2$ $P = 0.3$	$r = 0.4$ $P = 0.04^*$
	Δ LF	$r = 0.3$ $P = 0.1$	$r = 0.2$ $P = 0.3$	$r = 0.1$ $P = 0.6$	$r = -0.1$ $P = 0.6$	$r = 0.1$ $P = 0.5$	$r = -0.3$ $P = 0.2$	$r = 0.2$ $P = 0.3$
	Δ HF	$r = -0.05$ $P = 0.8$	$r = 0.2$ $P = 0.4$	$r = 0.4$ $P = 0.04^*$	$r = -0.2$ $P = 0.4$	$r = 0.1$ $P = 0.8$	$r = -0.02$ $P = 0.9$	$r = -0.1$ $P = 0.6$

*Statistically significant. Δ = The difference between pre- and postvalvuloplasty parameters (1 day); RAP = right atrial pressure; LAP = left atrial pressure; SPAP = systolic pulmonary artery pressure; Grad = right ventricle-pulmonary artery peak systolic pressure gradient; EF = left ventricle ejection fraction; RVWT = right ventricle wall thickness; RVD = right ventricle diameter; RAD = right atrial diameter; HR = heart rate; SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the 5-minute mean RR intervals; RMSSD = root mean square of successive differences; PNN50 = number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals; LF = low frequency; HF = high frequency.

*Statistically significant.

The most significant limitation of our study is the lack of plasma catecholamine concentrations in these patients.

As a result, proBNP levels were higher, and HRV lower, indicating sympathovagal imbalance in patients with PS compared to healthy individuals. Sympathetic overactivity or decreased parasympathetic activity and increased proBNP levels were associated with heart failure symptoms. Although HRV analysis does not allow the appraisal of individual mechanisms involved in the decrease in sympathetic activity and increase in HRV after PBV, our results demonstrated that the PBV yielded an improvement in the sympathovagal imbalance in the early period, associated with decrease in atrial pressures and proBNP levels.

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