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Ventricular Arrhythmias and Autonomic Profile in Patients with Primary Pulmonary Hypertension

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Abstract. The aim of our study was to assess the arrhythmic profile in patients with primary pulmonary hypertension (PPH) and its correlation with autonomic features, echocardiographic indexes and pulmonary function. We studied 9 subjects with a mean age of 42 ± 11 years. All underwent echocardiography, 24-hour Holter monitoring, and cardiopulmonary exercise testing. Left ventricle ejection fraction was normal (65 ± 6%). The right ventricle end diastolic volume was increased (108 ± 32 ml/m^2) with a slight reduction of ejection fraction (49 ± 5%). Right ventricle systolic pressure was increased (91 ± 25 mmHg). Heart rate variability analysis showed evidence of a reduced standard deviation of all NN intervals (SDNN) compared with the control group (102.8 ± 32 versus 156.1 ± 32, $p < 0.005$). Patients with significant ventricular arrhythmias had a lower SDNN, and lower baseline and effort PO_2 (SDNN: 87.0 ± 15 versus 115.4 ± 38; baseline PO_2: 63.2 ± 12% versus 78.8 ± 7%; effort PO_2: 50.7 ± 13% versus 68.7 ± 19%). The patients with SDNN lower than 90 ms were characterized by a higher right ventricle systolic pressure (115.0 ± 22.9 mmHg versus 79.2 ± 17.8 mmHg, $p = 0.035$). The patients who experienced syncope had higher SDNN (131.7 ± 36 versus 88.4 ± 20, $p < 0.05$), higher effort PO_2 (77.5 ± 14 mmHg versus 52.3 ± 14 mmHg, $p < 0.03$). The patients with PPH evidenced an increased sympathetic activity. Premature ventricular beats were more frequent in those subjects with higher adrenergic drive and lower oxygen saturation. Patients with episodes of syncope seem to have a relatively higher vagal activity, and effective mechanisms of adjustment in blood oxygenation during effort.

Key words: Primary pulmonary hypertension—Autonomic nervous system—Heart rate variability—Ventricular arrhythmias.

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Introduction

Primary pulmonary hypertension (PPH) is a rare disease characterized by an increase of pulmonary vascular resistance leading to an enhanced pulmonary arterial pressure and low cardiac output. With the progression of the disease, dilatation and hypertrophy of the right ventricle develops, usually associated with tricuspid insufficiency [14, 17, 22]. Increased metabolic needs related to augmented myocardial wall stress, and decreased perfusion due to a decreased diastolic coronary flow and an impaired capillary network, induce right ventricle myocardial ischemia, as seen in animal models and other diseases with pulmonary hypertension [5, 8]. Right ventricle dysfunction was recently demonstrated by myocardial scintigraphy to be associated in humans with myocardial ischemia [4].

The prognosis of this disease is usually poor, and the most frequent causes of death are heart failure and pneumonia. Sudden death also occurs, induced by a sudden increase in pulmonary resistance, due to vasoconstriction or massive thrombosis, pulmonary hemorrhage or acute right ventricle ischemia [1, 3].

In PPH a modulation of the autonomic activity could occur, induced by hemodynamic changes as well as by mechanical and metabolic alteration of the right ventricle.

Considering the well-documented correlations between the occurrence of arrhythmias and autonomic nervous system activity [19], the aim of our study was to assess the arrhythmic profile in PPH patients and its correlation with autonomic features, echocardiographic indices, and pulmonary function.

Patients and Methods

Patients

We studied 9 patients (2 males and 7 females), with a mean age of 42 ± 11 years, in whom PPH was diagnosed according to the criteria of the National Institute of Health registry for PPH. For the diagnosis all of them underwent an assessment including clinical history (the first manifestation was exertional dyspnoea in 6 patients and exertional syncope in 3), physical examination, chest X-ray, 12 lead electrocardiogram with leads V3r and V4r, two-dimensional echocardiography, pulmonary function tests, ventilation/perfusion lung scan, left and right heart catheterization with coronary angiography, and complete immunological screening [16].

All patients were treated with digoxin, anticoagulants, and diuretics. Only 2 subjects were treated with diltiazem after a demonstration of vasodilatation responsiveness.

Methods

For assessment of arrhythmias and heart rate variability analysis all the patients underwent a 24-hour Holter monitoring (3-channel Del Mar 461 recorder). The recordings were analyzed by a Del-Mar Avionics 563 Holter analysis system (operator-controlled analysis). Ventricular arrhythmias were considered as the absolute number of premature ventricular complexes (PVC) detected. In order to obtain time domain analysis of heart rate variability, normal and aberrant complexes were discriminated and all adjacent intervals between normal beats (NN) over the 24 hours were collected and computed. The parameters considered were as follows: the standard deviation (SD) of all NN intervals

(SDNN), the SD of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals (pNN50). The recordings, collections and elaboration of the results were made according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [21]. Twenty healthy subjects (mean age 39 ± 18 years) formed a control group for heart rate variability analysis.

The cardiopulmonary exercise testing with gas exchange measurements was performed by a bicycle stress test. A progressive, 2-minute incremental workload test, symptom limited, was adopted. Electrocardiogram and blood pressure were monitored throughout the test. Moreover, room air was breathed through a mouthpiece and a low-resistance valve connected to a volume turbine, which measured minute ventilation (VE). Expired air was sampled continuously, breath to breath, by oxygen and carbon dioxide analyzer. From the expired gas, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), and maximal oxygen consumption (VO_2) were derived. Oxygen pulse (O_2 P) was calculated by dividing VO_2 by the heart rate. The ventilatory equivalent of oxygen (VEO_2) was calculated by dividing VE by VO_2. Two capillary samples were obtained in order to measure PO_2, PCO_2, and hemoglobin saturation (HbS): the first at rest, the second at the peak exercise.

Statistical Analysis

The data are expressed as mean ± standard deviation. Differences between groups were examined for statistical significance by analysis of variance (ANOVA). Statistical significance was assumed with a level of $p < 0.05$.

Results

The echocardiographic study showed normal left ventricle functioning, whereas the right ventricle turned out to be dilated, with a slight reduction of output and a relevant increase of the right ventricle systolic pressure (Table 1).

During Holter monitoring, 4 patients showed a relevant number of isolated premature ventricular complexes, in 2 cases couples (cases 2 and 9), whereas the others had only rare ectopic activity (Table 2). In 3 cases, ventricular arrhythmias had right bundle branch block morphology, in one left bundle branch block morphology, and in the others, both morphology were present.

Heart rate variability analysis showed reduced SDNN and SDANN values compared with the control group. The other indexes did not show significant differences (Table 2).

The cardiopulmonary exercise test demonstrated a substantial exercise limitation, with a maximal workload of 80 W in 1 patient, 60 W in 4 patients, 54 W in another patient and 40 W in the other 3. The reasons for discontinuations were dyspnoea and physical exhaustion. The PO_2 showed a decrease with the exercise, while ventilation increased significantly (Table 3). Effort did not induce ventricular arrhythmias.

Patients with significant ventricular arrhythmias (PVC >700/24/h, patients 2, 3, 5, 8) had a lower value SDNN and SDANN, but without reaching the statistical significance. On the contrary, they evidenced a significantly lower baseline effort PO_2 (Table 4). The patients with the lowest values of SDNN (< 90 msec, 3

Table 1. Echocardiographic indexes

Patient	LVEDV (ml/m^2)	LVEF (%)	RVEDV (ml/m^2)	RVEF (%)	RVSP (mmHg)
1	43	70	93	53	135
2	28	57	162	42	97
3	36	66	78	51	90
4	28	69	132	43	97
5	45	69	80	55	65
6	47	70	90	55	77
7	42	68	81	53	53
8	51	66	151	48	120
9	39	52	108	44	85
Mean ± SD	39.9 ± 8	65.2 ± 6	108.3 ± 32	49.3 ± 5	91.2 ± 25

LVEDV: left ventricle end diastolic volume; LVEF: left ventricle ejection fraction; RVEDV: right ventricle end diastolic volume; RVEF: right ventricle ejection fraction: RVSP: right ventricle systolic pressure.

Table 2. Heart rate variability analysis and ventricular arrhythmias

Patient	Mean NN	SDNN	SDANN	RMSSD	pNN50	n. PVCs	Syncope
1	634	65.9	62	20.8	3.6	85	No
2	750	99.3	89	24	3.7	1210	No
3	666	80.6	75	12.1	0.7	710	No
4	945	167.6	152	53.2	21.3	7	Yes
5	821	100.2	94	28.2	8.5	720	No
6	807	133	120	24.1	4.4	4	Yes
7	882	94.6	79	32.2	7.1	1	Yes
8	709	68.1	53	52.2	10.1	3600	No
9	735	116.1	105	87.8	12.2	4	No
Mean ± SD	772.1 ± 101	102.8 ± 32	92.1 ± 30	37.2 ± 23	7.9 ± 16	–	–
Control group	819.9 ± 112	156.1 ± 32	139.9 ± 30	37.7 ± 16	11.7 ± 9	–	–
p	NS	<0.005	<0.005	NS	NS	–	–

For abbreviation see explanation in text

patients) were characterized by a higher right ventricle systolic pressure (115.0 ± 22.9 mmHg versus 79.2 ± 17.8 mmHg, $p < 0.05$).

The patients with syncope (cases, 4, 6 and 7) showed higher SDNN values (131.7 ± 36.5 versus 88.4 ± 20.0), higher effort PO_2 (77.5 ± 14 mmHg versus 52.3 ± 14 mmHg, $p < 0.03$), and lower effort ventilation (28.3 ± 4 l/min versus 36.4 ± 2 l/min, $p < 0.01$). These patients did not show significant changes of PO_2 during exercise (77 ± 10 mmHg versus 77.5 ± 14 mmHg), whereas the others showed a reduction of the same index (69 ± 13 mmHg versus 52 ± 14 mmHg). Moreover, these subjects were characterized by a lower number of PVCs at Holter monitoring.

Discussion

Patients with PPH have a poor survival expectancy, and often die young. Frequently the cause of death cannot be correctly determined.

Table 3. Cardiopulmonary exercise test

	Baseline	Peak exercise	*p*
PO_2 (mmHg)	71.9 ± 12.1	60.7 ± 18.0	< 0.01
HbS (%)	94.7 ± 4.3	89.0 ± 7.8	NS
VE (l/mm)	10.2 ± 1.8	33.7 ± 4.9	< 0.0001
VEO_2%Pr (%)	–	202.1 ± 35.4	–
O_2P%Pr (%)	–	76.3 ± 11.7	–

For abbreviation see explanation on text.

Table 4. Heart rate variability and cardiopulmonary exercise test in patients with different ventricular arrhythmias

	PVCs < 700/24 hour	PVCs > 700/24 hour	*p*
Patients (n)	5	4	NS
SDNN	115.4 ± 38.5	87.0 ± 15.5	NS
SDANN	103.6 ± 35.2	77.7 ± 18.3	NS
RMSSD	43.6 ± 27.7	29.1 ± 16.8	NS
pNN50	9.7 ± 7.3	5.7 ± 4.3	NS
Baseline PO_2	78.8 ± 7.2	63.2 ± 11.8	< 0.05
Baseline HbS	96.9 ± 1.3	92.0 ± 5.5	NS
Baseline VE	9.9 ± 2.3	10.7 ± 1.0	NS
Effort PO_2	68.7 ± 18.7	50.7 ± 12.6	NS
Effort HbS	92.3 ± 7.0	85.0 ± 7.5	NS
Effort VE	31.9 ± 5.8	35.9 ± 2.7	NS

For abbreviation see explanation on text.

Various studies have tried to identity new prognostic factors and to evaluate the efficacy of conventional and new therapies [11]. The introduction of prostacyclin has contributed to a significant reduction in mortality in these subjects [2, 12, 18, 24]. More recently, a clinical improvement was achieved with bosentan, a dual endothelin receptor antagonist [15].

A less studied aspect of the disease is the arrhythmic profile of these patients, as a possible cause of death. In our study we tried to characterize the arrhythmic profile in patients with PPH. Moreover, considering the well-demonstrated influence of the autonomic nervous system on the genesis of the arrhythmias, we also studied the autonomic activity of these subjects by heart rate variability analysis.

Right ventricular morphologic modifications, induced by the enhanced pressure, could represent an adequate substrate for arrhythmias. A recent study confirmed the theoretical assumption of the existence of right ventricle ischemia in PPH, which could be another important risk factor for ventricular arrhythmias. Besides this, both reduction of cardiac output and modifications of pulmonary pressure are able to induce a modulation of the autonomic activity, with an increase of the sympathetic drive, well known for its proarrhythmic effects.

In our study group we found no serious ventricular arrhythmias. Four patients showed more than 700 PVCs in 24 hour. Furthermore, the site of origin of the ectopic activity, on the basis of PVC morphology, is not confined to the right ventricle.

The reduction of the mean SDNN value that we found in our study group reflects increased sympathetic activity, probably related to reduced cardiac output, typical in PPH, and the consequent baroreflex activation.

The mechanoreceptors of the myocardial wall usually drive a reflex withdrawal of sympathetic activity when activated. On the contrary, in our cohort we found the lowest SDNN in subjects with the higher right ventricle systolic pressure. However, we could hypothesize that this inhibitory reflex is less effective than the reduced cardiac output in the modulation of the adrenergic tone.

In some cases the small number of patients studied preclude the achievement of the statistical significance, nevertheless, patients with more frequent ventricular PVC showed a higher sympathetic activity. The autonomic profile in arrhythmic patients was also confirmed by a reduction of vagal activity, reflected by a decreased pNN50. Unfortunately, all the patients had a very poor performance in terms of maximal workload during exercise testing, and no arrhythmias were induced by effort. For this reason, we cannot confirm the relevance of adrenergic activity on ventricular arrhythmias in these patients. It is noteworthy that the 3 patients who experienced exertional syncope were those with a higher mean SDNN. Several studies have attempted to demonstrate a correlation between indexes of heart rate variability and the occurrence of syncope in the general population, but the results are still controversial [6, 7, 13, 23].

The main factor involved in syncope in PPH patients is the defective cardiac output during physical activity [9]. On the other hand, we know that one of the most common mechanism for reflex syncope starts from a diminished left ventricular filling, induced by hypovolemia or by a reduction of venous return, with intense contractions around an empty cavity. The result is an increased stimulation of the mechanoreceptors located in the myocardial wall, that inducing a reflex efferent parasympathetic inhibitory discharge causes bradycardia and hypotension [10]. Similarly, PPH patients usually have a reduced left ventricular volume, as confirmed in our population. We could hypothesize that in these conditions if a similar mechanism is involved, starting from the reduced ventricular filling, the higher chronic vagal tone could facilitate the onset of the vagal reflex reaction.

The variation of oxygen saturation showed a different behavior in patients with or without syncope during exercise. In fact, the subjects suffering loss of consciousness showed stable values of PO_2 during effort. For this reason we could exclude hypoxia as one of the determinants of the syncope. The cardiopulmonary exercise test showed a decrease of PO_2 during physical activity, whereas ventilation increased significantly. These findings indicate that these patients have baseline and effort exaggerated ventilation, not proportional with the physical performance, but inadequate to compensate gas exchanges during effort [20]. The lowest baseline and effort PO_2 values were found in patients with most frequent ventricular arrhythmias; we could therefore hypothesize that a relative ischemia could be involved in the electrical instability.

In conclusion, in our study group we did not find life-threatening arrhythmias, even though frequent isolated PVCs were found in some cases. It may be that in these patients, an enhanced sympathetic activity and a relative oxygen saturation reduction combine their effects to induce ischemia-induced arrhythmias. The patients with episodes of syncope seem to have a relatively higher vagal activity and effective mechanisms of adjustment in blood oxygenation during effort.

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