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Research Article

"Right Ventricular Hypertrophy or Right Ventricular Dilatation in Pulmonary Hypertension: Is there a Difference in the Autonomic Balance"?

Gabriela Roncato[1,3,4], Karina Rabello Casali[2], Ana Amélia Machado Duarte[3], Bruna Doleys Cardoso[4], Guilherme Watte[4], Fabrício Fontoura[4], Juliessa Flarian[4], Fernanda Brum Spilimbergo[4], Gisela Martina Bohns Meyer[4], Katya Vianna Rigatto[1,3]*

[1]*Institute of Basic Health Sciences, Department of Physiology, Federal University of Rio Grande do Sul, Brazil*
[2]*Institute of Science and Technology, Federal University of São Paulo, Brazil*
[3]*Department of Basic Health Sciences, Federal University of Health Sciences of Porto Alegre, Brazil*
[4]*Pulmonary Hypertension Center, Santa Casa de Misericordia de Porto Alegre, Brazil*

***Corresponding author**
Katya Vianna Rigatto, Department of Basic Health Sciences, Federal University of Health Sciences of Porto Alegre, Sarmento Leite, 245, Porto Alegre, 90050-170, RS/ Brazil, Tel: 0 xx 55 51 3303-8753; Fax: 0 xx 55 51 3303-8753; E-mail: krigatto@gmail.com

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Abstract

Introduction: Even though autonomic nervous system imbalance is a common finding in several diseases, these imbalances often remain untreated. The prognosis of pulmonary hypertension (PH) depends upon the functional capacity of the right ventricle. Because an autonomic nervous system imbalance occurs in PH, our goal was to investigate whether the magnitude of this imbalance might provide valuable information regarding the diagnosis, prognosis and possibly the treatment of PH.

Objective: To investigate the sympathovagal balance in PH associated with right ventricular hypertrophy or right ventricular dilation.

Methods: An electrocardiogram was performed in two groups of patients with PH evaluation of autonomic responses by spectral analysis: group 1- PH patients with right ventricular hypertrophy (PH-H; n= 6) and group 2- PH patients with right ventricular dilatation (PH-D; n= 9). In addition, a group of healthy subjects was also studied (CO; n= 5).

Results: The autonomic balance, as determined by the ratio of the low (LF) and high frequency (HF) components (m/s2) of the electrocardiogram, was significantly impaired in the PH-D group (2±1.2) compared to the PH-H (0.5±0.4) and control (0.4±0.4) groups. In addition, there was significant variability in heart rates (m/s2) between all groups: PH-D (381±100), PH-H (1007±403) and control (1917±656).

Conclusion: For the first time, a sympathetic/parasympathetic imbalance was shown to exist in PH associated with dilated cardiomyopathy but not in PH associated with hypertrophic cardiomyopathy.

ABBREVIATIONS

PH: Pulmonary Hypertension; ANS: Autonomic Nervous System; BP: Blood Pressure; HR: Heart Rate; HRV: Heart Rate Variability; ECG: Electrocardiogram; RV: Right Ventricle; NYHA: New York Heart Association; PH-H: PH patients with right hypertrophic cardiomyopathy; PH-D: PH patients with right dilated cardiomyopathy; CO: Control group; PI: Pulse Interval; HF: High Frequency; SD: Standard Deviation; LFa: absolute Low Frequency; HFa: absolute High Frequency; LFnu: normalized Low Frequency; HFnu: normalized High Frequency; BPV: Blood Pressure Variability; y: years; PDE-5: Phosphodiesterase 5; WHO: World Health Organization; HIV: Human Immunodeficiency Virus.

INTRODUCTION

Pulmonary hypertension (PH) is a disease with a poor prognosis and is characterized by inappropriate elevations in pulmonary arterial pressure [1], endothelial dysfunction, coagulation abnormalities, vascular remodeling, vasodilator/vasoconstrictor imbalances [2] and autonomic nervous system (ANS) disturbances [3,4]. Progressive remodeling of the pulmonary vasculature leads to increased vascular resistance and, consequently, increased pulmonary arterial pressure, resulting in right ventricle failure [1].

The ANS plays an important role in the regulation of blood pressure (BP) and heart rate (HR) [5,6]. ANS changes are important prognosis indicators and are associated with several pathologies, including PH [4]. The assessment of heart rate variability (HRV) provides relevant information about ANS function and quantitatively expresses sympathetic and parasympathetic nervous system modulation of the cardiovascular system [7]. A reduction in HRV is associated with poorer outcomes [8-10] and is a precursor to the development of hypertension [11]. Moreover, a consensus of clinical opinion states that a higher HRV indicates better BP control. Because HRV can be assessed by a simple electrocardiogram (ECG), this relevant information could easily be obtained in clinical situations to aid in the diagnosis [12,13] of PH, evaluation of cardiovascular risk [14] and monitoring of the disease.

Right ventricle (RV) function is the major determinant of functional capacity and prognosis in PH. The RV is exposed to pressure overload caused by chronic HP, triggering an initial adaptive response, such as myocardial hypertrophy [15]. On the other hand, as very well described by McLaughlin et al. (2009), "…it remains unclear why some RVs compensate while others decompensate, manifest as thinning and dilatation of the wall,…" [16].

RV dilation may be an attempt to maintain systolic volume despite the reduction in fractional shortening [15]. However, the contractile strength of the RV progressively weakens, followed by symptoms of RV failure such as high filling pressure and diastolic dysfunction [17]. Thus, the RV function and size not only are indicators of the severity and chronicity of PH but also are an additional cause of a patient's symptoms and worsen a patient's prognosis [15].

In addition, it is well established in the literature that the predominance of sympathetic modulation correlates with disease severity [4]. On the other hand, the role of sympathetic and parasympathetic balance in the progression of cardiac dysfunction in PH is by no means clear.

Considering the relevance of sympathetic and parasympathetic modulation to patient evaluation and monitoring, HRV changes in PH patients with either right ventricular hypertrophy or right ventricular dilatation using ECG were investigated. Our primary goal is to better understand PH physiopathology. An additional goal is to focus attention on spectral analysis as a clinically unexplored method that can aid in PH risk evaluation, disease monitoring, and possibly treatment.

Table 1:

	Hypertrophy	Dilation
Patients, n	6	9
Age, y (mean)	41	41
Treatment, n		
Endothelin antagonists	1	2
PDE-5 inibitor	5	7
Functional class WHO (mean)	2	2
Diagnosis, n		
Idiopathic	2	2
Congenital heart disease	3	4
Chronic thromboembolic	1	1
Connective tissue disease		1
HIV		1

Abbreviations: **y:** years; **PDE-5:** phosphodiesterase 5; **WHO:** world health organization; **HIV:** human immunodeficiency virus.

MATERIALS AND METHODS

Patients

Fifteen patients with PH and five controls gave informed consent to participate in the study, which was approved by the Ethics Committee of Universidade Federal de Ciências da Saúde de Porto Alegre.

Patients with a mean pulmonary arterial pressure > 25 mmHg were included. Their functional status was scored according to the New York Heart Association (NYHA) classification. Patient characteristics are summarized in (Table 1).

Groups

1- Control (CO): Subjects without diagnosed disease (n = 5; 3 women);

2- PH-H: PH patients with right hypertrophic cardiomyopathy (n = 6; 5 women);

3- PH-D: PH patients with right dilated cardiomyopathy (n = 9; 8 women).

Electrocardiogram

All ECGs were recorded between 1 and 3 PM. During the data recording, the subjects were at rest in the supine position in a quiet room. They were advised to remain motionless in a comfortable position. Disposable electrodes were placed on the skin of the chest to collect electrocardiographic signals (derived: DI, DII and DIII), which reflect cardiac electrical activity [18]. Continuous ECG signals (sampling rate, 1 kHz) were recorded by a MP150 system (Biopac, California, USA) and used to perform spectral analysis using an autoregressive model (Table 2).

If a woman was of childbearing age, the ECG was performed between the 1st and 5th day of the menstrual cycle to standardize the data.

Autonomic modulation evaluation

The sympathetic and parasympathetic modulation of the heart was evaluated by spectral analysis of a time series of RR intervals (tachograms) extracted from the ECG signals through software provided by the manufacturer of the acquisition system (Acknowledge software, Biopac Systems Inc).

Table 2:

Spectral Analysis			
	CO	PH-H	PH-D
LFa (ms²)	316±89	222±107	87±11*
HFa (ms²)	1009±532	281±300#	73±45**
LFnu (%)	27±15	44±20	52±15
HFnu (%)	71±15	62±14	31±19&,*

Abbreviations: CO=control group; PH-H=PH patients with right dilated cardiomyopathy; PH-D=PH patients with right hypertrophic cardiomyopathy; LFa= low frequency in absolute values; HFa= high frequency in absolute values; LFnu= low frequency in normalized values; HFnu= high frequency in normalized values; *,#P≤0,01 *vs* CO; #P≤0,05 *vs* PH-D; **P≤0,001 *vs* CO; &≤0,01 vs CO.

After detecting the pulse intervals, the heart period was automatically calculated on a beat-to-beat basis as the time interval between two consecutive systolic peaks or a pulse interval (PI). All data were carefully checked to avoid erroneous detections or missed beats. Sequences of 200-300 beats were randomly chosen. If the randomly selected sequence included evident non-stationarities, the sequence was discarded, and a new random selection was performed. Frequency domain analysis of HRV was performed with an autoregressive algorithm [19-21] on the PI interval sequences (tachogram). In this study, two spectral components were considered: low frequency (LF), from 0.04 to 0.15 Hz, and high frequency (HF), from 0.15 to 0.5 Hz. The spectral components are expressed in absolute (s2 or mmHg2) and normalized units (nu). Normalization consisted of dividing the power of a given spectral component by the total power and multiplying the ratio by 100 [22] Moreover, the ratio of the absolute LF/HF values, known as cardiac sympathetic and parasympathetic balance, was also calculated for each stretch [23].

Statistical analysis

Data are expressed as the mean ± standard deviation (SD). The statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. Values were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

Examination of absolute frequency values indicated a significant reduction in sympathetic (LFa; 72%) and parasympathetic (HFa; 93%) modulation in the PH-D group compared to the CO group. On the other hand, only the HFa component was significantly decreased (72%) in the PH-H group relative to the CO group.

When frequency values were normalized as a percentage of ANS participation, sympathetic modulation (LFnu) was higher in the PH-D (92%) and PH-H (62%) groups compared to the CO group. These differences were not statistically significant. On the other hand, parasympathetic modulation (HFnu) was significantly lower in the PH-D group compared to the PH-H and CO groups.

The LF/HF ratio, reflecting the sympathetic and parasympathetic balance, was significantly higher in the PH-D (2.0±1.2) group compared with the PH-H (0.5±0.4) and CO (0.4±0.4) groups (Figure 1). These results are particularly important because they demonstrate a proportional reduction in the parasympathetic modulation of the heart only in PH-D patients.

Consistent with our observed LF/HF ratios, HR did not differ among the groups. However, the HRV was significantly lower in the PH-D (381±100 ms²) and PH-H (1007±403 ms²) groups when compared to the CO group (1917±656 ms²). On the other hand, there was also a decrease in HRV in the PH-D group relative to the PH-H group (Figure 2), indicating a worsening in autonomic modulation with disease progression.

This is the first study to demonstrate a significant difference in the reflex control of the heart in both hypertrophic and dilated cardiomyopathy associated with PH.

The main finding of this study was that the sympathetic modulation was significantly higher in the PH-D group when compared with the CO and PH-H groups. On the other hand, the HRV was significantly lower in the PH-D group compared to the PH-H and CO groups, demonstrating that ventricular dilatation is associated with impaired reflex control of the heart.

In this context, an important unanswered question regarding the physiopathology of PH is to determine why some right ventricles respond to pressure overload with hypertrophy and others show thinning and dilation of the wall and worsening of right ventricular function [16].

Although without specifying the type of cardiomyopathy, McGown et al. (2009) observed a reduction in the LF absolute spectral component in PH patients compared to controls [24]. These results are in agreement with our observed decreases in absolute values, indicating sympathetic and parasympathetic modulation. On the other hand, normalizing the data revealed that sympathetic modulation predominated, as indicated by the increase in LFnu and the LF/HF ratio.

Interpretation of our data allows us to conclude that there is a worsening in hemodynamic parameters in the PH-D group.

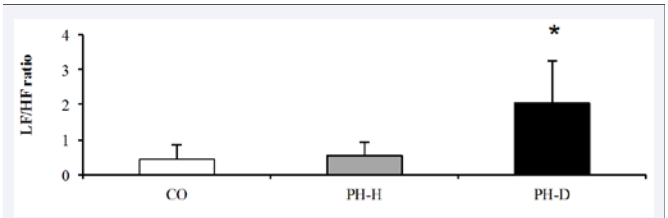

Figure 1 CO = control group; PH-H= hypertrophy group; PH-D= dilatation group; LF/HF ratio = low frequency/high frequency; *P≤0,05 *vs* CO and PH-D.

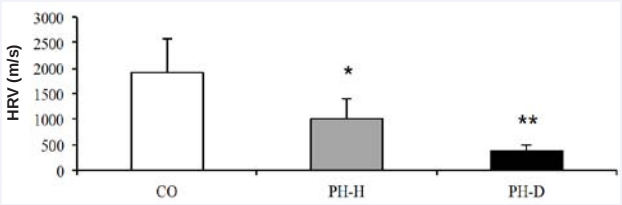

Figure 2 CO= control group; PH-H= hypertrophy group; PH-D= dilatation group; HRV= heart rate variability; *P≤0,05 *vs* CO and PH-D; **P≤0,001 *vs* CO.

Our observed decrease in HFnu indicates a reduc tion in parasympathetic stimulation of the cardiovascular system. This result was also confirmed experimentally by Rigatto et al. (2013) who, in studying rats with monocrotaline-induced PH, found a decrease in HFnu compared to control rats [25]. This result shows a reapportioning of control between the sympathetic and parasympathetic nervous systems in favor of sympathetic modulation.

These results are in complete agreement with our observed increases in the LF/HF ratio of 466% in the PH-D group and 380% in the PH-H group versus the CO group. There is a consensus that ANS is impaired in PH [26]. On the other hand, we did not find a difference in LF/HF ratios between the PH-H and CO groups. These results indicate that impairment of the sympathetic and parasympathetic balance occurs only in PH patients with dilated cardiomyopathy. These results are consistent with those of McGowan et al. (2009), which also showed a reduction in the LF/HF ratio in patients with PH; however, again, these authors did not specify whether hypertrophic or dilated [24] cardiomyopathy occurred.

In addition, Wensel et al. (2009) [4,27], Folino et al. (2003) [4,27], and Mustafa Can et al. (2013) [28] also demonstrated a reduction in HRV accompanied by sympathetic and parasympathetic imbalances in patients with PH. In our results, the HRV was significantly decreased in PH-D (80%) and PH-H (47%) patients when compared to the control group. These results show that the autonomic imbalance in PH patients with RV hypertrophy was almost half of that observed in PH patients with RV dilation. Velez Roa and colleagues (2004) also demonstrated that there is an association between sympathetic hyperactivity and the severity of PH [26].

Because increased sympathetic activity in PH can be detrimental to both the heart and the pulmonary vasculature [29] and decreased HRV is associated with a worse prognosis in cardiovascular disease, [8,9,30,31] we conclude that patients with right ventricular hypertrophy have most likely "adapted" to their condition. On the other hand, patients who have a maladaptive response to RV overload develop RV dilatation.

Moreover, it is important to consider that HRV is inversely associated with BP variability (BPV) [32]. Thus, it is reasonable to consider that decreases in HRV, accompanied by increases in BPV, are significant risk factors associated with cardiovascular disease development. There is also evidence that the BPV is most likely more important than BP *per se* [14]. If so, it is absolutely necessary to treat the HR disturbances in order to decrease the BPV and cardiovascular risk.

Furthermore, the use of a non-invasive method to quantify autonomic modulation and assess cardiovascular risks can be of great value to better understand PH. Discovering whether the "adaptation" is a cause or a consequence of the autonomic dysfunction can aid in the development of strategies to reduce the imbalances between the sympathetic and parasympathetic nervous systems. Use of ECG and treatment of ANS imbalances may represent important strategies to improve the quality of life of millions of people.

CONCLUSION

In conclusion, because HRV is a predictor of poor outcomes in PH patients [24] and treating the autonomic system can improve survival [28], future studies need to focus on the ANS as a possible therapeutic target to augment the conventional treatment of PH and thus improve survival. As emphasized by Rigatto et al. (2013), "…a drug that improves the ANS balance and decreases the ventricle pressure, certainly will postpone the transition from compensated hypertrophy to maladaptive remodeling and dilatation [25]."

Additional studies are needed to confirm these findings and to determine whether autonomic changes can be classified as a cause or consequence of cardiac remodeling in PH.

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