

# Cardiac sympathetic dysfunction in pulmonary arterial hypertension: lesson from left-sided heart failure

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## Abstract

Sympathetic nervous system hyperactivity has a well-recognized role in the pathophysiology of heart failure with reduced left ventricular ejection fraction. Alterations in sympathetic nervous system have been related to the pathophysiology of pulmonary arterial hypertension, but it is unclear whether cardiac sympathetic nervous system is impaired and how sympathetic dysfunction correlates with hemodynamics and clinical status in pulmonary arterial hypertension patients. The aim of this study was to evaluate the cardiac sympathetic nervous system activity by means of <sup>123</sup>Iodine-metaiodobenzylguanidine nuclear imaging in pulmonary arterial hypertension patients and to explore its possible correlation with markers of disease severity. Twelve consecutive pulmonary arterial hypertension patients (nine women, median age 56.5 (17.8), eight idiopathic and four connective tissue-associated pulmonary arterial hypertension) underwent cardiac <sup>123</sup>Iodine-metaiodobenzylguanidine scintigraphy. The results were compared with those of 12 subjects with a negative history of cardiovascular or pulmonary disease who underwent the same nuclear imaging test because of a suspected paraganglioma or pheochromocytoma, with a negative result (controls), and 12 patients with heart failure with reduced left ventricular ejection fraction. Hemodynamics, echocardiography, six-minute walking distance, cardiopulmonary exercise testing, and N-terminal pro brain natriuretic peptide were collected in pulmonary arterial hypertension patients within one week from <sup>123</sup>Iodine-metaiodobenzylguanidine scintigraphy. Cardiac <sup>123</sup>Iodine-metaiodobenzylguanidine uptake, assessed as early and late heart-to-mediastinum ratio, was significantly lower in pulmonary arterial hypertension compared to controls ( $p = 0.001$ ), but similar to heart failure with reduced left ventricular ejection fraction. Myocardial <sup>123</sup>Iodine-metaiodobenzylguanidine turnover, expressed as washout rate, was similar in pulmonary arterial hypertension and heart failure with reduced left ventricular ejection fraction and significantly higher compared to controls ( $p = 0.016$ ). In the pulmonary arterial hypertension group, both early and late heart-to-mediastinum ratios and washout rate correlated with parameters of pulmonary arterial hypertension severity including pulmonary vascular resistance, right atrial pressure, tricuspid annular plane systolic excursion, N-terminal pro brain natriuretic peptide, and peak  $\text{VO}_2$ . Although we evaluated a small number of subjects, our study showed a significant impairment in cardiac sympathetic nervous system in pulmonary arterial hypertension, similarly to that observed in heart failure with reduced left ventricular ejection fraction. This impairment correlated with indices of pulmonary arterial hypertension severity. Cardiac sympathetic dysfunction may be a contributing factor to the development of right-sided heart failure in pulmonary arterial hypertension.

## Keywords

pulmonary arterial hypertension, sympathetic nervous system, nuclear imaging, <sup>123</sup>I-metaiodobenzylguanidine

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## Introduction

Pulmonary hypertension (PH) is a pathophysiological disorder that characterizes several distinctive clinical

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conditions and can complicate the majority of cardiovascular and respiratory diseases.<sup>1</sup> PH is defined by the presence of a mean pulmonary arterial pressure equal or higher than 25 mmHg at rest as measured by right heart catheterization and is categorized in five groups based on similar etiology, clinical features, pathological findings, hemodynamic characteristics, and treatment strategy.<sup>1</sup> Group 1 refers to pulmonary arterial hypertension (PAH), a rare clinical condition that primarily affects the pulmonary vasculature leading to a chronic increase in right ventricular afterload.<sup>1</sup> Prognosis related to PAH is typically poor, and mortality is mainly related to the development of right heart failure.<sup>2</sup>

Recent advances in diagnosis, clinical management, and pharmacological treatment have improved the prognosis of PAH.<sup>3</sup> Nevertheless, the disease is still associated with marked morbidity and mortality, mainly related to the progressive development of right-sided heart failure that can progress despite reduction in pulmonary afterload with specific pulmonary vasodilator treatment.<sup>4</sup> A better understanding of the pathophysiological mechanisms that lead to right ventricular dysfunction represents an urgent unmet need. An alteration in neurohormonal signaling may act as candidate pathogenic contributor to the progressive pulmonary vascular remodeling process and the development of right heart failure.<sup>5</sup> The detrimental role of chronic sympathetic hyperactivation, and its implications on both disease progression and mortality, has been widely recognized in the field of left-sided heart failure and represents the rationale for adrenergic receptor blocker therapy.<sup>6</sup>

Nuclear imaging has a well-established role in the evaluation of sympathetic nervous activity in several clinical settings. In particular, cardiac nuclear imaging with <sup>123</sup>Iodine-metaiodobenzylguanidine (<sup>123</sup>I-MIBG) allows measurable assessment of sympathetic dysfunction of the left ventricle (LV) secondary to chronic systemic adrenergic hyperactivation, typically present in patients with heart failure with reduced LV ejection fraction (HFrEF).<sup>7</sup> Importantly, cardiac sympathetic dysfunction has prognostic significance in development of arrhythmia and sudden cardiac death in these patients.<sup>8–10</sup>

Some studies suggested an increased systemic sympathetic activity in patients with PAH,<sup>11,12</sup> highlighting an impairment of cardiac autonomic innervation by cardiac <sup>123</sup>I-MIBG study<sup>13–15</sup>; however, the impact of such alterations on clinical status and their correlation with hemodynamics and functional parameters have not been completely elucidated.

In the present study, we sought to (1) explore the presence and type of cardiac sympathetic dysfunction in patients with PAH in comparison to healthy subjects and patients with HFrEF; and (2) evaluate possible correlations with hemodynamic, clinical, and functional parameters.

Some of the results of this study have been previously reported in abstract form.<sup>16</sup>

## Methods

### Patients

Patients referred to the Pulmonary Hypertension Outpatient Clinic of the Federico II University of Naples for right heart catheterization (for diagnostic or follow-up evaluation) were prospectively enrolled between February 2015 and June 2016. Inclusion criteria were age  $\geq 18$  years and group 1 PAH diagnosis according to current guidelines' criteria (mean pulmonary artery pressure  $\geq 25$  mmHg at rest measured at right heart catheterization, along with a pulmonary capillary wedge pressure  $\leq 15$  mmHg and a pulmonary vascular resistance greater than 3 Wood units).<sup>1</sup> All patients with other causes of PH (i.e. due to heart disease, severe lung disease, chronic thromboembolic PH, etc.) were excluded. Furthermore, we excluded patients who presented any condition that could potentially interfere with the results of MIBG imaging (i.e. treatment with any medication interfering with norepinephrine neuronal uptake, diagnosis of diabetes mellitus, autonomic neurological disorders such as Shy Drager syndrome, pheochromocytoma, or any contraindication to nuclear imaging, such as pregnancy).

The results of <sup>123</sup>I-MIBG imaging in PAH patients were compared with healthy subjects (control group) who underwent <sup>123</sup>I-MIBG scintigraphy to rule out a paraganglioma or a pheochromocytoma; these patients were selected among those showing low clinical probability, and all had negative radionuclide imaging for paraganglioma or a pheochromocytoma and no evidence of neurological or cardiac diseases.

The results of <sup>123</sup>I-MIBG imaging in the study population were also compared with a group of patients with HFrEF (idiopathic dilated cardiomyopathy or due to ischemic heart disease), in NYHA class II or III, who underwent <sup>123</sup>I-MIBG because of enrollment in other research protocols.<sup>17</sup>

The study was performed in accordance with the Declaration of Helsinki on human research and the Good Clinical Practice standards. The local Ethical Committee approved the study protocol and all the patients included in the study gave their written informed consent after receiving an accurate explanation of the study protocol and of the potential risks related to the procedures provided by the study protocol.

### Procedures

At the time of enrollment, all PAH patients underwent complete clinical examination and assessment of serum N-terminal pro brain natriuretic peptide (NT-proBNP). Demographic data, medical history, and concomitant medications were also collected. The following procedures were performed within a one-week period.

**Transthoracic echocardiography.** Standard transthoracic echocardiography was performed at the Internal Medicine Echocardiography Laboratory using a Philips iE33 machine

with subjects in the left lateral decubitus position. Measurements were performed off-line by an experienced echocardiographer (VM) according to current guidelines for the left and right chambers evaluation.<sup>18</sup>

**Six-minute walking distance.** Six-minute walking test was performed according to the *American Thoracic Society* guidelines,<sup>19</sup> and the Borg scale dyspnea index was collected at the end of the test.

**Cardiopulmonary exercise testing (CPET).** Incremental symptom-limited CPET was performed using a bicycle ergometer according to the current guidelines under continuous 12-lead electrocardiographic monitoring and every 2 min noninvasive blood pressure measurement.<sup>19</sup> After a 3 min warm-up period at unloaded cycling, a ramp protocol at a workload established by the sex-, age-, height-, and weight-adjusted Wassermann formula [(predicted peak  $\text{VO}_2$  – predicted rest  $\text{VO}_2$ )/100] was started.

Respiratory gas exchange measurements were obtained breath-by-breath by means of a computerized metabolic cart (Ultima CardiO2, MedGraphics Cardiorespiratory Diagnostics). Peak  $\text{VO}_2$  was recorded as the mean value of  $\text{VO}_2$  during the last 20 s of the test and expressed in milliliters per kilogram per minute. The ventilatory anaerobic threshold was noninvasively detected by two experienced reviewers (GC and PP) using a “dual method approach” with the V-slope method and the ventilatory equivalent for  $\text{O}_2$  method.

**Right heart catheterization.** With patients resting in a supine position, a Swan-Ganz catheter was advanced through venous femoral access under fluoroscopic guidance to measure right atrial pressure, pulmonary arterial pressure, and pulmonary arterial wedge pressure at end-expiration. Cardiac output was measured by thermodilution using an average of three measurements. Pulmonary vascular resistance was calculated using the formula: [(mean pulmonary arterial pressure – pulmonary wedge pressure)/ cardiac output] and expressed in Wood Units.

**Cardiac  $^{123}\text{I}$ -MIBG imaging.** All enrolled patients underwent cardiac  $^{123}\text{I}$ -MIBG according to the recommendations of the European Association of Nuclear Medicine Cardiovascular Committee and the European Council of Nuclear Cardiology,<sup>20,21</sup> as previously described.<sup>17</sup>

An activity of 111 MBq  $^{123}\text{I}$ -MIBG (Covidien, Mallinckrodt) was intravenously administered over 1–2 min after thyroid blockade by oral administration of Lugol’s solution. Ten-minute planar images of the thorax in standard anterior view ( $256 \times 256$  matrix) were performed 15 min (early image) and 3 h and 50 min (late image) after tracer administration. Four hours after tracer administration, a SPECT study was performed; it was obtained in step and shoot mode, with 90 projections, an imaging time 30 min and stored in a  $64 \times 64$  matrix. Planar and

tomographic imaging was performed using a dual-head camera system (Skylight, Philips) equipped with a low-energy, parallel-hole, high-resolution collimator, and the camera peaked at 159 keV with a symmetrical 20% energy window. On the planar MIBG images, using dedicated post-processing software on a dedicated workstation (Philips), a cardiac region of interest (ROI), polygonal in shape, was manually drawn over the epicardial border including the left ventricular cavity. Care was taken to exclude lung and liver from the myocardial ROI. The mediastinal ROI with a square shape was placed on the upper half of the mediastinum and had a size of  $7 \times 7$  pixels. The location of the mediastinal ROI was determined using as landmarks the lung apex, the upper cardiac border, and the medial contours of the lungs. From early and late planar images, the heart-to-mediastinum (H/M) ratio was computed by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. The MIBG washout rate (WR), decay and background corrected, was calculated using the following formula: [(early heart counts per pixel – early mediastinum counts per pixel) – [late heart counts per pixel decay-corrected – late mediastinum counts per pixel decay corrected]]/(early heart counts per pixel – early mediastinum counts per pixel)  $\times 100$ . SPECT studies were processed with filtered back-projection and reconstructed into standard long-axis and short-axis images, perpendicular to the heart axis. The interpretation of images was done by consensus of two independent expert readers, with previously demonstrated excellent intra- and inter-observer reproducibility.<sup>17</sup> No patient was excluded for poor quality of  $^{123}\text{I}$ -MIBG images.

### Statistical analysis

Continuous variables are expressed as median (interquartile range) and were compared using ANOVA test and Mann–Whitney test followed by Bonferroni correction. Discrete variables are expressed as absolute numbers or percentage and compared using chi square test. Pearson correlation analysis was performed to evaluate the correlations between cardiac  $^{123}\text{I}$ -MIBG parameters and hemodynamics, instrumental, and serum data in PAH patients. All data were collected and entered in an Excel database, and statistical analysis was performed using SPSS (IBM SPSS Statistics 19 Version). A  $p$  value  $< 0.05$  was considered as statistically significant.

## Results

### Patient characteristics

Among the patients that were consecutively referred to our Pulmonary Hypertension Outpatient Clinic for right heart catheterization between February 2015 and June 2016, 12 PAH patients, 9 women and 3 men, median age of 56.5 (17.8) years gave their consent to participate in the study.

**Table 1.** Characteristics of enrolled subjects.

	PAH (n = 12)	HFrEF (n = 12)	Controls (n = 12)
Sex M/F (n)	3/9	3/9	4/8
Age (years)	56.5 (17.8)	60 (9.5)	54.5 (10)
BMI (kg/m <sup>2</sup> )	27.3 (7.3)	26 (10.5)	24 (7)
HR (bpm)	73.5 (17)	66.5 (20.8)	68 (12)
SBP (mmHg)	110 (17.5)	107.5 (36.3)	115 (20)
DBP (mmHg)	70 (20)	67.5 (18.8)	70 (10)

BMI: body mass index; DBP: diastolic blood pressure; HFrEF: heart failure with reduced left ventricular ejection fraction; HR: heart rate; PAH: pulmonary arterial hypertension; SBP: systolic blood pressure.

Data are expressed as median (interquartile range) or as absolute number. Group comparisons were performed using Mann–Whitney nonparametrical analysis for continuous variables and  $\chi^2$  statistics for categorical variables, as appropriate. A  $p < 0.05$  was considered as statistically significant. No significant differences among groups were observed ( $p = ns$ ).

Eight patients had idiopathic PAH and four had PAH associated with connective tissue disease (in two cases systemic sclerosis, one undifferentiated connective tissue disease, and one systemic erythematosus lupus). Five were incident cases who were referred for a diagnostic right heart catheterization, and seven were prevalent cases who needed a follow-up right heart catheterization. Control group included 12 subjects, 8 women and 4 men, with a median age of 54.5 (10) years. The group of HFrEF patients included 12 patients, 9 women and 3 men with a median age of 60 (9.5) years, in NYHA class II or III (6 in II and 6 in III) with a moderate reduction of left ventricular ejection fraction, with a median value of 34.5 (7.75)%. Eighty-three percent of them had ischemic etiology, and 17% were diagnosed with idiopathic dilated cardiomyopathy. The three groups were comparable in terms of age, sex, and anthropometrics characteristics (Table 1).

Clinical, hemodynamic, echocardiographic, and serologic data of the PAH patients are summarized in Table 2. Prevalent patients were receiving treatment with pulmonary vasodilator drugs, the majority of them as combination therapy with a phosphodiesterase-5 inhibitor (tadalafil) and an endothelin receptor antagonist (ambrisentan or bosentan). Hemodynamics revealed a high right atrial pressure, a severe increase in mean pulmonary arterial pressure, with a normal pulmonary capillary wedge pressure, and a low cardiac output. Pulmonary vascular resistance was severely increased. Echocardiographic evaluation of the right chambers revealed a dilated right atrium, a severe increase in estimated systolic pulmonary arterial pressure, and a borderline right ventricular systolic function (tricuspid annular plane systolic excursion (TAPSE) within the lower limits of normal and a reduced right ventricular S' wave). Six-minute walking distance was 380 (166.3)m and Borg dyspnea index 3.5 (3.3). At CPET, PAH patients had a low VO<sub>2</sub> peak and VO<sub>2</sub> pulse, with an increase in VE/VCO<sub>2</sub> slope and a reduced end-tidal pCO<sub>2</sub>.

**Table 2.** Clinical, hemodynamic, instrumental, and serum data of PAH patients.

	PAH patients (n = 12)
WHO functional class I/II/III/IV (n)	0/6/6/0
Pulmonary vasodilator treatment (n = 7)	
Phosphodiesterase-5 inhibitor	5
Endothelin receptor antagonist	6
Prostacyclin analogue	1
Combination therapy	5
Right heart catheterization	
Right atrial pressure (mmHg)	9.5 (3.3)
Mean pulmonary arterial pressure (mmHg)	48 (11.3)
Systolic pulmonary arterial pressure (mmHg)	65 (18.8)
Diastolic pulmonary arterial pressure (mmHg)	34 (10)
Cardiac output (l/min)	3.8 (2.2)
Cardiac index (l/min/m <sup>2</sup> )	2.1 (1.3)
Pulmonary vascular resistance (Wood Units)	9.5 (4.8)
Pulmonary capillary wedge pressure (mmHg)	9.5 (2)
Transthoracic echocardiography	
Right atrial area (cm <sup>2</sup> )	20.5 (5)
Estimated systolic pulmonary arterial pressure (mmHg)	77.5 (36.3)
TAPSE (mm)	17 (3)
Right ventricular S' wave (cm/s)	10 (2.6)
Six-minute walking distance (n = 10)	
Distance walked (m)	380 (166.3)
Borg scale dyspnea	3.5 (3.3)
Cardiopulmonary exercise testing (n = 10)	
VO <sub>2</sub> peak (ml/min/kg)	13.7 (4.2)
VE/VCO <sub>2</sub> slope	36.0 (8.5)
VO <sub>2</sub> pulse (ml/min/kg/bpm)	7.5 (3.3)
End-tidal pCO <sub>2</sub> (mmHg)	29 (6)
Serum biomarker	
NT-proBNP (pg/dl)	279.5 (153.5)

NT-proBNP: N-terminal pro brain natriuretic peptide; PAH: pulmonary arterial hypertension; pCO<sub>2</sub>: carbon dioxide partial pressure; TAPSE: tricuspid annular plane systolic excursion; VCO<sub>2</sub>: carbon dioxide production; VE: minute ventilation; VO<sub>2</sub>: oxygen consumption per kg/min; WHO: World Health Organization.

Data are expressed as median (interquartile range) or as absolute number.

### Cardiac <sup>123</sup>I-MIBG imaging

The results of <sup>123</sup>I-MIBG imaging are summarized in Table 3. The analysis of MIBG imaging parameters highlighted a significant difference in H/M ratios and WR among the groups. In particular, early H/M was significantly reduced in PAH patients in comparison to the control group (1.95 (0.50) versus 2.20 (0.20),  $p = 0.0259$ ), and there was no significant difference when compared with HFrEF patients (1.92 (0.24),  $p = ns$ ) (Fig. 1). Also, late H/M in PAH



**Table 3.** Cardiac  $^{123}\text{I}$ -MIBG findings in the enrolled patients.

$^{123}\text{I}$ -MIBG	PAH (n = 12)	HFrEF (n = 12)	Controls (n = 12)	ANOVA p value
Early H/M	1.95 (0.50)*	1.92 (0.24)**	2.20 (0.20)	0.008
Late H/M	1.65 (0.49)	1.74 (0.29)**	2.10 (0.28)	<0.0001
WR (%)	27.5 (30.8)	32.2 (11.2)**	18.5 (3.8)	0.019

ANOVA: analysis of variance; HFrEF: heart failure with reduced left ventricular ejection fraction; H/M: heart-to-mediastinum ratio;  $^{123}\text{I}$ -MIBG:  $^{123}\text{I}$ iodine-metaiodobenzylguanidine; PAH: pulmonary arterial hypertension; WR: washout rate.

Data are expressed as median (interquartile range) Group comparisons were performed using ANOVA test and Mann–Whitney analysis for continuous variables, and  $\chi^2$  statistics for categorical variables, as appropriate. A  $p < 0.05$  was considered as statistically significant.

\* $p < 0.05$  versus controls; \*\* $p < 0.005$  versus controls; \*\*\* $p < 0.0005$  versus controls.

patients was significantly reduced in comparison to controls (1.65 (0.49) versus 2.10 (0.28),  $p = 0.001$ ), and there was no significant difference with HFrEF patients (1.74 (0.29),  $p = ns$ ) (Fig. 1). Furthermore, WR was significantly increased in PAH patients in comparison to controls (27.5 (30.8)% versus 18.5 (3.8)%,  $p = 0.0156$ ) and similar to HFrEF patients (32.2 (11.2)%,  $p = ns$ ) (Fig. 1).

There was no statistically significant differences in  $^{123}\text{I}$ -MIBG parameters among incident and prevalent PAH patients or among different PAH etiologies.

### Correlation analysis in PAH patients

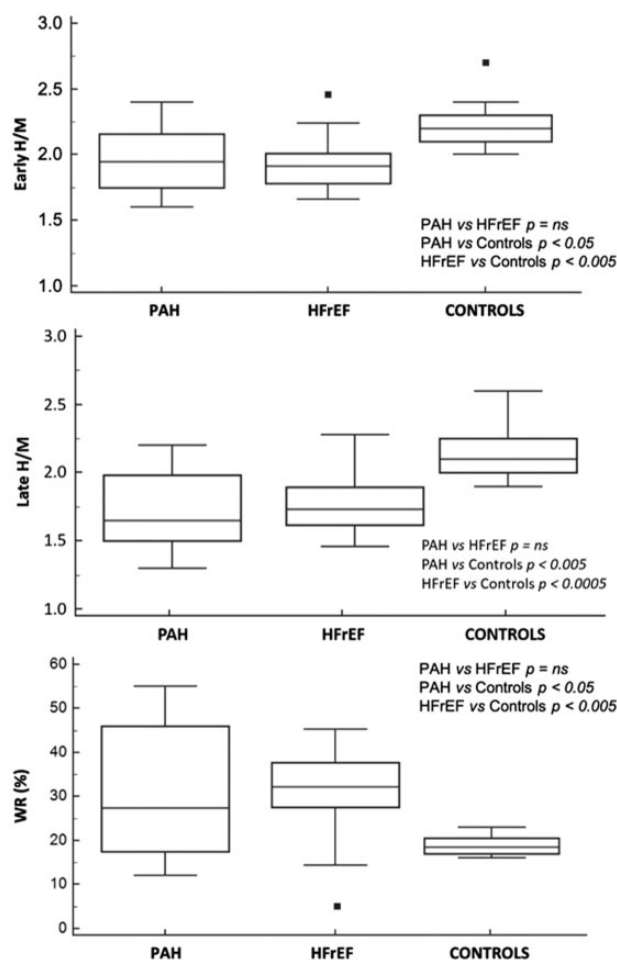
In Table 4 the results of the correlation analysis between  $^{123}\text{I}$ -MIBG and parameters deriving from hemodynamics, echocardiography, CPET, six-minute walking distance, and serologic data are summarized.

Although there was no significant correlation with early H/M, late H/M showed a significant positive correlation with cardiac index, TAPSE, and right ventricular  $S'$  wave, and an inverse correlation with pulmonary vascular resistance and with NT-proBNP (Fig. 2). Furthermore, WR was positively correlated with right atrial pressure and pulmonary vascular resistance, with NT-proBNP, and VE/ $\text{VCO}_2$  slope. There was a negative correlation with TAPSE and right ventricular  $S'$  wave, with  $\text{O}_2$  pulse,  $\text{VO}_2$  peak, and with distance walked (Fig. 3).

### Discussion

In this study we demonstrate the presence of significant impairment in cardiac sympathetic activation in a small but well-characterized cohort of patients with PAH using  $^{123}\text{I}$ -MIBG imaging. Furthermore, we found that this alteration is correlated with several parameters of disease severity.

Few prior studies, mainly performed on patients with heterogeneous etiologies of PH, demonstrated cardiac sympathetic dysfunction at  $^{123}\text{I}$ -MIBG imaging.<sup>13–15</sup>



**Fig. 1.** Box plots of cardiac  $^{123}\text{I}$ -MIBG early H/M, late H/M, and WR in PAH patients, HFrEF patients, and control subjects. HFrEF: heart failure with reduced left ventricular ejection fraction; H/M: heart-to-mediastinum; PAH: pulmonary arterial hypertension; WR: washout rate.

Moreover, as additional new finding, we compared the characteristics of cardiac sympathetic dysfunction in PAH patients with data derived from patients with HFrEF, and we showed that the alterations were similar between groups.

Sympathetic hyperactivity is a well-known hallmark of HFrEF. It represents a compensatory mechanism aimed at enhancing heart rate and contractility, and at raising systemic blood pressure by means of peripheral vasoconstriction. However, catecholamine overstimulation over time leads to a reduction in myocardial beta 1-adrenergic receptor expression and signaling.<sup>6</sup> This deregulation is implicated in the development of progressive cardiac adverse remodeling and represents the rationale for the use of beta-blockers for the treatment of HFrEF.<sup>6</sup> Nuclear imaging with  $^{123}\text{I}$ -MIBG can quantify the dysfunction of sympathetic drive. In particular, a decrease in H/M ratio indicates a downregulation of adrenergic receptors (norepinephrine transporter 1) due to chronic increase in sympathetic input, and an increase in WR is consequent to the increased turnover of postsynaptic noradrenalin.<sup>8</sup>

**Table 4.** Correlations between cardiac  $^{123}\text{I}$ -MIBG parameters (late H/M and WR) and hemodynamic, instrumental, and serum data in PAH patients.

Parameter	Late H/M		WR	
	Pearson	$p$	Pearson	$p$ value
Right atrial pressure	-0.5022	ns	0.7216	0.0081
Mean PAP	0.1945	ns	0.3242	ns
Cardiac index	0.7290	0.0072	-0.3295	ns
Pulmonary vascular resistance	-0.7373	0.0062	0.7490	0.0051
TAPSE	0.6830	0.0144	-0.6517	0.0217
Right ventricular S' wave	0.8604	0.0003	-0.6424	0.0243
Right atrial area	0.2440	ns	-0.5392	ns
Estimated SPAP	-0.2212	ns	0.1974	ns
Six-minute walking distance	0.3894	ns	-0.7683	0.0094
$\text{VO}_2$ peak	0.2732	ns	-0.7374	0.0149
$\text{VE}/\text{VCO}_2$ slope	-0.5914	ns	0.6447	0.0442
$\text{VO}_2$ pulse	0.1807	ns	-0.7047	0.0229
End-tidal $\text{pCO}_2$	0.1992	ns	-0.4419	ns
NT-proBNP	-0.6239	0.0302	0.6926	0.0125

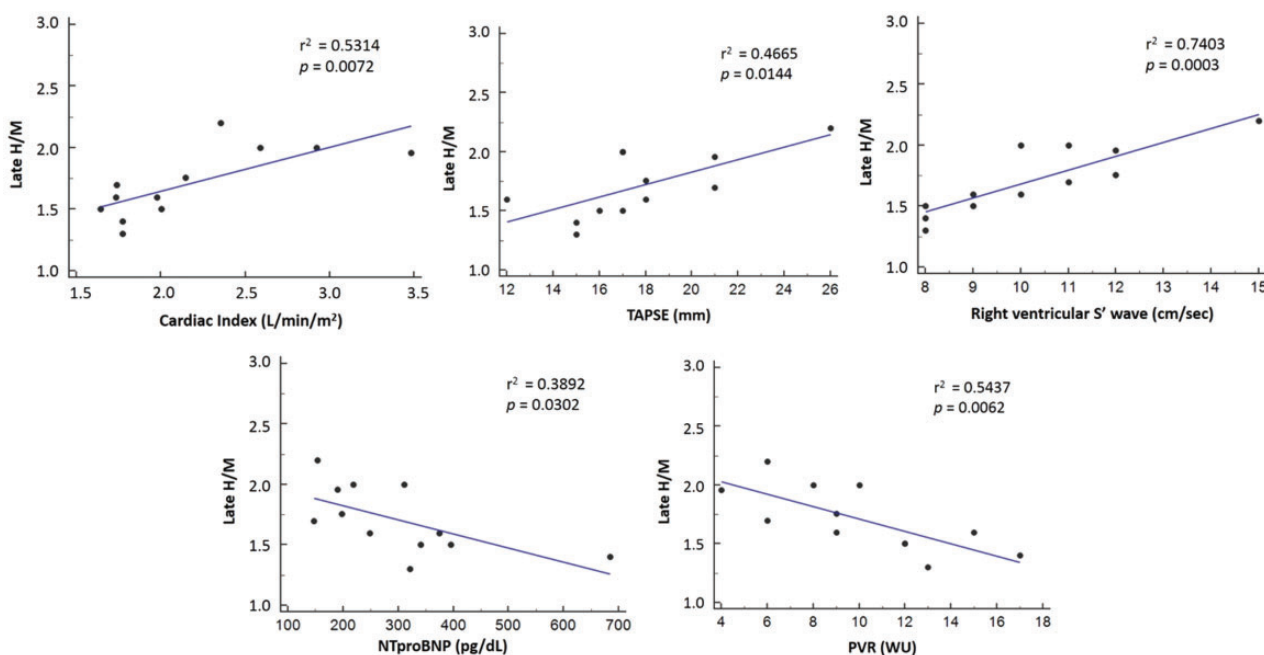
H/M: heart-to-mediastinum;  $^{123}\text{I}$ -MIBG:  $^{123}\text{I}$ iodine-metaiodobenzylguanidine; NT-proBNP: N-terminal pro brain natriuretic peptide; PAH: pulmonary arterial hypertension; PAP: pulmonary arterial pressure;  $\text{pCO}_2$ : carbon dioxide partial pressure; SPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion;  $\text{VCO}_2$ : carbon dioxide production per minute;  $\text{VE}$ : minute ventilation;  $\text{VO}_2$ : oxygen consumption per kg/min; WR: washout rate. A  $p < 0.05$  was considered as statistically significant.

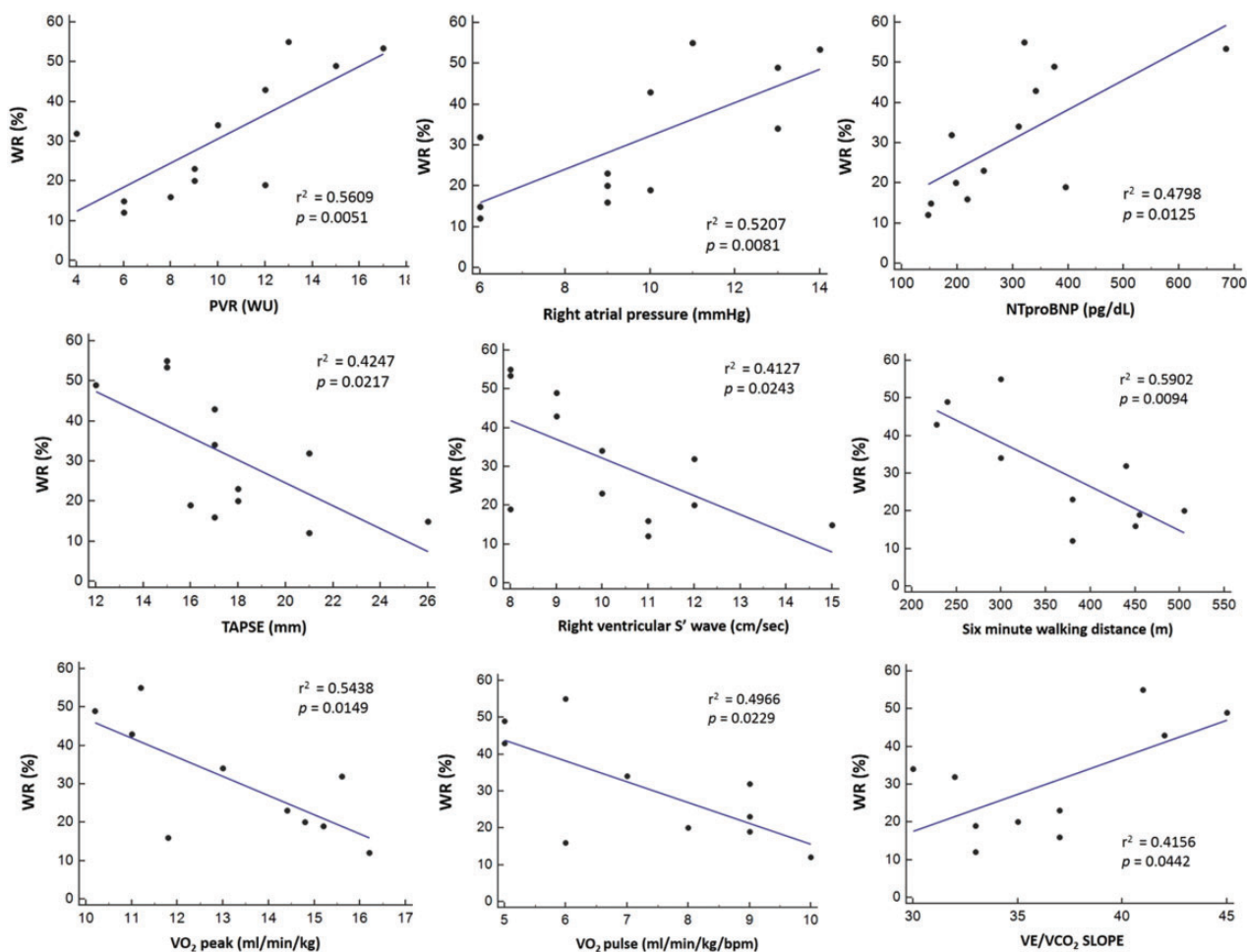
These alterations correspond to a decrease in myocardial norepinephrine content and an increase in its spillover.<sup>8</sup>

Our results confirm recent advances in the understanding of the possible role of sympathetic hyperactivity in the pathophysiology of PAH. Preclinical models of pulmonary vascular pressure overload highlighted a correlation between maladaptive right ventricular remodeling and dysfunction in cardiac sympathetic activity, evaluated both in vivo and noninvasively with  $^{123}\text{I}$ -MIBG cardiac imaging.<sup>22</sup> It has been demonstrated that the increase in sympathetic activity could be partially caused by increased chemo-sensitivity and increased right ventricular filling pressures.<sup>23</sup>

To date, whether circulating catecholamines are increased or normal in PAH remains controversial.<sup>24</sup> Nonetheless, muscle sympathetic nerve activity was found to be markedly increased in PAH,<sup>23</sup> and a reduction in heart rate variability, another marker of sympathetic hyperactivity, has been demonstrated in both experimental and clinical studies.<sup>25</sup> Furthermore, prolonged activation of the sympathetic nervous system (SNS), as measured by microneurographic recording, was associated with a poor prognosis in PAH.<sup>11</sup>

The main advantage of  $^{123}\text{I}$ -MIBG imaging is related to its organ-specificity in detecting cardiac alterations secondary to sympathetic system activation. Indeed, it is well known that the rate of spillover of noradrenaline to plasma is regional and organ-specific, with certain organs experiencing the greatest degree of sympathetic activation.<sup>26</sup> Furthermore, it has been demonstrated that increased cardiac adrenergic drive precedes generalized sympathetic

**Fig. 2.** Correlation between late H/M and hemodynamic, instrumental, and serum data in PAH patients. H/M: heart-to-mediastinum; NT-proBNP: N-terminal pro brain natriuretic peptide; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion.



**Fig. 3.** Correlation between WR and hemodynamic, instrumental, and serum data in PAH patients. NT-proBNP: N-terminal pro brain natriuretic peptide; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion; VCO<sub>2</sub>: carbon dioxide production per minute; VE: minute ventilation; VO<sub>2</sub>: oxygen consumption per kg/min; WR%: washout rate.

activation in human heart failure.<sup>27</sup> Therefore, the ability to investigate the state of cardiac-specific sympathetic activity makes <sup>123</sup>I-MIBG imaging a better technique for characterization of the role of cardiac-specific SNS in the pathophysiology of PAH, since its impairment may also precede sympathetic dysfunction in other organs. Moreover, <sup>123</sup>I-MIBG imaging has a validated role in the management of HF patients, particularly for the assessment of HF severity and prognosis of HF patients. Several studies have demonstrated the independent and incremental prognostic role of cardiac <sup>123</sup>I-MIBG imaging in HFrEF, thus helping in risk-stratification, in selection of therapeutic strategies, and in predicting long-term survival.<sup>28</sup>

In our analysis, cardiac sympathetic dysfunction in PAH patients correlated with echocardiographic measurements of right ventricular function and with hemodynamic measures (pulmonary vascular resistance and right atrial pressure) that are well known prognostic markers, thus supporting the notion that sympathetic activation is associated with worse prognosis. However, it remains unclear whether this is a cause or a consequence of right heart failure.<sup>11</sup>

Moreover, we demonstrated a significant correlation between WR% and CPET-derived parameters of exercise capacity and ventilatory efficiency (VO<sub>2</sub> peak and VE/VCO<sub>2</sub> slope, respectively): this is a novel observation suggesting that increased sympathetic nerve activation could be a physiologic adaptive mechanism to hypoxia contributing to the alveolar wasted hyperventilation typically observed in patients with PAH, thus leading to further impairment of exercise capacity and respiratory muscle function.<sup>29</sup>

We acknowledge that the <sup>123</sup>I-MIBG data obtained derive mainly from the ROI involving mainly the LV. Nevertheless, taking into account that PAH primarily originates as a “right heart” problem, the evidence of adrenergic dysfunction involving the “left side” of the heart in those patients may suggest that the process is ubiquitous.

To our knowledge, this is the first study comparing cardiac sympathetic dysfunction between PAH and HFrEF as demonstrated by <sup>123</sup>I-MIBG imaging. Our results are particularly relevant since they could represent a rationale for supporting novel therapeutic approaches for the treatment of PAH. In particular, it is well known that in patients with

chronic left-sided heart failure, sympathetic hyperactivation is associated with a higher risk of sudden cardiac death and ventricular arrhythmias,<sup>30</sup> and that this risk is significantly reduced with the use of beta-blockers.<sup>31</sup> Likewise, it is plausible that sympathetic dysfunction could be at least partly responsible for the higher incidence of sudden cardiac death in PAH patients.<sup>1</sup> The role played by the adrenergic nervous system in left-sided HFrEF is well established and the therapeutic effect of beta-blockers represents a cornerstone of modern treatment. While right ventricular failure is the main cause of mortality in PAH, there are several differences between the LV and RV related to their different shape, embryological origins, structure, circulatory environments, and pressure overload response.<sup>32</sup> In this respect, the use of beta- and alpha-blockers in PAH is controversial.<sup>33</sup> To date, the latest guidelines for treatment of PH discourage the use of beta-blockers in PAH,<sup>1</sup> particularly in portopulmonary PH, based on results from a small study showing improved exercise tolerance after beta-blocker withdrawal in these patients.<sup>34</sup> Nevertheless, preclinical studies showed some beneficial effects in PAH on right ventricle function, including reversal of RV remodeling, delayed RV failure,<sup>35</sup> and improvement of pulmonary vascular remodeling<sup>36</sup> in various models of PH. Recently, some small nonrandomized clinical studies aimed at evaluating the effects of beta-blockers in PAH suggest a possible beneficial effect of beta-blockers as well as their good tolerability.<sup>37,38</sup> The use of beta-blockers is a common practice in PH due to left-sided HFrEF and in PAH with cardiovascular comorbidities with up to 10–30% of these patients receiving one of this class of drugs.<sup>37,38</sup> Two recent randomized placebo-controlled studies using bisoprolol<sup>39</sup> or carvedilol<sup>40</sup> in small cohorts of PAH patients demonstrated good tolerability and safety, but no clear clinical benefit or better exercise capacity, suggesting a lack of clear efficacy in this setting.<sup>41</sup> Pharmacological modulation of the adrenergic system in selected patients with selected agents could be useful in PAH. Potential beneficial effects may include reverse RV remodeling and delayed development of RV failure. However, negative inotropic and chronotropic effects may limit their clinical use.<sup>42,43</sup> Further randomized trials are needed to better understand which strategy of adrenergic blockade might be effective in managing sympathetic hyperactivation in PAH.

### Study limitations

There are some limitations to this study. First, as mentioned in the “Discussion” section, the MIBG data presented derived mainly from the ROI involving the LV because of technical issues in visualization and identification of specific ROI for the right ventricular free wall. However, the ROI considered included also the interventricular septum, a portion “shared” between the two ventricles that is known to play a major role in the maintenance of right ventricular function,<sup>44</sup> which when impaired is associated with poor

prognosis in the setting of PH. Another limitation concerns the relatively small number of enrolled patients, which is related to the rare prevalence of PAH. Nevertheless, this limited number of patients does not particularly differ from other studies on PAH and SNS alterations,<sup>11–15</sup> or on other studies on <sup>123</sup>I-MIBG alterations in other noncommon diseases, such as hypertrophic cardiomyopathy, Anderson–Fabry disease, or Tako-Tsubo syndromes, which applied “not widely available” techniques for research purposes.<sup>28</sup> Despite the growing evidence of the important role of cardiac <sup>123</sup>I-MIBG as a tool to evaluate organ-specific sympathetic nervous dysfunction, its clinical use has remained very limited because of economic concerns relative to reimbursement and funding. Even if larger multicenter randomized trials on cardiac <sup>123</sup>I-MIBG use in the context of HF are emerging, current guidelines encourage the collection of small data in other fields not widely explored yet.<sup>28</sup> We did not enroll more patients since this was an exploratory study.

### Conclusions

Our results indicate that patients with PAH have cardiac sympathetic nervous dysfunction demonstrated with <sup>123</sup>I-MIBG imaging that is similar to the impairment observed in patients with HFrEF. Furthermore, these alterations were strongly correlated with well-recognized prognostic indices. <sup>123</sup>I-MIBG cardiac imaging could provide relevant information for better understanding of the pathophysiology of PAH. Additional larger studies with adequate follow-up periods are needed to better interpret the correlations with hemodynamic and functional parameters and to assess the prognostic relevance of this imaging technique. The triggers that induce these alterations in PAH and the role of SNS on the development of right ventricular dysfunction<sup>45</sup> in PAH with different etiologies (e.g. idiopathic versus connective tissue disease) need to be further investigated. The possible effect of therapeutic interventions targeting sympathetic activation in PAH patients remains to be clarified.

### Authors' contributions

Conception and design: VM, TP, MP, AC, DB. Collection of data: VM, TP, GC, PP, VP. Analysis and interpretation of data: VM, TP, GB, GC, PP, MP. Drafting of the article: VM, GC, PMH. Revision and final approval of the manuscript: VM, CGT, PMH, MP, AC, DB.

### Conflict of interest

The author(s) declare that there is no conflict of interest.

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