Prognostic Significance of Sympathetic Nervous System Activation in Pulmonary Arterial Hypertension

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Rationale: **The sympathetic nervous system has been reported to be activated in pulmonary arterial hypertension (PAH).**
Objectives: **We investigated the prognostic significance of muscle sympathetic nervous system activity (MSNA) in PAH.**
Methods: **Thirty-two patients with PAH were included in the study and underwent a measurement of MSNA over a 6-year period of time. They had undergone a concomitant evaluation of New York Heart Association (NYHA) functional class, a 6-minute walk distance (6MWD), an echocardiographic examination, and a right heart catheterization for diagnostic or reevaluation purposes. The median follow-up time was 20.6 months (interquartile range, 45.8 mo). Clinical deterioration was defined by listing for transplantation or death.**
Measurements and Main Results: **Seventeen patients presented with clinical deterioration. As compared with the 15 others, they had an increased MSNA (80 $\pm$ 12 vs. 52 $\pm$ 18 bursts/min; $P < 0.001$) and heart rate (88 $\pm$ 17 vs. 74 $\pm$ 12 bpm; $P = 0.01$), a lower 6MWD (324 $\pm$ 119 vs. 434 $\pm$ 88 m; $P < 0.01$) and a deteriorated NYHA functional class (3.6 $\pm$ 0.5 vs. 2.9 $\pm$ 0.8; $P < 0.001$). The hemodynamic variables were not different. MSNA was directly related to heart rate and inversely to 6MWD. A univariate analysis revealed that increased MSNA and heart rate, NYHA class IV, lower 6MWD, and pericardial effusion were associated with subsequent clinical deterioration. A multivariate analysis showed that MSNA was an independent predictor of clinical deterioration. For every increase of 1 burst/minute, the risk of clinical deterioration during follow-up increased by 6%.**
Conclusions: **Sympathetic nervous system activation is an independent predictor of clinical deterioration in pulmonary arterial hypertension.**

Keywords: prognosis; outcome; neurohumoral activation; pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a dyspnea–fatigue syndrome defined as an isolated increase in pulmonary vascular resistance leading to progressive right ventricular failure (1). In spite of progress achieved during the last two decades with the introduction of targeted medical therapies, the prognosis of PAH remains poor, with a median survival limited to 5 to 6 years (1). The outcome of patients with PAH can be to a certain extent predicted by a clinical and biological evaluation combined with echocardiographic and hemodynamic measurements (1). It is of interest that most predictors of outcome in PAH are related to right ventricular function rather than to the severity of pulmonary vascular disease as defined by pulmonary artery pressure (PAP) or pulmonary vascular resistance (1).

We previously reported on microneurographic measurements suggestive of a marked sympathetic nervous system activation in PAH (2, 3). The finding was in keeping with some (4, 5) but not all (6, 7) previous studies based on measurements of circulating catecholamines, but was confirmed by a report of disturbed spectral power of heart rate variability analysis in patients with PAH (8). A variable but significant correlation between indices of sympathetic nervous system activation and severity of the disease has emerged from some of these studies (3, 8). Whether sympathetic nervous system activation contributes to or reflects disease progression in PAH is presently unknown.

The purpose of the present investigation was to evaluate the impact of microneurographic measurement of sympathetic activation on the outcome of patients with PAH.

AT A GLANCE COMMENTARY

Current Scientific Knowledge on the Subject

There is an increasing amount of data on abnormal neurohumoral activation in pulmonary arterial hypertension.

What This Study Adds to the Field

This study gives further insight into neurohumoral activation in pulmonary arterial hypertension. It demonstrates that an abnormal increase in sympathetic nervous system activity is an important prognostic factor indicating an adverse outcome for pulmonary arterial hypertension.

METHODS

Patients

Thirty-three patients with PAH gave informed consent to the study, which was approved by the institutional review board. All of them had been admitted for reevaluation or diagnostic work-up between 2001 and 2007. Death and listing for transplantation were considered end points corresponding to severe clinical deterioration. One patient was on the waiting list for transplantation at the moment of muscle sympathetic nervous system activity (MSNA) recording and therefore was excluded from the study. The analysis was performed on 32 patients (11 men), aged 53 $\pm$ 16 years, with a body mass index of 23 $\pm$ 4 kg/m^2. The median follow-up was 20.6 months (interquartile range, 45.8 mo).

The diagnosis of PAH was made according to a standard algorithm including a right heart catheterization as previously reported (1). PAH was idiopathic in 22 patients, associated with intake of anorexigens in 5, congenital cardiac shunts in 3, and connective tissue disease in 2. At the moment of evaluation, patients were receiving standard therapy consisting of diuretics (furosemide, n = 13; spironolactone, n = 16; bumetanide, n = 7; thiazide, n = 2), digitalis (n = 6), and anticoagulants (n = 17). Specific treatment of PAH consisted of calcium antagonist (n = 3), prostacyclins (epoprostenol, n = 7; treprostinil, n = 7; beraprost, n = 3), endothelin receptor antagonists (bosentan, n = 6; sitaxsentan, n = 2; ambrisentan, n = 1), and phosphodiesterase inhibitors (n = 5). Thirteen patients were not under targeted therapy for PAH at the moment of enrollment in the study.

(*Received in original form December 14, 2009; accepted in final form February 24, 2010*)

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Am J Respir Crit Care Med Vol 181. pp 1269–1275, 2010
Originally Published in Press as DOI: 10.1164/rccm.200912-1856OC on March 1, 2010
Internet address: www.atsjournals.org

Measurements

All the patients underwent recording of MSNA by microneurography. Measurements were performed as described elsewhere (9). MSNA was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head. Electric activity in the nerve fascicle was measured with the use of tungsten microelectrodes. The neural signals were amplified, filtered, rectified, and integrated to obtain a mean voltage display of sympathetic nerve activity.

During the microneurographic recording, blood pressure was measured every minute with a Physiocontrol Colin BP-8800 sphygmomanometer (Colin Press Mate; Colin Corporation, San Antonio, TX). Arterial oxygen saturation (Sa_{O_2}) (Nellcor, N100C pulse oximeter; Medical Resource, Boulder, CO) and heart rate (HR) (ECG monitoring; Siemens Medical, Erlangen, Germany) were continuously monitored.

Clinical, Hemodynamic, and Echocardiographic Evaluation

A right heart catheterization was performed with a 7.5F flow-directed thermodilution Swan-Ganz catheter (Baxter, Deerfield, MI) inserted percutaneously under local anesthesia into an internal jugular vein. Measurements of resting right atrial pressure (RAP) and mean pulmonary artery pressure (mPAP) were obtained. Cardiac output (CO) was measured by the thermodilution method.

Standard echocardiography was performed with commercially available ultrasonographs, using standard views. On the basis of transvalvular pulmonary blood flow recorded with pulse wave Doppler, the pulmonary acceleration time was measured. The tricuspid regurgitation was recorded with continuous Doppler wave, with the ultrasound beam well aligned to regurgitant jet, to obtain the entire envelope of regurgitant flow. From this recording, the maximal instantaneous gradient between the right ventricle and right atrium was measured. Pericardial effusion was evaluated in the parasternal long- and short-axis views and the patients were classified into two groups according to the presence of pericardial effusion. The first group combined patients with no pericardial effusion or with small diastolic pericardial separation, whereas in the second group we included patients with circumferential pericardial effusion.

Exercise Capacity

Exercise capacity was determined by the 6-minute walk distance (6MWD), accompanied by dyspnea evaluation according to the Borg Scale.

Statistical Analysis

Results are presented as means ± SD. Variables between the groups (severely clinically deteriorated vs. not deteriorated) were compared by unpaired two-sample *t* test. Categorical data were compared by chi square test. Relation between MSNA and other variables was analyzed by Pearson correlation. Multivariate analysis based on the Cox proportional hazard model was used to examine the independent effect of variables on survival. Variables, which were significantly related to severe deterioration in the univariate Cox proportional hazard ratio analysis, were included in the multivariate model and the forward conditional method was used to define independent predictors of severe deterioration. Diagnostic performance of variables in predicting severe clinical deterioration in patients with PAH was determined with receiver operating characteristic curves. Survival curves were derived by the Kaplan-Meier method and groups were compared by log-rank test. The level of statistical significance was fixed at $P < 0.05$.

RESULTS

Baseline Patient Characteristics

Baseline clinical, hemodynamic, functional, and microneurographic data are summarized in Table 1. Patients presented with advanced PAH, characterized by low CO and increased mean PAP and RAP. The functional capacity of patients was largely impaired, as determined by 6MWD. Patients reported on perception of difficult breathing during the 6MWD test, as confirmed by high Borg dyspnea score. The majority of patients were classified in NYHA functional class III or IV. The echocardiographic examination revealed decreased pulmonary acceleration time and high maximal gradient of tricuspid regurgitation, which was consistent with increased pulmonary pressures. Circumferential pericardial effusion was noted in four patients. The microneurographic recordings showed a high level of sympathetic activation.

Clinical Outcome during Follow-up

During the follow-up period eight patients were listed for transplantation. Nine patients died during follow-up, which gave an overall mortality rate of 28%.

Comparison between Severely Deteriorated Patients and Nondeteriorated Patients

Comparisons between severely deteriorated patients (dead or listed for transplantation, n = 17) with those who did not deteriorate (n = 15) are presented in Table 2. Severely deteriorated patients, in comparison with the rest of the studied group, were more tachycardic, had increased MSNA, and achieved shorter 6MWD. Moreover, severely deteriorated patients more often presented circumferential pericardial effusion. No difference was noted in age, Sa_{O_2}, mean systemic arterial pressure, CO, mean PAP, RAP, pulmonary acceleration time, and maximal gradient of tricuspid regurgitation between the two groups.

Relation between MSNA and Clinical, Functional, and Hemodynamic Variables

MSNA was directly related to HR ($r = 0.66$; $P < 0.001$), whereas it was inversely related to 6MWD ($r = -0.42$; $P = 0.02$) and pulmonary acceleration time ($r = -0.42$; $P = 0.02$) (Figure 1). Patients in NYHA class IV presented with higher

TABLE 1. CLINICAL, FUNCTIONAL, HEMODYNAMIC, AND MICRONEUROGRAPHIC CHARACTERISTICS OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION AT BASELINE

Variable	Value
Clinical and functional variables	
NYHA class I, II, III, IV	1 (3%), 2 (6%), 16 (50%), 14 (41%)
6MWD, m	375 ± 118
Borg dyspnea score	5.5 ± 2.0
HR, bpm	82 ± 16
mSAP, mm Hg	84 ± 17
Sa_{O_2}, %	91 ± 6
Microneurography	
MSNA, burst/min	67 ± 20
Hemodynamic variables	
mPAP, mm Hg	55 ± 13
RAP, mm Hg	10 ± 4
CO, L/min	3.9 ± 1.5
Echocardiographic variables	
Circumferential pericardial effusion, number of patients	4 (13%)
Pulmonary AT, ms	74 ± 16
TR maximal gradient, mm Hg	43 ± 5

Definition of abbreviations: 6MWD = 6-minute walk distance; AT = acceleration time; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; MSNA = muscle sympathetic nerve activity; NYHA = New York Heart Association functional class; RAP = right atrial pressure; Sa_{O_2} = arterial blood oxygen saturation; TR = tricuspid regurgitation.

n = 32 patients.

TABLE 2. COMPARISON OF FUNCTIONAL, HEMODYNAMIC, AND MICRONEUROGRAPHIC VARIABLES BETWEEN SEVERELY DETERIORATED PATIENTS* AND NONDETERIORATED PATIENTS†

Variable	Severely Deteriorated Patients (Dead or Listed for Transplantation)	Nondeteriorated Patients	*P* Value
Age, yr	54 ± 16	52 ± 17	0.66
MSNA, burst/min	80 ± 12	52 ± 18	<0.001
HR, bpm	88 ± 17	74 ± 12	<0.01
Sa_{O_2}, %	90 ± 8	92 ± 3	0.33
mSAP, mm Hg	82 ± 14	86 ± 19	0.50
NYHA IV, number of patients (%)	10 (59%)	3 (20%)	0.07
6MWD, m	324 ± 119	434 ± 88	<0.01
Borg dyspnea score	5.8 ± 2.0	5.4 ± 2.1	0.64
mPAP, mm Hg	53 ± 12	57 ± 14	0.49
RAP, mm Hg	8 ± 4	11 ± 4	0.12
CO, L/min	3.7 ± 0.9	4.2 ± 2.0	0.33
Pulmonary AT, ms	70 ± 11	79 ± 20	0.11
TR maximal gradient, mm Hg	45 ± 4	42 ± 56	0.25
Circumferential pericardial effusion, number of patients (%)	4 (24%)	0 (0%)	<0.05

Definition of abbreviations: 6MWD = 6-minute walk distance; AT = acceleration time; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; MSNA = muscle sympathetic nerve activity; NYHA = New York Heart Association functional class; RAP = right atrial pressure; Sa_{O_2} = arterial blood oxygen saturation; TR = tricuspid regurgitation.

* Dead or listed for transplantation, n = 17.

† n = 15.

MSNA than those in NYHA class I to III (77 ± 14 vs. 60 ± 22 burst/min; $P = 0.02$).

Univariate and Multivariate Cox Regression Analysis

In the univariate analysis high MSNA, elevated HR, the presence of pericardial effusion, and NYHA class IV were associated with severe clinical deterioration (Table 3). In the multivariate analysis MSNA was the only independent predictor of severe deterioration (hazard ratio, 1.06; 95% confidence interval [CI], 1.02–1.10; $P = 0.001$). For every increase of one burst in sympathetic activation, the risk of death or listing for transplantation increased by 6%. An analysis of predictors of severe clinical deterioration in patients naive to specific treatment for PAH at the moment of microneurography (n = 13) revealed that MSNA only was related to severe clinical deterioration in this patient group (hazard ratio, 1.12; 95% CI, 1.01–1.24; $P = 0.03$).

Receiver Operating Characteristic Curves

According to receiver operating characteristic curves, the best predictor of severe clinical deterioration during the follow-up period was MSNA, followed by 6MWD and HR (Figure 2). The cutoff value of MSNA of 64 bursts/minute in predicting severe clinical deterioration, had a sensitivity and specificity of 94 and 80%, respectively.

Kaplan-Meier Analysis of Survival Time to Severe Clinical Deterioration

Patients were divided into groups based on the cutoff values (obtained from receiver operating characteristic curves), which

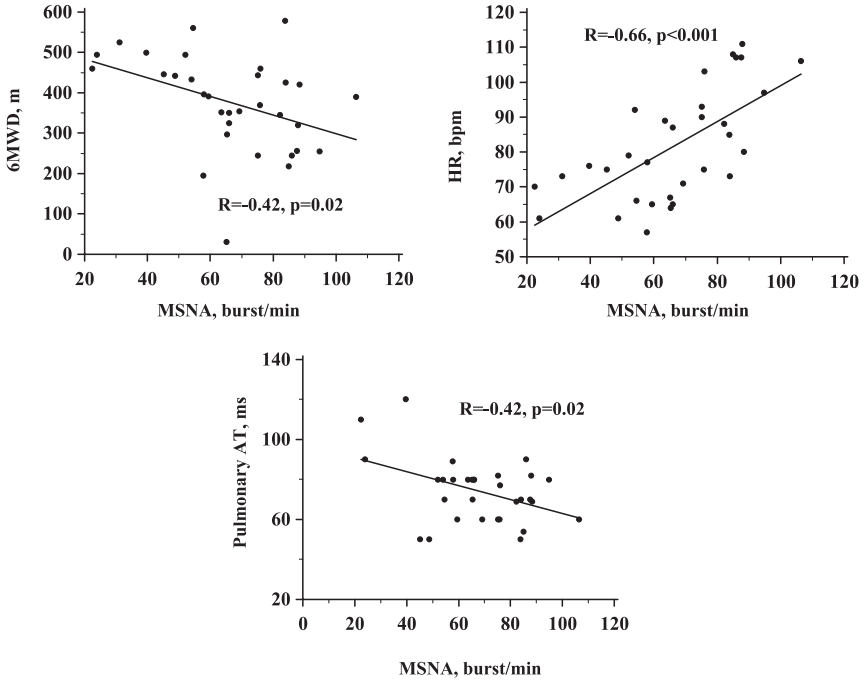

Figure 1. Muscle sympathetic nerve activity (MSNA) was directly related to heart rate (HR; *top right*) and inversely related to 6-minute walk distance (6MWD; *top left*) and pulmonary acceleration time (AT; *bottom*).

TABLE 3. UNIVARIATE COX PROPORTIONAL HAZARD RATIO ANALYSIS OF PREDICTORS OF SEVERE CLINICAL DETERIORATION

Variable	Hazard Ratio (95% CI)	*P* Value
MSNA, burst/min	1.06 (1.02–1.10)	0.001
HR, bpm	1.06 (1.02–1.10)	0.003
NYHA IV, number of patients	3.11 (1.25–7.72)	0.02
6MWD, m	0.995 (0.991–0.999)	0.01
Borg dyspnea score	1.13 (0.86–1.50)	0.38
mPAP, mm Hg	1.0 (0.96–1.04)	0.94
RAP, mm Hg	0.91 (0.80–1.03)	0.13
CO, L/min	0.90 (0.63–1.29)	0.58
Pulmonary AT, ms	0.98 (0.95–1.02)	0.21
TR maximal gradient, mm Hg	1.01 (0.99–1.02)	0.42
Circumferential pericardial effusion, number of patients	3.49 (1.12–10.90)	0.03

Definition of abbreviations: 6MWD = 6-minute walk distance; AT = acceleration time; CI = confidence interval; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; MSNA = muscle sympathetic nerve activity; NYHA = New York Heart Association functional class; RAP = right atrial pressure; Sa_{O_2} = arterial blood oxygen saturation; TR = tricuspid regurgitation.

predicted with highest sensitivity and specificity the severe clinical deterioration. The following cutoff values were used: 64 bursts/minute for MSNA, 93 bpm for HR, and 421 m for 6MWD. Kaplan-Meier curves were plotted for these variables (Figure 3). Similarly, Kaplan-Meier curves were also plotted to compare survival of patients in NYHA functional class IV and patients in NYHA functional class III or less (Figure 3). Patients with MSNA higher than 64 bursts/minute, a HR greater than 93 bpm, a 6MWD less than 421 m, and in NYHA functional class IV presented a shorter time to occurrence of severe clinical deterioration.

DISCUSSION

Our study investigated clinical outcome in a population of patients with advanced PAH, as evidenced by low cardiac output, substantial exercise capacity impairment, and high sympathetic activation. We report that sympathetic activation was related to progression of heart failure and the importance of exercise intolerance. Moreover, the sympathetic activation was higher in patients who subsequently severely deteriorated and either died or required listing for transplantation. Finally, our study showed that direct intraneural recordings of sympathetic activation were an independent predictor of severe deterioration in patients with PAH.

Neurohumoral activation in PAH is evidenced by investigations reporting on increased circulating catecholamine levels (4, 5), abnormally high MSNA (2, 3), and impaired heart rate variability (10). However, mechanisms of sympathetic activation in PAH have not been sufficiently investigated, and speculations on the origin of neurohumoral dysfunction in PAH are based on the current state of knowledge about neurohumoral imbalance in left heart failure (11). In this way, the assumption is made that the sympathetic activation in PAH is a consequence of impairment of right ventricular function with, as a result, low cardiac output and consequent activation of the sympathetic system. The following mechanisms are believed to contribute to sympathetic overactivation in left heart failure: attenuation of inhibitory stimuli from dysfunctional carotid, aortic, and cardiopulmonary baroreceptors (12, 13); abnormally increased response from metaboreceptors located in skeletal muscles (14); and increased sensitivity of

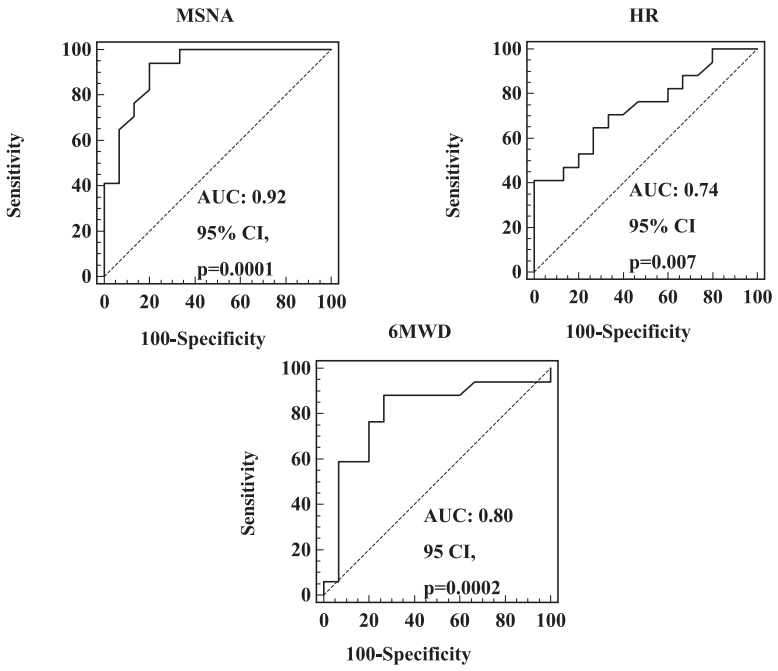

Figure 2. Receiver operating characteristic curves of muscle sympathetic nerve activity (MSNA; *top left*), heart rate (HR; *top right*), and 6-minute walk distance (6MWD; *bottom*) for prediction of severe clinical deterioration in patients with pulmonary arterial hypertension. AUC = area under curve; CI = confidence interval.

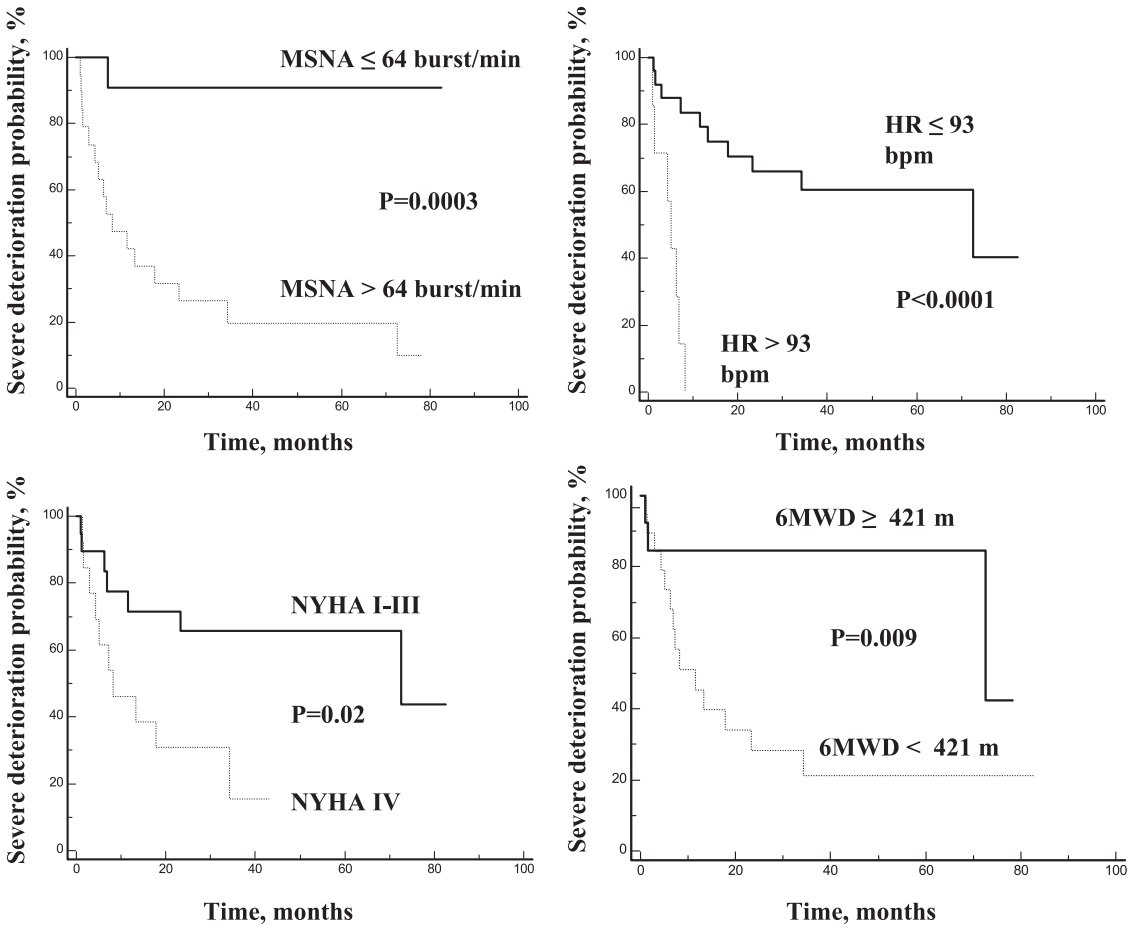

Figure 3. Kaplan-Meier curves for survival free from severe deterioration. Patients were divided into groups according to muscle sympathetic nerve activity (MSNA; *top left*), 6-minute walk distance (6MWD; *bottom right*), heart rate (HR; *top right*), and New York Heart Association (NYHA) functional class (*bottom left*). The cutoff values for the continuous variables were derived from receiver operating characteristic curves; for MSNA the cutoff chosen was 64 bursts/minute, for 6MWD it was 421 m, and for HR it was 93 bpm. Patients characterized by high MSNA, high HR, short 6MWD, and NYHA functional class IV presented with shorter time to occurrence of severe clinical deterioration.

central and peripheral chemoreceptors (15, 16). None of these mechanisms, apart from baroreceptor function (17), was specifically studied in patients with isolated right ventricular failure.

Moreover, it is still unclear whether sympathetic activation in right ventricular failure should be considered a marker or a factor contributing to right ventricular damage, or both. It could be argued that sympathetic activation in PAH can be deleterious both for the heart and lung vasculature.

Chronic sympathetic activation leads to changes in structure and function of the myocardium, as a result of down-regulation of β receptors (18), increased myocardial remodeling (19), and apoptosis (20). This increases also the susceptibility to life-threatening arrhythmias (21). Moreover, an effect of increased sympathetic activation cannot be excluded on the lungs. Indeed, human pulmonary arteries and arterioles present dense sympathetic innervation (22). The vasoactive effects of catecholamines (either circulating or released by nerve fibers) in the lungs are exerted by stimulation of α_1-adrenoreceptors located on pulmonary smooth muscles, endothelial α_2–adrenoreceptors, or β_1- and β_2-adrenoreceptors (23). Moreover, sympathetic nerve stimulation provokes pulmonary vasoconstriction, exacerbated by β-receptor blockade (24, 25). Finally, sympathetic stimulation contributes to basal pulmonary vascular tone, because denervation results in pulmonary vasodilation (26).

In light of the previously mentioned studies, our observation that sympathetic activation is related to disease severity and is a prognostic factor for severe deterioration is not unexpected. In our study we observed a relation between MSNA and the severity of PAH, as assessed by NYHA class, 6MWD, and pulmonary acceleration time. Although the correlation between sympathetic activity and NYHA class was already previously described (3), our study is the first to report a correlation between MSNA and exercise impairment, as assessed by 6MWD.

6MWD was found to be a predictive factor of adverse outcome in several different studies (27–30) and is the most commonly used parameter to evaluate the functional status of patients in numerous clinical trials. Barst and colleagues found that 6MWD distance was lower in the nonsuvivors versus survivors in a group treated with prostacyclin, but also in the group treated by conventional therapy only, and the 6MWD performance was found to be an independent factor of survival (27). Miyamoto and colleagues reported that 6MWD was an independent prognostic factor of mortality (29). Paciocco and colleagues concluded that pretreatment 6MWD in moderately symptomatic patients with PAH is predictive of survival; a distance less than 300 m increased the mortality risk by 2.4 (30). In our study the mean 6MWD was slightly higher than in the studies previously cited; however, our patient population was already undergoing a different specific treatment for PAH (60% of patients were taking prostacyclins) that affected 6MWD (27). Despite the fact that the majority of our patients were receiving different specific treatments, those who presented at baseline with a 6MWD less than 422 m also presented with a shorter time to death or listing for transplantation.

Patients in NYHA class IV in our study developed severe deterioration in a shorter time in comparison with patients in NYHA functional class III or less. There is strong evidence of the importance of NYHA functional class for the prognosis in PAH, as shown already in several different studies. The NIH cohort study showed that among 195 patients diagnosed with idiopathic PAH, the risk of death was higher among those who

were in NYHA classes III and IV in comparison with those in NYHA classes I and II (31). In a subsequent cohort study, with a small number of patients receiving epoprostenol therapy, patients in NYHA class IV at the time of the diagnosis had a significantly higher risk of death that patients in NYHA classes I–III (32).

Echocardiographic examination is a valuable tool to assess patients with PAH. In our study, the presence of circumferential pericardial effusion was related to the appearance of faster severe deterioration in patients with PAH. The importance of pericardial effusion on echocardiographic examination has already been appreciated in other studies (24), which demonstrated that pericardial effusion is a predictor of adverse outcome in patients with PAH.

We did not find differences in hemodynamic variables between patients who died or were listed for transplantation during follow-up in comparison with those who did not deteriorate. Although other studies report that hemodynamic variables such as CO, RAP, and mPAP are predictors of outcome in PAH (data from the NIH Registry Study [31]), these observations are less obvious in patients who are already receiving specific treatments. In a series of patients treated with epoprostenol, it was found that only RAP was predictive of survival on univariate analysis (33). There is still limited data on the prognostic value of hemodynamic variables in patients treated with other agents than epoprostenol. The sentence should be: There is still limited data on the prognostic value of hemodynamic variables in PAH patients treated with other agents than epoprostenol. We cannot exclude that targeted PAH therapy in the majority of patients in our study affected the prognostic relation between hemodynamic measurements and severe deterioration.

This is, to our knowledge, the first study to show the prognostic importance of sympathetic activation in patients with pulmonary arterial hypertension. This was obtained by use of direct recordings of sympathetic traffic, not affected by changes of reuptake and spillover, which may confound the interpretation of circulating catecholamine levels.

Our study presents, however, several limitations. It was conducted on a limited number of patients, who were treated with different specific agents for PAH. We did not intervene in therapeutic decisions during the study and physicians were free to change, stop, or associate different agents according to their clinical judgment. Our study population was heterogeneous in terms of origin of PAH, and it is known that a different etiology of PAH is associated with a different prognosis. However, in our studied population, the majority of patients presented either with idiopathic PAH or PAH associated with anorexigen intake, and these two entities are similar in terms of clinical evolution, histopathological findings, and response to treatment.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors acknowledge the support of the European Society of Cardiology, Funds for Cardiac Surgery, Foundation Horlait-Dapsens, Pfizer, Astra Zeneca, and Novartis.

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