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Exercise Hemodynamics in the Prognosis of Patients with Pulmonary Arterial Hypertension

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Keywords
Pulmonary arterial hypertension · Exercise testing · Survival · Pulmonary hemodynamics · Right ventricular function

Abstract
Background: Assessment of prognosis is of major importance when deciding on a therapeutic strategy in patients with pulmonary arterial hypertension (PAH). ***Objectives:*** The aim of this study was to investigate the prognostic value of pulmonary hemodynamics during exercise and changes during treatment in patients with PAH. ***Methods:*** Consecutive incident patients (n = 49) with PAH undergoing right heart catheterization at rest and during a constant workload cycle exercise in supine position were included. Predictors of survival were identified at baseline using Cox proportional hazard regression models in a univariate analysis unadjusted and adjusted for age and gender. ***Results:*** During a median follow-up period of 42 months, 13 (27%) of the 49 patients studied died. Two predictors of death were found: rest-to-exercise changes in heart rate and systolic pulmonary artery pressure. Adjusted hazard ratios were 0.92 (95% CI 0.86–0.99) and 0.93 (95% CI 0.88–0.99), respectively. These 2 variables were correlated with each other (r = 0.55, p < 0.001). ***Conclusions:*** Rest-to-exercise changes in heart rate and systolic pulmonary artery pressure measured at diagnosis are predictors of survival in patients with PAH. These measurements taken from an exercise test reflect right ventricular function.

Introduction

Pulmonary arterial hypertension (PAH) is a pulmonary vascular disease that leads without treatment to right ventricle (RV) failure and death [1, 2]. Evaluation of severity is an important step during the diagnostic proce-

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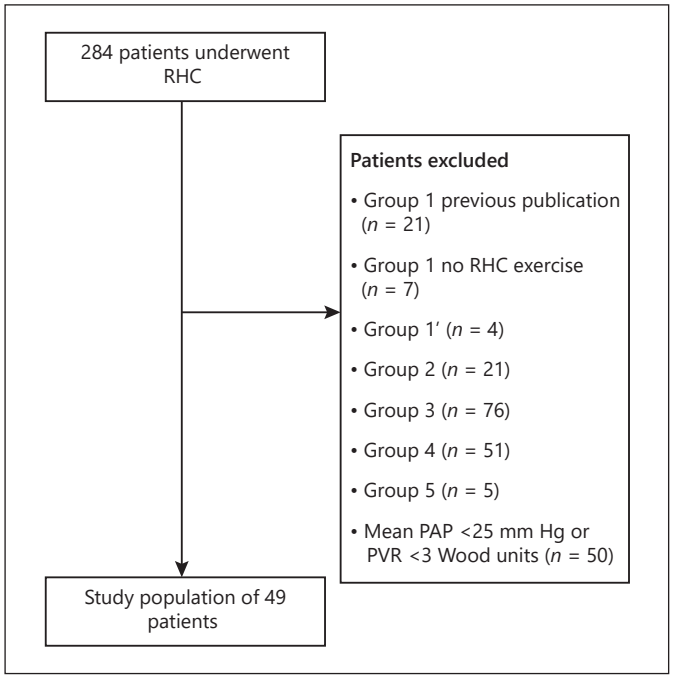

Fig. 1. Patient flowchart. RHC, right heart catheterization.

dure and during the follow-up of patients with PAH. A multidimensional assessment is recommended mainly based on variables related to RV function to estimate the risk of 1-year mortality [3].

In order to respond appropriately to an increase in metabolic demand, cardiac output increases with increasing heart rate (HR) and stroke volume during exercise in healthy subjects; in patients with PAH, these 2 ways of increasing cardiac output are impaired [4, 5].

Adaptive RV remodeling as opposed to maladaptive remodeling is characterized by preserved systolic and diastolic function. Consequently, adaptive remodeling in patients with PAH leads to minimally altered ventriculoarterial coupling ensuring a good prognosis [6]. Cardiopulmonary exercise testing during right heart catheterization evaluates the response of the pulmonary circulation to an increase in flow and the response of the heart to an increase in load, and differentiates patients with maladaptive RV remodeling from patients with adaptive remodeling.

In patients with PAH, due to structural changes in the distal pulmonary arteries, capillaries, and pulmonary veins of variable extent depending on the type of PAH, the lung vasculature has little ability, if any, to recruit or to vasodilate during exercise. Therefore, cardiopulmonary exercise tests in patients with severe PAH assess the ability of the RV to face an increase in its afterload which corresponds approximately to an evaluation of right ventriculoarterial coupling. Additionally, hemodynamic measurements during exercise could provide important information on treatment response which is not always revealed by measures at rest [7–10]. As a matter of fact, the RV function is dependent on its preload, which can be different in an individual from one measurement to another performed only at rest [11].

It is not definitively established whether pulmonary hemodynamics during exercise provide additional relevant information to the overall evaluation currently performed in PAH patients [3]. Thus, the aim of this study was to provide further evidence on the prognostic value of exercise hemodynamics at the time of diagnosis in patients with PAH and, second, to determine which hemodynamic variables play a predominant role. As exploratory analyses, we examined pulmonary hemodynamic changes in patients on PAH-specific drug therapies during exercise. Part of the study results have been reported at the 2015 European Respiratory Society (ERS) conference [12].

Methods

Additional details on the methods and results are available in the online supplementary Material (for all online suppl. Material, see www.karger.com/doi/10.1159/000509144).

Patients

We studied consecutive patients referred to the Nancy University Hospital, Nancy, France, for suspicion of pulmonary hypertension between March 1, 2006, and December 15, 2012. Forty-nine patients were selected for this study (Fig. 1). They all met hemodynamic criteria of group 1 of the clinical classification of pulmonary hypertension developed at the third World Symposium (2003) as well as 2015 European Society of Cardiology (ESC)/ERS guidelines [3]. All patients were evaluated for conditions known to be associated with pulmonary hypertension.

The population studied is part of the French PAH registry. Our data collection and analysis methods were approved by the *Commission Nationale Informatique et Liberté* (CNIL) on May 24, 2003 (approval No. 842063). All patients gave written informed consent to undergo a right heart catheterization with an exercise test.

Study Design

Data were collected prospectively in our database. Delay between the first expert advice and diagnosis did not exceed 4 weeks. All patients were incident cases and in accordance with our practice; PAH-specific therapy was started within 7 days after the baseline (T0) right heart catheterization.

The best standard of care was applied all along the follow-up, including PAH-specific drug therapies which were administered as recommended. The first follow-up evaluation included a right heart catheterization (T1) with an exercise test using the same workload as at baseline and was planned between 3 and 6 months after initiating PAH therapy but could be delayed.

Table 1. Characteristics of the study population (n = 49)

Variables	Mean ± SD or n	Median (interquartile range)
Age, years	53±16	52 (43–66)
Female/male ratio	33/16	
Body mass index, kg/m^2	26±7	25 (22–30)
PAH diagnosis, n		
Idiopathic/heritable	17/3	
Scleroderma/others[1]	10/19	
NYHA class, n		
I or II	12	
III	34	
IV	3	
6MWD, m	401±103	420 (325–470)
FVC, %	92±17	
FEV_1, %	97±16	
Resting pulmonary hemodynamics		
Heart rate, beats/min	75±14	73 (64–82)
RAP, mm Hg	6±4	5 (3–8)
Mean PAP, mm Hg	43±11	44 (34–51)
PAWP, mm Hg	8±3	7 (5–10)
Cardiac index, L/min/m^2	2.6±0.7	2.6 (2.0–3.7)
Cardiac output, L/min	4.7±1.6	4.4 (3.4–5.6)
PVR, Wood units	8.6±4.4	7.8 (5.3–11.1)
SvO_2, %	64±8	64 (58–70)
Exercise pulmonary hemodynamics		
Workload, W	20±10	20 (15–22)
<10 W	4	
10–20 W	33	
25–30 W	9	
>30 W	3	
Heart rate, beats/min	107±17*	105 (100–118)
Mean PAP, mm Hg	62±14*	64 (51–73)
PAWP, mm Hg	12±6*	11 (7–15)
Cardiac index, L/min/m^2	3.7±1.2*	3.5 (2.7–4.6)
PVR, Wood units	8.4±4.2	8.4 (5.2–10.8)
SvO_2, %	39±12	39 (31–48)
Exercise minus rest values		
ΔHeart rate, beats/min	32±12	32 (24–37)
ΔSystolic PAP, mm Hg	27±12	27 (18–37)
ΔMean PAP, mm Hg	19±8	19 (13–25)
ΔCardiac index, L/min/m^2	1.1±0.8	0.9 (0.5–1.6)
ΔSVI, mL/m^2	–0.1±5.6	–0.6 (–3.4 to 3.0)
Pressure-flow slope, mm Hg/L/min	12.9±8.4	9.6 (6.8–15.0)

PAH, pulmonary arterial hypertension; 6MWD, 6-min walk distance; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; RAP, right atrial pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance, SvO_2, mixed venous oxygen saturation; Δ, exercise minus rest values; SVI, indexed stroke volume. * $p < 0.001$, rest vs. exercise (paired t test).

[1] Portal hypertension (n = 6), congenital heart disease (n = 5), human immunodeficiency virus (n = 3), systemic lupus erythematosus (n = 3), and other connective tissue disease (n = 2).

Measurements

At baseline, all patients underwent right heart catheterization and the 6-min walk distance test before starting any treatment of pulmonary hypertension. Right heart catheterization was performed as previously described [9]. All pulmonary hemodynamic measurements were performed using a Swan-Ganz catheter in the supine position at rest and during exercise. Patients performed a cycling exercise with constant workload aiming for an exercise duration of 8 min (mean workload of 20 ± 10 W). Cardiac output was measured using the thermodilution technique first at rest and then during exercise, and 3 values differing <10% were averaged. Indexed stroke volume (SVI) was calculated as cardiac output divided by HR and was indexed to body surface area. Pressure-flow relationship was computed in each patient by the ratio of mean pulmonary artery pressure (mPAP) and cardiac output differences between end of exercise (one measure) and rest values. Isoflow mPAP was calculated as previously described by Provencher et al. [8]. This allows to compare the mPAP measured during exercise for the same value of cardiac output at 2 different examinations (e.g., after treatment) in the same patient (online suppl. Fig. 1). The 6-min walk distance was measured in all 49 patients as recommended in American Thoracic Society guidelines [13].

Statistical Analysis

We expressed data as means ± SD unless stated differently. Paired data were compared using paired t tests. Overall survival was assessed from the date of the right heart catheterization at T0 until December 15, 2014, using the Kaplan-Meier method. Predictors of survival were identified at baseline (T0) using Cox proportional hazard regression models in univariate analysis unadjusted and adjusted for age and gender. The assumption of proportional hazards was assessed graphically using log-minus-log survival plot.

We carried out receiver-operating characteristic (ROC) curve analysis for 36-month survival to determine threshold values of selected hemodynamic covariates. ROC curves were constructed with 40 uncensored patients (9 were censored alive before the 36-month follow-up).

Correlations were computed using Pearson's coefficients. p values <0.05 were considered significant. Statistical analyses were performed using IBM SPSS Statistics version 19 (Chicago, IL, USA).

Results

Pulmonary Hemodynamics at Baseline and after Treatment

Table 1 reports the characteristics of the 49 study subjects with a female to male ratio of 33:16. Of the 49 study subjects, 17, 3, and 29 patients had idiopathic PAH, heritable PAH, or PAH associated with the scleroderma spectrum or another disease, respectively. They were 53 ± 16 years of age, and 34 (69%) were in NYHA class III. Mean pulmonary hemodynamic data indicated that most patients had severe pulmonary hypertension. Exercise led to an increase in mPAP and cardiac index (CI), the latter

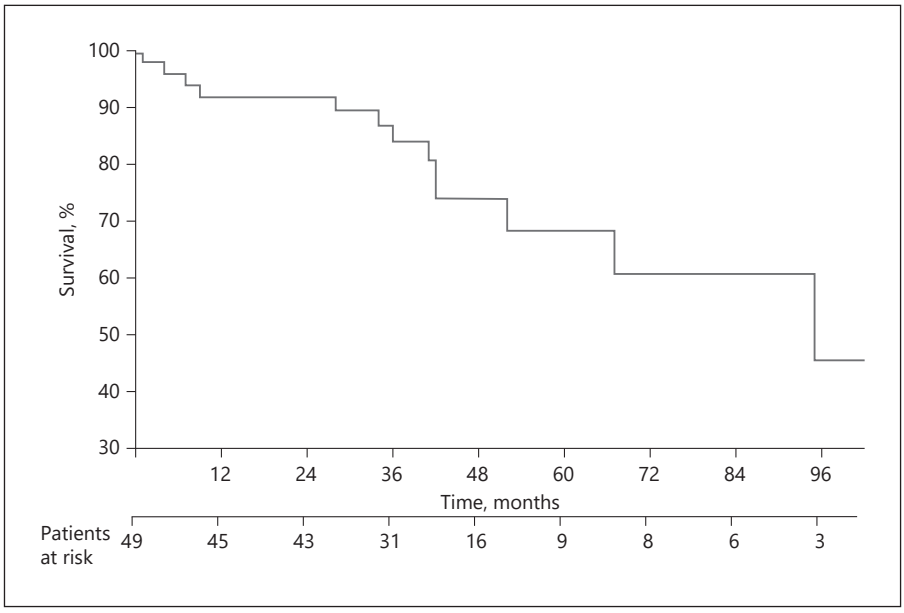

Fig. 2. Survival of the 49 patients estimated using the Kaplan-Meier method.

being due to an increase in HR and a remarkably unchanged SVI (Table 1).

Twelve patients did not undergo an exercise hemodynamic study at the follow-up evaluation. Rest-to-exercise change in HR (ΔHR), systolic pulmonary artery pressure (sPAP), CI, and SVI at T0 and resting hemodynamic data at T1 were not statistically different between the 12 patients who were not reassessed and the remaining 37 patients (data not shown). Pulmonary hemodynamics at rest and during exercise improved significantly under PAH-specific treatment (online suppl. Table 1): isoflow mPAP was significantly improved from T0 (62 ± 13 mm Hg) to T1 (49 ± 15 mm Hg; $p < 0.001$), as well as pressure-flow slope (14.1 ± 8.6 mm Hg/L/min at T0 vs. 11.0 ± 6.6 mm Hg/L/min at T1, $p = 0.02$). Rest to exercise changes in CI (ΔCI) were significant and improved from 1.0 ± 0.7 L/min/m^2 at T0 to 1.4 ± 0.8 L/min/m^2 at T1 ($p < 0.001$) due to an improvement in SVI (ΔSVI) from –0.9 ± 5.2 mL/m^2 at T0 to 1.1 ± 5.3 mL/m^2 at T1 ($p = 0.012$). ΔHR and ΔsPAP did not change significantly between T0 and T1. Remarkably, the improvement in SVI adaptation during exercise (exercise minus rest values) under PAH-specific treatment was strongly correlated with the decrease in RV afterload, the latter being measured by the decrease in isoflow mPAP ($r = –0.735$, $p < 0.001$; online suppl. Fig. 2).

Survival

Up till the last evaluation or death, all patients were receiving PAH therapy. Median follow-up among survivors was 42 months (range 18–102 months). Of the 49 patients, none was lost to follow-up or had lung transplant at the endpoint date; 13 patients died: among them, 8 died from RV failure, and 3 died from a reason unrelated to PAH. Survival rates after 1, 3, and 5 years were 92% (95% confidence interval [95% CI] 84–99), 84% (95% CI 73–95), and 68%, respectively (95% CI 51–85; Fig. 2).

Table 2 shows Cox proportional hazard univariate analysis. Statistically significant predictors of survival at baseline were age, gender, CI during exercise, SVI during exercise, ΔHR, ΔsPAP, and ΔCI. In univariate analysis adjusted for age and gender, only ΔHR and ΔsPAP remained predictors of survival. Adjusted hazard ratios were 0.92 (95% CI 0.86–0.99) and 0.93 (95% CI 0.88–0.99). Remarkably, ΔsPAP was correlated with ΔHR ($r = 0.55$, $p < 0.001$). In an exploratory way, we performed a stepwise multiple linear regression analysis, which showed that the only variable independently predicting ΔsPAP was ΔHR.

Nine patients were censored alive before the 36-month follow-up. As a result, ROC curves were plotted, and areas under the curve (AUC) for 36-month survival were calculated with 40 patients, 7 of whom had died (Fig. 3). The AUC for ΔsPAP (exercise minus rest values at T0) was 0.84 (95% CI 0.68–0.99). ΔsPAP >30 mm Hg had a sensitivity of 40% and a specificity of 100% to predict survival at 36 months. Accordingly, all the 11 patients who had ΔsPAP >30 mm Hg at baseline were alive 36 months after diagnosis. A similarly sig-

Table 2. Univariate Cox proportional hazard regression analysis related to covariates measured at baseline

Variables (n = 49)	Unadjusted hazard ratio (95% CI)
Age	1.05 (1.01–1.09)*
Gender	
Female	1
Male	4.83 (1.45–16.12)*
Diagnosis	
Idiopathic/heritable	1
Scleroderma/others	0.54 (0.16–1.83)
Resting hemodynamics	
6-min walking distance	0.76 (0.66–0.88)**
Heart rate	1.04 (0.99–1.08)
Right atrial pressure	1.15 (0.98–1.35)
Mean PAP	1.03 (0.98–1.08)
Cardiac index	0.76 (0.32–1.80)
Indexed stroke volume	0.96 (0.90–1.01)
Pulmonary vascular resistance	1.02 (0.90–1.16)
SvO_2	0.94 (0.88–1.00)
Exercise hemodynamics	
Heart rate	1.00 (0.97–1.04)
Systolic PAP	0.99 (0.96–1.01)
Mean PAP	0.99 (0.95–1.03)
Cardiac index	0.43 (0.23–0.81)*
Indexed stroke volume	0.94 (0.89–1.00)*
Pulmonary vascular resistance	1.07 (0.93–1.23)
Exercise minus rest values	
ΔHeart rate	0.92 (0.87–0.98)*
ΔSystolic PAP	0.91 (0.86–0.96)**
ΔCardiac index	0.25 (0.08–0.75)*
ΔIndexed stroke volume	0.93 (0.83–1.03)
Pressure-flow slope	1.04 (0.96–1.12)

CI, confidence interval; PAP, pulmonary artery pressure; SvO_2, mixed venous oxygen saturation; Δ, exercise minus rest values; Pressure-flow, pressure-flow relationships. * $p < 0.05$, ** $p < 0.001$ (Wald χ^2 statistics).

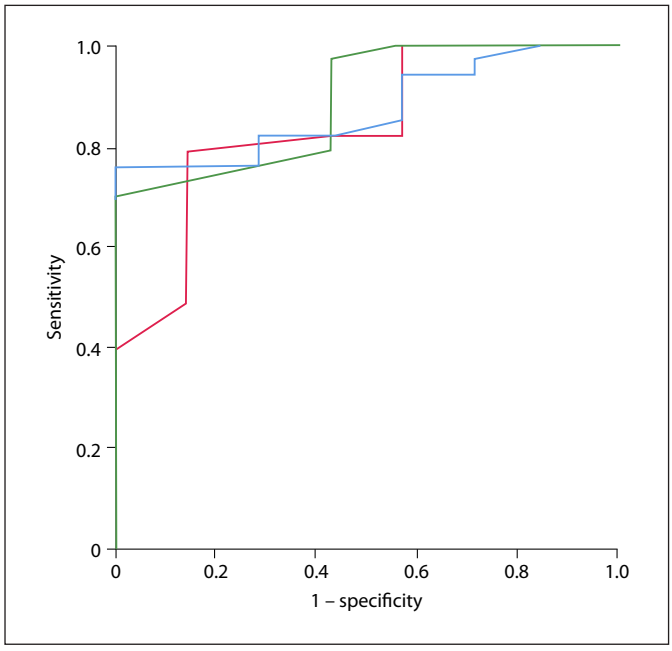

Fig. 3. Receiver-operating characteristic curve analyses of 36-month survival for rest-to-exercise change in heart rate (blue curve), systolic pulmonary artery pressure (red curve), and cardiac index (green curve) at baseline; areas under the curves: 0.87 (95% CI 0.76–0.98), 0.84 (95% CI 0.68–0.99), and 0.89 (CI 95% 0.77–1.00), respectively.

nificant result was found for ΔHR with an AUC of 0.87 (95% CI 0.76–0.98). ΔHR >30 beats/min provided 70% sensitivity and 100% specificity of being alive at 36 months.

Discussion

The present study shows that rest-to-exercise changes in pulmonary hemodynamic data measured at the time of PAH diagnosis predicted survival. ΔHR and ΔsPAP were the only variables predicting survival after adjustment for age and gender. It must be emphasized that in our study these 2 variables (HR and sPAP) were strongly correlated and that the increase in HR is the only way to increase CI during exercise in patients with severe PAH. Notably, we also show that ΔHR did not change after 5 months of PAH-specific drug therapies. However, ΔSVI improved due to a decrease in RV afterload indicating vasodilatation under treatment, which is demonstrated by a lower exercise isoflow mPAP. The findings of this study may help to differentiate between high-risk and low-risk patients and guide treatment decisions [3].

Population Studied

The patients were included prospectively at an expert center for the diagnosis and treatment of severe pulmonary hypertension. On inclusion, all patients were incident cases and naïve to PAH-specific therapy. The clinical and resting hemodynamic characteristics of the study population were consistent with recent papers devoted to PAH [14, 15]. At diagnosis, 76% (n = 37) of the patients studied were in NYHA class III or IV. Mean CI (2.6 ± 0.7 L/min/m^2) and mixed venous oxygen saturation (64 ± 8%) were also strongly altered, indicating advanced PAH in most of our patients. However, the average 6-min walk distance in our population (401 ± 103 m) was slightly

higher than in the French registry [16]. Therefore, the population of our study is representative of an incident population of PAH patients. This study confirms our previous results [9] from an independent series of patients. Since our previous study only included patients with idiopathic, heritable, or anorexigen-associated PAH, the study presented here broadens the scope of PAH associated with connective tissue disease and other conditions (Table 1).

Prognostic Value of Pulmonary Hemodynamics during Exercise at PAH Diagnosis

Our study shows that HR and sPAP changes during submaximal exercise at diagnosis were statistically significant prognostic factors. Notably, these 2 variables, HR and sPAP, are correlated, which is consistent with a recently published study [17]. Previous studies demonstrated that peak oxygen uptake during exercise [10, 18, 19] and exercise CI [9] were important prognostic factors. In the study by Wensel et al. [18], low peak oxygen uptake was one of the best predictors of mortality among several variables of cardiopulmonary exercise testing and pulmonary hemodynamic data. A significant correlation between CI and oxygen uptake during exercise has been established [20]. It can also be assumed that since SVI cannot be increased on exercise in such patients, it is very likely that the chronotropic incompetence revealed by a stress such as physical exertion must play a leading role in the prediction of clinical outcome in these studies [9, 10, 18, 19].

Hasler et al. [19] demonstrated that the pressure-flow slope was a good predictor of transplant-free survival. The discrepancy between these results and ours is mainly explained by a significant change in the pressure-flow slope under PAH drug therapies and an important variability in individual response to treatment (mean decrease of –3.0 ± 6.6 mm Hg/L/min) observed in our study. As a result, we found that some patients with a higher pressure-flow slope than average at baseline had a better survival than the average when the pressure-flow slope decreased significantly under PAH-specific therapy (data not shown), not allowing this covariate at baseline to be significantly related to survival. Moreover, our study, unlike that of Hasler et al. [19], consisted of exclusively incident patients, and we applied a 2-point calculation of the pressure-flow slope from the constant submaximal test whereas Hasler et al. [19] used a multipoint calculation from an incremental maximal exercise test. Thus, this made unlikely that the pressure-flow slope measured at baseline in our study could be a prognostic factor.

Exercise Pulmonary Hemodynamic Changes under PAH-Specific Drug Therapies

Follow-up exercise hemodynamic results under PAH-specific treatment show that after a median time of 5 months, exercise CI under the same workload increased significantly by 0.71 ± 0.82 L/min/m^2 (paired *t* test, $p < 0.001$). Although the resting HR at T1 was significantly lower, ΔHR was similar at T1 and T0. Therefore, the increase in exercise CI from T0 to T1 can only be explained by an increase in SVI. These results are important because they show that SVI during exercise can increase as long as the RV afterload is decreased by the treatment demonstrated by a lower mPAP at isoflow during exercise. It must be emphasized that SVI measured at rest and after a median treatment duration of 5 months was one of the 2 independent hemodynamic prognostic factors in a recently published study of nearly 1,000 patients with PAH [15]. This marked improvement in the SVI may be interpreted as a marked improvement in right ventriculoarterial coupling [17].

Clinical Implications

Our findings suggest that the chronotropic response to exercise at diagnosis should be tested as a prognostic factor in larger cohorts of patients with PAH. Compared with an increase in sPAP >30 mm Hg during exercise which was associated with a better survival in a previous study [21] as well as in the present study, the chronotropic response has the advantage to be simpler and independent of gender [22].

We also found that SVI, measured during submaximal exercise after 5 months (median time) of PAH-specific treatment, increased significantly. Although we did not assess the prognostic importance of hemodynamic variables after treatment, our results are in line with a paper showing that an SVI increase of about 10 mL/m^2 from rest to the first reevaluation was independently associated with survival without lung transplantation [15]. Further studies are warranted to identify variables with a high potential of change under PAH-specific therapies and to elaborate standardized and uniform exercise protocols. Adding a stress such as physical exertion may help to select such a variable [23]. Our hypothesis is that the decrease in RV afterload after several weeks of PAH-specific treatment leads to an improvement in right ventriculoarterial coupling, expressed by an SVI increase at rest and its capacity to further increase during physical efforts. Our findings are in line with the 2015 ERS/ESC guidelines for the diagnosis and treatment of pulmonary hypertension emphasizing the importance of assessing the risk of

death in individual patients [3]. No side effects occurred during exercise as part of right heart catheterization. However, due to cardiovascular limitation, some patients were unable to complete their exercise test and were, therefore, excluded from the analysis. In some patients, pulmonary artery wedge pressure could not be obtained during exercise.

Limitations of the Study

This study has several limitations. First, the sample size is small, and, therefore, all results must be confirmed in larger studies. However, the size is comparable to that of other studies in this field [9, 10, 18]. Second, exercise hemodynamics during right heart catheterization was performed with a single workload. Although, this simple test may be less accurate, the burden of such a test is less important compared to a stepwise incremental exercise test protocol [9]. Third, because of a small size, our study did not allow to determine the prognostic value of hemodynamic variables at the follow-up visit. Fourth, the study period is extended from 2006 to 2014, which could have led to significant changes in therapeutic strategies. However, it is important to mention that the 3 classes of drugs were available in 2005, and that initial oral combination therapy was started in our institution in 2015. It is important to keep in mind that our population is 67% female (n = 33), which is very similar to the French registry of pulmonary hypertension. Female predominance is usually observed in most PAH subgroups, particularly for idiopathic, heritable PAH and those associated with connective tissue disease [16]. Overall prognosis is better in women, and gender has, therefore, influenced our results on survival. The most likely hypothesis is an ability to preserve an adapted RV function in women, explained by the protective role of estrogens (anti-remodeling effects). On the other hand, testosterone could have pro-remodeling effects [24].

Despite these limitations, our study presents at least some strengths. First, we have a complete hemodynamic data set at baseline, and, second, no patient was lost to follow-up for the survival analysis. Again, although the number of patients is small and the number of deaths limited, our results are consistent with previously published studies and emphasize the importance of exercise measurements in predicting prognosis [23]. The small size also explains why right atrial pressure, CI, and mixed venous oxygen saturation measured at diagnosis were not significantly associated with survival in our study. However, this reinforces the discriminating role at the individual level of exercise measurements. Finally, although the variables of interest highlighted in our study were obtained invasively, it seems possible to obtain at least part of them by noninvasive tests.

Conclusions

At the time of diagnostic of PAH, the possibility of increasing HR and sPAP during submaximal exercise were indicators of better long-term survival. The fact that exercise SVI increased inversely with the decrease in RV afterload after few months of PAH-specific treatment is compatible with an improvement in right ventriculoarterial coupling under treatment. Our results stress the value of exercise hemodynamic measurements in predicting prognosis of PAH patients, which would warrant more studies in this area.

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Statement of Ethics

Our data collection and analysis methods were approved by CNIL on May 24, 2003 (approval No. 842063). All patients gave written informed consent to undergo a right heart catheterization with an exercise test.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to declare.

Author contributions

M.F. and A.C.: study design and development/data analysis, and interpretation/writing the paper/final approval of the submitted version; S.V. and F.C.: study design and development/data analysis, and interpretation/writing the paper/final approval of the submitted version; M.Z.: study design and development/writing the paper/final approval of the submitted version; O.S.: study design and development/final approval of the submitted version; L.P.: writing the paper/final approval of the submitted version; and A.G., E.G., O.H., and C.S.-S.: data analysis and interpretation/final approval of the submitted version.

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