

Pulmonary Arterial Hypertension in France

Results from a National Registry

Marc Humbert, Olivier Sitbon, Ari Chaouat, Michèle Bertocchi, Gilbert Habib, Virginie Gressin, Azzedine Yaici, Emmanuel Weitzenblum, Jean-François Cordier, François Chabot, Claire Dromer, Christophe Pison, Martine Reynaud-Gaubert, Alain Haloun, Marcel Laurent, Eric Hachulla, and Gérald Simonneau

Service de Pneumologie, Centre des Maladies Vasculaires Pulmonaires, Hôpital Antoine Bécère, Assistance-Publique-Hôpitaux de Paris, Université Paris-Sud, Clamart, France; Service de Pneumologie, Hôpital Hautepierre, Strasbourg; Service de Pneumologie, Hôpital Louis-Pradel, Lyon; Service de Cardiologie, Hôpital de la Timone; Service de Pneumologie, Hôpital Sainte Marguerite, Marseille; Actelion Pharmaceuticals France, Paris; Service de Pneumologie, Hôpital de Brabois, Vandoeuvre-les-Nancy; Service de Chirurgie Thoracique, Hôpital du Haut Levesque, Bordeaux; Département Médecine Aiguë Spécialisée, Hôpital Michallon, Grenoble; Service de Pneumologie, Hôpital Laennec, Nantes; Service de Cardiologie, Hôpital Pontchaillou, Rennes; and Service de Médecine Interne, Hôpital Claude Huriez, Lille, France

Rationale: Pulmonary arterial hypertension (PAH) is an orphan disease for which the trend is for management in designated centers with multidisciplinary teams working in a shared-care approach.

Objective: To describe clinical and hemodynamic parameters and to provide estimates for the prevalence of patients diagnosed for PAH according to a standardized definition.

Methods: The registry was initiated in 17 university hospitals following at least five newly diagnosed patients per year. All consecutive adult (≥ 18 yr) patients seen between October 2002 and October 2003 were to be included.

Main Results: A total of 674 patients (mean $\pm$ SD age, 50 ± 15 yr; range, 18–85 yr) were entered in the registry. Idiopathic, familial, anorexigen, connective tissue diseases, congenital heart diseases, portal hypertension, and HIV-associated PAH accounted for 39.2, 3.9, 9.5, 15.3, 11.3, 10.4, and 6.2% of the population, respectively. At diagnosis, 75% of patients were in New York Heart Association functional class III or IV. Six-minute walk test was 329 ± 109 m. Mean pulmonary artery pressure, cardiac index, and pulmonary vascular resistance index were 55 ± 15 mm Hg, 2.5 ± 0.8 L/min/m², and 20.5 ± 10.2 mm Hg/L/min/m², respectively. The low estimates of prevalence and incidence of PAH in France were 15.0 cases/million of adult inhabitants and 2.4 cases/million of adult inhabitants/yr. One-year survival was 88% in the incident cohort.

Conclusions: This contemporary registry highlights current practice and shows that PAH is detected late in the course of the disease, with a majority of patients displaying severe functional and hemodynamic compromise.

Keywords: cardiopulmonary hemodynamics; prevalence; pulmonary arterial hypertension registry; six-minute walk test

Pulmonary arterial hypertension (PAH) is characterized by remodeling of the small pulmonary arteries leading to a progressive increase in pulmonary vascular resistance and right ventricular failure (1–3). PAH can be idiopathic, familial, or associated with a number of conditions or diseases, such as connective tissue disease; congenital heart disease; portal hypertension; HIV infection; and exposure to toxins and drugs, including appetite suppressants (4). PAH is an orphan disease for which the trend is

for management in designated centers with multidisciplinary teams working in a shared-care approach (5).

Information relative to the natural history of PAH is derived from a national registry conducted in the United States in the early 1980s, where 187 patients with primary pulmonary hypertension (corresponding to idiopathic PAH in the recent classification) were described and followed for up to 5 yr (6, 7). This study confirmed that “primary” pulmonary hypertension bears a poor prognosis, with a median survival of 2.8 yr after diagnosis (7). Significant medical advances have occurred in the last 15 yr that include a more systematic assessment of patients with objective parameters (e.g., 6-min walk test and acute vasodilator challenge) and availability of new treatments (e.g., prostacyclin, endothelin receptor antagonists, and type 5 phosphodiesterase inhibitors) (8, 9). Prompted by the rapid evolution of knowledge in the field of PAH and the absence of multicenter registry since the 1980s, the French Reference Center for Pulmonary Arterial Hypertension (Hôpital Antoine Bécère, Clamart, France) set up a French Network on Pulmonary Arterial Hypertension in 2000. This network initiated a national prospective registry to collect data on patients with PAH in the modern era and to describe the evolution of PAH during a 3-yr follow-up. In this article, we report data at the time of diagnosis of PAH from the 674 patients who have been entered in the registry, provide an estimate for the prevalence and incidence of PAH in the adult French population, and describe 1-yr survival in the incident cohort of patients.

METHODS

This clinical research network consisted in 17 French university hospitals following at least five newly diagnosed patients per year, according to a standardized diagnostic approach for PAH. The registry was opened in 2002. All consecutive adult (≥ 18 yr of age) patients with PAH seen in these centers between October 2002 and October 2003 were to be included. This registry was set up in agreement with the Commission Nationale de l'Informatique et des Libertés, the organization dedicated to information technology and civil rights in France. All patients gave informed consent to be entered in the registry.

PAH was defined as the presence of a mean pulmonary arterial pressure greater than 25 mm Hg at rest and a pulmonary artery wedge pressure less than 15 mm Hg at right heart catheterization (6). Our goal was to assess a homogeneous population; therefore, patients with known severe pulmonary function abnormalities (defined as pulmonary function test results for FVC, total lung capacity, or FEV₁ < 60%) were excluded because they are prone to develop another type of pulmonary hypertension secondary to chronic respiratory diseases (4). In agreement with the recent clinical classification (4), PAH was classified as idiopathic, familial, or associated with anorexigen exposure, connective tissue disease, congenital heart disease, portal hypertension, or HIV infection. Newly diagnosed patients (incident cases) were those for whom diagnosis was first made during the recruitment phase of the

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Correspondence and requests for reprints should be addressed to Pr. Marc Humbert, M.D., Ph.D., Centre National de Référence de l'Hypertension Artérielle Pulmonaire, UPRES EA 2705, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Bécère, Assistance Publique-Hôpitaux de Paris, Université Paris-Sud, 157 rue de la Porte de Trivaux, 92140 Clamart, France. E-mail: marc.humbert@abc.aphp.fr

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registry (October 2002–October 2003). Patients with a known diagnosis of PAH were those for whom diagnosis had been established before enrollment in the registry (prevalent cases). Date of diagnosis corresponded to that of confirmatory right heart catheterization. Acute vasodilator challenge was performed during right heart catheterization with inhaled nitric oxide or intravenous prostacyclin as previously described (10, 11). A positive vasodilator response was defined as a reduction of mean pulmonary arterial pressure of greater than 10 mm Hg leading to a value less than 40 mm Hg, with a normal or high cardiac output (8, 11, 12).

Statistics and 1-yr Survival Analysis

Quantitative variables were described using mean, SD, median, minimum, and maximum. For the comparisons between two groups, quantitative data were analyzed using Student's *t* test. For multiple comparisons, quantitative data were analyzed using analysis of variance or Kruskal-Wallis nonparametric tests. Qualitative variables were described by the usual measures (frequencies and percentages) and analyzed using χ^2 tests or Fisher's exact test ($n < 5$). The significance level was set at $p = 0.05$. Statistics were performed using SAS software (version 8; SAS Institute, Cary, NC). Incidence and prevalence of PAH were calculated as the ratio of newly diagnosed or all patients and the total French adult population as per the latest demography survey performed in 2002.

None of the 121 incident cases included in the registry were lost to follow-up, and 1-yr survival could be assessed in this population. We also compared survival observed in the subset of 56 incident idiopathic, familial, or anorexigen-associated PAH with the expected survival calculated for each patient based on the National Institutes of Health (NIH) formula (7).

RESULTS

Study Population

A total of 674 cases of PAH were included in the registry. The national reference center (Hôpital Antoine Bécère, Clamart) contributed 64% of the study population ($n = 431$). Clinical and hemodynamic data at the time of diagnosis are shown in Table 1. The female/male sex ratio was 1.9. The mean ($\pm$ SD) age of

patients enrolled was 50 ± 15 yr and was similar for women and men. A significant proportion of the population was older than 70 yr at the time of diagnosis (9.1%). Distribution of patients according to age and sex is shown in Figure 1. Body mass index (BMI) was normal (24.4 ± 5.5). A BMI above 30 was observed in 14.8% of the cases, a proportion similar to that of the adult French population (13).

In the whole cohort of patients, delay between onset of symptoms and diagnosis was 27 mo, and a majority of patients had severe symptoms at presentation, with 75% in New York Heart Association (NYHA) functional class III or IV (1% in class I, 24% in class II, 63% in class III, and 12% in class IV). Exercise capacity (Table 2) had been evaluated at the time of diagnosis in 548 patients (82.2%) through a 6-min walk test, which was abnormal in most patients (as low as 60 and 55% of reference values for men and women, respectively) (14). Six-minute walk distance correlated with NYHA functional class (Table 2) in all forms of PAH except for HIV-associated PAH, possibly due to the small size of the subgroup (Figure 2).

Right heart catheterization was available in 649 patients (96%) at the time of diagnosis. Of the 25 patients for whom hemodynamic data were not available at the time of diagnosis, 18 underwent right heart catheterization at enrollment in the registry, and the remaining seven patients with congenital heart diseases were diagnosed by echocardiography only. Results are shown in Tables 1–4, demonstrating a severe hemodynamic compromise, which correlated with clinical severity assessed with NYHA functional class. Acute vasodilator challenge was performed in 551 patients (85.6%) with inhaled nitric oxide (95.8%), intravenous prostacyclin (2.4%), or both (1.8%). As previously described (8, 11), the rate of acute vasodilator response was low (5.8%), slightly higher in NYHA functional class I or II patients (9.8%), as compared with patients in functional class III (4.8%) or IV (3.0%). Data at diagnosis for patients followed in the reference center and for patients followed in the other centers are shown in Table 3.

TABLE 1. CLINICAL AND HEMODYNAMIC DATA AT THE TIME OF DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION

	All Cases (<i>n</i> = 674)	Incident Cases (<i>n</i> = 121)	Prevalent Cases (<i>n</i> = 553)	<i>p</i> Value*
Clinical data				
Female patients, %	65.3	57.0	67.1	0.035
Age, yr (range)	50 ± 15 (18–85)	53 ± 17 (19–85)	50 ± 14 (18–82)	0.06
NYHA III–IV, %	75	81	73	0.08
6-min walk distance, m	329 ± 109	312 ± 114	333 ± 108	0.09
Hemodynamic data				
RAP, mm Hg	8 ± 5	8 ± 5	8 ± 5	< 0.0001
mPAP, mm Hg	55 ± 15	49 ± 14	56 ± 15	
PAWP, mm Hg	8 ± 3	8 ± 3	8 ± 3	
Cardiac index, L/min/m ²	2.5 ± 0.8	2.4 ± 0.9	2.5 ± 0.8	
SvO ₂ , %	63 ± 9	63 ± 8	63 ± 9	
PVRI, mm Hg/L/min/m ²	20.5 ± 10.2	19.2 ± 9.3	20.7 ± 10.4	
Disease subtype, %				
Idiopathic (<i>n</i> = 264)	39.2	40.5	38.9	
Familial (<i>n</i> = 26)	3.9	2.5	4.2	
Connective tissue diseases (<i>n</i> = 103)	15.3	18.2	14.6	
Congenital heart diseases (<i>n</i> = 76)	11.3	4.1	12.8	
Portal hypertension (<i>n</i> = 70)	10.4	14.9	9.4	
Anorexigens (<i>n</i> = 64)	9.5	3.3	10.8	
HIV infection (<i>n</i> = 42)	6.2	9.9	5.4	
Two coexisting risk factors (<i>n</i> = 29)	4.3	6.6	3.8	

Definition of abbreviations: mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PAWP = pulmonary arterial wedge pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SvO₂ = venous oxygen saturation. Data expressed as mean $\pm$ SD unless otherwise indicated.

* Comparisons are for incident versus prevalent cases of pulmonary arterial hypertension.

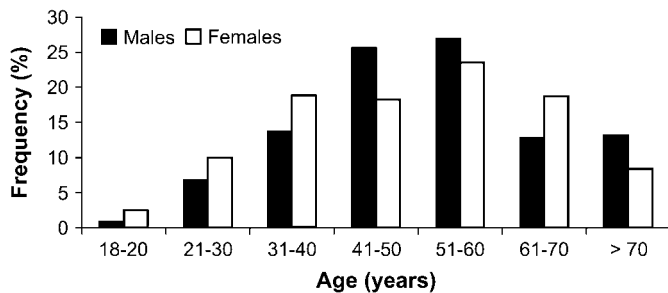


Figure 1. Distribution of patients with pulmonary arterial hypertension according to age based on sex.

Subgroups of PAH

The distribution of patients across the various types of PAH is given in Table 1. More than half of enrolled patients (52.6%) presented with idiopathic (39.2%), familial (3.9%), or anorexigen-associated PAH (9.5%). Connective tissue diseases, congenital heart diseases, portal hypertension, and HIV infection corresponded to 15.3, 11.3, 10.4, and 6.2% of the population, respectively. Among connective tissue diseases, systemic sclerosis and systemic lupus erythematosus were the leading causes, representing 76 and 15% of the cases, respectively. Two-thirds of the systemic sclerosis cases were limited forms, and one-third were diffuse forms. Twenty-nine patients (4.3%) displayed two coexisting conditions known to be associated with PAH. HIV infection and portal hypertension were the most common coexisting conditions ($n = 13$). Other associations consisted in appetite-suppressant exposure in patients with congenital heart diseases ($n = 4$), systemic sclerosis ($n = 4$), HIV infection ($n = 3$), or portal hypertension ($n = 2$). Connective tissue diseases could coexist with portal hypertension ($n = 2$) or HIV infection ($n = 1$).

Clinical and hemodynamic data at diagnosis for each subgroup of PAH are displayed in Tables 4 and 5. Irrespective of the PAH subtype, a majority of the patients were diagnosed in NYHA functional class III or IV, even in the setting of diseases such as systemic sclerosis, congenital heart diseases, or portal hypertension, where screening for PAH using Doppler echocardiography may be performed (9). The proportion of responders to acute vasodilators was low and mainly restricted to idiopathic and anorexigen-associated PAH.

A history of anorexigen exposure was found in 9.5% of patients with PAH; 77% of cases corresponded to fenfluramine derivatives. Duration of exposure to fenfluramine derivatives ranged from 1 to 300 mo; 15.3% were exposed for less than 3 mo, 19.4% were exposed from 3 to 6 mo, 36.1% were exposed from 6 to 12 mo, and 29.2% were exposed for more than 12 mo. Delay between last appetite suppressant intake and the first symptoms of pulmonary hypertension was within 2 yr of exposure in 24.2% of cases, 2 to 5 yr in 32.3%, and more than 5 yr in 43.5%.

Incident versus Prevalent Cases of PAH

One hundred twenty-one patients (18%) were diagnosed during the recruitment period and enrolled immediately (incident cases). The remaining patients had a known diagnosis of PAH before the opening of the registry (prevalent cases). Mean delay between diagnosis and enrollment was of 66 ± 86 mo. Clinical and hemodynamic data for incident versus prevalent cases are summarized in Table 1.

Prevalence and Incidence

Based on the 674 PAH cases in our registry, the low estimate of prevalence in France is of 15.0 cases/1 million adult inhabitants. The low estimate of prevalence for idiopathic PAH is 5.9 cases/1 million inhabitants. Regional prevalence was evaluated according to the region where the patients lived. A wide range of PAH regional prevalence was observed, from 5 to 25 cases/1 million adult inhabitants. In 2002–2003, the low estimate of PAH incidence was 2.4 cases/1 million adult inhabitants/yr.

One-Year Survival

One-year survival was 88.4% in the whole incident group ($n = 121$) and 89.3% in the group of 56 incident patients with idiopathic, familial, and anorexigen-associated PAH. This survival compared favorably with the estimated 1-yr survival calculated with the NIH equation (71.8%) (7).

DISCUSSION

The present registry represents the largest population of patients with PAH since the availability of a novel diagnostic classification of the condition and the development of disease-specific therapies, allowing an updated description of this orphan disease in the Western world. In 1981, the National Heart, Lung, and Blood Institute of the NIH created a national registry of patients

TABLE 2. SIX-MINUTE WALK DISTANCE AND HEMODYNAMIC PARAMETERS ACCORDING TO NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS AT DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION

	NYHA I-II	NYHA III	NYHA IV	p Value
6-min walk test				
n	134	359	55	
Distance, m	415 $\pm$ 86	319 $\pm$ 92	192 $\pm$ 96	< 0.0001
Percentage of reference values				
Male patients	68.1 $\pm$ 14.1	58.8 $\pm$ 14.7	36.5 $\pm$ 17.9	< 0.0001
Female patients	67.9 $\pm$ 22.2	53.9 $\pm$ 16.4	34.1 $\pm$ 15.8	< 0.0001
Hemodynamic parameters, n	162	405	77	
RAP, mm Hg	6 $\pm$ 4	9 $\pm$ 5	11 $\pm$ 7	< 0.0001
mPAP, mm Hg	50 $\pm$ 17	56 $\pm$ 15	56 $\pm$ 13	0.0002
PAWP, mm Hg	8 $\pm$ 3	8 $\pm$ 3	8 $\pm$ 4	0.75
Cardiac index, L/min/m ²	2.9 $\pm$ 0.9	2.4 $\pm$ 0.7	2.1 $\pm$ 0.8	< 0.0001
SvO ₂ , %	67 $\pm$ 8	62 $\pm$ 8	54 $\pm$ 9	< 0.0001
PVRI, mm Hg/L/min/m ²	15.8 $\pm$ 9.7	21.5 $\pm$ 9.8	25.1 $\pm$ 10.1	< 0.0001

For definition of abbreviations, see Table 1.

Data expressed as mean $\pm$ SD.

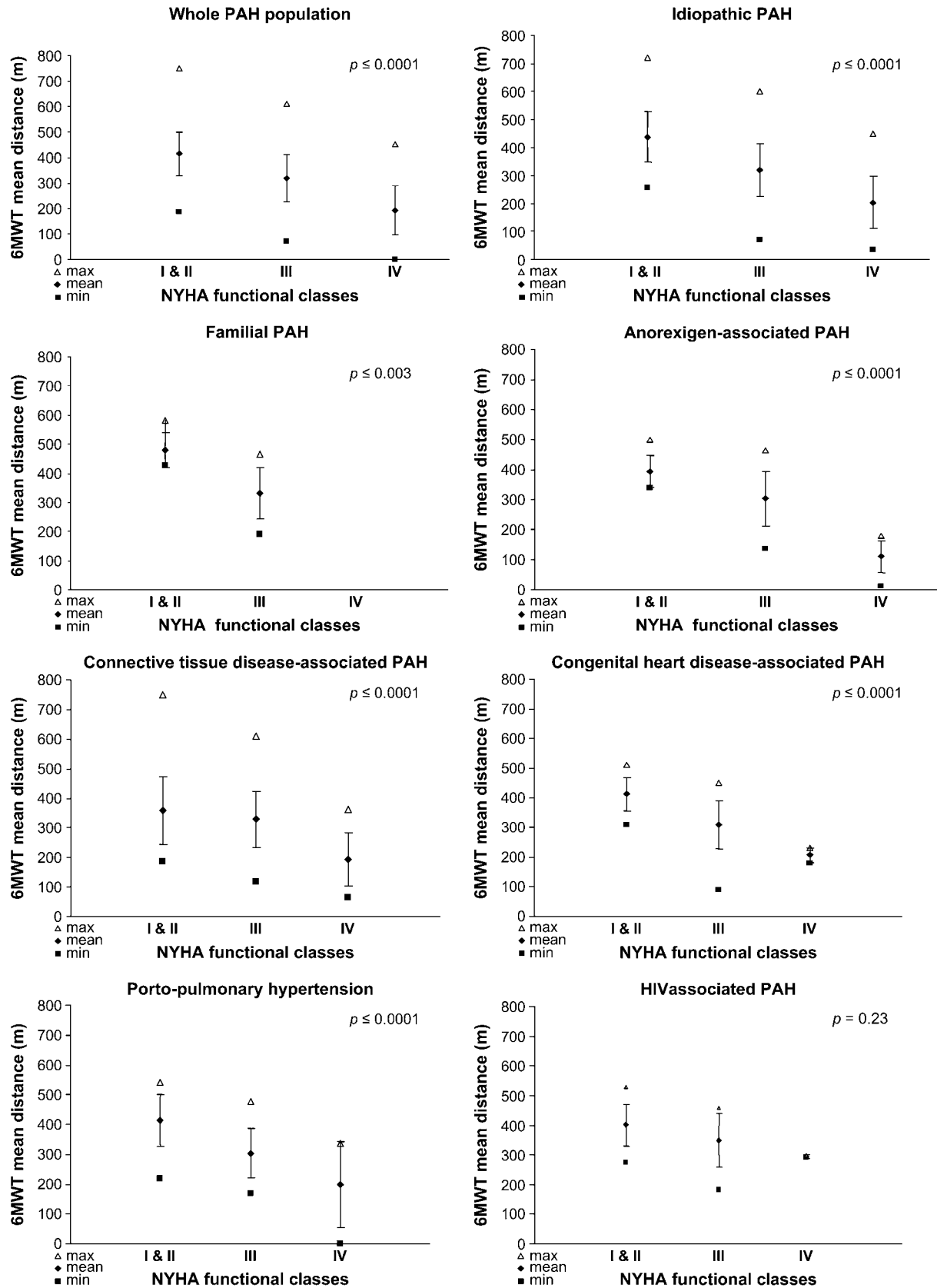


Figure 2. Six-minute walk distance according to New York Heart Association (NYHA) functional class in the whole pulmonary arterial hypertension (PAH) population and in the different subgroups of patients. Data are presented as mean $\pm$ SD. 6MWT = 6-min walk test.

TABLE 3. CLINICAL AND HEMODYNAMIC DATA AT THE TIME OF DIAGNOSIS FOR PATIENTS FOLLOWED AT THE REFERENCE CENTER AND IN THE OTHER CENTERS

	Reference Center (n = 431)	Other Centers (n = 243)	p Value
Clinical data			
Females, %	65.4	65	0.92
Age, yr	49 ± 14	53 ± 16	< 0.0001
NYHA III–IV, %	77.1%	70.2%	0.051
6-min walk distance, m	329 ± 102	330 ± 126	< 0.98
Pulmonary arterial hypertension subtype, n (%)			
Idiopathic	175 (40.6)	89 (36.6)	
Familial	20 (4.6)	6 (2.5)	
Connective tissue diseases	50 (11.6)	53 (21.8)	
Congenital heart diseases	40 (9.3)	36 (14.8)	
Portal hypertension	48 (11.1)	22 (9.1)	
Anorexigens	39 (9.0)	25 (10.3)	
HIV infection	36 (8.4)	6 (2.5)	
Two risk factors	23 (5.3)	6 (2.5)	
Hemodynamic parameters			
RAP, mm Hg	8 ± 5	8 ± 5	
mPAP, mm Hg	57 ± 15	50 ± 15	< 0.0001
PAWP, mm Hg	7.7 ± 3.2	8.3 ± 3.6	0.03
Cardiac index, L/min/m ²	2.6 ± 0.8	2.4 ± 0.8	0.003
SvO ₂ , %	63 ± 9	62 ± 10	0.35
PVRI, mm Hg/L/min/m ²	21 ± 10	20 ± 10	0.23

For definition of abbreviations, see Table 1.

Data expressed as mean ± SD.

with “primary” pulmonary hypertension (6, 7). By the time the registry closed in 1987, 187 patients were included, leading to major advances in the understanding of this rare condition. In the last 20 yr, it has become recognized that several conditions and diseases could be associated with PAH and that they shared similar pathologic and clinical features with “primary” pulmonary hypertension (4). In addition, disease-specific therapies are now available that allow improved quality of life, exercise capacity, and survival (8). Thus, it seemed timely to propose a novel registry that included all cases of PAH referred to pulmonary vascular centers in a given country. In our present registry, 674 adult patients (121 novel “incident” cases and 553 known “prevalent” cases; see Table 1) were included in a 1-yr period in France, with approximately half idiopathic, familial, and anorexigen-associated cases and half associated with various diseases, emphasizing increasing awareness and knowledge of this condition with better identification and characterization of cases. Familial cases represented 3.9% of the population. There were no distinc-

tive features of familial PAH, as compared with idiopathic PAH, with the exception of less severe clinical impairment at first presentation (no class IV and better walk test at diagnosis), although hemodynamic compromise was similar to that of idiopathic cases (Tables 4 and 5, Figure 2).

Prevalent cases of PAH correspond to survivors; this may therefore poorly represent PAH as a whole (the most severe patients being lost in the prevalent subgroup). To check whether there were significant differences between prevalent cases and incident cases when they were first evaluated, we compared clinical and hemodynamic parameters in both groups. At initial presentation, prevalent and incident cases had similar clinical and hemodynamic presentation (Table 1). This registry shows that despite advances in understanding and treating PAH, and presumably better awareness, patients are still diagnosed with a severe clinical impairment. Indeed, 75% of patients are identified when dyspnea can be classified in NYHA functional class III or IV. Accordingly, hemodynamic characteristics of this population

TABLE 4. HEMODYNAMIC DATA OBTAINED BY RIGHT HEART CATHETERIZATION AT DIAGNOSIS FOR EACH SUBTYPE OF PULMONARY ARTERIAL HYPERTENSION

Subgroup of Pulmonary Arterial Hypertension (n = 649)	RAP (mm Hg)	mPAP (mm Hg)	PAWP (mm Hg)	CI (L/min/m ²)	SvO ₂ (%)	PVRI (mm Hg/L/min/m ²)	Acute Vasodilator Responders (%)
Idiopathic (n = 259)	9 ± 5	56 ± 14	8 ± 3	2.3 ± 0.7	61 ± 10	22.8 ± 10	10.3
Familial (n = 26)	7 ± 4	61 ± 12	8 ± 3	2.3 ± 0.7	63 ± 9	24.7 ± 8.5	0
Associated with one risk factor (n = 336)							
Connective tissue diseases (n = 97)	8 ± 6	45 ± 14	8 ± 3	2.5 ± 0.7	63 ± 8	16.5 ± 8.8	2.6
Congenital heart diseases (n = 66)	6 ± 4	68 ± 18	7 ± 4	2.7 ± 1.1	68 ± 8	26.0 ± 15.2	3.3
Portal hypertension (n = 69)	8 ± 5	52 ± 14	8 ± 4	2.9 ± 1.0	65 ± 7	16.8 ± 8.1	1.6
Anorexigens (n = 63)	9 ± 5	56 ± 12	8 ± 4	2.5 ± 0.7	63 ± 9	20.0 ± 8.3	6.8
HIV infection (n = 41)	9 ± 6	49 ± 11	7 ± 3	2.7 ± 0.7	60 ± 8	17.2 ± 6.6	0
Associated with two risk factors (n = 28)	9 ± 5	49 ± 15	8 ± 3	3.0 ± 1.0	64 ± 8	15.3 ± 8.4	0

Definition of abbreviations: CI = cardiac index; mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PAWP = pulmonary arterial wedge pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SvO₂ = venous oxygen saturation.

Data expressed as mean ± SD.

TABLE 5. CLINICAL DATA OBTAINED AT DIAGNOSIS FOR EACH SUBGROUP OF PULMONARY ARTERIAL HYPERTENSION

Subgroup of Pulmonary Arterial Hypertension	Males (%)	Females (%)	Age (yr)*	NYHA III–IV (%)	6-min Walk Distance (m)*
Idiopathic	37.9	62.1	52 ± 15	80.5	328 ± 112
Familial	30.8	69.2	37 ± 11	69.2	368 ± 103
Associated with one risk factor					
Connective tissue diseases	20.4	79.6	56 ± 15	73.8	315 ± 111
Congenital heart diseases	32.9	67.1	39 ± 14	64.4	337 ± 91
Portal hypertension	60.0	40.0	52 ± 12	64.3	340 ± 110
Anorexigens	6.3	93.7	57 ± 11	78.1	289 ± 120
HIV infection	54.8	45.3	42 ± 8	81.0	364 ± 88
Associated with two risk factors	37.9	62.1	48 ± 11	62.1	348 ± 107

* Data expressed as mean ± SD.

are identical to those reported in the 1980s in the registry of the NIH (6). More than 80% of incident cases with PAH in 2002–2003 were in NYHA functional class III or IV with a marked hemodynamic impairment (Table 1), showing no improvements in patients' severity at first presentation, as compared with prevalent cases detected in the previous years. Because baseline NYHA functional class is a recognized predictor of outcome in PAH, this information indicates that awareness is insufficient in the field of PAH. One may hypothesize that because of the availability of oral drugs in treating PAH, less specialized centers may delay referral to pulmonary vascular centers. However, at the time of the French registry, sildenafil therapy was not approved in France for PAH, and bosentan therapy had just been approved for PAH in NYHA functional class III with restricted prescription to respiratory, cardiology, or internal medicine specialists. In 2002, there was no difference between the date of initial diagnosis and the referral to the specialty center between patients who were treated with oral drugs versus those who were not. Whether this is the case at present remains to be tested. A recent unpublished analysis of epoprostenol, treprostinil, iloprost, and bosentan prescription indicates that, in 2004, more than 95% of French epoprostenol-, treprostinil-, and iloprost-treated patients were treated in a center contributing to this registry, as compared with two-thirds of French bosentan-treated patients.

The 6-min walk test is a submaximal exercise test that can be performed by patients incapable of tolerating maximal exercise testing (15). It is straightforward, safe, and reproducible and does not require expensive equipment. The distance walked in 6 min has a strong independent association with mortality in idiopathic PAH (15, 16). The present registry is the first to extensively describe objective exercise capacity by means of 6-min walk test in a large multicenter population. Absolute value and percentage of theoretic values were used, highlighting an objective impairment of exercise capacity in this population (14). Our data also indicate that the 6-min walk test results correlate with NYHA functional class in all forms of PAH (Figure 2). Last, we show that incident cases had severe exercise limitation, confirming no improvement in patients' severity at first presentation, as compared with prevalent cases (Table 1).

Our registry confirms the female predominance in most subtypes of PAH including idiopathic, familial, anorexigen-, connective tissue disease-, and congenital heart disease-associated cases. PAH associated with portal hypertension or HIV infection were characterized by a moderate male predominance, presumably reflecting the epidemiology of portal hypertension and HIV infection in France. This registry also underlines that PAH may develop at all ages, with a quarter of cases occurring after the

age of 60, and that the condition may be first detected in patients in their 80s (Figure 1).

The use of anorexigens (mainly aminorex and fenfluramine derivatives) was associated with an increased risk of PAH in studies performed in Europe and North America (17–20). Our report is the first addressing the issue of anorexigen-related PAH in France since the withdrawal of fenfluramine derivatives in 1997. Of the patients included in the registry in 2002–2003, 11.4% had a history of anorexigen intake (alone or in the context of another condition known to be associated with PAH); a majority of cases were related to fenfluramine derivatives. This proportion was 3% in incident cases in 2002–2003, more than 5 yr after fenfluramine derivatives were withdrawn from the French market (Table 1). As previously indicated by Abenhaim and colleagues (19), obesity was not a confounding factor explaining appetite suppressant exposure in our population because the distribution of BMI was similar in patients with idiopathic and anorexigen-associated PAH, a proportion similar to that of the adult French population (13). Duration of exposure and delay between last anorexigen intake and the first symptoms of PAH varied markedly between cases, indicating that anorexigen-associated PAH could be described even after short exposures of less than 3 mo and a long time after last anorexigen intake.

Systemic sclerosis was the leading cause of PAH among connective tissue diseases. In systemic sclerosis, the occurrence of PAH is known to have a major impact on outcome and survival (21–23). Because more than 10% of patients with systemic sclerosis develop PAH, it is recommended that early identification of this complication be obtained by means of a systematic echocardiography-based screening program (9, 24). When such strategies are widely applied, it is likely that larger numbers of PAH will be reported, thus increasing prevalence of this condition. Similarly, congenital heart diseases were underrepresented in the present registry performed in pulmonary vascular centers. This presumably reflects the fact that these patients have a relatively stable course and that they are rarely referred to pulmonary vascular centers, unless they require to be listed on a heart–lung transplantation program or treated with complex specific PAH therapies, such as continuous intravenous epoprostenol. Thus, we assume that only a subset of patients with systemic sclerosis or congenital heart diseases with PAH was followed in pulmonary vascular centers in France in 2002–2003.

PAH can complicate the course of HIV infection (25, 26) and portal hypertension (27, 28). It represents a significant cause of mortality in these populations (25, 27, 28). Improved awareness should lead to increased referral to pulmonary vascular centers to initiate specific management (25–28). Two risk factors were identified in 4.3% of patients included in this registry, the most common being the coexistence of HIV infection and portal

hypertension, presumably because of shared behavioral risks. Despite the fact that our registry was begun at a time when awareness was presumably supported by the recent availability of novel therapeutic strategies, a large majority of patients presented with severe hemodynamic impairment. Because one of the centers contributed 64% of all of the patients (French referral center), we compared patients referred to this hospital with patients followed in regional university hospitals (Table 3). This comparison indicated that patients from the French referral center were slightly more severe in terms of NYHA functional class and hemodynamic parameters. Hemodynamic impairment correlated with NYHA functional class and 6-min walk distance in all subgroups of patients. In addition, this large multicenter registry confirmed that acute responders to vasodilator challenge represented a small minority of patients and that acute responders mainly belonged to idiopathic and anorexigen-associated subtypes of PAH. Because acute vasodilator challenge identifies patients who may benefit from calcium channel blocker therapy, this study confirms that these agents are useful only in a small minority of patients presenting with PAH (8, 11). Less than 20% patients were on chronic calcium channel blocker therapy when first referred to the national referral center or to one of the university hospitals. Thus, some patients with a good response to calcium channel blocker therapy may have been treated empirically in the community and never referred in such expert centers, and the rate of long-term responders to calcium channel blocker therapy might be underestimated (11).

This registry was conducted in a network of pulmonary vascular centers, allowing the calculation of a low estimate of PAH prevalence of 15.0 cases/1 million adult inhabitants. We believe that awareness is insufficient, as demonstrated by marked differences in regional prevalence, ranging from 5 to 25 cases per 1 million inhabitants, while these populations are homogeneous and that the French Network on Pulmonary Arterial Hypertension has connections in all French regions. This indicates that many patients are unidentified or not referred to specialized centers. Not all patients are referred to pulmonary vascular centers, especially in the context of associated conditions such as congenital heart disease or systemic sclerosis. In addition, availability of oral drugs may lead to late referral to pulmonary vascular centers, as suggested by the fact that most if not all epoprostenol-treated patients were followed in a pulmonary vascular center, although this was the case of only two-thirds of bosentan-treated patients. Thus, the incidence/prevalence data we present are likely underestimated and represent a lower estimate.

In conclusion, this contemporary registry provides novel information on PAH. This registry highlights current practice and data that are both similar and different from the NIH Registry in an era when treatment options are different from 20 yr ago (6, 7). It shows that PAH is still detected late in the course of the disease, with a majority of patients displaying severe functional and hemodynamic compromise. Novel strategies, such as systematic screening in an at-risk population, need to be tested to allow earlier management of this severe condition. Last, the contemporary nature of this report is of major importance, with novel medical strategies widely available. The 1-yr survival analysis of our incident cohort exceeds 88%. This observed survival compares favorably with the 71.8% estimated 1-yr survival calculated with the NIH equation. Whether modern management and novel treatment strategies (8) will yield a better prognosis will be evaluated in the ongoing 3-yr follow-up of this large patient cohort.

Conflict of Interest Statement: M.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.S. does not have a financial relationship with a commercial entity that has an interest

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