experimental and clinical data from patients with PAH of varied clinical presentations.

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Daniel Ranayhossaini, B.S.
Patrick J. Pagano, Ph.D.
Department of Pharmacology and Chemical Biology
University of Pittsburgh
Pittsburgh, Pennsylvania
and
Vascular Medicine Institute
University of Pittsburgh
Pittsburgh, Pennsylvania

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Evolving Epidemiology of Pulmonary Arterial Hypertension

Epidemiology, the science of diseases in populations, views a disease through the prism created by an aggregate of incidence, prevalence, demographics, and outcomes. The product of a high-quality epidemiological survey is a rich phenotypic characterization of a disease. Far from a dry science, epidemiology offers a dynamic portrait of the "beast," pulmonary arterial hypertension (PAH). Although there are no large prospective epidemiologic studies of PAH, the longitudinal study by Ling and colleagues in this issue of the *Journal* (pp. 790–796) is a significant contribution (1). Conducted at all eight PAH centers in the United Kingdom (UK) and Ireland between 2001 and 2009, their report contributes to the understanding of evolving epidemiology of PAH. Their evaluation of a treatment-naive, incident cohort allows confident determination that the epidemiology of PAH is indeed changing.

World Health Organization (WHO) category I pulmonary hypertension (PH) (PAH) is defined as mean pulmonary artery pressure $>$ 25 mm Hg with a pulmonary capillary wedge pressure (PCWP) $<$ 15 mm Hg. It includes idiopathic and familial PH, as well as PH associated with conditions such as collagen vascular disease, congenital shunts, portal hypertension, anorexigens, HIV, hemoglobinopathies, and schistosomiasis. The diagnosis of PAH is largely a diagnosis of exclusion (i.e., excluding categories 2–5 PH) (2). WHO category 2 PH is defined as mean pulmonary artery pressure $>$ 25 mm Hg with a PCWP $\geq$ 15 mm Hg, and it includes PH due to left heart failure with preserved or reduced ejection fraction, restrictive cardiomyopathies, and valvular heart disease (2).

Recent registry data suggest that the epidemiology of PAH has changed dramatically over the past three decades. The patients in the landmark National Institutes of Health (NIH) registry conducted in the 1980s were predominantly young (mean age of 36 at presentation) and female (1.7:1) and had idiopathic, familial, or anorexigen-associated PAH (3). Their 1-, 3-, and 5-year survival were 67, 45, and 37%, respectively (4). Modern PAH registries include the REVEAL registry (multicenter U.S.-based registry), the pulmonary hypertension connections

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TABLE 1. CHARACTERISTICS OF PAH REGISTRIES

PH Registry	Date of Enrollment	Sample Size	PH Population (%)	Age (*Mean* ± *SD*)	Female (%)	Incident Cases (%)	Incidence (*cpm/yr*)	Prevalence (*cpm*)	Treatment Status on Enrollment (%)	Mortality at 1 yr (%)	Mortality at 5 yr (%)
NIH registry (3)	1981–1988	194	IPAH FPAH Anorexigen	36 ± 15	62.5	64	NA	NA	No PAH-specific therapies available	32	66
PH connection (6)	1982–2006	578	IPAH: 44 CTD: 30 CHD: 11 Portal HTN: 7 Anorexigen: 3 FPAH: 4 HIV: 1	48 ± 14	77	14	NA	NA	ERA: 3 PDE-5 Inh: 0.8 Prostacyclin: 2	16	42
French registry (7)	2002–2003	674	IPAH: 39.2 CTD: 15.3 CHD: 11.3 PHTN: 0.4 Anorexigen 9.5 FPAH: 3.9 HIV: 6.2	50 ± 15	65	15*	2.4	15	ERA: 43 PDE-5 Inh: 7 Prostacyclin: 23	17	42
REVEAL Registry (5)	2006–2007	2525	IPAH: 46.2 CTD: 25.3 CHD: 9.9 Portal HTN: 5.3 Anorexigen 5.2 FPAH: 2.9 HIV: 1.9	53 ± 14	80	14	NA	NA	ERA: 47 PDE-5 Inh: 49 Prostacyclin: 42	9	43
PAH registry in China (8)	1999–2004	72	IPAH: 94.4 FPAH: 5.6	36 ± 12	71	NA	NA	NA	No PAH-specific therapies available	32	79
PAH registry in UK and Ireland (1)	2001–2009	482	IPAH: 92.9 FPAH: 5.4 Anorexigen 1.7	50 ± 17	70	100	1.1	6.6	ERA: 44 PDE-5 Inh: 29 Prostacyclin: 18	7	40

Definition of abbreviations: CHD = congenital heart disease; cpm = cases/million adults; CTD = connective tissue disease; ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; HIV = human immunodeficiency virus; HTN = hypertension; IPAH = idiopathic pulmonary arterial hypertension; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PDE-5 Inh = phosphodiesterase 5 inhibitor; PH = pulmonary hypertension; PHTN = pulmonary hypertension; SD = standard deviation.

*Based on IPAH population.

(PHC—single-center U.S.-based registry), and the French national registry (5–8) (Table 1). Compared with the NIH registry, patients enrolled in these registries were older (mean age at presentation ranging from 48 to 53 yr) and had better survival rates in the modern era (9–11). However, the contemporary cohorts were predominated by *prevalent* cases of PAH (~85%). Overrepresentation of *prevalent* cases, who have survived for reasons including intrinsic variation in disease lethality and/or the effects of therapy, could potentially introduce survivor bias. In contrast, Ling and colleagues' treatment-naive, incident cohort should provide a more accurate estimate of what a newly diagnosed PAH patient might expect, in terms of death and disability. Although the PHC and the French registry addressed this question, the paucity of true incident cases of idiopathic, familial, and anorexigen-associated PAH patients in these registries (14 and 15%, respectively) limits the robustness of their conclusions.

The centralization of the diagnosis and management of PAH patients in the UK and Ireland to eight designated PAH referral centers, starting in 2001, provided the opportunity to study true incident cohort. Ling and colleagues wisely used this opportunity to define the epidemiology of 482 treatment-naive, incident cases of idiopathic, familial, and anorexigen-associated PAH and determine whether there was indeed a change in the disease characteristics over the decade of their study.

The mean age at the time of diagnosis in this incident cohort was 50 years, similar to the other contemporary PAH registries. Based on age, they identified two PAH subtypes: the younger group, with age at diagnosis < 50 years, and the older group, with at age at diagnosis ≥ 50 years. Compared with the younger group, older patients had a greater delay between onset of symptoms and diagnosis, poorer functional capacity, and more comorbidities (systemic hypertension, diabetes, obesity, and ischemic heart disease). The presentation of patients also varied by age (more edema in older patients vs. more syncope and presyncope in the younger group). The older group had less severe PAH by hemodynamic criteria (i.e., lower mean pulmonary artery pressure and pulmonary vascular resistance) but had worse outcomes. The difference in the phenotypic manifestation between the young and the old patients persisted even when the data were divided into quartiles based on the age at presentation, confirming a true biological relationship. These findings confirm and extend the observation of an earlier study by Shapiro and colleagues (12). Ling and coworkers also confirm that the epidemiology of PAH is evolving rapidly. Patients diagnosed with idiopathic, familial, and anorexigen-associated PAH in the UK and Ireland during 2007–2009 were more likely to be of the older subtype when compared with those diagnosed during 2001–2003.

As in the other modern registries, the NIH equation did not accurately predict survival in this UK–Irish registry, confirming that the epidemiology of PAH has changed over the past three decades. The risk predication equations derived from both REVEAL and the PHC accurately predicted survival in this UK–Irish registry. In contrast, the French equation for mortality in incident cases underestimated survival in this UK–Irish registry.

Several intriguing questions remain unanswered. When patients > 50 years of age with several coexisting comorbidities for left heart disease are diagnosed to have WHO group 1 PH (PAH), this rests on an accurate measurement of PCWP < 15 mm Hg. Are these patients truly a different phenotype of group 1 PH, or are they a form of group 2 PH (pulmonary venous hypertension associated with preserved ejection fraction)? The differentiation between these two entities is important because the underlying mechanism and therapeutic implications are different. The diagnosis often turns on a single measurement of the PCWP, and this measurement is fraught with error. First, it can be difficult to obtain an accurate PCWP in the presence of intrinsic pulmonary vascular disease (13, 14). Second, the PCWP can sometime be discrepant from the left ventricular end diastolic pressure (LVEDP) (15). The common practice of using the digitally measured mean PCWP, instead of the end-expiratory PCWP, can significantly underestimate LVEDP (16). In cases where patients with proven pulmonary venous hypertension develop severe right ventricular failure, PCWP can be <15 mm Hg (17). Recent analysis from our group suggests that when an elderly patient presents with pulmonary hypertension and comorbidities for left heart disease such as hypertension, diabetes, obesity, and coronary artery disease, it is more likely to reflect pulmonary venous hypertension than PAH (18). Ideally, LVEDP should be measured at the time of diagnosis to ensure that the post "A-wave" pressure is <15 mm Hg. Otherwise, with an aging cohort of PAH patients with prevalent hypertension and diabetes, there will be misclassification of group 2 PH as group 1. Classification drift would be problematic because of the much higher prevalence of group 2 PH (2, 19). In addition, the therapies for group 1 and 2 PH differ. Pulmonary vasodilator therapy, which forms the cornerstone for group 1 therapy, can potentially increase PCWP in patients with group 2 PH. Moreover, key drugs approved for group 1 PH are either ineffective (endothelin antagonists) or harmful (prostanoids) in patients with group 2 PH associated with reduced left ventricular function (20, 21). The role of approved PAH drugs in group 2 PH associated with preserved left ventricular function is currently unclear.

Future epidemiologic studies should include hemodynamic and functional data (including LVEDP) to differentiate the aging group 1 PH cohort from group 2 PH patients. In the meantime, this useful report reminds us that the face of PAH has changed and alerts physicians to carefully considerer group 1 PH in patient over age 50 who present with dyspnea or impaired exercise tolerance.

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Thenappan Thenappan, M.D.
John J. Ryan, M.B.B.Ch.
Stephen L. Archer, M.D.
University of Chicago
Chicago, Illinois

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