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Epidemiology of pulmonary hypertension in the elderly

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1 Introduction

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC).[1] It can be due to a primary elevation of pressure in the pulmonary arterial system alone (pulmonary arterial hypertension), or secondary to elevations of pressure in the pulmonary venous and capillary systems (pulmonary venous hypertension). PH can be a progressive, fatal disease if untreated, although the rate of progression is highly variable.

The clinical classification of PH is intended to categorize multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, and haemodynamic characteristics.[2,3] Pulmonary arterial hypertension (PAH) describes group 1, while pulmonary hypertension (PH) describes group 2 through group 5.

Group 1: PAH. PAH is a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance (PVR) > 3 Wood units, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases.[1] It consists of sporadic idiopathic PAH (iPAH), heritable PAH (also known as familial PAH), and PAH associated (aPAH) with drugs and toxins, connective tissue diseases (CTD), human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), and schistosomiasis.[3]

Group 2: PH due to left heart disease (PH-LHD). PH due to LHD is characterized PH associated with an elevated left atrial and pulmonary venous pressure. PH due to left ventricular (LV) systolic or diastolic dysfunction, valvular heart disease, inflow/outflow tract obstruction, congenital cardiomyopathies and pulmonary veins stenosis are included in this group.[3]

Group 3: PH due to lung diseases and/or hypoxia. PH due to lung diseases and/or hypoxemia includes PH due to chronic obstructive pulmonary disease (COPD), interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, and other conditions associated with hypoxemia.[3] The underlying lung disease in this group as a whole is usually severe.

Group 4: chronic thromboembolic PH (CTEPH) and other pulmonary artery obstructions. Chronic thromboembolic PH is due to chronic thromboembolic occlusion of the proximal or distal pulmonary vasculature. Pulmonary hypertension in this group has the potential for improvement or cure with pulmonary thromboendarterectomy.

Group 5: pulmonary hypertension with unclear and/or multifactorial mechanisms. Pulmonary hypertension with unclear and/or multi-factorial mechanisms included patients with PH caused by chronic hemolytic anemia [e.g., sickle cell disease (SCD), beta-thalassemia, or spherocytosis], myeloproliferative disorders, systemic disorders (e.g., sarcoidosis), metabolic disorders (e.g., glycogen storage disease), chronic kidney disease, or miscellaneous causes. PH is, in general, an uncommon manifestation of these disorders.

2 Incidence and prevalence

The true prevalence of PH in the general population is unknown, likely because of the broad classification and multiple etiologies. In rare diseases, such as PAH, registries provide important information about the epidemiology, baseline characteristics and outcomes of the disease. In some of the earlier registries, definition and assessment of PAH were not standardized, numbers were small, and a significant number of patients did not have RHC to confirm the diagnosis.[4,5] Although PAH was a rare disease and tra-

ditionally considered to affect young women, it is now known that PAH affects all age groups as well as both genders.

The epidemiology of PH varies among the five groups. Best studied is group 1 PAH; idiopathic and familial PAH (fPAH) is rare in the general population and estimated to be 5 to 15 cases per one million adults.[6,7] In registries, around half of PAH patients have idiopathic, heritable or drug-induced PAH.

Data about the true prevalence of PH in the elderly are more limited. Registries have provided information about the epidemiology of elderly patients in the last ten years. The diagnosis and management of PAH has undergone significant changes since the National Institutes of Health (NIH) conducted the first registry of iPAH in the early 1980s. According to NIH registry, less than 10% of patients were older than 60 years and the mean age of patients was 36 ± 15 years.[8] PAH is now more frequently diagnosed in elderly patients, resulting in a mean age at diagnosis between 50 ± 14 and 65 ± 15 years in current registries.[9] It is unclear whether elderly patients diagnosed with PH have the same epidemiologic characteristics as younger patients.

Data from current registries and studies associated with epidemiology of PAH in elderly are discussed below: (1) the American surveillance organ of PH has clearly shown the evolution of frequency in the diagnosis of any kind of PH among hospitalized patients who were 65 years and older. Since 1995, the increase was determined particularly among patients older than 85 years. Between 1990 and 2002, the prevalence of PH diagnosis increased by 3.4 times in older than 65 years.[10]

(2) Results from a National Registry in France [674 patients newly and previously diagnosed as PAH (age: 50 ± 15 years)] confirmed the increasing proportion of elderly patients at the time of diagnosis with 12.8% patients older than 65 years.[6] Idiopathic (the most common type), familial, anorexigen, CTD, CHD, portal hypertension, and HIV-associated PAH accounted for 39.2%, 3.9%, 9.5%, 15.3%, 11.3%, 10.4%, and 6.2% of this population, respectively.

(3) Multi-center observational US-based REVEAL (Registry Early and Long-term PAH Disease Management) included 2525 adults showed that the mean age at diagnosis was 53 ± 14 years and nearly 17% of the patients with PAH were over 65 years.[11] 46.2% iPAH, 2.7% fPAH and 50.7% aPAH patients (subgroups: 19.5% CHD, 49.9% CTD, 10.6% portal HT, and 10.5% drugs/toxins) were diagnosed.

(4) Results from the Pulmonary Hypertension Registry of the United Kingdom and Ireland showed that the median age at diagnosis of PAH was 50 years, with 13.5% of incident cases in patients aged ≥ 70 years.[7] A total of 482 patients (93% idiopathic, 5% heritable, and 2% anorexigen-associated PAH) were diagnosed, giving rise to an estimated incidence of 1.1 cases per million per year and prevalence of 6.6 cases per million in 2009.

(5) To SPANISH Registry, 866 patients with PAH (mean age 45 ± 17 years) and 162 (mean age 61 ± 15 years) with CTEPH were included. Estimated prevalence were as follows: PAH, 16 and CTEPH, 3.2 cases per million and incidences were as follows PAH, 3.7 CTEPH 0.9 cases per million per year, respectively.[12] Mean age of patients with CTEPH was highest (61 ± 15 years). iPAH was the most common diagnosis (30%). Among patients with aPAH, CTD, scleroderma, was the most common diagnosis (61%) and had second highest mean age range (54 ± 15 years).

(6) In ASPIRE (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre) registry included 1344 patients with PH (Group 1–5), the mean age at diagnosis was 59 ± 17 years with 44% aged > 65 years.[13] Assuming a stable referral population of 15 million, between 2001 and 2009, the incidence of patients diagnosed as PAH increased from 0.9 to 6.1, iPAH from 0.3 to 2.1, PAH-CTD from 0.3 to 2.4 and CTEPH from 0.3 to 3.7 cases per million per year. The most common disease in all of patients was group 1 PAH (44.5%) and the most common subgroups, in Group 1 PAH, were CHD (33%) and CTD (31%). Among patients with PH (Group 2–5), CTEPH was diagnosed the highest percentage (32.5%). The highest age range was 69 ± 10 years in the patient diagnosed as WHO group 2 PH. Among patients with group 1 PAH, the highest age range was 66 ± 9 years in the patient diagnosed as scleroderma.

(7) COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) was a prospective registry completed in 28 centers in six European countries. 2654 patients were included this registry. 71% of all patients had PAH, 29% had non PAH-PH. Only the patients accepted as PAH were detailed evaluated. 65% of patients with PAH had iPAH and 56.8% of patients with aPAH had CTD. The patients diagnosed as iPAH divided into two groups, namely younger and elderly (≥ 65 years). This registry found 63% of patients in a cohort of iPAH were aged ≥ 65 years.[14] The median age at diagnosis was 71 years. 98% of elderly patients with PAH had iPAH.

Results of above mentioned registries showed that PAH was now more frequently diagnosed in elderly patients, compared NIH Registry. Proportions of elderly patients were 63% (highest, COMPERA), 44% (ASPIRE), 13.5% (UK, Ireland), 17% (REVEAL), and 12.8% (French), in chronological order. COMPERA is latest registry. When it was considered the dates of these registries, the prevalence

of elderly patients with PH was observed to be increasing over time. Current registries, except ASPIRE, showed that iPAH was most common type. In addition, among the patients with aPAH, scleroderma was most frequent diagnosis and the elderly patients with scleroderma were older than others. In ASPIRE registry evaluated all PH types, it was seen the patients with PH-LHD had highest age range.

These registries were not designed to evaluate exclusively elderly patients. Among these registries, data associated with elderly patients were commented by way of comparison with younger patients in only COMPERA. The current registries, except ASPIRE, evaluated the patients with only PAH.[6,7,11,12] Although patients belonging to groups 2 and 3 represent an important part of the clinical practice, especially in elderly patients, there is disproportionately little information about the epidemiology from current literature. In brief, a detailed description of the causes of PH (group 1-5) in elderly patients is lacking.

To investigate the causes of PH in the elderly, several studies evaluated exclusively elderly patients were designed in recent years. In one of these studies, Shapiro, *et al*.[15] compared elderly (age > 65 years) *vs*. younger patients with clinically suspected iPAH (n = 197). The elderly patients represented 24% of the patients, however, most of these patients (56%) did not meet standard hemodynamic criteria for PAH [pulmonary artery wedge pressure (PAWP) ≥ 15 mmHg]. Thus, they may have had another cause for PH, especially LHD. These patients evaluated as suspected iPAH had a normal ejection fraction (EF), and no left-sided valve. Elevated estimated systolic pulmonary artery pressure (sPAP) by echocardiography and increased left ventricular diastolic pressures are common in elderly patients, and PH associated with heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized cause of PH in older adults. Shapiro, *et al*.[15] suggested 56% of elderly patients may have Group 2 PH.

In another study, Pugh, *et al*.[16] evaluated exclusively elderly patients (n = 246, ≥ 65 years, mean age, 72.9 years) referred for evaluation of PH. WHO group 2 PH was the most frequent diagnosis (28%) while 17% had mixed group, known as 2/3 PH, that was disproportionate to the underlying cardiopulmonary disease. Only 15% of 246 elderly patients had PAH. Most PAH (78%) was associated with CTD (OR: 27.2; 95% CI: 9.5–77.6). Pugh, *et al*.[16] concluded that WHO group 2 PH and secondly mixed disease were common causes of PH, while PAH was an uncommon cause of PH and most frequently associated with CTD.

The results of these studies[15,16] disagree with results of above mentioned registries.[6,7,11–14] Left heart disease is believed to be the most common cause of PH in general population,[17] however the true prevalence of PH-LHD is unclear because of a lack of a standard definition. According to results of latest registry named COMPERA evaluated elderly, iPAH was most common type.[14] One might argue that many of patients of COMPERA could have been misclassified as iPAH while they in fact had other causes, such as LHD, lung disease, or chronic thromboembolic disease. Nevertheless, these patients provided all the hemodynamic criteria for pre-capillary PH in COMPERA. Most of the participating centers have not routinely performed volume or exercise challenge during RHC, so that it might have missed some patients with LV diastolic dysfunction. One should also be cautious about possible misclassifications between PAH and non-PAH (particularly with HFpEF), which may occur, particularly in elderly patients as a consequence of uncertainties in the current definitions and difficulties in the measurement of the PAWP.[9] Also, other national and international PAH registries ruled out Group 2 and 3 PH before confirming PAH diagnosis, but unfortunately, most of the registries did not mentioned fluid challenge, exercise testing or LV end diastolic pressure measurement by left heart catheterization. Such tests have not been standardized and normal values are lacking to provide a clear recommendation to clinicians, currently not recommended as part of the diagnostic work-up of patients. In addition, it has been suggested that patients with a diagnosis of PAH may present an abnormal increase in PAWP in response to fluid loading.[18] Consequently, it is possible that some patients with HFpEF might have been missed, even if the proportion of misdiagnosed patients cannot be estimated.

PH due to diastolic dysfunction may be more difficult to assess and diastolic dysfunction, despite being very common among the elderly, may have been itself relatively asymptomatic, dyspnea being unrecognized or considered as related to age.[19] In this condition, echocardiographic evaluations reveal left atrial enlargement, LV hypertrophy, or elevated filling pressure indices despite the latter reliability has recently been questioned.[20] HFpEF-PH is associated with various very frequent cardiovascular diseases and risk factors such as old age, female gender, systemic hypertension, coronary artery disease, diabetes mellitus, hypertrophic or restrictive cardiomyopathy, and obesity.[21] Interestingly, a cross-sectional study suggested that PAH and HFpEF-PH could be more accurately differentiated by using predictive modeling. Old age, the presence of hypertension and coronary heart disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output best differentiated PAH from HFpEF-PH.[21] Although no single variable can

can differentiate PH-LHD from pre-capillary PH, the presence of multiple risk factors and findings should raise suspicion for PH-LHD.[22]

3 Gender

One striking finding is the marked female preponderance in most of registries. NIH Registry reported showed female preponderance (64%) and female: male ratio, 1.8: 1.[8] The Surveillance of Pulmonary Hypertension in America registry, conducted from 1998 to 2001 in the United States, reported a female/male ratio: 4.3: 1.[10] The contemporary French[6] and Scottish[23] registries reflect a similar female preponderance and female: male ratio to that seen in the NIH registry (65% and 66%, respectively; female: male ratio, 1.9: 1). REVEAL registry has a higher female preponderance (79.5%) and demonstrates a 3.6: 1 female-to-male ratio among patients with iPAH, and a 3.8: 1 ratio among those with aPAH.[11] Spanish registry has 71% female preponderance in patents with PAH and 60% in patents with CTEPH.[12] Registry of the United Kingdom and Ireland showed a female preponderance (66.5%) in patients at age > 50 years.[7] ASPIRE registry had a female preponderance of 62%.[13] In COMPERA registry, younger patients showed a female-to-male ratio of 2.3: 1 whereas the gender ratio in elderly patients was 1.2: 1 (55% female).[14] It was observed that female predominance was quite variable among registries. It was emphasized in the previous section that the mentioned registries, except COMPERA, were not designed to evaluate exclusively elderly patients. According to results of latest registry named COMPERA evaluated elderly, men and women are almost equally affected. If results of COMPERA are considered, it can reach the conclusion that the ratio of male patients increased in recent years.

4 Risk factors

A number of risk factors for the development of PAH has been identified and are defined as any factor or condition that is suspected to play a predisposing or facilitating role in disease development. Risk factors were classified as definite, likely or possible, based on the strength of their association with PH and their probable causal role.[24] An etiological link between exposure to anorectic agents such as fenfluramine, dexfenfluramine as known definite risk factors and PH, which has been demonstrated between the 70 s and the 80 s.[25,26] Despite these molecules having been withdrawn from the market several years or even decades ago, benfluorex, a molecule that shares similar structural and pharmacological characteristics with anorectic agents, was widely prescribed until recently as an oral anti-diabetic, a class of treatment that is prone to be prescribed to elderly patients. Recent study suggests an etiological link between benfluorex and the development of PAH and mitral or aortic valvular diseases.[27] Data from the French registry showed that patients presenting benfluorex-related PAH ranged between 51 and 61 years.[6] The delay between first exposure and PAH diagnosis ranged between 5 and 12 years, suggesting that new incident cases can be expected in the next years, particularly in the elderly.[28]

5 Clinical characteristics and survival

A median survival of 2.8 years and the survival rates at 1 and 3 years were 68% and 48%, respectively, for patients with primary PH was documented in the NIH registry.[29] Whereas the data from the REVEAL registry suggest that patients with PAH with a profile similar to those in the NIH registry in the United States can expect a median survival time of > 7 years.[30] Kaplan-Meier survival estimates for the full REVEAL Registry cohort diagnosed after November 2001 were 85%, 68%, 57% and 49% at 1, 3, 5, and 7 years from diagnosis, respectively.[30]

Results from a National Registry in France showed that 1-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 anorexigenic-associated PAH. The estimated 1- and 3-year survival rates of the subgroup of patients with iPAH/fPAH/ anorexigenic-associated PAH for whom 3-year follow-up results were reported were 82.9% and 58.2%, respectively.[6]

Results from the Pulmonary Hypertension Registry of the United Kingdom and Ireland showed that older patients (age > 50 years) had longer duration of symptoms, more comorbidities, worse functional and exercise capacity, less severe hemodynamic impairment, but worse survival compared with younger patients. Younger patients (aged < 50 year) had better survival with 1-, 2-, 3-, and 5-year survival of 94.7%, 91%, 87.2%, and 74.7% compared with 1-, 2-, 3-, and 5-year survival of 90%, 75.5%, 57.1%, and 43.7% in patients aged more than 50 years.[7] In comparison with the earlier cohorts, patients diagnosed in 2007–2009 were older, more obese, and more comorbidities, but better survival.

In Spanish Registry, 1-, 3-, and 5-year survival were 87%, 75% and 65%, respectively.[12] ASPIRE registry showed that the 1- and 3-year survival rates were 88% and 68% for group 1, 90% and 73% for group 2, 65% and 44% for group 3, 89% and 71% for group 4 and 84% and 59% for group 5.[13] Compared with group 1, survival in group 3 was inferior and in group 4 was superior.

COMPERA showed following results:[14] At the time of diagnosis, older patients presented more often in functional class IV, had lower 6-minute walk test, higher PAWP and PVR and lower mean PAP. In the whole group (n = 587), all cause mortality was 18.4%. Mortality rate was 12.0% in the younger cohort and 22% was in the older one. For the whole group, the estimated survival rates 1, 2, and 3 years after diagnosis were 92.0%, 83.1% and 73.6%, respectively. The expected 1, 2 and 3-year survival rates for an age/gender matched population were 99.6%, 99.1% and 98.5% for the younger cohort and 96.5%, 92.8% and 88.9% for the elderly cohort, respectively. COMPERA Registry shows worse survival in elderly patients with iPAH. The limited response to medical therapy in the elderly and the lower survival rates may be explained in part by the observation that elderly patients were treated less aggressively, as evidenced by the reduced likelihood of receiving combination drug regimens compared to younger patients.

Shapiro, *et al*.[15] suggested that elderly patients were more likely to have cardiovascular disease, increased vascular and LV diastolic stiffness, and higher PAWP. Among patients with normal PAWP, elderly patients had worse survival (risk ratio, 1.5; confidence limits, 1.1 to 2.0), while among patients with an elevated PAWP, elderly patients had better survival (risk ratio, 0.6; confidence limits, 0.4 to 0.9).

Pugh, *et al*.[16] suggested that comorbid conditions were common in this elderly cohort, with cardiovascular and metabolic diseases seen most commonly in patients with WHO group 2 PH. WHO group 2 cohort, most patients had no significant valvular heart disease and a normal left ventricular ejection fraction (>50%).

Recent reports from contemporary registries suggested that the patients with PAH are now older[6,7,9–14] and show a increase proportion of male patients[14] and have better survival[6,7,13,14,30] and compared with patients from the first registry.[29] The reasons for the increase in the mean age of patients with iPAH in clinical trials are not clear. This may be related to increased use of echocardiography in the elderly, increases in the age of the population with patients surviving other diseases such that their PH becomes manifestation, or increased physician willingness to refer elderly patients for consideration of a growing number of less complicated PH therapies. In addition, elderly patients show worse clinic and hemodynamic characteristics and survival compared younger patients.[7,14,15] The poorer survival in the elderly may reflect the greater prevalence of cardiovascular disease in the elderly, a different natural history of a "late-onset" variant of the iPAH, or that older patients have another disease, such as heart failure with secondary PH.

The progressive decline in lung function with normal aging has been demonstrated. The pulmonary vascular bed may be affected by age-related vascular stiffening. A decrease in left heart compliance is also observed, leading to progressive LV diastolic dysfunction. Because of these changes, sPAP show a significant age-related increase.[28] Age-related physiological changes of the cardiovascular and respiratory systems should be kept in mind when PH is suspected in the elderly. In fact, normal aging could either lead to an over-diagnosis of PH or an underestimation of PAH in this population. The main issue of PAH diagnosis in the elderly is to discriminate potential pulmonary vascular disease from the expected consequences of aging and from the frequent causes of PH secondary to left heart failure or lung disease.

6 Conclusions

Understanding the causes and characteristics of PH in elderly patients, particularly distinguishing between HFpEF and PAH, is very important for choosing appropriate PH therapies. The importance of appropriate diagnosis of PH in the elderly has major implications, given the cost of PAH therapies and the potential risks of these medications when used inappropriately. Therefore, it should be performed adequate evaluation and detailed haemodynamic investigation in the patients and, when needed, elderly patients with severe unexplained PH should be sent to expert centers.

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