Causes of Pulmonary Hypertension in the Elderly

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BACKGROUND: Pulmonary hypertension (PH) is common in elderly patients, but a detailed analysis of the causes of PH in the elderly has not been performed. We hypothesized that pulmonary arterial hypertension (PAH) is rare in elderly patients and sought to describe the characteristics of these patients at a large referral center.

METHODS: Clinical and hemodynamic data were collected on consecutive patients ≥ 65 years of age referred for evaluation of PH. The subtype of PH was determined after standard evaluation using the World Health Organization (WHO) classification. Patients with PH not meeting criteria for PAH with “out-of-proportion” PH related to group 2 or group 3 disease were classified as “other/mixed PH.” A model using age, presence of connective tissue disease, and left atrial size was developed to predict the probability of PAH diagnosis.

RESULTS: Two hundred forty-six elderly patients were evaluated (mean age, 72.9 ± 5.5 years, 78% women); 36 had PAH (15%). Idiopathic PAH was rare (four patients, 1.6%). WHO group 2 PH was the most frequent diagnosis ($n = 70$, 28% of cohort); mixed/other PH ($n = 43$, 17%) and WHO group 3 PH ($n = 34$, 14%) were also common diagnoses. Connective tissue disease strongly predicted PAH diagnosis (OR, 27.2; 95% CI, 9.5-77.6).

CONCLUSIONS: PAH is an uncommon cause of PH in elderly patients, most frequently associated with connective tissue disease. WHO group 2 PH and mixed disease are common, highlighting a need for careful phenotyping of elderly patients with PH prior to initiating PAH therapy.

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ABBREVIATIONS: HFpEF = heart failure with preserved ejection fraction; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PH = pulmonary hypertension; WHO = World Health Organization

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Pulmonary hypertension (PH) is increasingly recognized in the elderly population; however, the causes and characteristics of PH in the elderly population are not well established. Data from a multicenter observational US registry suggest that idiopathic pulmonary arterial hypertension (IPAH) has an older age at diagnosis compared with the National Institute of Health registry study performed in the 1980s, with nearly 17% of the cohort ≥ 65 years of age at the time of diagnosis in the last decade.¹⁻³ A report from a multinational European registry found 63% of patients in a cohort of IPAH were aged ≥ 65 years,⁴ and an analysis of incident cases of pulmonary arterial hypertension (PAH) in the United Kingdom and Ireland reported 13.5% of patients were diagnosed with PAH at age ≥ 70 years.⁵ Elderly patients (aged ≥ 65 years) represented 24% of the patients with presumed IPAH seen at one large center; however, most of these patients (56%) did not meet standard hemodynamic criteria for PAH (pulmonary capillary wedge pressure ≤ 15 mm Hg) and, thus, may have had another cause

for PH.⁶ Elevated estimated systolic pulmonary artery pressure by echocardiography and increased left ventricular diastolic pressures are common in elderly patients,⁷ and PH associated with heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized cause of PH in older adults.⁸ Understanding the causes and characteristics of PH in elderly patients, particularly distinguishing between HFpEF and PAH, is especially important for choosing appropriate PH therapies and evaluating the implications of PH registries and clinical trials.

A detailed description of the causes of PH in elderly patients referred for treatment of PH is currently lacking in the literature. We hypothesized that among elderly patients undergoing systematic clinical evaluation for PH, PAH (World Health Organization [WHO] group 1 PH) would be rare and that non-WHO group 1 PH would be more common. Here we describe the clinical and hemodynamic characteristics of a large cohort of patients aged ≥ 65 years referred for evaluation of PH at our center and develop a model to predict PAH in elderly patients.

Materials and Methods

Study Patients

This study was approved by institutional review board at Vanderbilt University Medical Center (protocol 110199). Consecutive patients aged ≥ 65 years at the time of initial visit to the Vanderbilt Pulmonary Vascular Center for evaluation of known or suspected PH between January 1995 and September 2011 were included. Only incident cases of PH are included in this cohort; patients with an established diagnosis of PH prior to age 65 years (prevalent PH cases) and those with established PH transferring care from another PH center were excluded. Patients underwent standard evaluation for PH according to published guidelines⁹ to determine the presence, severity, and cause of PH. Right-sided heart catheterization in addition to other standard testing (pulmonary function testing, chest imaging, ventilation-perfusion scanning, and echocardiography) was used to definitively determine the cause of PH in accordance with consensus guidelines.^{9,10} When indicated, provocative measures to diagnose diastolic dysfunction (rapid IV administration of 500 mL 0.9% normal saline as a “fluid challenge” or nitroprusside administration) or to determine vasoreactivity (inhaled nitric oxide at 40 parts per million) were performed during cardiac catheterization using standard protocols as previously reported.^{11,12} Relevant data from the medical record were collected and managed using RedCap (Research Electronic Data Capture), a secure, web-based application for translational research studies.¹³ Obesity was defined as a BMI ≥ 30 kg/m².

Definitions and Classification

PH was defined as mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. Patients not meeting this criterion were classified as “No PH.” WHO group 1 disease or PAH was defined as PH with a pulmonary artery occlusion pressure (PAOP) ≤ 15 mm Hg and exclusion of other causes of PH after standard evaluation.⁹ WHO group 2 disease (PH owing to left-sided heart disease) was defined as PH with a PAOP or left ventricular end-diastolic pressure > 15 mm Hg at baseline or an increase in PAOP > 7 mm Hg to > 15 mm Hg after IV fluid challenge.^{11,14} Patients with PH and clinically significant restrictive lung disease (total lung capacity $< 60\%$ predicted), obstructive lung disease (FEV₁/FVC $< 70\%$, FEV₁ $< 60\%$ predicted), or a diffusing capacity $< 60\%$ predicted with

more than mild lung disease seen on high-resolution chest CT scan received a diagnosis of WHO group 3 disease (PH owing to lung disease, hypoxia, or both). PH secondary to chronic thromboembolic disease was diagnosed according to published criteria¹²: patients in whom imaging (ventilation-perfusion scan or CT angiography followed by pulmonary angiography) demonstrated multiple perfusion defects in the presence of precapillary PH (mPAP ≥ 25 mm Hg, PAOP ≤ 15 mm Hg). Patients with more than one potential cause for PH (eg, a patient with total lung capacity $< 60\%$ predicted plus PAOP > 15 mm Hg with group 2 and group 3 PH) or those with evidence for group 2 or 3 disease with PH that was believed to be “out of proportion” (transpulmonary gradient ≥ 15 mm Hg) were classified as “other/mixed PH” for the purposes of this study. When evaluation for PH was incomplete, such that a definitive cause for PH could not be ascertained (ie, patient did not complete right-sided heart catheterization or declined full evaluation), patients were characterized as “unknown.” In each case, the diagnostic classification according to the previous criteria was completed by one of two PH specialists (I. M. R. and A. R. H.) during prospective clinical evaluation.

Statistical Analysis

Demographic data were presented as mean with 95% CI or percentages as appropriate. The Kruskal-Wallis test was used to compare differences between groups for continuous variables. To assess the difference in continuous variables between WHO group 1 PH and WHO group 2 PH, the Mann-Whitney *U* test was applied. Differences in categorical variables between groups were examined using a χ^2 test. Spearman rank correlation was used to examine correlations between age and hemodynamic variables. A logistic regression model was developed to predict the probability of PAH diagnosis using prespecified risk factors of age, connective tissue disease, and left atrial size (continuous variable in centimeters) by echocardiography. Both unadjusted and adjusted ORs were determined from this model with age, connective tissue disease, and left atrial size. We internally validated and calibrated the model using bootstrapping technique.¹⁵ All *P* values were two-sided, and a *P* value $< .05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics 19.0 (IBM), Prism 4.0 software (GraphPad Software, Inc), and statistical programming language R version 2.13.1 (R Development Team).

Results

There were 246 consecutive patients aged ≥ 65 years with a presumptive diagnosis of PH referred for evaluation at our center. The mean age at initial visit was 72.9 years (95% CI, 72.2-73.6 years), and 192 were women (78%).

Demographics and Causes of PH

Figure 1 shows the causes of PH in our elderly cohort after full evaluation. PH owing to left-sided heart disease (WHO group 2) was the most common type of PH in our cohort (70 patients, 28%). Patients with mixed/other PH included those with out-of-proportion group 2 PH ($n = 17$) and group 3 PH ($n = 9$), those with mixed group 2 and group 3 disease ($n = 12$), and others with miscellaneous causes of PH ($n = 5$). PAH (WHO group 1) was diagnosed in 36 patients (15%), and IPAH was rare, with only four patients meeting criteria for this diagnosis. Most PAH (28 of 36 patients, 78%) was associated with connective tissue disease. Table 1 shows the demographic and hemodynamic characteristics for the four most common causes of PH. Age, sex, BP, and 6-min walk distance were similar between groups. There was no significant difference in mPAP or cardiac index

between the four major causes of PH, although the mean pulmonary vascular resistance was different across groups and was significantly higher in patients with PAH compared with patients with WHO group 2 PH (Table 1). Comorbid conditions were common in this elderly cohort, with cardiovascular and metabolic diseases seen most commonly in patients with WHO group 2 PH (Table 2).¹⁶ PAH-specific therapies were used more commonly in WHO group 1 patients but were not restricted to this group (Table 3).

Clinical Predictors of WHO Group 1 PH Diagnosis

We fit a logistic model to predict the probability of WHO group 1 PH (PAH). We selected age, presence of connective tissue disease, and echocardiographic assessment of left atrial size to be included in the model based on clinical relevance. The unadjusted and adjusted ORs and 95% CIs for the three predictors' influence on the risk of PAH diagnosis are presented in Figure 2. Among the three predictors, presence of connective tissue disease (OR, 27.2; 95% CI, 9.5-77.6) met statistical significance at an α level of 0.05 in our adjusted model. The model has good discriminative ability for predicting risk of PAH, with the area under the receiver operating

Figure 1 – Causes of PH. This chart shows the final diagnoses of PH in this elderly cohort after complete clinical evaluation. PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

TABLE 1] Demographic Characteristics of the Most Common PH Groups

Characteristic	Group 1 PAH (n = 36)	Group 2 PH Owing to Left-Sided Heart Disease (n = 70)	Group 3 PH Owing to Lung Disease and/or Hypoxia (n = 34)	PH Due to Other or Mixed Disease (n = 43)	P Value
Age, y	71.4 ± 4.5	73.8 ± 9.1	72.6 ± 6.3	72.9 ± 5.9	.16
Women, No. (%)	31 (86)	58 (83)	23 (68)	32 (74)	.18
Systolic BP, mm Hg	123.7 ± 17.4	128.0 ± 20.6	124.7 ± 17.9	124.7 ± 18.3	.62
Diastolic BP, mm Hg	70.0 ± 10.7	67.6 ± 10.3	71.4 ± 10.6	65.7 ± 11.5	.08
Resting heart rate, bpm	80.3 ± 15.0	74.8 ± 15.4	82.2 ± 13.6	78.8 ± 15.8	.05
6-min walk distance, m	267 ± 109	272 ± 124	239 ± 116	212 ± 119	.11
Hemodynamic variables					
Right atrial pressure, mm Hg	6.9 ± 5.4	10.8 ± 5.5	9.0 ± 7.2	9.6 ± 5.8	.01
PA systolic pressure, mm Hg	74.4 ± 23.3	65.0 ± 22.3	66.3 ± 14.8	70.8 ± 20.7	.27
PA diastolic pressure, mm Hg	25.4 ± 8.5	21.7 ± 7.9	25.1 ± 6.7	25.1 ± 10.5	.29
Mean PA pressure, mm Hg	44.1 ± 13.3	38.8 ± 11.5	40.1 ± 7.8	41.3 ± 12.3	.48
PAOP, mm Hg	8.1 ± 4.8	18.3 ± 6.6	10.1 ± 5.1	14.1 ± 6.9	<.001
PA diastolic to PAOP gradient, mm Hg	17.5 ± 9.4	7.2 ± 6.4	17.3 ± 10.0	11.9 ± 10.8	<.001
Cardiac index, L/min/m ²	2.7 ± 0.8	3.1 ± 1.3	2.5 ± 0.7	3.0 ± 1.3	.20
PVR, Wood units	9.3 ± 5.1	4.7 ± 3.0	8.0 ± 5.6	6.2 ± 4.7	<.001
PA saturation, %	66.0 ± 9.3	67.4 ± 8.0	63.9 ± 11.0	67.8 ± 8.2	.42

Values are presented as mean ± SD unless otherwise noted. bpm = beats per min; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.

characteristic curve of 0.87 (95% CI, 0.8-0.93), as shown in Figures 3 and 4. Sensitivity and specificity for several cutpoints for the model are shown in Table 4. We used bootstrapping to validate and calibrate the fitted model. The apparent Somers Dxy was 0.73, and the bias-corrected Dxy was 0.71. The mean absolute calibration error was 0.03, and the 0.9 quantile of the absolute error was 0.05.

Discussion

Our results show that at a large referral center for pulmonary vascular disease, PH owing to left-sided heart disease (WHO group 2), mixed PH, and PH owing to lung disease, hypoxia, or both (WHO group 3) are the most common causes of PH in patients ≥ 65 years of age and that PAH is an uncommon cause of PH in this age group. We identified the presence of connective tissue disease as the major risk factor for a diagnosis of PAH in this elderly cohort with suspected PH. Our logistic model using age, echocardiographic-determined left atrial size, and diagnosis of connective tissue disease had good discriminative ability to predict the risk of PAH in elderly patients. Furthermore, we found that in many patients (17%), multiple causes of PH or out-of-proportion PH were identified, constituting a robust proportion of this elderly group with mixed PH. The rarity of PAH and IPAH in particular in patients ≥ 65 years of age has

relevance for tailoring appropriate diagnostic evaluation in this age group and underscores the critical need for careful phenotyping of patients in this age range prior to enrollment in PAH registries or clinical trials as well as initiation of PAH-specific therapy.

Elevation of estimated pulmonary arterial systolic pressure on echocardiography is a common finding in patients ≥ 65 years of age,⁷ and PAH registry information has suggested that the mean age of patients with PAH is increasing over time. In the 1987 National Institutes of Health registry, the mean age of patients with primary PH, now called IPAH, was 36 ± 15 years,³ whereas the IPAH subgroups in more recent registries from the United States and France show a mean age at diagnosis of 50 ± 15 years and 52 ± 15 years, respectively.^{2,17} The median age at diagnosis of idiopathic, heritable, and anorexigen-associated PAH was 50 years in a cohort from the UK and Ireland, with 13.5% of incident cases in patients aged ≥ 70 years.⁵ Several reports have highlighted potential differences in the characteristics of PAH in the elderly, including a higher PAOP,^{4,6} lower mPAP,^{4,18} more medical comorbidities,¹⁸ and lower female-to-male ratio of disease.⁴ Each of these studies sought to describe PAH in an elderly cohort, but the characteristics of alternative causes for PH in the elderly population have not been well described. Our cohort

TABLE 2] Medical Comorbidities of This Elderly Cohort

Comorbid Condition	Group 1 PAH (n = 36)	Group 2 PH Owing to Left-Sided Heart Disease (n = 70)	Group 3 PH Owing to Lung Disease and/or Hypoxia (n = 34)	PH Due to Other or Mixed Disease (n = 43)
Cardiovascular				
Systemic hypertension	14 (39)	55 (79)	18 (53)	26 (61)
Dyslipidemia	11 (30)	27 (39)	11 (32)	15 (36)
CAD/PVD	10 (27)	25 (36)	14 (41)	12 (29)
Atrial fibrillation	3 (8)	32 (46)	3 (9)	17 (41)
Metabolic				
Obesity	6 (16)	28 (40)	2 (6)	12 (29)
Diabetes mellitus	5 (14)	29 (41)	9 (27)	16 (38)
Metabolic syndrome ^a	4 (11)	24 (34)	4 (12)	9 (21)
Pulmonary				
COPD	5 (14)	11 (16)	17 (50)	14 (33)
Interstitial lung disease	3 (8)	0	16 (47)	8 (19)
OSA	4 (11)	27 (39)	3 (9)	9 (21)
Sarcoidosis	0	1 (1)	0	1 (2)
Rheumatologic				
Scleroderma	21 (58)	0	3 (9)	4 (9)
Rheumatoid arthritis	1 (3)	2 (3)	0	1 (2)
SLE	2 (6)	2 (3)	0	0
Other				
DVT/pulmonary embolus	1 (3)	5 (7)	3 (9)	6 (14)

Data are presented as No (%). CAD/PVD = coronary artery disease/peripheral vascular disease; SLE = systemic lupus erythematosus. See Table 1 legend for expansion of other abbreviations.

^aMetabolic syndrome¹⁶ defined as presence of three or more of the following conditions: obesity (BMI > 30 kg/m²), dyslipidemia, hypertension, insulin resistance, or diabetes mellitus.

includes all elderly patients referred for PH evaluation and demonstrates that despite registry data showing increasing age at diagnosis of PAH, incident PAH as a cause for PH in the elderly remains uncommon overall. This has significant impact for clinicians evaluating and treating these patients.

Our study aimed to classify the causes of PH in elderly patients referred to a specialized center for evaluation. We chose to define elderly patients as those > 1 SD

above the mean age of diagnosis of PAH from recent registries and, thus, used the age of ≥ 65 years. In our WHO group 2 cohort, most patients had no significant valvular heart disease and a normal left ventricular ejection fraction (> 50%) (ie, HFpEF). Prior work has suggested that pulmonary venous hypertension in HFpEF may be especially common in patients aged ≥ 65 years,⁷ and this may underlie the elevated frequency of this diagnosis in our cohort. The increased prevalence of features of the metabolic syndrome in this elderly cohort with WHO group 2 PH is consistent with previous observations.¹¹ As waist circumference and markers of insulin resistance were not measured in our cohort, metabolic syndrome may be underrecognized in this cohort. The high prevalence of patients with PH who were ultimately classified as out-of-proportion PH or more than one cause of PH (other or mixed PH) was not surprising, given the comorbidities in this cohort and prior publications from referral centers.^{11,19} This mixed group constitutes a particular diagnostic and therapeutic challenge, as it is unclear if PAH-specific

TABLE 3] Use of PAH Therapies

PH Type	ERA	PDE5-I	Prostaglandin
Group 1 (n = 36)	18 (50)	27 (75)	14 (39)
Group 2 (n = 70)	2 (3)	7 (10)	0
Group 3 (n = 34)	6 (18)	5 (15)	0
Mixed/other PH (n = 43)	6 (14)	23 (54)	6 (14)

Data are presented as No (%). ERA = endothelin receptor antagonist; PDE5-I = phosphodiesterase-5 inhibitor. See Table 1 legend for expansion of other abbreviations.

Figure 2 – Association of variables with PAH diagnosis. Plot of adjusted and unadjusted ORs for our logistic regression model predicting a diagnosis of PAH. Probability of WHO group 1 PH = $1/[1 + \exp(-X\beta)]$, where $X\beta = 6.42 - 0.0995(\text{age}) + 3.3(\text{CTD}) - 0.495(\text{left atrial size})$. CTD = 1 if CTD is present, 0 if CTD is not present. CTD = connective tissue disease; WHO = World Health Organization. See Figure 1 legend for expansion of other abbreviation.

therapy improves outcomes in this group. Although use of PAH-specific therapy was not common overall in non-group 1 PH, phosphodiesterase-5 inhibitors were commonly used in the mixed PH group. Although this mixed group is widely recognized among PH clinicians, there is no standardized definition, and consensus statements regarding identification and treatment of this

Figure 3 – Receiver operating characteristics curve for full model predicting WHO group 1 PH (PAH). AUC = area under the curve. See Figure 1 and 2 legends for expansion of other abbreviations.

Figure 4 – Receiver operating characteristics curve for the full model and individual variables predicting WHO group 1 PH (PAH). LA = left atrium. See Figure 1 and 2 legends for expansion of other abbreviations.

group are lacking. Additional study of these mixed patients is needed, especially as use of PAH-specific therapies in this group is not uncommon.

PAH was an uncommon diagnosis in this elderly population, occurring in 15% of the patients; IPAH was diagnosed in only four of 256 total patients (1.6%). Strengthening the observation that IPAH is unusual in this cohort, our logistic model confirmed that the presence of a connective tissue disease was the strongest predictor of the diagnosis of PAH. Accordingly, 78% of patients with PAH had associated connective tissue disease. Our predictive model had good discriminative ability for PAH and suggests that simple clinical variables (age, diagnosis of connective tissue disease, and left atrial size) may be used to risk stratify elderly patients for PAH. Although right-sided heart catheterization is

TABLE 4] Sensitivity and Specificity of the Model to Predict Risk of PAH

Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (%)	Negative Predictive Value (%)
0.15	71 (53-84)	88 (82-92)	51	95
0.40	68 (50-81)	92 (87-96)	60	94
0.50	58 (41-74)	94 (89-97)	63	93
0.60	42 (26-59)	97 (93-99)	72	91

See Table 1 legend for expansion of abbreviation.

required for definitive diagnosis of PAH, application of this model could potentially limit the need for more invasive testing in certain groups with low probability for PAH.

It is presently unknown if patients with PAH $\geq$ 65 years of age respond as well to PAH therapy as their younger counterparts; however, data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) have demonstrated that men $\geq$ 60 years of age with PAH have higher mortality than those $<$ 60 years,²⁰ and the publication from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA Registry) shows worse 1-, 2-, and 3-year survival in elderly patients with IPAH.⁴ Studies of PAH therapies in this age range will need to include careful phenotyping, perhaps with provocative maneuvers such as volume challenge or exercise during right-sided heart catheterization, given our findings of relative rarity of PAH in this cohort. Outside of clinical trials, 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.

There are several limitations to this study. First, it is retrospective analysis; however, the diagnostic classifications and evaluation was carried out in a prospective manner by treating clinicians. It is a single-

center study; however, the large number of patients completing rigorous evaluation strengthens the observations. As several patients in this cohort had echocardiography at outside institutions, we did not uniformly have other echocardiographic parameters that may also be useful in prediction of PAH including tricuspid annular plane systolic excursion and qualitative assessment of right ventricular function. These data do not shed light on the prevalence of PAH in the general population aged $\geq$ 65 years, as PAH, although uncommon, is likely overrepresented in our cohort because patients were screened by referring physicians and referred for suspicion of PAH. Last, our classification scheme included a mixed/other PH group, which is not uniformly agreed upon and lacks inclusion in current PH classification schema, although these patients with multiple potential causes for PH or out-of-proportion disease represent a common dilemma for specialists in this field.²¹

In conclusion, we found that the majority of patients aged $\geq$ 65 years referred for PH evaluation at our center have WHO group 2 PH, WHO group 3 PH, or mixed disease. PAH was a relatively rare diagnosis, and the presence of connective tissue disease was a strong predictor of PAH diagnosis. Further study of the outcome of PAH therapies in this age range outside that reported in modern registries is warranted and will need to focus on meticulously phenotyped patients.

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