Frequency, Predictors, and Prognostic Impact of Pulmonary Artery Aneurysms in Patients With Pulmonary Arterial Hypertension

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Detection of pulmonary artery aneurysms (PAA) in pulmonary arterial hypertension (PAH) is increasing. We sought to determine the frequency of PAA in a PAH cohort, variables related to its development and its prognostic impact. We conducted a retrospective analysis of PAH patients who underwent a computed tomography or magnetic resonance. PAA was defined as a pulmonary artery >40 mm. Baseline, echocardiographic, and hemodynamic findings at PAH diagnosis were compared. Freedom from death or lung transplant was estimated by Kaplan−Meier method and compared by log-rank test. Predictors of PAA development were analyzed with multivariate models. Two-hundred patients underwent a computed tomography and/or magnetic resonance. In 77 (38%), a PAA (48.3 ± 7.2 mm) was detected. Time-course (months) of PAH was an independent risk factor for PAA (hazard ratio 1.01; 95% confidence interval 1.002 to 1.019; p = 0.016) whilst connective tissue disease was associated with a lower risk (hazard ratio 0.236; 95% confidence interval 0.060 to 0.920; p = 0.037). PAA patients showed lower rates of death and lung transplant from PAH diagnosis (p = 0.005), but no differences appeared when survival analysis was performed from first imaging test (p = 0.269). PAA patients presented a nonsignificant higher rate of sudden death (5% PAA vs 1% no-PAA; p = 0.073). In conclusion, the frequency of PAA was 38%. PAH time-course was an independent risk factor for PAA development whereas connective tissue disease -related PAH patients showed a lower risk. PAA patients showed lower rates of death or lung transplant from PAH diagnosis but no differences were found from imaging test. PAA patients had a nonsignificant higher rate of sudden death. **(Am J Cardiol 2019;123:474−481)**

Pulmonary arterial hypertension (PAH) is a rare disease with an estimated prevalence of 15 to 26 cases per million.[1] In the last 20 years, the prognosis of PAH has improved due to the development of new therapies.[2] This improvement in survival has turned PAH into a chronic disease in a significant proportion of patients. As a consequence, several conditions related to PAH, which could determine patient's outcomes, have been identified.[3] Pulmonary artery aneurysm (PAA), defined as a main pulmonary artery (PA) diameter >40 mm,[4] has emerged as one of the above mentioned entities. PAA prevalence in PAH patients is unknown, probably due to its usual asymptomatic course. Hence, the reported frequency of PAA in PAH patients range from 1.3% to 24%.[5,6] Complications related to PAA have been described, such as PA thrombosis,[7] airway compression,[8] PA dissection,[9] severe pulmonary regurgitation,[10] and left main coronary artery compression.[11] The occurrence of these PAA-related complications may severely impact patient's prognosis.[12,13] In the present study, we aimed to determine the detection rate of PAA in a cohort of PAH patients. Likewise, we sought to describe potential predictors of PAA development as well as PAA prognostic implications.

Methods

We performed a retrospective cohort study of patients with PAH followed up at a national referral centre for PAH from 1984 to 2015. Inclusion of patients in our database was prospective from 2000 and retrospective before then.[2] Patients were evaluated and treated according to standard

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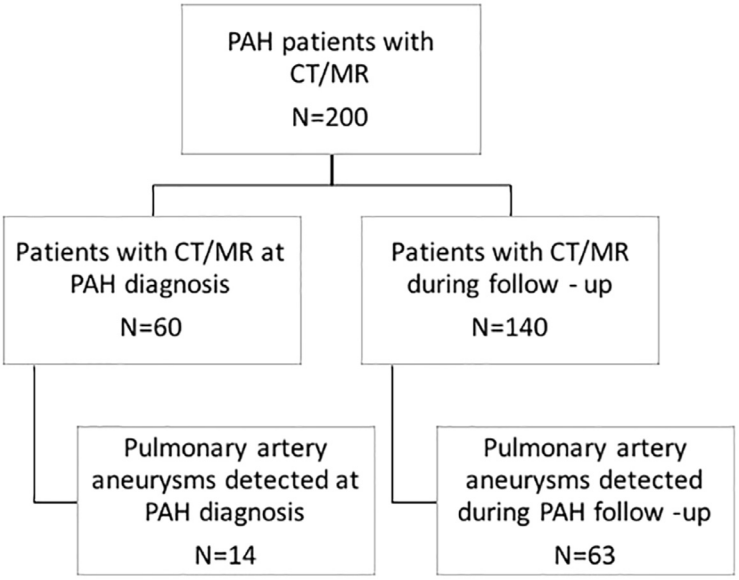

Figure 1. Study flowchart. CT = computed tomography; MR = magnetic resonance; PAH = pulmonary arterial hypertension.

recommendations at that moment[14] and the institutional protocol.[2] PAH was defined as an invasive mean pulmonary artery pressure ≥25 mmHg at rest, pulmonary capillary wedge pressure ≤15 mm Hg and a pulmonary vascular resistance ≥3 Wood Units.[14]

The study population was conformed by patients who underwent a high-resolution thoracic imaging technique (computed tomography [CT] or magnetic resonance [MR]), either shortly after PAH diagnosis (first 6 months after first right heart catheterization) or at any moment during follow-up (Figure 1).

The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

The first available thoracic high-resolution imaging test from the diagnosis of PAH was analyzed. Time-course of PAH was defined as the time between invasive diagnosis of PAH and imaging test performance.

From 2010, all patients underwent a CT at PAH diagnosis[14] as part of the institutional protocol. Before then, CT was performed based on the following indications: suspicion of parenchymal lung disease; symptoms suggesting intrathoracic complications (chest pain, hemoptysis, persistent cough, and atelectasis); ergometry positive for myocardial ischemia; suspected PAA on chest X-ray or echocardiography; protocol for lung transplantation.

MR was performed in selected cases to assess the presence of congenital heart disease, to evaluate right ventricular function before lung transplant, in cases with poor echocardiographic window or in patients with contrast media allergy.

Echocardiogram was performed to all patients on a yearly basis since PAH diagnosis. However, measurement of PA not included in echocardiogram protocol and so it was not included in the available reports.

PAA was defined as a main PA diameter >40 mm.[4] The widest PA diameter perpendicular to its long axis was measured with computer callipers at the level of the bifurcation.[15] Right and left pulmonary arteries diameters were measured at their widest portions, 2 cm before the branching of the lobar arteries.[15] Right and left pulmonary arteries diameter upper limits were established at 19.8 mm, and 22.1 mm respectively.[16]

Follow-up was established from PAH diagnosis until December 2015. Patients were regularly evaluated at the outpatient clinic according to protocol. Specific PAH treatment was chosen according to state-of-the-art recommendations.[14] Before the availability of these recommendations, treatment choice was established according to clinician's discretion and "best practice" at that time.

Clinical data was obtained from hospital records. Cause of death was established according to the information gathered from the institutional database. Sudden deaths that occurred out of the hospital were reported by family members or other treating physicians. Selection of candidates for lung transplant was established according to standardized inclusion criteria.[17] PAA was neither an indication nor a contraindication for lung transplant.

Kolmogorov-Smirnov test was used to test the normality of data distribution. Continuous variables are reported as mean ± standard deviation or as medians (Q1-Q3) as appropriate. Categorical variables are presented as numbers and frequencies (%). Categorical variables were compared using the Chi-squared test or the Fisher exact test and continuous variables with the Student's *t-test* or the Mann-Whitney *U-test* when appropriate. Freedom from death or lung transplant from PAH diagnosis and from imaging test performance were estimated by the Kaplan−Meier method and compared by log-rank test between groups. Predictors of PAA were assessed with univariate logistic regression analysis. Independent predictors of PAA development were analyzed with multivariate analysis using a backward stepwise selection. Variables with a p-value <0.20 were initially included. At each step, the least significant variable was removed from the model, until all variables reached a p-value <0.20. All tests were 2-sided and a p-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 21.0.0.0 (SPSS Inc, Chicago, Illinois).

Table 1
Baseline clinical, echocardiographic, and hemodynamic characteristics at PAH diagnosis and imaging test findings

Variable	All (n = 200)	Pulmonary artery aneurysm		p-value
		Yes (n = 77)	No (n = 123)	
Age (years)	48 (38−59)	44 (33−53)	40 (32−58)	0.706
Male sex	65 (33%)	26 (34%)	39 (32%)	0.762
PAH etiology				
Familial	17 (9%)	3 (4%)	14 (11%)	0.073
BMPR2 mutation	7 (4%)	1 (1%)	6 (5%)	0.253
KCNK3 mutation	3 (2%)	0 (0%)	3 (2%)	0.286
TBX4 mutation	3 (2%)	1 (1%)	2 (2%)	0.853
Idiopathic	58 (29%)	25 (33%)	33 (27%)	0.393
Congenital heart disease	34 (17%)	21 (27%)	13 (11%)	0.002
Connective tissue disease	40 (20%)	6 (8%)	34 (28%)	0.001
Toxic oil syndrome	16 (8%)	12 (16%)	4 (3%)	0.002
Portal hypertension	12 (6%)	2 (3%)	10 (8%)	0.134
HIV-related	4 (2%)	3 (4%)	1 (1%)	0.160
Rendu−Osler	2 (1%)	1 (1%)	1 (1%)	1.000
Veno-occlusive disease	17 (9%)	4 (5%)	13 (11%)	0.297
EIF2AK4 mutation n	8 (4%)	2 (25%)	6 (75%)	0.713
WHO Functional class III−IV	135 (68%)	59 (79%)	76 (64%)	0.035
Chest pain	39 (20%)	18 (24%)	21 (19%)	0.370
Echocardiographic parameters				
Tricuspid regurgitation III/IV	70 (35%)	35 (49%)	35 (29%)	0.008
End-diastolic right ventricle diameter (mm)	43.7 ± 8.08	46.4 ± 7.7	42.4 ± 7.9	0.006
Pericardial effusion	43 (22%)	17 (23%)	26 (21%)	0.747
6-minutes walking test distance (m)	397 ± 118	392 ± 126	400 ± 115	0.702
Hemodynamic parameters				
Right atrial pressure (mm Hg)	8.5 (5−12)	8 (5−12)	8.5 (5−11)	0.926
Systolic pulmonary artery pressure (mm Hg)	89.7 ± 24.4	93.7 ± 26.4	87.1 ± 22.7	0.072
Mean pulmonary artery pressure (mm Hg)	56.9 ± 15.2	60.3 ± 16.0	54.7 ± 14.3	0.012
Pulmonary vascular resistance (Wood Units)	11.4 (7.5−16.3)	12.2 (8.2−17)	11 (7.3−15.9)	0.298
Cardiac index (l/min/m^2)	2.5 ± 0.8	2.3 ± 0.7	2.5 ± 0.9	0.137
Imaging test findings				
Time course of PAH at imaging test performance (months)	29 (1.2−82)	62 (6−115)	18 (1−51)	0.001
Main pulmonary artery diameter (mm)	39.4 ± 8.9	48.3 ± 7.2	33.9 ± 4.2	<0.001
Right pulmonary artery diameter (mm)	26.8 ± 8.7	32.4 ± 10.2	23.5 ± 4.6	<0.001
Left pulmonary artery diameter (mm)	25.7 ± 6.8	29.4 ± 8.8	22.6 ± 5.3	<0.001

The primary end point of this study was to determine the detection rate of PAA assessed by CT and/or MR in patients with PAH followed-up according to standard protocols. The secondary end points were to detect predictors of PAA development and to determine the prognostic impact of PAA.

Results

A total of 200 PAH patients (age: 48.03 ± 14.47 years, 65 [32%] male) underwent a high-resolution imaging technique and conformed the study population. In 77 (38%), a PAA (48.3 ± 7.2 mm) was detected (Figure 2). The rate of detection of PAA was higher in those patients in whom imaging test was performed during follow-up (63 [45%] PAAs during follow-up vs 14 [23%] PAAs at diagnosis; p = 0.004) (Figure 1). Baseline characteristics at PAH diagnosis are summarized in Table 1.

PAA was more frequently detected in patients with congenital heart disease (27% PAA vs 11% no-PAA; p = 0.002) and toxic oil syndrome (16% PAA vs 3% no-PAA; p = 0.002). On the contrary, PAA was less frequent in patients with connective tissue disease (CTD)-related PAH (8% PAA vs 28% no-PAA; p = 0.001). Imaging test findings are presented in Table 1.

The time-course of PAH was longer in the PAA group as compared with patients without PAA (62 [6 to 115] vs 18 [1 to 51] months; p = 0.001). As shown, patients with PAA presented dilated right and left pulmonary arteries. We did not find significant differences in PAH time-course between patients with CTD-related PAH and those with other different etiologies (30 months [2 to 60] CTD-related PAH vs 29 months [2 to 86] non−CTD-related PAH; p = 0.76).

At PAH diagnosis, patients who developed a PAA had a higher mean PA pressure. In addition, they presented more often moderate or severe tricuspid regurgitation, functional class III/IV and a larger end-diastolic right ventricular diameter.

To determine variables potentially related to the development of PAA, univariate and multivariate analysis were performed (Table 2).

CTD-related PAH remained independently associated with a lower risk of developing a PAA (hazard ratio 0.236; 95% confidence interval 0.060 to 0.920; p = 0.037) and

Table 2
Univariate and multivariate regression analysis of the variables associated with development of PAA

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
PAH time-course	1.006	1.002−1.010	0.003	1.01	1.002−1019	0.016
Familial PAH	0.316	0.088−1.137	0.078			
Idiopathic PAH	1.131	0.704−2.442	0.393			
Congenital heart disease	3.173	1.480−6.804	0.003			
Connective tissue disease	0.221	0.088−0.556	0.001	0.236	0.060−0.920	0.037
Veno-occlusive disease	0.464	0.145−1.478	0.194			
Toxil oil syndrome	5.492	1.702−17.719	0.004	6.289	0.936−42.624	0.064
Portal hypertension	0.301	0.064−1.414	0.128			
HIV-related pulmonary hypertension	4.946	0.505−48.429	0.170			
Rendu Osler	1.605	0.099−26.046	0.739			
Identified mutation	0.272	0.059−1.260	0.096	0.142	0.017−1.121	0.074
WHO functional-class III-IV	2.038	1.044−3.977	0.037			
Tricuspid regurgitation III-IV	2.324	1.267−4.263	0.006			
End-diastolic right ventricular diameter	1.068	1.018−1.121	0.008	1.054	0.997−1.115	0.064
Pericardial effusion	1.121	0.560−2.245	0.747			
6 minutes walking test distance	0.999	0.997−1.002	0.700			
Right atrial pressure	1.000	0.948−1.056	0.992			
Systolic pulmonary artery pressure	1.011	0.999−1.024	0.074	0.968	0.929−1.009	0.120
Diastolic pulmonary artery pressure	1.015	0.991−1.040	0.219			
Mean pulmonary artery pressure	1.025	1.005−1.046	0.013	1.053	0.988−1.122	0.114
Pulmonary vascular resistances	1.019	0.977−1.064	0.384			
Cardiac index	0.749	0.503−1.116	0.156			

CI: confidence interval; HR = hazard ratio; HIV = human immunodeficiency virus; PAH= pulmonary arterial hypertension; WHO = World Health Organization.

time-course of PAH remained as an independent risk factor for PAA development (hazard ratio 1.01; 95% confidence interval 1.002 to 1.019; p = 0.016) (Table 2).

During a median follow-up of 63 (34 to 125) months from PAH diagnosis 60 (30%) patients met the composite end point (38 [19%] death and 22 [11%] lung transplant). Median time from PAH diagnosis to event was 66 (31 to 119) months. In patients with PAA, the composite end point occurred in 29 (38%) patients (20 [26%] deaths and 9 [12%] lung transplant). Patients with PAA had a longer median follow-up time from PAH diagnosis to death, lung transplant or end of follow-up (98 [55 to 163] months PAA vs 50 [29 to 84] months; p <0.001). Survival analysis from PAH diagnosis showed higher rates of the composite end point death and lung transplant in patients without PAA compared with those with PAA (p = 0.005). However, analysis from time of imaging test performance showed no differences between groups with regard to the composite end point (p = 0.269; Figure 3). Mortality data is detailed in Table 3.

PAA patients had a nonsignificant higher rate of sudden death (5% PAA vs 1% no-PAA; p = 0.073) with no differences in mortality due to heart failure (13% PAA vs 7% no-PAA; p = 0.119) or noncardiovascular death (8% PAA vs 7% no-PAA; p = 0.901).

Complications related to PAA were detected in 10 patients (13% of the PAA group). In 6, CT and/or MR was indicated based on symptoms suggesting a complicated PAA, whereas in 4 complicated PAAs were incidentally detected at follow-up. In 7 patients, left main coronary artery compression was suspected by CT, requiring 4 of them percutaneous revascularization; 2 patients suffered a pulmonary artery dissection; 1 severe pulmonary regurgitation and 1 lung compression with recurrent pneumonia (Figure 4).

Discussion

PA dilatation is common in PAH patients.[6] However, PAA frequency in PAH remains unclear.[5] PAA are often asymptomatic,[3,18] resulting in a significant proportion of undiagnosed patients. Furthermore, there is lack of consensus regarding the definition of PAA in studies.[5,11,18,19]

In the present study, a PAA was detected in 77 patients (38% of the study population). Importantly, only 8% presented symptoms related to PAA during follow-up. In current clinical practice, the indication of performing high-resolution imaging tests during PAH follow-up often relies on the presence of symptoms. Consequently, a significant number of PAA in asymptomatic patients might be overlooked.[3] According to current PAH guidelines, performing a CT might be reasonable at the time of PAH diagnosis.[14] However, specific recommendations of patients under follow-up are lacking. Based on our results, performing a CT and/or MR may be useful to detect PAA in PAH patients, irrespectively of the presence of symptoms, not only at PAH diagnosis but also during follow-up. Patient with long-standing PAH might specially benefit from this strategy.

The mechanisms leading to the development of PAA remain unclear. Severe PAH is present in up to 66% of reported PAA.[20] The existence of PAA leads frequently to a PAH diagnosis.[21] In a recent study, patients with PAH and PAA on echocardiogram who underwent simultaneous right heart catheterization presented higher pulmonary

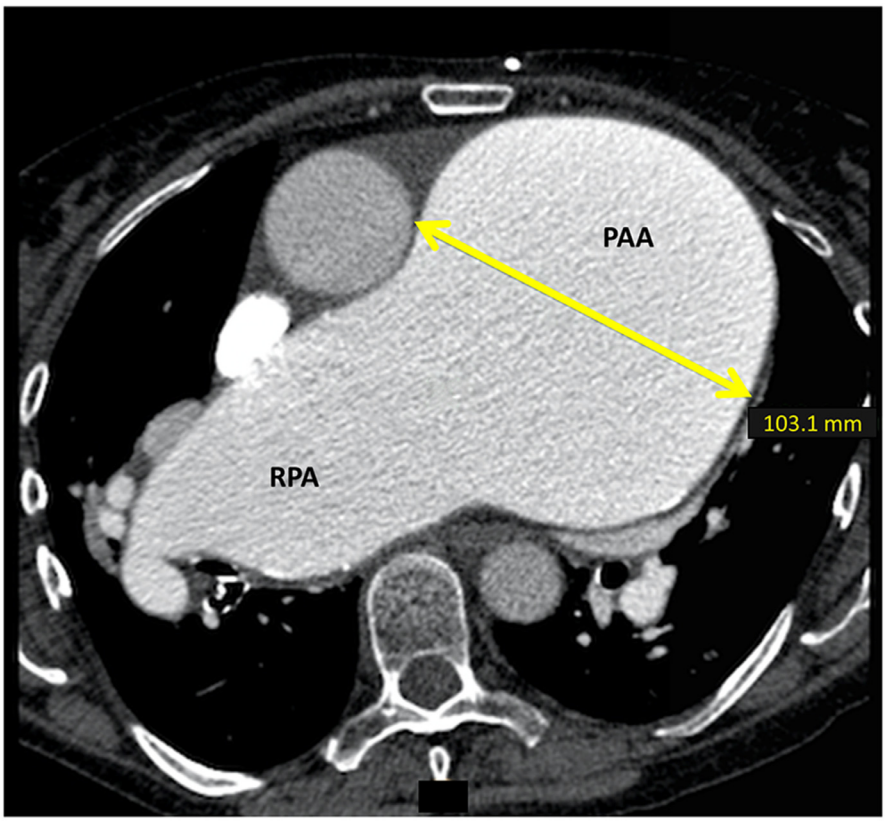

Figure 2. CT angiography axial view of a giant PAA with concomitant dilatation of the right pulmonary artery. PAA = pulmonary artery aneurysm; RPA = right pulmonary artery.

pressures and a worse right ventricle function.[19] However, the progression of PAA has been showed to be independent from pulmonary pressures during follow-up.[22] In the absence of PAH, PAA may be detected associated to infections, Behçet disease or Marfan syndrome,[5] possibly due to intrinsic PA wall abnormalities.[4] We were unable to find an association of PAA with any invasive hemodynamic parameter at diagnosis. However, the duration of elevated PA pressure, reflected as PAH time-course, was an independent risk factor for the development of PAA, as previously speculated.[5] Furthermore, we found a higher frequency of PAA in those patients who underwent an imaging test during follow-up. This reinforces the hypothesis that PAA is a condition proper of long-standing PAH.

CTD-related PAH was independently associated with a lower risk of PAA. PAH in CTD patients may result from complex pathophysiological processes leading to endothelial dysfunction and vascular remodeling.[23] Although the lower survival in CTD-related PAH patients could explain the lower incidence of PAA in these population,[2] in our study group, PAH time-course of CTD patients was no shorter than in patients with other causes for PAH. Disease-specific histopathological changes associated to CTD-related PAH have been described.[24] We speculate whether structural changes in the pulmonary artery wall in patients with CTD-related PAH may prevent the development of a PAA.

We found a lower incidence of the composite end point of death and lung transplant in PAA patients compared with patients without PAA from PAH diagnosis. The longer follow-up periods in PAA patients illustrate the fact that PAA is associated with long-standing forms of PAH, as reflected by the higher proportion of patients with PAH associated to congenital heart disease or toxic oil syndrome. Thus, the lower rate of death and lung transplant in PAA patients may actually indicate that PAH patients with a longer survival are precisely those who develop a PAA during follow-up. Conversely, survival analysis from imaging test performance showed no differences between groups. This finding might suggest that PAA actually do not have any prognostic influence in PAH patients.

However, it should be highlighted that PAA-related complications were detected in a 13% of PAA patients. Severe consequences, including sudden cardiac death, linked to complicated PAA have been described.[7–13] In addition, PA dilatation has been described as an independent risk factor for sudden cardiac death in PAH patients.[25]

Symptoms suggesting a complicated PAA may allow prompt detection and treatment. However, up to 40% of complicated PAA from our cohort were incidentally detected during follow-up. In a recent study, only 23% of patients with complicated PAA detected by CT presented associated symptoms.[3] Patients with asymptomatic complicated PAA might therefore be at risk of sudden death due to ventricular arrhythmias or PA dissection.[3,26] Sudden death represents up to 30% of the causes of death in patients with PAH.[27] We previously described a rate of sudden death of 11% in the overall population of patients with

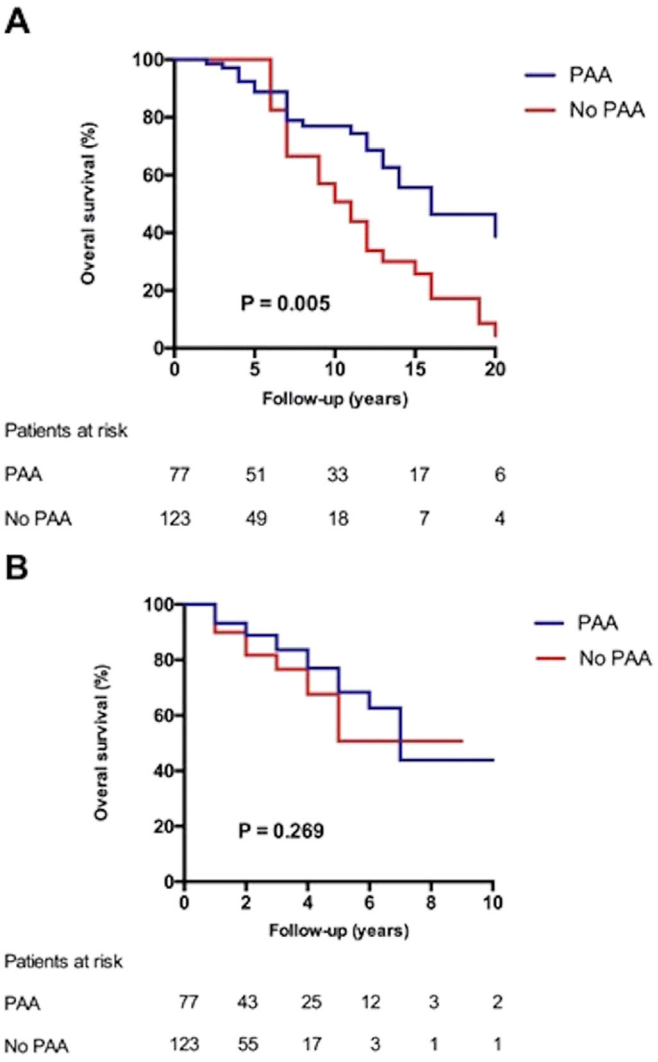

Figure 3. Kaplan-Meier survival curves of freedom from death or lung transplant in patients with PAA versus patients without PAA from PAH diagnosis (*A*) and from imaging test (*B*). PAA = pulmonary artery aneurysm.

PAH under follow-up in our centre.[2] In the present study, patients with PAA presented a nonsignificant higher rate of sudden death compared with their counterparts (PAA 5% vs no-PAA 1%; p = 0.073). The rate of sudden death reported in our series is lower than that reported in other series[27] and in our global population.[2] This may be explained, at least in part, by the revascularization of severe left main coronary artery compression. However, sudden death resulting from asymptomatic complicated PAA in patients who were not screened for PAA cannot be excluded. In consequence, the impact of undetected complicated PAA in PAH patients might be not trivial.

Table 3
Differences in mortality and cause of death in patients with PAA versus patients without PAA

Variable	All (n = 200)	Pulmonary artery aneurysm		p-value
		Yes (n = 77)	No (n = 123)	
Deaths	38 (19%)	20 (26%)	18 (15%)	0.047
Age at death (years)	57 (48–66)	59 (49–69)	56 (47–65)	0.260
Male sex	12 (32%)	7 (35%)	5 (28%)	0.632
Follow-up (months)	63 (29–148)	88 (52–169)	45 (24–75)	0.003
Sudden death	5 (2%)	4 (5%)	1 (1%)	0.073
Heart failure	18 (9%)	10 (13%)	8 (7%)	0.119
Noncardiovascular death	15 (8%)	6 (8%)	9 (7%)	0.901

Based on these findings, PAA development may be a consequence of long-term PAH, appearing in those PAH patients with a longer survival. However, PAA may lead as well to fatal consequences in this population. The development of PAA screening programs in PAH patients, irrespectively of their clinical status, is therefore mandatory. Surgical treatment of PAA has been proposed as a therapeutic option. In light of our results, a conservative approach with regular follow-up could be an appropriate option for PAH patients with a PAA, especially considering the high surgical risk of this population.

This study has several limitations that should be acknowledged. This is a retrospective single-centre

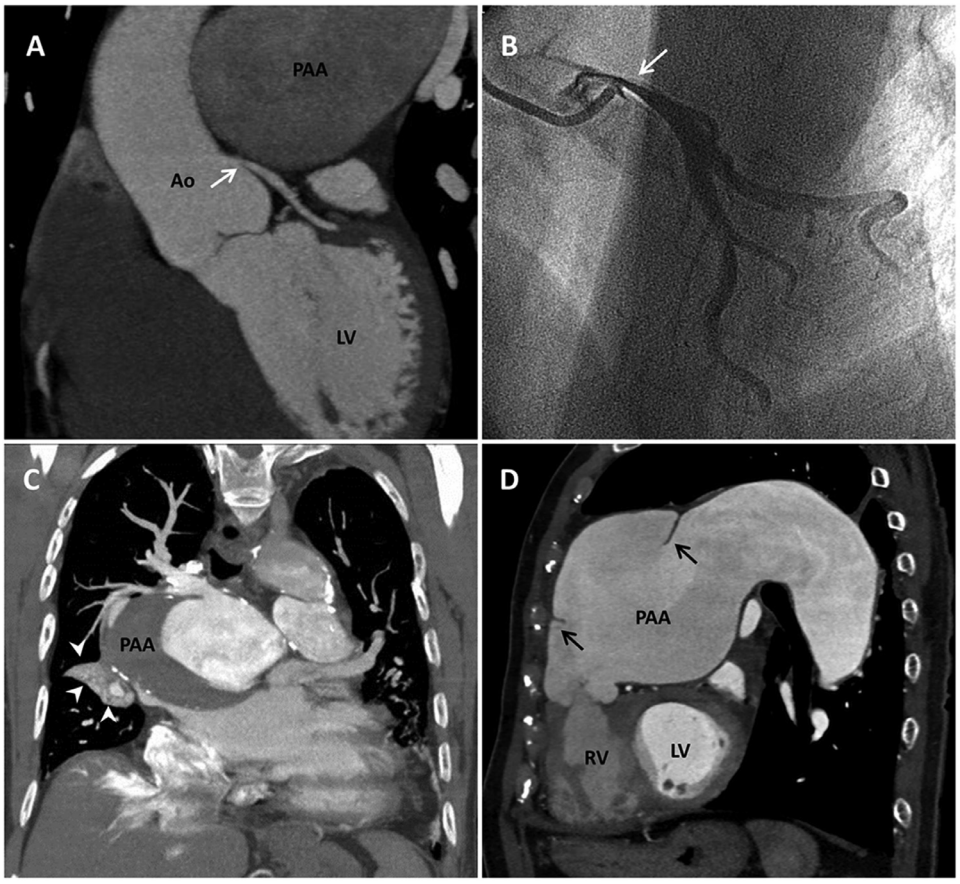

Figure 4. PAA-related complications. (***A***) CT coronary angiography oblique coronal view showing left main coronary artery compression (*arrow*) by a PAA; (***B***) coronary angiography demonstrating ostial left main coronary artery compression (*arrow*); (***C***) giant PAA with concomitant dilatation of right pulmonary artery compressing the right lung middle lobe (arrow heads); (***D***) PAA dissection (*arrows*). Ao = aorta; LV = left ventricle; PAA = pulmonary artery aneurysm; RV = right ventricle.

study analyzing the frequency of PAA detection in a PAH population. Patients with PAH under follow-up did not systematically undergo an imaging test, which might determine a selection bias. However, our data emerge from the application of standard protocols of PAH, illustrating current clinical practice. Imaging tests were performed at different moments of the evolution of the disease, which prevent us of assuming a clear correlation of PAA with hemodynamic data. A prospective study, including systematic imaging test performance at PAH diagnosis and during follow-up is required to elucidate the actual prevalence of PAH and to identify those patients at higher risk of developing a PAA. Strategies in order to prevent sudden cardiac death in patients at high risk (i.e. complicated PAA) are needed.

In conclusion, the frequency of detection of PAA in patients with PAH who underwent high-resolution imaging techniques was 38%. PAH time-course was an independent risk factor for PAA development whereas CTD-related PAH patients showed a lower risk. Compared with patients without PAA, PAA patients showed lower rates of the composite end point death and lung transplant during follow-up, but nonsignificant higher rates of sudden death.

Acknowledgment

JN, JMMC, and PES contributed to conception and design of the study, drafting and final approval of the manuscript. CJLG, MTVM, SAC, YRO, and FAY contributed to drafting and final approval of the manuscript.

Disclosures

The authors have no conflict of interest to report related to this manuscript.

1. Escribano-Subias P, Blanco I, Lopez-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gomez-Sanchez MA, Barbera JA, Investigators R. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J* 2012;40:596–603.
2. Quezada Loaiza CA, Velazquez Martin MT, Jimenez Lopez-Guarch C, Ruiz Cano MJ, Navas Tejedor P, Carreira PE, Flox Camacho A, de Pablo Gafas A, Delgado Jimenez JF, Gomez Sanchez MA, Escribano Subias P. Trends in pulmonary hypertension over a period of 30 years: experience from a single referral centre. *Rev Esp Cardiol* 2017;70:915–923.
3. Lee SE, Im JH, Sung JM, Cho IJ, Shim CY, Hong GR, Chung N, Jung JW, Chang HJ. Detection of mechanical complications related to the potential risk of sudden cardiac death in patients with pulmonary

arterial hypertension by computed tomography. *Int J Cardiol* 2017;243:460–465.
4. Kreibich M, Siepe M, Kroll J, Hohn R, Grohmann J, Beyersdorf F. Aneurysms of the pulmonary artery. *Circulation* 2015;131:310–316.
5. Duijnhouwer AL, Navarese EP, Van Dijk AP, Loeys B, Roos-Hesselink JW, De Boer MJ. Aneurysm of the Pulmonary Artery, a Systematic Review and Critical Analysis of Current Literature. *Congenit Heart Dis* 2016;11:102–109.
6. Badagliacca R, Poscia R, Pezzuto B, Papa S, Nona A, Mancone M, Mezzapesa M, Nocioni M, Sciomer S, Valli G, Cedrone N, Fedele F, Vizza CD. Pulmonary arterial dilatation in pulmonary hypertension: prevalence and prognostic relevance. *Cardiology* 2012;121:76–82.
7. Hernandez V, Ruiz-Cano MJ, Escribano P, Sanchez MA. Complications of proximal pulmonary artery aneurysm in patients with severe pulmonary arterial hypertension. *Rev Esp Cardiol* 2010;63:617–618.
8. Terris MH, Mainwaring RD, Pransky SM. Airway compromise secondary to vascular compression in a neonate. *Int J Pediatr Otorhinolaryngol* 1994;28:193–197.
9. Khattar RS, Fox DJ, Alty JE, Arora A. Pulmonary artery dissection: an emerging cardiovascular complication in surviving patients with chronic pulmonary hypertension. *Heart* 2005;91:142–145.
10. Metras D, Ouattara K, Quezzin-Coulibaly A. Aneurysm of the pulmonary artery with cystic medial necrosis and massive pulmonary valvular insufficiency. Report of two successful surgical cases. *Eur J Cardiothorac Surg* 1987;1:119–124.
11. Galie N, Saia F, Palazzini M, Manes A, Russo V, Bacchi Reggiani ML, Dall'Ara G, Monti E, Dardi F, Albini A, Rinaldi A, Gotti E, Taglieri N, Marrozzini C, Lovato L, Zompatori M, Marzocchi A. Left main coronary artery compression in patients with pulmonary arterial hypertension and angina. *J Am Coll Cardiol* 2017;69:2808–2817.
12. Arena V, De Giorgio F, Abbate A, Capelli A, De Mercurio D, Carbone A. Fatal pulmonary arterial dissection and sudden death as initial manifestation of primary pulmonary hypertension: a case report. *Cardiovasc Pathol* 2004;13:230–232.
13. Demerouti EA, Manginas AN, Athanassopoulos GD, Karatasakis GT. Complications leading to sudden cardiac death in pulmonary arterial hypertension. *Respir Care* 2013;58:1246–1554.
14. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903–975.
15. Frazier AA, Galvin JR, Franks TJ, Rosado-De-Christenson ML. From the archives of the AFIP: pulmonary vasculature: hypertension and infarction. *Radiographics* 2000;20:491–524; quiz 530-1, 532.
16. Bozlar U, Ors F, Deniz O, Uzun M, Gumus S, Ugurel MS, Yazar F, Tayfun C. Pulmonary artery diameters measured by multidetector-row computed tomography in healthy adults. *Acta Radiol* 2007;48:1086–1091.
17. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG, Snell GI, Verleden GM, Zamora MR, Glanville AR. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015;34:1–15.
18. Deterling RA Jr., Clagett OT. Aneurysm of the pulmonary artery; review of the literature and report of a case. *Am Heart J* 1947;34:471–499.
19. Sakata K, Satoh T, Isaka A, Uesugi Y, Furuya M, Matsushita K, Yoshino H. Cardiac dysfunction of pulmonary artery aneurysm in patients with pulmonary arterial hypertension. *Int J Cardiol* 2017;228:1035–1040.
20. Boyd LJ, McGravack TH. Aneurysm of pulmonary artery. *Am Heart J* 1939;18:562–578.
21. Grubstein A, Benjaminov O, Dayan DB, Shitrit D, Cohen M, Kramer MR. Computed tomography angiography in pulmonary hypertension. *Isr Med Assoc J* 2008;10:117–120.
22. Boerrigter B, Mauritz GJ, Marcus JT, Helderman F, Postmus PE, Westerhof N, Vonk-Noordegraaf A. Progressive dilatation of the main pulmonary artery is a characteristic of pulmonary arterial hypertension and is not related to changes in pressure. *Chest* 2010;138:1395–1401.
23. Kahler CM, Colleselli D. Pulmonary arterial hypertension (PAH) in connective tissue diseases. *Rheumatology* 2006;45(Suppl 3): iii11-3.
24. Sasaki N, Kamataki A, Sawai T. A histopathological study of pulmonary hypertension in connective tissue disease. *Allergol Int* 2011;60:411–417.
25. Zylkowska J, Kurzyna M, Florczyk M, Burakowska B, Grzegorczyk F, Burakowski J, Wieteska M, Oniszh K, Biederman A, Wawrzynska L, Szturmowicz M, Fijalkowska A, Torbicki A. Pulmonary artery dilatation correlates with the risk of unexpected death in chronic arterial or thromboembolic pulmonary hypertension. *Chest* 2012;142:1406–1416.
26. Montero Cabezas JM, Nuche Berenguer J, Velazquez Martin MT, Escribano Subias P. Left main extrinsic compression in pulmonary arterial hypertension: from identification to percutaneous coronary intervention optimization. *J Am Coll Cardiol* 2017;70:2459–2460.
27. Delcroix M, Naeije R. Optimising the management of pulmonary arterial hypertension patients: emergency treatments. *Eur Respir Rev* 2010;19:204–211.