



Idiopathic, heritable and veno-occlusive pulmonary arterial hypertension in childhood: computed tomography angiography features in the initial assessment of the disease

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Received: 21 March 2018 / Revised: 22 October 2018 / Accepted: 12 December 2018
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Abstract

Background In children, idiopathic and heritable pulmonary arterial hypertension present echocardiographic and heart catheterization findings similar to findings in pulmonary veno-occlusive disease.

Objective To provide a systematic analysis of CT angiography anomalies in children with idiopathic or heritable pulmonary arterial hypertension, or pulmonary veno-occlusive disease. We also sought to identify correlations between CT findings and patients' baseline characteristics.

Materials and methods We retrospectively analyzed CT features of children with idiopathic and heritable pulmonary arterial hypertension or pulmonary veno-occlusive disease and 30 age-matched controls between 2008 and 2014. We compared CT findings and patient characteristics, including gene mutation type, and disease outcome until 2017.

Results The pulmonary arterial hypertension group included idiopathic ($n=15$) and heritable pulmonary arterial hypertension ($n=11$) and pulmonary veno-occlusive disease ($n=4$). Median age was 6.5 years. Children with pulmonary arterial hypertension showed enlargement of pulmonary artery and right cardiac chambers. A threshold for the ratio between the pulmonary artery and the ascending aorta of ≥ 1.2 had a sensitivity of 90% and a specificity of 100% for pulmonary arterial hypertension. All children with pulmonary veno-occlusive disease had thickened interlobular septa, centrilobular ground-glass opacities, and lymphadenopathy. In children with idiopathic and heritable pulmonary arterial hypertension, presence of intrapulmonary neovessels and enlargement of the right atrium were correlated with higher mean pulmonary artery pressure ($P=0.011$) and pulmonary vascular resistance ($P=0.038$), respectively. Mediastinal lymphadenopathy was associated with disease worsening within the first 2 years of follow-up ($P=0.024$).

Conclusion CT angiography could contribute to early diagnosis and prediction of severity in children with pulmonary arterial hypertension.

Keywords Adolescents · Children · Computed tomography angiography · Familial primary pulmonary hypertension · Pulmonary veno-occlusive disease · Telangiectasia

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00247-018-04331-y>) contains supplementary material, which is available to authorized users.

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Introduction

Paediatric pulmonary hypertension has an estimated incidence of 63.7 cases per million children per year [1]. Pulmonary hypertension is classified into five groups according to clinical, pathological and haemodynamic characteristics. Group 1 pulmonary arterial hypertension includes diseases previously classified as primary pulmonary hypertension [2], whereas groups 2 through 5 are less frequent in children. The latter include pulmonary hypertension from left heart disease (group 2), chronic lung disease or hypoxia (group 3), chronic thromboembolic pulmonary disease (group 4) and unclear multifactorial mechanisms (group 5). In children, 57% with pulmonary arterial hypertension have idiopathic or heritable pulmonary arterial hypertension — from mutations of the bone morphogenic protein receptor type 2 (*BMPR2*) in 70% of cases, or from other rare mutations such as activin-like receptor kinase-1 (*Alk-1*) (hereditary hemorrhagic telangiectasia syndrome), T-box transcription factor-4 (*TBX4*) (small patella syndrome), endoglin (*ENG*), or mothers against decapentaplegic homolog 9 (*SMAD9*). Pulmonary veno-occlusive disease falls into group 1 [3], although it is less prevalent. Pulmonary veno-occlusive disease can initially be misdiagnosed as idiopathic pulmonary arterial hypertension but with a worse prognosis, and specific pulmonary arterial hypertension therapy can be deleterious in some cases [4]. These three entities — idiopathic and heritable pulmonary arterial hypertension and pulmonary veno-occlusive disease — constitute a group of heterogeneous disorders with similar initial clinical and haemodynamic data [5].

In children with clinical suspicion of pulmonary arterial hypertension, right heart catheterization is mandatory for accurate diagnosis and guidance of medical therapy [2], and chest CT angiography is also recommended in the initial assessment of the disease to exclude other underlying diseases that might be missed by transthoracic echocardiography and heart catheterization [6].

To the best of our knowledge, the literature about chest CT angiography features of pulmonary arterial hypertension in children is scarce; only one retrospective study to date included a systematic description of parenchymal anomalies [7]. Authors described cardiac, vascular and parenchymal CT angiography anomalies including peripheral vasculopathy and centrilobular opacities in children with idiopathic pulmonary arterial hypertension.

In adults with pulmonary arterial hypertension, CT features have been explored more extensively, and the ratio of the main pulmonary artery diameter to the ascending aorta diameter is a widely used sign for pulmonary hypertension, with a threshold value of 1 [6–13]. Lung parenchymal anomalies, such as centrilobular ground-glass nodules and tiny serpiginous intrapulmonary vessels, have also been described [6, 14]. CT findings in pulmonary veno-occlusive disease are

suggestive of the disease [4, 8, 9], but diagnosis is still based on lung biopsy analysis and, more recently, on genetic screening for *EIF2AK4* biallelic mutation [10].

In this study, we estimated the contribution of CT angiography in the initial assessment of the disease by providing a systematic analysis of CT angiography anomalies in a cohort of children with idiopathic and heritable pulmonary arterial hypertension and pulmonary veno-occlusive disease. We sought (1) to assess threshold values of pulmonary artery and right cardiac chambers enlargement compared to normal age-matched controls; (2) to perform a descriptive analysis of lung parenchymal anomalies; and (3) to identify potential correlations between CT findings and patient/disease characteristics, including gene mutation type and disease outcome.

Materials and methods

Study design and population

We retrospectively reviewed all consecutive children diagnosed with pulmonary arterial hypertension in our tertiary referral centre between 2008 and 2014. We received approval of the institutional review board (CEPRO 2013-012) for the retrospective analysis of case records and imaging data.

We included children diagnosed with idiopathic or heritable pulmonary arterial hypertension or pulmonary veno-occlusive disease according to the updated clinical classification [2]. Children with other types of pulmonary hypertension, particularly pulmonary arterial hypertension associated with congenital heart disease, were not included. CT angiography scan was performed during the initial assessment of the disease, as was right heart catheterization, with a maximum delay between procedures of 3 months. Diagnosis of pulmonary arterial hypertension was established on the basis of right catheterization according to the European guidelines [11]. Diagnosis of heritable pulmonary arterial hypertension was based on family history or a mutation in one of the known genes for pulmonary arterial hypertension [1, 12, 13]; specifically, *BMPR2*, *Alk-1*, *TBX4*, *ENG* or *SMAD9* was identified in the patient or a first-degree relative [14]. Diagnosis of pulmonary veno-occlusive disease was established upon histological examination of lung biopsy or lung explant or upon identification of an *EIF2AK4* biallelic mutation [10]. Diagnosis of idiopathic pulmonary arterial hypertension was established after exclusion of other causes of pulmonary arterial hypertension in children with no family history of pulmonary arterial hypertension. We collected clinical and haemodynamic data including patient age, gender, New York Heart Association class, mean pulmonary artery pressure and pulmonary vascular resistance measured by right catheterization. We collected follow-up data until January 2017. We defined early worsening outcome as death; heart or lung

transplantation; or right-side heart failure requiring Potts procedure, a palliative surgical technique of anastomosis between the left pulmonary artery and the descending aorta to decompress the right ventricle [15], occurring within 2 years of follow-up.

The control group included 30 age-matched children without known cardiac or pulmonary disease, selected from our radiology database.

Chest computed tomography angiography acquisition and analysis

Images were obtained with a 64-row multidetector CT scanner (LightSpeed VCT; GE Healthcare, Milwaukee, WI). CT angiographies were performed according to the usual protocol in our department. Chest was scanned from the lung apex to the base without electrocardiographic (ECG) gating. Scan parameters included z-axis automatic tube current modulation from 50 mA (mAs) to 300 mAs; tube voltage of 80 kV (kV) or 100 kV for children younger or older than 6 years, respectively; and collimation of 1.25 mm. An intravenous injection of 1.5 mL/kg of body weight of nonionic iodinated contrast medium (Iomeron 350; Bracco SpA, Milan, Italy) was performed, followed by a bolus of normal saline (0.5 mL/kg of body weight), infused with an automatic injector; flow rates were heterogeneous, ranging 1–2 mL/s depending on child age and catheter diameter. Acquisition time was adapted to the end of saline injection, ranging 25–40 s, depending on volume injected and flow rates.

The 60 CT studies were anonymized. Two paediatric radiologists with 12 and 2 years of experience in thoracic imaging, blinded to clinical and genetic data, reviewed all CT images independently and randomly. In cases of disagreement between the observers, a consensus opinion was reached.

Image post-processing was done on an ADW 4.5 workstation (GE Healthcare), at mediastinal and parenchymal window settings (width 400 Hounsfield units [HU] and level 40 HU; and width 1,600 HU and level 600 HU, respectively) in multiplanar reformats in axial and coronal axes; maximum- and minimum-intensity-projection reconstructions were also used.

We measured the diameter of the main pulmonary artery at the level of the pulmonary artery bifurcation, the diameter of ascending aorta, the diameters of right and left atria, and the diameters of right and left ventricles on four-chamber view, using electronic calipers. We calculated the ratio of main pulmonary artery diameter/ascending aorta diameter, right atrium diameter/left atrium diameter and right ventricle diameter/left ventricle diameter [16]. We compared the medians of these ratios between pulmonary arterial hypertension and control groups.

We defined and reported lung parenchyma anomalies according to the Fleischner Society glossary [17]: ground-glass

opacities or nodules, airspace consolidations, micronodules, thickened interlobular septa, intralobular lines, bronchiectasis, lung cysts, honeycombing and mosaic attenuation pattern. We also reported intrapulmonary neovessels, defined as tiny, micronodular, serpiginous intrapulmonary vessels coursing in directions inconsistent with known arteriolar anatomy [18], dilatation of bronchial arteries [19, 20], and mediastinal lymphadenopathy (short axis >1 cm), and evaluated pleural or pericardial effusion, as well as any other anomaly.

In the children with pulmonary arterial hypertension, we correlated mediastinal and pulmonary CT lesions and patterns with genetic diagnosis, New York Heart Association class at diagnosis, pulmonary vascular resistance and mean pulmonary artery pressure as measured by right heart catheterization, and outcome at follow-up (as defined in study design).

Statistical analysis

For statistical analysis we used The R Project statistical software V3.3 (The R Development Core Team, The R Foundation, Vienna, Austria). We described categorical data as numbers and continuous variables as mean (standard deviation) or median (range) according to their distribution.

We performed statistical analyses on the results of the mean of the two observers for quantitative values and on the results of consensus review for qualitative variables. We performed comparisons between the two groups using Wilcoxon test for quantitative variables and Fisher exact test for qualitative variables. For all tests, a *P*-value less than 0.05 was considered statistically significant. Youden index in conjunction with receiver operating characteristic analyses were performed for the ratios of main pulmonary artery diameter/ascending aorta diameter, right atrium diameter/left atrium diameter, and right ventricle diameter/left ventricle diameter, to estimate the diagnostic performance and the optimal threshold values [21] of these ratios between children with pulmonary arterial hypertension and the control group. When this threshold was not unique, we retained the threshold with the greater specificity. Finally, we estimated the hazard ratio of each anomaly. Receiver operating characteristic curve confidence intervals were determined by 2,000 stratified bootstrap replicates.

Results

Study population

Thirty children (8 boys/22 girls, median age at CT 6.5 years, range 11 months to 15 years) fulfilled the criteria and were included in the pulmonary arterial hypertension group. The median time elapsed between catheterization and CT was 3.5 days (range 0–88 days). Clinical, haemodynamic and evolution data of the pulmonary arterial hypertension group are

summarized in Table 1. Median follow-up was of 52 months (range 6–117 months).

The control group included 30 children (13 boys/17 girls, median age 6.5 years, range 11 months to 15 years). In this group CT angiographies were performed for extrapulmonary tumor staging ($n=10$), suspicion of tuberculosis ($n=12$) and polytrauma ($n=8$). None of them presented with any thoracic lesion or injury.

Computed tomography angiography analysis

The pulmonary arterial hypertension group showed a statistically significant increase in diameter ratios between the pulmonary artery and the ascending aorta (main pulmonary artery diameter/ascending aorta diameter), right and left atria (right atrium diameter/left atrium diameter) and right and left ventricle (right ventricle diameter/left ventricle diameter) compared to the control group (Fig. 1; Table 2). The best ratio thresholds to discriminate pulmonary arterial hypertension and control groups are summarized in Table 3 (receiver operating characteristic curves and their confidence interval in additional contents).

Patterns of lung and mediastinal anomalies were heterogeneous. Anomalies are summarized in Supplementary-table 1, in additional contents. All children from the pulmonary arterial hypertension group presented with parenchymal anomalies except one 13-year-old girl with a diagnosis of idiopathic pulmonary arterial hypertension. One child with a mutation in *TBX4* had only a few thickened interlobular septa.

The most frequently reported anomaly was a mosaic attenuation pattern ($n=23$). For 19 children it consisted of areas of decreased attenuation with normal or increased peripheral vessel dimensions, which was better detected in minimum-intensity projection reconstructions (Fig. 2). This was the only parenchymal anomaly reported for two children with idiopathic pulmonary arterial hypertension. For the four children with pulmonary veno-occlusive disease, the anomaly consisted instead of diffuse areas of decreased attenuation associated with decreased pulmonary vascularization resulting in associated mosaic perfusion (Fig. 3).

Ground-glass opacities were frequent but with heterogeneous distribution and extent: one isolated peripheral area of ground-glass opacity in 3 children with idiopathic pulmonary arterial hypertension, isolated peri-arteriolar or peri-arteriovenous fistula opacity in 2/4 children with mutation in *Alk-1*, diffuse peri-arteriolar ground-glass nodules in 3/3 children with mutation in bone morphogenetic protein receptor type 2 (Fig. 4) and 4/15 children with idiopathic pulmonary arterial hypertension, and diffuse centrilobular or confluent ground-glass nodules in 4/4 children with pulmonary veno-occlusive disease (Fig. 4).

Consolidations were rare and consisted of one isolated peripheral nonspecific area in three children.

Signs of neovascularization, such as tiny serpiginous intrapulmonary peripheral neovessels (Fig. 5) and dilated bronchial arteries (Fig. 6), were frequent (14/30) and could be seen in any aetiology except pulmonary veno-occlusive disease. No other abnormal collateral vessels (anterior thoracic, diaphragmatic or intercostal dilated arteries) were described.

Micronodules, isolated or with a tree-in-bud aspect (Fig. 4), presented an arteriolar distribution. In two children with mutation in *Alk-1*, the aspect of the nodules, in contact with both an artery and a vein, suggested pulmonary arteriovenous fistula, as shown in Fig. 7.

When present, interlobular lines were smooth. The extent and localization varied a lot from one child to another (perihilar, peripheral, diffuse).

Correlation between computed tomography angiography anomalies, genotype, baseline characteristics and worsening disease

All children with pulmonary veno-occlusive disease presented with a typical pattern (Fig. 3): diffuse centrilobular ground-glass opacities, thickened interlobular septa with variable extent, mosaic perfusion and lymphadenopathy. Two of them had lung hyperinflation. This pattern was not present in any of the other children in the pulmonary arterial hypertension group.

In contrast to pulmonary veno-occlusive disease, we could not highlight a CT pattern of parenchymal anomalies typical enough for differentiating between children with mutation in *BMPR2*, *Alk-1*, *TBX4* or idiopathic pulmonary arterial hypertension; however, in children with *Alk-1* mutation, lesions suggesting intrapulmonary arteriovenous fistulas (Fig. 7) or hepatic telangiectasia (Fig. 8) were present in three of four cases.

We found a positive correlation between right atrium diameter/left atrium diameter and pulmonary vascular resistance ($\rho=0.9$, $P=0.038$). We also found a correlation between the presence of peripheral neovessels and mean pulmonary artery pressure: median mean pulmonary artery pressure in children with neovessels was 72 mmHg (range 44–103 mmHg) versus 56 mmHg (range 25–73 mmHg) in children without this feature ($P=0.011$). There was no other significant correlation between baseline characteristics and other parenchymal or mediastinal CT anomalies. Presence of enlarged mediastinal lymphadenopathies correlated with early worsening events during follow-up (median length of follow-up 52 months, range 6–117 months, z value=2.3, $P=0.024$).

Table 1 Clinical, haemodynamic and evolution data of the pulmonary arterial hypertension group (n=30)

Patient	Age ^a	Diagnosis ^b	Family history	New York Heart Association class ^c	Mean pulmonary artery pressure (mmHg)	Pulmonary vascular resistance (MPa·s/m ³)	Worsening events	Delay from CT (months) ^d	Follow-up (months)
1	6 years	Idiopathic arterial hypertension	None	II	49	16	None		87
2	1 year 4 months	Idiopathic arterial hypertension	None	II	60	15	None		117
3	2 years 11 months	Idiopathic arterial hypertension	None	III	50	7	None		11
4	13 years 1 month	Idiopathic arterial hypertension	None	III	49	15	None		40
5	4 years 2 months	Idiopathic arterial hypertension	None	II	84	16	None		62
6	4 years 0 months	Idiopathic arterial hypertension	None	III	84	14	Deceased	6	6
7	15 years 7 months	Idiopathic arterial hypertension	None	II	59	18	None		24
8	13 years 2 months	Idiopathic arterial hypertension	None	III	63	18	None		56
9	1 year 5 months	Idiopathic arterial hypertension	None	III	71	14	Need for Potts procedure	0	53
10	3 years 7 months	Idiopathic arterial hypertension	None	IV	41	6,7	None		27
11	8 years 11 months	Idiopathic arterial hypertension	None	II	53	16	None		70
12	12 years 9 months	Idiopathic arterial hypertension	None	II	71	21	None	0	63
13	5 years 4 months	Idiopathic arterial hypertension	None	III	56	10	Need for Potts procedure	16	45
14	4 years 7 months	Idiopathic arterial hypertension	None	IV	70	12	Need for Potts procedure	1	89
15	2 years 6 months	Idiopathic arterial hypertension	None	II	75	14,3	None		68
16	11 years 9 months	Heritable pulmonary arterial hypertension	Brother deceased from pulmonary arterial hypertension	III	68	22	Need for Potts procedure	62	83
17	11 years 10 months	<i>Alk-1</i> hypertension	Brother deceased from pulmonary arterial hypertension	N/A	36	7	None		0
18	13 years 10 months	<i>Alk-1</i>	None	IV	90	22	Heart transplantation	10	28
19	12 years 5 months	<i>Alk-1</i>	None	II	49	12	None		47
20	11 months	<i>Alk-1</i>	None	III	69	10	Need for Potts procedure	12	44
21	2 years 9 months	<i>BM/PR2</i>	None	IV	103	18	None		69
22	13 years 3 months	<i>BM/PR2</i>	Mother deceased from pulmonary arterial hypertension	IV	68	41	Need for Potts procedure	67	78
23	2 years 2 months	<i>BM/PR2</i>	None	IV	76	16	None		51
24		<i>TBX4</i>	None	N/A	60	14,4	None		91

Table 1 (continued)

Patient	Age ^a	Diagnosis ^b	Family history	New York Heart Association class ^c	Mean pulmonary artery pressure (mmHg)	Pulmonary vascular resistance (MPa·s/m ³)	Worsening events	Delay from CT (months) ^d	Follow-up (months)
25	9 years 2 months	<i>TBX4</i>	None	III	73	23	None		49
26	14 years 10 months	<i>TBX4</i>	One sister and one cousin with pulmonary hypertension	III	44	5	None		61
27	1 year 6 months	Pulmonary veno-occlusive disease	None	III	41	6,2	Need for Potts procedure	0	47
28	8 years 8 months	Pulmonary veno-occlusive disease	Sister deceased from and one brother with pulmonary arterial hypertension	III	25	12	Heart transplantation	22	22
29	11 years 1 months	Pulmonary veno-occlusive disease	Sister deceased from pulmonary arterial hypertension	IV	73	21	Heart transplantation	6	99
30	6 years 9 months	Pulmonary veno-occlusive disease	None	N/A	54	27	Heart transplantation	0	0
	15 years 3 months	Pulmonary veno-occlusive disease							

N/A data not available

^a Age at initial assessment by CT angiography

^b Final diagnosis after genetic testing: idiopathic or heritable pulmonary arterial hypertension, mutation in activin-like receptor type 2, T-box transcription factor type 4 and pulmonary veno-occlusive disease

^c New York Heart Association class at CT: I: Mild symptoms and no limitation in ordinary physical activity. II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. III: Marked limitation in activity from symptoms, even during less-than-ordinary activity, comfortable only at rest. IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

^d Delay from initial assessment by CT angiography and the worsening event

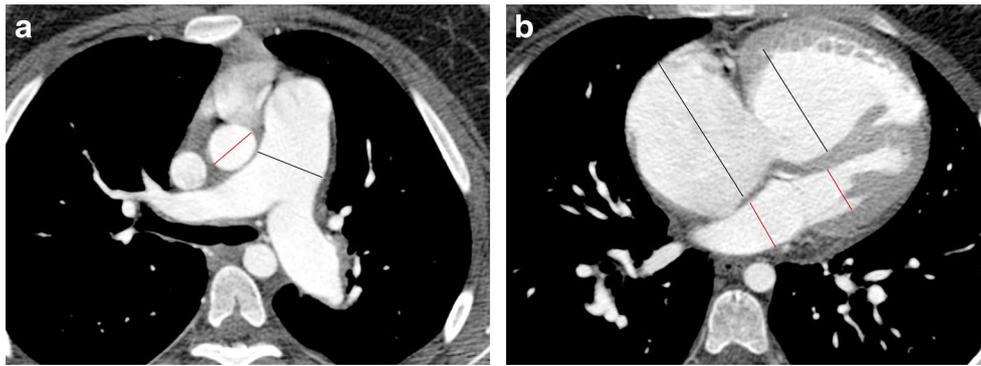


Fig. 1 Pulmonary arterial hypertension from a mutation in bone morphogenetic protein receptor 2 in a 12-year-old girl. Axial CT angiography in mediastinal window. **a** Image at the level of the main pulmonary artery shows enlargement of main pulmonary artery

(diameter marked by *black line*) compared to the aorta (diameter marked by *red line*). **b** On four-chamber view, there is enlargement of the lumen of right (*black lines*) compared to left (*red lines*) cavities

Table 2 Comparison between pulmonary arterial hypertension group and control group for right-to-left vascular and heart chamber ratios^a

	Pulmonary arterial hypertension	Control	Wilcoxon <i>P</i>
Age (months)	91.5 (11–183)	91.0 (11–186)	
Diameter of main pulmonary artery/diameter of ascending aorta	1.43 (0.97–2.05)	0.98 (0.74–1.15)	2.6·10 ⁻¹⁰
Diameter of right atrium/diameter of left atrium	1.54 (1.01–2.44)	1.02 (0.70–1.59)	1.2·10 ⁻⁷
Diameter of right ventricle/diameter of left ventricle	1.32 (0.87–3.22)	0.81 (0.63–1.10)	7.7·10 ⁻¹⁰

^aMedian (range)

Table 3 Optimal threshold values and diagnostic performance of right-to-left vascular and cardiac chambers ratios

Ratio	Value	Youden index	Sensitivity	Specificity	95% confidence intervals for the receiver operating curve
Diameter of main pulmonary artery/diameter of ascending aorta	1.2	0.90	0.90	1.00	0.92–1.00
Diameter of right atrium/diameter of left atrium	1.3	0.67	0.76	0.90	0.81–0.96
Diameter of right ventricle/diameter of left ventricle	1.1	0.80	0.80	1.00	0.91–0.99

Fig. 2 Idiopathic pulmonary arterial hypertension in a 13-year-old boy. Axial CT in lung window shows low-attenuation regions (*asterisks*). **a** Thin slice. **b** Minimum-intensity projection allows for better detection of areas of decreased attenuation and their limits (*dotted lines*)

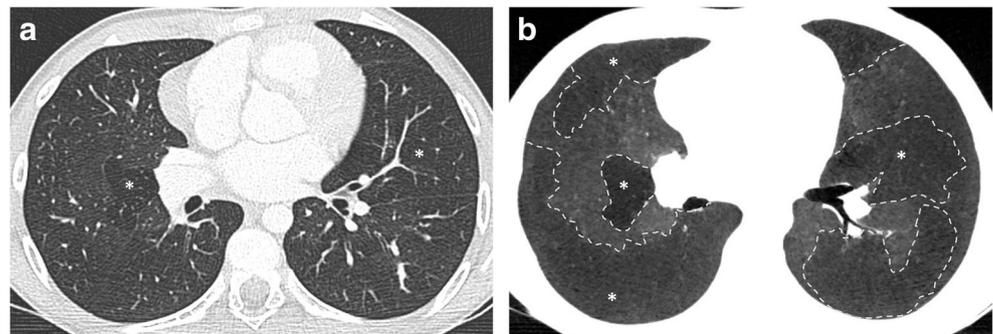
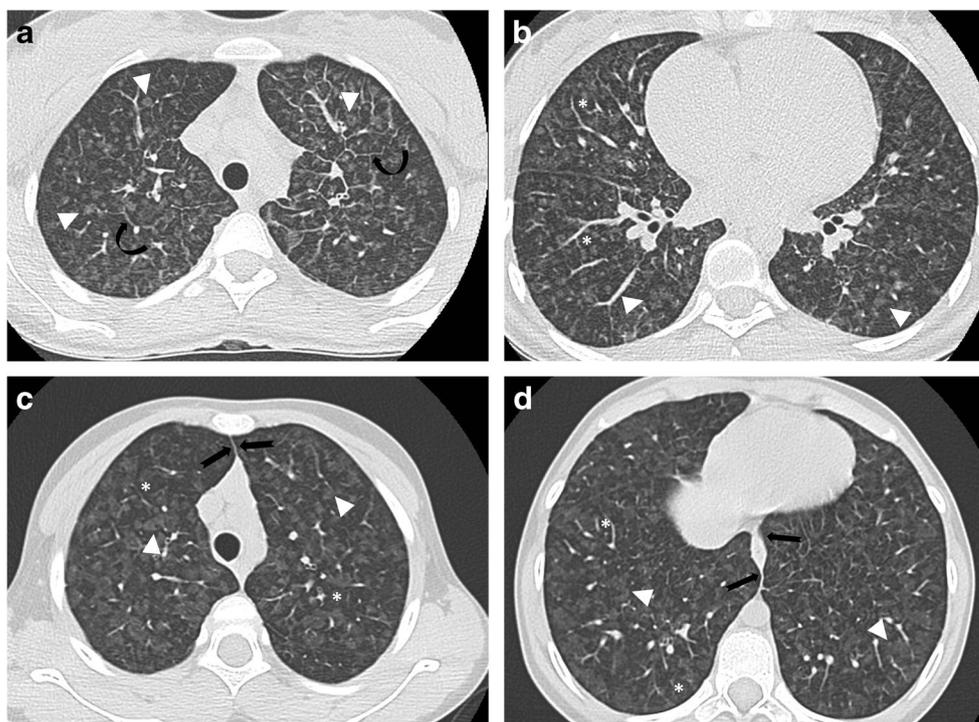


Fig. 3 Axial CT angiography (lung window) of pulmonary veno-occlusive disease. **a, b** In a 15-year-old girl, slices through the upper lobes (**a**) and lower lobes (**b**) demonstrate a mosaic pattern with areas of decreased attenuation (*asterisks*) and centrilobular ground-glass nodules (*arrowheads*) with smooth interlobular lines (*arrows*). **c, d** In a 7-year-old-girl, slices through the upper lobes (**c**) and lower lobes (**d**) demonstrate similar findings, and also hyperinflation of the lungs (*arrows*)



Discussion

Idiopathic and heritable pulmonary arterial hypertension represent major causes of pulmonary arterial hypertension in childhood. With pulmonary veno-occlusive disease, they constitute a heterogeneous group of diseases that can be difficult to distinguish on the basis of clinical, ultrasound or heart catheterization data while treatment and prognosis might be dramatically different. A systematic analysis and better understanding of CT angiography anomalies could contribute to earlier detection and better disease classification, allowing for tailored treatment of pulmonary arterial hypertension in children.

The diagnosis of pulmonary hypertension, which is usually suspected on echocardiography, is confirmed by right heart catheterization. Yet noninvasive tools with high sensitivity

and specificity could be useful for detecting at-risk patients. In our study, detection by CT angiography of enlargement of pulmonary arteries and right heart chambers showed high sensitivity and specificity in children with pulmonary arterial hypertension, as compared to normal patients. Recently, Caro-Dominguez et al. [22] determined main pulmonary artery diameter/ascending aorta diameter ratios in a cohort of 44 children affected with pulmonary arterial hypertension, and compared them to a control group. The authors proposed a main pulmonary artery diameter/ascending aorta diameter ratio of 1.3, which provided a positive likelihood ratio of 34, a specificity of 98%, and a receiver operating characteristic area under the curve of 94%. Our study has led us to propose a threshold value of 1.2, which had a better sensitivity (90%), a specificity of 100%, and a receiver operating characteristic area under the curve of 97.5%. This result suggests that an

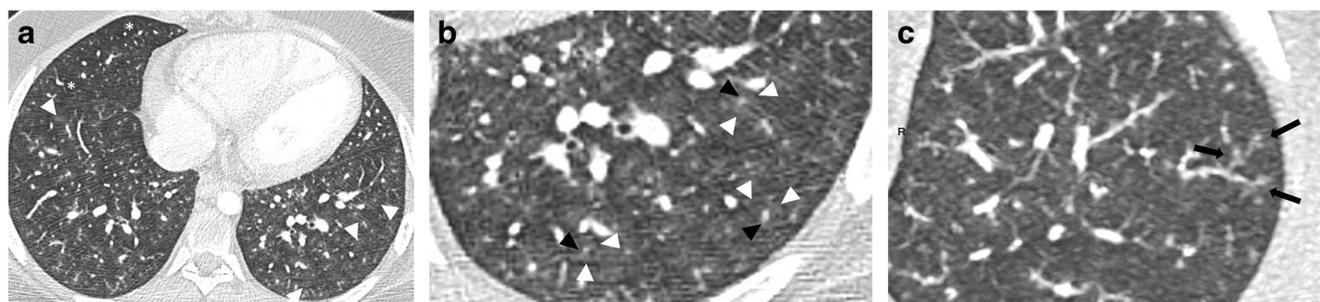


Fig. 4 Axial CT angiography in a 12-year-old girl with pulmonary arterial hypertension caused by a mutation in bone morphogenetic protein receptor 2. **a** There is a mosaic pattern of attenuation with areas of decreased attenuation (*asterisk*) and diffuse low-density ground-glass

nodules (*arrowheads*) **b, c** Detail images show ground-glass nodules (*white arrowheads*) centred around arterioles (*black arrowheads*), and enlargement of peripheral arteries. Arteriolar tree-in-bud micronodules (*arrows*) are also evident



Fig. 5 Severe pulmonary arterial hypertension in a 14-year-old girl with hereditary hemorrhagic telangiectasia syndrome from a mutation in activin-like receptor kinase-1. Thin maximum-intensity projection axial CT (lung window) shows neovessels (arrows)

increased main pulmonary artery diameter/ascending aorta diameter ≥ 1.2 at CT angiography performed for any reason in children should raise suspicion for pulmonary arterial hypertension, with indication for heart ultrasound, as reported in adults in a recent meta-analysis (1,350 adult subjects) [23]. In that study, Shen et al. [23] reported a sensitivity and specificity of 74% and 81%, respectively, to detect pulmonary hypertension in adults for a main pulmonary artery diameter/ascending aorta diameter threshold value of 1.

Chaudry et al. [7] described a large variety of imaging findings including peripheral vasculopathy, centrilobular opacities, cardiomegaly and central pulmonary arterial

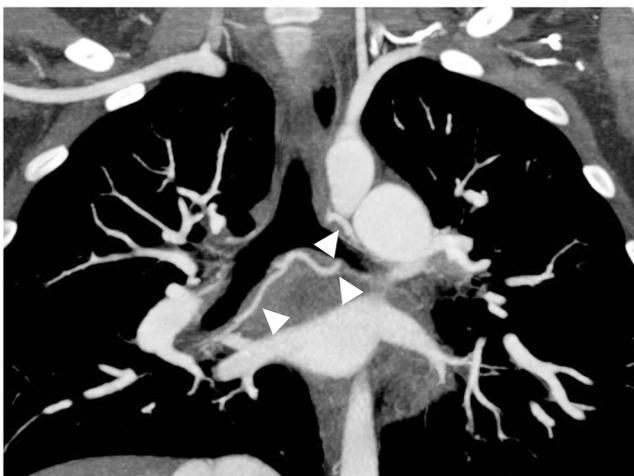


Fig. 6 Idiopathic pulmonary arterial hypertension in a 12-year-old boy. CT angiography shows dilatation of bronchial arteries (arrowheads), seen as vascular structures emerging from the aorta, running along the bronchial structures and with a diameter greater than 1.5 mm

enlargement in 17 idiopathic children ages 1 month to 17 years, excluding those with pulmonary veno-occlusive disease, which is consistent with our results. Mosaic attenuation and perfusion were rare (respectively 3 and 1 patients) in Chaudry’s cohort, whereas they were the most frequent anomaly in our patients. Griffin et al. [24] reported mosaicism in seven of eight adults with idiopathic pulmonary hypertension, which is more consistent with our results.

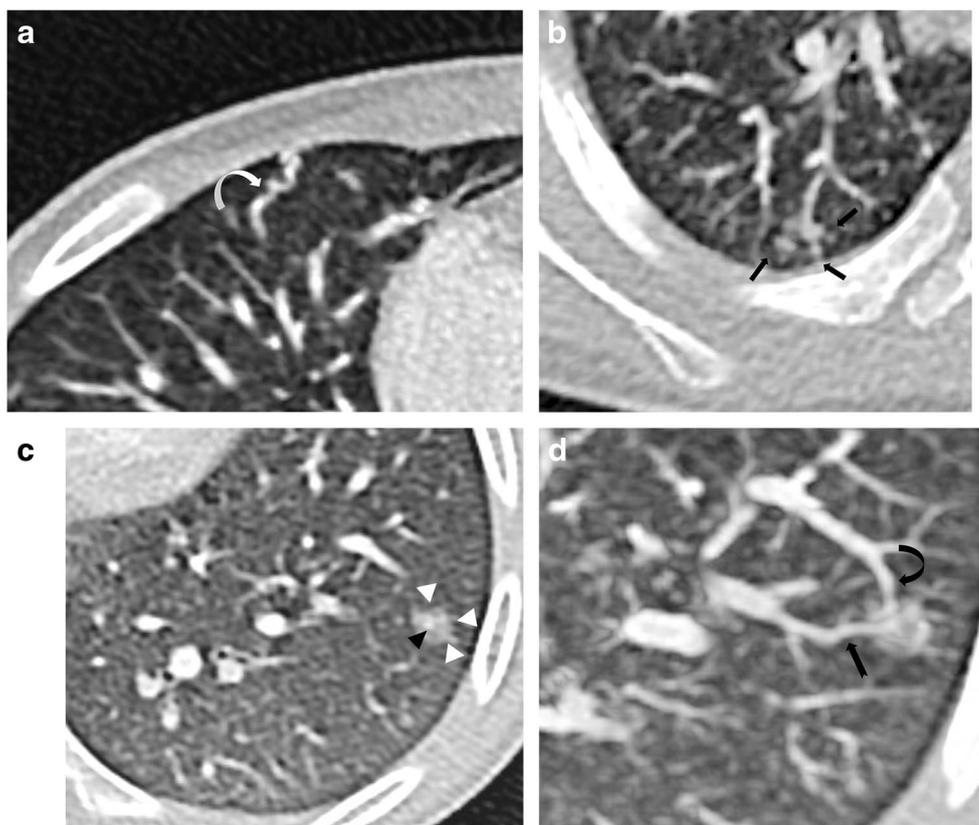
We found a typical pattern in children affected with pulmonary veno-occlusive disease, a pattern that was not observed in any of the other 26 children. This pattern, consisting of thickened interlobular septa, poorly defined centrilobular nodular opacities, and lymphadenopathy, was also reported in children with pulmonary veno-occlusive disease by Woerner et al. [9] in nine paediatric patients. In addition, we found a mosaic perfusion with poor parenchymal vascularization. Mineo et al. [8] described this pattern in adults and found a diagnostic accuracy of CT of 90.5% in identifying people with pulmonary veno-occlusive disease in a cohort of 96 adults with pulmonary arterial hypertension. These results are particularly important to guide genetic research and ensure the correct therapeutic management of these patients [4, 10].

Other genotype-phenotype correlations were difficult to establish in this small series, but children with *Alk-1* mutation had images suggesting lung fistula or liver telangiectasia [25]. It might be interesting to further define CT angiography phenotypes in children with no identified mutations to attempt to differentiate them.

Intrapulmonary peripheral neovessels were described by Sheehan et al. [18] as tiny, micronodular, serpiginous intrapulmonary vessels, coursing in directions inconsistent with known arteriolar anatomy, which could match the histological report of abnormally dilated, muscular arteries within alveolar septa in people with Eisenmenger syndrome. In our cohort and in Chaudry et al.’s [7] cohort, it was described in 13 (43%) and 6 (35%) children, respectively, and was correlated in our cohort with higher mean pulmonary artery pressures. We thus believe that neovascularity is a manifestation of severe pulmonary arterial hypertension regardless of cause, as also suggested by Devaraj and Hansell [16].

In a cohort of 85 adults with idiopathic pulmonary arterial hypertension, 20% presenting with mediastinal lymphadenopathies, Moua et al. [26] hypothesized that mediastinal lymphadenopathies might be caused by elevated right-side pressures in people with idiopathic pulmonary arterial hypertension. In our study, mediastinal lymphadenopathies were present in 33% of the children and correlated with poor outcome of the disease. The presence of mediastinal lymphadenopathies might therefore be a new predictor of outcome in paediatric pulmonary arterial hypertension and should be explored in future studies to understand its physiopathological significance.

Fig. 7 Pulmonary arterial hypertension in an 11-month-old boy with hereditary hemorrhagic telangiectasia syndrome caused by a mutation in activin-like receptor kinase-1. Parenchymal details are seen in excerpts from axial CT in lung window. **a** Peripheral subpleural neovessels (*arrow*). **b** Branching micronodules with a tree-in-bud figure (*arrows*). **c** A micronodule is observed in the left lower lobe (*black arrowhead*) surrounded by ground-glass nodule (*white arrowheads*). **d** Maximum-intensity projection reconstruction shows that this micronodule is in contact with both an artery (*curved arrow*) and a vein (*straight arrow*), suggesting an intrapulmonary arteriovenous fistula



Limitations of this study include its retrospective design, a possible selection bias at the time of referral to our institution, and the small number of patients.



Fig. 8 Pulmonary arterial hypertension caused by a mutation in activin-like receptor kinase-1 in an 11-year-old girl. CT angiography demonstrates enhancing nodules (*white arrowheads*) and a larger lesion (*black arrowheads*) in the liver in the arterial phase of acquisition, evocative of telangiectasia and confluent vascular masses, respectively, which suggest hereditary hemorrhagic telangiectasia in the context of pulmonary arterial hypertension

However, we could conduct further study using a larger cohort of patients despite the low prevalence of the disease because our institution is a tertiary referral centre for paediatric pulmonary arterial hypertension. Furthermore, our patients exhibited a wide range of disease severity.

Conclusion

Chest CT angiography, realized for any indication in children, can play a crucial role in raising suspicion for pulmonary arterial hypertension and leading to further investigations. Our study suggests that in children with pulmonary arterial hypertension CT angiography is helpful in correctly guiding to the diagnosis of pulmonary veno-occlusive disease, and evaluating initial severity and predictors of worse outcome. Further studies are necessary to confirm these data.

Compliance with ethical standards

Conflicts of interest None

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