Original Article

Decreased Pulmonary Artery Bifurcation Angle: A Novel Imaging Criterion for the Diagnosis of Chronic Pulmonary Thromboembolism

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Received: 17 October 2020
Revised: 06 March 2021
Accepted: 07 June 2021

Abstract

Background: Chronic pulmonary thromboembolism (CTEPH) is an unusual complication of acute pulmonary embolism (PE), which is now considered to be treatable. In modern multi-detector scanners, a detailed evaluation of pulmonary artery geometry is currently possible. This study aimed to evaluate the changes in pulmonary artery bifurcation angle (PABA) in the follow-up computed tomography angiography (CTA) of patients with acute PE.

Methods: In this cross-sectional study, the records of two tertiary-level academic hospitals were gathered from 2012 to 2019. Pulmonary artery (PA) bifurcation angle and diameter were measured. Chi-square test, independent samples *t* test, Mann-Whitney, and Pearson's tests were employed to compare data. To evaluate the cut-off point, we utilized receiver operating characteristic (ROC) curve analysis. The accuracy, sensitivity, and specificity of pulmonary artery bifurcation angle changes were calculated. A P value <0.05 was considered to be significant.

Results: Forty-six patients were included in the study. No significant differences were found between patients with and without CTEPH, and PABA in the dimeters of PA trunk, right PA, and left PA in the first CTA images (P values of 0.151, 0.142, 0.891, and 0.483, respectively), while in the secondary CTA, the mean PABA was significantly smaller in patients with CTEPH (P=0.011). In the receiver operating characteristic (ROC) analysis, delta angle revealed an area under the curve of 0.745 and an optimal cutoff of 0, leading to a sensitivity of 64%, specificity of 87%, and accuracy of 76% for diagnosing CTEPH.

Conclusion: We showed a significant decrease in PABA in patients developing CTEPH. This parameter can be easily measured in lung CTA.

Please cite this article as: Abbasi B, Darvish A, Akhavan R, Pezeshki Rad M, Farrokh D, Emadzadeh M, Dehghani S. Decreased Pulmonary Artery Bifurcation Angle: A Novel Imaging Criterion for the Diagnosis of Chronic Pulmonary Thromboembolism. Iran J Med Sci. doi: 10.30476/IJMS.2021.88058.1926.

Keywords ● Pulmonary artery ● Computed tomography angiography ● Pulmonary embolism

What's Known

- The diagnostic value of pulmonary artery bifurcation angle in the diagnosis of chronic pulmonary embolism has never been evaluated in the literature.

What's New

- Decreased pulmonary artery bifurcation angle is significantly smaller in the imaging follow-up of patients developing chronic pulmonary embolism.
- The findings of the current study may be considered novel for diagnosing the progression of the disease to chronic form.

Introduction

Pulmonary thromboembolism (PE) is a life-threatening condition and a leading cause of morbidity and mortality. Although most cases of PE resolve without any sequelae, in some patients thrombi do not resolve entirely and may go on to organize inside

the vessels, eventually leading to endothelialized fibrotic obstructions of the vascular bed and pulmonary hypertension. In this condition, which is known as chronic thromboembolic pulmonary hypertension (CTEPH), the blood flow will shift towards other healthy parts of the pulmonary vasculature, leading to the remodeling of these previously healthy vascular structures. The eventual result is pulmonary hypertension and cor pulmonale.[1] In recent years, the emergence of novel treatment techniques, such as pulmonary endarterectomy, has increased the chance of early treatment in patients with CTEPH.[2] Additionally, this condition, previously known only on autopsy series, is now considered curable through the use of pulmonary thromboendarterectomy and disease-modifying medical therapies.[3]

For unclear reasons, the natural history of the acute PE is not predictable and the pathogenesis and time courses remain unclear.[3] Clinical symptoms in patients with CTEPH are non-specific and related to the development of pulmonary hypertension.[4] Unfortunately, the physical examination findings are entirely unremarkable early in the course of the disease, and timely diagnosis demands a high level of clinical suspicion. The condition is usually diagnosed during the workup of unexplained pulmonary hypertension. Digital subtraction angiography (DSA), which has long been the main diagnostic modality is not commonly applied in modern medical practice. Ventilation/perfusion (V/Q) scintigraphy has a reported sensitivity of 97.4% in diagnosing CTEPH, but is still unavailable in some centers.[3] On the other hand, due to its wide availability and low invasiveness, CTPA tends to be overused. With the new multi-detector computed tomography (CT) scanners, high-speed helical computed tomography angiography (CTA) of lungs has replaced angiography in most centers and has demonstrated a promising sensitivity of 83%-100% and a specificity of 89%-96%.[5]

A variety of parenchymal and vascular abnormalities have been described in the CTA of patients with CTEPH.[5-7] CTA also has the advantage of ruling out other parenchymal and mediastinal causes of pulmonary hypertension, such as pulmonary fibrosis, fibrosing mediastinitis, pulmonary artery sarcoma. A positive CTA may be utilized as a basis for surgical planning in selected patients. The ability of 3D reconstruction and thin-slice acquisition provides the opportunity for a detailed evaluation of vascular structures. The main pulmonary artery and its branches were considered to be parts of right cardiac structures, and any change in the pulmonary vasculature had direct effects on the physiology and anatomy of these vessels.[8] There have been some data concerning the changes of pulmonary arterial size in pulmonary hypertension;[9] however, there is no information about the geometry of pulmonary artery bifurcation in the setting of CTEPH. Herein, we retrospectively evaluated the changes in the pulmonary artery bifurcation angle (PABA) in CT angiographic follow-up of patients with the initial diagnosis of acute PE.

Methods

Patient Selection

This study was approved by our institution's ethics committee (approval code: IR.MUMS.MEDICAL.REC.1397.511). We retrospectively collected the records of patients, who presented with non-specific respiratory symptoms from three weeks to three years after an initial event of acute PE. The hospital records of two tertiary-level academic hospitals at Mashhad University of Medical Sciences were gathered from 2012 to 2019. All the patients fulfilling the inclusion criteria at the specified time entered the study, which included patients older than 18 years old, who underwent repeated pulmonary CTAs for the clinical suspicion of CTEPH. The patients with any of the following findings were excluded: para-cardiac tumoral lesions, mediastinal infiltrations, severe hilar lymphadenopathy (subjectively defined by a radiologist), severe motion artifacts, diffuse parenchymal lung disease, and severe scoliosis (subjectively defined by a radiologist, as scoliosis preventing proper measurement of pulmonary artery bifurcation angle).

Two vascular and interventional radiologists with five and 10 years of experience examined the images and categorized the follow-up CTAs as the presence or absence of CTEPH. They were not informed about the target variable studied in the research (PABA). They evaluated the images regarding the presence of findings suggestive of CTEPH as below:[6]

- Vascular findings: intravascular filling defect, intravascular band or web, arterial narrowing, arterial wall thickening, presence of collateral vessels, reflux of contrast into hepatic veins, straightening of the interventricular septum, and arterial wall calcification.
- Parenchymal findings: mosaic lung attenuation, signs of previous lung infarct, and pleural thickening.

Any discrepancies were tackled via discussion. The patients were divided into two groups based on the main outcome, which was defined as the presence (patient group) or

absence (control group) of imaging findings of CTEPH on the second pulmonary CTA. A final impression of no PE/acute PE/chronic PE was also recorded for each examination.

Image Acquisition

All the pulmonary CTA studies were performed in a caudocranial direction utilizing a commercially available 16-slice CT scanner (NeuViz 16 Essence, Neusoft Medical Systems, China). All the scans were done with the patients in the supine position extending their arms over the head. Intravenous contrast material (100 cc) was injected and followed by 50 mL of saline chaser at a rate of 4 mL/s.

Image Analysis and Measurements

The initial CTA (at the time of acute PE event) and follow-up CTA studies of each patient were transferred from Picture Archive and Communicating System (PACS) into a dedicated workstation. The scans were anonymously analyzed by use of OSIRIX MD™ (version 10.0.1) software (Pixmeo, Switzerland) and a medical monitor. From each dataset, multiplanar reconstructions were generated in order to make the angle of the axial images completely perpendicular to the trachea (figure 1a). The bifurcation angle was measured at a level that made it possible to visualize the greatest possible diameter of the right and left pulmonary arteries (PAs) (figure 1b). In order to measure the PA trunk, we used an image, in which the ascending aorta and PA trunk were magnified until constituting at least 50% of the display. In the axial image, at the pulmonary bifurcation level, the maximum diameter at the axis perpendicular to the long axis of PA was recorded as the pulmonary artery diameter. The right and left PAs were measured at an axis perpendicular to the longitudinal axis and within a distance of 1 cm from the bifurcation site. The difference between PABA in the first and the second CTA studies (delta angle) was calculated as follows:
Delta Angle=PABA in the initial CTA-PABA in the followup CTA

In the initial CTAs depicting acute PE, the level of PA involvement (saddle, main, lobar, segmental, subsegmental) and the presence/absence of right heart failure signs (reflux of contrast into the inferior vena cava and straightening of the interventricular septum) were recorded.

Statistical Analysis

We applied SPSS (version 22 for Windows®, IBM Statistics, Chicago, IL) to analyze the data. Descriptive statistics were determined for all the variables. Kolmogorov-Smirnov test was employed initially to check the normal distribution of data. Chi-square test, independent samples *t* test, and Mann-Whitney test were applied to

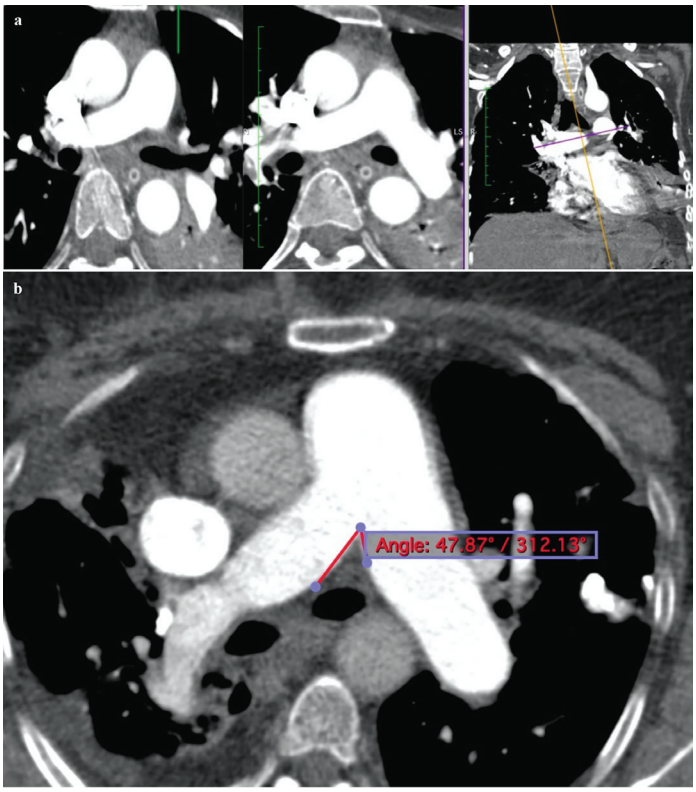

Figure 1: Axial pulmonary CT angiography (a) shows the reconstruction technique of the axial CTA images; the bifurcation angle measurement (b) is performed on axial lung CTA images at the level of pulmonary artery bifurcation.

compare the data between groups of patients. To evaluate a cut-off point for diagnosing chronic PE, we used ROC curve analysis. The correlation between quantitative variables was evaluated utilizing Pearson's test. A P<0.05 was considered to be of statistical significance in all the tests.

Results

Demographics

Among the 46 patients included in the study, the imaging signs of PE in 25 of them (54.3%) were completely resolved in the second CTA while 21 patients (45.6%) showed the imaging findings signs of chronic PE in their second CTA. Basic demographic and imaging data of patients are summarized in table 1. There were no significant differences in sex and age between the two groups.

Imaging Findings in the Initial CTA

The location of involvement was significantly different between the case and control groups (P<0.001), as the initial clot was located more centrally in the patients with subsequent progression to CTEPH (table 1).

According to the frequency of imaging signs of right ventricular strain, contrast reflux showed no significant differences between cases and controls; however, there was a significant difference in the frequency of interventricular septal straightening between the two groups (table 1). The pulmonary artery geometric parameters revealed no statistically significant difference between the two groups (table 1).

Imaging Findings in the Follow-Up CTA

Imaging findings in the repeated pulmonary CTA scans are summarized in table 2. The median time between the two scans was 50 (IQR 26-315) days for the control and 64 (IQR 38-246) days for the case group (P=0.708). There was no significant correlation neither between the time interval and delta angle (P=0.812, Pearson's test), nor between the time interval and PABA (P=0.12). The frequency of interventricular septum straightening was significantly different between the two groups (P<0.001). However, this was not the case for the reflux of contrast into the inferior vena cava (table 2).

The pulmonary artery size measurements, including diameters of the pulmonary trunk, right PA, and left PA, were not significantly different between the two groups (table 2). The pulmonary bifurcation geometric measurements, including

Table 1: Patient demographics and findings in the initial CTA

Variable			Case (n=21)	Control (n=25)	P value
Age (years , Mean±SD)			56.54±16.58	58.9±19.2	0.591*
Women, n (%)			13 (61.90)	9 (36.00)	0.202**
Time between two CTAs, days (median, (IQR))			64 (38-246)	50 (26-315)	0.714***
Initial pulmonary CT	Location of acute PE, n (%)	Saddle emboli	5 (23.81)	1 (4.00)	<0.001**
		Main pulmonary arteries	13 (61.90)	5 (20.00)	
		Lobar arteries	3 (14.28)	8 (32.00)	
		Segmental arteries	0 (0.00)	11 (44.00)	
	PA measurements, median (IQR)	PA bifurcation angle, degrees	68 (60-92)	87 (70-97)	0.142***
		PA trunk diameter, mm	28 (27-31)	27 (23-29)	0.151***
		Left main PA diameter, mm	21 (18-23)	20 (17-23)	0.891***
		Right main PA diameter, mm	21 (19-23)	20 (918-24)	0.483***
	Imaging signs of RVS, n (%)	Contrast reflux	6 (28.57)	4 (16.00)	0.248**
		Interventricular septum straightening	13 (61.90)	7 (28.00)	0.019**
	Pulmonary infarct, n (%)		5 (23.81)	11 (44.00)	0.111**

PE: Pulmonary thromboembolism; CPE: Chronic pulmonary thromboembolism; RVS: Right ventricular strain; PA: Pulmonary artery; SD: Standard deviation; *Independent samples *t* test; **Chi-square test; ***Mann-Whitney U test

Table 2: Findings of follow-up pulmonary CTA

Variable			Case (n=21)	Control (n=25)	P value
Follow-up pulmonary CTA	Imaging signs of RVS, n (%)	Contrast reflux	6 (28.57)	4 (16.00)	0.271**
		Interventricular septum straightening	11 (52.38)	3 (12.50)	<0.001**
	PA measurements, median (IQR)	PA bifurcation angle, degrees	71 (41-94)	91 (83-101)	<0.001**
		PA trunk diameter, mm	28 (25-31)	27 (23-31)	0.771**
		Left main PA diameter, mm	21 (19-23)	20 (18-22)	0.653**
		Right main PA diameter, mm	20 (19-24)	19 (16-23)	0.218**
	Delta Angle, median (IQR)		5 (-4-25)	-3 (-22- 0)	<0.001*

PE: Pulmonary thromboembolism; CPE: Chronic pulmonary thromboembolism; RVS: Right ventricular strain; PA: Pulmonary artery; SD: Standard deviation; *Independent samples *t* test; **Chi-square test; ***Mann-Whitney U test

mean PABA and delta angle, were of significant difference between the case and control groups (table 2, figure 2).

ROC analysis of delta angle showed an area under the curve of 0.745 and an optimal cutoff 0, leading to a sensitivity of 64% (CI, 41%-83%), specificity of 87% (CI, 68%-97%), and accuracy of 76% (CI, 61%-87%) for diagnosing chronic PE. ROC analysis of PABA in the follow-up CTA revealed an AUC of 0.739 and showed that a PABA smaller than 80 degrees could diagnose chronic PE with a sensitivity of 62% (CI, 38%-82%), specificity of 80% (CI, 59%-93%), and accuracy of 72% (CI, 56%-84%) (figure 3).

Discussion

In this article, a significant decrease of PABA in patients, who developed CTEPH in comparison to those, in whom acute PE completely resolved over time was observed. This finding can be evaluated in the subsequent pulmonary CTA of patients with acute PE, who are being followed up and may play an important role in the early diagnosis of the disease. The importance of the pulmonary vessels as prognostic indices in chronic lung diseases has been described in the literature. The main pulmonary artery diameter[9] and the pulmonary artery/aorta ratio[10] are known to predict the likelihood of pulmonary hypertension. However, to our knowledge, the geometry of pulmonary artery bifurcation has never been described in adults.

The cause of decreasing pulmonary artery bifurcation angle in CTEPH patients might be discussed to be pulmonary artery hypertension. Meanwhile, our study demonstrated no significant differences in the diameter of these arteries neither between the images taken in the acute and chronic phases of the disease in patients with CTEPH, nor between the two groups of patients. Considering that the main pulmonary artery diameter is the most discussed imaging finding in pulmonary artery hypertension,[11-13] bifurcation angle reduction does not seem to be related to pulmonary artery pressure alone. Unfortunately, the pulmonary artery pressure measurement was not performed in a considerable number of our patients, and we were not able to evaluate the relationship between pulmonary artery pressure and pulmonary bifurcation angle directly. However, this is the first time that pulmonary artery bifurcation angle measurement is described in the literature, and its significance needs further evaluation.

Literature suggests that many inflammatory processes are involved in PE. Many researchers

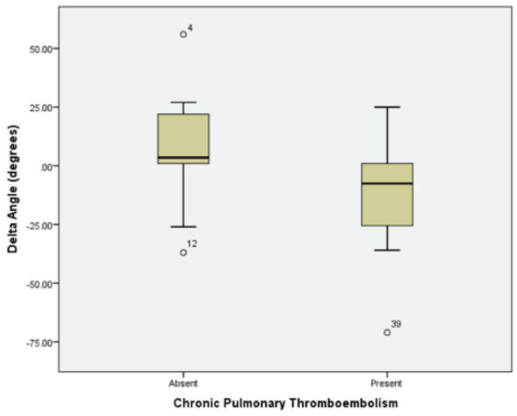

Figure 2: Boxplot depicts the changes in pulmonary artery bifurcation angle in patients with and without CPE.

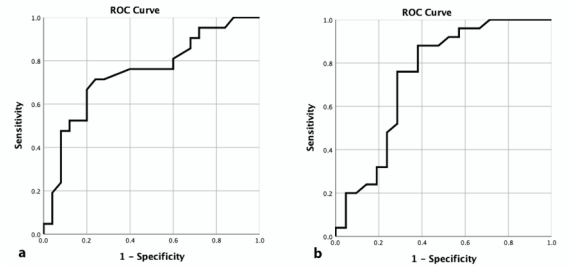

Figure 3: ROC curves for the accuracy of delta angle for diagnosing chronic PE (a) and PABA in the follow-up CTA for ruling out chronic PE (b) are represented.

believe that the underlying processes, including trauma, hypoxia, and other problems with elevated inflammatory cytokines, such as cancers or rheumatic diseases, are the initiators of thromboembolic events.[14] In fact, changes in the vascular endothelium trigger the production of several cytokines responsible for a majority of thrombotic problems. It has been revealed that patients with PE may present with leukocytosis and elevated levels of neutrophil-to-lymphocyte ratio (NLR).[15] Venetz and others reported that the leukocyte count of more than 9.8×109 /L were significantly associated with a higher mortality rate even in the presence of prompt anticoagulant treatment.[16] Among these mentioned cytokines, the tumor necrosis factor is also the main player. Tumor necrosis factor triggers extrinsic coagulation through VIIa activation. In addition, the aforementioned factor is responsible for fibrogenesis.[17] Zhang and colleagues reported that the level of TNF-α is higher in patients with pulmonary thromboembolism.[18] Kooiman also reviewed the higher levels of this factor in patients with chronic PE compared to the acute cases.[19] Furthermore, these cytokines make the patients prone to developing CTEPH. The cytokines probably trigger fibrogenesis and remodeling, leading to higher rates of CTEPH.[20] This fibrogenesis and remodeling process might be involved in the imaging finding of

decreased pulmonary artery bifurcation angle. In fact, chronic inflammation can cause vascular fibrosis and remodeling, which does not affect the luminal diameter of the pulmonary artery and only further spreads and bulges the walls, therefore tightening the bifurcation angle.

Although pulmonary artery bifurcation angle was significantly smaller in the patients developing CTEPH than the other group, we cannot readily consider a small bifurcation angle as an imaging sign of the disease, since we did not include the other causes of chronic lung disease and pulmonary artery hypertension (chronic obstructive pulmonary disease) in the present work. Herein, it is suggested that a decreased pulmonary artery bifurcation angle in the imaging follow-up of patients with acute PE could be considered as a warning sign of progression to CTEPH.

To the best of our knowledge, this is the first work to suggest a novel criterion in the follow-up CTA of patients with acute PE for diagnosing CTEPH through the measurement of PABA. The results of this study may be of potentially unique interest for pulmonologists, who focus their attention on the diagnostic importance of pulmonary bifurcation geometry.

However, this study had some limitations. Our present work had a modest sample size, which is due to the tight inclusion criteria and only including the PE patients with at least two CTA studies. Moreover, we were unable to assess the possible associations of PABA with PA hypertension as discussed above. Further studies with a prospective design, assessing PA pressure in PE patients, can be valuable in this regard.

Conclusion

Decreased pulmonary artery bifurcation angle in the imaging follow-up of patients with acute PE might be considered as a novel criterion for diagnosing chronic PE. Pulmonary artery bifurcation angle has not been previously evaluated as a diagnostic criterion for the progression of chronic PE. Designing similar studies with larger sample sizes and evaluating the correlation between PABA and pulmonary artery pressure may lead to interesting results.

Acknowledgement

This research was supported by the Chancellor for Research of Mashhad University of Medical Science, Mashhad, Iran. This is derived from the Radiology Specialty thesis number 970272 conducted by Afrouz Darvish, in Mashhad University of Medical Sciences.

Conflict of Interest: None declared.

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