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Role of Computed Tomography Pulmonary Angiography in diagnosing COPD-associated Pulmonary Hypertension

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Abstract: Chronic obstructive pulmonary disease (COPD) is a progressive lung disease associated with significant morbidity and mortality. Pulmonary hypertension (PH) is a common complication of COPD that adversely impacts patients' outcomes. Early identification of COPD-associated PH is crucial, yet its diagnosis remains challenging due to overlapping symptoms with COPD and limitations of conventional diagnostic methods. While right heart catheterization remains the gold standard for PH diagnosis, its invasive nature limits its routine application. Transthoracic echocardiography, although recommended as the initial imaging modality, may be hindered by technical difficulties in COPD patients. Computed tomography pulmonary angiography (CTPA) offers a comprehensive assessment of pulmonary vasculature and cardiac structures, making it a valuable tool in diagnosing COPD-associated PH. This review aims to explore the role of CTPA in identifying COPD-associated PH and emphasize the CTPA parameters employed for evaluating this condition

Keywords: *Pulmonary Hypertension; Computed Tomography Pulmonary Angiography; COPD.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive incurable lung disease **(1)**. It is a leading cause of morbidity and mortality worldwide, primarily caused by inhalation of toxic agents such as cigarette smoke, indoor and ambient air pollutants, and occupational exposures **(1-3)**. Pathological hallmarks of COPD include bronchoconstriction, small airway remodeling, and alveolar destruction, resulting in chronic bronchitis and pulmonary emphysema **(2,4)**.

Chronic hypoxia, a common sequel of COPD, induces pulmonary vascular remodeling, leading to pulmonary hypertension (PH) **(4,5)**. According to the current guidelines from the European Society of Cardiology (ESC)/European Respiratory Society (ERS), PH is defined as elevated mean pulmonary arterial pressure (PAP) greater than 20 mmHg at rest, as measured by right heart catheterization (RHC) **(6)**. PH is categorized into different groups, with COPD-associated PH classified as group III (pre-capillary PH) **(6)**.

COPD-associated PH is an important and common complication, with a prevalence ≥ 50% in patients with advanced COPD **(7)**. While often presenting with mild to moderate severity and gradual progression, it can significantly impact patients' survival. Severe PH occurs less frequently, yet COPD patients' survival is inversely

related to the severity of PH **(7)**. Early identification of COPD-associated PH is crucial for optimal patient management. However, differentiating its symptoms from those of COPD is challenging, especially in its mild form **(7)**.

RHC is the gold standard for the diagnosis of COPD-associated PH. However, it is not recommended in the routine assessment of COPD patients due to its invasive nature **(7)**. Non-invasive imaging modalities play an essential role in the diagnosis of COPD-associated PH **(8)**. Current guidelines recommend transthoracic echocardiography (TTE) as the first-line imaging in the case of suspecting PH **(6)**. Nevertheless, its diagnostic efficiency can be limited by technical difficulties due to chest overinflation in COPD patients **(7)**.

Computed tomography pulmonary angiography (CTPA) can provide a more comprehensive assessment of pulmonary vasculature and cardiac chambers in patients with clinical suspicion of PH, making it an integral investigation in the diagnostic pathway of COPD-associated PH **(9)**. Accurate identification of COPD-associated PH through CTPA can improve patients' outcomes.

This review will explore the role of CTPA in the diagnosis of COPD-associated PH, highlighting the key CTPA parameters essential for evaluating this condition.

CTPA image acquisition

Purpose and Principles

The purpose of CTPA is to provide detailed visualization of the main pulmonary artery (MPA) and its branches **(10)**. This is achieved by administration of intravenous contrast agent to opacify the right side of the heart and pulmonary arteries while avoiding simultaneous opacification of the aorta **(10)**. Precise timing is crucial for achieving good optimal image quality, as delayed imaging can hinder the differentiation between pulmonary arteries and veins **(10)**, affecting the accuracy of image interpretation.

Contrast agent's injection techniques

Two primary methods of contrast injection are employed:

1) Test bolus: A small amount of contrast agent is initially injected (20-25 mL), followed by low-dose scanning through the MPA to generate a time-density curve. This helps to determine the optimal timing for the CTPA scan based on peak contrast enhancement in MPA **(9,10)**.

2) Bolus tracking: A region of interest (ROI) is positioned over the MPA. Then, scan acquisition begins when a threshold contrast density is reached (120-150 HU). This method is generally preferred due to its reliability. However, in patients with congenital heart disease or severe cardiac impairment, test bolus injection may be necessary, as the delay time can be exceedingly long **(9,11)**.

Imaging protocols

CTPA protocols can vary significantly between institutions due to factors such as CT scanner type, ECG-gating capabilities, and injector pump technology **(9)**.

1-Non-ECG gated CTPA: Typically acquired as a helical scan from diaphragm to lung apices during deep inspiration to minimize diaphragmatic motion artifact. Approximately 80 mL of contrast agent is injected at a rate of 4-5 mL/second, with image acquisition initiated 5 seconds post peak MPA enhancement **(9)**.

2-ECG-gated CTPA: Commonly performed using retrospective ECG-gating with dose adjustment to reduce radiation exposure. Image acquisition is primarily focused on the diastolic phase of the cardiac cycle. A cranio-caudal scan direction is used with a trigger delay of 2 seconds post peak MPA enhancement **(9)**. ECG gating improves assessment of cardiac parameters such as cardiac chambers enlargement and hypertrophy **(12)**. Recently, high-pitch ECG-synchronized CTPA protocol is suggested for better contrast opacification of the pulmonary vessels at reduced radiation dose **(13)**.

3-Dual energy CTPA: Similar to non-ECG gated CTPA but includes a saline flush to reduce superior vena cava related artifact. Simultaneous data acquisition at dual energy levels (e.g.,140 and 80 kVp) is used to create an iodine perfusion map of the lung parenchyma through a subtraction technique **(9)**.

Image reconstruction and evaluation

Images are typically reconstructed with 1-2 mm axial sections and 1 mm overlap. For image evaluation, different window settings are employed **(9,10)**:

-Mediastinal window (width 400 HU/level 40 HU).

-Lung window (e.g. width 1500 HU/level -500 HU).

-Pulmonary embolism-specific window (e.g. width 700 HU/level 100 HU).

CTPA parameters

Various CTPA parameters have been described to diagnose PH, irrespective of its underlying cause **(9)**. These parameters can be classified as quantitative and qualitative parameters. When combined, these parameters can facilitate accurate diagnosis of COPD-associated PH. Radiologists can employ these parameters in their routine clinical practice to assist in diagnosis of COPD-associated PH.

Quantitative CTPA parameters

Various static and dynamic quantitative CTPA parameters can be used to predict PH **(14)**.

Static quantitative parameters

1-MPA diameter

Persistent elevation of the PAP causes vascular remodeling and MPA dilatation **(15)**. The maximum width of MPA is measured on axial mediastinal CTPA images, at the level of its bifurcation orthogonal to its long axis **(9) (Figure 1).** A dilated MPA with a mean diameter ≥ 29 mm demonstrates 87% sensitivity, 89% specificity, and 97% positive predictive value for PH diagnosis **(16)**, making it a commonly employed cut-off value in the literature and clinical practice. However, it is essential to recognize that a normal PA diameter (below 29 mm) does not definitively rule out PH **(17)**. Normal MPA diameter is frequently seen in cases of mild PH **(18)**.

Three-dimensional (3D) volume measurement of the MPA on CTPA have been shown to be more effective predictor of PH than axial diameter measurement of the MPA **(19)**. Although uncommon finding in PH, a dilated MPA can potentially compress the left main coronary artery **(20,21)**.

2-MPA-to-ascending aorta (AAo) diameters ratio

Various factors such as patient's age, body surface area, and vascular compliance can impact the diameter of MPA **(22)**. Therefore, depending solely on MPA diameter may not precisely reflect variations in PAP between individuals **(22)**. In addition, diameter of the MPA larger than that of the ascending aorta (AAo) has been identified as an indicator for moderate to severe PH **(16,18)**. Thus, the AAo is measured at the same axial level as the MPA diameter and then compared to it **(23) (Figure 1)**. A MPA-to-AAo ratio > 1 shows strong correlation with PAP rather than using MPA diameter alone, as variables affecting MPA diameter will affect both measurements equally **(23).**

3- MPA-to-descending aorta (DAo) diameters ratio

The descending aorta (DAo) can be measured at the same axial level as the MPA diameter and then compared to it **(24) (Figure 1)**. The MPA-to-DAo ratio has been established as a significant predictor of PH. A MPA-to-DAo ratio ≥1.29 demonstrates 89.6 % specificity and 77.4% sensitivity for the diagnosis of PH **(24)**.

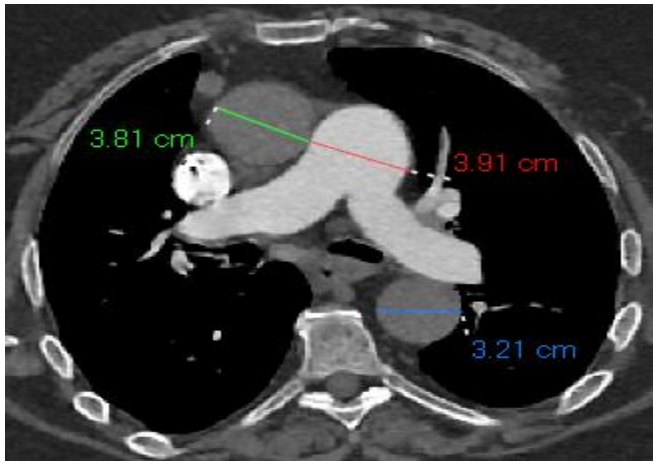

Figure (**1**) Axial CTPA image (mediastinal window) showing measurements of MPA (red measurement), ascending aorta diameter (green measurement), and descending aorta (blue measurement) in a patient with COPD-associated PH. The calculated MPA-to-AAo is 1.03 and the MPA-to-DAo is 1.22

4-Right and left pulmonary artery diameters.

Diameters of both the right pulmonary artery (RPA) and left pulmonary artery (LPA) can be measured 1.5 cm distal from the bifurcation of the MPA **(19) (Figure 2)**. Specifically, diameters of 16 mm for RPA and 21 mm for LPA are associated with a high probability of PH **(19)**.

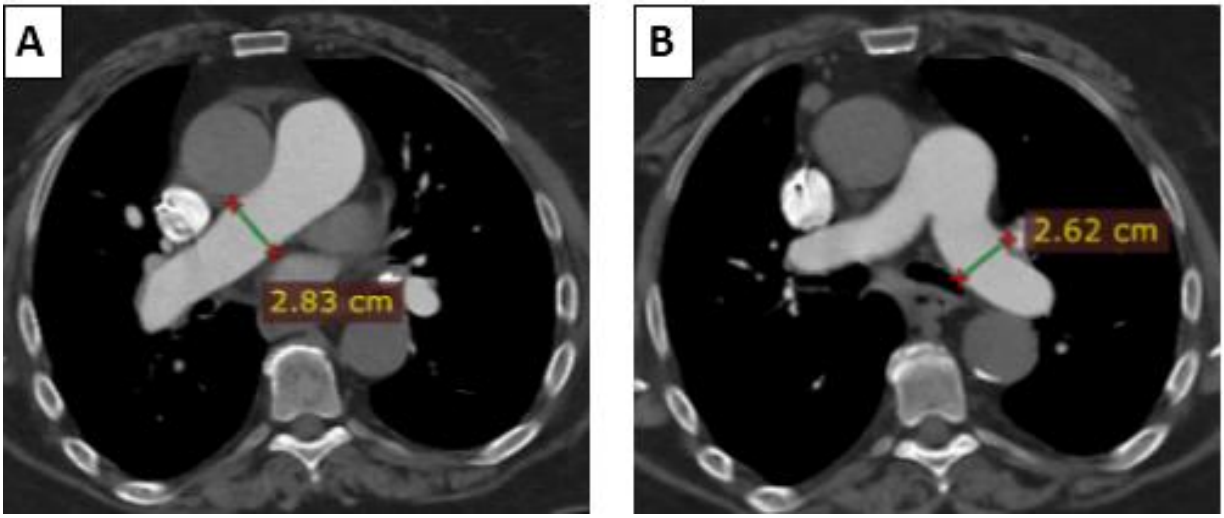

Figure (2) Axial CTPA images (mediastinal windows) showing measurement of the RPA (**A)**, and LPA diameters (**B**) in a patient diagnosed with COPD-associated PH.

5-Ratio of segmental PA-to-accompanying bronchus

The diameter of the segmental PA is typically equivalent to that of the adjacent bronchus **(25) (Figure 3A)**. In cases of PH, dilatation of the segmental PA with an increased segmental PA-to-accompanying bronchus ratio exceeding 1.25 in at least three lobes has been observed **(16) (Figure 3B)**. This sign, in combination with MPA dilatation, has been reported to have a specificity of 100% for PH **(16)**.

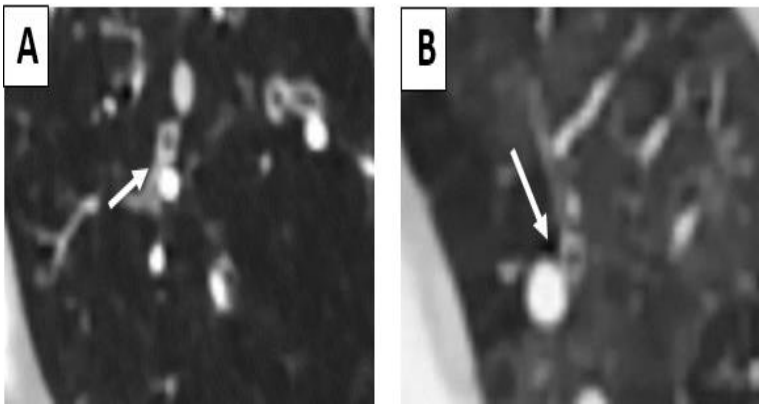

Figure (3) Axial CTPA images (lung windows) showing normal broncho-arterial ratio (**A**) and increased broncho-arterial ratio (**B**) (white arrows)**.**

6-Size of the right ventricle (RV) lumen

In response to prolonged PH, the right ventricle (RV) initially hypertrophies, then dilates, and eventually fails **(17,26)**. The size of RV lumen is frequently determined by measuring the maximal distance between the ventricular free wall and the interventricular (IV) septum, perpendicular to the long axis of the heart at the mid-ventricular level **(9) (Figure 4).** A RV lumen diameter ≥ 30 mm is associated with 92.9% sensitivity and 73% specificity for predicting PH **(24)**. RV size can be also estimated on CTPA images using two-dimensional (2D) area or 3D volume measurements. While one-dimensional measurements are simple and can be obtained manually, 2D and 3D measurements require specialized software for image processing and analysis.

7-Size of the left ventricle (LV) lumen

The size of left ventricle (LV) lumen is typically assessed at the mid-ventricular level by measuring the maximal distance between the LV free wall and the IV septum, perpendicular to the long axis of the heart **(24) (Figure 4)**. A LV lumen diameter ≥ 57 mm is associated with 76.2% sensitivity and 88.9% specificity for predicting PH **(24)**. Additionally, LV size can be calculated on axial CTPA images by measuring its area at the mid-ventricular level.

8-RV lumen-to-LV lumen ratio

In normal individuals, the RV lumen typically has a smaller size than the LV lumen. However, in the presence of PH, RV dilatation significantly changes the RV lumen-to-LV lumen ratio. A RV lumen-to-LV lumen ratio ≥ 1 is suggestive of PH **(26) (Figure 4)**.

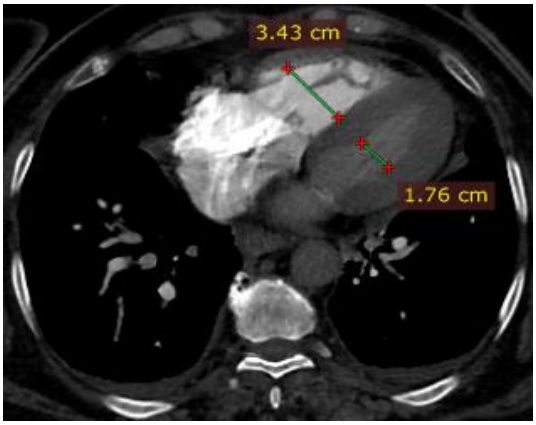

Figure (4) Axial CTPA image (mediastinal window) shows measurements of RV and LV diameters, measured at mid-ventricular level in a patient with COPD-associated PH. The calculated RV lumen-to-LV lumen ratio is 1.95

9- RV area-to-LV area ratio

The RV area-to-LV area ratio has been found to differ significantly between individuals with and without PH **(27).** Further research is needed to establish specific cut-off value and prognostic utility of this ratio in diagnosing PH.

10-RV free wall thickness

RV hypertrophy develops gradually as a sign of chronic pressure overload in PH **(27)**. The normal RV free wall thickness, measured at the mid-ventricular level, is less than 4 mm **(26) (Figure 5)**. Increased RV free wall thickness is a valuable predictor of PH, with a value of 6 mm or more demonstrating 81% sensitivity and 91.9% specificity for predicting PH **(24)**.

11- LV free wall thickness

The LV free wall thickness is also measured at the mid-ventricular level **(24) (Figure 5)**. A LV free wall thickness ≥15 mm demonstrates 85.7% sensitivity and 83.8% specificity for predicting PH **(24)**.

12-RV wall-to-LV wall ratio

Comparing the thickness of the RV wall to the LV wall can also aid in PH diagnosis **(Figure 5)**. A RV wall-to-LV wall ratio ≥ 0.32 is indicative of PH, with 73.6% sensitivity and 83.8% specificity **(24)**.

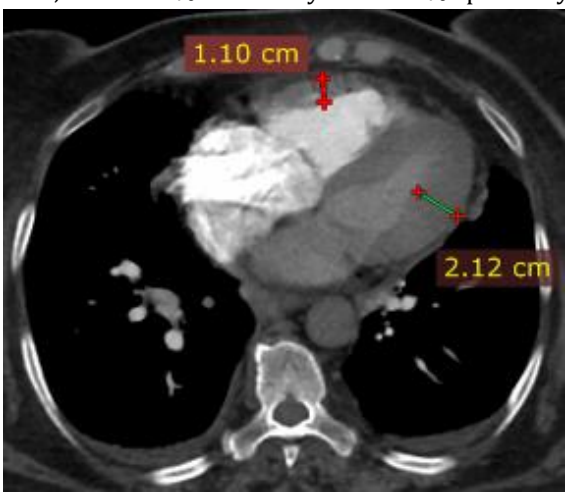

Figure (5) Axial CTPA image (mediastinal window) shows increased RV and LV wall thickness in a patient with COPD-associated PH. The calculated RV wall-to-LV wall ratio is 0.52.

13- RV muscle area/LV muscle area ratio

Comparing the RV and LV muscle areas might provide further insights into PH diagnosis. Research has demonstrated a significant difference in RV muscle area/LV muscle area ratio between individuals with and without PH, suggesting its potential as a diagnostic marker **(27)**. However, additional research is required to establish specific cut-off value for this ratio and determine its prognostic value.

14-RV outflow tract (RVOT) thickness: The musculature of the RV outflow tract (RVOT) is compact and easier to measure than the RV free wall. It can be measured anteriorly 1 cm below the pulmonary arterial valve **(28) (Figure 6)**. It has been found that RVOT thickness differs significantly between individuals with and without PH, signifying its diagnostic potential **(27)**. Nevertheless, more research is necessary to determine specific cut-off value and prognostic value of this parameter.

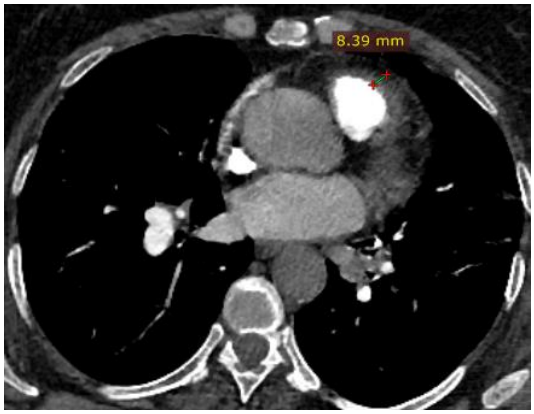

Figure (6) Axial CTPA image (mediastinal window) showing measurement of RV outflow tract thickness in a patient with COPD-associated PH.

15-Septal angle

The septal angle is defined as the angle formed between the interventricular (IV) septum and the line connecting the sternum mid-point and thoracic spinous process **(15)**. Septal angle is increased in patients with PH due to RV overload **(15) (Figure 7)**. However, further research is needed to determine specific cut-off value and prognostic significance of this parameter.

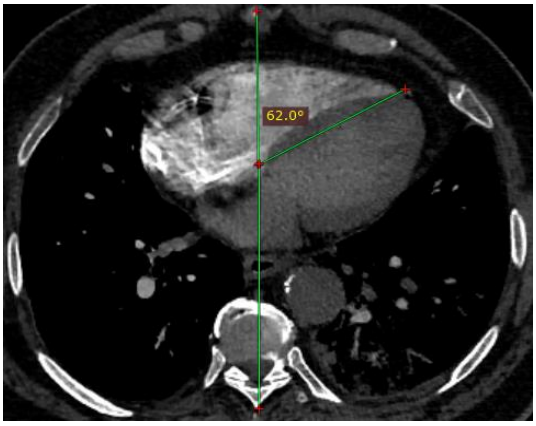

Figure (7) Axial CTPA image (mediastinal window) showing measurement of septal angle (62°) in a patient with COPD-associated PH.

16-Size of the right atrium

Enlargement of the right atrium (RA) is a common but non-specific observation in patients with PH **(9)**. Typically assessed by measuring anterior-posterior diameter, which exceeds 3.5 cm in PH patients **(9) (Figure 8)**. A more detailed evaluation of the RA size involves measuring RA area. RA area been shown to differ significantly between individuals with and without PH, suggesting its diagnostic utility **(27)**. Additional research is required to establish specific cut-off value for RA area and to determine its diagnostic role in combination with other CTPA parameters.

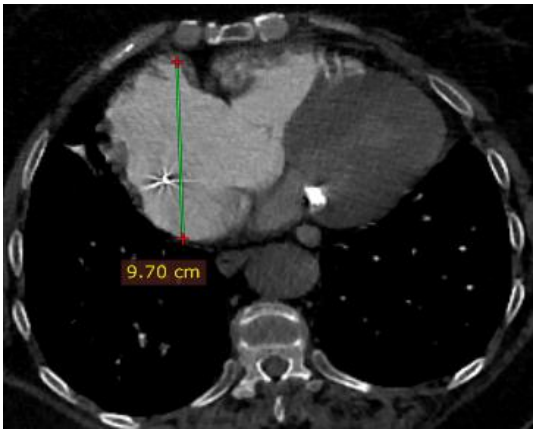

Figure (8) Axial CTPA image (mediastinal window) showing RA enlargement (antro-posterior diameter 9.7 cm) in a patient diagnosed with COPD-associated PH.

Dynamic quantitative parameters

Dynamic changes in the MPA on CTPA have not been extensively explored in the literature **(14)**.

1- Density of contrast (HU) in the MPA

By analyzing a ROI in the MPA on CTPA images, the contrast density can be determined **(14) (Figure 9)**. Research has shown significant differences in MPA contrast density between individuals with and without PH **(14)**.

2-MPA-to-AAo density ratio

Calculated by dividing the HU value in the MPA by the HU value in the AAo at the level of the MPA **(14) (Figure 9)**. This ratio is considered one of the most sensitive and specific dynamic parameters to diagnose PH **(14)**. A MPA-to-AAo density ratio ≥1.5 has shown a 73% sensitivity and 91.7% specificity for predicting PH **(14)**.When combined with an MPA diameter of ≥29 mm, the sensitivity increases to 84.6%, but with 62.5% specificity (**14**).

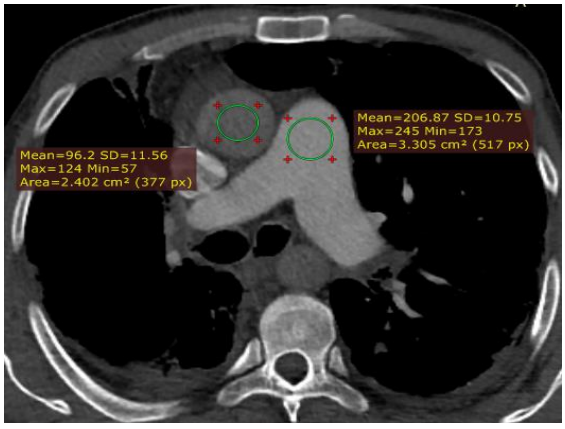

Figure (9) Axial CTPA image showing density measurements in both MPA and AAo, with MPA-to-AAo density ratio=1.98 in a patient diagnosed with COPD-associated PH.

3- Time to trigger threshold (seconds)

This parameter indicates the duration taken for the contrast density in the MPA to reach the trigger threshold of 120 HU during monitoring (**14**). Research has identified significant differences in the time to trigger threshold between individuals with and without PH (**14**). A time to trigger of ≥ 8 seconds provides a sensitivity of 61.5% and specificity of 79.2% for diagnosing PH. Moreover, the combination of time to trigger of ≥8 seconds and an MPA-to-AAo density ratio ≥1.5 demonstrates 88.5% sensitivity and 79.2% specificity in predicting PH (**14**).

Qualitative CTPA parameters

1-RV strain or dysfunction

Various CTPA findings can be used to assess the severity of RV dysfunction in cases of PH. In addition to changes in the measurements of RV, changes in the IV septum and reflux of contrast agent from the RA into the inferior vena cava (IVC) are also significant findings to consider PH **(29)**.

In normal individuals, the IV septum typically demonstrates a slight convex bowing towards the RV **(9)**. However, in the case of PH, the IV septum exhibits flattening or reverse bowing towards the LV **(9) (Figure 10)**.

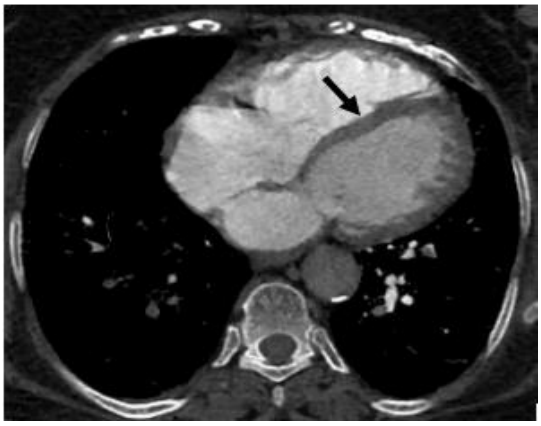

Figure (10) Axial CTPA image (mediastinal window) shows flattening of the IV septum (black arrow) in a patient diagnosed with COPD-associated PH.

Reflux of contrast from the RA into the IVC and hepatic veins occurs in PH secondary to RV dilatation **(30)**. The severity of reflux of contrast into the IVC or hepatic veins can be classified into: grade 1= no reflux; 2= trace reflux into IVC only; 3= reflux into IVC but not hepatic veins; 4= reflux into IVC and proximal hepatic veins; 5= reflux into IVC and hepatic veins down to the mid-portion of the liver; 6= reflux into IVC with opacification of distal hepatic veins **(30) (Figure 11)**.

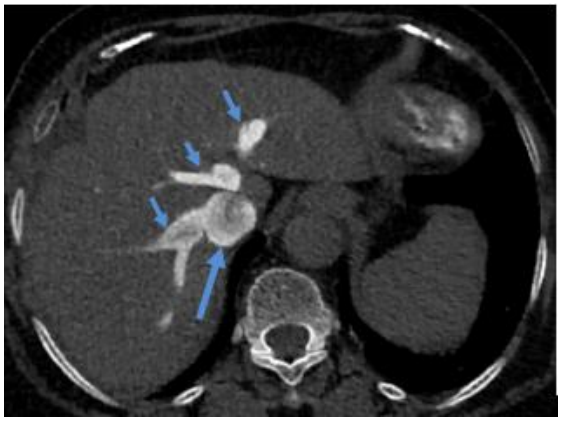

Figure (11) Axial upper abdomen CTPA image shows grade 4 reflux of contrast agent into the dilated IVC (long arrow) and proximal hepatic veins (short arrows) in a patient diagnosed with COPD-associated PH.

2- Pericardial effusion and thickening

Pericardial effusion and thickening of the pericardium (>4 mm) may be seen in PH of any underlying etiology (**9**). The presence of a pericardial effusion in patients with PH reflects elevated RA pressure and considered a significant predictor of mortality in these patients **(31) (Figure 12)**.

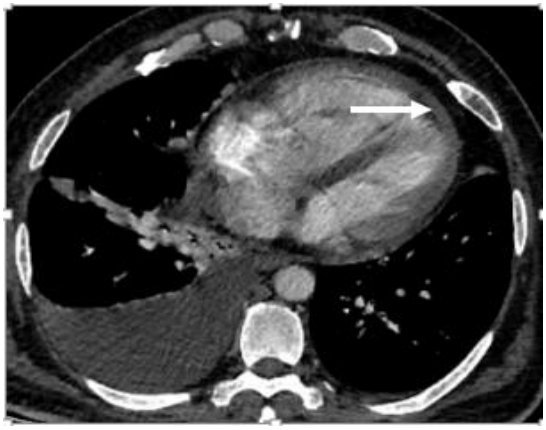

Figure (12) Axial CTPA image (mediastinal window) shows small amount of pericardial effusion (white arrow) in a patient diagnosed with COPD-associated PH

Conclusion

CTPA plays a crucial role in the detection and evaluation of PH in patients with COPD. It offers a comprehensive assessment of both pulmonary vasculature and cardiac chambers, with various CTPA parameters tailored for the diagnosis of COPD-associated PH. These parameters can be readily used by radiologists in routine clinical practice to better diagnose COPD-associated PH.

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