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Abstract

Acute pulmonary embolism (APE) is one of the leading causes of cardiovascular (CV) morbidity and mortality. To select appropriate therapeutic strategy and/or to minimize the mortality and morbidity, rapid and correct identification of life-threatening APE is very important. Also, right ventricular (RV) failure usually precedes acute hemodynamic compromise or death, and thus the identification of RV failure is another important step in risk stratification or treatment of APE. With advances in diagnosis and treatment, the prognosis of APE has been dramatically improving in most cases, but inadequate therapy or recurrent episodes of pulmonary embolism (PE) may result in negative outcomes or, so called, chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a condition with the remaining of chronic thromboembolism in the pulmonary vasculature which induces chronic pulmonary hypertension.

Various imaging modalities include chest computed tomography pulmonary angiography

(CTPA), echocardiography, magnetic resonance imaging, and nuclear imaging and each are used for the assessment of varying status of PE. Assessment of thromboembolic burden by chest CTPA is the first step in the diagnosis of PE. Hemodynamic assessment can be achieved by echocardiography and also by chest CTPA. Nuclear imaging is useful in discriminating CTEPH from APE.
Better perspectives on diagnosis, risk stratification and decision making in PE can be provided by combining multimodality cardiovascular imaging. Here, the advantages or pitfalls of each imaging modality in diagnosis, risk stratification, or management of PE will be discussed.
Key words: pulmonary embolism, imaging

Introduction

Acute pulmonary embolism (APE) refers to a condition in which the pulmonary vasculatures are abruptly occluded by abnormal thrombi or emboli, usually originating from deep veins of the lower extremities. Because APE may result in right ventricular (RV) dysfunction and hemodynamic compromise, APE is one of the major causes of mortality worldwide [1, 2]. The rapid and correct diagnosis of APE is essential in selecting an appropriate therapeutic strategy and to reduce mortality from APE. In this regard, multi-modality cardiovascular (CV) imaging, including chest computed tomography (CT), computed tomography pulmonary angiography (CTPA) and echocardiography are useful not only in the diagnosis of APE, but also in the evaluation of hemodynamic significance of APE and thus clinical decision making and therapeutic strategy [3]. The evaluation of therapeutic efficacy is another important role of CV imaging in APE.

With the advances in diagnosis, treatment and prognosis of APE has been dramatically improved in most of cases. Inadequate therapy or recurrent episodes of pulmonary embolism (PE) may result in a serious negative outcomes, including so called chronic thromboembolic pulmonary hypertension (CTEPH). Although the pathogenesis of CTEPH is not completely understood, unresolved organized fibrotic thrombi or emboli, subsequent endothelial dysfunction and abnormal vascular remodeling seem to be involved in the development of pulmonary hypertension (PH). In case of CTEPH, RV can initially adapt to the increased afterload by PH through the process of RV dilatation and hypertrophy, but a progressive or

sustained significant increase of pulmonary artery pressure results in RV failure and death [4]. Contrary to the evanescent role of nuclear imaging in APE, ventilation/perfusion (V/Q) scan is an imaging of choice in the detection of CTEPH [5].

In this review, the advantages and pitfalls of each imaging modality in diagnosis, risk stratification, and/or management of PE will be discussed.

Role of TTE

Although transthoracic echocardiography (TTE) is the most widely used CV imaging modality in the assessment of cardiac function and structure, it plays a limited role in the diagnosis of APE because TTE cannot directly visualize the location or extent of pulmonary arterial thrombi or emboli in many cases. However, TTE has a critical role in evaluating hemodynamic significance of APE, including RV dysfunction, and thus TTE is the most useful CV imaging modality in risk stratification, clinical decision making of therapeutic strategy, or evaluating the prognosis of APE [6]. Furthermore, TTE can provide the first indications for diagnosing APE frequently, because it is the most widely used CV imaging modality in patients with dyspnea or chest pain.

The presence of RV dysfunction in APE is a hallmark of higher risk patients and an independent predictor of adverse clinical outcomes, and sometimes it can advocate emergency reperfusion treatment for APE. Therefore, the echocardiographic evaluation of RV function is an important step in the evaluation of APE [7]. Echocardiographic findings suggesting RV dysfunction include RV dilatation, hypokinesia or akinesia of the RV free wall and relative sparing of RV apical wall motion (Mc Connell's sign), decreased tricuspid annulus plan systolic excursion (TAPSE) or fractional area change (FAC), and diminished RV longitudinal strain (Fig. 1) [8–13]. In addition, an increased RV systolic pressure assessed by measuring the peak velocity of tricuspid regurgitation (TR) jet or the increased size of the inferior vena cava or the change of an inferior vena cava size of less than 50% with inspiration can be a supportive sign of RV dysfunction [14]. Despite RV hypokinesia and pulmonary hypertension, RV hypertrophy is not a finding of APE because of the acute nature of the illness. Contrary to APE, RV hypertrophy with moderate to severe PH is a common finding in CTEPH as a consequence of adaptation of RV to an elevated afterload. Accordingly, RV hypertrophy on TTE is a simple qualitative clue for chronic PE [15].

In summary, the role of TTE in PE can be summarized as follows; 1) TTE is an imaging of choice in the evaluation of hemodynamic significance including RV dysfunction and thus

risk stratification or clinical decision making of therapeutic strategy of known APE; 2) TTE can provide the first indication for suspecting APE in some patients; 3) RV hypertrophy with PH in patients with known PE may suggest a finding of CTEPH.

Chest CTPA

Rapid availability and reliability in diagnosis, has made chest CTPA the gold standard CV imaging for the evaluation of suspected APE, and actually it replaced the role of the V/Q scan in the diagnosis of APE. According to the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) II trial, CTPA appeared to have high negative predictive value (96%) in patients with low clinical probability for APE and also has a high positive predictive value (96%) in patients with high clinical probability for APE [16]. Hence, current guidelines recommend performing CTPA in patients highly suspected for APE or even in patients with low to intermediate clinical probability for APE when they have hypotension or shock.

Besides the role in diagnosing APE, chest CTPA can provide information about hemodynamic significance of APE. Previous studies have shown that RV enlargement of chest CTPA is a marker for RV dysfunction in patients with APE (Fig. 2A) [17, 18]. RV enlargement can be evaluated by measuring RV dimension to left ventricular dimension (RVD/LVD) ratio in a 4-chamber view of the chest CTPA, and RVD/LVD ratio greater than 1.0 is suggested as a reliable marker for RV dysfunction in a meta-analysis [19]. RVD/LVD ratio greater than 0.9 on chest CTPA was used as a marker for RV dysfunction in another prospective cohort study [20]. In a previous study, the optimal cut-off value of RVD/LVD ratio on CTPA for predicting RV dysfunction was 1.12 [21]. Leftward ventricular septal bowing and contrast reflux to the inferior vena cava on CTPA are also considered as suggestive findings of RV dysfunction in APE (Fig. 2B–D), but the diagnostic sensitivity and/or specificity of these findings are lower than those of RVD/LVD ratio. For these reasons, the measurement of RVD/LVD ratio has proved to be the most reliable predictor of mortality in patients with APE among CTPA measurements [21–23].

Chest CTPA also enables assessment of the presence, location, and degree of thrombi burden in APE (Fig. 3). Several scoring systems have been developed to evaluate the severity of a current episode of APE by measuring PA clot loads (Table 2) [24–28]. Qanadli index is a scoring system that evaluates the embolic burden by combining the total number of involved pulmonary vascular segments and degree of embolic obstruction [25]. Some studies

demonstrated that the Qanadli index was a good predictor of RV dysfunction or mortality in APE, but it was not a predictor of RV dysfunction or mortality from APE in other studies [29–32]. Therefore, the clinical significance of these PA clot load scoring systems for the prediction of RV dysfunction or mortality in patients with APE should be clarified through further and larger studies.

With recent advances in processing of CT images, dual energy CT (DECT) has become available for the assessment of pulmonary parenchyma perfusion, by using iodine-subtraction techniques [33]. Perfusion defect or hypo-perfused region corresponding to the vascular obstruction is indicative of PE (Fig. 4). Thus, DECT can be useful in the assessment of PE without evidence of overt thrombus on CTPA. However, the diagnostic or prognostic role of DECT in APE remains poorly defined. Further research should be conducted to investigate the role of quantitative DECT on clinical outcomes in patients with APE.

Chest CTPA is an imaging of choice for the diagnosis of APE, but CTPA alone cannot exclude or confirm CTEPH completely. In the current guidelines, V/Q lung scan still remains the first-line imaging modality for the detection of CTEPH because V/Q scans demonstrate better sensitivity and specificity for the diagnosis of CTEPH as compared to those of chest CTPA [3, 34]. Nevertheless, several findings of chest CTPA can be useful in differentiating CTEPH from APE and CTEPH. The eccentric wall-adherent or mural thrombi, which are often calcified, is a relatively specific finding of CTEPH on CTPA (Fig. 5A, B). Complete vessel cutoff with convex margin due to organized thrombi is another specific feature of CTEPH, which is different from the concave margin of acute PE with a tapering of thrombus (Fig. 5C, D). An additional finding of CTEPH is the abrupt narrowing of the vessel distal to complete obstruction, due to contraction of the thrombus in chronic PE. Intraluminal webs or band and intimal irregularities by organized thrombi are not pathognomic but suggestive that findings with CTPA are consistent with CTEPH as well. In the chronic type of PE, development of collateral systemic circulation such as bronchial artery dilatation is frequently observed [35–37]. In addition, a non-uniform arterial perfusion pattern and mosaic pattern of lung attenuation can be observed on CTPA in CTEPH (Fig. 5E, F). When chest CTPA revealed these findings, the possibility of CTEPH should be carefully monitored even in patients who were first diagnosed as PE.

In summary, the role of chest CTPA in PE can be summarized as follows; 1) chest CTPA is a gold standard CV imaging for the evaluation of suspected APE, and it has replaced the role of V/Q scan in the diagnosis of APE; 2) chest CTPA is useful in the evaluation of RV

dysfunction in APE and thus risk stratification or clinical decision making of therapeutic strategy, especially before performing TTE or when TTE is not available; 3) chest CTPA enables a quantitative assessment of PA clot loads by using a scoring system and DECT allows an assessment of pulmonary parenchyma perfusion, but the significance of these techniques should be validated through larger, future studies; 4) several findings of CTPA can be useful in differentiating CTEPH from APE, even though a V/Q scan is an imaging of choice in the diagnosis of CTEPH.

Nuclear imaging: Ventilation/perfusion scintigraphy

V/Q scan is an established diagnostic test for suspected PE. The main finding of V/Q scans in PE is that of perfusion (Q) defect without corresponding ventilation (V) defect, which is recognized as a V/Q mismatch (Fig. 6). Interpretation of the V/Q scan is important, considering the fact that there are other medical conditions that might cause a V/Q mismatch, such as veno-occlusive disorder, vasculitis, congenital pulmonary vascular abnormalities, pulmonary artery sarcoma, fibrosing mediastinitis, malignancy and mediastinal lymphadenopathy. Currently, the modified PIOPED II and prospective investigative study of acute pulmonary embolism diagnosis (PISAPED) criteria are most commonly used in the interpretation, with a sensitivity of 85% vs. 80% and specificity of 93% vs. 97%, respectively [38, 39].

These systems classify studies as high probability, very low probability, normal and non-diagnostic. Current guideline recommends excluding PE when the study has been classified as normal, and to confirm PE when the study has been classified as high probability [3].

Presently, the V/Q scan is one of the most useful imaging modalities in screening CTEPH in patients with PH in the absence or disappearance of PE. In CTEPH, V/Q scans reveal at least one segmental perfusion defect despite normal ventilation. According to the current guidelines, V/Q scan is recommended as a first-line imaging modality for CTEPH, with 96–97% sensitivity and 90–95% specificity for diagnosis [3].

Recently, the introduction of single photon emission computed tomography (SPECT) into V/Q scintigraphy has emerged, which enables defining the size and location of perfusion defects more accurately, using a 3-dimensional imaging technique [40]. Accordingly, the diagnostic performance of SPECT V/Q has been increasing with higher reproducibility and lower indeterminate rate compared to V/Q scanning [41–43].

In summary, the role of the V/Q scan can be summarized as follows; 1) V/Q scan has high

diagnostic accuracy in the evaluation of PE; 2) V/Q scan is useful in the discrimination of CTEPH from APE, and is recommended as a first-line diagnostic tool for CTEPH.

Magnetic resonance pulmonary angiography

Magnetic resonance pulmonary angiography (MRPA) is another non-invasive imaging modality that can provide information about not only morphological assessment, but also functional assessment in patients with PE.

With MRPA, vascular deformities such as vascular filling defects, complete absence of vessel enhancement, post-stenotic dilatation, and dilatation of a main pulmonary artery can be detected [44]. As with CTPA, irregular luminal filling defects, intraluminal webs and bands, vessel cutoffs and organized thrombi are indicative findings of CTEPH [45].

Recent research have shown that pulmonary artery flow can be assessed using phase contrast magnetic resonance [46]. Three- and four-dimensional phase contrast magnetic resonance imaging provides visualization of vortex flow changes in pulmonary arteries [46, 47].

However, MRPA has lower sensitivity of PE compared to CTPA, especially in peripheral involvements [48]. The Main advantages of MRPA are that it is free of ionizing radiation and can provide information on structure and flow mechanics [49–51].

Nevertheless, MRPA is not recommended for routine investigation of PE, because of its limited availability, technically inadequate studies, reduced robustness and higher cost [3]. MRPA is anticipated as a promising imaging tool in the diagnosis of PE, however further studies are warranted for the clinical use of MRI in the diagnosis of PE.

Role of conventional pulmonary angiography

Pulmonary angiography provides direct visualization of obstructed vasculature or thrombi and also hemodynamic measurements [52]. It offers better visualization of peripheral pulmonary vessels, which can go undetected with other non-invasive imaging modalities, such as CTPA or MRPA. Filling defect or loss of pulmonary arterial branch is an indicative sign of PE. Currently, pulmonary angiography is more useful in patients suspected for CTEPH. Similar to CTPA findings, complete vessel cutoff with convex contour of thrombi, abrupt vessel narrowing, luminal irregularity and intravascular bands or webs are indicative signs of CTEPH rather than APE [36].

In patients with APE with shock or hypotension, prompt catheter-directed thrombolysis or

thrombectomy can be performed after diagnosis of APE. Otherwise in patients with PH with suspected CTEPH, pulmonary balloon angioplasty followed by diagnostic pulmonary angiography can be performed for PH relief [3, 34, 53, 54].

Role of venous compression ultrasonography

The role of lower extremity venous compression ultrasonography (CUS) in the routine diagnostic strategy is limited because of its low sensitivity for PE [3, 55].

With the advancements in technology, CTPA has shown better diagnostic performance in detecting PE compared to CUS [56]. However, it is useful to perform a CUS in diagnosing PE, in cases where it is difficult to obtain CTPA, such as pregnant women, patients with chronic kidney disease or with an allergy to contrast media [57, 58].

Imaging modalities in special cases

Pregnancy

The imaging modality of choice in the diagnosis of deep vein thrombosis (DVT) of the lower limb in pregnancy is CUS. Abnormal D-dimer and proximal DVT founded by lower extremity compressive venous sonography warrants anticoagulation therapy and makes thoracic imaging unnecessary.

Guidelines recommend performing a V/Q scan over CTPA in the diagnosis of PE in pregnant women. The V/Q scan protocol can be adjusted to lower fetal and maternal radiation exposure. A low dose perfusion scan can be performed with a half dose of routine radiopharmaceutical agents. It is not fully established, but V/Q scan may offer less maternal radiation exposure and higher diagnostic accuracy compared to that of CTPA [3, 59, 60].

Impaired renal function

Computed tomography pulmonary angiography is not a good option for the diagnosis of PE in patients with high risk for radio-contrast induced nephropathy. Magnetic resonance angiography carries a better renal safety profile and no radiation exposure [61]. However, gadolinium-related nephrogenic systemic fibrosis could occur [62]. V/Q scan is preferred over CTPA in patients with impaired renal function and suspicions of PE to avoid contrast mediated injury of the kidneys [63].

Conclusions

Despite many advances in medical technology, there is still uncertainty about decisions in the diagnosis and prognosis of PE and treatment plans in clinical practice. A high index of clinical suspicion and selection and use of optimal CV imaging are essential in the diagnosis of PE. Physicians, therefore, should be familiar with the major advantages or pitfalls of various CV imaging modalities used in the evaluation of PE (Table 1). The optimal use of multimodality CV imaging enables the comprehensive assessment of anatomical and functional severity of PE and the prediction of prognosis as well as the decision for choosing therapeutic strategy.

Conflict of interest: None declared

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Table 1. Comparisons of various cardiovascular imaging modalities in the assessment of pulmonary embolism (PE).

Modality	Advantages	Disadvantages
Transthoracic echocardiography (TTE)	1. Bedside evaluation is possible 2. Useful in the evaluation of treatment efficacy by serial exam 3. Allows assessment of hemodynamics 4. Relatively inexpensive cost 5. Widely available equipment 6. No radiation	1. Operator-dependent 2. Cannot identify the thrombus extent 3. High sensitivity, low specificity 4. Suboptimal in patients with poor imaging windows
Computed tomography pulmonary angiography (CTPA)	1. High diagnostic accuracy 2. Diagnostic modality of choice 3. Directly visualize the extent and burden of the thrombus 4. Visualize thromboembolic resolution after treatment 5. Allows assessment of other cardiac structures	1. Radiation exposure 2. Contrast administration precludes use in patients with advanced renal disease
V/Q scan	1. High diagnostic accuracy 2. Helps to distinguish CTEPH from acute PE	1. Limited availability 2. High cost 3. Radiation exposure
Magnetic resonance imaging (MRI)	1. Free from ionizing radiation 2. Can provide information on structure and flow mechanics	1. Limited availability 2. Gadolinium administration precludes use in patient with advanced renal disease 3. High cost

CTEPH — chronic thromboembolic pulmonary hypertension; V/Q — ventilation/perfusion

Table 2. Various scoring systems assessing pulmonary arterial clot load

Pulmonary Artery Clot Load Scores

Miller score [24, 28]

n — number of obstructed arterial segments

1 point for filling defects on any one of segmental branches

Max.16 points: according to the involved lobal region

— right: max. 9 points (upper 3, middle 2, lower 4)

— left: max. 7 points (upper 2, middle 2, lower 3)

Walsh score [27, 28]

n — number of obstructed arterial segments

1 point for segmental filling defect or obstruction

Max. 18 points: according to the involved lobal region

— max. 9 points for each lobe (upper 3, middle or lingular 2, lower 4)

— max. 3 points for single central region

Qanadli score [25]

Qanadli index = $\sum (n * d)/40 * 100$ (CT obstruction index)

n — number of obstructed arterial segments

— 1: presence of embolus in a segmental artery

d — degree of vascular obstruction

— 0: no occlusion

— 1: partial occlusion

— 2: total occlusion

— max. 40 points: 10 segmental arteries for each lobe

Mastora score [26]

n — number of obstructed arterial segments

d — degree of vascular obstruction

— 1: < 25% obstruction

— 2: 25~49% obstruction

— 3: 50~74% obstruction

— 4: 75~99% obstruction

— 5: 100% obstruction

Scoring in each location level

— central score (5 mediastinal and 6 lobar)

— peripheral score (20 segmental)

— global score (central and peripheral)

Max. 155 points

Max — maximal

FIGURES LEGENDS

Figure 2. Chest computed tomography angiography suggesting right ventricular (RV) dysfunction. RV dimension is greater than left ventricular dimension (**A**). Leftward ventricular septal bowing (**B**). Contrast reflux (arrows) to the inferior vena cava (**C**) and hepatic veins (**D**).

Figure 3. Chest computed tomography angiography shows multifocal small filling defects in both pulmonary arteries (arrows) (**A**) and large filling defects resulting in near total occlusion of the left pulmonary artery (wide arrow) and filling defect in right pulmonary artery (narrow arrow) (**B**).

Figure 4. Dual energy computed tomography (DECT) in a 55-year-old female with acute pulmonary embolism. Pre-treatment DECT shows multi-focal hypoperfused regions (dark-brown color) corresponding to the location of vascular obstruction (**A**). Follow up DECT shows the disappearance of hypoperfused regions after 6-months of anticoagulation (**B**).

Figure 5. Chest computed tomography angiography (CTPA) suggesting chronic thromboembolic pulmonary hypertension (CTEPH). Calcific thrombi (arrows) in right pulmonary artery on pre-enhance (**A**), post-enhance CTPA (**B**), eccentric (crescentic shape) thrombi (arrow heads; **C**, **D**), and nonuniform arterial perfusion pattern and mosaic pattern of lung attenuation (**E**, **F**).

Figure 6. Ventilation/perfusion (V/Q) scans demonstrating pulmonary embolism. Moderate to large mismatch on V/Q scan: normal ventilation scan (**A**) and moderate-sized perfusion

defect in right middle lung and large-sized perfusion defect in left upper lung on perfusion scan (**B**). A large-sized perfusion defect in right upper lung, and two, small-sized perfusion defects in left upper lung and a missed perfusion defect in anterior basal segment of right lower lung on perfusion planar image in perfusion single photon emission computed tomography-computed tomography (SPECT-CT; **C**); LPO — left posterior oblique; RPO — right posterior oblique.

Figure 1.

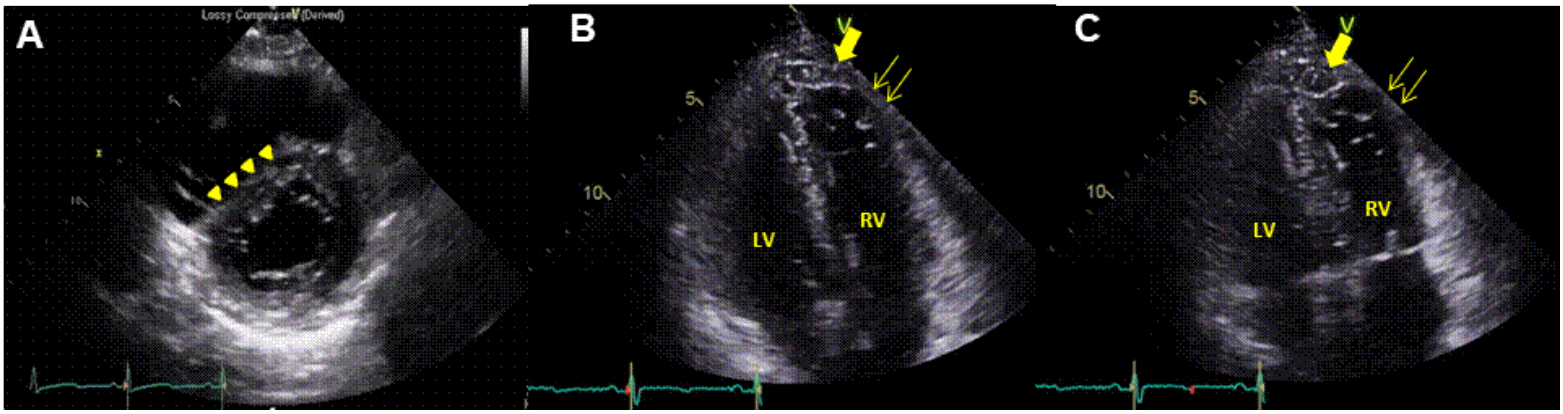
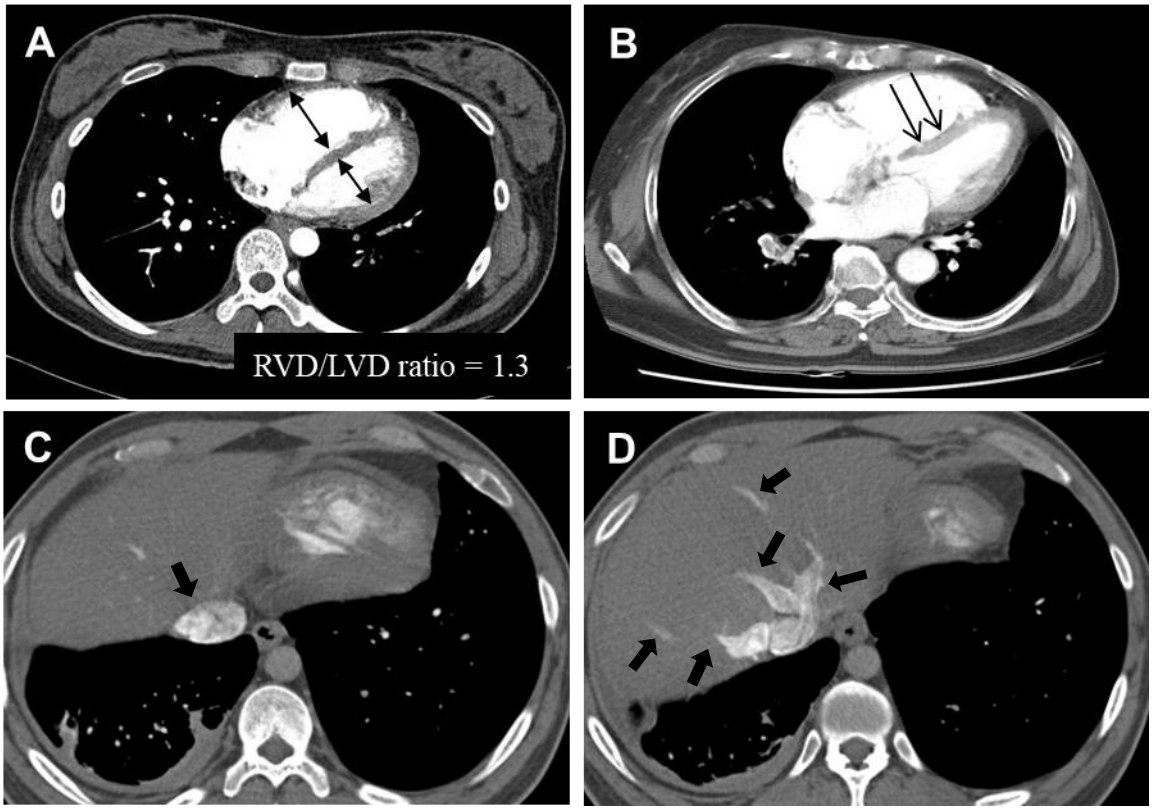


Figure 2.



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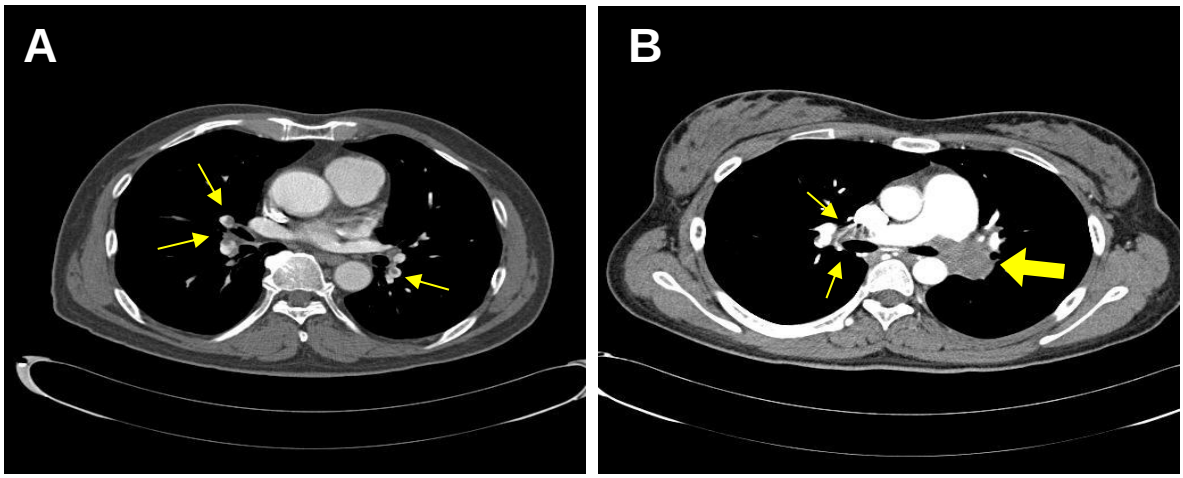

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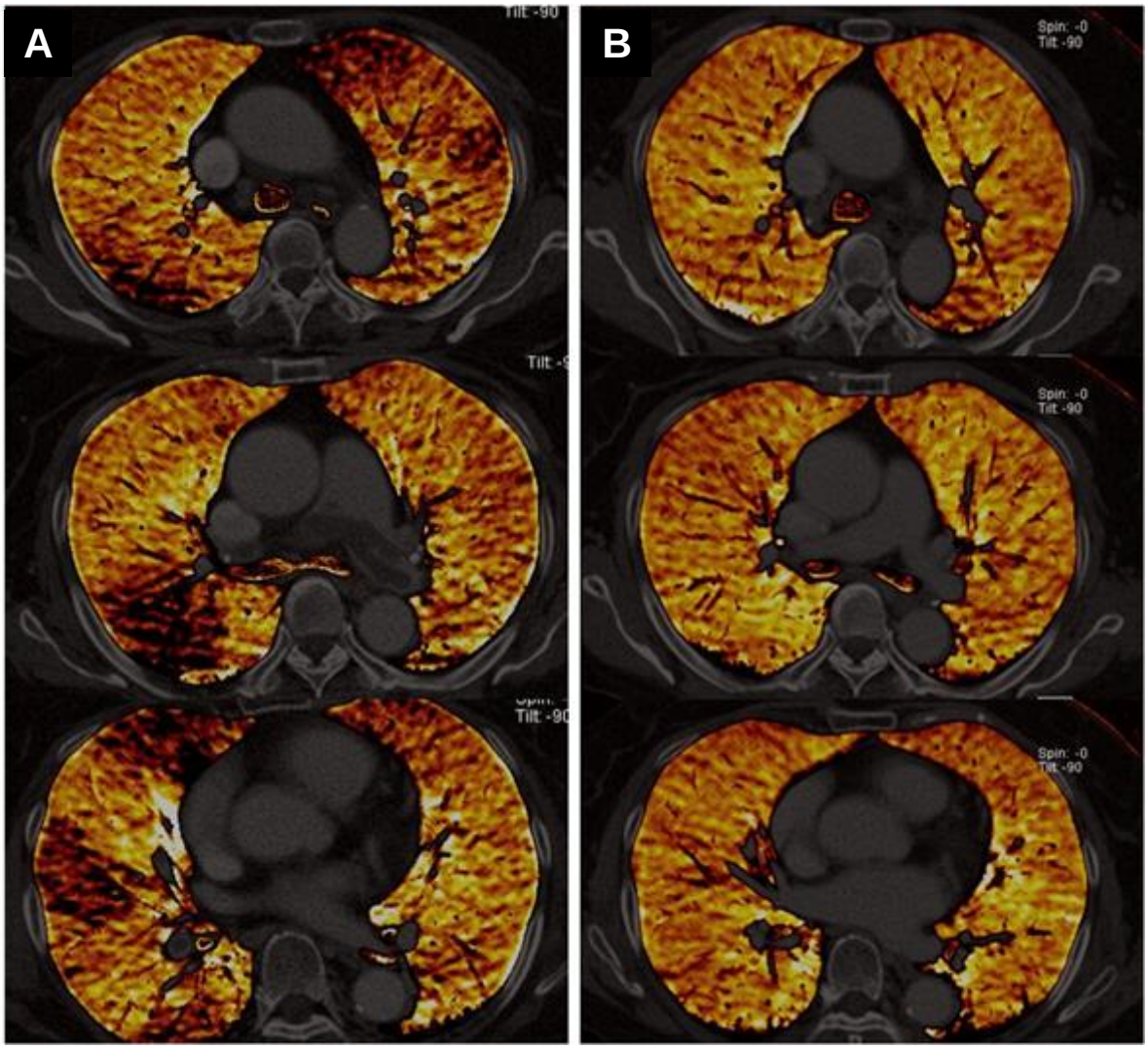


Figure 5.

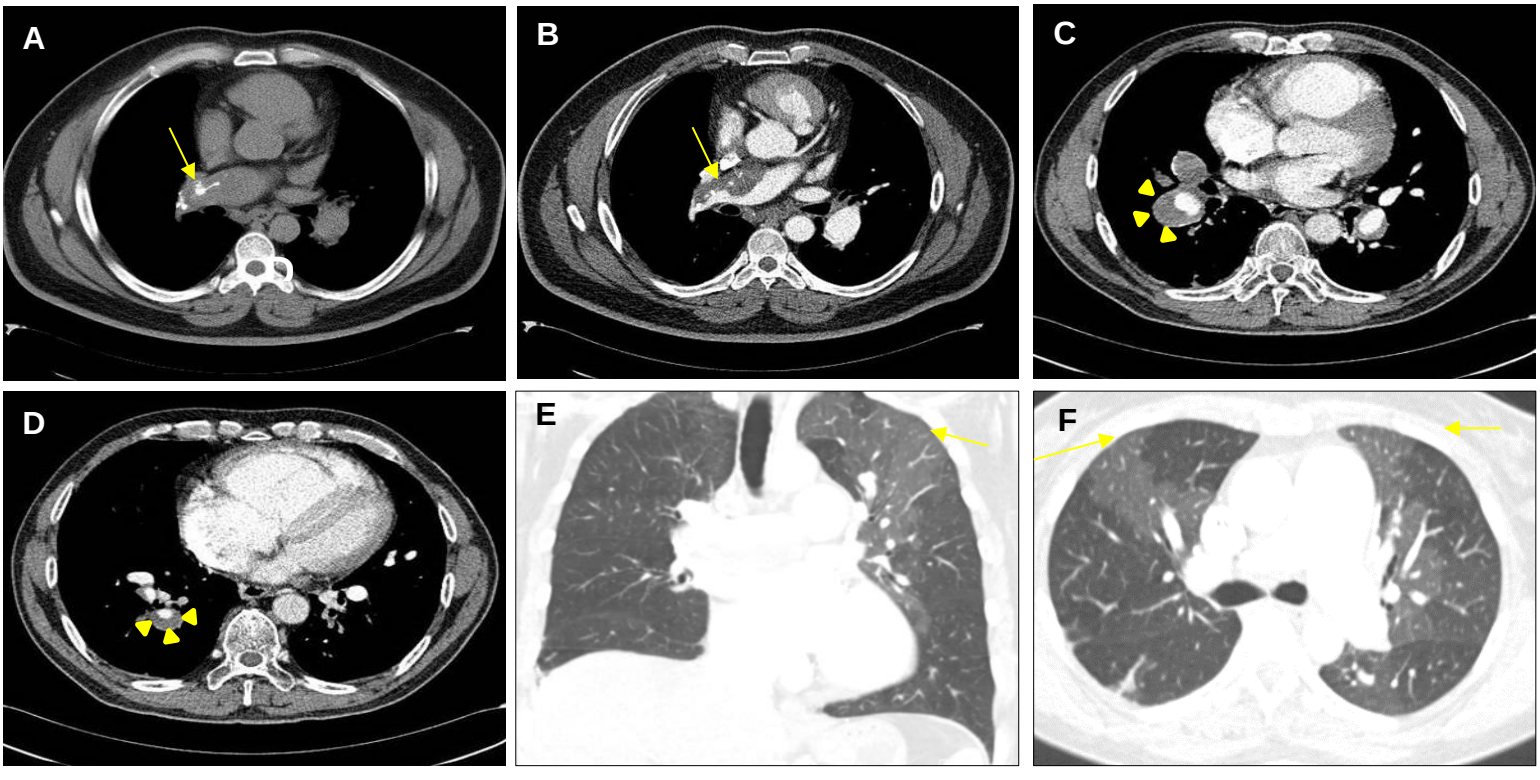
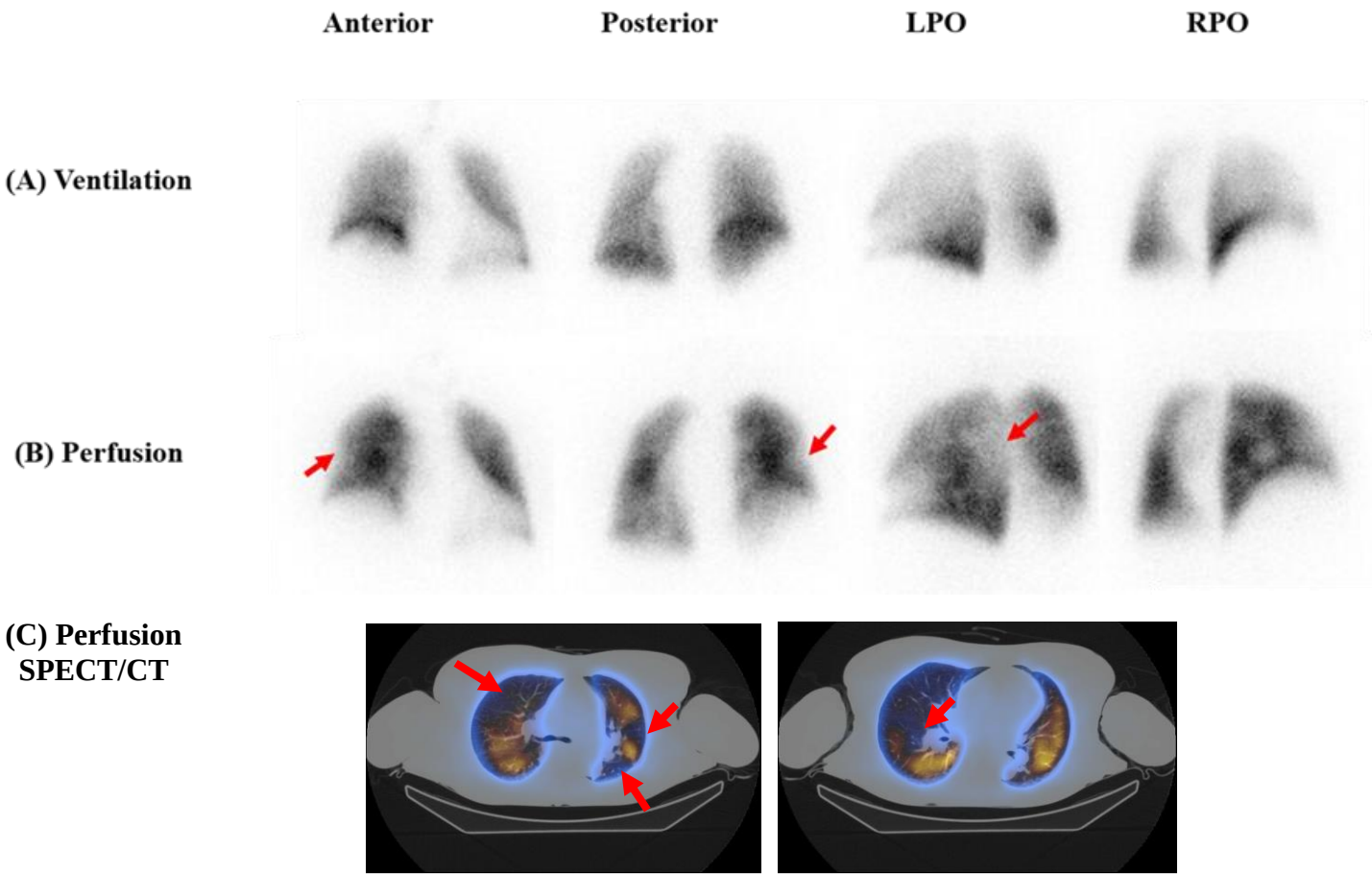


Figure 6.


Anterior
Posterior
LPO
RPO
(A) Ventilation
(B) Perfusion
(C) Perfusion SPECT/CT