The role of computed tomography in the diagnosis of acute and chronic pulmonary embolism

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ABSTRACT

Pulmonary embolism (PE) is a potentially life threatening condition requiring adequate diagnosis and treatment. Computed tomography pulmonary angiography (CTPA) is excellent for including and excluding PE, therefore CT is the first-choice diagnostic imaging technique in patients suspected of having acute PE. Due to its wide availability and low invasiveness, CTPA tends to be overused. Correct implementation of clinical decision rules in diagnostic workup for PE improves adequate use of CT. Also, CT adds prognostic value by evaluating right ventricular (RV) function. CT-assessed RV dysfunction and to lesser extent central emboli location predicts PE-related mortality in normotensive and hypotensive patients, while PE embolic obstruction index has limited prognostic value. Simple RV/left ventricular (LV) diameter ratio measures >1.0 already predict risk for adverse outcome, whereas ratios <1.0 can safely exclude adverse outcome. Consequently, assessing the RV/LV diameter ratio may help identify patients who are potential candidates for treatment at home instead of treatment in the hospital. A minority of patients develop chronic thromboembolic pulmonary hypertension (CTEPH) following acute PE, which is a life-threatening condition that can be diagnosed by CT. In proximal CTEPH, involving the more central pulmonary arteries, thrombectomy usually results in good outcome in terms of both functional status and long-term survival rate. CT is becoming the imaging method of choice for diagnosing CTEPH as it can identify patients who may benefit from thrombectomy. New CT developments such as distensibility measurements and dual-energy or subtraction techniques may further refine diagnosis and prognosis for improved patient care.

Acute pulmonary embolism (PE) is the third most common cardiovascular condition, after coronary artery disease and stroke (1). Due to lack of specific sets of symptoms that accurately predict or exclude the diagnosis of acute PE, the diagnosis strongly relies on noninvasive imaging techniques. Diagnostic strategies for evaluating PE have undergone important changes over the past decades (2). Due to rapid technical advances in speed and spatial resolution, the utility of computed tomography (CT) angiography has been recognized in vascular imaging. Particularly, after the development of multidetector row CT in 1998 (3), CT pulmonary angiography (CTPA) has become the imaging method of choice in the diagnosis of acute PE (4). CTPA has advantages over conventional invasive X-ray pulmonary angiography and nuclear ventilation-perfusion (V/Q) imaging. CT is a widely available, fast and noninvasive technique, has the capability to directly visualize emboli, and may provide alternative diagnoses (4).

Despite adequate diagnosis and anticoagulant therapy, death rate after a diagnosis of acute PE is still 8%–15% (5, 6). The prognosis of acute PE mainly depends on residual pulmonary circulation and the severity of right ventricular (RV) dysfunction (7). Recent studies have shown that CT permits the assessment of acute right-sided heart failure. Furthermore, CT can predict adverse clinical outcome by using the RV/left ventricular (LV) diameter ratio (8, 9) or RV ejection fraction in patients with PE (10).

The aim of this review is to discuss the developments of CT in PE diagnosis, and to analyze the added value of CT in estimating PE severity and prognosis. Furthermore, CT findings of chronic thromboembolic pulmonary arterial hypertension (CTEPH) as a complication of acute PE will be discussed.

CT developments in PE diagnosis

Historically, pulmonary angiography and nuclear planar V/Q-imaging were the main imaging methods used for diagnosing PE. Both methods have recognized limitations. Pulmonary angiography has previously been regarded as reference standard, but the method

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is invasive and involves right heart catheterization. Moreover, its sensitivity is not 100% as recurrent venous thromboembolic events have been observed in a limited number of patients with normal angiograms (11). Interobserver agreement rates for detection of subsegmental emboli with pulmonary angiography ranged from 45% to 66% (12, 13). For multidetector CT this is in the range of 56%–85% (14, 15).

Until the 1990s, planar V/Q-imaging was the imaging method of choice in patients with suspected PE. However, the PIOPED I study showed that with V/Q-imaging in more than 65% of cases an indeterminate probability for PE was reported, and reliable diagnosis of PE could not be made (16). Of note, in as many as 40% of indeterminate V/Q-scans, PE was shown by invasive pulmonary angiography (17). Nowadays, planar V/Q-imaging has largely been replaced by CTPA. Since the emergence of multiple-head cameras, V/Q single-photon emission CT (SPECT) was proposed to improve the diagnostic performance with better sensitivity and/or specificity and lower nonconclusive test results (18). However, its advantages have not yet been validated by outcome studies that use V/Q SPECT as part of a diagnostic strategy to rule out PE (18).

With the introduction of fast-speed helical CT in the early nineties, its potential in vascular imaging and diagnosing PE has been recognized (19). Multidetector CT enabled isotropic voxel imaging that led to routine utilization of three-dimensional

Main points

- CT pulmonary angiography (CTPA) is the first-choice diagnostic imaging technique in the diagnostic algorithm for pulmonary embolism.

- The high accuracy and easy accessibility increased the CTPA orders; however, the indication for CTPA should outweigh its potential risk of X-ray induced malignancy.

- Implementation of clinical decision rules (like Wells and Geneva score) can decrease CTPA orders and increase the number of positive CTPA and therefore is recommended by the European Society of Cardiology guidelines.

- CT adds prognostic value by evaluating right ventricular (RV) function; simple RV/left ventricular (LV) diameter ratio > 1.0 predicts risk for adverse outcome, whereas ratios <1.0 can safely exclude adverse outcome.

- CT is becoming the imaging method of choice for diagnosis and follow-up of chronic thromboembolic pulmonary hypertension (CTEPH) as it can identify patients who may benefit from thrombectomy.

imaging. CT angiography has now become an established technique for minimally invasive vascular imaging (20). The 4- or 16-slice CTPA already provides a high level of image quality resulting in a diagnostic performance that equals or surpasses that of conventional pulmonary angiography (21), with sensitivity and specificity varying between 83%–100% and 89%–96%, respectively (22–24). Also, the sensitivity of CT for identifying PE in small pulmonary arteries (92%) is superior to that of invasive pulmonary angiography (56%) (22, 25). Reassessment of 20 causes of discordant CTPA readings from the PIOPED II study showed PE detection sensitivity of 87% for CT and 32% for angiography (26). Because of its high sensitivity and specificity, CTPA has nowadays replaced invasive pulmonary angiography as the reference standard for diagnosing PE (4).

CT diagnosis of PE

CTPA is currently the imaging test of choice for diagnosing PE (23). Due to the high sensitivity of CT, the number of false negatives is low. If the test is negative, PE is ruled out. Also, because of the high specificity, the proportion of false positives is low. If the CTPA test is positive, PE is diagnosed and anticoagulant therapy can be started (27).

With an overall PE prevalence of 15%–38%, the negative predictive value of CTPA for ruling out PE is 96.2%–99.1%; a negative CTPA alone can safely exclude PE in patients with high clinical pretest probability or low to intermediate clinical probability and elevated D-dimer levels (28, 29). The afterward incidence of venous thromboembolism (VTE) has been shown to be about 1%. Furthermore, the three-month fatal risk after a normal CTPA has been shown to be very low (0.41%–0.6%), making it safe to withhold anticoagulant therapy in case of negative CTPA results (28, 29). The CTPA studies show much better negative predictive values for ruling out PE (96.2%) than those that can be obtained by V/Q imaging (75.9%), which is clinically important as to safely withhold anticoagulant therapy (30, 31).

CT diagnosis of subsegmental PE

With the use of multidetector CTPA instead of single-detector CT techniques, the number of subsegmental PE diagnoses has increased (32). Clinical relevance of subsegmental PE (presence of PE on subsegmental level only) has been the topic of discussion

for many years. The definition of subsegmental PE has yet to be standardized and a single subsegmental PE probably does not have the same clinical relevance as multiple subsegmental emboli (33). One meta-analysis that included 2657 patients with PE showed that multidetector CTPA increased the proportion of subsegmental PE diagnoses to 9.4%, as compared to 4.7% with single-detector CTPA, but without lowering the three-month risk of VTE in patients with normal multidetector CTPA. The authors therefore speculated that subsegmental PE may not be clinically relevant (32). A recent multicenter study of 3728 consecutive patients with clinically suspected PE identified 748 patients with proven PE, 116 of whom having subsegmental PE, and directly investigated the outcome for three-month follow-up risk of recurrent VTE and mortality. Between patients with subsegmental PE and those with more proximal PE, no statistical differences were seen in the prevalence of VTE risk factors, the three-month risk of recurrent VTE (3.6% vs. 2.5%), or mortality (10.7% vs. 6.5%). Also, when compared with patients without PE, patients with subsegmental PE were at an increased risk of VTE during follow-up (hazard ratio, 3.8; 95% CI, 1.3–11.1). The study indicates that in contrast to the common belief that subsegmental PE represents a benign subset of VTE, patients with symptomatic subsegmental PE have comparable prognosis as patients with segmental or more proximal PE regarding short-term clinical course (34). Thus, subsegmental PE is clinically relevant and should be reported when present. However, the positive predictive value of CT and interobserver agreement is low. The European Society of Cardiology (ESC) 2014 guidelines suggest that compression ultrasonography of the legs may be used to identify deep vein thrombosis (DVT) that would require treatment. In case of an isolated subsegmental PE and no DVT, the decision on whether to treat should be made on an individual basis, taking into account the clinical probability and the bleeding risk (33).

CT in clinical decision rules for diagnosing PE

The high accuracy and easy accessibility of CT increased the numbers of CTPA examinations up to five-fold within six years, but also resulted in a decrease in PE prevalence (35). In the U.S., the percentage of positive PE diagnoses decreased from 15% in the year 2000 to around 7%–8% in 2005

(36). Clinical decision rules (CDRs) that use pretest probability estimations for the presence of PE are highly effective in selecting patients for further work-up by CTPA. It has been shown that the implementation of a CDR decreases the number of CTPA requests by 20%, and increases the number of positive CTPA examinations by 69% (35). The best validated and widely used CDRs are the Wells and Geneva scores (Table 1), mainly valid for outpatients (37, 38). Since 2008, the European Society of Cardiology guidelines on the diagnosis and management of acute PE recommend using a pretest clinical probability test like the Wells score (21). Standardized assessments of pretest clinical probability allow patients to be classified into three groups. After diagnostic testing (V/Q imaging or compression ultrasonography of the legs or invasive pulmonary angiography), the estimated prevalence of PE is ≤10% for low clinical probability, 30% as a midpoint for intermediate clinical probability, and ≥70% for high clinical probability (37, 39). While the Geneva score and the original Wells score classify PE probability into three groups, the revised Well score uses a dichotomized version i.e., PE likely (score of >4), or PE unlikely (score of ≤4) (40).

The value of CT in diagnosing PE after applying CDRs has been evaluated in many studies (41). The largest study to date was PIOPED II (824 patients), where Wells score and CTPA results were compared with V/Q imaging, invasive pulmonary angiography or ultrasonography for DVT (23). PIOPED II concluded that the predictive value of CTPA for diagnosing or excluding PE is high in case of concordant clinical probability assessment, but additional testing is needed when clinical probability is inconsistent with the CTPA results, although these results are mainly applicable for four-detector row CT (23).

In the Christopher study the effectiveness of revised Wells score, D-dimer testing, and CT was assessed (42). PE was safely excluded by revised Wells score ≤4 and low D-dimer testing (<500 ng/mL); only one DVT (0.1%) and four nonfatal PEs (0.4%) occurred among 1028 untreated patients. They concluded that patients with high Wells score (>4), or low Wells score (≤4) but positive D-dimer test should undergo CTPA. In such cases, a negative CTPA was shown to safely exclude PE, with a low incidence of DVT (0.6%), nonfatal PE (0.2%), and fatal PE (42–44). Of note, among patients with a high pretest probability for PE but normal

Table 1. The Wells rule and the revised Geneva score			
Wells rule	Score	Revised Geneva score	Score
Clinical signs of DVT	3	Age >65 years	1
Previous DVT or PE	1.5	Previous DVT or PE	3
Surgery or immobilization within 4 weeks	1.5	Surgery or fracture within 1 month	2
Active malignancy	1	Active malignancy	2
Alternative diagnosis less likely than PE	3	Unilateral lower limb pain	3
Hemoptysis	1	Hemoptysis	2
Heart rate >100 beats/min	1.5	Heart rate 74–95 beats/min	3
		Heart rate >95 beats/min	5
		Pain on lower limb deep vein palpation and unilateral edema	4
Clinical probability (revised Wells score)		Clinical probability	
Low	<2	Low	0–3
Intermediate	2–6	Intermediate	4–10
High	>6	High	≥11
PE unlikely	≤4		
PE likely	>4		
DVT, deep venous thrombosis; PE, pulmonary embolism.			

D-dimer, the CTPA showed PE in 19%–28% of patients when using quantitative rapid ELISA technique for determining D-dimers or even 24%–36% when using a semiquantitative latex agglutination technique (45, 46). Therefore, a negative D-dimer cannot be used for safely excluding PE in patients with a high pretest probability.

In the current diagnostic work-up of patients with suspected PE, the combination of low clinical probability and normal D-dimer level safely excludes PE (47). A high (>500 ng/mL) plasma D-dimer level is a highly sensitive but nonspecific screening test for suspected PE. Elevated D-dimer levels are present in almost all patients with PE but are also present in many other conditions, including advanced age, pregnancy, trauma, postoperative period, inflammation, and cancer (48).

A low D-dimer rules out PE in 60% of patients below 40 years of age, but only in 5% of patients older than 80 years. Recently an age-adjusted D-dimer cutoff (age × 10 µg/L, above 50 years) was associated with a higher number of patients in whom PE could be ruled out (from 6.4% [95% CI, 4.8%–8.5%] to 29.7% [95% CI, 26.4%–33.3%]), with a low likelihood of subsequent clinical VTE. The age-adjusted D-dimer cutoff can help excluding the need for CTPA in the elderly with compromised renal function (49).

Radiation exposure in CTPA

Since CTPA has replaced V/Q imaging, and the number of CTPA examinations has increased exponentially, concern has been raised about the risks that are associated with the radiation exposure. CTPA delivers a higher absorbed dose to breast tissue than V/Q imaging (typically 10–70 mSv for CTPA vs. <1.5 mSv for V/Q imaging) (50). The variation in values is related to CT parameter settings, differences in size and configuration of breast tissue, and the methods to calculate or directly measure radiation dose. For comparison, these doses greatly exceed the American College of Radiology recommendation of an equivalent dose in breast tissue of 3 mSv or less for standard two-view mammography (51). Patient risk also depends on age, with lower risk for patients above 40 years (52), due to the relative shorter life expectancy after 40 years and the latency period of radiation-induced tumors.

Actual data on the carcinogenic potential at the relatively low dose level at which CTPA is performed are lacking. Most authors have drawn conclusions of increased cancer risk based on the outcomes of victims surviving the atomic bombings in Hiroshima and Nagasaki by extrapolating effects that have been observed at a relatively high dose to supposed effects at a low dose (51). The excess stochastic risk of fatal cancer induction

in a standard person is estimated as five deaths per 100,000 persons per mSv (53), meaning 15–30 excess deaths per 100,000 persons undergoing CTPA with the current effective dose of 3–6 mSv for CTPA (54). There have been substantial achievements in dose reduction for CT in general and for CTPA in particular. Automatic exposure control adapts the output of the scanner to the size and build (posture) of each individual patient, over ranging of helical scans can be reduced with dynamic collimators, iterative reconstructions and advanced noise reduction allows for radiation reduction whilst retaining image quality, and CT scans with intravenous iodine contrast like CTPA, can be optimized by using a lower tube voltage (e.g., 80 or 100 kV). Lowering the tube voltage and tube current and anatomic coverage can lower the dose by 81% (55). Mean effective chest radiation dose reduction of 27.6% in patients more than 60 kg can be achieved when adaptive statistical iterative reconstruction is used (56).

Major risks of radiation exposure during CTPA are developing breast and lung carcinoma. The lifetime attributable risk for breast cancer has been estimated by phantom studies to be 20 excess cases per 100,000 in 55-year-old women undergoing a single CTPA examination. These risk calculations are suggested to be higher in young peripartum women (57). Both CTPA and a nuclear medicine perfusion imaging have high diagnostic performance in pregnant women and can be used without substantial risk to the fetus (21). However, there is evidence that CTPA results in lower radiation dose to the fetus in the first or second trimester as compared to nuclear perfusion imaging (24). The estimated equivalent dose for the fetus in first, second, and third trimester of pregnancy is 0.003–0.02 mSv, 0.008–0.08 mSv, 0.0051–0.13 mSv, respectively, in case of CTPA, while this is 0.06–0.12 mSv for nuclear lung perfusion imaging (21). In young women, some authors recommend use of V/Q imaging above CTPA because of the lower radiation dose to the breast (50). In pregnant women, the current guidelines on the diagnosis and management of acute PE favor nuclear lung perfusion imaging as far as exposure of the breasts to radiation is concerned (21). However, the evidence to recommend either CTPA or nuclear lung perfusion is complex and effects to the mother and fetus should be taken into consideration. As an initial imaging study a chest film is recommended by the American Thoracic Society (58), and compression ultrasonography of the legs may be suggested in case of leg symptoms; if the ultrasound exam is positive for deep-vein thrombosis the need for radiographic imaging is eliminated (21). When the chest film is normal a nuclear lung scintigraphy is recommended; however, if the chest film is abnormal or the lung scintigraphy is non-diagnostic, a CTPA is recommended (58). CTPA and nuclear perfusion scanning have equivalent clinical negative predictive value (99% for CTPA and 100% for perfusion scanning) and have equivalent image quality in the care of pregnant patients. Overall, the PE prevalence in series of PE suspicion during pregnancy is lower than in the general population (only 3.7% as compared to 5%–25% in the general population) (59). There are no known mutagenic or teratogenic effects of iodinated contrast. Recent study has shown that a single, high dose *in utero* exposure to iodinated contrast is unlikely to give suppression of neonatal thyroid function (60).

Potential adverse effects related to the use of iodinated contrast agent administration include contrast material allergy and contrast material induced nephropathy. V/Q imaging may be an alternative imaging tool in patients with allergy to iodine or severe renal insufficiency (21).

CT in estimating PE severity and prognosis

PE obstruction index and embolus location

Several studies have focused on the performance of multidetector CT in the diagnosis of PE and its ability to determine the embolus burden, which can be calculated by either applying conventional angiographic scores adapted for CT (Miller and Walsh scores) or dedicated CT scores (Qanadli and Mastora scores) (61).

The prognostic role of embolic burden as a marker for short-term clinical outcome is a topic of discussion (62). In a meta-analysis, exploring short-term (30-day or three-month) prognostic value of embolic burden on CT by Qanadli obstruction index (16 studies, 3884 patients) and by embolic location, classified as central (at least lobar branches) or distal (segmental and subsegmental branches), three studies involving 1309 patients demonstrated that the location of emboli in the central pulmonary artery branches was associated with a two-fold increased risk of 30-day mortality, (OR, 2.24; 95% CI, 1.29–3.89) (62). However, no association was found between the Qanadli obstruction in-dex and 30-day or three-month mortality. The meta-analysis included a variety of studies, mostly with hemodynamically stable and some with hemodynamically unstable patients. The main difference between the two methods (embolic burden by Qanadli obstruction index and embolic location) is that the Qanadli score includes the total number of pulmonary vascular segments and the degree of embolic obstruction that allows calculation of the percentage of blocked pulmonary arteries. The location method includes the more proximal emboli, but disregards the degree of obstruction. According to the authors, the differences in prognostic value observed in this study between the location of emboli and Qanadli score may reflect their effect on RV dilatation (62). While multiple small emboli by Qanadli score may not have been able to induce RV dysfunction, central emboli may present more often with RV dysfunction (62). Thus, the location of emboli seems to be more important in predicting the short-term mortality than the percent embolic obstruction of the pulmonary arterial bed.

RV dysfunction

Whereas prognosis in PE patients is only weakly correlated with embolus-load, it is highly dependent on RV function (Fig. 1). Pulmonary artery obstruction causes an increase in RV afterload, release of neurohumoral factors, and RV enlargement and dysfunction (63). Elevated RV pressure leads to interventricular septum shift and compression of the left ventricle. This may result in LV diastolic failure, underfilling, and ultimately in LV systolic dysfunction and cardiogenic shock (64, 65). Secondary to increased RV afterload, wall stress and myocardial damage, cardiac troponins and brain natriuretic protein (BNP) or its precursors (NT-pro-BNP) increase (66). The mechanism and pathophysiologic pathway of PE and RV dysfunction are shown in Fig. 2.

International echocardiographic multicenter studies have shown that in PE patients, RV dysfunction is a major determinant of short-term mortality (67, 68). RV dysfunction can also be recognized on CT, e.g., by measuring the ratio of RV/LV diameters (8, 9) or by volumetric measurements, that can be obtained with or without electrocardiography (ECG)-gating (69, 70). Several multidetector CT studies have shown the prognostic value of RV dysfunction that may help to identify those patients at risk and may facilitate selecting therapeutic strategies (9).
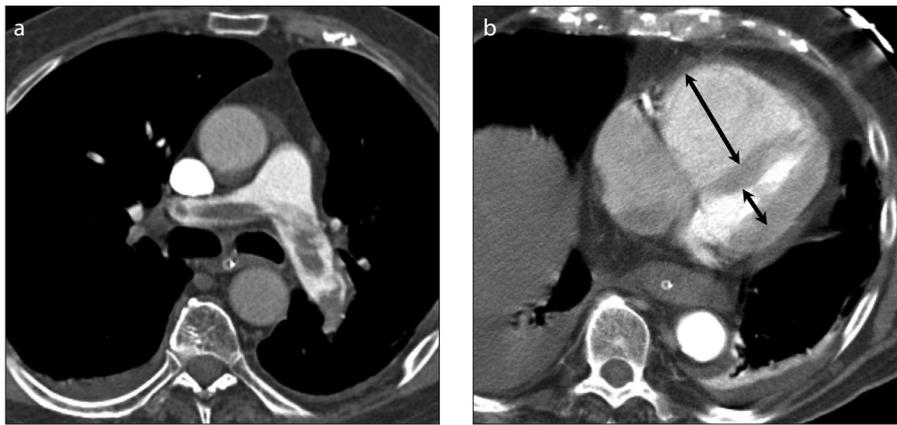
Figure 1. a, b. A 82-year-old man presenting with hypoxemia, hypotension, sinus tachycardia and ECG-changes suggesting right ventricular strain. Multidetector CT **(a)** shows a saddle embolism, with signs of right ventricular dysfunction with high RV/LV diameter ratio of 2.8 (*arrows* in **b;** *arrow* in the LV cavity is partly overlying the papillary muscle). The patient was treated with thrombolysis which resolved the pulmonary embolism **(b)**, however, the patient finally died of ventilation-associated pneumonia and septic shock.
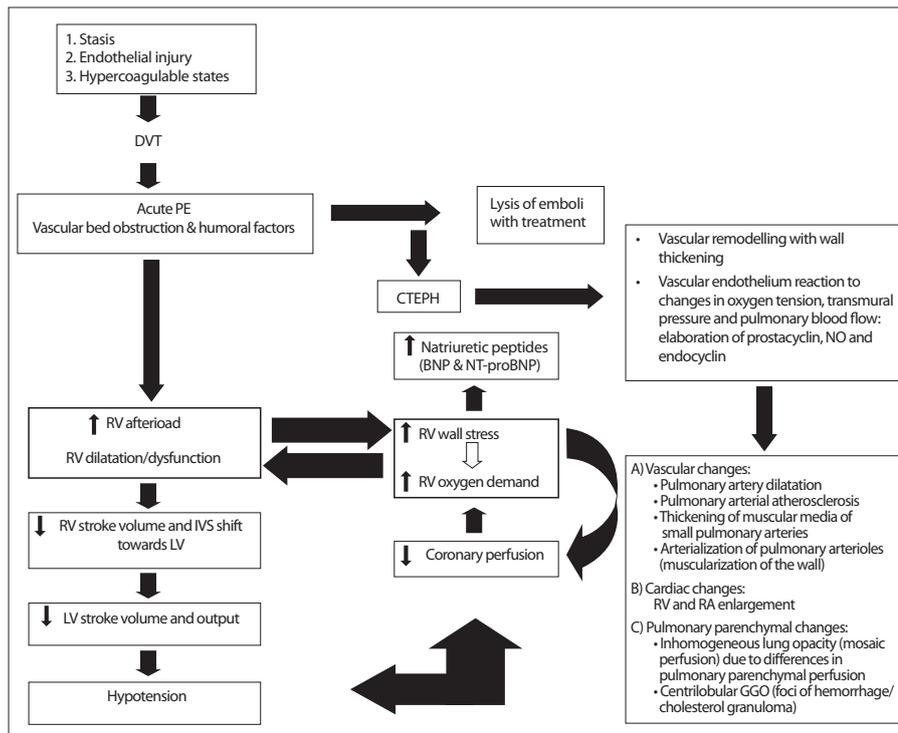
Figure 2. Pathophysiology of hemodynamic instability due to pulmonary embolism, development of CTEPH, and its cardiovascular and pulmonary parenchymal changes. Predisposing factors may cause DVT that can dislodge and cause pulmonary embolism. Pulmonary embolism can cause RV failure directly or indirectly after inadequate lysis of emboli and development of CTEPH. Right lower box shows morphologic changes that may be observed on CT. DVT, deep vein thrombosis; PE, pulmonary embolism; RV, right ventricular; LV, left ventricular; IVS, interventricular septal; CTEPH, chronic thromboembolic pulmonary hypertension; BNP, brain natriuretic peptide; NT-proBNP, aminoterminal-probrain natriuretic peptide; NO, nitric oxide; RA, right atrial; GGO, ground glass opacity.

A RV/LV diameter ratio cutoff value of >1.0 is commonly considered to represent RV dysfunction and has been shown to predict short-term adverse outcome and mortality (10, 71, 72). Axial and four-chamber view measurements of RV/LV diameter ratio >1.0 are comparable for predicting 30-day mor-tality (10, 73). Normotensive patients with PE and a RV/LV diameter ratio <1.0 have excellent short-term outcomes with a neg-ative predictive value (NPV) of 98%–100% (10, 73). This means that patients without RV dysfunction have a very low risk for in-hospital death or adverse outcome and could be candidate for home-treatment. Conversely, normotensive PE patients with a RV/LV diameter ratio >1.0 have been as-sociated with a three-month mortality risk of 3%–15%, but only a low positive predic-tive value (PPV) of 9%–15% was observed. This implies that many patients with RV/LV diameter ratio >1.0 will not have severe short-term complications (10, 73).

It has been suggested that volumetric measurements, obtained with or without ECG-gating may be more useful as a mark-er for RV dysfunction in patients with acute PE (69, 71). In a study with 260 PE patients, a RV/LV volume ratio >1.2 resulted in a six-fold increased risk for 30-day mortal-ity, while 97.8% survived with a ratio <1.2 (71). Non-ECG-gated volumetric analysis seems to be slightly superior to identify high-risk patients with adverse clinical out-come compared to RV/LV diameter ratio measurements (71, 74). Furthermore, axial and four-chamber view measurements of RV/LV diameter ratio have shown consid-erable interobserver variability, while vol-umetric measurements have shown better reproducibility (71). In another study of 60 patients, a RV/LV volumetric ratio >1.28 measured in non-ECG-gated CTPA showed 89% sensitivity, 75% specificity, 42% PPV and 97% NPV to predict adverse clinical outcome (74).

A recent study, in which an additional low-dose ECG-gated cardiac scan was per-formed in 113 patients with PE, showed that RV ejection fraction <47% was the best predictor of adverse clinical outcome, with a sensitivity of 100% (95% CI, 52%–100%) and specificity of 60% (95% CI, 50%–70%). The PPV was 13% (95% CI, 5%–26%) and NPV 100% (95% CI, 93%–100%) (10). How-ever, no significant additional value of RV ejection fraction <47% compared with axial RV/LV diameter ratio >1.0 was shown (10). Thus, measuring simple RV/LV diameter ra-tio >1.0 on standard axial CTPA was shown to be as prognostic as RV ejection fraction <47% by ECG-gated cardiac CT. The limited PPV of adverse outcome will probably not outweigh the additional radiation dose associated with ECG-gating for function analysis. Thus, it can be helpful to estimate patient prognosis in PE by RV/LV diameter ratio measures that can be made directly on the CTPA investigation. By ESC consensus criteria, RV/LV diameter ratio <1 in combi-nation with advantageous clinical parameters may be used as to help select patients who may be treated at home instead of hospital

(21). However, the recent Hestia Study has suggested that hemodynamically stable patients with asymptomatic RV dysfunction as assessed by RV/LV diameter ratio >1.0 may also be treated safely at home when appropriately selected based on the Hestia criteria risk checklist (75).

Many other secondary CT signs of RV dysfunction such as interventricular septum bowing, inferior vena cava reflux, and pulmonary artery diameter exceeding that of the aorta have been recognized, although without direct association with short- term mortality in acute PE (76).

To conclude, regarding prognosis in PE, RV function is more important than embolus load. RV function represented by RV/LV diameter ratio can be helpful in estimating prognosis and, with further selection based on clinical parameters, this may be used for safely selecting patients for treatment at home.

Prognostic value of cardiac biomarkers

Elevated cardiac biomarkers like NT-pro-BNP, secondary to increased RV afterload and wall stress have shown a higher discriminative power and clinical utility as predictor of adverse events after PE than the RV/LV diameter ratio (77). NT-pro-BNP increased to > 600 pg/mL may be superior to RV/LV ratio >1.0 in predicting adverse events after PE. The NPV is excellent for both (99% vs. 98%) (77).

CT findings of CTEPH as a complication of acute PE

CTEPH is defined as mean pulmonary artery pressure greater than 25 mmHg that persists six months after an acute PE and pulmonary vascular resistance of 3 Wood units (240 dyne·s/cm^5) or greater with persistent pulmonary arterial thrombotic obstruction despite at least three months of effective, uninterrupted anticoagulation therapy (78). The pathogenesis of CTEPH is poorly understood, although a clinical history of VTE has been recorded in 80% of patients. Inadequate anticoagulation, large thrombus mass, residual thrombi and recurrence of VTE may contribute to development of CTEPH (79).

Pathologically, CTEPH is characterized by wall-adherent or intraluminal organized thrombus, forming vascular channels interspersed with connective tissue (80). Peculiar finding is that a history of symptomatic VTE is lacking in 31%–42% of patients diagnosed with CTEPH (81). A prospective follow-up study of 834 consecutive patients suspected for PE (and 320 proven PE) reported a CTEPH incidence of 1% (82). Another study comprised 866 unselected, consecutive patients after acute PE (83). Patients without known pulmonary hypertension underwent echocardiography. Patients with echocardiographically suspected pulmonary hypertension had total diagnostic work-up for CTEPH, including V/Q imaging and invasive pulmonary artery pressure measurements (83). After an average follow-up period of 34 months of all 866 patients, CTEPH incidence was found as 0.57%.

Diagnosing CTEPH is relevant to guide potential treatment options. Patients with predominantly proximal vascular distribution may be treated with pulmonary artery endarterectomy, while more distally located CTEPH is not amenable to surgery and must be treated medically (84). Endarterectomy can lead to major health improvement. Studies have shown that before thrombectomy, over 95% of CTEPH patients were in poor functional New York Heart Association (NYHA) class III or IV, i.e., only comfortable at rest or severe limitation with symptoms even at rest (85). One year after thrombectomy, 93%–95% of patients were found to have NYHA class I or II, i.e., no limitations or mild symptoms during normal activity (85, 86). Thrombectomy improved not only the functional status, but also long-term survival (six-year survival of 75%) (86).

CT diagnosis of CTEPH

CT imaging is the method of choice for diagnosis and follow-up CTEPH (87). CT sensitivity (86%) exceeds that of invasive pulmonary angiography (70%) and MRI (27%–44%) (88), and CT has been found more specific than nuclear scintigraphy (89). CT has advantages in evaluating CTEPH patients as it provides direct information over wall-adherent thrombus, RV function and changes in lung parenchyma (88).

The primary diagnostic CT criteria for CTEPH are listed in Table 2. These diagnostic criteria include the demonstration of intraluminal filling defects (intravascular web), signs of pulmonary hypertension such as dilatation of the pulmonary arteries and RV, and RV hypertrophy (87). The peripheral pulmonary vessels show decreased diameters (80).

Secondary signs of CTEPH include mosaic perfusion pattern, referring to hetero-

Table 2. Summary of diagnostic criteria for CTEPH

Criteria		Pathologic findings	CT findings
Primary (87)			
	Changes in pulmonary arteries:	Organizing thrombus	1. Eccentric wall-adherent filling defect which may calcify (calcification in ≤10%)
			2. Stenosis or obstruction
			3. Post-stenotic dilatation
	Changes due to PH:	Intravascular webs (due to recanalization)	Linear intraluminal filling defects
		Dilatation and atherosclerotic changes (due to increased pressure and turbulent flow)	1. Dilatation of PA (29 mm in men and 27 mm in women) and/or atherosclerotic calcification of PA (92)
			2. RV hypertrophy/dilatation
			3. Tortuous vessels
			4. Systemic collateral arterial supply: e.g., bronchial arterial collaterals towards pulmonary post-obstructive vessels
			5. Pericardial fluid (109)
Secondary (85)		Small-vessel arteriopathy due to shear stress, pressure, inflammation, and the release of cytokines	Mosaic lung perfusion (due to decreased perfusion) and variation in the size of segmental vessels

References (85, 87, 92, 109) were used in preparing this table.
CTEPH, chronic thromboembolic pulmonary hypertension; CT, computed tomography; PH, pulmonary hypertension; PA, pulmonary artery; RV, right ventricular.

Figure 3. a–c. CTPA and HRCT reconstruction in CTEPH and mosaic perfusion. A 53-year-old man with CTEPH who presented with persistent dyspnea and dyspnea on exertion lasting several months, known with a history of adequately treated acute PE six years before. Blood analysis was unremarkable except elevated NT-proBNP (1212 ng/mL), echocardiography showed severe RV and right atrial dilatation with moderate tricuspid insufficiency and an estimated pulmonary artery pressure of 62 mmHg. Right-sided catheter measurements showed a pulmonary vascular resistance of 781 dyne·s/cm⁵ and a mean pulmonary artery pressure at rest of 46 mmHg. CTPA with high resolution reconstructions in lung setting **(a)** shows mosaic perfusion with hyperperfused pulmonary areas of high attenuation associated with larger vessels, and areas of hypoperfusion with low attenuation that contain smaller vessels. In soft tissue setting **(b)**, the diameter ratio of the main pulmonary artery to the aorta is >1, indicative for pulmonary hypertension. Also note the wall-adherent thrombus and atherosclerotic calcification of the main pulmonary arteries, as signs of pulmonary hypertension. There is intraluminal web in the segmental artery to the left upper lobe. Dilated RV and flattening of the ventricular septum indicate RV dysfunction **(c)**. Figure is published with patient's permission and courtesy of Dr. I. Bahce and Dr. A. Boonstra, Department of Pulmonary Diseases at the VU University Medical Center Amsterdam, the Netherlands.

geneous lung attenuation due to heterogeneous blood flow (90), and enlargement of bronchial or non-bronchial collateral systemic arteries (Fig. 3) (85). Not all features are required to be diagnosed as CTEPH (84).

Regarding the size of the main pulmonary artery at the level of pulmonary artery bifurcation, a variety of "upper limits" of normal diameter have been published (91, 92). A practical rule-of-thumb is the diameter ratio of the main pulmonary artery to that of the (normal) aorta measured on CT. A ratio >1 strongly suggests pulmonary hypertension, with 92% specificity and 96% PPV (93). The main pulmonary artery (PA) diameter is measured at the level of the bifurcation of the right PA and perpendicular to its long axis. This is easy to define anatomically and highly reproducible on axial CT images (92). At the same location, the ascending aorta can be measured to provide the ratio of PA diameter to that of the aorta (92). A PA diameter of 29 mm or more was determined to have 97% PPV, 87% sensitivity, and 89% specificity for the presence of pulmonary hypertension (94). Specificity increases to 100% if accompanied by findings of a segmental artery-to-bronchus ratio greater than one in three of four pulmonary lobes (94). However, a diameter less than 29 mm does not rule out pulmonary hypertension (94).

Recently, the Framingham Heart Study reported a sex-specific 90th percentile cutoff value with risk for pulmonary hypertension above a PA diameter of 29 mm in men and 27 mm in women on ECG-gated CT. Increase with diameter was associated with higher risk for self-reported dyspnea (ad-justed odds ratio, 1.31) (92). Regarding patient size, only a moderate correlation has been observed between body surface area and PA diameter (for men: r=0.41; for women: r=0.42). Moreover, the correlation between PA diameter and age was poor (men: r=0.10; women: r=0.07), indicating that the PA size does not significantly increase with age (92).

Mosaic perfusion is common and occurs in 77%–100% of patients with CTEPH (95). Distinction of mosaic pattern in chronic PE from that of small airway disease may be made by assessing the diameter of the main PA that may be typically dilated in chronic PE (88), but is usually normal in patients with airway disease (96). Both airway disease and CTEPH have decreased size and number of vessels in lucent lungs compared with higher-attenuation lung. Associate signs that help differentiate are direct signs of airways disease such as bronchial wall thickening and bronchiectasis (97). Also, air trapping will be present in airway disease but not in CTEPH (98). In CTEPH, chronic thrombi may be observed.

As compared to patients with CTEPH, mosaic perfusion is seen significantly less often in patients with idiopathic or cardiac or pulmonary disease-associated pulmonary arterial hypertension (90).

The normal pulmonary circulation is a low-pressure, low-resistance, and highly distensible system (99). In CTEPH, pulmonary vascular remodeling results in increased vascular resistance and decreased vascular compliance (i.e., increased wall stiffness) (100). Consequently, the distensibility of the pulmonary arteries will decrease. The duration and the extent of increased PA pressure seem crucial in vessel wall remodeling. PA distensibility has been suggested to be a sensitive (83%) and specific (82%) marker for PH, even in early or mild clinical stages (101, 102). Moreover, decreased PA distensibility was shown to be related to mortality (99). Measurement of PA distensibility is possible from ECG-gated CT and can be calculated from the change in cross-sectional PA area between diastole and systole, as the maximal cross-sectional area minus the minimal cross-sectional area divided by the maximal cross-sectional area (103). Studies have demonstrated that the PA distensibility was lowest in PH (6.0%±2.7%), but also decreased in PE (12.9%±3.4%) as compared with normal controls (25.9%±5.7%) (102). In PE patients, anticoagulant therapy significantly improves PA distensibility (102). Including functional approach of PA distensibility evaluation next to anatomic CT measurements of main PA diameter may better identify patients with PH (102). In patients with PH, CT measurements of PA distensibility have shown good interobserver reproducibility (r>0.7) (104). Measuring PA distensibility may be helpful in patients with CTEPH. These patients eventually die due to RV failure. Diagnosing decreased distensibility could help to identify CTEPH patients who may benefit from thrombectomy by reducing RV afterload (105).

Some studies have suggested that innovative CT techniques such as contrast-enhanced dual-energy or subtraction tech-

niques may provide further functional information on blood volume by assessing the pulmonary iodine distribution as a marker for pulmonary perfusion (106). CT-perfusion may help differentiate between various forms of pulmonary hypertension, i.e., chronic thromboembolic vs. nonembolic pulmonary hypertension (107). Iodine mapping by using dual-energy may be complementary to thin-section CTPA and may be used to study the impact of CTEPH on regional pulmonary perfusion, which seems strongly correlated to mosaic attenuation patterns, where iodine mapping may also identify systemic collateral supply in CTEPH (108). The ability to characterize perfusion parameters next to anatomic evaluation by dual-energy or subtraction CT techniques may further refine diagnostic accuracy and prognosis in the assessment of acute PE and CTEPH (108).

Conclusion

PE is a potentially life threatening disease with a challenging diagnosis. CTPA requests from emergency departments are increasing. Considering the risk of X-ray induced malignancy (e.g., breast carcinoma in women of child-bearing age), the indication for CTPA should outweigh its risk. To avoid useless patient radiation exposure, CTPA should not be overused. Correct implementation of clinical decision rules in diagnostic workup for PE improves adequate use of CT. CTPA is excellent for including and excluding PE, therefore CT is the first-choice diagnostic imaging technique in patients suspected of having acute PE. Also, CT adds prognostic value by evaluating RV function. CT-assessed RV dysfunction and to lesser extent central emboli location predicts PE-related mortality in normotensive and hypotensive patients, while PE embolic obstruction index has limited prognostic value. Simple RV/LV diameter ratio measures >1.0 already predict risk for adverse outcome, whereas ratios <1.0 can safely exclude adverse outcome. Consequently, assessing the RV/LV diameter ratio may help identify patients who are potential candidates for treatment at home instead of treatment in the hospital. A minority of patients develop CTEPH following acute PE, which is a life-threatening condition that can be diagnosed by CT. In proximal CTEPH involving the more central pulmonary arteries, thrombectomy usually results in good outcome in terms of both functional status and long-term survival rate. CT is becoming the imaging method of choice for diagnosing CTEPH as it can identify patients who may benefit from thrombectomy. New CT developments such as distensibility measurements and dual-energy or subtraction techniques may further refine diagnosis and prognosis for improved patient care.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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