CT Angiography for Diagnosis of Pulmonary Embolism: State of the Art

In daily clinical routine, computed tomography (CT) has practically become the first-line modality for imaging of pulmonary circulation in patients suspected of having pulmonary embolism (PE). However, limitations regarding accurate diagnosis of small peripheral emboli have so far prevented unanimous acceptance of CT as the reference standard for imaging of PE. The development of multi–detector row CT has led to improved visualization of peripheral pulmonary arteries and detection of small emboli. The finding of a small isolated clot at pulmonary CT angiography, however, may be increasingly difficult to correlate with results of other imaging modalities, and the clinical importance of such findings is uncertain. Therefore, the most realistic scenario to measure efficacy of pulmonary CT angiography when PE is suspected may be assessment of patient outcome. Meanwhile, the high negative predictive value of a normal pulmonary CT angiographic study and its association with beneficial patient outcome has been demonstrated. While the introduction of multi–detector row technology has improved CT diagnosis of PE, it has also challenged its users to develop strategies for optimized contrast material delivery, reduction of radiation dose, and management of large-volume data sets created at those examinations.

Where do we stand now with regard to the optimal diagnostic imaging tool for pulmonary embolism (PE)? Increasingly sophisticated clinical algorithms for bedside exclusion of PE are being developed. These algorithms are based mainly on negative results of a D-dimer test (1–4), which is a highly sensitive, albeit nonspecific, means for ruling out PE. Still, there is a high and increasing demand for imaging tests when PE is suspected, although actual numbers are difficult to establish.

Some still regard conventional pulmonary angiography as the standard technique for diagnosis of PE, but in reality it is infrequently performed (5–8). Conventional angiography is an invasive procedure, although the incidence of complications with contemporary technique is low (9,10). More important, there is accumulating evidence illustrating the limitations of this technique for unequivocal diagnosis of isolated peripheral pulmonary emboli: Two recent analyses of the interobserver agreement rates for detection of subsegmental emboli with selective pulmonary angiography ranged from only 45% to 66% (11,12). Given such limitations, use of this method as an objective and readily reproducible tool for the verification of findings at competing imaging modalities regarding the presence of PE seems questionable, and the status of pulmonary angiography as the standard of reference for diagnosis of PE is in doubt (11,12).

Use of nuclear medicine imaging, once the first study in the diagnostic algorithm for PE, is in decline (13,14) owing to the high percentage of indeterminate studies (73% of all studies performed [15]) and poor interobserver correlation (16). Revised criteria for the interpretation of ventilation-perfusion scans (17,18) and newer technologies in nuclear medicine, such as single photon emission computed tomography, (19,20) can help decrease the ratio of indeterminate scintigraphic studies but cannot offset the limitations inherent to a functional imaging test (21).

Contrast material–enhanced magnetic resonance (MR) angiography has been evaluated...
for use in the diagnosis of acute PE (22–25). However, the acquisition protocols that are currently available for pulmonary MR angiography lack sufficient spatial resolution for reliable evaluation of peripheral pulmonary arteries (24,25). More important, this modality has not seen widespread use in acutely ill patients suspected of having PE, owing to lack of general availability, relatively long examination times, and difficulties in patient monitoring.

That leaves us with computed tomography (CT), which for most practical purposes has become the first-line imaging test in daily clinical routine for patients suspected of having PE. The most important advantage of CT over other imaging modalities is that both mediastinal and parenchymal structures can be evaluated, and thrombus can be directly visualized (26,27) (Fig 1). Investigators have shown that up to two-thirds of patients in whom there is an initial suspicion of PE receive another diagnosis (28), including some potentially life-threatening diseases such as aortic dissection, pneumonia, lung cancer, and pneumothorax (29). Most of these diagnoses are amenable to CT demonstration so that, in many cases, a specific origin for the patient’s symptoms and important additional diagnoses can be established (21).

Interobserver agreement for CT is better than that for scintigraphy (30). In a study published in 2000 (16), the interobserver agreement for the diagnosis of PE was excellent for spiral CT angiography ($\kappa = 0.72$) and only moderate for ventilation-perfusion lung scanning ($\kappa = 0.22$). Moreover, a diagnostic algorithm for PE that includes CT appears to be more cost-effective than algorithms that do not include CT but are based on other imaging modalities (ultrasonography [US], scintigraphy, pulmonary angiography) (31). In addition, there are some indications that CT not only may be used for evaluating thoracic anatomy in cases where PE is suspected but also could, to some degree, allow derivation of physiologic parameters on lung perfusion at single–detector row electron-beam and multi–detector row CT (32–34).

The main impediment to the unanimous acceptance of CT as the modality of choice for the diagnosis of acute PE has been the limitation of this modality for accurate detection of small peripheral emboli. Results of early studies (35–38) in which single–detector row CT was compared with selective pulmonary angiography demonstrated the high accuracy of CT for detection of PE to the segmental arterial level but suggested that subsegmental pulmonary emboli may be overlooked on CT scans. The degree of accuracy that can be achieved for the visualization of subsegmental pulmonary arteries and for the detection of emboli in these vessels with single–detector row, dual–detector row, and electron-beam CT scanners was found to range from 61% to 79% (37,39–41), limitations that have been overcome by developments in CT technology.

ADVANTAGES OF MULTI–DETECTOR ROW CT FOR IMAGING PE

The past few years have seen decisive dynamic developments in CT technology, mainly brought about by the advent of multi–detector row CT (42,43). The current generation of four–, eight–, and 16–detector row CT scanners now allow for coverage of the entire chest with 1-mm or submillimeter resolution within a short single breath-hold—now less than 10 seconds in the case of 16–detector row CT (Fig 2; Movie 1, rsanajnl.radiology.org/cgi/content/full/2302021489/DC1).

The ability to cover substantial anatomic volumes with high in-plane and through-plane spatial resolution has brought a number of clear advantages. Shorter breath-hold times have been shown to benefit imaging of patients suspected of having PE and underlying lung disease by reducing the percentage of nondiagnostic pulmonary CT angiographic studies (44). The near isotropic nature of high-spatial-resolution multi–detector row CT data lends itself to two- and three-dimensional visualization. This may, in some instances, improve diagnosis of PE (45) (Fig 3) but is generally of greater importance for conveying information to

Figure 1. Extensive acute central PE with “saddle embolus” extending into both central pulmonary arteries in a 72-year-old man. Contrast material–enhanced 16–detector row CT yielded coronal volume renderings in (a) anterocranial and (b) anterior perspectives, which allow intuitive visualization of the location and extent of embolus (arrows).
referring clinicians on the location and extent of embolic disease in a more intuitive display format (Fig 1). Probably the most important advantage is improved depiction of small peripheral emboli. It has been shown that single-detector row CT with thinner sections (e.g., 2 vs 3 mm) can provide superior demonstration of segmental and subsegmental pulmonary arteries (39). With single-detector row CT, however, the range of coverage with thin section widths within one breath hold was limited (39,41). The high spatial resolution of 1-mm- or submillimeter-collimation data sets now allows evaluation of pulmonary vessels down to sixth-order branches (46) and substantially increases the detection rate of segmental and subsegmental pulmonary emboli (47). This improved detection rate is likely due to reduced volume averaging and accurate analysis of progressively smaller vessels by use of thinner sections. These results are most striking in peripheral arteries with an anatomic course parallel to the scan plane; such vessels tend to be most affected by volume averaging when thicker sections are used (47). The high spatial resolution along the scan axis of a thin-collimation multi-detector row CT data set, however, allows an accurate evaluation of the full course of such vessels (Fig 4). The interobserver correlation for confident diagnosis of subsegmental emboli with thin-section multi-detector row CT by far exceeds the reproducibility of selective pulmonary angiography (11,12,47).

Figure 2. Normal pulmonary vessels in a 56-year-old man who presented with mild chest pain after a long-distance flight. A contrast-enhanced 16-detector row CT examination covers the entire chest within 10 seconds, allowing analysis of even the most peripheral pulmonary vessels with exquisite detail. Coronal reconstruction using (a) maximum intensity projection and (b) volume-rendering techniques. The entire scanned volume is shown in Movie 1 (rsnajnl辐射ology.org/cgi/content/full/2302021489/DC1).

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While traditional technical limitations of CT in the diagnosis of PE appear to have been successfully overcome by multi-detector row CT, we are now facing new challenges that are a direct result of our high-resolution imaging capabilities. In our recent experience, small peripheral clots that might have gone unnoticed in the past are now frequently detected, often in patients with minor symptoms (Figs 5, 6).

Although there may be no doubt in the mind of the interpreting radiologist as to the presence of a small isolated clot on a good quality multi-detector row CT scan, such a finding will be increasingly difficult to prove in a correlative manner. Animal experiments with artificial emboli used as an independent standard indicate that thin-collimation four-detector row CT is at least as accurate as conventional pulmonary angiography for the detection of small peripheral emboli (48). However, it appears highly unlikely that pulmonary angiography will be performed in a patient merely to prove the presence of an isolated small (2–3 mm) embolus. In addition, given the limited interobserver correlation for pulmonary angiography discussed earlier (11,12), it appears doubtful that this test, even if performed, would provide proof as useful and conclusive as that of thin-section multi-detector row CT. Investigators in broad-based studies such as the Prospective Investigation of Pulmonary Embolism Diagnosis II study, who set out to establish the efficacy of multi-detector row CT in cases where PE is suspected, account for this latter fact by using a composite reference test based on ventilation-perfusion scanning, US of the lower extremities, pulmonary angiography, and venography to establish the PE status of the patient (49).

Perhaps more important, there is a growing sense of insecurity within the clinical community as to how to care for patients in whom a diagnosis of isolated peripheral embolism has been established. It has been shown that 6% (15) to 30% (50) of patients with documented PE have clots only in subsegmental and smaller arteries, but the clinical importance of small peripheral emboli in subsegmental pulmonary arteries in the absence of a central embolus is uncertain. It is assumed that one important function of the lung is to prevent small emboli from entering the ar-
Such emboli are thought to form even in healthy individuals, although this notion has never been substantiated (51). Controversy also exists regarding whether the treatment of small emboli, once detected, may result in a better clinical outcome for patients (38,52,53). There is little disagreement though, that the presence of peripheral emboli may be an indicator of concurrent deep venous thrombosis (DVT), thus potentially heralding more severe embolic events (28,50,54). A burden of small peripheral emboli may also have prognostic relevance in individuals with cardiopulmonary restriction (26,50,53) and for the development of pulmonary infarction.

Figure 3. Contrast-enhanced pulmonary CT angiography in a 43-year-old woman suspected of having acute PE. Lymphatic tissue (arrows) in mediastinum and pulmonary hilum may be misinterpreted as embolic filling defects in central pulmonary vessels by less experienced observers if (a) transverse sections alone are used for diagnosis, while (b) coronal multiplanar reformations from four-detector row CT allow better differentiation of lymphatic tissue and vessels and may reduce sources of diagnostic error.

Figure 4. Contrast-enhanced thin-section pulmonary CT angiography in a 52-year-old man after right lung transplantation. Transverse 1-mm-thick sections show isolated pulmonary emboli (arrows) in segmental and subsegmental arteries in the right middle lobe of the lung and allow detailed visualization of course of obliquely oriented vessels and of isolated filling defects in segmental and subsegmental branches.

Figure 5. (a) Transverse contrast-enhanced 16-detector row CT image obtained with 0.75-mm collimation in a 62-year-old man with chest pain. Isolated peripheral pulmonary embolus (arrow) in sixth-order pulmonary arterial branch in segment 8 of the right lung is shown. (b) Lung window display of more caudal transverse section from same study shows subsequent pulmonary infarct (arrow) in the corresponding vascular territory in the right lower lobe. (c) Coronal volume-rendered display (anterior view) shows isolated peripheral filling defect (arrow) in otherwise normal pulmonary vascular tree.
chronic pulmonary hypertension in patients with thromboembolic disease (50).

Perhaps the most practical and realistic scenario for studying the efficacy of CT for the evaluation of patients in whom PE is suspected is to assess patient outcome. There is a growing body of experience concerning the negative predictive value of a normal CT study and patient outcome if anticoagulants are subsequently withheld (16,44,53–59). According to these retrospective investigations, the negative predictive value of a normal CT study is high, approaching 98%, regardless of whether multi–detector row technology was used (44) or underlying lung disease was present (58). The frequency of a subsequent clinical diagnosis of PE or DVT after a negative pulmonary CT angiogram is low; the frequency is even lower than that after a negative or low-probability ventilation-perfusion scan (53). Thus, even single–detector row CT appears to be a reliable imaging tool for excluding clinically relevant PE, and it appears that anticoagulants can be safely withheld when the CT scan is normal and of good diagnostic quality (53,59).

**PROBLEMS AND LIMITATIONS OF CT FOR DIAGNOSIS OF PE**

**Contrast Material Injection and Artifacts**

Despite advances in CT technology, there are still several factors that can render pulmonary CT angiographic images inconclusive. The most common reasons for nondiagnostic CT images are poor contrast enhancement of pulmonary vessels, patient motion, and increased image noise due to excessive patient obesity.

The advent of multi–detector row CT necessitates an extensive revision of contrast material injection protocols. Faster scanning times allow acquisition during maximal contrast enhancement of pulmonary vessels (41) but pose an increased challenge for precise timing of the contrast material bolus. Strategies that have the potential to improve the delivery of contrast material for high and consistent vascular enhancement during pulmonary CT angiography currently in-
clude use of a test bolus or automated bolus-triggering techniques (60). Saline chasing (61,62) has been used for effective utilization of contrast material and for reduction of streak artifacts arising from a dense concentration of contrast material in the superior vena cava. Multiphasic injection protocols have proved to be beneficial for general CT angiography (63,64) but, to our knowledge, have not been scientifically evaluated for the pulmonary circulation.

Another limitation that, in some instances, results in suboptimal diagnostic quality of pulmonary CT angiographic images is motion artifact due to patient respiration or transmitted cardiac pulsation. The shorter breath-hold times that are possible with multi–detector row CT should facilitate investigation in dyspneic patients (44) and reduce the occurrence of respiratory motion artifacts. Similarly, artifacts arising from transmitted cardiac pulsation appear amenable to decreased temporal resolution with fast CT acquisition techniques (41). Electrocardiographic (ECG) synchronization of the CT acquisition allows effective reduction of cardiac pulsation artifacts that might interfere with the unambiguous evaluation of cardiac structures, the thoracic aorta, and pulmonary structures (65,66).

However, the spatial resolution that could be achieved with, for example, a retrospectively ECG–gated technique with the previous generation of four–detector row CT scanners was limited by the relatively long scanning duration inherent to data oversampling (66). Thus, a thin-section acquisition could only be achieved for relatively small volumes (eg, coronary arterial tree) but not for extended coverage of the entire chest. The advent of 16–detector row scanners now effectively eliminates these previous tradeoffs. With 16–detector row CT, it is now possible to cover the entire thorax with submillimeter resolution in a single breath hold with retrospective ECG gating, effectively reducing transmitted pulsation artifacts (Fig 7). This way, potential sources of diagnostic pitfalls arising from cardiac motion can be averted. It needs to be shown whether this technology will be able to further increase the accuracy of CT for detection of small emboli in the vicinity of the heart.

**Radiation Dose**

Use of thin-section multi–detector row CT protocols has been shown to improve the visualization of pulmonary arteries (46) and the detection of small subsegmental emboli (47). When PE is suspected, the establishment of an unequivocal diagnosis regarding the presence of emboli or other disease on the basis of high-quality multi–detector row CT scans may reduce the overall radiation burden in patients, since further work-up with other tests that involve ionizing radiation may be less frequently required. However, if a four–detector row CT protocol with 1-mm collimation is chosen to replace a single–detector row CT protocol with 5-mm collimation, the increase in radiation dose ranges between 30% (67) and 100% (42).

Similar increases in radiation dose, however, are not to be expected with the introduction of 16–detector row CT technology with submillimeter resolution capabilities. The addition of detector elements should improve tube output utilization, compared with that of current four–detector row CT scanners, and reduce the ratio of excess radiation dose that does not contribute to image generation (68). As sophisticated technical devices become part of clinical practice—devices that modulate and adapt tube output relative to the geometry and x-ray attenuation of the scanned object (ie, the patient) (69–71)—substantial dose savings can be realized without compromising diagnostic quality (72). The specific effect of such devices on the detection of PE, however, has not been scientifically evaluated to date, to our knowledge.

The most important factor for ensuring
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Fig. 8. CT-based algorithm for imaging evaluation of patients clinically suspected of having PE. If diagnosis of DVT can be established in a patient suspected of having PE, the therapeutic regimen is usually predetermined and no further diagnostic work-up of pulmonary circulation is pursued. If no diagnosis of DVT can be established, CT angiography (CTA) of pulmonary circulation is performed; if results are positive for PE, the patient is treated. If a good quality CT study does not reveal PE, work-up can usually stop at this point. In the unlikely case of persistent high clinical suspicion of PE despite a negative good-quality pulmonary CT angiogram, there is the theoretical option of pursuing definitive diagnosis by means of conventional pulmonary angiography to exhaust all diagnostic means available. In cases where a poor-quality CT study does not allow one to establish or rule out with confidence PE or other sources of the patient's symptoms, repeat pulmonary CT angiography is usually attempted.

The responsible utilization of the technical prowess of multi-detector row CT is increased awareness by technologists and radiologists with regard to radiation exposure to patients. It has been shown that the diagnostic quality of chest CT is not compromised if tube output is adjusted to the body type of the individual patient (73). Also, with multi-detector row CT, radiologists are increasingly adapting to the concept of volume imaging. There is a trade-off between increased spatial resolution and image noise when thinner and thinner sections are acquired with fast CT techniques. Given the great flexibility and diagnostic benefit that a thin-section, nearly isotropic multi-detector row CT data set provides, radiologists are increasingly willing to compromise on the degree of image noise that they are willing to accept on an individual transverse thin section in order to keep radiation dose within reasonable limits.

Data Management

Multi-detector row CT increases our diagnostic capabilities; however, the massive amount of data that are generated with this technique puts a substantial strain on any image analysis and archiving system. A thin-section 16-detector row CT study in a patient suspected of having PE routinely results in 500–600 transverse images. Three-dimensional display of multi-detector row CT data in such a patient may aid diagnosis in some instances and help prevent diagnostic pitfalls, allowing, for example, correct interpretation of hilar lymphatic tissue adjacent to central pulmonary arteries (74) (Fig 3). There are indications that focal lung disease can be diagnosed accurately by using maximum intensity projection reconstructions that beneficially “condense” large-volume multi-detector row CT data sets (75). In contrast, a diagnosis of PE is usually most beneficially established on the basis of individual transverse sections, although extensive (Fig 1) or isolated findings of PE (Figs 5, 6), as well as normal pulmonary vasculature (Fig 2, Movie 1 [snajnl.radiology.org/cgi/content/full/2302021489/DC1]), can be visualized in a comprehensive manner by means of three-dimensional reconstructions based on thin-section multi-detector row CT data. Interpretation of such large-volume studies is only feasible with use of digital workstations that allow viewing in “scroll-through” or cine modes.

Development of dedicated algorithms for computer-aided detection (76) may be helpful in the future for identification of pulmonary emboli in large-volume multi-detector row CT data sets. Large and accessible storage capacity is an essential requirement for successful routine performance of multi-detector row CT in a busy clinical environment. Adaptation of this environment to the new demands generated by the introduction of ever-faster scanning techniques is not a trivial task. New modalities for data transfer, data archiving, and image interpretation will have to be devised to make full use of the vast potential of multi-detector row CT imaging.

CT ALGORITHM FOR EVALUATION OF PATIENTS WHO MAY HAVE PE

We propose a simple CT-based algorithm, which is based on our beneficial experiences with thin-section multi-detector row pulmonary CT angiography, for the imaging evaluation of patients in whom there is clinical suspicion of PE (Fig 8). This algorithm reflects the clinical reality at our institution and works well in our hands for establishment of a definitive diagnosis in the majority of cases.

Before proceeding to imaging, the most important first-line clinical tool at our institution for diagnosis of PE is D-dimer testing, the results of which, if negative, are usually accepted for ruling out PE (3), especially if other causes for the patient's signs and symptoms can be established during further work-up. In clinically stable patients, the same regimen of anticoagulants is usually chosen for treatment of both PE and DVT. Therefore, if a diagnosis of DVT can be established (eg, by means of positive findings at lower extremity US) in a patient in whom PE is clinically suspected, usually no further diagnostic work-up of the pulmonary circulation is pursued (Fig 8). If no diagnosis of DVT can be established in such a patient, CT angiography of the pulmonary circulation is performed and, if the results are positive for PE, the patient is treated accordingly (Fig 8). If a good-quality CT angiographic study does not reveal PE, the work-up for PE can ordinarily stop at this point (Fig 8), and other diagnostic routes for elucidation of the source of the patient's signs and symptoms should be pursued.

In the unlikely case of a persistent high clinical suspicion of PE despite a negative good-quality pulmonary angiogram, there is the theoretical option of pursuing a definitive diagnosis by means of conventional pulmonary angiography as the last resort to exhaust all diagnostic means available. To date, however, this has not occurred in our practice. In those few cases where a poor quality CT angiographic study does not allow us to establish or rule out with confidence a diagnosis of PE as the source of the patient's symptoms, we usually attempt repeat pulmonary CT angiography, if at all feasible in view of the patient's clinical presentation. In many instances, analysis and remedying of factors for failed pul-
monary CT angiography (eg, improved intravenous access, higher rate of contrast material injection, use of automated bolus-triggering techniques, adaptation of tube output to patient’s body type, use of ECG-gated acquisition) result in diagnostic studies at repeat CT angiography.

CONCLUSION

With multi–detector row CT technology, past limitations of CT for the diagnosis of PE should be effectively overcome; for all practical purposes, CT has become the first-line modality for imaging in patients suspected of having PE. CT is now an attractive means for establishing a safe, highly accurate, and cost-effective diagnosis of PE. The lack of a clinically available performance standard for the diagnosis of PE suggests that the medical community should replace theoretical and academic discussions on the relative value of different imaging modalities with more realistic approaches based on patient outcome. Retrospective studies (16,44,53,55–59) already indicate the high negative predictive value for a normal multi–detector row CT pulmonary angiographic study. However, prospectively acquired patient outcome studies are still needed. Once this type of investigation has confirmed that a negative CT scan can be used to safely rule out PE, we believe use of CT to aid in diagnosis of PE will be unani-

References

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