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ORIGINAL ARTICLE

Efficacy of Iodine Perfusion Maps from Dual-energy Computed Tomography of the Pulmonary Arteries in Pulmonary Embolism Assessment

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ABSTRACT

Introduction: *There has been increasing availability and use of dual-energy computed tomography (DECT) over recent years. The aim of this study was to evaluate the sensitivity, specificity, and accuracy of iodine perfusion maps in diagnosing pulmonary embolus (PE) using a DECT scanner.*

Methods: *A retrospective study was performed comparing the detection of PE and correlation of PE types (central vs. segmental and occlusive vs. non-occlusive) on computed tomographic pulmonary angiography (CTPA) and iodine perfusion maps. Diagnostic performance parameters were calculated for each reader and for the different types of PE. Interobserver variability was measured for the two techniques.*

Results: *Both radiologists demonstrated consistent diagnostic performance in detecting PEs on CTPA. However, diagnostic performance varied widely in the detection of a defect on iodine perfusion maps. Iodine perfusion scans demonstrated a high sensitivity for occlusive and central PE but a low sensitivity for non-occlusive and segmental PE, whereas their specificity in the detection of central PE was similar to that of segmental PE. Positive predictive value (PPV) of iodine perfusion scans was higher for central PE than for segmental PE, whereas negative predictive value (NPV) was lower for segmental PE than for central PE. Occlusive PE had a low PPV and a high NPV, whereas non-occlusive PE had a lower PPV and NPV. Interobserver agreement was high in the interpretation of CTPA and fair in the interpretation of iodine perfusion maps.*

Conclusion: *Iodine perfusion maps should be read in conjunction with CTPA. A normal iodine perfusion map excludes a central or occlusive PE.*

Key Words: *Iodine; Observer variation; Perfusion imaging; Pulmonary embolism; Tomography, X-ray computed*

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中文摘要

雙能電腦斷層掃描碘灌注圖評估肺栓塞肺動脈的效果

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引言：近年，雙能電腦斷層掃描（DECT）的使用日益增加。本研究旨在評估使用DECT碘灌注圖對診斷肺栓塞的敏感性、特異性和準確性。

方法：回顧性研究比較電腦斷層掃描肺血管造影（CTPA）和CT碘灌注圖檢測肺栓塞和肺栓塞類型的相關性（中央型和節段型肺栓塞、閉塞型和非閉塞型肺栓塞）。為每位放射科醫生和不同類型肺栓塞計算診斷性能參數，以及記錄兩種技術的觀察者間差異。

結果：兩位放射科醫生通過CTPA診斷肺栓塞表現一致，但通過碘灌注圖診斷時卻有較大差異。碘灌注圖顯示對閉塞型和中央型肺栓塞敏感度高，但對非閉塞型和節段型肺栓塞敏感度低；診斷中央型肺栓塞的特異性與節段型肺栓塞相似。碘灌注圖掃描的陽性預測值（PPV）方面，中央型較節段型肺栓塞高，而節段型肺栓塞的陰性預測值（NPV）低於中央型肺栓塞。閉塞型肺栓塞的PPV較低而NPV較高，非閉塞肺栓塞的PPV和NPV則均低。觀察者對CTPA判斷有高度一致性，對碘灌注圖判斷的一致性一般。

結論：應結合碘灌注圖與CTPA進行分析。正常碘灌注圖可排除中央型或閉塞型肺栓塞。

INTRODUCTION

Computed tomographic pulmonary angiography (CTPA) is considered the imaging modality of choice and the reference standard in assessing a patient with suspected pulmonary embolism (PE).[1] Recently, there has been increase in the use of dual-energy computed tomography (DECT), a technique which simultaneously acquires images at two different energies, typically 80 kVp and 140 kVp. This is achieved either via having two pairs of X-ray tubes and detectors that rotate around patient or a single-source DECT with rapid kVp switching.[2,3] Iodine content of the administered intravenous iodinated contrast possesses the unique quality of attenuating the X-ray spectra differently at the different energies, thus enabling derivation of iodine content in each imaged voxel, and hence as a result, an iodine perfusion map. The perfusion maps in turn are considered reflective of regional blood flow/pulmonary microcirculation.[4] Defects in these iodine maps have been demonstrated to represent proximal vascular occlusion.[5-8] The benefits of DECT include faster scan times, high spatial resolution, and a wide range of available post-processing techniques.[7]

Simultaneous acquisitions enable assessment of material composition to generate material density images using two absorption spectra.[2,3] Thus, contrast uptake maps or 'perfusion' maps are produced in addition to routine monochromatic CTPA images.[9] These perfusion maps refer to pulmonary vascular enhancement visible at one point in time,[7] which approximates the pulmonary blood flow.[10]

Routine monochromatic CTPA and perfusion maps complement each other. Routine CTPA provides morphologic information of the pulmonary embolus.[7,10-12] In contrast, perfusion maps provide a more functional assessment.[7,11,12] In recent studies, Weidman et al[13] found that iodine maps provide a small incremental benefit over CTPA, and Grob et al[14] found iodine maps to be equivalent to routine CTPA.

A study by Kim et al[15] suggested a blockage in overall perfusion >30% detected on perfusion imaging correlates with poor clinical outcome. A separate study by Apfalter et al[16] concluded similarly, that higher perfusion defect volume correlated with more adverse outcomes in patients with pulmonary emboli. Perfusion defects, however, are not necessarily specific to an embolic aetiology and have been reported to be secondary to a myriad of non-vascular as well as vascular causes.[16] In addition, streak and motion artefacts may mimic perfusion defects.[2,7,8,11,17]

Most of the literature to date comment on the use of dual-source DECT. Very little data exist on single-

source DECT with fast kVp switching.[10] The aim of this retrospective study was to evaluate the sensitivity, specificity, and accuracy of iodine perfusion maps in diagnosing PE using a single-source, fast switching DECT scanner.

METHODS

Patients

The study was aligned with the institutional review board guidelines. All consecutive adult patients referred for CTPA were included in this study over a period between 1 January 2013 and 31 August 2013. Patients who had poor renal function and did not receive iodinated contrast, or whose images were very degraded due to motion artefacts were excluded. Patients who did not undergo dual-energy CTPA scans were also excluded from the study. The consecutive CTPA reports were reviewed by a research coordinator who determined positive and negative CTPA studies based on the reports. The first 53 consecutive positive and the first 50 consecutive negative dual-energy CTPA scans were assessed.

Computed Tomography Scanning and Image Reconstruction

Patients were scanned with a 64-detector single-source DECT scanner using fast kVp switching (Discovery HD 750 CT scanner, GE Healthcare, Milwaukee [WI], United States). The scanning parameters included 80 kVp and 140 kVp acquisitions via fast kVp switching, automatic exposure control ranging from 216 to 440 mAs, 1.375 pitch, 0.625 mm collimation, 0.5-s rotation time. Up to 75 mL of iodinated intravenous contrast (iohexol 370 mg I/mL) was given via a cannula in the cubital fossa. Scans were performed between 8 s and 13 s after contrast bolus injection with the use of bolus tracking. The scan was triggered when the attenuation value of contrast in the pulmonary trunk reached 250 Hounsfield units.

The tube current was matched to patient size by the automatic exposure control; averaging 216 mAs for a small patient, 315 mAs for a medium-sized patient, and 440 mAs for a larger patient.

The amount of contrast injected, and injection rate was also varied for different patient size; 30 to 50 mL at 4 to 5 mL/s for small patients, 40 to 60 mL at 5 to 5.5 mL/s for medium sized patients and 50 to 70 mL at 5 to 6 mL/s for larger patients (Table 1).

A standard orthogonal multiplanar reconstruction algorithm was used to generate routine grayscale CTPA images. Maximal intensity projection images were also generated. Iodine perfusion maps were subsequently generated using spectral information from different energies which measured iodine distribution in the lungs.

Table 1. Computed tomography scanner parameters.

Adverse event	Patient size		
	Small	Medium	Large
kVp		80 and 140	
Collimation (mm)		40	
Pitch		1.375:1	
Time delay between contrast bolus injection and scan (s)		8-13	
Current (mAs)	216	315	440
Amount of contrast injected (mL)	30-50	40-60	50-70
Injection rate (mL/s)	4-5	5-5.5	5-6

The first 53 consecutive patients (26 female, 27 male, mean age 64 years) diagnosed with PE (identified from the hospital's PACS reports) on a dual-energy scan between 1 January 2013 and 31 August 2013 were selected as study subjects. A further consecutive age-matched 50 patients (29 female, 21 male; mean age 62 years) who had undergone CTPA on the same scanner without PE were selected as controls. All patient information was collected retrospectively from the Centricity PACS system (GE Healthcare). Diagnosis of PE was based on reports derived from the extracted PACS data and subsequently verified by an independent radiologist before selecting study subjects.

Radiologist Readers

Two senior radiologists with 20 and 10 years of chest CT experience, respectively, were blinded to the patient and scan details. The readers randomly reviewed the CTPA images in one session, and then randomly reviewed the perfusion maps in another session, independent of each other.

Data Collection

Readers were required to complete a data form as they read each study. Information collected on the reader form included presence/absence of a PE on routine CT pulmonary angiogram, location of the embolism (right/left/bilateral, which lobe and which segment), and nature of the embolism (occlusive/non-occlusive and central/peripheral). The main pulmonary trunk, right and left main pulmonary arterial, and proximal lobar location was classified as 'central'; a segmental/subsegmental location was classified as 'peripheral'. The readers then

assessed the perfusion maps independent of the CTPA images for presence/absence of perfusion defect(s). Lung windows were also reviewed to assess for the presence of any parenchymal abnormality which could account for a perfusion defect, such as consolidation, fibrosis, or pleural effusion. Wedge-shaped perfusion defects in the absence of an underlying parenchymal abnormality were ascribed to embolic aetiology. The locations of the perfusion defects were tabulated.

Collected data were entered into Excel 2016 (Microsoft Corporation, Redmond [WA], United States) for analysis.

Data Analysis

A PE was considered as 'true positive' when the number of PEs and their locations denoted by both readers were in agreement. When both readers did not detect any PE, the study was considered as true negative. For any discrepant results, the images were reviewed by the two radiologists with a third radiologist in a consensus meeting. The diagnostic performance parameters (accuracy, sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) were then generated. These were assessed separately for central versus peripheral emboli on a per-segment basis and compared between the two readers.

Cohen's kappa statistic was used to compare interobserver variability. Kappa value (κ) $\leq$0.2 indicated poor agreement, κ between 0.21 and 0.4 indicated fair agreement, κ between 0.41 and 0.6 indicated moderate degree of agreement, κ between 0.61 and 0.8 indicated substantial agreement, and κ >0.8 indicated good agreement.

RESULTS

A total of 103 patients (55 female, 48 male) were included in the study with a mean age 62 (range, 20-97) years.

In all, 53 of the studies demonstrated a pulmonary embolus on CTPA, 16 of which were peripheral emboli and 37 were central emboli. Of the studies that demonstrated pulmonary emboli, 29 were bilateral, 17 were in the right lung and 7 were in the left lung.

On a segmental basis, there were a total of 69 segments that demonstrated an occlusive pulmonary embolus, of which 57 had corresponding perfusion defects. In total, 15 segments had abnormalities on perfusion scan with no evidence of a pulmonary embolus on CTPA. These consisted of streak artefact, emphysematous change, motion artefact, interstitial lung disease, pleural effusion, or pulmonary artery compression.

Both readers in our study demonstrated consistent diagnostic performance in detecting a pulmonary embolus on CTPA; accuracy, specificity, sensitivity, PPV and NPV of 100%. However, these parameters varied widely in the detection of a filling defect on iodine perfusion maps and are demonstrated in Table 2. Reader 2 had a higher accuracy (72%), specificity (67%), PPV (70%) and NPV (74%) than reader 1 (accuracy of 61% and specificity of 48%) whereas reader 1 had a higher sensitivity (75%) compared with reader 2 (53%) [Table 2].

Iodine perfusion scans demonstrated a high sensitivity (83%) for occlusive pulmonary emboli but a low sensitivity (57%) for non-occlusive pulmonary emboli (Table 3). The specificity of iodine perfusion scans in the detection of central pulmonary emboli was similar to that of segmental pulmonary emboli, measuring 93%. The finding of 'occlusive pulmonary emboli' had a low PPV and a high NPV whereas 'non-occlusive pulmonary emboli' had a lower PPV and NPV.

Mean sensitivity of iodine perfusion scan in detecting a PE is 64% whereas mean specificity is 58%.

High interobserver agreement was observed between the readers in the interpretation of CTPA, with an agreement rate of 100% and kappa (κ) = 1. However, interpretation

Table 2. Comparison of readers' diagnostic performance in detection of a pulmonary embolus on iodine perfusion maps.

	Accuracy	Sensitivity	Specificity	PPV	NPV
Reader 1	61%	75%	48%	57%	68%
Reader 2	72%	53%	67%	70%	74%
Mean	66%	64%	58%	63%	71%

Abbreviations: NPV = negative predictive value; PPV = positive predictive value.

Table 3. Performance of iodine perfusion scan in the detection of pulmonary emboli on a per-segment basis.

	Sensitivity	Specificity	PPV	NPV
Occlusive PE	83%	93%	79%	94%
Non-occlusive PE	57%	48%	35%	70%

Abbreviations: NPV = negative predictive value; PE = pulmonary embolus; PPV = positive predictive value.

of iodine perfusion maps only yielded a fair agreement of 69% and κ of 0.38.

DISCUSSION

Separate studies have demonstrated the use of perfusion maps in identifying perfusion defects associated with PE, particularly for small[3] peripheral pulmonary emboli[2] and chronic pulmonary emboli,[11,12] as well as quantifying the severity of the PE.[9,11,12] Our study demonstrated that iodine perfusion maps are more likely to demonstrate a defect in an occlusive and central pulmonary embolus. An occlusive pulmonary embolus is unlikely if there is no perfusion defect on iodine maps.

A 'perfusion defect' in our study did not necessarily correspond to a PE. Various mimickers of pulmonary emboli in our study included: streak artefact, emphysematous change, motion artefact, interstitial lung disease, pleural effusion, and pulmonary artery compression. Apart from pleural effusions, none of these pathologies could be differentiated on iodine perfusion maps. The susceptibility of perfusion maps to artefacts such as movement and streak artefact from dense iodinated contrast in the heart and mediastinum has been documented in various literature.[2,7,8,11,17,18] Cardiac gating methods, reviewing all multiplanar reconstructions,[2] and having a basic understanding of artefacts assist in reducing misinterpretation of perfusion maps. In addition, perfusion defects consistent with acute pulmonary embolus tend to be wedge-shaped[2,12] and take on either a segmental or lobar distribution.

Previous studies documented perfusion maps demonstrating a high sensitivity (76.7%-100%) and specificity (76%-100%) on a per-patient basis and variable values on a per-segment basis (40%-82.9% sensitivity and 66.7%-99.6% specificity).[8,17,19-21] NPV in excluding the presence of an occlusive pulmonary emboli is high for perfusion maps.[2,7,21] Interobserver and intraobserver correlation in reading perfusion maps are good (κ = 0.806-1.000).[7,17] High accuracy and interobserver agreement are also demonstrated in animal studies.[22,23] Nakazawa et al[17] found perfusion maps to be comparable to pulmonary scintigraphy in evaluating pulmonary perfusion.

Overall reader diagnostic performance in our study was excellent for CTPA but varied widely for iodine perfusion maps. This is mainly because interpretation of the iodine maps was more subjective and there was no set measurable surface area or density. In addition, multiple other different pathologies resulted in false positive and false negative findings.

It is recommended that iodine maps be read in conjunction with CTPA. This guides localisation of pulmonary embolus and eliminates false positives and false negatives from other causes.

The study was performed on a limited number of patients due to time and facility constraints. Future studies with a larger, age- and population-matched group would increase the statistical power of the study.

CONCLUSION

Interobserver agreement is high for CTPA and fair for iodine perfusion maps. Iodine perfusion maps should be read in conjunction with CTPA. A normal iodine perfusion map excludes a central or occlusive pulmonary embolus or other lung pathologies such as emphysema, interstitial lung disease, pleural effusion, and pulmonary artery compression.

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