Acute and subacute dual energy CT findings of pulmonary embolism in rabbits: correlation with histopathology

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Objective: The purpose of this study was to describe quantitative dual energy CT (DECT) findings and their accuracy in the detection of acute and subacute pulmonary embolism (PE) in rabbits.

Methods: Pulmonary emboli were created in 24 rabbits by gelatin sponge femoral vein injection. Conventional CT pulmonary angiography (CTPA) and DECT were obtained at either 2 h, 1 day, 3 days or 7 days after embolisation ($n=6$ rabbits for each time point). The location and number of PEs in the different stages were recorded at CTPA and iodine maps from DECT on a per-lobe basis. With histopathology as the reference standard, sensitivity and specificity of CTPA and DECT were calculated. CT and iodine map overlay values of the embolic and non-embolic areas were measured for each scan.

Results: With histopathology as the reference standard, the overall sensitivity and specificity of CTPA were 98% and 100% and those of iodine maps were 100% and 95%, respectively. Conventional CT and iodine map values of the embolised and non-embolised areas were significantly different between 2 h and 1 day ($p<0.001$), but not between 3 days and 7 days ($p>0.05$). A statistical difference was found for overlay values measured in the embolic and non-embolic regions for four groups.

Conclusion: Iodine maps derived from DECT show alterations in lung perfusion for acute and subacute PE in an experimental rabbit model and show comparable sensitivity for PE detection and conventional CTPA.

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In the USA, more than 650 000 cases of pulmonary embolism (PE) occur each year, resulting in as many as 300 000 annual fatalities [1, 2]. Despite the high morbidity, the diagnosis of PE may be delayed in the absence of typical clinical symptoms or when emboli are subsegmental and such scenarios may delay the treatment and increase the mortality of PE. Imaging plays an important role in the diagnosis and follow-up of PE. With improvements in multidetector row CT, CT pulmonary angiography (CTPA) has largely replaced digital subtraction angiography (DSA) for the diagnosis and follow-up of PE and has been recommended as the reference of standard for diagnosis of acute PE [3]. However, CTPA has shortcomings, such as a limited sensitivity to detect peripheral or subsegmental emboli of the pulmonary artery and an inability to show lung perfusion impairment resulting from acute or chronic PE.

With the development of dual source CT (DSCT), in which two orthogonally mounted detectors and tubes arrays operate simultaneously and can be set to different tube potentials to allow for dual energy CT (DECT) acquisitions with minimal patient motion registration artefact, DECT imaging has been used to investigate

iodine distribution maps in clinical and pre-clinical studies [4–13]. Such iodine maps, which have been termed blood flow imaging (BFI), have been shown to be valuable supplements to conventional anatomic CTPA for the evaluation of distal pulmonary artery emboli [4–13]. Many studies have focused on the feasibility or diagnostic accuracy of DECT iodine maps to improve the detection of PE, with CTPA, scintigraphy or histopathology as a reference standard in the clinical and experimental studies [5–13], or the evaluation of image quality of dual energy CTPA [14,15]. However, to the best of our knowledge, there are no reports that describe the evolution of CT and DECT imaging findings of PE over time after an embolic event with histopathological correlation. Histopathology correlation is most ethically obtained using an animal model. Therefore, we evaluated DECT findings with histopathology correlation in a rabbit model of PE with different time delays after embolisation and assessed the diagnostic accuracy of DECT in the detection of PE at these different time points.

Materials and methods

Animal model

The study protocol was approved by our institutional animal experimental committee and performed according to Chinese animal care guidelines. A total of 30 New Zealand white rabbits with a mean body weight of

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2.5 kg (Jinling Hospital Laboratories, Nanjing, Jiangsu Province, China) were used for DECT imaging. Rabbits were anaesthetised with 44 mg kg^{-1} of intravenous ketamine hydrochloride (Hengrui Medical, Nanjing, Jiangsu Province, China). Pulmonary emboli were created in 24 rabbits by injecting 4 embolised gelatin sponge plugs measuring $4 \times 4 \times 10 \text{ mm}$ ($n=2$) and $2 \times 4 \times 10 \text{ mm}$ ($n=2$) into a 4- or 3-French custom-made catheter *via* the right femoral vein. Gelatin sponge was chosen as the embolic material in this study because of its clinical availability, simple preparation and rapid distension resulting in acute pulmonary vascular occlusions [7]. Benzylpenicillin (2.5 U kg^{-1}) was injected to prevent infection. For another six rabbits 5 ml of saline was injected into the right femoral vein; these animals served as a control group. All procedures were performed by one experienced interventional radiologist (XBH with 5 years of experience of small animal intervention), who was not involved in the subsequent histopathological or DECT evaluation.

Imaging protocols

Pre-embolisation CT scans were performed for each rabbit before the injection of gelatin sponge plugs, and these CT scans were used as a reference for subsequent post-embolisation scans. To assess pulmonary emboli of different temporal acuity, the rabbits were divided into four groups consisting of six rabbits each and were imaged at the following times after embolisation: Group A imaged at 2 h, Group B at 1 day, Group C at 3 days and Group D at 7 days. Groups A and B were considered to be "acute" PE and groups C and D were considered to be "subacute". All CT examinations were performed using a DSCT scanner (Somatom Definition; Siemens Healthcare, Erlangen, Germany). The rabbits were centred in the scanner to ensure that the entire thorax was covered by the field of view (FOV) of both the larger and smaller tube detector arrays; the size of the FOV of the smaller tube detector array was 260 mm. A contrast-enhanced CT (CECT) with the dual energy mode was obtained after 1.8 mL s^{-1} injection of Ultravist (300 mg mL^{-1} , Bayer Schering Pharma, Berlin, Germany, 2 mL kg^{-1}) followed by 10 ml of saline solution into an internal jugular vein *via* an 28-gauge catheter. The CT was triggered by a bolus tracking technique with the region of interest (ROI) placed in the pulmonary trunk and image acquisition started 3 s after the signal attenuation reached the pre-defined threshold of 100 HU. The other CT parameters were as follows: tube voltages of 80 kVp and 140 kVp and tube currents of 183 mA and 51 mA for the smaller and larger X-ray tubes, respectively; gantry rotation time of 0.33 s, detector collimation of $14 \times 1.2 \text{ mm}$, pitch 0.5, FOV 260 mm.

Image reconstruction and analysis

From the raw spiral projection data of both tubes, images were then automatically reconstructed into three conventional CT image data sets (80 kVp, 140 kVp and average weighted 120 kVp images, with 30% density information from the 80 kVp image and 70% from the 140 kVp image) with slice thickness of 0.75 mm and intervals of 0.50 mm.

Then, all images were transferred to a commercially available workstation (Syngommvvp VE23A; Siemens Healthcare). Average weighted 120 kVp images were post-processed to obtain sliding maximum intensity projection CTPA reformations in the axial, coronal and sagittal planes and dedicated dual energy iodine maps of the perfused blood volume/BFI in the axial, coronal and sagittal planes were obtained using 80 and 140 kVp data sets. For the iodine maps, the colour coding was as follows: red represented the highest iodine concentrations and high contrast-enhanced blood volume; yellow represented intermediate iodine concentrations and intermediate contrast-enhanced blood volumes; blue represented low iodine concentrations and low contrast-enhanced blood volume; and black represented absence of iodine and a defect in contrast-enhanced blood volume.

The diagnostic accuracy of DECT for the diagnosis of PE in the different stages was evaluated. All images were independently evaluated by two radiologists (YEZ and XC, with 3 and 2 years of experience in CTPA interpretation, respectively) who were unaware of the pathological findings. When inconsistent readings were present, the third radiologist (IJZ with 10 years of experience in CTPA interpretation) evaluated the cases as final results. For each of the 30 rabbits, the pulmonary findings were assessed for each of the 5 lung lobes (right upper, middle and lower lobe and left upper and lower lobes) using previously described diagnostic criteria. Briefly, a normal iodine map was defined as showing symmetric and homogeneous lung iodine distribution in the normal range (colour-coded red or yellow). Pulmonary emboli on iodine maps were defined as segmental or lobar areas of heterogeneous diminished or absent iodine (colour-coded blue and black, respectively). For CTPA and iodine map images, the presence, numbers and locations of PE were recorded on a per-lobe basis. The lung lobes with a solitary embolus or multiple emboli (or iodine map abnormalities) within the same lobe were regarded as a true positive result, while the lobes without emboli or iodine map abnormalities as a true negative.

For quantification of imaging findings, the CT numbers of the embolised and non-embolised lung lobes were measured for the post-embolisation conventional fused CT images on representative lung parenchyma of each lobe in areas of relatively normal and, if present, areas of heterogeneous or increased/decreased lucency with care to avoid visible blood vessels and bronchi. For the iodine maps, the "overlay value", which is a DECT measure of iodine concentration on iodine maps developed by Siemens, was measured to quantify iodine contents in the embolised and non-embolised lung lobes using similar circular 1 cm^2 ROIs as used for the conventional fused CT images. ROIs were manually placed by a radiologist with 3 years of experience in the interpretation of pulmonary DECT imaging. CT numbers (HU) in lung window and overlay values from iodine maps were measured in three separate locations and these measures were averaged for the final measurement.

Histopathological processing

Histopathological analysis was used as the standard of reference in this study. Immediately after the

post-embolisation CT scan, each rabbit was anticoagulated by iv injection of 10 000 U of heparin (Shanghai Honghao Medical Inc., Shanghai, China), sacrificed by an overdose of pentobarbital and the pulmonary vasculature was then perfused with formalin (1:10 dilution of formaldehyde in 0.01 mmol l⁻¹ phosphate-buffered saline) to fix the lungs *in vivo*. The lungs and heart were subsequently removed *en bloc* and fixation was continued until serial sectioning of the lungs was performed (2–5 days after formalin perfusion). Pathological sectioning at 1 mm intervals was performed to verify the presence and location of pulmonary artery branches with and without emboli. Haematoxylin and eosin staining was performed to confirm the presence of gelatin sponge within the pulmonary arteries to diagnose pulmonary emboli.

Statistical analysis

Statistical analysis was performed using the software SPSS version 13.0 [IBM Corporation (formerly SPSS Inc.), Armonk, NY]. Quantitative variables were expressed as mean ± SD and categorical variables as frequencies or percentages. The Kolmogorov–Smirnov test was used to analyse the distribution of CT and overlay value in the embolic and non-embolic regions. When this test for normality indicated abnormal data the Mann–Whitney test was used and when the data were normal, a two independent sample *t*-test was used to analyse the difference of CT number and overlay value in the embolised and non-embolised regions. Using the histopathological results as the standard of reference, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CTPA

and BFI images for the detection of pulmonary emboli were determined for all and each group in the different stages on a per-lobe basis. The McNemar test was performed to compare the accuracy of the iodine maps and CTPA for the detection of pulmonary emboli on a per-lobe basis. Kappa statistics were used to quantify the intertechnique variability for the detection of PE using CTPA, BFI and interreader agreement for the detection of PE for two readers. κ -values <0.20 were interpreted as poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate, 0.61–0.80 as good and 0.81–1.00 as very good agreement. *p*-values <0.05 were regarded as statistically significant.

Results

Diagnostic accuracy of dual energy CT in the detection of pulmonary embolism

Numbers and location of lung lobes with emboli detected on CTPA, iodine maps and histopathology are shown in Table 1. With histopathological findings as the reference standard, CTPA showed 98% sensitivity and 100% specificity while iodine maps showed 100% sensitivity and 95% specificity for PE on a per-lobe basis. Sensitivities, specificities, PPVs, NPVs and accuracies of CTPA and iodine maps for pulmonary emboli detection in the different stages of PE on a per-lobe basis are provided in Table 2. Three lung lobes were misdiagnosed as having pulmonary emboli by the iodine maps and one lung lobe with PE was missed by CTPA (Table 2). The McNemar test showed no statistical difference for diagnostic accuracy of iodine maps and CTPA for pulmonary embolus detection on a per-lobe basis (*p*>0.05). Kappa analysis indicated

Table 1. Locations and numbers of pulmonary emboli detected by CTPA, BFI and histopathology

	Right lung			Left lung		Total
	Upper	Middle	Lower	Upper	Lower	
2 h (n=6)						
CTPA	1	1	6	0	5	13
BFI	1	1	6	1	6	15
Histopathology	1	1	6	0	6	14
1 day (n=6)						
CTPA	0	0	6	0	6	12
BFI	0	0	6	0	6	12
Histopathology	0	0	6	0	6	12
3 days (n=6)						
CTPA	0	2	6	2	6	16
BFI	2	2	6	2	6	18
Histopathology	0	2	6	2	6	16
7 days (n=6)						
CTPA	0	1	5	0	6	12
BFI	0	1	5	0	6	12
Histopathology	0	1	5	0	6	12
Control (n=6)						
CTPA	0	0	0	0	0	0
BFI	0	0	0	0	0	0
Histopathology	0	0	0	0	0	0
Total						
CTPA	1	4	23	2	23	53
BFI	3	4	23	3	24	57
Histopathology	1	4	23	2	24	54

BFI, blood flow imaging; CTPA, CT pulmonary angiography.

Table 2. The diagnostic performance of BFI on a per-lobe basis ($n=120$)

Group	Results (n)				Statistics (%)				PPV	NPV	Accuracy	kappa value	p-value	
	TP	FP	TN	FN	Sensitivity	Specificity								
CTPA														
2 h	13	0	16	1	93 (13/14)	100 (16/16)	100 (13/13)	94 (16/17)	97 (29/30)	0.933	<0.001			
1 day	12	0	18	0	100 (12/12)	100 (18/18)	100 (12/12)	100 (18/18)	100 (30/30)	1.000	<0.001			
3 days	16	0	14	0	100 (16/16)	100 (14/14)	100 (16/16)	100 (14/14)	100 (30/30)	1.000	<0.001			
7 days	12	0	18	0	100 (12/12)	100 (18/18)	100 (12/12)	100 (18/1)	100 (30/30)	1.000	<0.001			
Control	0	0	30	0	–	100 (30/30)	–	100 (30/30)	100 (30/30)	1.000	<0.001			
Total	53	0	96	1	98 (53/54)	100 (96/96)	100 (53/53)	99 (96/97)	99 (149/150)	0.980	<0.001			
BFI														
2 h	14	1	15	0	100 (14/14)	94 (15/16)	93 (14/15)	100 (15/15)	97 (29/30)	0.933	<0.001			
1 day	12	0	18	0	100 (12/12)	100 (18/18)	100 (12/12)	100 (18/18)	100 (30/30)	1.000	<0.001			
3 days	16	2	12	0	100 (16/16)	86 (12/14)	89 (16/18)	100 (12/12)	94 (28/30)	0.870	<0.001			
7 days	12	0	18	0	100 (12/12)	100 (18/18)	100 (12/12)	100 (18/18)	100 (30/30)	1.000	<0.001			
Control	0	0	30	0	–	100 (30/30)	–	100 (30/30)	100 (30/30)	1.000	<0.001			
Total	54	3	93	0	100 (54/54)	95 (93/96)	95 (54/57)	100 (93/93)	98 (147/150)	0.950	<0.001			

BFI, blood flow imaging; CTPA, conventional CT pulmonary angiography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

excellent agreement between dual energy iodine maps, CTPA and histopathology (Table 2). Excellent inter-reader agreement was found when BFI images were used to evaluate the presence of PE ($\kappa=0.929$, $p=0.001$).

Dual energy CT and correlation with pathological findings

Pre-embolisation CT scans of experimental and control rabbits did not show abnormal pulmonary findings and showed homogeneous iodine maps for the lung parenchyma without visible lobar or segmental decreased iodine map defects (Figure 1), except in the superior lung lobes where differential gravity-dependent lung perfusion was expected and seen in some rabbits.

2 h after embolisation, pulmonary emboli were detected in 14 lung lobes by histopathology. Lobar or segmental lucencies were seen in the lobes with pulmonary emboli on the CECT images; iodine map defects were seen in the lobes with pulmonary emboli on iodine maps. At histopathology, purple discolouration of the gross lung specimens was seen in the lobes with emboli. No gross pathological abnormalities were observed except in the distribution of emboli (Figure 2).

1 day after embolisation, pulmonary emboli were detected in 12 lung lobes by histopathology. Lobes with PE showed iodine map defects. Pathologically, pulmonary emboli were found in the pulmonary arteries of the lower lung lobes in Group B. The congestion, haemorrhage, inflammatory cell infiltration, alveolar gas reduction and structural integrity of gas space were observed in the embolic pulmonary interstitium; the gelfoam embolus was also seen in the corresponding pulmonary arteries (Figure 3).

3 days after embolisation, pulmonary emboli were detected in 16 lung lobes by histopathology. Lobes with PE showed increased CT number on conventional CT images and defects on iodine maps. Haemorrhage, alveolar septal widening, a large number of inflammatory cell infiltrations and some mild lung tissue necrosis can be observed except in pulmonary arteries with gelfoam embolus (Figure 4).

7 days after embolisation, pulmonary emboli were histopathologically detected in 12 lung lobes. Bilateral lower lobes with PE in five rabbits showed increased CT number on conventional CT images and defects on iodine maps. An iodine map defect was noted in the right middle lung lobe in one rabbit with PE and in the left lower lobe in another rabbit with PE. Pathological findings showed lung tissue necrosis and filling of the alveolar space with a large amount of exudate; gelatin sponge was also observed in the corresponding pulmonary arteries (Figure 5). Table 3 illustrates the percentage of CT findings in different stages of PE.

Quantitative analysis of pulmonary embolism on dual energy CT imaging

For groups A and B (acute PE), the conventional CECT images showed lower CT numbers from ROIs taken from the embolised than from non-embolised lobes (mean CT numbers of -683.63 ± 121.82 HU for embolised and

Figure 1. Lung CT images in one rabbit before embolisation. (a) Lung window of conventional enhanced chest CT image shows a homogeneous appearance of the pulmonary parenchyma without focal findings. (b) Coronal maximum intensity projection image of CT pulmonary angiography shows normal tapering of the bilateral pulmonary arteries. (c) Coronal iodine map shows a homogeneous iodine map, colour-coded as red.

Figure 2. Lung CT and histopathological images in one rabbit 2 h after embolisation. (a) Lung window of chest CT shows increased lucency in bilateral lung bases (arrows). (b) Thin coronal maximum intensity projection image of CT pulmonary angiography shows cut-off appearance of bilateral lower lobe pulmonary arteries (arrows). (c) Coronal iodine map shows decreased overlay values (iodine concentrations), colour-coded as blue to black, in the bilateral lung bases (arrows) compared with other lung fields. (d) Photograph of the gross lung specimen shows a dark red discolouration of the lower lobes bilaterally (arrow). (e) Histological section shows gelatin sponge in the pulmonary artery (arrow), mild alveolar exudate of red cells and white cells and thickened alveolar septa; no necrosis was noted (haematoxylin and eosin staining, $\times 100$).

Figure 3. Lung CT and histopathological images in one rabbit 24h after embolisation. (a) Lung window of chest CT shows increased lucency in the bilateral lung fields (arrows). (b) Thin coronal maximum intensity projection image of CT pulmonary angiography shows cut-off appearance of the bilateral lower lobe pulmonary arteries (arrows). (c) Iodine map shows decreased iodine concentrations, colour-coded as blue to black, in the bilateral lung bases (arrows) compared with other lung fields. (d) Photograph of gross lung specimen shows a dark red discolouration of the bilateral lower lobes (arrows). (e) Histological section shows congestion, haemorrhage, inflammatory cell infiltration and reduction in alveolar gas in the embolised pulmonary tissue (arrow), the gelfoam embolus was also seen in the corresponding pulmonary arteries (arrowhead) (haematoxylin and eosin staining, $\times 100$).

-456.98 ± 39.24 HU for non-embolised lobes for group A, -607.07 ± 29.66 HU for embolised and -422.58 ± 51.36 HU for non-embolised lobes for Group B, both $p < 0.05$) indicating pulmonary oligoemia in the embolised regions. But for Groups C and D (subacute PE), the average CT numbers of the embolised regions (-222.00 ± 369.26 HU and -157.95 ± 329.54 HU for Groups C and D, respectively) were similar to those of the normal lung regions (-462.11 ± 37.39 HU for Group C and -455.10 ± 32.53 HU for Group D, both $p > 0.05$) corresponding to areas of pulmonary consolidation or infarcts at histopathology. Table 4 shows the mean CT numbers and iodine map overlay values for the embolised and non-embolised lung lobes. Figure 6 illustrates the CT numbers and iodine map overlay values for the embolised and non-embolised lobes over the four imaged time points. The mean CT numbers of the embolic region became increasingly higher and the iodine map overlay value of the embolised lobes gradually decreased to zero over time, corresponding to changes in histopathological findings from early lung pulmonary oligoemia to consolidation and infarction in the experimental PE rabbit model.

Discussion

Our study demonstrates that iodine maps derived from DECT have a comparable diagnostic accuracy compared with conventional CTPA for the assessment of PE across a range of acuity from 2 h to 7 days after emboli in rabbits with histopathology as the reference standard.

DSCT imaging has opened new horizons for dual energy contrast-enhanced applications because the 2 simultaneously operating source and detector arrays can be set to different tube potentials, 1 at 80 kVp and 1 at 140 kVp, allowing for DECT acquisitions with minimal patient motion registration artefact [16]. The resultant dual peak kilovoltage datasets can be reformatted using the dedicated dual energy post-processing software to extract maps of iodine contrast-material content without the need for complex image registration which is invariably present with conventional single source CT and generally requires separate acquisitions of unenhanced and enhanced CT scans to determine pulmonary perfusion [17, 18]. Our findings add to the current literature. While Woo et al [19] described histopathological correlation of pulmonary fat emboli with CT

Figure 4. Lung CT and histopathological images in a rabbit 3 days after embolisation. (a) Lung window of chest CT shows increased lucency in the left lower lung base (red arrow) and consolidation in the right lower lobe (yellow arrow). (b) Coronal maximum intensity projection image of CT pulmonary angiography shows cut-off appearance of the bilateral lower pulmonary arteries (arrows). (c) Iodine map shows decreased iodine concentrations, colour-coded as blue to black, in the bilateral lower lobes (arrows) compared with other lung parenchyma. (d) Photograph of gross lung specimen shows a dark red to black discolouration (yellow arrow) in the right lower lobe and a dark red discolouration (red arrow) of the left lower lobe. (e) Histological section shows diffuse haemorrhage, a large inflammatory cell infiltrate and some mild lung tissue necrosis (haematoxylin and eosin staining, $\times 100$).

findings in a rabbit model, they did not describe DECT iodine map findings.

In our DECT study, 2h after embolisation defects on iodine maps correlated to histopathological findings of an absence of alveolar exudate and other histopathological findings except for the presence of sponge plugs in the pulmonary arteries. 1 day after embolisation, iodine map defects corresponded to histopathological areas of scattered congestion, haemorrhage, inflammatory cell infiltration and decreased alveolar air space. 3 days after embolisation, iodine map defects correlated to areas of diffuse pulmonary congestion, haemorrhage, prominent inflammatory cell infiltration and partial necrosis in the embolic lung regions. Finally, 7 days after embolisation, iodine map defects correlated to histopathological findings of diffuse congestion, haemorrhage and necrosis of the embolic lung tissues. Quantification of the overlay values measured in the embolic lung regions showed a gradual decrease in the overlay values of the embolised lung with increased elapsed time, corresponding to the

histopathological evolution from early lung pulmonary oligoemia to consolidation and infarction. For acute PE (2h and 1 day after embolisation), decreased blood flow resulting from pulmonary artery occlusion but without significant alveolar changes appeared as decreased but not zero iodine content iodine map images, possibly related to compensatory systemic blood flow from aortic arterial branches, which are part of the known dual blood supply of the lung. For subacute PE (3 or 7 days after embolisation), lung consolidation and infarct resulted in increased CT numbers on conventional CT images because of diffuse pulmonary congestion, haemorrhage, prominent inflammatory cell infiltration and necrosis in the embolic lung regions. By contrast, the iodine map overlay value of the embolic regions was decreased to zero and we hypothesise that this decrease reflected a reduction of systemic arterial flow to these lung regions. It should be noted that the overlay values were variable at 3–7 days after embolisation, with some instances of persistently high overlay values, and the

Figure 5. Lung CT and histopathological images in a rabbit 7 days after embolisation. (a) Transverse and (b) coronal lung window images of the chest CT show consolidation in the left lung lower lobe (arrow). (c) Thin coronal maximum intensity projection image of CT pulmonary angiography shows cut-off appearance of left lower pulmonary arteries (arrow). (d) Fused coronal iodine map and (e) transverse iodine map show decreased iodine concentrations, colour-coded as blue to black, in the left lower lobe (arrow) compared with other lung parenchyma. (f) Photograph of gross lung specimen shows a black discolouration of the left lower lobe (arrow). (g) Histological section shows the pulmonary parenchymal necrosis and filling of the alveolar space with exudates (haematoxylin and eosin staining, $\times 100$). Note the gelatin sponge in the corresponding pulmonary artery (arrow).

mechanism for this variability needs to be further evaluated. Potentially, DECT may be helpful to elucidate the cause of these findings.

The advantage of DECT over conventional CT is that the presence of relatively large pulmonary perfusion defects can be assessed on iodine maps in addition to the anatomic evaluation for small pulmonary artery filling defects at CTPA [5–13]. Owing to practical clinical

concerns, most published reports used either CTPA or nuclear scintigraphy [7–13] rather than pathology as the standard of reference for the diagnosis of pulmonary embolus, leading to some uncertainty as to the accuracy of the final diagnoses and preventing a more definitive comparison of CTPA and iodine map assessment of pulmonary perfusion. Animal models can largely overcome such uncertainties. Zhang et al's experimental

Table 3. Percentage of CT findings in different stages of pulmonary embolism

Stages	Normal	Oligaemia	Consolidation	Infarction
2 h ($n=30$)	16	14	0	0
1 day ($n=30$)	18	8	4	0
3 days ($n=30$)	14	8	8	0
7 days ($n=30$)	18	4	5	3
Control ($n=30$)	30	0	0	0
Overall ($n=120$)	66	34	17	3

Table 4. The average CT and overlay value of the embolic and non-embolic areas after embolisation

Group	Embolised lung parenchyma (range; unit, HU)	Non-embolised lung parenchyma (range; unit, HU)	p-value
CT value			
2 h (n=6)	-683.63 ± 121.82 (-754.03–437.83)	-456.98 ± 39.24 (-498.40–396.33)	0.002
1 day (n=6)	-607.07 ± 29.66 (-664.03–581.90)	-422.58 ± 51.36 (-486.93–367.60)	<0.001
3 days (n=6)	-222.00 ± 369.26 (-698.63–27.85)	-462.11 ± 37.39 (-512.55–413.77)	0.173
7 days (n=6)	-157.95 ± 329.54 (-671.33–64.20)	-455.10 ± 32.53 (-505.20–420.93)	0.078
Overlay value			
2 h (n=6)	19.09 ± 6.05 (14.53–29.87)	131.96 ± 27.44 (104.30–168.90)	<0.001
1 day (n=6)	2.21 ± 26.10 (-33.00–34.60)	197.42 ± 38.26 (166.33–271.47)	<0.001
3 days (n=6)	7.48 ± 11.58 (0.00–22.43)	123.33 ± 33.18 (72.10–165.90)	<0.001
7 days (n=6)	9.17 ± 15.14 (0.00–35.77)	202.56 ± 33.86 (148.60–233.63)	<0.001

study [5] in rabbits showed that the diagnostic sensitivity of dual energy iodine maps alone for the detection of PE was 89% and showed good agreement with histopathological findings. In contrast with the iodine maps, CTPA had a lower sensitivity of 67% for pulmonary emboli in that study. Zhang and his colleagues [6] also compared the accuracy of DECT and perfusion planar scintigraphy in detecting pulmonary emboli and showed that BFI derived from DECT improves the diagnostic accuracy of PE compared with perfusion planar scintigraphy in an experimental rabbit model. The present study found 100% sensitivity and 95% specificity to detect pulmonary embolus for BFI with the histopathological findings as the standard of reference. In this study, some false-positive results in BFI were seen although repeated detailed observations were performed. We speculate that these false-positive PEs could have been caused by ignoring gravity effect to the two superior leaves of the lung on perfusion images, respiration motion artefacts or reader inexperience. Beam-hardening artefacts caused by a high concentration of contrast agent in the thoracic veins may result in artificial hyperiodine distribution state (high iodine concentration) in local pulmonary

tissues and must be noted when BFI or fused images were interpreted. Therefore, preferential gravity-dependent lung perfusion in a ventrodorsal direction is a normal finding and must be kept in mind when BFI or fused images are interpreted [20]—it will help improve the detection value of PE and avoid false-positive results.

We acknowledge our study has some limitations. Firstly, each rabbit underwent a single post-embolisation CT scan immediately prior to being sacrificed and so the evolution of DECT findings in individual rabbits was not assessed. This study design was necessitated by the need to obtain histopathology correlation for each CT scan. Secondly, the small sample size limits the power of our study; larger studies are needed to demonstrate the findings of the present study. Nevertheless, we identified general trends in DECT findings that help define what may be seen clinically. Thirdly, large gelatin sponge clots resulted in segmental or subsegmental pulmonary artery emboli, causing the typical findings of cut-off of enhanced pulmonary arteries on CTPA images. More distal peripheral clots needed to be created to demonstrate the possible role of DECT in detecting small peripheral pulmonary emboli [5]. Fourthly, caution

Figure 6. CT number and overlay value changes of the embolised and non-embolised pulmonary parenchyma. (a) The CT numbers obtained from conventional CT images of the embolised lung parenchyma gradually increased while (b) the overlay value obtained from iodine maps of the embolised lung parenchyma gradually decreased to approximately 0 HU as the time interval from embolisation increased from 2 h to 7 days. These findings corresponded to the evolution of histopathological changes from early lung pulmonary oligoemia to consolidation and infarction. However, the CT and overlay values of the non-embolised areas did not change significantly with elapsed time. PE, pulmonary embolism.

should be exercised in the translation of our findings to clinical subjects because a histopathological gold standard for pulmonary emboli is not generally available to define the presence or absence of PE in human patients. Last, we did not choose a contrast-enhanced single energy technique, such as 100 kVp/120 kVp for conventional CTPA, which is used in many clinics who do not have a dual energy Siemens CT, but instead average weighted 120 kVp images were used to evaluate PE in previous published papers [8–13].

In conclusion, iodine maps derived from contrast-enhanced DECT can be quantified and correspond to the histopathological changes seen in the lung over time after PE and DECT has a comparable diagnostic sensitivity in the detection of PE in the different stages with the histopathological findings as a standard of reference.

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