Quantitative lung-perfused blood volume imaging on dual-energy CT: capability for quantitative assessment of disease severity in patients with acute pulmonary thromboembolism

[Abbreviated Short Title]

Quantitative assessment of disease severity in acute pulmonary thromboembolism using dual-energy CT

Abstract

Background: Regional iodine distribution assessment on dual-energy CT (DECT) has been suggested as useful for management of acute pulmonary thromboembolism (APTE) patients. However, no reported studies have made a direct comparison between quantitatively assessed DECT and right -to-left ventricular (RV/LV) ratio on CT for differentiation of right heart dysfunction (RHD) from non-right heart dysfunction (NRHD) in APTE patients.

Purpose: To determine the capability of DECT for differentiation of RHD from NRHD in APTE patients.

Material and Methods: Thirteen APTE patients underwent DECT and echocardiography at onset of APTE. Patients were divided into RHD (n = 7) and NRHD (n = 6) groups based on echocardiography. A normalized lung perfused blood volume map was generated, and two kinds of overall perfusion (OP) index were determined, one placed over each lung field (OP index A) and as the average from six ROIs placed over each lung field (OP index B). The heterogeneity index was also determined as the standard deviation for the six ROIs. RV/LV ratio evaluations were also performed. To assess differences between the two groups, each index was statistically compared with the Mann–Whitney U test. The ROC-based positive test was then performed to determine the feasible threshold value for dividing patients into the two groups. Finally, differentiation capabilities of the indexes were compared using McNemar's test.

Results: Significant differences between the two groups were found for both OP indexes and RV/LV ratio ($p<0.05$). For each of the feasible threshold values, accuracy of each OP index with and without RV/LV ratio was better than that of the RV/LV ratio.

Conclusion: Quantitative DECT has good potential for differentiation of APTE patients with and

without right heart dysfunction.

Key words: Lung, CT, pulmonary thromboembolism, perfusion, dual-energy CT

Introduction

Acute pulmonary thromboembolism (APTE) is a common and potentially fatal disease, with an overall 30-day mortality rate that exceeds 10% (1, 2). Although most late deaths are due to underlying diseases, the main cause of death within 30 days is right ventricular (RV) failure (3). Rapid risk stratification is thus paramount for identifying high-risk patients and facilitating the selection of the appropriate treatment strategy. Thrombolysis or surgical embolectomy as adjuncts to anticoagulation may rapidly reverse right heart dysfunction and reduce the risk of death. In recent years, many attempts have been made to stratify patients according to their risk of death. While the results of large retrospective registries (2) and randomized trials of thrombolytic treatment (4) have identified the clinical presentation of the patients as the most powerful predictor of death, further risk stratification of patients has been attempted by using imaging methods.

Among the imaging modalities, multidetector-row CT (MDCT) can be used to evaluate RV failure in terms of the right ventricular-to-left ventricular (RV/LV) diameter ratio and identify clots within pulmonary arteries (PAs) with high sensitivity and specificity, and can also indicate underlying lung disease. Various parameters have been used to evaluate the CT scoring systems for PA clot assessment and to assess right heart dysfunction (5–12), while recent technical advances in MR imaging have made possible time-resolved or four-dimensional (4D) contrast-enhanced MR angiography or dynamic contrast-enhanced (CE-) perfusion MR imaging for APTE patients (13–15).

Dual-energy CT (DECT) has been used for evaluation of various pulmonary diseases since 2007 (16). Compared with conventional CT, DECT can generate maps that provide perfusion- or ventilation-weighted information for patients with APTE and various pulmonary diseases (17–19). In this situation, there have been no reports to make a direct comparison between quantitatively assessed DECT and RV/LV ratio on CT for evaluating disease severity, although several investigators have suggested that regional iodine distribution assessment on DECT may be used to diagnose or manage APTE.

We hypothesized that quantitatively assessed DECT can be as effective as RV/LV ratio for evaluating disease severity in APTE patients. The purpose of this study was therefore to determine the capability of DECT for evaluating disease severity and for differentiating between APTE patients with and without right heart dysfunction.

Material and Methods

Study group

This study was approved by the Institutional Ethics Committee of Nara Medical School (reference number: 563). All data were analyzed retrospectively, and our Institutional Review Boards Committee did not require written informed consent from each patient at this time. This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

A total of 18 consecutive patients (9 men and 9 women; mean age, 62.6 years; age range, 27–93 years) with suspected APTE underwent contrast-enhanced DECT (CE-DECT) and echocardiography. Exclusion criteria for CT were a history of adverse reaction to iodinated contrast media and renal failure. In addition, patients who were younger than 18 years or pregnant were excluded. The final diagnosis of APTE for all patients was made by consensus of board-certified radiologists, nuclear medicine physicians, pulmonary physicians, and cardiologists on the basis of the results of all examinations. All APTE patients with estimated systolic pulmonary arterial pressure (sPAP) > 35 mmHg and/or tricuspid velocity > 2.7 m/s on echocardiography were suspected of having right heart dysfunction (20). To evaluate the severity of right heart dysfunction, echocardiographically obtained tricuspid regurgitation pressure gradient (ΔP) values were also assessed. Five patients were excluded because a lack of echocardiographic data at onset of APTE. The final enrolment was therefore 13 APTE patients (8 men and 5 women; mean age, 66.1 years; age range, 39–85 years). All radiological examinations were performed within a 15-day period (mean, 2.6 days; range, 0–15 days). Based on the echocardiographic data, all patients were divided into two groups: right heart dysfunction (RHD) (n = 7) and non-right heart dysfunction (NRHD) (n = 6).

DECT scanning protocols

All patients were examined with CE-DECT using one of two dual-source CT scanners (SOMATOM Definition or SOMATOM Definition Flash; Siemens Healthcare, Forchheim, Germany) in dual energy mode. Details of the scan protocols are shown in Table 1. The field-of-view of the B detector was limited to 26 cm with the SOMATOM Definition and to 33 cm with the SOMATOM Definition Flash, while the field-of-view of the A detector was 50 cm.

Contrast medium was administered as described in previous studies (21): 80 mL of iodinated contrast media, iopamidol 300 (Iopamiron 300 mgI/mL; Bayer Pharma, Osaka, Japan) for patients with body weight (BW) < 65 kg, or iopamidol 370 (Iopamiron 370 mgI/mL; Bayer Pharma) for patients with BW ≥ 65 kg via the cubital vein at 4 ml/s, followed by a third-strength dose of contrast agent diluted with saline solution (mixture of 20 mL of contrast media and 40 mL of saline solution), and finally 60 mL of saline solution, all at the same rate. DECT scanning was started 20 seconds after the start of contrast medium administration, from caudal to cranial direction and under full inspiration.

Next, three CT pulmonary angiography (CTPA) image series were routinely reconstructed from the dual energy data: one series each at 80 kV and 140 kV, and one weighted-average series combining data from the high- and low-kV series in such a way as to create the image impression of a regular 120 kV CT examination (Definition: 70% of the 140 kV and 30% of the 80 kV data; Flash: 60% of the 140 kV + SN filter and 40% of the 80 kV data). Different kernels were used in reconstruction of the DECT data as lung window images (Definition, B60f; Definition Flash, B60f) and as CTPA images at each kV (Definition, D30f; Definition Flash, D30f). Diagnosis of PE was made on the virtual 120 kV images during clinical routine reading on our PACS workstation (SYNAPSE; Fujifilm, Tokyo, Japan).

Cardiac echocardiography

All subjects underwent Doppler echocardiography examinations by board-certified and experienced cardiologists according to the standard technique established by the American Society of Echocardiography (22). sPAP and ΔP were determined for each subject.

Image analysis

DE-CT

To generate a lung-perfused blood volume (PBV) map for assessment of lung perfusion in every patient, the high- and low-kV data sets were simultaneously transferred to a multi-modality workplace (MMWP; Siemens Healthcare, Forchheim, Germany), and analyzed using dedicated post-processing software (Lung PBV, *Syngo* Dual Energy; Siemens, Erlangen, Germany) by a board-certified chest radiologist (S.M) with 14 years of experience. When the Lung PBV map of a patient was generated, the post-processing parameters preset by the vender were not modified. Each patient's lung PBV map was then assessed as a color-coded iodine distribution map of the lung parenchyma.

Although all CE-DECT imaging was obtained using the same protocol and the same scan time, it was necessary to reduce inter-patient differences to achieve direct comparison of Lung PBV among patients. *Syngo* Dual Energy software on MMWP (Siemens, Germany) was therefore used to automatically normalize all Lung PBV maps with reference to the maximum CT number of the main trunk of the pulmonary artery. A normalized lung PBV (nLung PBV) map expressing the percentage of iodine distribution within the lung was generated for each patient by means of pixel-by-pixel analysis and by dividing the maximum enhancement within the lung parenchyma by the maximum value of the main trunk of the pulmonary artery.

As the first method for evaluating disease severity and cardiac condition from the nLung PBV maps, a region-of-interest (ROI) was automatically positioned over both lung fields (Fig. 1A) by using *Syngo* Dual Energy software, to automatically determine the mean PBV value within the total lung, which was termed overall perfusion index type A (OP index A).

As the second method for determining regional differences in lung parenchymal perfusion changes as well as evaluating disease severity and cardiac condition, three ROIs of the same volume were automatically placed on each lung field (a total of six ROIs for each subject) using *Syngo* Dual Energy software (Fig. 1B). The average PBV value and standard deviation (SD) were then calculated from the six ROIs. This averaged value, determined from the regional PBV for each of the subjects was termed overall perfusion index type B (OP index B), and the resulting SD determined from the regional PBV was termed the heterogeneity index.

RV/LV diameter ratio

The RV/LV diameter ratio was measured on axial CECT images by the same chest radiologist who analyzed the DECT.

Based on past findings (10, 23), the RV/LV diameter ratio was then calculated as follows:

$$\text{RV/LV diameter ratio (\%)} = \text{diameter of RV} \div \text{diameter of LV} \quad [1]$$

The short axis of the right ventricle was measured from inner wall to inner wall at the level of the tricuspid valve, and the short axis of the left ventricle was measured from inner wall to inner wall at the level of the mitral valve (23).

Statistical analysis

The Mann–Whitney U test was used to evaluate the differences between the RHD and NRHD groups for all indexes.

To evaluate the capability of all perfusion indexes for assessment of disease severity, they were correlated with the echocardiographically determined RV/LV diameter ratio and the ΔP values by means of Pearson's correlation. The RV/LV diameter ratio was also correlated with ΔP values.

To differentiate the RHD and NRHD groups, feasible threshold values for RV/LV diameter ratios and each DECT index that was significantly different for the RHD and NRHD groups and correlated significantly with RV/LV diameter ratio and ΔP value were determined with the ROC-based positive test (24). Finally, McNemar's test was used for statistical comparison of the sensitivity, specificity, and accuracy of each index with the applied feasible threshold value.

A p value less than 0.05 was considered as significant for each of the statistical analyses.

Results

Representative cases are shown in Figs. 2 and 3. No adverse effects were observed in this study.

Comparison of all indexes between the RHD and NRHD groups is shown in Table 2.

Significant differences were found for OP index A ($p=0.008$), OP index B ($p=0.008$) and RV/LV diameter ratio ($p=0.004$).

The results of Pearson's correlation between each index and ΔP are shown in Fig. 4. When correlated with ΔP, OP index A ($r = –0.68$, $p = 0.01$), OP index B ($r = –0.67$, $p = 0.01$) and RV/LV diameter ratio ($r = 0.75$, $p = 0.003$) demonstrated significant correlations. In addition, OP index A ($r = –0.72$, $p = 0.005$) and OP index B ($r = –0.71$, $p = 0.007$) had correlated significantly with RV/LV diameter ratio respectively (Fig. 5).

Results of the ROC-based positive test are shown in Fig. 6. The Feasible threshold values were: OP index A, 70%; OP index B, 70%; RV/LV diameter ratio, 1.2.

The differentiation capabilities of all CT indexes are shown in Table 3. When feasible threshold values were used, OP index A and B showed better sensitivity (SE) and accuracy (AC) (SE: 85.7 % [6/7]; AC: 92.3% [12/13]) than did the RV/LV diameter ratio (SE: 57.1 % [4/7]; AC: 76.9 % [10/13]). In addition, when each OP index was combined with the RV/LV diameter ratio, SE (85.7% [6/7]) and AC (92.3% [12/13]) of the combined two indexes were higher than those of the RV/LV diameter ratio only. However, there were no significant differences among any of the diagnostic performances ($p>0.05$).

Discussion

This report concerns the preliminary results of an assessment of the capability of quantitatively assessed DECT for evaluating disease severity and for distinguishing between APTE patients with and without RHD, and of a direct comparison of the capability of DECT with conventional RV/LV diameter ratio in this setting. The results indicate that the OP index is at least as reliable as the

RV/LV diameter ratio and has the potential to improve the capability of the RV/LV diameter ratio to differentiate APTE patients with, from those without RHD. To the best of our knowledge, no previous study has directly compared the capabilities of quantitatively assessed DECT and the RV/LV diameter ratio for evaluating disease severity and distinguishing RHD from NRHD patients with APTE.

A comparison of all the indexes for the RHD and NRHD groups showed that both the OP indexes as well as the RV/LV diameter ratio were significantly different. Although it has been suggested that the RV/LV diameter ratio is an important parameter for evaluation of RV dysfunction or failure (23, 25), our results suggest the capability of the OP indexes used in this study to evaluate RV dysfunction or failure is as good as that of the RV/LV diameter ratio. When the indexes were correlated with the RV/LV diameter ratio and ΔP, OP indexes assessed from a single ROI (i.e. OP index A) and from six ROIs (i.e. OP index B) showed significant and good correlations, while the heterogeneity index assessed from the six ROIs showed no significant correlation with both the RV/LV diameter ratio and ΔP. The hemodynamic response to PE generally depends on the size of the embolus, coexistent cardiopulmonary disease, and neurohumoral effects. Hemodynamic decompensation occurs not only because of physical obstruction of blood flow, but also because of the release of humoral factors such as serotonin from platelets, thrombin from plasma, and histamine from tissue. Furthermore, acute PE increases pulmonary vascular resistance, which is partly attributable to hypoxic vasoconstriction. In addition, increased right ventricular afterload can lead to right ventricular dilatation, hypokinesis, tricuspid regurgitation with annular dilatation of the tricuspid valve, and ultimately right heart dysfunction (26). In view of these physiopathologic aspects, our results can be considered to be compatible and to indicate that the OP index may be as capable as the RV/LV diameter ratio and ΔP to function as one of the biomarkers for assessment of APTE patients.

The results of the comparison of the capability to distinguish RHD and NRHD APTE patients, indicated that the OP index was more accurate than the RV/LV diameter ratio and can even enhance the performance of the RV/LV diameter ratio. In addition, use of the OP index A is a simple method that features slightly better correlation and a similar capability for differentiation than does OP index B, which is slightly more complicated and time-consuming. Our results therefore indicate that, when DECT is performed in routine clinical practice, the OP index from a single ROI on DECT image could be as good as the RV/LV diameter ratio for disease severity assessment and differentiation of RHD from NRHD APTE patients.

Several limitations apply to the present study. First, this study was a single center study with a small enrolment. Moreover, our study group was comprised of APTE patients with various degrees of APTE, and did not include normal subjects or patients with other pulmonary diseases. Therefore, the present study could not determine differences between the diagnostic performance of DECT for APTE and other patients. Moreover, we did not classify patients into subgroups according to history of associated cardiopulmonary disease and intensive care unit admission. These limitations constitute the major cause of possible bias in this study.

Second, we used the same protocol for bolus injection of contrast media administration for all patients, and normalized contrast enhancement with reference to the main trunk of the pulmonary artery. However, normalization would be more accurate if the total amount of iodine were adjusted according to patient characteristics such as body weight, body mass index, height, and cardiac output, as is standard practice for contrast-enhanced CT examination of the liver (21). In addition, Sueyoshi et al. considered that distribution of contrast media into the lung field depended on various factors, including cardiopulmonary status as well as contrast media injection protocol, and suggested that establishment of a fixed method was difficult (27). Therefore, our OP indexes may have been influenced not only by dynamic perfusion status but also by the extent of perfusion defect.

Third, although our findings indicate that quantitatively assessed DECT index is at least as reliable as the RV/ LV ratio, it has been suggested that the radiation dose of DECT is higher than that of conventional CE-MDCT examinations (17-19, 27). In addition, several techniques including newly developed reconstruction algorithms have been proposed for reducing the radiation dose for not only conventional CE-MDCT, but also DECT examinations (28, 29). However, we did not use any radiation dose reduction techniques for DECT examination in this study, and could not determine the actual significance of DECT for APTE patient management because the differentiation capability of the DECT index was almost equal to that of the RV/ LV ratio. Therefore, further investigations are warranted to determine the actual significance of DECT in this setting.

Fourth, it has been suggested during the last a few decades that time-resolved MR angiography, dynamic CE-perfusion MR imaging, phase-contrast MR imaging, or other nuclear medicine studies are useful for assessment of APTE patients (13-15). Since we did not compare our indexes with parameters assessed by other modalities, a large-scale prospective study may be needed to assess the actual value of quantitatively assessed DECT. In addition, a comparative study is needed of cost effectiveness and the influence of any diseases not related to APTE that could affect lung perfusion and OP index measurements from DECT data.

In conclusion, quantitatively assessed DECT is thought to be capable of accurate evaluation of disease severity and differentiation of APTE patients with and without right heart dysfunction. In addition, the OP index assessed by means of a single ROI placed over the entire lung yields satisfactory results in this setting when compared with that assessed either by placement of several ROIs or by evaluation of heterogeneity within the lung, and may enhance the differentiation capability of the RV/LV diameter ratio in routine clinical practice.

Declaration of Conflicting Interests: The authors declare that there is no conflict of interest.

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Table 1. Scanning protocols

	SOMATOM Definition	SOMATOM Definition Flash
Detector collimation	64 × 0.6 mm	128 × 0.6 mm
Slice thickness	1 mm	1 mm
Helical pitch	0.5	0.55
Rotation time	0.33 seconds	0.33 seconds
Kernel	D30f kernel	D30f kernel
Reference mAs and kV	100 mAs at 140 kV 500 mAs at 80 kV	200 mAs at Sn140 kV 471 mAs at 80 kV
Dose modulation	CARE Dose4D	CARE Dose4D
Average CTDIvol	13.17 mGy	12.56 mGycm
Average DLP	467 mGy	426 mGycm
Patient position	Supine	Supine

CARE Dose4D: the automatic tube current modulation technique provided by Siemens Healthcare.

Table 2. Comparison of all indexes for the RHD and NRHD groups

	RHD	**NRHD**
Mean ΔP (range)	44.9 (30 to 60) mmHg	20.2 (15 to 23) mmHg
OP index A	56.1 ± 21.7%*	109.3 ± 36.1%
OP index B	57.3 ± 20.6%*	109.6 ± 36.9%
Heterogeneity index	12.8 ± 8.1%	11.0 ± 8.7%
RV/LV diameter ratio	1.39 ± 0.3*	0.95 ± 0.12

*: Significant difference between RHD and NRHD ($p<0.05$)

Table 3. Capability of each index to differentiate non-right heart dysfunction from right heart dysfunction subjects

	TV (%)	SE (%)	SP (%)	PPV (%)	NPV (%)	AC (%)
OP index A	70	85.7	100	100	85.7	92.3
		(6/7)	(6/6)	(6/6)	(6/7)	(12/13)
OP index B	70	85.7	100	100	85.7	92.3
		(6/7)	(6/6)	(6/6)	(6/7)	(12/13)
RV/LV ratio	1.2	57.1	100	100	66.7	76.9
		(4/7)	(6/6)	(4/4)	(6/9)	(10/13)
RV/LV ratio + OP index		85.7	100	100	85.7	92.3
		(6/7)	(6/6)	(6/6)	(6/7)	(12/13)

TV: threshold value; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; AC: accuracy.

Figure legends

Fig. 1. Examples of ROI placement on DECT

A: region-of-interest (ROI) (white line) was automatically positioned over both lung fields. Three ROIs of the same volume were automatically placed on each lung field. B: Three ROIs of the same volume were automatically placed on each lung field.

Fig. 2. A 76-year-old female with APTE and right heart dysfunction

A: Coronal contrast-enhanced multiplanar reformatted (MPR) CT image demonstrates thrombus in the main trunk, bilateral main, and bilateral interlobar pulmonary arteries (arrows). B: Coronal nLung PBV image fused with contrast-enhanced MPR CT image at mediastinal window setting shows thrombi in the main trunk, bilateral main and bilateral interlobar pulmonary arteries. It also markedly low and heterogeneous iodine distribution in the lung field. The mean value of overall perfusion was 26% and ΔP was 51 mmHg.

Fig. 3. A 63-year -old male with APTE but without right heart dysfunction

A: Coronal contrast-enhanced multiplanar reformatted (MPR) CT image demonstrates thrombus in the subsegmental pulmonary artery in the right medial segment (arrow). B: Coronal nLung PBV image fused with contrast-enhanced MPR CT image at mediastinal window setting shows thrombus in the subsegmental pulmonary artery and low iodine distribution in the right medial segment alone. Other lung segments show near-homogeneity. The mean value of overall perfusion was 101% and ΔP was 16 mmHg.

Fig. 4. Correlations between each index and ΔP for all APTE patients

A: OP index A showed significant and good correlation with ΔP ($r = –0.68$, $p = 0.01$). B: OP index B showed significant and good correlation with ΔP ($r = –0.67$, $p = 0.01$). C: Heterogeneity index showed no significant correlation with ΔP ($r = 0.23$, $p = 0.44$). D: RV/LV ratio showed significant correlation with ΔP ($r = 0.75$, $p = 0.003$).

Fig. 5. Correlations between each index and RV/LV ratio

A: OP index A showed significant correlation with RV/LV ratio ($r = –0.72$, $p = 0.005$). B: OP index B showed significant correlation with RV/LV ratio ($r = –0.71$, $p = 0.007$). C: Heterogeneity index showed no significant correlation with RV/LV ratio ($r = 0.42$, $p = 0.16$).

Fig. 6. Results of ROC-based positive test for OP index A and B and RV/LV ratio

A: Feasible threshold value, sensitivity, specificity, and accuracy of OP index A and B were : 70%, 85.7%(6/7), 100%(6/6), and 92.3%(12/13). B: Feasible threshold value, sensitivity, specificity, and accuracy of RV/LV ratio were determined as follows: 1.2, 57.1%(4/7), 100%(6/6), and 76.9%(10/13).