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Computed tomography pulmonary angiography and venography with a low dose of contrast medium

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Abstract
The authors developed a method to ensure sufficient opacification of pulmonary vasculature for separate depiction of arteries and veins in three-dimensional form with a small dose of contrast medium utilizing a test injection to determine optimal timing of computed tomography (CT) scanning. The dose was determined by a simulation based on a pharmacokinetic model. The contrast medium was administered at a rate of 5.0 mL/s for 3 s, followed by helical scanning at the timing determined by a dynamic CT scanning following the test injection. Images of 20 consecutive patients acquired with a 64-row CT scanner were evaluated. Quality of vessel depiction was assessed on the basis of the following: HU values at the main pulmonary artery (MPA) and left atrium (LA), distance between the pleural surface and the distal end of the pulmonary vessels on three-dimensional CT pulmonary arteriography and venography (3D-CTPAV), and subjective visual assessment of quality of the 3D-CTPAV images. Time to generate the 3D-CTPAV images was recorded. The mean ± standard deviation (SD) of the HU values at MPA/LA and the distances to the pleural surface for pulmonary arteries/veins were 448.0 ± 123.1/277.3 ± 60.85 HU and 9.21 ± 3.60/10.7 ± 5.45 mm, respectively. The image quality was visually rated as excellent for all of the patients. The mean time ± SD to generate 3D-CTPAV images was 13.6 ± 6.7 min. In conclusion, three-dimensional images of the pulmonary vasculature can be created using 21 mL (including 6 mL for the test injection) of contrast medium.

Keywords Pulmonary artery · Computed tomography angiography · Pulmonary veins · Image processing · 3D reconstruction

1 Introduction

Pulmonary lobectomy performed by video-assisted thoracoscopic surgery (VATS) is widely used in the treatment of peripheral lung cancer [1, 2]. The branching patterns of the pulmonary arteries and veins vary from patient to patient; thus, preoperative assessment of these patterns is essential for patient safety [3]. Thoracic surgeons cannot palpate organs directly during VATS because of its non-invasive nature; therefore, it is difficult to evaluate anatomic relationships when using this procedure. Computed tomography (CT) pulmonary angiography can reveal the distance and positional relationship between the primary tumor and the intersegmental veins, thereby allowing an adequate safety margin to be established around the primary tumor. This anatomical information is fundamental for preoperative planning [4]. For this purpose, contrast-enhanced CT of the chest with volume rendering of pulmonary vessels, i.e., three-dimensional CT angiography and venography (3D-CTPAV), is an effective procedure [5, 6], and is less

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invasive than conventional pulmonary angiography. Two 3D-CTPAV methods have been reported thus far. In the first method, data acquisition by CT is repeated twice during the passage of contrast medium from the right atrium to the left atrium (LA). This method allows for selection of an appropriate phase for 3D-CTPAV [7]. The second method involves single-phase data acquisition at an appropriate time point when the pulmonary arteries and veins are both well-opacified [8]. The former method has a higher probability of capturing optimum 3D-CTPAV images; however, radiation exposure increases with the number of scans. The single-phase method has a relatively low probability of capturing images suitable for 3D-CTPAV, which requires sufficient enhancement as well as differences in enhancement between the pulmonary arteries and veins. A recently reported software for creating 3D-CTPAV images [9] is capable of separating pulmonary arteries and veins from single-phase data, regardless of the skill or experience of the operator, in a matter of minutes. Thus, imaging at the most suitable time point might become less critical to the success of 3D-CTPAV.

Renal toxicity of contrast medium is dose-related [10]. It is, therefore, essential to reduce the dose of the contrast medium [11]; this can be achieved by imaging with dual-source CT [12] at a low tube voltage. Previous studies have reported contrast medium doses of 40 mL [13] and 20 mL with low tube voltage scanning [14] for CT pulmonary angiography. The purpose of this study was to further reduce the volume of the contrast medium without dual-energy scanning, while enabling separate 3D rendering of the pulmonary arteries and veins.

2 Materials and methods

2.1 Estimation of the contrast medium dose for low-dose 3D-CTPAV

The contrast medium dose was estimated based on the simulation of the time-enhancement curve in the pharmacokinetic analysis [15]. The human body was modeled with six compartments, assuming a body height, weight, body mass index (BMI), and cardiac index of 175 cm, 70 kg, 24.2, and 2.7 L/min/m^2, respectively. The input and output for each component were expressed as simultaneous differential equations and solved by the fourth-order Runge–Kutta method. The pharmacokinetic analyses were performed with free statistical software (GNU Octave, version 4.0.0; http://www.octave.org/). The six compartments were the right heart system (expressed as suffix "R"), pulmonary circulation (suffix "P"), left heart system (suffix "L"), aorta (suffix "A"), peripheral artery (suffix "c"), and venous system (suffix "V"). Suffix "0" represents the contrast medium to be infused.

The following mass-balance equations are true:

$$\text{Right heart system } V_R \cdot \frac{dC_R}{dt} = Q_0 C_0 - Q_R C_R + Q_V C_V, \quad (1)$$

$$\text{Pulmonary circulation } V_P \cdot \frac{dC_P}{dt} = Q_R C_R - Q_P C_P, \quad (2)$$

$$\text{Left heart system } V_L \cdot \frac{dC_L}{dt} = Q_P C_P - Q_L C_L, \quad (3)$$

$$\text{Aorta } V_A \cdot \frac{dC_A}{dt} = Q_L C_L - Q_A C_A, \quad (4)$$

$$\text{Peripheral artery } V_C \cdot \frac{dC_C}{dt} = Q_A C_A - Q_C C_C, \quad (5)$$

$$\text{Venous system } V_V \cdot \frac{dC_V}{dt} = \frac{Q_C C_C}{k_P} - \frac{Q_C C_V}{kp}, \quad (6)$$

where V is the compartment volume (blood volume); Q is the volumetric flow rate (blood k_p flow volume) between compartments; C is the concentration of iodine and represents the tissue/blood distribution coefficient, which was set to 1.

The cardiac output is approximated by the following equation:

$$\text{Cardiac output (L/min)} = 2.7 \times 0.007184 \times H^{0.725} \times W^{0.425}.$$

The calculated cardiac output set to Q_R, and $Q_R = Q_P = Q_L = Q_A = Q_C = Q_V$ is true.

The circulating blood volumes were approximated by the following equation: [16]

$$\text{Circulating blood volumes (L)} = 0.168 \times (H \div 100)^3 + 0.05 \times W + 0.444.$$

We assumed a blood volume distribution as follows: 3.6% in the right heart system, 8.8% in the pulmonary circulation, 3.6% in the left heart system, 6.0% in the aorta, 8.0% in the peripheral artery, and 70% in the venous system [17].

Derived iodine concentrations of the compartments were converted into HU values via multiplication by 25.6 HU/mg, which was derived from the HU values of a contrast medium of known concentration, imaged using the same CT scanner as in this study. The contrast-medium dose and injection rate (Q_0) were set to 15 mL and 2.5 or 5 mL/s (370 mg iodine/mL for both), respectively.

2.2 Patients

This prospective study was approved by the ethics committee of our hospital. Written informed consent was obtained from all 20 patients over a period of 6 months. The inclusion

criteria were as follows: referred for 3D-CTPAV by a physician on the basis of clinical indications; 3D-CTPAV performed between January and June 2017; diagnosis or strong suspicion of lung cancer; planned thoracoscopic lobectomy, and aged > 18 years. The exclusion criteria were as follows: inability to provide written informed consent; contraindication for iodinated contrast medium, or inability to hold breath for a period adequate for 3D-CTPAV.

2.3 3D-CTPAV procedure

All CT images were acquired using a dual-source CT scanner (Somatom Definition Flash, Siemens, Forchheim, Germany). A dual-head power injector (Dual Shot GX7, Nemoto-kyorindo, Tokyo, Japan) was used for intravenous injection of the contrast medium. Volume rendering of the CT images was performed on a workstation (AZE Virtual Place Plus, Aze Corporation, Tokyo, Japan). The contrast medium used in this study was iopamidol (370 mg iodine/mL; Iopamiron 370, pre-filled syringe, Bayer Pharmaceuticals, Osaka, Japan).

All images were acquired during breath hold after full inspiration, using the following consecutive steps:

Anteroposterior and lateral topograms of the chest were obtained.

Using the topograms, the CT operator determined a slice to scan at a height of two-vertebrae below the tracheal bifurcation that could depict the MPA and the LA in one cross section.

The patient was injected with a test bolus and imaged in non-helical scan mode (*test scan*): tube voltage, 100 kVp; tube current, 20 mA; detector row configuration, 10 rows at 1 mm intervals; gantry rotation, 0.36 s/rotation; reconstruction kernel, B45f; and reconstruction slice thickness, 10 mm at the selected slice location. The test bolus was administered by simultaneous injection of contrast medium at a rate of 2 mL/s for 3 s from one injector head and saline at a rate of 3 mL/s for 3 s from another injector head, thus creating a diluted test bolus [18], followed by injection of a saline chaser (5 mL/s) for 4 s. The image acquisition was started 6 s after the start of the contrast injection and repeated at 1 s intervals until attainment of maximum enhancement of the LA, which was determined by visual inspection of the images on the CT console.

The CT operator measured the time to the peak enhancement at the MPA and the LA on serial images reconstructed from the *test scan*.

For each patient, the actual scan (the scan that produced images for diagnosis and reporting) was acquired twice, starting 2 s before the time to the peak enhancement obtained by the *test scan* of the MPA and LA. For the actual scan, contrast medium was administered at a rate of 5 mL/s for 3 s, followed by injection of a saline chaser (5 mL/s) for 4 s. The CT parameters were as follows: scanning mode, adaptive 4D spiral [19] helical mode; tube voltage, 100 kVp; tube current, 150 mA; exposure index ($CTDI_{vol}$), including exposure in the arterial and venous phases, 14.6 mGy (7.05 mSv); detector row configuration, 64 rows at 0.6 mm intervals; gantry rotation speed, 0.28 s/rotation; scan range, 381 mm; variable pitch to maintain a scan duration of 2.5 s; reconstruction kernel, B45f, and reconstruction slice thickness, 1.0 mm with a slice interval of 0.5 mm.

2.4 3D volume rendering

The 3D-CTPAV images were rendered with commonly used basic functions (thresholding, manual cutting, object selection, opacity manipulation, and subtraction between volumes) as illustrated in Fig. 1. From each set of actual scan images acquired, the pulmonary arteries and veins were processed separately and fused to create a 3D-CTPAV image depicting color-coded pulmonary arteries (red) and veins (blue).

2.5 3D-CTPAV image processing time

The time required to create the 3D-CTPAV image on the workstation was measured to verify whether image creation is possible within a period of time comparable to that of dedicated software. The mean of the measurements determined by two radiological technologists with ≥ 7 years of experience was adopted.

2.6 Assessment of image quality of 3D-CTPAV

The image quality was assessed both quantitatively and qualitatively using the three methods outlined below:

1. Based on assumption that greater enhancement is an index of higher image quality, degree of enhancement (HU values) was measured by one of the authors at the MPA in the arterial phase; those of the LA and pulmonary veins (superior and inferior pulmonary veins on both sides) were measured in the venous phase. The points of the measurements and the settings of the regions-of-interest are provided in Fig. 2. For the HU values of the pulmonary arteries and veins of the upper or lower lobes, the mean HU values of the right and left were used for comparison.
2. In addition, based on the assumption that good opacification of the peripheral vessel is an index of higher image quality, the distance between the pleural surface and the distal end of the pulmonary artery and vein was measured in S4 and S5 of the tumor-harboring lungs, in the middle of the scan range. The nearest vessel ends were selected visually, and the distance between the pleural surface and the selected distal end was manually

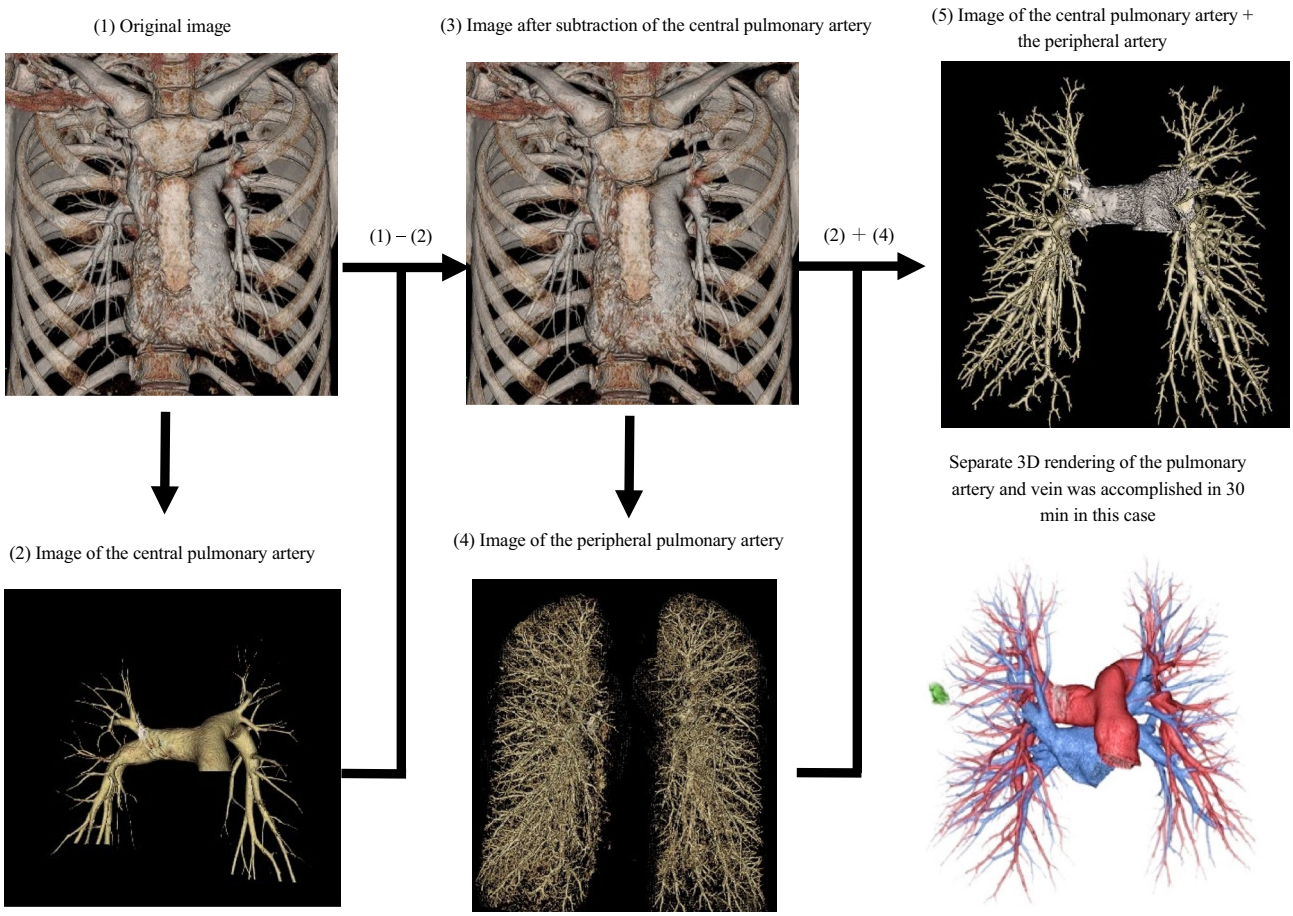

Fig. 1 Processing of three-dimensional CT pulmonary arteriography and venography data for distinct depiction of pulmonary arteries and veins. The pulmonary arterial tree (1) was extracted from source images by applying the CT value of the MPA as the threshold. A portion of the MPA was cut off from the arterial tree (2). Image dataset 2 (2) was subtracted from image dataset 1 (1) to create image dataset 3 (3). The opacity of image dataset 3 was adjusted to show the peripheral part of the pulmonary arterial tree (4). The addition of image datasets 2 and 4 resulted in a complete image of the pulmonary arterial tree (5). Using the same procedure, the source images of the pulmonary venous phase were processed to create an image of the pulmonary venous tree. Note that numerals in parentheses in italics correspond to those in the figure

measured on oblique sagittal or coronal images until the value of the measurement became minimal [20].

3. Using the created 3D image, two radiological technologists visually evaluated the degree of depiction of the pulmonary vasculature and arteriovenous separation using a four-point scale: 1, better than the best result of the clinical routine during the study; 2, better than the mean result of the clinical routine; 3, below the mean; 4, unacceptable for review by doctors. Differences were resolved by consensus.

2.7 Statistical analysis

Differences in HU values among the pulmonary arteries, LA, and pulmonary veins were analyzed using the Mann–Whitney *U* test.

3 Results

3.1 Estimation of the dose of contrast medium

The calculated HU values of the pulmonary artery and the LA were 216 and 174 HU for an injection rate of 2.5 mL/s, and 412 and 219 HU for an injection rate of 5 mL/s, respectively, (Fig. 3) in the simulation. We elected to use a 15-mL dose of contrast medium at an injection rate of 5 mL/s for 3D-CTPAV, based on the results.

3.2 Patients

This study included 20 consecutive patients (13 males) with a mean age, body weight, and BMI of 55 years (range 50–85 years), 58 kg (range 50–84 kg), and 21.7 (range 15.0–27.4), respectively. No patient was excluded from the

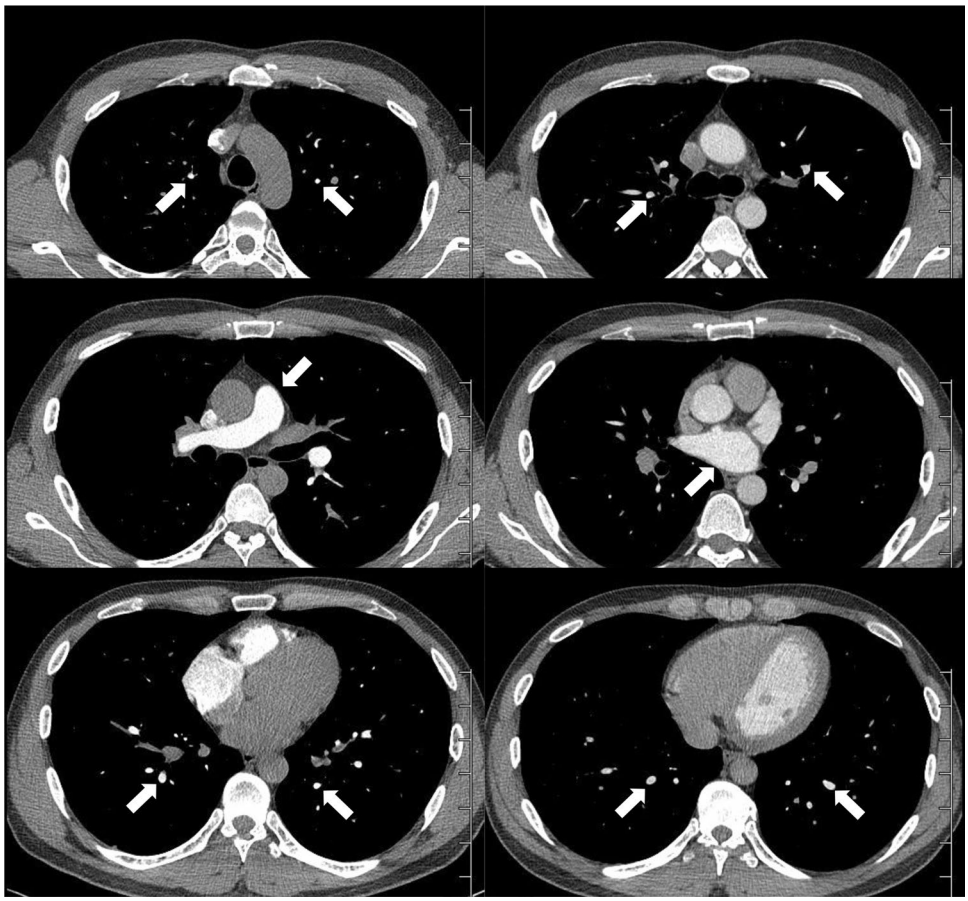

Fig. 2 Measurement points for HU values in pulmonary arteries and veins. Measurement points in the pulmonary artery (upper left) and vein (upper right) of the upper lobe, MPA (middle left), LA (middle right), and pulmonary artery (lower left), and vein (lower right) of the lower lobe are shown. For measurement, elliptical regions of interest not extruding into the vessel boundary were manually placed. The arrows indicate the measured sites. *MPA* Main pulmonary artery, *LA* left atrium

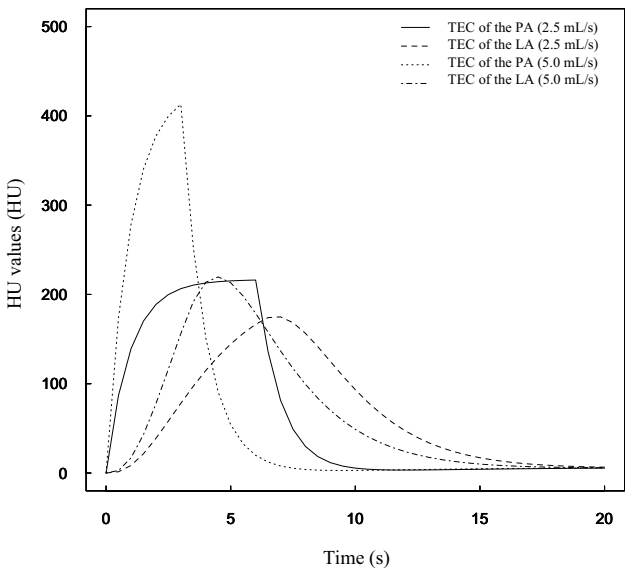

Fig. 3 Results of the simulation of contrast-medium dynamics, with time-enhancement curves shown according to blood vessels. The simulation points and assumed injection rates of contrast medium are shown in the right upper part of the figure. Because the contrast-medium dose was 15 mL, the injection durations were 6 and 3 s for injection rates of 2.5 and 5 mL/s, respectively. At a constant dose, rapid injection will result in higher HU values in the vessel. PA, main pulmonary artery; LA, left atrium; HU, Hounsfield unit

study after enrollment. VATS was performed for 12 of the 20 cases. Their operation reports revealed that the created 3D-CTPAV images were utilized during the VATS to determine the extent and sites of resection in these 12 cases.

The peak enhancement times of the arterial and venous phases obtained in the test scan were 5–10 s (mean 7.75 s) and 11–18 s (mean 13.8 s), respectively. There were no instances of poor breath holding or scan failure that required additional scanning.

3.3 Image processing time

The mean ± standard deviation (SD), median, 25th-percentile, and 75th-percentile processing times of 3D-CTPAV images on the workstation were 13.6 ± 6.7, 12.5, 7.0, and 18.5 min.

3.4 Assessment of image quality of 3D-CTPAV

1. In the arterial phase, the mean HU values ± SD of the MPA and pulmonary arteries of the upper and lower lobes were 448.0 ± 123.1, 477.9 ± 116.5, and 415.5 ± 119.5 HU, respectively ($P = 0.1457$). In the venous phase, the mean HU values ± SD of the LA and pulmonary veins of the upper and lower lobes were 277.3 ± 60.85, 262.4 ± 76.78,

and 269.1 ± 75.51 HU, respectively ($P = 0.631$). Differences between the arterial and venous phases were statistically significant (all $P < 0.001$).

2. The mean distances ± SD between the pleural surface and the distal end of the vessel were 9.21 ± 3.60 and 10.7 ± 5.45 mm for pulmonary arteries and veins, respectively.
3. For all 20 cases, a score of 1 was assigned for both the visually evaluated vessel depiction and the arteriovenous separation.

Representative examples of 3D-CTPAV images of a patient of mean size (weight, 58 kg; BMI, 22.8) and those of an overweight patient (weight, 84 kg; BMI, 27.4) are provided in Fig. 4. We concluded that BMI had no effect on the image quality of 3D-CTPAV.

4 Discussion

We have demonstrated that 3D-CTPAV images of the pulmonary vasculature can be created using a 15-mL dose of contrast medium with an additional dose of 6 mL for a test scan (21 mL in total), a 64-row multi-detector CT scanner, and a basic function of an image processing workstation with < 20 min of user interaction. The resultant 3D-CTPAV images exhibited high image quality, as suggested by the high HU values of the MPA (448.0 ± 123.1 HU) and LA (277.3 ± 60.85 HU), and by the short distances between the pleural surface and the distal end of the vessel (9.21 ± 3.60 and 10.7 ± 5.45 mm for pulmonary arteries and veins, respectively); these distances were shorter than similar measurements found in a study of cone-beam CT (11.9 ± 3.5) and CT (15.2 ± 4.0) [20]. Although the study was conducted on 20 patients who were suspected of pulmonary hypertension, three exhibited no pulmonary hypertension. The image quality was also rated as excellent by subjective visual assessment.

To acquire optimum 3D-CTPAV images using 15 mL of contrast medium, it is necessary to accurately identify the peak enhancement time. In our study, the injection protocols of the test scan and actual scans differed only in the iodine concentration of the bolus. With the same injection duration, the time to peak enhancement is estimated accurately, because the injection duration is a major determinant of the time to peak enhancement [17]. Moreover, for both scans,

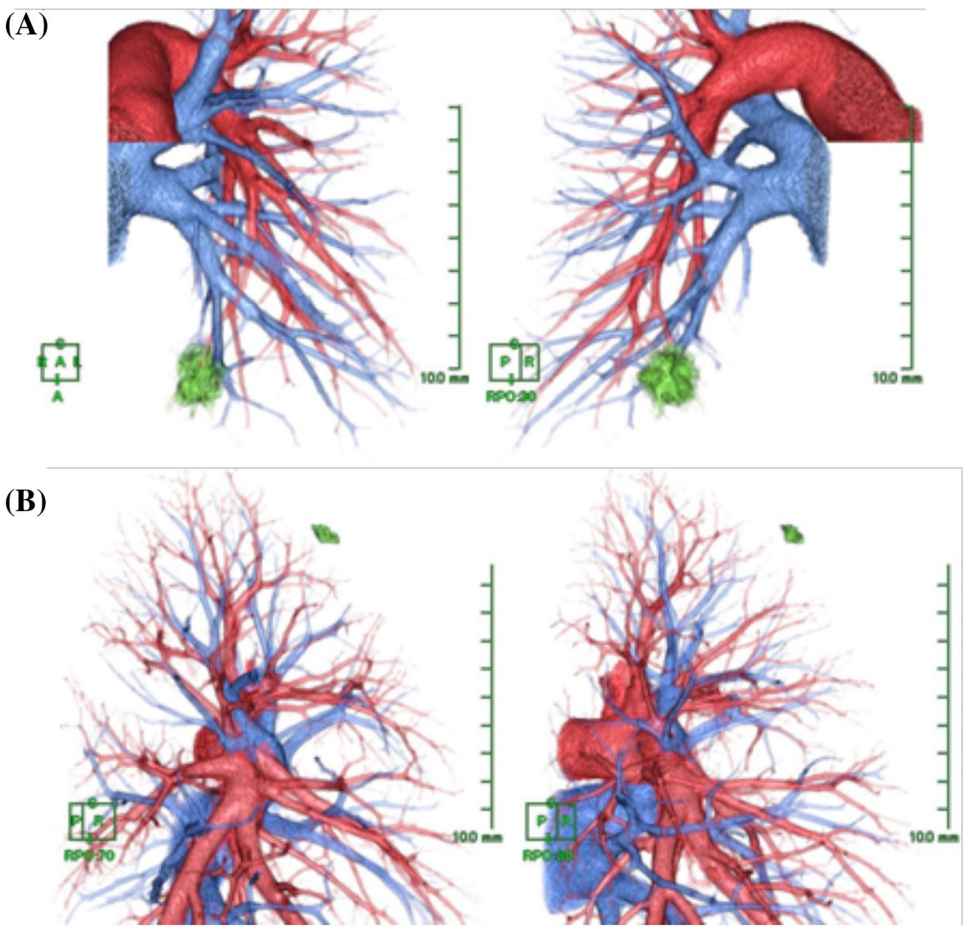

Fig. 4 Clinical examples of 3D visualizations in our approach. A left S10 nodule in a 57-year-old woman with a body weight of 58 kg and a body mass index of 22.8 (**a**). A right S1 nodule in a 35-year-old man with a body weight of 84 kg and a body mass index of 27.4 (**b**)

image acquisition was performed during breath holding after full inspiration, which also minimized any difference in the effect of the breathing pattern on pulmonary and systemic circulation [21]; this improved the reproducibility of the peak enhancement time between the two scans. By adopting a shorter injection duration than the time required for pulmonary circulation, we believe that it was possible to create a 3D image with clear separation between the pulmonary artery and the pulmonary vein.

A further reduction in the contrast medium and radiation doses would be possible if the diluted test bolus could be omitted. However, there are individual differences in peak enhancement times of the arterial and venous phases. Therefore, omitting the test scan will increase the number of images with poor contrast. Another possibility for contrast medium dose reduction is low-kV scanning and iterative reconstructions [14]. Low tube-voltage scanning was not utilized in this study to make this method widely applicable, although we used a dual-source CT scanner. From the results of this study and those of prior studies, further reduction in the contrast medium dose might be attained with combined use of our method and low-kV scanning.

The data acquisition protocol of this study required two instances of radiation exposure. The magnitude of the exposure index is lower than the diagnostic reference level in Japan (15 mGy). With the use of advanced software [9], only one exposure is sufficient, leading to the possibility of further dose reduction. Additionally, the use of an iterative reconstruction algorithm, a low kV setting (e.g., 70 kV), or a dual-energy technique will further reduce the radiation dose; further studies are required in this regard. Although this study employed a dual-source CT scanner, the data acquisition protocol does not require dual-energy mode scanning. Therefore, this protocol is universally applicable in institutions using 64-row multi-detector CT scanners and a basic image processing workstation and is effective in decreasing the volume of contrast medium to 21 mL, which might contribute to reducing nephrotoxicity.

In conclusion, we have demonstrated in 20 cases that 3D-CTPAV images of the pulmonary vasculature can be created using 21 mL (test scan, 6 mL; actual scan, 15 mL) of contrast medium, a 64-row dual-source CT scanner, and a basic function of an image processing workstation, with < 20 min of user interaction. The timing of the start of the two actual scans in the pulmonary arterial and venous phases during the breath hold after full inspiration was determined by the test injection of 6 mL of contrast medium. The resultant 3D-CTPAV images appeared suitable for clinical purposes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies performed in animals.

Informed consent Informed consent was obtained from all the study participants.

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