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Detection of pulmonary embolism on CT-angiography using contrast attenuation of pulmonary veins

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Abstract

Introduction: *In areas of pulmonary embolism (PE), the enhancement of pulmonary veins on computed tomography pulmonary angiography (CTPA) should be decreased due to reduced arterial perfusion.*
The purpose of this study was to investigate the accuracy of contrast density measurements (differences) in all pulmonary veins and the left atrium for the prediction of PE.

Material and methods: *Seventy-five patients with PE and 22 patients without PE on CTPA were included. Four readers measured the enhancement of the blood in the pulmonary vein immediately before the entrance to the left atrium, right after the aperture, in the center of the left atrium, in the pulmonary trunk and in the aorta. Enhancement of the pulmonary veins with and without upstream PE, and ROC curves with HU thresholds for optimal sensitivity and specificity for PE were calculated.*

Results: *More PEs were found in the right and lower lobes. PE-affected lobes demonstrated 13.8 ± 45 HU less enhancement in the pulmonary vein, compared to a paired non-affected pulmonary vein of the same patient ($P < 0.0001$). On average, non-affected pulmonary veins demonstrated no difference in enhancement compared to each other: 0.2 ± 21 HU. The optimal cutoff level in the ROC curve analysis for PE affection proved to be decreasing enhancement in the pulmonary vein of more than 10 HU compared to the atrium.*

Conclusion: *Decreasing enhancement in the pulmonary vein of more than 10 HU compared to the atrium could provide additional information and confidence in the diagnosis of PE.*

Key words: pulmonary embolism detection, CT-pulmonary angiography, enhancement and perfusion of pulmonary veins

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Introduction

Pulmonary embolism (PE) is a common disease with a potentially poor patient outcome. A thrombus occluding the pulmonary artery causes obstruction of lung circulation and can result in cardiogenic shock and death. Often, PE is not clinically recognized because the symptoms can be very unspecific and therefore can have low diagnostic value [1, 2]. Symptoms by themselves do not make it possible to exclude PE or to confirm it [1, 2]. To decide on diagnostic steps and additional therapy, risk stratification is crucial [1]. Established clinical

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scores, such as the Wells score [3, 4] or the Geneva score [5, 6], classify patients into low-, intermediate- and high-risk categories. These scores include patients' risk factors for PE, symptoms and clinical signs [3–6].

Correct and immediate diagnosis, as well as management and initiation of treatment, is important for patient outcomes [7].

In intermediate- and high-risk patients, multidetector row computed tomography pulmonary angiography (CTPA) is the procedure of choice and has become the gold standard when PE is suspected [2, 8–11]. The overriding characteristics of PE in CTPA are an occlusive or non-occlusive filling defect inside a pulmonary artery [12, 13]. When the vessel is fully occluded, it can appear expanded, and the thrombus can form an acute angle with the artery wall [12–14]. A partial filling defect, in which the thrombus is surrounded by a contrasting agent, is called a "polo mint sign", occurring on images perpendicular to the long axis of the vessel [12]. On longitudinal images of the vessels, it is called the "railway track sign" [12].

Secondary findings in CTPA, such as an enlarged diameter of the pulmonary artery ("Pallas Sign"), atelectasis, pulmonary infarction ("Hamptons hump"), pleural effusion and oligemia ("Westmark sign") can provide additional proof of PE in cases of uncertainty, but they are unspecific [13, 15–17]. Furthermore, the signs of pulmonary hypertension and cardiac congestion — such as right ventricular dilation, horizontalization or deviation of the interventricular septum and contrast reflux into liver veins — can facilitate detecting or confirming the PE diagnosis. The PE sensitivity of these right ventricular congestion signs was reported as being as high as 78% [2]. Filling defects in pulmonary veins adjacent to PE was recently described by Souza et al [18]. This "Pulmonary Vein Sign" was defined as presence of homogeneous filling defect in a pulmonary vein in the last 2 cm from the left atrium. This visual sign only reached a PE sensitivity of 36% by radiologists.

The purpose of this study was to investigate the accuracy of contrast density measurements (differences) in all pulmonary veins and the left atrium for the prediction of pulmonary embolism since the contrast in pulmonary veins should be decreased due to reduced arterial perfusion in areas of PE.

Material and methods

IRB approval was waived due to the retrospective nature of the study with irreversible anonymization.

Inclusion/exclusion of patients

Our Radiology Information System (Centricity RIS-i 6, General Electric Company, GE Healthcare, Chicago, IL, USA) was searched for the diagnosis of PE. Over a time period of 2 years (2016 and 2017), 82 consecutive patients with pulmonary embolisms were submitted to CTPA at our institution. Two senior radiologists with 10 and 12 years of experience in chest imaging reviewed the images for diagnosis confirmation and mapping of the PE (see ground truth below). In 3 patients, the diagnosis of PE could not be verified on CTPA, and these patients were excluded (low contrast or beam hardening artifacts). Of the remaining 79 patients, 4 had to be excluded due to lobectomy or severe motion artifacts. Twenty-three patients demonstrated embolisms in the drainage locations of all four pulmonary veins and were used for PE distribution and arterial enhancement statistics, but were excluded from the work-up of different enhancement in the pulmonary veins (Fig. 1). Twenty-two age- and sex-matched patients with normal CTPA exams and without PE findings were added as a control group.

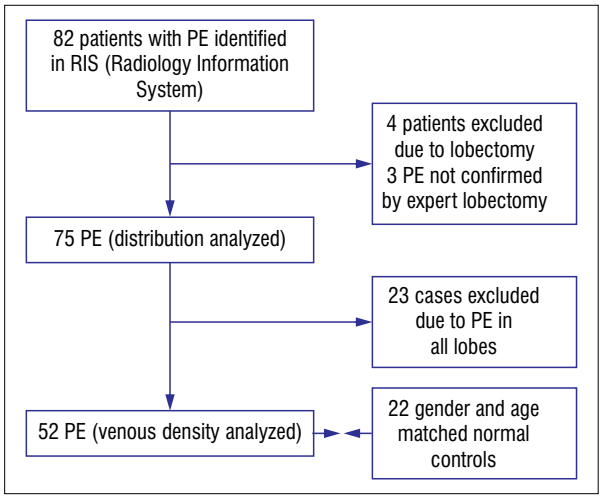

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) with the inclusion of 82 patients and exclusion of 7 and 23 patients

CT imaging

CT images were acquired by two CT scanners (both by Siemens Healthcare, Erlangen, Germany): a SOMATOM Definition Flash (128 × 0.6 mm, pitch 0.6, slice thickness 1 mm) and a SOMATOM Definition Edge (128 × 0.6 mm, pitch 0.6, slice thickness 1 mm). A CT tube voltage of 100 kVp and a reference CT current time product of 100 mA were used. Standard contrast medium with 300 mg/mL iodine concentration was used at a flow rate of 4 mL/s (Xenetix 300; Guerbet, Aulnay-sous-Bois, France). A region of interest (ROI) was placed in the pulmonary trunk. Image acquisition started 4 seconds after the threshold of 100 Hounsfield units (HU) was reached in the ROI. Iterative recon-

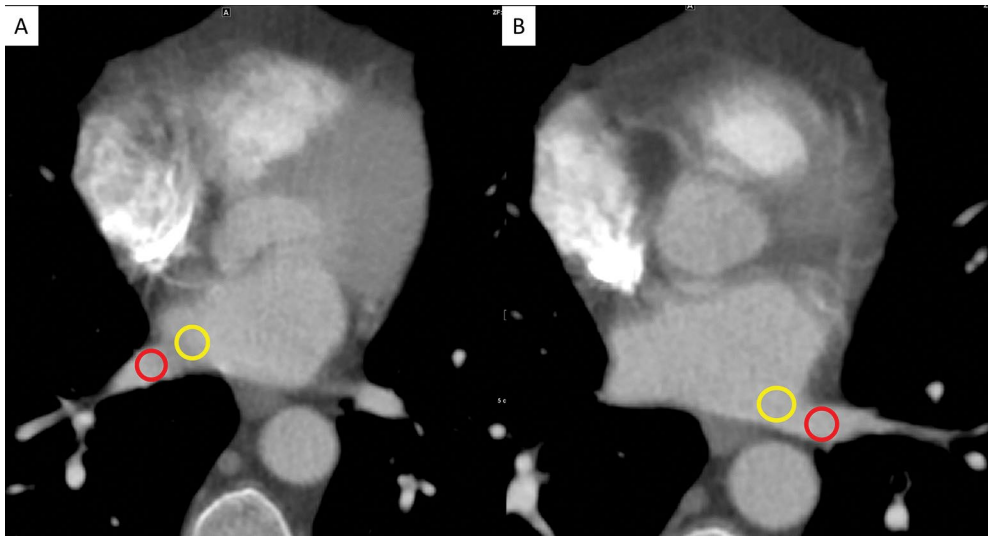

Figure 2. Density measurement in: **A** — the right inferior pulmonary vein; and **B** — the left inferior pulmonary vein. The readers in group 1 placed the ROI (region of interest, red circle) in the vein immediately before the entrance into the left atrium, and the readers in group 2 set the ROI in the atrium, as close as possible to the venous aperture (yellow circle)

struction (SAFIRE, level 3) was performed using kernels I26f and I70f.

Ground truth

In the remaining 75 cases, the mapping of the PE was reported in consensus by two senior radiologists with 10 and 12 years of experience in chest imaging. The PEs were classified as follows: central (involving the right or left main pulmonary artery), lobar, segmental or subsegmental PEs in the upper or lower lobe on the right or left side. Every embolus was counted separately and was noted with the most proximal affection of the pulmonary artery. Since the middle lobe and the lingula drain into the upper pulmonary veins, they counted as the upper lobes. In case of an additional lingular or middle lobe vein (normal variants), the mean densities of the upper lobe vein and the additional vein were calculated. Any aforementioned location of PE counted as a positive lobar result.

CT image analysis

The readouts were generated using a Picture Archiving and Communication System (PACS Philips, Amsterdam, Netherlands and Sectra, Linköping, Sweden). Group 1 consisted of two readers with 10 and 3 years of chest imaging experience, and group 2 consisted of two radiologists with 8 and 1 year(s) of chest imaging experience; both groups measured the 4 pulmonary veins in 97 cases (388 ROIs). The readers from group 1 placed the ROI (region of interest) into the vein immediately before the entrance into the left atrium, and the readers in group 2 set the ROI in the atrium, as close as possible to the venous aperture (Fig. 2). In addition, the readers also measured the density of the blood in the center of the left atrium, in the pulmonary trunk and in the middle of the aortic arc. After 4 weeks, the two groups remeasured the 4 pulmonary veins in half of the cases (n = 50) for intra-reader variability.

Statistics

Any form of embolism, even an isolated subsegmental PE, counted as affected pulmonary vein with an upstream PE. The mean enhancement of the pulmonary veins with and without upstream PE was calculated and compared to each other using Wilcoxon's unpaired rank sum test. In addition, the paired enhancement of the 1 to 3 normal veins and the 1 to 3 embolism-affected veins per patient were analyzed using Wilcoxon's paired rank sum test. Additionally, the average density difference of the veins within the same patient and the difference in the density to the atrium were calculated and analyzed by Wilcoxon's test. The results of both readers in the groups counted separately for the reader correlation, and the mean of their results was used for Wilcoxon's test. For the determination of the best cutoff level for (1) enhancement differences between atrium and pulmonary veins and (2) enhancement differences of the veins (normal vs. upstream embolism) receiver operator characteristic curves (ROC) were generated to find the area under the curve (AUC) and the optimal sensitivity and specificity (confidence interval included).

Table 1. Distribution of pulmonary emboli (total emboli load)

PE		R	L	R+L
Central*		14	10	24
Lobar	UL	11	7	
	LL	14	11	
	UL+LL	25	18	43
Segmental	UL	11	8	
	LL	17	17	
	UL+LL	28	25	53
Subsegmental	UL	4	8	
	LL	14	21	
	UL+LL	18	29	47
Total UL				73
Total LL				94
Total	UL+LL	85	82	
			Number of patients	
1 lobe PE (1 drainage vein)			21	
2 lobes PE (2 drainage veins)			22	
3 lobe PE (3 drainage veins)			9	
4 lobes PE (all drainage veins)			23	

*pulmonary trunk or main pulmonary artery
UL: upper lobe; LL lower lobe; R: right; L: left; PE: pulmonary embolism

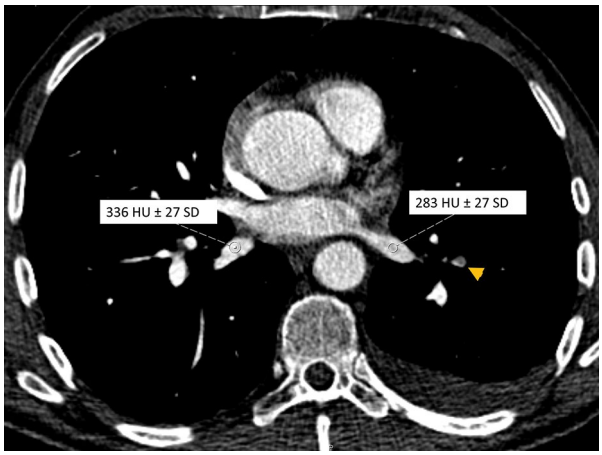

Figure 3. A 57-year-old male patient with a segmental pulmonary embolism in the anterior-lateral artery of the left lower lobe (orange arrow). The left pulmonary vein of the lower lobe demonstrated less enhancement than the right side

Intra- and inter-reader correlations were determined with Pearson's correlation coefficient.

All tests of significance were two-tailed, and a P-value of < 0.05 was considered to indicate statistical significance. Calculations were performed with MedCalc® software, version 16.4.3 (MedCalc Software, Ostend, Belgium).

Results

Seventy-five patients with pulmonary embolism (male:female = 40:37, mean age = 61.6 ± 16.2 years old) and 22 normal control patients (m:f = 11:11, mean age 60.2 ± 16.2 years old) were included. The emboli were classified as follows: 24 central, 43 lobar, 53 segmental and 47 subsegmental (Table 1). More PEs were found in the right and lower lobes, and more isolated subsegmental PEs were found on the left side (Table 1). In 21, 22, 9 and 23 patients one, two, three or four lobes, respectively, were affected by PEs.

Group 1: on average, the pulmonary vein of a PE-affected lobe was 13.8 ± 45 HU less enhanced than a paired non-affected pulmonary vein of the same patient ($P < 0.0001$, Fig. 3). Group 2: these paired measurements did not demonstrate significant differences (mean difference = 7.8 ± 48 HU, $P = 0.336$).

In group 1, the mean and median enhancement differences from an *affected* vein to the atrium (HUatrium-HUpv) were 5.1 ± 3.8 and 8.5 (CI: –4.2 to 15.0), respectively; meanwhile the mean and median enhancement differences from an *unaffected* vein to the atrium (HUatrium-HUpv) were –3.1 ± 2.1 HU and –2 HU (CI: –7.9 to 1.0), respectively. These enhancement differences were significant (affected vs. unaffected: $P = 0.0052$).

The optimal cutoff level in the ROC analysis for PE affection proved to be decreasing enhancement in the pulmonary vein of more than 10 HU, compared to the atrium (Fig. 4). The AUC for this ROC curve was 0.57 (CI: 0.51 to 0.63) with sensitivity of 47.8% (37.3–58.5%) and specificity of 74.7% (67.4–81.1%). Group 2, who measured in the left atrium closest to the venous aperture did not score significantly different enhancements between veins with or without upstream PEs ($P = 0.31$). Figure 5 demonstrates the venous enhancement differences (HUatrium-HUpv) depending on the number of embolism-affected lobes with the largest distinction found between patients without PE and with one PE. A specific ROC curve analysis (Fig. 6) of these patient selections found an AUC of 0.785 (CI: 0.70 to 0.86) with the best sensitivity of 85.7% (63.6–96.8%) and specificity of 63.5% (53.1–73.1%) using the criterion of > 3 HU (difference in HU between atrium and pulmonary vein). Again, no significant differences were found for group 2.

Generally, the blood density in the pulmonary trunk (PT) was higher than that in the left atrium (LA), and it was higher in the LA than in the aorta in both groups (Table 2). In patients with pulmonary embolisms, the

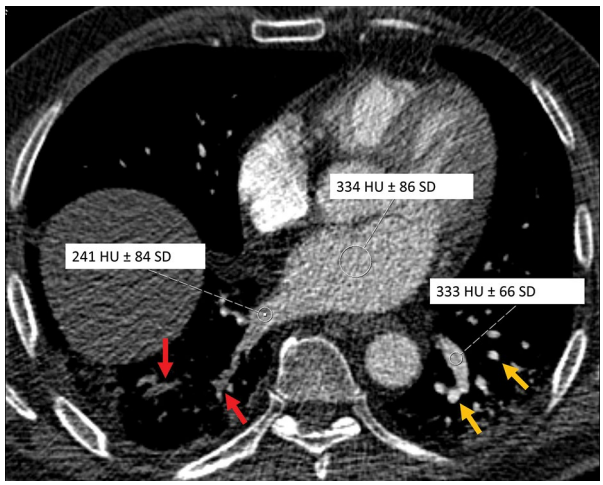

Figure 4. A 63-year-old male patient suffering from lobar and segmental pulmonary embolisms in the right lower lobe (red arrows). The right lower pulmonary vein demonstrated less enhancement than the normal left lower pulmonary vein and the atrium. Note the regular enhancement/perfusion of the segmental arteries of the left lower lobe (yellow arrows)

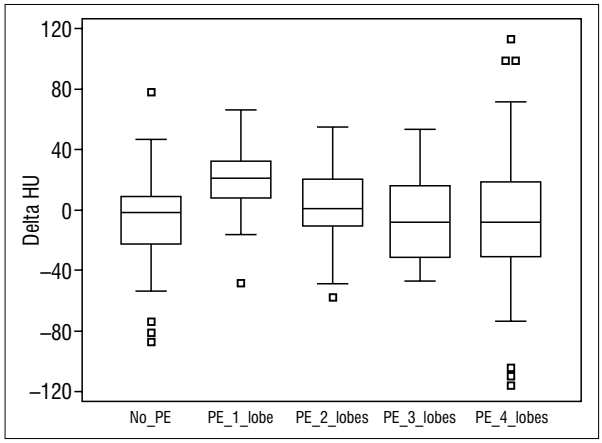

Figure 5. Box-and-whisker plot of the enhancement difference from an affected vein to the left atrium (HUatrium-HUpv) in patients without PE and patients with 1 to 4 affected lobes

density along this track was at each point higher than in the patients without embolisms ($P = 0.046$ for all 3 measurements in the PT, LA and aorta in both groups combined).

There was no significant difference in the mean absolute pulmonary vein density (non-paired), whether in cases with or without pulmonary embolisms ($P > 0.1742$). The means and medians of the pulmonary vein density in groups 1 and 2 for the different embolism categories are indicated in Table 3.

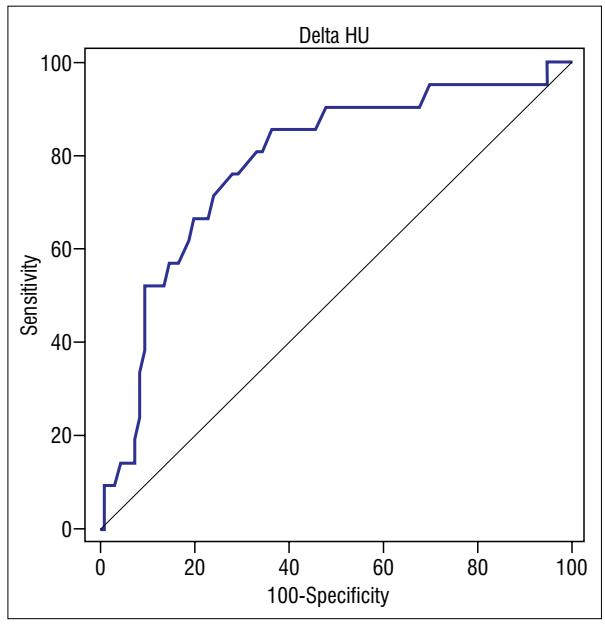

Figure 6. Patients with PE affecting only one lobe: ROC curve analysis of enhancement differences between the left atrium and pulmonary vein (HUatrium-HUpv). Best sensitivity and specificity of 85.7% and 63.5%, respectively, were found for a threshold of a > 3 HU difference

Both the inter- and intra-reader correlations were very high: the intra-reader correlations of the 4 readers were ≥ 0.93 (CI: 0.91 to 0.95). The inter-reader correlations in the groups and between the groups were ≥ 0.92 (CI: 0.91 to 0.94), although the ROIs were set slightly differently.

Discussion

In this study, we found that the veins in the drainage area of the PEs had, on average, 14 HU less enhancement than the veins of unclogged areas ($P < 0.0001$). For practical reasons, we also provided results for the measurement differences between the atrium and pulmonary veins (when comparing veins, one never knows whether the vein compared is free of embolisms). An attenuation difference of +10 HU indicates PE when applying this technique, with the strength clearly lying in the 75% specificity. Especially difficult to find are solitary PEs for radiologists, and for these embolisms, the accuracy increased to a sensitivity of 86% (threshold: HUatrium-HUpv > 3 HU). Our results indicate up to 50% higher sensitivities than the "Pulmonary Vein Sign". There could be different reasons for that: First, Souza et al. [18] set the ROI into the left atrium to trigger the CT exam, in our study the pulmonary trunk was used as trigger reference leading to an earlier CT phase.

Table 2. Central vascular enhancement dependent on PE

	HU (aorta)			HU (pulmonary trunk)			HU (atrium)		
	Mean ± SD	Median	(min to max)	Mean ± SD	Median	(min to max)	Mean ± SD	Median	(min to max)
PE (all 4 PV with upstream PE)	284 ± 82	293	438 to 144	407 ± 100	398	597 to 190	332 ± 75	324	476 to 211
PE (1 to 3 PV with upstream PE)	303 ± 84	294	608 to 142	392 ± 105	372	673 to 154	325 ± 85	315	597 to 132
Patients without PE	277 ± 92	268	527 to 128	380 ± 132	352	633 to 135	310 ± 99	288	527 to 125

PE: pulmonary embolism; PV: pulmonary veins; SD: standard deviation; HU: Hounsfield Units

Second, we measured HU differences between veins and atrium and computed the best cut-off levels for PE, while Souza et al. used a visual sign with probably rather large enhancement differences that could have led to a shift from sensitivity toward specificity.

As mentioned in the introduction, CTPA is the method of choice when detecting PE. It has very high sensitivity (90%) and specificity (94%) [14, 19–23]. In CTPA, PE is diagnosed by detecting a partial or fully occluded artery. Generally, the vessel density before (pulmonary trunk) and after the PE (left atrium) was higher, compared to the non-embolic cases. Pulmonary embolisms increase the pulmonary arterial resistance and pressure and can lead to a certain delay in circulation, which in turn can lead to accumulation of contrast media in the heart/lung. Therefore, one could expect high pulmonary vessel density in patients with PE. However, the clogged lobes are prone to lesser perfusion with less intravascular contrast media, which might be why the absolute vein density did not differ between any of the clogged and non-clogged lobes. The difference could only be found by comparing the veins in the same patient. In cases in which all four lobs are affected, there should be no HU difference. However, in these patients the diagnosis of PE requires no further sign for confidence boosting since all of the lobes are affected, and PE can usually be found easily.

More isolated subsegmental PEs were found on the left side (Table 1), likely because, on the right side, the subsegments were already occupied by larger segmental or lobar PEs.

Group 2 demonstrated a larger SD of the focal density measurement in the region of interest (ROI), indicating that the ROI was set larger due to larger space within the atrium (compared to the measurement within the veins for group 1); therefore, there was more noise and a larger SD.

Secondary findings can help in evaluation, especially in cases of uncertainty, and they have been described as predictors of severity and outcome [24]. However, there is disagreement in the literature in regard to their value in detecting PE, as well as predicting severity and outcome. They can distract from and interfere with the diagnosis of PE, thus presenting a potential pitfall [24]. Engelke et al. described sporadic secondary findings in cases of PE diagnosis that did not contribute to its detection [24]. They found PE burden to have the highest value for detection. However, they excluded pleural effusion from their study, which is more closely associated with PE. Similarly, contrast density differences between the pulmonary veins could be used to detect PE, especially, when there is doubt.

Other parameters can be utilized for the prediction of PE severity and outcome. Blood clot burden

Table 3. Enhancement of pulmonary veins dependent on upstream embolism

GROUP 1		Pulmonary veins (HU)		
		Mean ± SD	Median	(min to max)
PE (all 4 PV with upstream PE)		335 ± 79	331	(169 to 536)
PE (1 to 3 PV with upstream PE)	**Affected PV**	312 ± 75	310	(125 to 564)
	Non-affected PV	326 ± 85	326	(110 to 586)
Patients without PE		315 ± 103	303	(111 to 554)
GROUP 2		**Mean ± SD**	**Median**	**(min to max)**
PE (all 4 PV with upstream PE)		336 ± 79	329	(214 to 534)
PE (1 to 3 PV with upstream PE)	**Affected PV**	321 ± 82	313	(135 to 605)
	Non-affected PV	328 ± 89	315	(132 to 598)
Patients without PE		310 ± 106	291	(115 to 554)

PE: pulmonary embolism; PV: pulmonary veins; SD: standard deviation; HU: Hounsfield Units

was described as a predictor of severity by Ghaye et al. [25] and Araoz et al. [26], yet it cannot predict clinical outcomes. Another predictor of severity but not outcome is right ventricular failure [26]. Previous studies have found cardiac parameters to be superior in predicting the patient's clinical outcomes [26]. According to Bilj et al., the best predictor of clinical illness-specific outcomes is the right to left ventricular ratio [27]; nevertheless, the sample size in this study was very small. The vein enhancement measurements applied in this study could also be used in the future to help predict severity and outcome.

There are some limitations in our study: No classifications according to PE severity, secondary cardiopulmonary diseases or patient outcome were made. Anatomical anomalies of pulmonary vessels, such as the normal variants of pulmonary veins (e.g., additional veins), bronchopulmonary sequester, lung transplantation, dystelectasis, and structural lung disease, for example fibrosis, COPD or tissue scars, could perhaps account for the reduction in contrast density and are potential reasons for wrong density values. These pitfalls can be easily detected with CT and must be considered when interpreting contrast density reductions in pulmonary veins.

Additionally, CT-tube voltage plays a role in the absorption fraction and the density measurements of contrast media and must be kept constant. For example, low-dose CTPA for pregnant women can detect different venous enhancement due to lower CT-tube voltage and different blood volumes [28–34]. Enhancement of the pulmonary veins is highly dependent on the delay phase of the scan; therefore, the mean density did not prove to be useful, but the differences in enhancement within the same patent kept this variable out of the equation. All of these factors must be considered before utilizing this technique since they can distort density values and affect measurements.

In conclusion, decreasing enhancement in the pulmonary vein can provide additional information and confidence in the diagnosis of PE.

It is important to measure the blood density within the pulmonary veins right before the aperture and not after the aperture into the left atrium; and subtract it from the blood density in the center of the left atrium. An attenuation difference of >10 HU indicates PE when applying this technique, with the strength clearly lying in the 75% specificity.

Conflict of interest

None.

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