European Journal of Radiology Open 7 (2020) 100280

Contents lists available at ScienceDirect

European Journal of Radiology Open

journal homepage: www.elsevier.com/locate/ejro

Improving Contrast Enhancement in Pulmonary CTA: The value of breathing maneuvers

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ARTICLE INFO

Keywords:
Pulmonary embolism
Computed tomography angiography
Pulmonary arteries
Contrast density
Image quality
Breathing

ABSTRACT

Purpose: To investigate contrast dynamics and artifacts associated with different breathing maneuvers during pulmonary computed tomography angiography (pCTA) in a prospective randomized clinical trial.

Method: Three different breathing maneuvers (inspiration, expiration, Mueller) were randomly assigned to 146 patients receiving pCTA for suspected pulmonary embolism (PE). Contrast enhancement of central and peripheral arteries and imaging quality of lung parenchyma were compared and analyzed. Results were compared by using the analysis of variances (ANOVA) and Kruskal-Wallis-Test.

Results: Mean enhancement in the pulmonary trunk was highest during breath-hold in inspiration (293 HU, range 195–460 HU) compared to Mueller (259 HU, range 136–429 HU, $p = 0022$) and expiration (267 HU, range 115–376 HU). This was similar for the right pulmonary artery (inspiration 289 HU, range 173–454 HU; Mueller 250 HU, range 119–378 HU; $p = 0.007$; expiration 257 HU, range 114–366 HU; $p = 0.032$) and left pulmonary artery (inspiration 280.3 HU, range 170–462 HU; Mueller 245 HU, range 111–371 HU; $p = 0.016$; expiration 252 HU, range 110–371 HU).

Delineation of peripheral arteries was significantly better in inspiration vs Mueller ($p = 0.006$) and expiration ($p = 0.049$). Assessment of the lung parenchyma was significantly better in inspiration vs Mueller ($p = 0.013$) or expiration ($p < 0.001$).

Conclusions: Resting inspiratory position achieved the highest enhancement levels in central and peripheral pulmonary arteries and best image quality of the pulmonary parenchyma in comparison to other breathing maneuvers. It is necessary to train the maneuver prior to the examination in order to avoid deep inspiration with the risk of suboptimal opacification of the pulmonary arteries.

1. Introduction

Contrast-enhanced computed tomography angiography (CTA) has been accepted as gold standard for detecting pulmonary embolism (PE) [1]. In clinical practice, inspiratory breath-hold is the standard for chest CT also very common for pulmonary CTA (pCTA) [2].

A number of parameters influence the vascular enhancement in CTA, amongst them are tube voltage (kV setting), iodine delivery rate (IDR), scan time, and scan timing. Optimal results can be achieved with large central catheters, but usually peripheral lines (18−20 G) in an antecubital or palmar vein are used for contrast agent injection.

Determination of the contrast bolus arrival time is individualized applying either the test-bolus method or bolus tracking. The best patient's breathing maneuver during data acquisition of pCTA, however, is still a matter of debate [2–5]. Deep inspiration might lead to increased influx of non-contrast-enhanced blood from the inferior vena cava (IVC) to the right atrium, thus diluting or even interrupting the contrast material influx [4]. During Valsalva maneuver the intrathoracic pressure

Abbreviations: pCTA, pulmonary computed tomography angiography; PE, pulmonary embolism; IDR, iodine delivery rate; IVC, inferior vena cava; GCP, good clinical practice; IRB, institutional review board; ROI, region of interest; MPR, multiplanar reformations; ANOVA, analysis of variances; ICC, intraclass correlation coefficient; SVC, superior vena cava.

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https://doi.org/10.1016/j.ejro.2020.100280
Received 7 August 2020; Received in revised form 3 October 2020; Accepted 6 October 2020

rises and decreases inflow of contrast enhanced blood (Fig. 1). Both can lead in insufficient contrast enhancement within the pulmonary arteries.

A small prospectively randomized clinical trial, including 28 patients with suspected PE, suggested pCTA should be performed in resting expiratory state [5]. Attenuation of the blood pool in the cardiac chambers, pulmonary artery and ascending aorta was measured and compared in a larger, but retrospective study including 145 pCTA-examinations in inspiratory and 181 in expiration [2]. The authors concluded, that pCTA can be successfully performed in expiratory state, however inferior parenchymal imaging needs to be accepted. This is in line with [5]. In a retrospective analysis of 1361 pCTA examinations performed in inspiration, only 18 examinations were identified as non-diagnostic and had to be repeated in expiration, suggesting reimaging in expiration in patients with an initial non-diagnostic pCTA [3]. Gutzeit et al. [6] randomized patients without the suspicion of pulmonary embolism to four groups, performing either Valsalva, Mueller maneuver, inspiration or expiration during pCTA. Each group consisted of 15 patients, the authors concluded that significantly higher enhancement within the pulmonary arteries can be achieved performing Mueller maneuver [6].

The aim of the present study was to test the different methods in a real-world emergency setting in patients with the clinical suspicion of acute pulmonary embolism.

2. Material and methods

2.1. Patients

Power analysis was performed (Cohen's f was calculated prospectively with a medium size effect f of 0.265 and a sample size power of 80.0 %) resulting in a sample size of 141 subjects. Because of potential drop-outs 150 patients were recruited for this study.

150 patients with the indication for pCTA for the clinical suspicion of PE were prospectively enrolled between January and December 2017 either from the emergency department (ED) or as part of their inpatient stay. Two observers blinded to the imaging protocol and clinical results independently reviewed the scans. Each observer has clinical experience in interpreting CTA (6 and 8 years respectively).

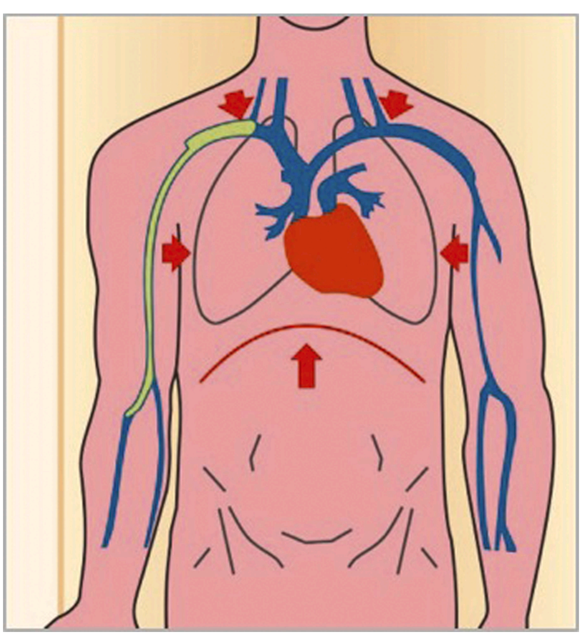

Fig. 1. Transient interruption of contrast column.
Demonstration of the "transient interruption" of the contrast column, usually injected via upper extremity. During Valsalva maneuver, pressure in the chest rises and interrupts the contrast-column. Insufficient contrast enhancement within the pulmonary arteries can mimic false positive embolus or may result in a lack of differentiation between the intravascular contrast and the embolus.

The study protocol was approved by the local institutional review board (IRB) and the study was performed according to Declaration of Helsinki and "good clinical practice" (GCP) guidelines. Before enrollment, each patient provided written informed consent prior to inclusion to this observational study.

Indication for performing CTA was based on clinical results, elevated D-dimer levels (>0.5 mg/l), ECG (signs of acute cor pulmonale) and blood gas analysis (arterial carbon dioxide tension $PaCO_2 < 36$ mmHg, arterial oxygen tension $PaO_2 < 80$ mmHg) [7,8]. Contraindications were renal insufficiency, manifest hyperthyroidism and pregnancy. Patients with language barrier, intubation, tracheostomy and difficulty in performing the Mueller maneuver were excluded from the study.

To prevent selection bias, the different breathing maneuvers were randomly assigned by online available randomization software (Randomization in Treatment Arms-RITA) [9].

2.2. Imaging procedure

All scans were performed with a 64 slice CT scanner (Definition AS 64, Siemens Healthcare, Erlangen, Germany). All patients were examined on the same CT scanner with an identical protocol, despite the breathing maneuver. The scan protocol was as follows: 64 × 0.6 collimation, 1.2 pitch, 0.5 s gantry rotation speed, 120 kVp tube voltage and 100 ref.mAs tube current (AEC enabled). The bolus tracking technique with a region of interest (ROI) placed in the center of the pulmonary trunk used with a triggering threshold of 140 HU and a delay of 5 s after reaching the trigger value. Contrast medium (Solutrast 300, 300 mg iodine/mL, Bracco, Konstanz, Germany) was injected via a cubital vein (20 G venous access catheter) using a power injector (Inject CT Motion, Ulrich medical, Ulm, Germany) with a weight-adapted contrast dose of 1 mL/kg (minimum of 60 mL and maximum 120 mL) at a flow rate of 4 cc/sec. Saline flush of 40 mL followed contrast medium injection with a rate of 4 cc/sec.

Images were reconstructed with a slice thickness of 1.0 mm, increment of 0.7 and a medium reconstruction kernel (I40f) using iterative reconstruction (SAFIRE 3). Multiplanar reformations (MPR) in coronal and sagittal plane were reconstructed with a slice thickness of 3 mm. For the assessment of the lung parenchyma, a high-resolution kernel (I70f) was used to reconstruct 1 mm and 5 mm axial slices.

2.3. Breathing maneuvers

Patients were divided into three groups, the "inspiration group" was instructed to breathe in normally and hold the breath (apnea) without exercising a Valsalva maneuver. The "expiration group" was instructed to breathe out and hold the breath. The "Mueller group" was instructed to use a device (see Fig. 2) and breathe in to generate negative pressure of -20 mm Hg.

The manometer [6] allowed to perform standardized and reproducible Mueller maneuvers.

All patients were instructed how to perform their breathing maneuver before the examination by a technician multiple times.

A quantitative ranking score (1 – optimal, 2 – good, 3 – adequate, 4 – suboptimal and 5 – poor; see Fig. 3) was used for the evaluation of imaging quality of the lung parenchyma. A standardized scale demonstrating levels of quality of the peripheral vessels (1 – all vessels are easy to asses, 2 – subsegment arteries still sufficiently assessable, 3 - segmental arteries still sufficiently assessable, 4 – lobar arteries still sufficiently assessable, 5 – vessels cannot be assessed) enabled an independent assessment by the two radiologists.

The attenuation of the central pulmonary vasculature was measured by a quantitative ROI measurement (HU). The central pulmonary vasculature was divided into the central pulmonary trunk, the right and left pulmonary artery. At each level the region of interest in each

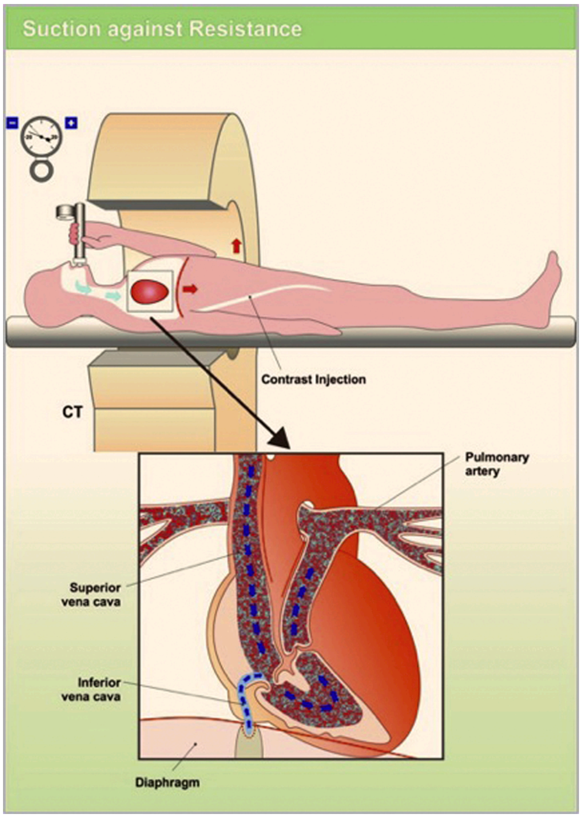

Fig. 2. Suction against resistance.
This schematic diagram shows the functional changes between diaphragm, heart, IVC, SVC and the pulmonary trunk caused by Mueller maneuver.

anatomical area was standardized as follows: 200–300 mm^2 for the central pulmonary trunk and the main pulmonary arteries (see Fig. 4). A minimal opacification of approximately 100 HU is required for identification of acute emboli [10].

2.4. Statistics

Data were expressed as mean values ± one-fold standard deviation (SD). For the data analysis commercially available software was used (IBM SPSS Statistics, Version 25). The normality of data distribution was assessed using Levene's test. Data showing a Gaussian distribution were evaluated by an analysis of variances (ANOVA) with a post-hoc analysis of Gabriel. The Kruskal-Wallis test was applied, where ordinal data distribution was present. A p-value less than 0.05 was considered to indicate a significant result for the tests that were performed. Agreement between the observers for quantitative data was assessed for intraclass correlation using 95 % confidence intervals. Interpretation of agreement was as follows: less than 0.2 was poor, 0.2–0.4 was fair, 0.4–0.6 was moderate, 0.6 – 0.8 was good and 0.8–1 was very good. Statistical power analysis was performed prospectively with an online available statistical power analysis software (G*Power) [11].

3. Results

146 of 150 examined patients were successfully included in the final data analysis, four patients who were randomly assigned to Mueller maneuver could not perform the procedure and were excluded. The protocol used for these four patients was inspiration since this was the standardized protocol at our institution. One patient assigned for inspiration practiced Valsalva maneuver during the examination, which yielded inadequate results. After evaluation of the overall clinical patient's condition, the on-call radiologist repeated the examination in expiratory position.

In 27 patients the diagnosis of pulmonary embolism could be verified, seven of them had additional pulmonary infarction (see Fig. 5). The other patients had pleural effusion (25 %), tumor ($n = 31$ patients), or pneumonia ($n = 51$ patients). There were no statistically significant differences within the three groups in age, BMI, weight and gender (Table 1).

Enhancement of the pulmonary trunk was 294HU/259HU/267HU (inspiration/Mueller/expiration). The difference between inspiration and Mueller was statistically significant ($p = 0.022$). Attenuation of the right pulmonary artery was higher in inspiration (289 HU; $p = 0.007$) compared to Mueller (250 HU) and expiration (257 HU; $p = 0.032$), attenuation of the left pulmonary artery was higher in inspiration (280.31 HU) as compared to Mueller (244.7 HU; $p = 0.016$). There were no statistical significances between attenuation values from inspiration and expiration (268.4 HU) scans (Tables 2 and 3, Fig. 6).

Enhancement of the more peripheral pulmonary arteries was significantly higher in inspiration compared to expiration ($p = 0.049$) and also in Mueller compared to expiration ($p = 0.006$). There was no statistically significant difference between Mueller and inspiration.

Imaging quality of the lung parenchyma was rated significantly higher during inspiration compared to the other breathing maneuvers (Mueller $p = 0.013$; expiration $p < 0.000$). Image quality was rated higher in scans performed during Mueller maneuver compared to expiration ($p < 0.000$).

The intraclass correlation coefficient (ICC) and correlation

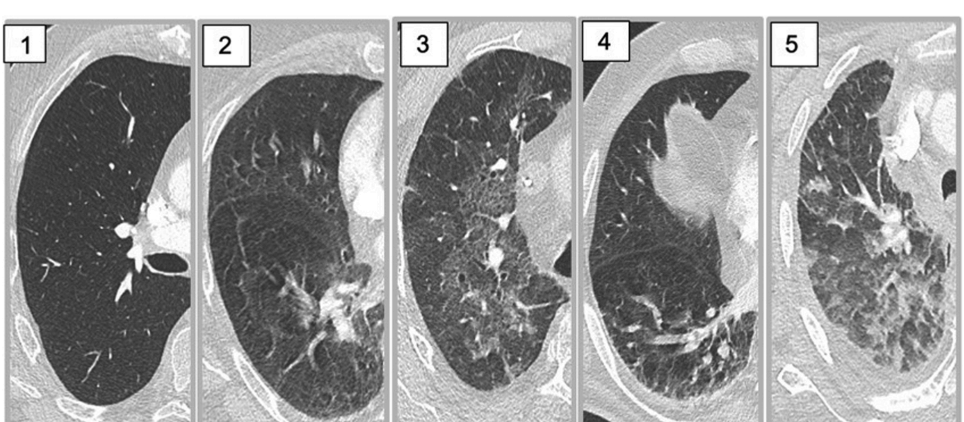

Fig. 3. Quantitative ranking score for the evaluation of lung parenchyma.
Standardized scale demonstrating levels of quality of lung parenchyma during CTA.

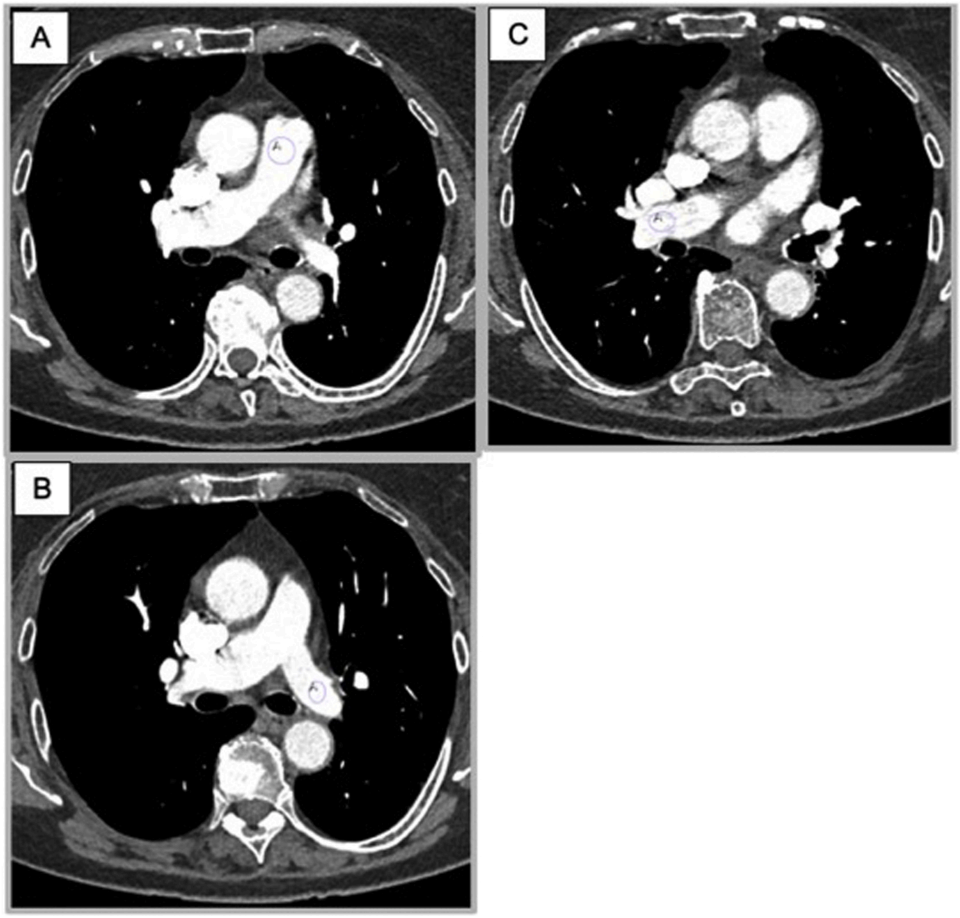

Fig. 4. Demonstration of ROI in the central pulmonary arteries.
Demonstration of ROI in the pulmonary trunk (A), the left PA (B) and right PA (C).

coefficient (Pearson) between the two radiologists were 0.849 – 0.884 ICC and κ = 0.85-0.886.

4. Discussion

Pulmonary CTA is the imaging modality of choice in patients with suspected acute pulmonary embolism. Confirmation or exclusion of hemodynamically relevant emboli can be performed with a high degree of certainty [12]. As opposed to V/Q scans, CTA provides visualization of the entire chest and allows diagnosis of alternative pathologies that mimic the symptoms of PE [13]. Recent advances in CT technology allows for so-called triple-rule-out examinations, which are aimed to detect or exclude coronary artery disease, PE, and aortic dissection [14].

Limitations in the diagnostic performance of pulmonary or the more complex triple-rule-out CTA are motion artifacts (breathing and cardiac motion), streak artifacts from highly concentrated contrast material in the superior vena cava, and low arterial enhancement. This can result in up to 4% of suboptimal or insufficient pulmonary CTA examinations [15,16].

There are a number of reasons for insufficient vascular enhancement, amongst them are incorrect scan timing, suboptimal injection or scan protocol, venous access complications and altered intrathoracic hemodynamics. The inflow of "native" blood from the IVC to the right heart can cause physiological interruption of contrast influx from the SVC [4]. During inspiration the diaphragm descends, increasing venous return from IVC and SVC [6]. Both increased (inspiration) or decreased (Valsalva maneuver) venous return can negatively affect pulmonary artery attenuation [2,3,5]. CT in expiration on the other hand negatively affects the assessment of the lung parenchyma. Mortimer at al [2]. concluded (145 inspiratory and 181 expiratory pulmonary CTA) that expiratory scanning should be reserved for failed inspiratory breath-hold CTA, due to inferior parenchymal depiction, especially at the base of the lung, although expiratory scans showed higher attenuation of the pulmonary trunk, right and left pulmonary artery, lobar and segmental PAs. A major limitation of this study is the retrospective design without randomization. Chen et al. [3] retrospectively analyzed 1361 pCTA in inspiration from patients with suspected PE and reported similar findings. 18 CTA were non-diagnostic and re-imaged in expiration position, with statistically significant higher attenuation in both the central and peripheral pulmonary arteries [3]. In contrast to these studies, our patients were prospectively randomized to the different breathing maneuvers and the technicians extensively trained the specific breathing maneuver with each patient. Besides vascular enhancement of the central pulmonary arteries, enhancement of the peripheral arteries as well as visualization of the lung parenchyma was assessed in our study.

Raczeck et al. [5] performed a prospective randomized clinical trial to evaluate two different respiratory positions (inspiratory and expiratory) during CTA data acquisition. In accordance to our results, resting expiratory pCTA was identified as being superior, but only 14 patients were included in each group. In contrast to our results no difference in parenchymal assessment was found [5].

Inspiration against resistance (=Mueller maneuver) has been reported to be a promising technique to improve contrast density within the pulmonary arteries, especially the peripheral arteries [3,6]. Gutzeit et al. prospectively randomized 60 patients to one of 4 breathing maneuvers (inspiration, expiration, Valsalva, Mueller Maneuver) [6], but none of them had the suspicion of acute pulmonary embolism.

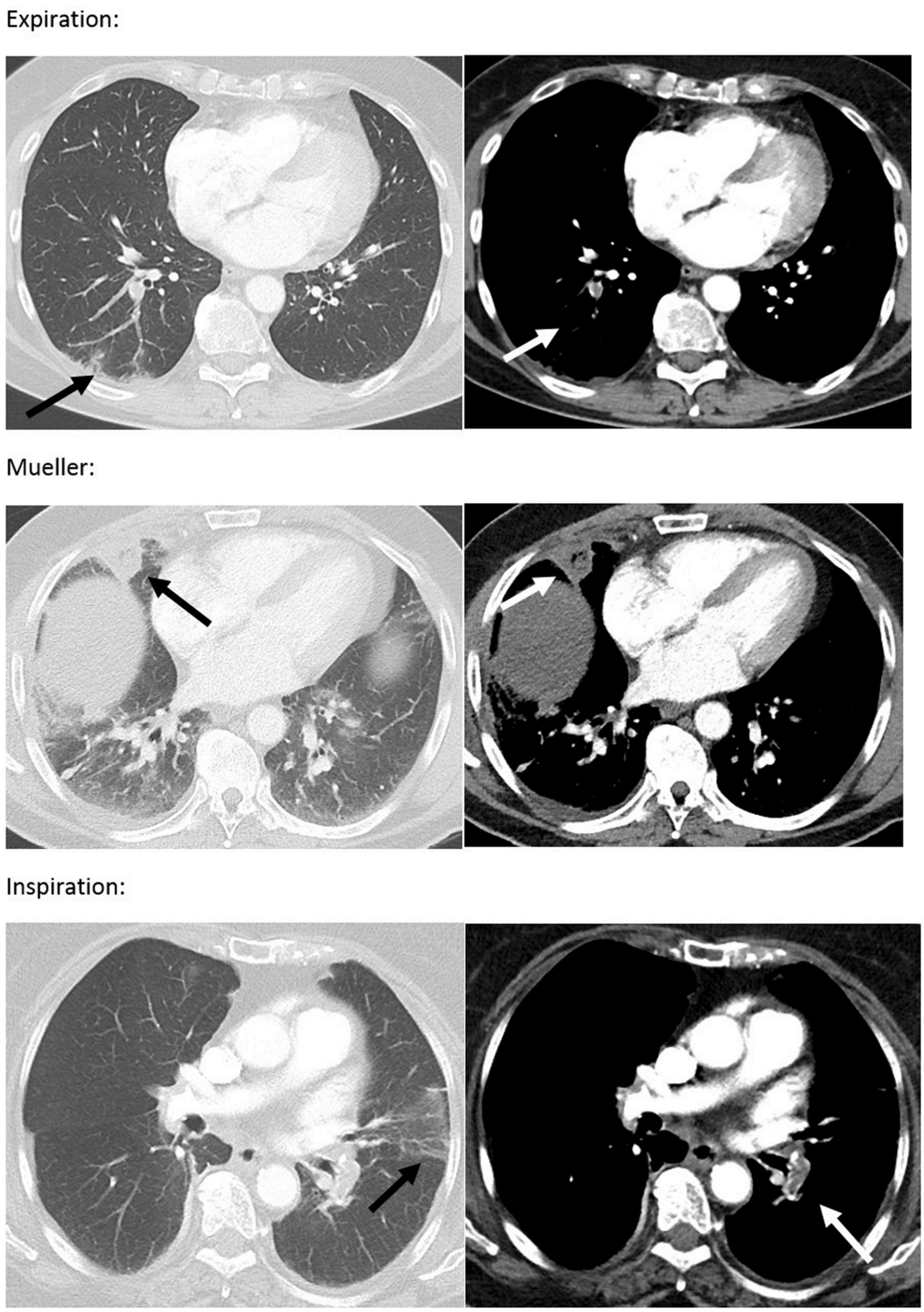

Fig. 5. Demonstration of PE and infarction in the different respiratory maneuvers. Arrows indicating the areal of infarction and the embolus.

To the best of our knowledge, our study is the first prospective, randomized and sufficiently powered clinical trial to evaluate differences between the three most promising breathing maneuvers (inspiration, expiration and Mueller) in patients with dyspnea and clinical suspicion of acute pulmonary embolism. Assessment was focused on vascular enhancement of the central and peripheral pulmonary arteries, and the lung parenchyma. We did not include Valsalva maneuver in the study, since this maneuver has been repeatedly reported as being inferior.

Most patients were able to perform the specific breathing maneuver after the individual training. Despite training, adherence to the Mueller maneuver was difficult for many patients, properly holding the device and performing the maneuver required a higher level of cooperation compared to the other maneuvers.

As a result, the device was repeatedly within in the examination field and generated artifacts. In contrast to Gutzeit et al. [6], we could not find an advantage of the Mueller maneuver in our cohort of dyspneic patients. A minimal attenuation 100 HU [10] in the central pulmonary arteries could be achieved with each breathing maneuver, providing representative data for clinical and statistical analysis. Our results suggest that pCTA during inspiration have less artifacts and higher attenuation levels. An explanation for this discrepancy to previously published data might be that expiratory breath hold is more difficult to perform when suffering from dyspnea.

It has been repeatedly demonstrated, that Valsalva maneuver with increased intrathoracic pressure leads to insufficient vascular

Table 1
Comparison of patient's characteristics: Descriptive characterization of the three groups in gender, weight, age and body mass index (BMI). No significant statistical difference between the groups was found.

	Breathing maneuver			
	Mueller (N = 46)	Inspiration (N = 51)	Expiration (N = 49)	p
Gender				$\chi^2 =$ 0.958
male	25	28	28	
female	21	23	21	
Weight in KG	83.22(SD 25.05)	75.94 (SD 19.96)	83.18 (SD 20.62)	0.165
Age in years	58.85 (SD 16.74)	63.61 (SD 15.22)	61.39 (SD 17.32)	0.365
BMI in kg/m^2	28.40 (SD 7.61)	25.69 (SD 5.54)	27.84 (SD 5.77)	0.085

enhancement, therefore technicians were alerted to train the patients to hold the breath in inspiration avoiding Valsalva's maneuver. During the one-year study period only one patient assigned to inspiratory breath-hold presumably performed Valsalva's maneuver despite adequate instruction.

We diagnosed PE in only 18.5 % of the patients, but this is in line with other reports (14 %–22 % [17]). Pleural effusion, tumor and pneumonic consolidation were the most frequent alternative diagnoses explaining the patients' symptoms, stressing the need for optimal assessment of the lung parenchyma.

It could be considered a limitation of our study that we did not apply automated tube voltage selection or low-kV scanning. We intentionally fixed the tube voltage at 120 kV in order to reduce variables of contrast enhancement other than the breathing maneuver.

A further limitation is the lack of correlation with clinical scores like the Wells score, but our primary goal was to test different breathing maneuvers and not the likelihood of a positive diagnosis. Quantitative measurement of the enhancement in the small peripheral vessels was not performed, because of the high risk of inadequate ROI placement due to the small vessel diameter. Therefore, we performed a subjective evaluation of the peripheral vessels with a quantitative ranking score.

5. Conclusion

Our results indicate that CTA during inspiratory breath-hold is the most beneficial breathing maneuver to consistently obtain high arterial enhancement, optimal parenchyma assessment and least artifacts. Besides that, it was the easiest maneuver for the patients, but training is necessary before data acquisition in order to avoid Valsalva maneuver with the risk of insufficient contrast enhancement.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

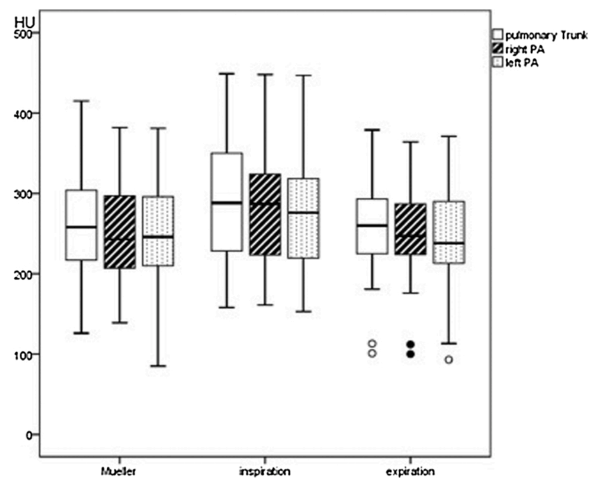

Fig. 6. Boxplots as graphical representations of the variability of the data. Boxplots with the distribution of the attenuation (HU) in the pulmonary trunk, the right and left PA in the three different breathing maneuvers.

Table 2
Radiodensity (HU) of the central parts of the pulmonary vessel system: Contrast density results of the pulmonary trunk, the right and left pulmonary artery in the three different breathing maneuvers. Reported values are estimated mean values (HU), standard deviation (SD), error of SD, 95 % confidence interval (CI), the Range with minimum and maximum values.

vessel	Breathing position	N	mean	SD	SD Error	95 % CI	Range	
Pulmonary trunk	Mueller	46	25,924	5824	859	241,94–276,53	136	429
	Inspiration	51	29,359	6984	978	273,95–313,23	195	460
	expiration	49	26,694	5729	818	25,048	115	376
Right pulmonary artery	Mueller	46	2,503,913	6129	904	232,19–268,59	119	378
	inspiration	51	28,886	6612	926	270,26–307,46	173	454
	expiration	49	25,747	5449	778	255,94–276,48	114	366
Left pulmonary artery	Mueller	46	24,465	6011	886	226,80–262,50	11,100	37,100
	Inspiration	51	28,031	6764	947	261,29–299,34	17,000	46,200
	expiration	49	25,196	5720	817	235,53–268,34	11,000	37,100

Table 3
Contrast density results of the central parts of the pulmonary vessel system: Contrast density results of the pulmonary trunk, the right and left pulmonary artery in the three different breathing maneuvers. Reported values are estimated mean differences between the breathing methods, error of standard deviation (SD), p-value and 95 % confidence interval (CI).

Vessel	Breathing method versus		Mean difference	SD Error	P value	95 % CI
Pulmonary trunk	Inspiration	Mueller	3435	1266	0022	3,79–64,91
		expiration	2665	1245	0098	−3,42–56,72
Right pulmonary artery	Inspiration	Mueller	3847	1238	0007	8,58–68,36
		expiration	3139	1218	0032	1,98–60,81
Left pulmonary artery	Inspiration	Mueller	3566	1259	0016	5,26–66,06
		expiration	2835	1238	0069	−1,56–58,27

Compliance with ethical standards

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.

Informed consent

The IRB at our institution approved this single center prospective randomized study. Before enrollement, each patient provided wirtten informed consent prior to inclusion.

The scientific guarantor of this publication is Dr. med. Panagiota Manava and Dr. med. univ. Maximilien Bruch.

Credit authorship contribution statement

Conceptualization, Supervision, Validation, Visualization: Manava, Galster, Lell. Data curation, formal analysis, Investigation, Methodology: Manava, Galster, Bruch, Schoen. Project administration: Manava, Galster, Lell, Ficker, Adamus. Writing: Manava, Lell.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

This research did not receive any specific grant from funding.

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