Feasibility of a Single Contrast Bolus High-Pitch Pulmonary CT Angiography Protocol Followed by Low-Dose Retrospectively ECG-Gated Cardiac CT in Patients with Suspected Pulmonary Embolism

Evaluation eines high pitch CT Pulmonalisangiografieprotokolls mit unmittelbar folgender niedrigdosis retrospektiv getriggerter Herz CT Spirale unter Verwendung eines einzigen Kontrastmittelbolus bei Patienten mit Verdacht auf Lungenarterienembolie

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ZUSAMMENFASSUNG

Einleitung Ziel dieser Studie war die Evaluierung eines high pitch CT Pulmonalis-Angiografie (CTPA) Untersuchungsprotokolls mit unmittelbar folgender niedrigdosis retrospektiv EKG getriggerter Herz CT Spirale unter Verwendung eines einzigen Kontrastmittel (KM) Bolus bei Patienten mit Verdacht auf eine akute Lungenembolie (LE) zur detaillierten Analyse der rechtsventrikulären Funktion.


Ergebnisse Die mittlere effektive Dosis lag bei 4,22 ± 2,05 mSv. Die höchsten Dichtewerte in der CTPA wurden im Truncus pulmonalis gemessen (442,01 ± 187,64), in der 4D-cCT in der Aorta descendens (560,59 ± 208,81). Analog dazu zeigten sich in der CTPA im Truncus pulmonalis (CNR = 12,43 ± 4,57; SNR = 15,14 ± 4,90) und in der 4D-cCT in der deszendierenden Aorta (CNR = 10,26 ± 5,57; SNR = 10,86 ± 5,17) das höchste CNR und SNR. Die LVEF lag bei 60,73 % ± 14,65 %, die RVEF bei 44,90 % ± 9,54 %. Der RVEF/LVEF Quotient lag bei 0,79 ± 0,29. Es zeigte sich für keinen Parameter ein signifikanter Unterschied zwischen der LE- und Nicht-LE-Gruppe.

Schlussfolgerungen Das vorgestellte CT Protokoll ermöglicht die Evaluation der RV Funktion bei Patienten mit akuter LE. Das Ziel künftiger Studien sollte der Vergleich zwischen EKG-synchronisierten und nicht synchronisierten Messungen sein im Hinblick auf einen potentiellen Mehrwert für die Risikostratifizierung von Patienten mit akuter LE.
Introduction

Mortality among patients with non-high-risk pulmonary embolism (PE) varies from 2% to 8% [1], depending on possibly existing right ventricular dysfunction (RVD). RVD is the main predictor of short-term mortality in patients with acute PE, leading to secondary hemodynamic instability [2]. Patients with acute RVD require intensive care unit monitoring and might benefit from early thrombolysis or invasive therapies [3]. Therefore, it is essential to assess RV function shortly after the diagnosis of PE. The current ESC guidelines (2014) recommend imaging techniques (computed tomography (CT), echocardiography) and cardiac laboratory biomarkers (Troponin I or T, brain-natriuretic peptide (BNP)) to assess the degree of RV strain. Biomarkers for RVD show a high negative predictive value (NPV) with a low positive predictive value (PPV) [4]. For risk stratification, biomarkers should be combined with CT or echocardiographic measurements [4]. One advantage of echocardiography is the possibility to monitor the clinical course and therapeutic success [5]. On the other hand, echocardiography might not be available 24/7 in every hospital and requires skilled examiners. Within this context, it has been demonstrated that patients with PE who are admitted on weekends have a significantly higher short-term mortality than patients admitted on weekdays [6].

Computed tomography pulmonary angiography (CTPA) signs of RVD, such as RV/left ventricular (LV) ratio > 0.9, are associated with an adverse outcome [7]. The main advantage of a CT-based assessment of RVD is that the data is already available after the diagnosis of PE. However, CTPA images are not ECG-synchronized and picture the heart at an accidental point during the R-R’ interval. This might lead to a possible over-/underestimation of the real RV load.

Several studies tried to solve this problem in the past few years. The potential benefit of additional cardiac ECG-synchronized imaging always weighed against the additive amount of contrast agent and radiation dose [8, 9]. With the introduction of ultra-high pitch imaging, CTPA studies can be performed in less than 1 second. These fast acquisition techniques open the field for additional cardiac ECG-synchronized imaging. The potential benefit of additional cardiac ECG-synchronized imaging always weighed against the additive amount of contrast agent and radiation dose [8, 9].
The aim of this study was to evaluate a high-pitch CTPA protocol that is subsequently followed by low-dose ECG-gated cardiac CT with a reduced tube current used for the assessment of RVD.

Materials and Methods

Patient population

The HIPAA-compliant study protocol, which is in accordance to the Declaration of Helsinki, was approved by our local ethics committee. Written informed consent was obtained from all patients following a full explanation of the purpose of the study as well as of the risks and discomforts associated with participation.

62 patients (33 female, age 65.1 ± 17.5 years) who presented in our emergency department with suspected PE were prospectively included in this study. All patients underwent CT imaging including high-pitch CTPA that was subsequently followed by a low-dose retrospectively ECG-gated functional cardiac examination (4D-cCT).

Age, preexisting conditions and risk factors for deep venous thrombosis or PE were recorded. Exclusion criteria were pregnancy, clinical instability and age < 18y. ▶ Table 1 summarizes the patients’ baseline characteristics.

CT protocol

A high-pitch CTPA examination that was subsequently followed by 4D-cCT was performed in all patients included in the study. Contrast enhancement was achieved by injecting a single contrast bolus of 80 cc (Iomeron 400, Bracco Imaging S.p.A., Milan, Italy) via an antecubital vein access followed by a saline flush of 30 cc, both at a flow rate of 4 ml/s. One bolus was used for both parts of the protocol (▶ Fig. 1).

55 examinations were performed on a 2nd generation 2 × 128 slice dual-source CT (DSCT) system (SOMATOM Definition Flash, Siemens Healthineers, Forchheim, Germany). The remaining 7 examinations were performed on a 3rd generation 2 × 192-slice DSCT scanner (SOMATOM Force, Siemens Healthineers, Forchheim, Germany).

Table 1

<table>
<thead>
<tr>
<th>Preexisting conditions</th>
<th>% of all patients</th>
<th>Number of patients with PE</th>
<th>Number of patients without PE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting DVT</td>
<td>11.7</td>
<td>5</td>
<td>2</td>
<td>0.0004*</td>
</tr>
<tr>
<td>CHF</td>
<td>38.3</td>
<td>3</td>
<td>20</td>
<td>1.0000</td>
</tr>
<tr>
<td>RHI (without preexisting PE)</td>
<td>20.0</td>
<td>0</td>
<td>12</td>
<td>0.1823</td>
</tr>
<tr>
<td>Cardiac decompensation (not PE-related)</td>
<td>18.3</td>
<td>0</td>
<td>11</td>
<td>0.1888</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8.3</td>
<td>1</td>
<td>4</td>
<td>0.5768</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>38.3</td>
<td>2</td>
<td>21</td>
<td>0.4598</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>3.3</td>
<td>1</td>
<td>1</td>
<td>0.2797</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>28.3</td>
<td>4</td>
<td>13</td>
<td>0.2564</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.0</td>
<td>4</td>
<td>8</td>
<td>0.0689</td>
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<tr>
<td>COPD</td>
<td>26.7</td>
<td>1</td>
<td>15</td>
<td>0.4215</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>48.3</td>
<td>5</td>
<td>24</td>
<td>0.7270</td>
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<tr>
<td>Arterial hypertension</td>
<td>61.7</td>
<td>6</td>
<td>31</td>
<td>1.0000</td>
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<tr>
<td>Nicotine abuse</td>
<td>23.3</td>
<td>1</td>
<td>13</td>
<td>0.6705</td>
</tr>
<tr>
<td>Malignoma</td>
<td>28.3</td>
<td>3</td>
<td>14</td>
<td>0.7035</td>
</tr>
<tr>
<td>Recent surgery (within 3 months)</td>
<td>11.7</td>
<td>1</td>
<td>6</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism, DVT = deep vein thrombosis, CHF = congestive heart failure, RHI = right heart insufficiency, COPD = chronic obstructive pulmonary disease.

PE = Lungenembolie, DVT = Tiefe Venenthrombose, CHF = Herzinsuffizienz, RHI = Rechtsherzinsuffizienz, COPD = Chronisch obstruktive Lungenkran- kung.
CT pulmonary angiography

The scan parameters for the 2nd generation DSCT system were as follows: 120 kV tube voltage, 80 mAs reference tube current using automated tube current modulation, pitch factor of 3, collimation of 128 × 0.6 mm, gantry rotation time of 0.28 s and reconstructed slice thickness of 1 mm. The scan parameters for the 3rd generation DSCT system were: 70 kV tube voltage, 140 mAs reference tube current using automated tube current modulation, pitch factor of 3, collimation of 192 × 0.6 mm, gantry rotation time of 0.25 s and reconstructed slice thickness of 1 mm.

Bolus tracking was used to define the onset of scanning (> 80 HU in the pulmonary trunk).

4D-cCT

Cardiac ECG-gated scanning started with a delay of 5 s after the end of the CTPA acquisition and was performed during inspiratory breath-hold. In contrast to standard retrospectively ECG-gated coronary CTA, the tube current of the ECG-gated tube current modulation was reduced by 80 % throughout the entire cardiac cycle without any tube current peak in order to solely evaluate cardiac function with a minimum radiation dose.

The scan parameters for the 2nd generation DSCT system were: 120 kV tube voltage, 50 mAs reference tube current using automated tube current modulation, pitch factor of 0.23, collimation of 128 × 0.6 mm, gantry rotation time of 0.28 s and reconstructed slice thickness of 1.5 mm. The scan parameters for the 3rd generation DSCT system were as follows: 70 kV tube voltage, 20 mAs reference tube current using automated tube current modulation, pitch factor of 0.38, collimation of 192 × 0.6 mm, gantry rotation time of 0.25 s and reconstructed slice thickness of 1.5 mm.

Image post-processing

For image reconstruction, iterative reconstruction algorithms were used (SAFIRE (Siemens Healthineers, Forchheim, Germany) for the 2nd generation DSCT system with a dedicated soft tissue kernel (I31f) and a lung kernel (I79f) for CTPA and an I26f kernel for 4D-cCT, ADMIRE (Siemens Healthineers, Forchheim, Germany) for the 3rd generation DSCT system with a Bv36 and Bv40 kernel for CTPA and a Bv40 kernel for 4D-cCT.

The 4D-cCT data was reconstructed in 5 % intervals throughout the cardiac cycle.

Measurements

CT examinations were analyzed by 2 radiologists (7 years and 2 years of CT imaging experience) using Osirix Pro (Version 5.0.2; Aycan, Würzburg, Germany). PE was diagnosed in the case of the presence of at least one filling defect of contrast material in the pulmonary artery tree on the CTPA study.

The volume CT dose index (CTDI vol) and dose length product (DLP) were recorded in all patients. To calculate the effective dose, the DLP was multiplied by a conversion coefficient (k) of 0.014 mSv/(mGy×cm) as recommended by the European Guidelines of Multislice Computed Tomography [10].
For the assessment of objective image quality, the attenuation was measured as Hounsfield units (HUs) within various regions of interest (ROIs). On CTPA, one ROI was set in each of the main pulmonary arteries, an apical sub-segmental branch of the right pulmonary artery, a basal sub-segmental branch of the left pulmonary artery and the autochthonous back muscles. On 4D-cCT, one ROI was set in each of the cardiac chambers (right atrium (RA), right ventricle (RV), left atrium (LA) and left ventricle (LV)) as well as the descending aorta and liver. These ROIs were used to subsequently calculate the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). The subjective image quality for CTPA and 4D-cCT was assessed by a board-certified radiologist with 10 years of cardiac CT imaging experience. Visualization of the ventricular cavities/pulmonary arteries and image noise were evaluated using a five-point Likert scale (a score of 1 indicated poor visualization/unacceptably high image noise; a score of 2 fair visualization/above-average image noise; a score of 3 moderate visualization/average image noise; a score of 4 good visualization/less than average image noise; and a score of 5 excellent visualization/minimal image noise), artifacts were evaluated using a four-point Likert scale (a score of 1 indicated no artifacts; a score of 2 slight artifacts; a score of 3 definite artifacts; and a score of 4 strong artifacts); and a score of 5 excellent). Ventricular function was assessed on the dynamic 4D-cCT images using a dedicated post-processing workstation (Syngo.Via VA30, Siemens Healthineers, Forchheim, Germany). Images were adjusted to a 2-chamber and 4-chamber view of the heart. End-systolic and end-diastolic volumes of both the right ventricle (RV) and left ventricle (LV) were measured and used to calculate the ejection fraction (EF). End-systole was defined as the smallest...
Correspondingly, end-diastole was defined as the point during the cardiac cycle at which the ventricle showed its largest dimension. For volumetric measurements, endocardial contours were drawn automatically. Papillary muscles were included in the ventricular cavity. If necessary, manual corrections of the automatically drawn contours were made.

After the measurement of the EF of both ventricles, the ratio of right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) (RVEF/LVEF) was calculated to rule out the influence of gender, age and body surface area on EF.

**Statistical analysis**

Statistical analysis was performed using JMP 11.0 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are presented as frequencies with percentages. To prove normal distribution of continuous variables, the Shapiro-Wilk test was used. If data were normally distributed, a two-tailed Student's t-test was used to compare two groups. Otherwise, the Mann-Whitney U-test was used. A p-value < 0.05 was considered statistically significant.

**Results**

**PE diagnosis**

A total of 62 CT studies were performed. Two patients were excluded from statistical analysis. One study was of non-diagnostic image quality because of insufficient contrast enhancement of the ventricular cavities – for an automated analysis as well as for manual assessment. The other study was performed in a patient with status post PE (one month ago) and so retrospectively did not fulfill the inclusion criteria. 60 CT studies remained for the data analysis.

**Radiation dose**

The mean effective dose was 4.22 mSv ± 2.05 mSv (3.72 mSv – 5.29 mSv), the mean overall DLP was 301.39 mGy×cm ± 146.71 mGy×cm (262.81 mGy×cm – 339.97 mGy×cm) and the mean overall CTDI vol was 18.23 mGy ± 8.76 mGy (15.92 mGy – 20.53 mGy). For additional dose parameters, see ▶ Table 2.

The chest and heart scan contributed similarly to the overall effective dose. There was a statistically significant difference between the 2nd and 3rd generation DSCT systems for all dose values except for the tube voltage and tube current on 4D-cCT (▶ Table 2).

**Image quality**

Attenuation measurements on the high-pitch CTPA images (▶ Table 3) showed the highest attenuation values in the main pulmonary artery followed by the apical and basal sub-segmental branches.

In the 4D-cCT images, the attenuation values were highest in the descending aorta followed by the left cardiac chambers (▶ Table 4). The RA and RV had the lowest attenuation values of all cardiac chambers. However, the mean attenuation within both atria was still above 400 HU, which was sufficient for the evaluation of cardiac function.

According to the attenuation values, the contrast-to-noise ratio and signal-to-noise ratio on CTPA showed the highest values.

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within the main pulmonary artery, followed by the left basal sub-segmental branch. The right apical sub-segmental branch showed the lowest CNR and SNR on CTPA images (Table 5).

On 4D-cCT images, the highest SNR and CNR could be measured in the descending aorta followed by the LV and LA. The lowest SNR and CNR appeared in the RV and RA (Table 5).

Assessment of the qualitative image quality (Table 5) revealed slightly better visualization for CTPA than for 4D-cCT (5 (3 – 5) vs. 4 (2 – 5)) with lower image noise (4 (3 – 5) vs. 3 (2 – 5)) and equal motion artifacts (both: 1 (1 – 3)). However, both parts of the protocol showed sufficient image quality for the assessment of pulmonary embolism and the evaluation of right ventricular function. Artifacts were mostly caused by implanted cardioverter defibrillators and pacemakers.

**RVEF, LVEF, RVEF/LVEF ratio**

The mean LVEF was 60.73 % ± 14.65 % (56.95 % – 64.52 %), and the mean RVEF was 44.90 % ± 9.54 % (42.44 % – 47.36 %). The mean RVEF/LVEF was 0.79 ± 0.29 (0.71 – 0.86). There was no significant difference between the PE and non-PE group for either of the parameters (Table 6).

**Discussion**

The aim of this study was to evaluate the feasibility of a novel high-pitch CTPA protocol followed by low-dose retrospectively ECG-gated cardiac CT for the assessment of RVD using a single contrast bolus. Our results demonstrate that the protocol is feasible without the use of an additional contrast bolus and allows a detailed analysis of cardiac function. In contrast to a standard retrospectively ECG-gated coronary CT protocol with a high radiation dose, the radiation dose of our protocol was significantly lower since we manually reduced the tube current of the ECG-dependent tube current modulation throughout the whole cardiac cycle.

Echocardiographic findings of RVD have long been reported to be associated with higher mortality rates [11]. Patients with RV hypokinesis on echocardiography showed a doubling of the mortality rate at 14 days compared to patients without RVD [11]. CT measurements of RV/LV ratios obtained on transverse sections and reconstructed 4-chamber view. Previous studies have reported a higher accuracy for the RV/LV ratio assessed on 4-chamber view images than on transverse sections compared with echocardiography [7]. RV enlargement on CT has been correlated with a 5-fold increase in the risk of death within 30 days [7]. There are previous studies that also assessed the additional value of ECG-synchronized measurements in patients with acute PE [8, 9]. Despite showing a potential benefit compared to standard CTPA measurements, the additional radiation dose and contrast agent did prevent a recommendation of ECG-synchronized protocols for routine clinical use. Our study showed a mean effective radiation dose of 4.22 mSv (1.91 mSv for cardiac scanning alone). In contrast, Dogan et al. reported a notably higher effective radiation dose of 3.0 – 4.2 mSv for cardiac scanning alone [9].

Due to the fast image acquisition of high-pitch CTPA in our study, it was possible to use only one 80-ml contrast material bolus for both parts of the protocol. During the functional cardiac examination, contrast medium was mostly concentrated in the left atrium (LA), LV and descending aorta (Table 4). However, there was still sufficient contrast material left within the right cardiac chambers to allow functional RV analysis. The CNR and SNR values for RV and LV were comparable to those published by Takx et al. in a study evaluating a prospectively ECG-triggered coronary CT angiography protocol with an 80 % dose reduction [12]. It has to be pointed out that two different scanner generations with
notable differences in radiation dose (and attenuation values) were used in our study. However, images of both scanners were of sufficient image quality to assess right ventricular function. The suggested protocol is also transferable to other high-end CT systems, even non-DSC systems that allow rapid thoracic CT of less than 2 s (e.g. CT systems with larger detector coverage instead of high-pitch imaging).

Using the remaining contrast medium for additional cardiac scanning allowed us to evaluate not only RV but also LV function.

In our study, we did not include echocardiography or cardiac MRI as a reference standard. It could be proven in previous studies that ECG-synchronized CT scanning is comparable to magnetic resonance imaging (MRI) in the evaluation of RV and LV function [13]. This also allowed the examination of differential diagnoses for dyspnea, such as cardiac decompensation, etc., in addition to PE confirmation/exclusion.

For the evaluation of right ventricular function, only the ejection fraction was assessed, without paying additional attention to regional wall motion abnormalities, since the aim of this study was simply to prove the feasibility of the proposed CT protocol. Over all patients, RVEF showed no statistically significant difference between PE and non-PE patients. This might be due to the fact that the non-PE group included 12 patients (23.5 %) with preexisting right heart insufficiency. RV function and the standard value for RVEF depend on age, gender and body surface area [14] and therefore can show significant variability. This also applies to LV function [15]. To rule out these influences, we calculated the ratio of RVEF and LVEF.

Our study has three main limitations, which have to be considered. First, we had a relatively small sample size – which was, however, adequate to assess the feasibility of our CT protocol. Second, we did not correlate CT findings of LV function with transthoracic echocardiography as a gold standard for the assessment of RV function in patients with acute PE. Third, there was no correlation of our results with clinical outcome, since this was merely a feasibility study, as already mentioned above. Thus, further studies have to evaluate the additional value of ECG-synchronized measurements with regard to their potential additional benefit in risk stratification and correlation with clinical outcome. It might be of additional value to compare end-systolic and end-diastolic parameters regarding their diagnostic accuracy for determining RVD in patients with acute PE.

### CLINICAL RELEVANCE OF THE STUDY

The novel CT protocol evaluated in this study allows the diagnosis of PE and detailed analysis of RV function at the same time. This might help with respect to rapid risk stratification in patients with acute PE, especially when echocardiography is not directly available. It shows good image quality and an acceptable radiation dose when compared to standard CTPA protocols.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### References


