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Original Article

The benefit of personalized hybrid SPECT/CT pulmonary imaging

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Abstract: Hybrid pulmonary imaging in the present day has seen a fusion of various uses of CT scans, including angiography (CTAG), diagnostic CT, low dose CT (LDCT), and perfusion or ventilation scintigraphy in tomographic or planar imaging. Determining the most effective individualized test for the complete diagnostics of patients with pulmonary symptoms for various groups of patients is a major issue. The aim of the present study was to assess the effectiveness of the implementation of hybrid imaging in current methods of nuclear medicine in differential diagnostics of pulmonary embolism (PE). 326 patients were examined for symptomatology of PE. Patients were initially examined with SPECT perfusion scintigraphy. SPECT finding without sub-segmental or segmental defects was considered unproven PE but the finding of more segments or sub-segments in various lung parts was considered nearly proven PE. In the case of unclear findings, LDCT was added and in the case of a higher suspicion of PE, a ventilation examination was applied. It was possible to determine 83% of patients with the occurrence or exclusion of PE only on the basis of the perfusion SPECT examination and an X-ray or LDCT. LDCT was determined with 26% of the patients. With 41% of them, the use of LDCT resulted in an alternative diagnosis, explaining perfusion abnormalities. The research proved that use of SPECT/LDCT for differential diagnosis of lung symptoms brings about improvement in the diagnosis of pulmonary embolism or the identification of other lung diseases when lung perfusion abnormalities are recorded.

Keywords: Pulmonary embolism, ventilation-perfusion scan, SPECT/CT, hybrid imaging

Introduction

Pulmonary embolism (PE) includes a characteristic blocking of the main artery of the lung or its branches due to foreign particles coming through the blood stream. PE is known to be the third most influential disease among cardiovascular diseases and venous thromboembolism is considered as the main cause of PE [1].

Diagnosis of pulmonary embolism ranks among the most important tasks for imaging methods with respect to the significant consequences of the disease including the risk of mortality, the negative and positive findings. The clinical symptoms of paraneoplastic pulmonary embolism can be covered up in the case of breast cancer patients with metastatic pulmonary disease or other complications of the disease and treatment (changes in the parenchyma after radiotherapy and fluidothorax in cardiac decompensation). Helical CT is considered as an efficient noninvasive diagnostic tool for PE in moderate to high risk condition. The other imaging techniques being incorporated are ventilation/perfusion (V/Q) scan, pulmonary arteriography, MRI and echocardiography [2]. CT angiography (CTA) is currently considered the best option for pulmonary vasculature imaging in PE suspected patients, as it provides sufficient visualization of pulmonary arteries to segmental level [3-5].

Multidetector CTA combined with venous-phase imaging (CTA-CTV) is also used for diagnosing acute PE and shows higher sensitivity than CTA alone [6]. CTA-CTV was found with 90 percent sensitivity and 95 percent specificity in the mentioned research. SPECT (V/Q) lung scans

are known to present high diagnostic accuracy and also facilitate advanced image-processing. The 3-dimensional aspects of SPECT data enable the objectified and automated analysis of lung scans, thus helping develop personalized imaging systems for PE. Studies have shown the automated diagnosis of PE with SPECT and image processing techniques is successful [7, 8]. The approach of diagnosing pulmonary embolism with hybrid SPECT/CT pulmonary imaging is considered to be revolutionary in most nuclear medicine departments due to the high sensitivity and specificity of this dual modality technique. SPECT/CT enables, during differential diagnosis of pulmonary embolism, among other things, the complete examination of the lungs with the assessment of parenchymal changes [9]. The combination of the scintigraphic examination and the morphologic method is currently the latest step in nuclear medicine development which, in the case of PE diagnosis, began with the planar ventilation-perfusion scan.

This historically significant shift in the diagnostic value of the lung scintigraphic examination was caused by the implementation of tomographic-SPECT perfusion imaging itself, later also SPECT ventilation imaging (APEs ^{99m}Tc DTPA or Technegas) and the assessment of the X-ray image at the same time. An extremely high negative predictive value was achieved for PE-98.5% [10] with a minimum of uncertain studies (3%). The sensitivity of the SPECT examination in contrast with common planar scintigraphy was increased to 97% (in comparison with 76%), the specificity to 91% (in comparison with 85%), and the diagnostic accuracy to 94% (in comparison with 81%). At the level of subsegments, the number of detected perfusion defects grew to 83%.

Involving hybrid gamma cameras with low dose CT, Gutte [11] demonstrated an improvement to the specificity of the ventilation-perfusion SPECT scan with a low dose CT in comparison with the ventilation-perfusion SPECT scan without a low dose CT from 88% to 100%, with the same sensitivity of examination for PE, 97%. The computed tomography pulmonary angiography (CTPA) itself (16 slice CT) also had a specificity of 100% but the sensitivity was only 68%.

The demonstrated significant benefit of low dose CT has led to thinking about the possible simplification of ventilation-perfusion scintigraphy. It has been shown, however, that if the ventilation examination was omitted, the perfusion SPECT/low dose CT (sensitivity 91-96%, specificity 83%-94%) is better than the planar ventilation-perfusion SPECT scan but worse than the tomographic ventilation-perfusion SPECT scan (a false positive in 17%) [12-14].

In hybrid pulmonary imaging the various examinations of the CT including angiography (CTPA), diagnostic CT, low dose CT (LDCT), and perfusion or perfusion-ventilation scintigraphy in tomographic or planar scan are combined. The routine combination of the ventilation-perfusion SPECT scan with low dose CT or CTPA for the exact diagnosis of pulmonary embolism is connected, however, with a logistic, economic and radiation burden. It is therefore of ongoing concern to find the most effective local test for the complete diagnosis of patients with pulmonary symptoms for various groups of patients.

The aim of the study was to assess the effectiveness of the implementation of hybrid imaging in the current methods of nuclear medicine in differential diagnosis of pulmonary embolism amongst patients without a known tumor and with patients with breast carcinoma, with respect to the diagnosis of other diseases.

Materials and methods

Patients

326 patients, including 24 patients with breast carcinoma, were examined for a different degree of symptomatology of thromboembolic disease in 2014 (from low risk to high risk patients). The group was characterized by an average age of 65 (±17.5, from 19 to 95) and included 199 women (61%). The group of 24 patients with breast carcinoma was characterized by an average age of 66 (±13.2, from 31 to 87), with 22 women (92%), and the group of 302 patients without breast carcinoma by an age of 64.9 (±17.9, from 19 to 95), with 177 (58%) women. The patients were monitored for at least one year.

Data acquisition

All patients were scanned by Anyscan® SPECT/CT system (dual head cameras, 16-slice CT, Mediso Ltd., Budapest, Hungary). Perfusion

SPECT was mostly performed 5-10 minutes after the injection of 150-200 MBq ^{99m}Tc- macro aggregated albumins (^{99m}Tc-MAA). Ventilation SPECT was delivered after inhalation of a dose up to 500 MBq ^{99m}Tc DTPA aerosol from APE® device (M.N.T. Kwint International, Holland)-particles were declared less than 0.3 micrometer. Both SPECT datasets were obtained with 30 projections per head over 180°, using 6° angular sampling, a 128 × 128 matrix, and 55 s per step, with the patient supine, LEHR collimator. Data were processed by using iterative reconstruction (MOSEM, without attenuation correction). CT was performed in immediate sequence with SPECT (120 kV, 100 mAs/slice, 500 mm FOV, collimation 20 mm (16 × 1.25 mm), 512 × 512 matrix, 2.5 mm/slice, rotation time 1 s, pitch 1).

Examination method

Thromboembolic disease was excluded on the basis of SPECT perfusion scintigraphy without typical perfusion defects (see the demonstrated high negative predictive value of perfusion SPECT scintigraphy in the introduction). Thromboembolic disease was, in contrast, diagnosed on the basis of typical multiple segmental and sub-segmental perfusion defects in various localizations without parenchymal changes. We chose (based on the above-mentioned analysis in the introduction) the combination of tomographic ventilation and perfusion scanning with a low dose CT as the gold standard. Parenchymal changes were assessed in an entry X-ray image and a low dose CT of lungs was indicated in case of an atypical perfusion without corresponding X-ray changes.

The main clinical reason for the examination with imaging methods was the recording. This was followed by a string of personalized examinations according to the algorithm: 1) pulmonary X-ray imaging with perfusion SPECT, 2) according to the finding of atypical perfusions without X-ray corresponding changes low dose CT was applied, 3) in case of an uncertain finding SPECT-ventilation imaging was added.

Data analysis

We reviewed all image data SPECT with or without LDCT scans done on patients referred to the Department of Nuclear Medicine in 2014 for suspected PE. Demographic and clinical information was obtained from interviews or from the hospital information system. We recorded presenting symptoms, D-dimers value and ECG changes and final clinical diagnosis given by the attending physician. Twelve-month follow-up status was ascertained from the hospital information system or from a control of the SPECT/CT study.

V/Q SPECT and LDCT were reported by two experienced nuclear medicine physicians with respect to clinical data, one radiologist blinded only to the LDCT scan, and classified by consensus as positive or negative for PE using predefined criteria (SPECT finding without sub-segmental or segmental defects was considered unproven PE but the finding of more segments or sub-segments in various lung parts was considered nearly proven PE. In the case of unclear findings, low dose CT was added for pulmonary abnormalities exclusion. In the case of unclear findings after LDCT scan a ventilation examination was applied. PE was diagnosed in the presence of >50% perfusion-ventilation mismatch in an anatomical segment or 2 regions of perfusion-ventilation mismatch regardless of size).

Twelve-month follow-up was used as a control. The diagnosis of PE was accepted if the result from SPECT/CT examination was PE. No other (gold) standard test was used for verification. The reference diagnosis was not PE if the final physician diagnosis was not PE and there was no occurrence of PE during 12 months.

Statistical analysis

Data were analyzed on the patient level in relation to the breast cancer subgroup. The effectiveness of the examination algorithm in terms of percentage of examinations or their combination success for both PE diagnosis and PE exclusion was calculated after each step from the increment of positive and negative findings in comparison with total number of patients. We did not calculate sensitivity, specificity or predictive values of the combination of using imaging methods due to the patient-guided algorithm and different frequency of imaging modalities.

Results

The main clinical reasons for the examination and the frequency of clinical symptoms in the

Table 1. The list of the main symptoms amongst the patients examined for PE suspicion (also more symptoms with one patient)

Number of patients	Symptoms	Dyspnea in %	Thoralgy in %	Palpitation in %	Collapse in %	Trombosis in %	ECG changes in %
All patients							
302	Without BC	52	24	17	20	14	15
24	With BC	58	33	25	8	17	0
Patients with PE							
46	Without BC	48	12	4	8	40	20
4	With BC	50	25	25	0	50	0

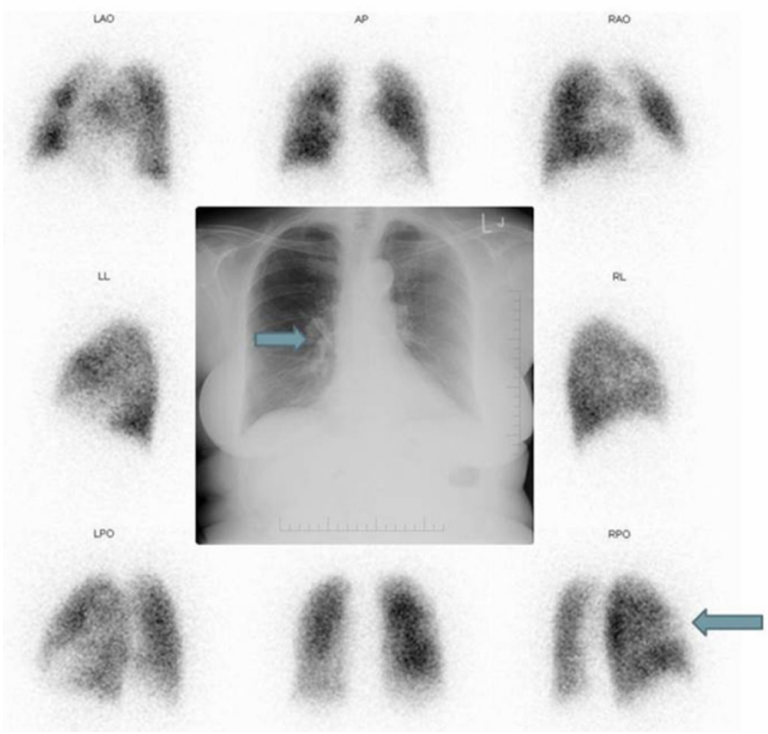

Figure 1. A basic perfusion scintigraphy with an X-ray image. Representative perfusion images (anterior posterior and right posterior oblique-arrow) show the perfusion reduction in the right lower/mid-zone to correspond with the X-ray abnormality (arrow). AP, Anterior posterior projection; PA, Posterior anterior; LPO, Left posterior oblique; RPO, Right posterior oblique; RL, Right lateral; LL, Left lateral; LAO, Left anterior oblique; RAO, Right anterior oblique.

demonstrated PE are summarized in **Table 1**. Dyspnea and chest pain appeared amongst the patients with breast carcinoma during the introduction of the examination, which are also two leading symptoms in metastatic lung disease. Dyspnea and chest pain and pre-collapse symptoms were also evident in the patients without known carcinoma involvement. **Figure 1** shows a basic perfusion scintigraphy with an X-ray image and **Figure 2** shows SPECT perfusion assessment with the same patient.

Fusion SPECT perfusion with a low dose CT with the above mentioned patient is shown in **Figure 3**. **Table 2** contains the data concerning the success in the personalized combination of imaging techniques for obtaining the final diagnosis. The diagnostic value of SPECT perfusion scintigraphy with an X-ray image for PE excluding is similar for the group of patients with or without breast carcinoma. The effectiveness of the personalized algorithm of the examination for the entire group is also evident from the chart in **Figure 4**. It is apparent that the occurrence or exclusion of PE could be decided with 83% of the patients only on the basis of perfusion SPECT imaging and an X-ray or low dose CT. 13 patients were examined during the follow-up interval for the relapse of pulmonary symptomatology in the group of 276 patients without pulmonary embolism. Pulmonary embolization was not diagnosed for any of them.

In the monitored group, a low dose CT was carried out with 26% patients. With 41% of them (11% of all the patients) the use of low dose CT resulted in an alternative diagnosis explaining perfusion abnormalities.

With breast cancer patients the participation of the indicated addition of low dose CT with a

Figure 2. SPECT helps to characterise the shape of the perfusion reduction region from the planar scans. Representative perfusion SPECT images (3D, transaxial, coronal and sagittal) show sub-segmental perfusion defect in the case shown in **Figure 1** as well.

high information value about the findings of other diseases, including significant metastatic pulmonary involvement, pneumonia and fluidothorax was higher (at 80% of the indicated CT). The share of the diagnosis of non-embolic etiology in the entire group is shown in **Figure 5**.

Discussion

This study provides information about the success of imaging method combination available in daily clinical practice for diagnosis of PE from low to high clinical suspicion according to main recorded symptoms. The majority of patients (70%) were identified as PE negative with relative simple imaging methods without a special patient preparation and without possible side effects of diagnostic methods.

The reference method for diagnosis of PE was, based on the results of new studies, the combined examination of tomographic perfusion, tomographic ventilation and low dose CT (sensitivity 97%, specificity 100%). Due to logistic and economic reasons and radio hygienic aspects a decision was made to carry out the individualized indication of imaging methods based on the results of a basic perfusion scintigraphy with a chest X-ray image.

There are some limitations within this study. The main limitation relates to reference diagnosis. The reference method (combination V/Q SPECT and low dose CT) was not used in all patients. The follow up is sufficient standard for clinical diagnosis but, in the case of very small PE, can be inaccurate especially when the cause of PE has passed away. There are 5% unclarified perfusion abnormalities (non-segmental or with hypoventilation) after full diagnostic protocol-of course they can be caused by small (originally sub-segmental) old PE. However, no serious disease was detected in follow up interval in this group. The follow up was also limited for those patients without PE (negative results of imaging methods) who visited our regional hospital (the only one for the region) with serious health problems or for control during the past 12 months. However, we have recorded the possibility that a Q SPECT/low dose CT scan can overestimate diagnosis of PE and the high predictive negative value of Q SPECT.

The group of breast carcinoma patients with clinical symptoms of pulmonary involvement of paraneoplastic etiology (thromboembolic disease or metastatic etiology) examined by hybrid SPECT/CT is still not large enough. It is also evident with a smaller group of patients that it is necessary to count with both significant causes of difficulties in the case of pulmonary symptoms. It is therefore advantageous to carry out the perfusion SPECT/low dose CT, completed with ventilation SPECT in case of the suspicion of pulmonary embolism. Another possible use of hybrid imaging of the lungs with regards to

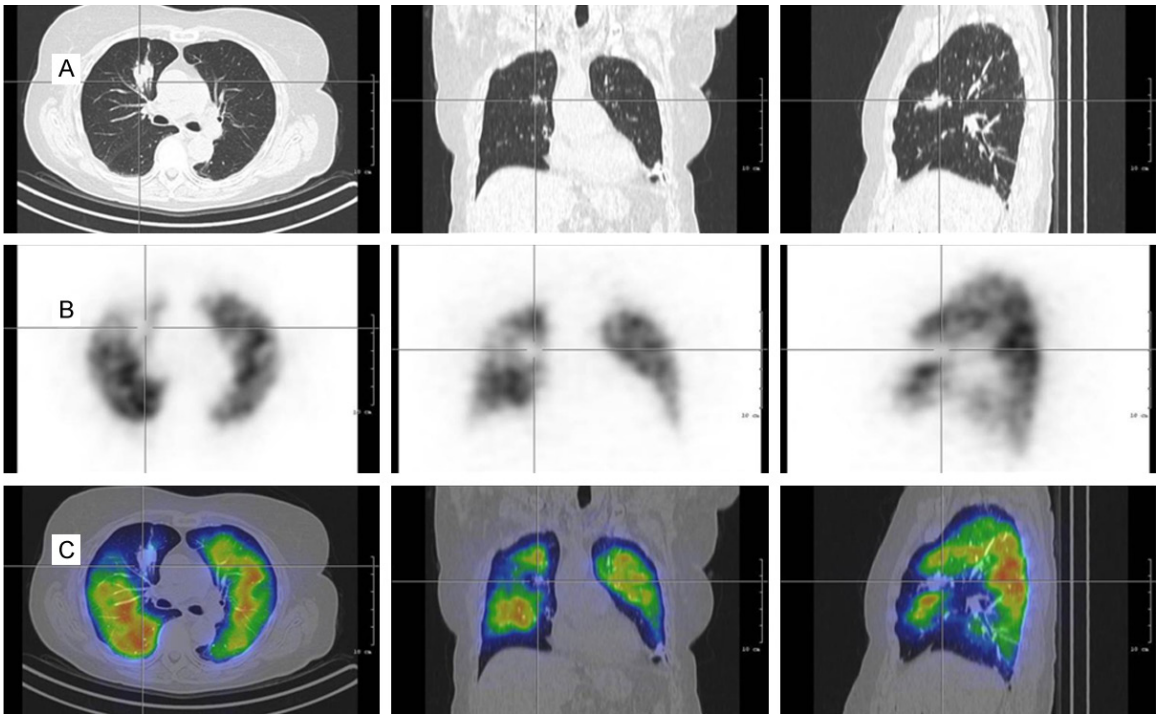

Figure 3. CT scan (line A-transaxial, coronal and sagittal slice) helps to characterize the cause of SPECT perfusion abnormalities (line B). The fused SPECT/CT images (line C) show the perfusion defect to correspond with parenchymal consolidation in this case (shown in **Figures 1** and **2** as well). The perfusion defect does not correspond to pulmonary embolism but corresponds to parenchymal changes.

Table 2. Comparison of the effectiveness of the examination algorithm amongst all patients and based on the breast carcinoma appearance

	All patients	In %	Patients without breast carcinoma	In %	Patients with breast carcinoma	In %
The number of patients	326	100	302	100	24	100
Negative for PE after perfusion scintigraphy and X-ray	227	70	209	69	18	75
The number of CT examinations	86	26	76	25	10	42
PE after perfusion scintigraphy in combination with X-ray	44	13	40	13	4	17
PE after perfusion and ventilation scintigraphy and CT	50	15	46	15	4	17
Another diagnosis after CT	35	11	27	9	8	33
Another diagnosis after CT on the number of realized CT	35	41	27	36	8	80

breast carcinoma is the possibility of a parallel assessment of the chest skeleton or hepatic parenchyma which is the issue of this study.

Low dose CT scans showed an alternative diagnosis to PE in 11% of exanimated patients without breast cancer and in 33% of breast cancer patients in our study. Le Roux 2015 [15] refers 24% of alternative diagnoses in retrospective analyses of 393 patients. Nevertheless, the incremental value of SPECT/CT device for alternative diagnosis can be probably dependent on the composition of patients in a group, and so further investigation is necessary.

The adjusted examination algorithm of perfusion SPECT with X-ray-low dose CT-ventilation SPECT is not necessarily available or optimal in every department. A number of medical facilities also prefer CTPA as the most frequent method. The diagnostic process is therefore dependent on regional conditions with respect

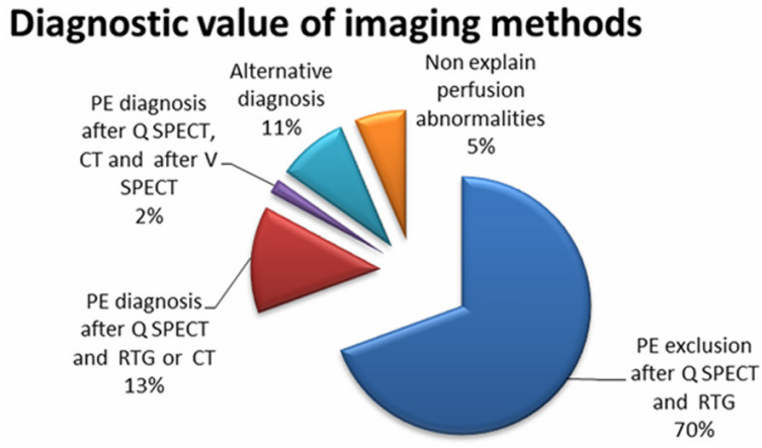

Figure 4. The effectiveness of the single steps of the algorithm for the use of imaging methods for differential diagnosis of pulmonary symptomatology in the entire group of patients. The exclusion of PE could be decided with 70% of the patients only on the basis of perfusion SPECT imaging and an X-ray. The occurrence of PE could be decided with 13% of the patients only on the basis of perfusion SPECT imaging and an X-ray or low dose CT. The V SPECT showed incremental value for diagnosis of PE in 2% after Q SPECT and CT examinations. PE, Pulmonary embolism; Q SPECT, Perfusion SPECT; V SPECT, Ventilation SPECT; RTG, Chest X-ray.

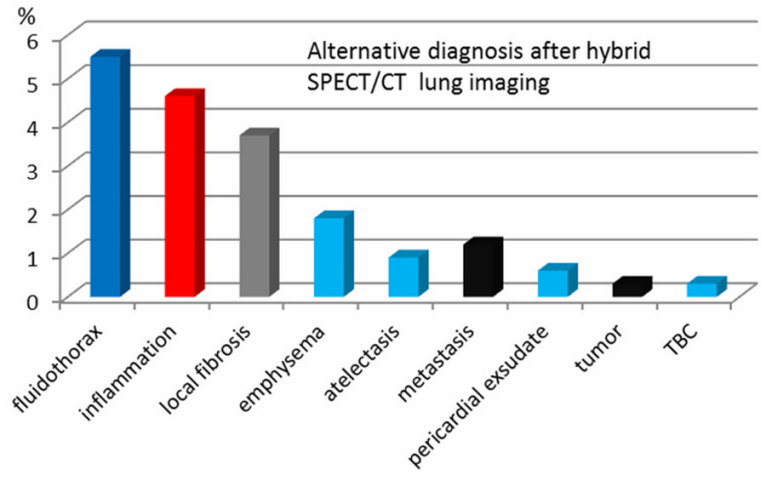

Figure 5. The alternative diagnosis after hybrid SPECT/CT lung imaging. Fluidothorax and inflammation were the most frequent diagnoses of non-embolic etiology with therapeutic consequences. Tumors or significant metastatic pulmonary involvement were very important diagnostic results of the hybrid SPECT/CT examination.

to imaging equipment and should be optimized to avoid excessive costs and also excessive irradiation of patients.

Conclusion

Hybrid imaging techniques have increased the potentials of tools and approaches available for imaging complex diseases. The present study concludes that use of SPECT/low dose CT for differential diagnosis of lung symptoms brings about improvement in the diagnosis of pulmonary embolism or the identification of other lung diseases to a significant number of patients when lung perfusion abnormalities are recorded. The fused examination of tomographic perfusion, tomographic ventilation and low dose CT is successfully demonstrated to diagnose PE among the target patient group. The presented approach paves the path for further successful demonstration of imaging in diagnosis of diseases.

The perfusion SPECT in combination with X-ray examination is very efficient for the exclusion of pulmonary embolism as an initial method. Use of the hybrid perfusion and ventilation SPECT/CT pulmonary imaging can be optimized according to the results of initial diagnostic methods to avoid excessive costs and also excessive irradiation of patients.

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