Lung Scintigraphy in Differential Diagnosis of Peripheral Lung Cancer and Community-Acquired Pneumonia

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Abstract. Ventilation/perfusion lung scintigraphy was performed in 39 patients with verified diagnosis of community-acquired pneumonia (CAP) and in 14 patients with peripheral lung cancer. Ventilation/perfusion ratio, apical-basal gradients of ventilation (U/L(V)) and lung perfusion (U/L(P)), and alveolar capillary permeability of radionuclide aerosol were determined based on scintigraphy data. The study demonstrated that main signs of CAP were increases in ventilation/perfusion ratio, perfusion and ventilation gradient on a side of the diseased lung, and two-side increase in alveolar capillary permeability rate for radionuclide aerosol. Unlike this, scintigraphic signs of peripheral lung cancer comprise an increase in ventilation/perfusion ratio over 1.0 on a side of the diseased lung with its simultaneous decrease on a contralateral side, normal values of perfusion and ventilation gradients of both lungs, and delayed alveolar capillary clearance in the diseased lung compared with the intact lung.

Keywords: ventilation-perfusion lung scintigraphy, alveolar capillary permeability, peripheral lung cancer, community-acquired pneumonia

INTRODUCTION

Morbidity rate of community-acquired pneumonia (CAP) in Russia ranges from 14‰ to 15‰ and annual number of sufferers exceeds 1.5 million people [1]. Modern diagnostics of this disease is a relevant problem of pulmonology [2]. Main cause of challenges consists in similarity of clinical presentation of CAP and other diseases manifesting with development of infiltrative processes in the lungs (malignant neoplasms, infiltrative pulmonary tuberculosis, pulmonary embolism, etc.) [3–6]. The process for developing a differential diagnosis between CAP and peripheral lung cancer is associated with particular difficulties [3]. There is evidence that at least 15% of all oncological morbidity accounts for lung cancer. Moreover, the number of patients suffering from this disease increases by 3.5% annually and the efficacy of comprehensive treatment of pulmonary neoplasms directly depends on the timing of their detection [7].

Unfortunately, 60% to 90% of initial patients with lung cancer undergo wrongful treatment for pneumonia, tuberculosis, and some other diseases [4, 6]. The causes of late diagnosis of lung cancer generally comprise symptom non-specificity resulting in high likelihood of false negative results of chest X-ray examination [4].

As known, X-ray methods mainly characterize morphological changes in the lungs. Due to this, radionuclide methods of study are of special interest for clinicians because they allow for evaluating not only anatomical structures, but also functional features of the pathological process in respiratory organs [5, 8, 9].

Radionuclide pulmonary studies proved their diagnostic value in pulmonary embolism and in nonspecific acute and chronic lung diseases [2, 5, 10]. Noninvasiveness, relatively low radiation exposure, convenience for patients, and comparative simplicity of the procedure allow for administering this study even at an outpatient stage [11].

Physics of Cancer: Interdisciplinary Problems and Clinical Applications (PC'16)
AIP Conf. Proc. 1760, 020037-1–020037-5; doi: 10.1063/1.4960256
Published by AIP Publishing. 978-0-7354-1418-1/$30.00

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The weight of evidence suggests that ventilation/perfusion scintigraphy may be considered an essential approach for acquiring additional information in establishing the differential diagnosis at a stage of infiltrative changes in pulmonary parenchyma in CAP and in peripheral lung cancer [5, 8, 9].

The aim of this study was to elucidate new capabilities of ventilation/perfusion scintigraphy in differential diagnosis of CAP and peripheral lung cancer.

MATERIALS AND METHODS

The study comprised 53 men with pulmonary infiltrates. Patients suffering from CAP of different localizations were assigned to group 1 (mean age of 35.4 ± 6.8 years, $n = 39$). Patients with verified diagnosis of peripheral lung cancer were assigned to group 2 (mean age of 56.5 ± 3.2 years, $n = 14$). Patients of group 1 were non-smokers; patients of group 2 were smokers. Consistently, control group ($n = 20$) comprised healthy volunteers including 10 non-smokers and 10 smokers of similar age and gender. This design of control group was based on the fact that smoking significantly affects alveolar capillary permeability (ACP), one of the most essential scintigraphic parameters of lung parenchyma [9].

All subjects underwent ventilation/perfusion lung scintigraphy examination. Scintigraphy studies were performed using emission computed tomography system with rotating dual head gamma-camera (Forte, Philips). Images were recorded to 128×128 matrix on specialized computer. Acquired scintigrams were processed using application software package SCINTI (NPO HELMOS, Russia). Initially, ventilation lung scintigraphy was performed; then, perfusion lung scintigraphy was conducted. All radionuclide studies were approved by the local ethics committee of the authors' institute; informed consent was received from all patients.

Technetium-99m (99mTc)-labeled macroaggregated human serum albumin was used as a radiopharmaceutical in perfusion lung scintigraphy. The studies were performed in four standard projections 5 min after the injection in sitting patients. Scintigram registration was done in static regime and lasted until accumulation of 300,000 counts per each position. Based on lung perfusion scintigraphy data, lung shape and sizes, radiopharmaceutical distribution homogeneity, presence of perfusion defects, and percentage of radiopharmaceutical accumulation by an individual lung were determined.

Lung ventilation scintigraphy was performed immediately after aerosol inhalation using ^{99m}Tc-labeled diethylenetriamine pentaacetate (DTPA). To prepare radioactive aerosol, 3 mL of the radiopharmaceutical with specific activity of 74-111 MBq were placed in a nebulizer. Inhalation mixture was supplied under pressure of 0.5–0.7 MPa. Scintigraphic images were registered in posterior frontal projection (POST) at 1 min after inhalation and, then, in anterior frontal (ANT) and lateral projections (LL 90°, RL 90°). At 10 and 30 min after finishing radiopharmaceutical inhalation, static lung scintigraphy was repeated only in posterior frontal. Exposure time was 2 min for each projection.

After completing the study, visual analysis of scintigraphic images was performed aimed at detection of ventilation defects in radiopharmaceutical accumulation. To calculate percentage of agent accumulation by each individual lung, mathematical analysis of ventilation scintigrams was performed. Alveolar capillary permeability was assessed by original technique developed by us [9, 10].

Acquired data were statistically processed by using STATISTICA 6.0 software for Windows. Quantitative parameters are presented as X ± m. Most numerical variables were not normally distributed. Therefore, significance of differences for independent data sets was determined based on Mann–Whitney U test (or Wilcoxon test in case of dependent data sets). Values were considered statistically significant when $P < 0.05$.

RESULTS AND DISCUSSION

Results of the study showed that main parameters of lung ventilation/perfusion scintigraphy in healthy smokers and non-smokers were comparable and did not significantly differ between each other both for right and left lungs. Taking this into account, specified parameters were calculated for both lungs together. Depending on the fact of smoking, differences were observed only in ACP (Table 1). In smokers, this parameter was significantly higher both at 10 and 30 min of the study. This observation agrees with literature data. Similar changes in ACP were registered by G.L. Hungon et al. (1984) and Kanazava et al. (1993) [12–14] when they performed lung ventilation scintigraphy studies. Increase in the clearance rate of unhalted radiopharmaceutical can be explained by toxic effects of tobacco smoke on alveolar-capillary membrane.

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TABLE 1. Parameters of ventilation/perfusion lung scintigraphy in healthy non-smokers and smokers ($X \pm m$, p)

Parameters	Healthy non-smokers* (n = 10)	Healthy smokers* (n = 10)	p
V/Q	0.98 ± 0.03	0.96 ± 0.03	0.7
$U/L(P)$	0.68 ± 0.03	0.64 ± 0.05	0.17
$U/L(V)$	0.66 ± 0.04	0.68 ± 0.08	0.49
ACP, % (10 min)	10.6 ± 2.9	17.1 ± 3.8	0.03
ACP, % (30 min)	21.3 ± 4.3	37.5 ± 5.2	0.004

V/Q—ventilation perfusion ratio, $U/L(P)$—apical-basal ventilation gradient, $U/L(P)$—apical-basal perfusion gradient, ACP—alveolar capillary permeability, *—values are presented for both lungs together in control group, p—significance value for intergroup differences.

In patients with CAP, ventilation/perfusion ratio (V/Q) was elevated in the diseased lung compared with that in the control group by about 8% (p = 0.01) (Table 2). In the healthy lung, V/Q did not exceed 1.0 (Table 2). Perfusion and ventilation gradients in the lung with infiltrate were significantly higher than corresponding values in control individuals (Table 2). The values of alveolar capillary permeability in both the diseased and intact lungs of CAP individuals significantly exceeded the control values.

Increase in ventilation/perfusion ratio in the diseased lung of CAP patients suggested predominance of vasoconstrictor mechanism in the development of alveolar hypoxia. Significant increases in the apical-basal perfusion ($U/L(P)$) and ventilation ($U/L(V)$) gradients in the diseased lung as well as the accelerated ACP represented a compensatory reaction of alveolar capillary system in order to prevent the development of arterial hypoxemia in such patients [9, 10].

In patients of group 2 with peripheral lung cancer, V/Q ratio on a side of the diseased lung was significantly higher compared with the corresponding value in healthy smokers (Table 3). This observation suggests the predominance of microcirculatory disorders over ventilation disorders. At the contralateral side (reference intact lung), the V/Q ratio was decreased suggesting the compensatory vasodilation of pulmonary vessels. Alveolar capillary permeability in the diseased lung was attenuated compared with the corresponding value in control individuals (Table 3). Observed changes also represent one of the mechanisms preventing the development of arterial hypoxemia due to an increase in blood oxygenation time in the diseased lung.

The results of a comparative analysis of scintigraphy studies in patients with CAP and peripheral lung cancer are presented in Table 4. As can be seen from Table 4, main differences were observed in the changes of ventilation-perfusion matching and alveolar capillary permeability on a side of the diseased lung. For example, in patients with peripheral lung cancer, V/Q ratio was significantly higher on a side of the diseased lung compared with the corresponding value in CAP patients. Besides, apical-basal perfusion gradient ($U/L(P)$) was decreased and alveolar capillary permeability was attenuated suggesting more severe microcirculatory abnormalities in patients with lung cancer.

TABLE 2. Parameters of ventilation/perfusion lung scintigraphy in patients with community-acquired pneumonia and in healthy non-smokers ($X \pm m$, p)

Parameters for diseased and intact lungs		CAP patients (n = 39)	Healthy non-smokers* (n = 10)	p
V/Q	Diseased	1.06 ± 0.01	0.98 ± 0.03	0.04
	Intact	0.97 ± 0.03	0.98 ± 0.03	0.6
$U/L(P)$	Diseased	0.80 ± 0.02	0.68 ± 0.03	0.04
	Intact	0.69 ± 0.02	0.68 ± 0.03	0.93
$U/L(V)$	Diseased	0.77 ± 0.03	0.66 ± 0.04	0.05
	Intact	0.69 ± 0.02	0.66 ± 0.04	0.41
ACP, % (10 min)	Diseased	20.37 ± 1.41	10.6 ± 2.9	0.001
	Intact	18.11 ± 1.34	10.6 ± 2.9	0.006
ACP, % (30 min)	Diseased	35.86 ± 1.73	21.3 ± 4.3	0.001
	Intact	32.00 ± 1.71	21.3 ± 4.3	0.001

V/Q—ventilation perfusion ratio, $U/L(P)$—apical-basal ventilation gradient, $U/L(P)$—apical-basal perfusion gradient, ACP—alveolar capillary permeability, CAP—community-acquired pneumonia, *—values are presented for both lungs together in control group, p—significance value for intergroup differences.

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TABLE 3. Parameters of ventilation/perfusion lung scintigraphy in patients with peripheral lung cancer and in healthy non-smokers ($X \pm m$, p)

Parameters for diseased and intact lungs		PLC patients (n = 14)	Healthy non-smokers* (n = 10)	p
V/Q	Diseased	1.13 ± 0.02	0.96 ± 0.03	0.001
	Intact	0.88 ± 0.02	0.96 ± 0.03	0.03
$U/L(P)$	Diseased	0.53 ± 0.08	0.64 ± 0.05	0.5
	Intact	0.57 ± 0.09	0.64 ± 0.05	0.35
$U/L(V)$	Diseased	0.84 ± 0.11	0.68 ± 0.08	0.054
	Intact	0.71 ± 0.05	0.68 ± 0.08	0.506
ACP, % (10 min)	Diseased	14.39 ± 2.84	17.1 ± 3.8	0.508
	Intact	14.00 ± 2.98	17.1 ± 3.8	0.691
ACP, % (30 min)	Diseased	24.54 ± 3.67	37.5 ± 5.2	0.006
	Intact	33.23 ± 3.14	37.5 ± 5.2	0.7

V/Q—ventilation perfusion ratio, $U/L(P)$—apical-basal ventilation gradient, $U/L(P)$—apical-basal perfusion gradient, ACP—alveolar capillary permeability, PLC—peripheral lung cancer, *—values are presented for both lungs together in control group, p—significance value for intergroup differences.

In summary, presented data suggest that the assessment of main parameters of lung ventilation/perfusion scintigraphy allows for extending the capabilities of differential diagnosis of CAP and peripheral ling cancer.

CONCLUSION

Main scintigraphic signs of CAP comprise increase in ventilation/perfusion ratio, perfusion gradient, and ventilation gradient on a side of the diseased lung compared with the corresponding values on the contralateral side as well as two-sided increase in ACP.

Scintigraphic signs differentiating peripheral lung cancer from CAP are as follows:

(i) Increase in ventilation/perfusion ratio over 1.0 on a side of the diseased lung.

(ii) Decrease in V/Q ratio in the healthy lung.

(iii) Normal values of ventilation gradient in both lungs and perfusion gradient of the intact lung.

(iv) Attenuated alveolar capillary permeability in the diseased lung compared with the corresponding value in the intact lung.

TABLE 4. Parameters of ventilation/perfusion lung scintigraphy in patients with community-acquired pneumonia and peripheral lung cancer ($X \pm m$, p)

Parameters for diseased and intact lungs		PLC patients (n = 14)	CAP patients* (n = 39)	p
V/Q	Diseased	1.13±0.02	1.06±0.01	<0.001
	Intact	0.88±0.02	0.97±0.03	0.006
$U/L(P)$	Diseased	0.53±0.08	0.80±0.02	0.009
	Intact	0.57±0.09	0.69±0.02	0.168
$U/L(V)$	Diseased	0.84±0.11	0.77±0.03	0.955
	Intact	0.71±0.05	0.69±0.02	0.929
ACP, % (10 min)	Diseased	14.39±2.84	20.37±1.41	0.037
	Intact	14.00±2.98	18.11 ±1.34	0.161
ACP, % (30 min)	Diseased	24.54±3.67	35.86 ±1.73	0.06
	Intact	33.23±3.14	32.00 ±1.71	0.7

V/Q—ventilation perfusion ratio, $U/L(P)$—apical-basal ventilation gradient, $U/L(P)$—apical-basal perfusion gradient, ACP—alveolar capillary permeability, CAP—community-acquired pneumonia, PLC—peripheral lung cancer, *—values are presented for both lungs together in control group, p—significance value for intergroup differences.

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ACKNOWLEDGMENTS

The study reported in this article was conducted according to accepted ethical guidelines involving research in humans and/or animals and was approved by an appropriate institution or national research organization.

The study is compliant with the ethical standards as currently outlined in the Declaration of Helsinki.

All individual participants discussed in this study, or for whom any identifying information or image has been presented, have freely given their informed written consent for such information and/or image to be included in the published article.

REFERENCES

1. *Rational Pharmacotherapy of Respiratory Diseases*, edited by A. G. Chuchalin (Litterra, Moscow, 2004), pp. 302–324.
2. M. Bajc, J. B. Neilly, M. Miniati, C. Schuemichen, M. Meignan, and B. Jonson, EANM guidelines for ventilation/perfusion scintigraphy: Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. EANM Committee, Eur. J. Nucl. Med. Mol. Imaging **36**(8), 1356–1370 (2009).
3. A. N. Okorokov, *Diagnosis of Respiratory Diseases* (Medical Literature, Moscow, 2000), pp. 157–232.
4. Y. Lu, A. Lorenzoni, J. J. Fox, J. Rademaker, Els. N. Vander, R. K. Grewal, H, W. Strauss, and H. Schöder, Noncontrast perfusion single-photon emission CT/CT scanning: a new test for the expedited, high-accuracy diagnosis of acute pulmonary embolism, Chest. **145**(5), 107910–10788 (2014).
5. K. Palmowski, U. Oltmanns, M. Kreuter, F. M. Mottaghy, M. Palmowski, and F. F. Behrendt, Diagnosis of pulmonary embolism: conventional ventilation/perfusion SPECT is superior to the combination of perfusion SPECT and nonenhanced CT, Respiration **88**(4), 291–297 (2014).
6. L. S. Marinho, N. P. Sousa, C. A. Barros, M. S. Matias, L. T. Monteiro, A. Beraldo Mdo, E. L. Costa, M. B. Amato, and M. A. Holanda, Assessment of regional lung ventilation by electrical impedance tomography in a patient with unilateral bronchial stenosis and a history of tuberculosis, J. Bras. Pneumol. **39**(6), 742–746 (2013).
7. P. V. Vlasov, Med. Vizualizats. **2**, 49–59 (2005).
8. M. Prokop, Lung cancer screening: the radiologist's perspective, Eur. Radiol. **21**(12), 2445–2454 (2011).
9. A. V. Dubodelova, Ventilation/perfusion lung scintigraphy in differential diagnosis of community-acquired pneumonias and thromboembolisms of distal pulmonary arteries, Ph.D. thesis, Tomsk, 2007.
10. *Radionuclide Diagnostics of Pulmonary Circulation*, edited by Yu. B. Lishmanov and N. G. Krivonogov (STT, Tomsk, 2007).
11. M. P. Rubin, Ter. Arkh. **80**, 10–16 (2008).
12. G. J. Huchon, J. A. Russell, L. G. Barritault, A. Lipavsky, and J. F. Murray, Am. Rev. Respir. Dis. **130**, 457–460 (1984).
13. M. Kanazawa, Y. Suzuki, A. Ishizaka, N. Hasegawa, S. Fujishima, T. Kawashiro, T. Yokoyama, A. Kubo, and S. Hashimoto, Nihon Kyobu Shikkan Gakkai Zasshi **31**, 593–600 (1993).
14. D. Köhler, G. Coates, M. Dolovich, M. Newhouse, and H. Matthys, Nuklearmedizin **22**, 115–119 (1983).

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