Annals of Nuclear Medicine Vol. 18, No. 7, 573–577, 2004

Detection of alveolar epithelial injury by ^{99m}Tc-DTPA radioaerosol inhalation lung scan following blunt chest trauma

Berna OKUDAN,* Serdar HAN,** Makbule BALDEMİR** and Mustafa YILDIZ*

*Department of Nuclear Medicine and **Department of Thoracic Surgery,
Ankara Numune Research and Training Hospital

DTPA clearance rate is a reliable index of alveolar epithelial permeability, and is a highly sensitive marker of pulmonary epithelial damage, even of mild degree. In this study, ^{99m}Tc-DTPA aerosol inhalation scintigraphy was used to assesss the pulmonary epithelial membrane permeability and to investigate the possible application of this permeability value as an indicator of early alveolar or interstitial changes in patients with blunt chest trauma. A total of 26 patients was chest trauma (4 female, 22 male, 31–80 yrs, mean age; 53 ± 13 yrs) who were referred to the emergency department in our hospital participated in this tsudy. Technetium-99m diethylene triamine pentaacetic acid (DTPA) aerosol inhalation scintigraphy was performed on the first and thirtieth days after trauma. Clearance half times ($T_{1/2}$) were calculated by placing a mono-exponential fit on the curves. Penetration index (PI) was calculated on the first-minute image. On the first day, mean $T_{1/2}$ value of the whole lung was 63 ± 19 minutes (min), and thirtieth day mean $T_{1/2}$ value was 67 ± 21 min. On the first day, mean PI values of the lung and 30th day mean PI value were 0.60 ± 0.05, and 0.63 ± 0.05, respectively. Significant changes were observed in radioaerosol clearance and penetration indices. Following chest trauma, clearance of ^{99m}Tc-DTPA increased owing to breakdown of the alveolar-capillary barrier. This increase in the epithelial permeability of the lung appears to be an early manifestation of lung disease that may lead to efficient therapy in the early phase.

Key words: ^{99m}Tc-DTPA aerosol inhalation scintigraphy, clearance, blunt chest trauma

INTRODUCTION

A NUMBER of pathological conditions alter the integrity of alveolar epithelial barrier and lead to patient morbidity and mortality. Investigators are interested in finding an accurate and reliable method for diagnosing these disorders, following their course, and helping with treatment planning.[1]

^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) aerosol inhalation lung scintigraphy is a simple, sensitive, non-invasive method for the evaluation of various kinds of pulmonary diseases.[2] Particularly, it provides information about lung and can also detect obstructive airway disease early.[3] The clearance rate is a reliable index of alveolar epithelial permeability, and is a highly sensitive marker of pulmonary epithelial damage, even of mild degree.[4,5] Alterations in lung clearance of ^{99m}Tc-DTPA aerosol have been shown in persons who smoke and in those with various lung disorders, including patients with asthma toxicity of chemotherapeutic agents, as weel as in diabetics and in hepatitis C virus antibody positive patients.[6–10] However, to our knowledge, alterations of pulmonary epithelial membrane permeability have not been described in patients with blunt chest trauma in the literature.

In this study, ^{99m}Tc-DTPA aerosol inhalation scintigraphy was used to assess the pulmonary epithelial membrane permeability and to investigate the possible application of this permeability value as an indicator of early alveolar or interstitial changes in patients with blunt chest trauma.

Received July 24, 2003, revision accepted June 21, 2004.

For reprint contact: Berna Okudan, M.D., Ankara Numune Research and Training Hospital, P.K:104 ISPARTA/TURKIYE.
E-mail: okudanb@yahoo.com

MATERIAL AND METHODS

A total of 26 patients with chest trauma (4 female, 22 male, 31–80 yrs, mean age; 52.73 ± 13.14 yrs) who were referred to the emergency department in our hospital participated in this study. Informed consent was obtained from all the patients. Patients with non-complicated chest trauma according to the "Revised Trauma Score" with values of three of higher were included.[11] The revised Trauma Score (RTS) is the most widely used trauma scale. It is based on the Glasgow Coma Scale, systolic blood pressure, and respiratory rate. For the evaluation of in-hospital outcome, coded values of the coma scale systolic blood pressure and respiratory rate are weighted and summed (Table 1). A better prognosis is associated with higher values. Absence of fracture, hemorrhage and pneumothorax were confirmed by computed tomography and chest x-ray in all patients. None of the patients had clinical or laboratory evidence of past or present chronic respiratory disease. All of the patients had been ex-smokers for at least 1-year. Any patients who showed a change in smoking habits during the study were also excluded. Twenty-one patients were nonsmokers and the others were ex-smokers. Patients were evaluated on admission and on the thirtieth day with physical and radiological examination and laboratory tests, and were followed for 6 months. Also, all patients were assessed from the aspect of discomfort by visual analog scale (VAS). Blood creatinine kinase (CK), creatinine kinase-MB (CK-MB), and arterial blood gas values (arterial oxygen saturation, PCO_2, HCO_3, pH) were obtained. DTPA aerosol inhalation scintigraphy was performed on the first and 30th days. All patients were administered 75 mg/day Diclofenac Sodium, which is a non-steroidal anti-inflammatory agent (NSAIDs) for pain control.

Table 1 Revised trauma score

Glasgow Coma Scale (GCS)	Systolic Blood Pressure (SBP) (mmHg)	Respiratory Rate (RT) (Breaths/min)	Coded Value
13–15	>89	10–29	4
9–12	76–89	>29	3
6–8	50–75	6–9	2
4–5	1–49	1–5	1
3	0	0	0

Table 2 Clearance half times ^{99m}Tc-DTPA and PI values and other parameters of patients on first and 30th days

Parameters	First day	Thirtieth day	p
$T_{1/2}$ (min)	62 ± 19	67 ± 21	0.03
PI	0.60 ± 0.05	0.63 ± 0.05	0.009
PO_2 (mmHg)	70 ± 9.2	78 ± 9.4	0.001
PCO_2 (mmHg)	38 ± 6.5	34 ± 6	0.01
HCO_3 (mEq/lt)	23 ± 2.5	24 ± 3.5	0.15*
PEFR (1/sn)	179 ± 31	206 ± 37	0.001
O_2 sat. (%)	92 ± 3.6	94 ± 3.5	0.001
pH	7.40 ± 0.01	7.38 ± 0.03	0.04
CK (U/*l*)	199 ± 88	63 ± 21	0.001
CK-MB (U/*l*)	20.03 ± 13	19 ± 9.1	0.30*
VAS	8.2 ± 1.4	1.3 ± 1.3	0.001

*Not significant ($p > 0.05$).

^{99m}Tc-DTPA (CIS bio international, France) was prepared from a freeze-dried kit according to the manufacturer's instructions. The quality control of ^{99m}Tc-DTPA was performed using instant thin-layer chromatography. The Ventiscan Biodex III aerosol delivery system, which produces submicronic particles (MMAD, 0.5 mm; GSAD, 18), was used at an O_2 flow rate of 10–12 $l \cdot min^{-1}$. Four to five milliliters of 1110 MBq (30 mCi) ^{99m}Tc-DTPA were placed into the nebulizer reservoir. Patients inhaled the radioaerosol in the supine position for 4 min at normal tidal breathing and then were disconnected from the system. Approximately 10% of total activity was administered to the patients during the 4 min inhalation. Immediately after the inhalation, scintigraphic

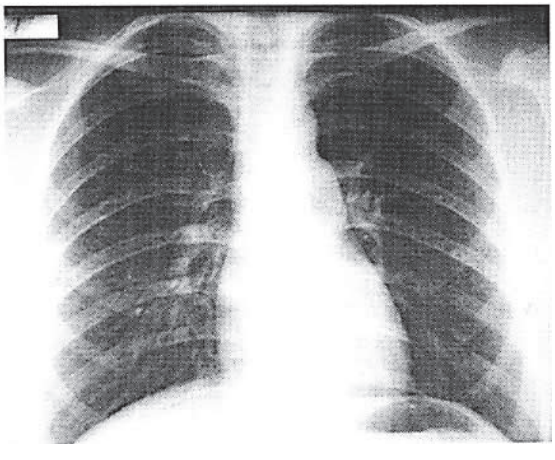

Fig. 1

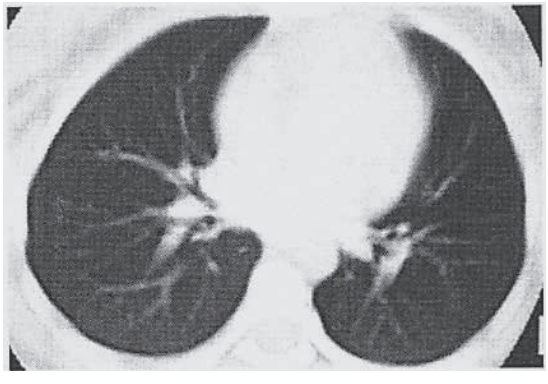

Fig. 2

Examples of normal anteroposterior thoracic X-ray and CT.

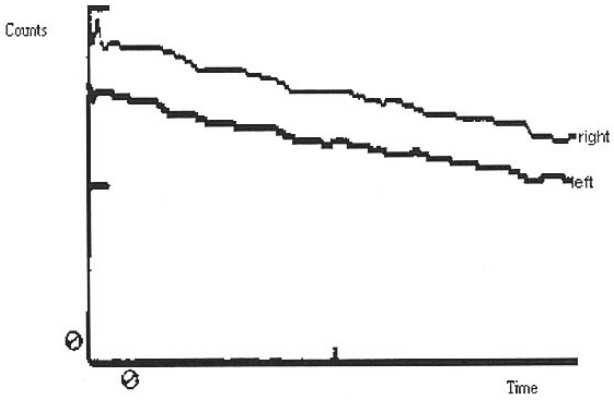

Fig. 3 Characteristic time-activity curves for clearance of ^{99m}Tc-DTPA of right and left lung on the first day.

data were recorded dynamically (1 frame/min) in posterior projection on a 64 × 64 matrix for a 45 min period using a single-headed rotating gamma camera (Elsint, SPX-6, Israel) equipped with a low-energy all-purpose parallel hole collimator interfaced to an Elsint Computer System. During the imaging period, the supine position was preferred to decrease patient motion.

Regions of interest (ROIs) were drawn around the periphery of the right and left lung and on the major airways on the first-minute image. To obtain a pure alveolar ROI and to exclude the entire bronchial activity, the outer third of each lung was used as a peripheral lung region. The inner two-thirds of the lungs was defined as the central lung region. The brightness of the image was increased to visualize body background and the lung periphery. The same peripheral and central ROIs were used as both first and last lung images for each patient to reproduce the ROI drawing at the interval of 1 month. Time-activity curves were generated and corrected for Tc-99m decay. $T_{1/2}$ was calculated by placing a mono-exponential fit on the curves. $T_{1/2}$ of whole lung was calculated as a mean of the $T_{1/2}$ of left lung and right lung. Penetration index (PI) was also calculated by dividing the peripheral total counts by the sum of the peripheral and central total counts on the first minute image, in order to quantify the distribution of the inhaled radioaerosol. Also, scintigraphic data were evaluated regarding to distribution of radiotracer in the lungs as diffuse, homogeneous, symmetric or localized distribution.

Each patient underwent pulmonary function test (PFTs) for peak expiratory flow rate (PEFR) using a vitalograph, astra, dry flowmetry on the same days as the ^{99m}Tc-DTPA-aerosol lung scintigraphy. ^{99m}Tc-DTPA inhalation scintigraphy was performed twice to calculate the changes in pulmonary clearance rates between the first and 30th day lung scintigraphy. We compared the values of the lung clearance of ^{99m}Tc-DTPA with the results of PEFR, VAS and the aforementioned laboratory tests.

Statistical analysis. The Wilcoxon Signed test was

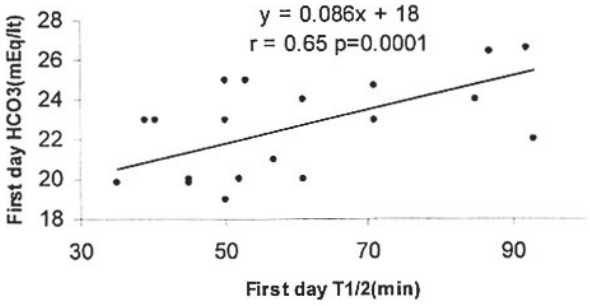

Fig. 4 Correlation between HCO_3 value and $T_{1/2}$ of ^{99m}Tc-DTPA on the first day.

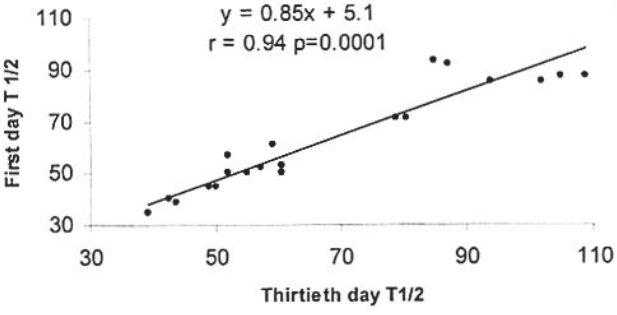

Fig. 5 Correlation between $T_{1/2}$ of ^{99m}Tc-DTPA of first day and $T_{1/2}$ of ^{99m}Tc-DTPA of thirtieth day values.

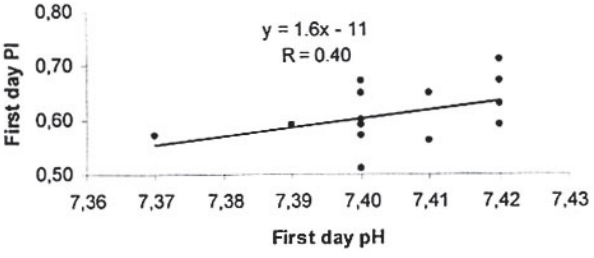

Fig. 6 Correlation between PI of ^{99m}Tc-DTPA of first day and pH of first day values.

used to compare PEFR, arterial blood gas values (oxygen saturation, PO_2, PCO_2, HCO_3, pH) radioaerosol clearance and PI values for paired data. Spearman test and regression analysis were used for correlations. All analyses were performed using the statistical package SPSS 9.5 for Windows, and a p value less than 0.05 was considered statistically significant.

RESULTS

The quantitative results of clearance half times ^{99m}Tc-DTPA and PI values on the first and 30th days were summarized in Table 2. The labeling efficiency of ^{99m}Tc-DTPA was found to be more than 95% as judged by thin layer chromatography. All of the patients had normal thoracic x-ray and computerized tomography findings on

the first day (Figs. 1, 2). Time-activity curves were generated separately from right and left lung on the first and thirtieth day. The ^{99m}Tc-DTPA clearance curves were mono-exponential in all patients (Fig. 3). The significant changes were determined in PI, $T_{1/2}$ values, arterial blood gases, PEFR and VAS score between the first and 30th days. On the first day, mean $T_{1/2}$ value of the whole lung was 62 ± 19 min while the thirtieth day mean $T_{1/2}$ value was 67 ± 21 min. The mean PI values of the lung on the first day and 30th day were 0.60 ± 0.05, and 0.63 ± 0.05, respectively. Significant changes were observed in radioaerosol clearance and penetration indices. Also, there was a correlation between $T_{1/2}$ and PI and blood HCO_3 value and pH (Figs. 4, 5, 6). Besides, distribution of radiotracer was found to be diffuse in 22 patients, in contrast to non-homogeneous in 4 patients. Although significant changes were observed in arterial blood gases, oxygen saturation and PEFR between the first and 30th day values, all of them were within the normal limits. But, there was no correlation between PI, $T_{1/2}$ values and PEFR.

DISCUSSION

Blunt injury to the lung is common after chest trauma, and is associated with mortality rates of 10% to 25%.[12,13] A blow anywhere to the chest wall can be transferred to the adjacent lung with the alveoli becoming injured and filled with fluid, leading to the localized site of pulmonary edema and impairment of oxygen exchange.[14] Early detection of these changes in alveolar-capillary permeability is crucial so as to commence therapy immediately to avoid irreversible damages.

^{99m}Tc-DTPA aerosol scintigraphy is a sensitive marker of the changes of the permeability characteristics of the lung parenchyma.[15] This test has not only generated considerable physiological interest but has also been proposed as a valuable means of detecting and quantifying a wide range of subtle to clinically obvious degrees of lung injury.[2,15,16]

A normal clearance certifies the absence of inflammation in lung from any cause. Similarly, the increase of clearance of ^{99m}Tc-DTPA may be a sensitive indicator of ongoing damage in interstitial lung disease and other pathologies.[5] Clearance of ^{99m}Tc-DTPA is increased in patients with diseases known to involve the alveolar-capillary membrane, including adult respiratory distress syndrome and interstitial lung diseases.[15]

We showed in our study that the ^{99m}Tc-DTPA clearance rate increased in the acute period in patients after blunt chest trauma and PI also increasing on the 30th day. This connotes that ^{99m}Tc-DTPA was deposited more in the peripheral lung region after therapy. Clearance of ^{99m}Tc-DTPA from the bronchial mucosa is slower than clearance from the alveolar epithelium, and mucociliary clearance may have an important role in removing ^{99m}Tc-DTPA from ciliated airways.[17] A correlation was found between blood HCO_3 values and $T_{1/2}$ of ^{99m}Tc-DTPA values on the first day which may suggest a compensatory rise in blood HCO_3 levels secondary to increased alveolocapillary permeability.

The mechanisms that increase the clearance of ^{99m}Tc-DTPA are not understood clearly. However, some hypotheses have been proposed to explain the increased clearance. One of the most commonly implicated mechanisms is related to with surfactant pathologies.

Pulmonary surfactant is a complex mixture of phospholipids and proteins that spreads in a thin film on the alveolar surface. Before reaching the epithelial cell membrane, ^{99m}Tc-DTPA must pass through this surfactant layer. Inflammation, as well as mechanical trauma is associated with alveolar septal damage due to which surfactant leaks into the bloodstream leading to reduced deficiency of pulmonary surfactant levels.[18] Evander et al. reported that the clearance of ^{99m}Tc-DTPA is increased in experimental models of surfactant dysfunction.[19]

The other mechanism is activation of the inflammatory cascade. This cascade increase of ^{99m}Tc-DTPA is the activation of the posttraumatic inflammatory cascade.[20] Several recent studies demonstrated that activation of such a posttraumatic inflammatory cascade led to progressive alveolar injury.[21–23] Besides, it is known that non-steroidal anti-inflammatory drugs (NSAIDs) affect the inflammatory cascade, particularly inhibiting cyclooxigenase-2 (COX-2) and cyclooxigenase-1 (COX-1). Therefore, NSAIDs are useful to control the signs and symptoms of established inflammation especially pain.[24] We consider that NSAIDs not only control pain but also improve $T_{1/2}$ and PI after therapy, likely mediated by inhibition of the inflammatory cascade via COX-2 and COX-1.

In our study, although statistically significant increases were seen in the values of the pulmonary function tests in all patients, we could not find any correlation between PI, clearance of ^{99m}Tc-DTPA and pulmonary function tests. This finding was consistent with the study of Tsai et al. indicating that radionuclide alveolar permeability was not related to the traditional pulmonary function tests.[25] But, it was known that, pulmonary function tests are affected in the acute period of blunt chest trauma. Total respiratory resistance increased 2 hours after trauma because of an increase in chest wall resistance. Pulmonary resistance was not significantly increased.[26]

CONCLUSION

We concluded that following chest trauma, clearance of ^{99m}Tc-DTPA increased owing to breakdown of the alveolar-capillary barrier. This increase in the epithelial permeability of the lung may be an early manifestation of lung disease may provide hints to efficient therapy in the early phase.

ACKNOWLEDGMENT

The authors would like to thank Baha Oral, M.D., Füsun Eroğlu, M.D., Ahmet Akkaya, for their assistance in editing the manuscript and Mustafa Öztürk, M.D., for his statistical assistance.

REFERENCES

1. Freeman LM. *Nuclear Medicine Annual*. Krasnow AZ, Isıtman AT, Collier BD, et al. Diagnostic applications of radioaerosols in Nuclear Medicine. New York; Raven Press, Inc., 1993: 123–193.
2. Coates G, O'Brodovich H. Pulmonary alveolar capillary permeability and fluid exchange. In: Loken MK, ed. *Pulmonary Nuclear Medicine*. Los Altos, CA; Appleton and Lange, Inc., 1987: 304–326.
3. Taplin GV, Tashkin DP, Chopra SK, et al. Early detection of chronic obstructive pulmonary disease using radionuclide lung-imaging procedures. *Chest* 1977; 71: 567–675.
4. Staub NC, Hyde RW, Crandall E. NHLBI workshop summary. Workshop on techniques to evaluate lung alveolar-microvascular injury. *Am Rev Respir Dis* 1990; 14: 1071–1077.
5. Suskind H. Technetium-99m-DTPA aerosol to measure alveolar-capillary membrane permeability. *J Nucl Med* 1994; 35: 207–209.
6. Jones JG, Minty BD, Lawler P, Hulands G, Crawley JC, Veall N. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980; 12: 66–68.
7. Wang SJ, Kao CH, Lin WY, Hsu CY, Chang CP, Lan JL. Effects of inhalation of steroids on lung permeability in patients with asthma. *Clin Nucl Med* 1995; 20: 494–496.
8. Lin WY, Kao CH, Wang SJ, Yeh SH. Lung toxicity of chemotherapeutic agents detected by Tc-99m DTPA radioaerosol inhalation lung scintigraphy. *Neoplasma* 1995; 42: 133–135.
9. Caner B, Ugur O, Bayraktar M, Ulutuncel N, Mentes T, Telatar F, et al. Impaired lung epithelial permeability in diabetics detected by technetium-99m-DTPA aerosol scintigraphy. *J Nucl Med* 1994; 35: 204–206.
10. Kula M, Gulmez I, Tutus A, Coskun A, Gursoy S, Oymak S. Impaired lung epithelial permeability in hepatitis C virus antibody positive patients detected by ^{99m}Tc-DTPA aerosol scintigraphy. *Nucl Med Commun* 2002; 23: 441–446.
11. Bongard FS, Sue DY. Philosophy and Principles of Critical Care. In: *Current Critical Care Diagnosis and Treatment*. Bongard FS, Sue DY (eds), 1st ed., Norwalk, Connecticut; Appletion and Lange, Inc., 1994: 1–12.
12. Clark GC, Schecter WP, Trunkey DD. Variables affecting outcome in blunt chest trauma: flail chest vs. pulmonary contusion. *J Trauma* 1988; 28: 298–304.
13. Pepe PE. Acute post-traumatic respiratory physiology and insufficiency. *Surg Clin North Am* 1989; 69: 157–173.
14. Shin B, McAslan TC, Hankins JR, Ayella RJ, Cowley RA. Management of lung contusion. *Am Surg* 1979; 45: 168–175.
15. O'Doherty M, Peters AM. Pulmonary technetium-99m diethylene triamine penta-acetic acid aerosol clearance as an index of lung injury (review). *Eur J Nucl Med* 1997; 24: 81–87.
16. O'Brodovich H, Coates G. Pulmonary clearance of ^{99m}Tc-DTPA: a noninvasive assessment of epithelial integrity. *Lung* 1987; 165: 1–16.
17. Capa Kaya G, Durak H, Yemez B, et al. Technetium-99m DTPA inhalation ascintigraphy in patients treated with fluoxetine and maprotiline: preliminary results. *Eur J Nucl Med* 2000; 27: 1402–1404.
18. Ishida K, Zhu B, Quan L, Fujita MQ, Maeda H. Pulmonary surfactant-associated protein A levels in cadaveric sera with reference to the cause of death. *Forensic Sci Int* 2000; 109: 125–133.
19. Evander E, Wollmer P, Johnson B, Lachmann B. Pulmonary clearance of inhaled ^{99m}Tc-DTPA: effects of surfactant depletion by lung lavage. *J Appl Physiol* 1987; 62: 1611–1614.
20. Davis KA, Fabian TC, Ragsdale DN, Trenthem LL, Proctor KG. Endogenous adenosine and secondary injury after chest trauma. *J Trauma* 2000; 49: 892–898.
21. Hellinger A, Konerding MA, Malkusch W, et al. Does lung contusion affect both the traumatized and the noninjured lung parenchyma? A morphological and morphometric study in the pig. *J Trauma* 1995; 39: 712–719.
22. Davis KA, Fabian TC, Croce MA, Proctor KG. Prostanoids: early mediators in the secondary injury that develops after unilateral pulmonary contusion. *J Trauma* 1999; 46: 824–831, discussion 831–832.
23. Obertacke U, Neudeck F, Majetschak M, et al. Local and systemic reactions after lung contusion: an experimental study in the pig. *Shock* 1998; 10: 7–12.
24. Ruddy S, Harris ED, Stedge CB, et al. *Kelley's Textbook of Rheumatology*. Sabagun ES, Weisman MH. Non-steroidal anti-inflammatory drugs. Philadelphia; WB Saunders, 2001: 799–822.
25. Tsai SC, Kao CH, Lee JK, Wang SJ. Kaohsiung. The relationships between the radionuclide alveolar integrity study and the pulmonary function test. *J Med Sci* 1996; 12: 88–92.
26. Sprung J, Mackenzie CF, Green MD, O'Dwyer J, Barnas GM. Chest wall and lung mechanics during acute hemorrhage in anesthetized dogs. *J Cardiothorac Vasc Anesth* 1997; 11: 608–612.