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Clearance of technetium-99m-labeled DTPA in hyperthyroidism without clinical evidence of lung disease, and relation to pulmonary function

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Objective: The mechanisms of dyspnea and exercise intolerance have not been fully elucidated. We aimed to investigate the clearance rate of technetium-99m diethyltriaminepentaaceticacid (Tc-99m DTPA) from lungs in hyperthyroid patients without clinical evidence of lung disease and to explore the interactions between their Tc-99m DTPA radioaerosol lung scintigraphy, spirometric measurements, and the levels of thyroid hormones. ***Methods:*** We studied 19 hyperthyroid patients and 16 sex- and age-matched controls. Thyroid hormone levels were assessed. Spirometric lung function tests, diffusing capacity of the lung for carbon monoxide (DLCO) and the clearance rate of Tc-99m DTPA were performed in all participants. Ratio of DLCO value to the alveolar ventilation (DLCO/VA) and the means of half-time ($T_{1/2}$) of Tc-99m DTPA clearance rate, which were used to evaluate alveolar-capillary membrane permeability, were calculated. ***Results:*** There were no statistical differences between spirometric parameters (VC, FVC, FEV_1/FVC, FEF 25–75) of the two groups ($p > 0.05$). Although the mean FEV_1 level was significantly lower in the hyperthyroid patients than the control subjects ($p < 0.01$), in five patients FEV_1 was only less than 80 percent of the predicted value. No significant difference in the means of DLCO, DLCO/VA or $T_{1/2}$ values of Tc-99m DTPA clearance was observed between the two groups ($p > 0.05$). In hyperthyroid patients, there was a positive relation between DLCO/VA, DLCO/VA % and $T_{1/2}$ values of Tc-99m DTPA clearance ($p < 0.01$, $r = 0.732$, $p < 0.01$, $r = 0.742$, respectively). The lung volumes and the levels of thyroid hormones did not show a significant relationship to $T_{1/2}$ values of Tc-99m DTPA clearance in hyperthyroid group ($p > 0.05$). ***Conclusions:*** We conclude that increased thyroid hormones have no effect on permeability of alveolar-capillary membrane in hyperthyroid patients.

Key words: hyperthyroidism, pulmonary function, Tc-99m DTPA aerosol scintigraphy, alveolar-capillary permeability

INTRODUCTION

PATIENTS with hyperthyroidism frequently complain of dyspnea, exercise intolerance and breathlessness despite elevated resting cardiac output.[1,2] In several studies, numerous abnormalities such as skeletal muscle myopathy,[2] respiratory muscle weakness,[3,4] reduction in lung volumes[5] and left heart failure[6] have been considered as the causes of these symptoms in hyperthyroidism. It is well known that abnormalities of diffusion capacity of lungs may be also responsible for the respiratory symptoms in the early phase of lung diseases.[7] Experimental studies showed that thyroid hormones might play a potent role in lung surfactant metabolism, which is important for diffusion capacity of lungs, in the rat.[8,9] However, to our knowledge, evaluation of alveolar-capillary membrane permeability in patients with hyperthyroidism where a radioaerosol scintigraphy method is used has not been

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reported in the literature.

Technetium-99m-diethyltriaminepentaaceticacid (Tc-99m DTPA) radioaerosol scintigraphy is well defined as a sensitive and non-invasive method for evaluation of the alveolar-capillary barrier in different interstitial lung diseases or lung toxicities.[10–16] Tc-99m DTPA is deposited in the lining layer of the pulmonary epithelial surface, and transfer of this hydrophilic solute across the alveolar-capillary barrier depends on passive diffusion through the intercellular junctions of the epithelium and endothelium.[11,12,17] The overall change in alveolar clearance of the solute is determined by interplay of the surface area for transfer, the concentration gradient across the alveolar-capillary membrane, and the distance of the diffusion pathway of the solute.[12]

The objective of this study was to evaluate the permeability of the pulmonary alveolar-capillary in patients with hyperthyroidism by using Tc-99m DTPA radioaerosol scintigraphy, and to assess the relationship between Tc-99m DTPA radioaerosol scintigraphy and the spirometric measurements in hyperthyroid patients.

MATERIAL AND METHOD

We enrolled 19 (13 female, 6 male, mean age; 48.3 ± 13.7 years old) hyperthyroid patients and age-matched, sex-matched 16 (11 female, 5 male, mean age; 50.5 ± 8.5 years old) healthy subjects in this study. Smokers, alcoholics, and patients having any respiratory disease, cardiac failure, severe arrhythmias, diabetes mellitus, chest deformity, or obesity (body mass index > 30 kg/m^2) were excluded from the study. Chest x-rays were interpreted by the same pneumologist who was masked to judge the scan results. The study was approved by the local ethics committee and all participants were informed according to the Helsinki Committee requirements.

The diagnosis of hyperthyroidism was made by clinical examination and confirmed by measuring free triiodothyronine (fT_3), free thyroxine (fT_4) and thyroid-stimulating hormone (TSH). Thyroid hormones were assessed by chemiluminescent immunoassay methods (Immulite-DPC, USA). Patients with above normal fT_4 and/or fT_3 levels and low TSH levels were regarded as hyperthyroid (the normal range fT_3: 1.8–4.2 pg/m*l*, fT_4: 0.8–1.9 ng/d*l*, TSH: 0.4–4 μIU/m*l*). Control subjects had normal thyroid hormone levels.

The breathing rates of all participants were measured on arrival. Then, spirometric lung function tests were performed using a dry spirometer (V-Max 22 device, Sensor Medics, CA) by one technician who was blinded to the patient's clinical data. Measurements were performed at the time of diagnosis before any treatment. Patients were taught how to perform the test, and it was repeated to obtain at least two identical readings. All tests were performed in the resting state with the subject seated and nose clip in place. Spirometric pulmonary function tests such as vital capacity (VC), force vital capacity (FVC), 1-s forced expiratory volume (FEV_1), FEV_1/FVC, and mean forced expiratory flow during the middle of FVC (FEF 25–75) were evaluated. All parameters were calculated automatically for age, sex, height and weight of each participant and expressed as the percentage of predicted values (predicted %).[18] A value below 80% of the predicted value was considered abnormal for spirometric measurements.

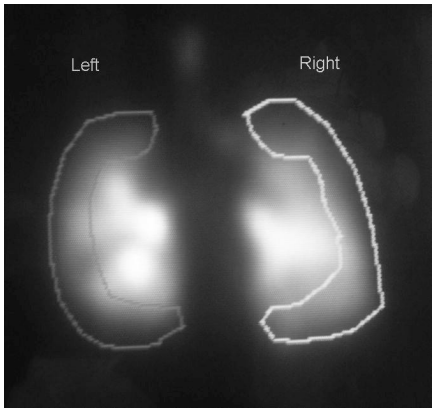
Table 1 Thyroid hormone levels and results of the spirometric measurements and Tc-99m DTPA radioaerosol scintigraphy of hyperthyroid and control group

	Hyperthyroid group	Control group	p
fT_3 (pg/m*l*)	9.7 ± 4.9	3.1 ± 0.6	< 0.001
fT_4 (ng/d*l*)	4.2 ± 1.6	1.3 ± 0.2	< 0.001
TSH (μIU/m*l*)	0.013 ± 0.02	1.5 ± 0.7	< 0.001
Breathing rate (min)	20 ± 3	19 ± 4	*
VC	3.0 ± 0.9	3.2 ± 0.8	*
VC %	90.3 ± 16.3	96.8 ± 12.4	*
FEV_1	2.5 ± 0.8	2.7 ± 0.6	*
FEV_1 %	92.6 ± 8.9	99.7 ± 12.8	*
FVC	2.9 ± 0.9	3.2 ± 0.8	*
FVC %	89.4 ± 16.6	99.1 ± 13.2	*
FEV_1/FVC	84.2 ± 13.2	83.9 ± 5.7	*
FEF 25–75	2.9 ± 1.2	2.8 ± 0.7	*
FEF 25–75%	78.8 ± 18.4	87.5 ± 17.0	*
DLCO	21.3 ± 5.2	23.1 ± 6.9	*
DLCO %	80.9 ± 22.2	95.7 ± 18.4	*
DLCO/VA	5.0 ± 1.2	4.8 ± 1.7	*
DLCO/VA %	99.4 ± 22.4	105.1 ± 15.7	*
$T_{1/2}$ (min)	149.1 ± 79.2	172.1 ± 83.0	*

* $p > 0.05$

The diffusing capacity of the lung for carbon monoxide (DLCO) was assessed by the Single Breath method. After a 30 min resting period, 0.3% CO, 21% O_2, and 10% helium mixture was inhaled during normal respiration. The patient inspired the mixture of gas from residual volume to total lung capacity, holding his breath 10 sec, and then rapidly exhaled to residual volume. A value of below 80% or above 120% was considered abnormal for DLCO. Ratio of DLCO value to the alveolar ventilation (DLCO/VA) was used to evaluate alveolar-capillary membrane permeability.[19]

Tc-99m DTPA (CIS bio international, France) aerosols were chelated by introducing 1,480 MBq of sodium Tc-99mO_4-into 5 m*l* of normal saline. Tc-99m DTPA was placed in the nebulizer reservoir of a commercially available system (VENTICIS Biodex III). Aerosols with a mass median diameter of 0.8 μ were produced with oxygen in flow of 10–12 *l*/min. Patients, while they are in a sitting position, inhaled the Tc-99m DTPA aerosols for 3 min period. Approximately 10% total activity was administered to patients during the 3-min inhalation. The subjects were placed over a gamma camera (Orbiter;



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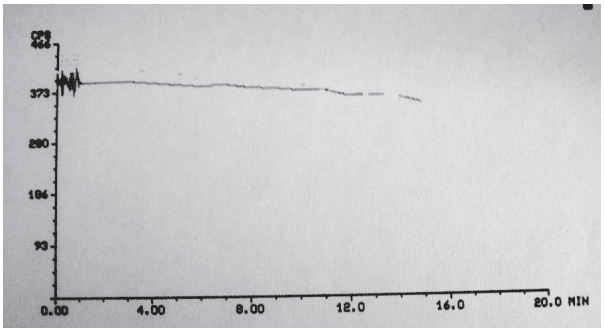

B

Fig. 1 This figure shows (A) regions of interest and (B) time activity curve from a subject in hyperthyroid group from posterior view of both lungs on Tc-99m DTPA radioaerosol inhalation lung scintigraphy.

Siemens Corp., Iselin, NJ, USA) with low-energy; all-purpose collimator and lung fields were imaged in posterior projection. One-minute frames were acquired in a 64 × 64 matrix for a 30 min period. Regions of interest (ROIs) were drawn around the periphery of the left and right lung, and on the major airways on the first-minute image (Fig. 1). To obtain a pure alveolar ROI and to exclude the entire bronchial activity, the outer one-third of each lung was used as the peripheral lung region. The inner two-thirds of the lung was defined as the central lung region. The brightness of the image was increased to visualize background of the body and the lung periphery, thereby permitting correct definition of the peripheral ROIs. Time-activity curves from each lung were generated and curves were corrected for Tc-99m DTPA decay. Then, the mean of half-time ($T_{1/2}$) of Tc-99m DTPA clearance rate for each lung was calculated by placing a mono-exponential fit on the curves.[20] In our laboratory, the coefficient of variation (CV) values for Tc-99m DTPA clearance rate were estimated to be 1.0% (Mean Centered), 1.1% (Median Centered) on the same image, and 13.4% (Mean Centered), 13.5% (Median Centered) on repeated scan of the same patient.

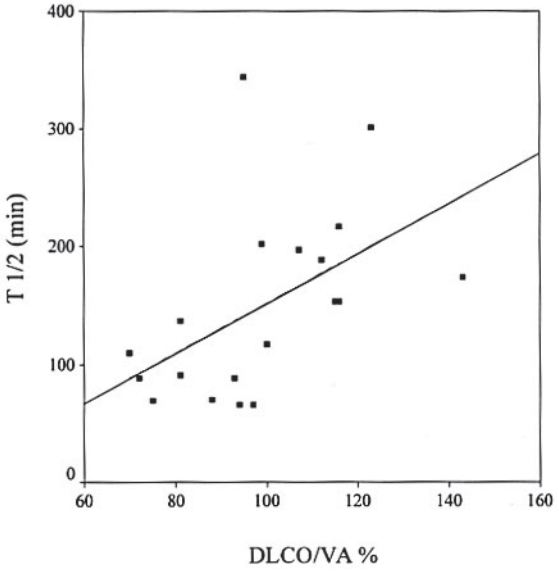

Fig. 2 Relationship between the values of clearance rate ($T_{1/2}$) of Tc-99m DTPA and DLCO/VA % in patients with hyperthyroidism.

Statistical Analysis

The SPSS 10.0 version was used in data analysis. Data are presented as mean ± SD. The results of the hyperthyroid and control groups were compared using Mann Whitney-U test. Spearman rank correlation was used to assess the relation between the $T_{1/2}$ values of Tc-99m DTPA clearance, spirometric lung function parameters and, thyroid hormones levels. $P < 0.05$ was considered statistically significant.

RESULTS

The hyperthyroid group had significantly higher serum levels of fT_3 ($p < 0.001$), fT_4 ($p < 0.001$), and lower serum levels of TSH ($p < 0.001$), compared with those of the control group. All participants had normal chest-x ray findings. The results of spirometric lung function tests, DLCO, DLCO/VA and $T_{1/2}$ values of Tc-99m DTPA clearance of hyperthyroid patients and control subjects were shown in Table 1. There were no statistical differences between the spirometric parameters (VC, FVC, FEV_1/FVC, FEF 25–75) of the two groups ($p > 0.05$). Although the mean FEV_1 (mean 86.8%, range 64%–105%) level was significantly lower in the hyperthyroid patients than the control subjects ($p < 0.01$), in five patients FEV_1 was only less than 80 per cent of the predicted value. No significant difference in the means of DLCO, DLCO/VA or $T_{1/2}$ values of Tc-99m DTPA clearance, which determine alveolar-capillary membrane permeability, was observed between the two groups ($p > 0.05$). In hyperthyroid patients, there was a positive relation between DLCO/VA, DLCO/VA % and $T_{1/2}$ values of Tc-99m DTPA clearance ($p < 0.01$, $r = 0.782$, $p < 0.01$,

r = 0.742, respectively) (Fig. 2). The lung volumes and the levels of thyroid hormones did not show a significant relationship to $T_{1/2}$ values of Tc-99m DTPA clearance in hyperthyroid group ($p > 0.05$).

DISCUSSION

In this study, we found no differences in the spirometric lung function measurements or clearance of Tc-99m DTPA between patients with hyperthyroidism and control subjects. In addition, the clearance of Tc-99m DTPA was correlated with the values of DLCO/VA in hyperthyroid patients. We did not find a relationship between thyroid hormone levels and the clearance of Tc-99m DTPA, and spirometric parameters. These results indicate that the permeability of the alveolar-capillary membrane may be normal in hyperthyroidism.

Tc-99m DTPA technique provides a sensitive index for evaluation of changes in the alveolar-capillary permeability.[21] It is well known that diffusion capacity depends on numerous factors such as surfactant, lung oxygen consumption, capillary blood volume available for gas exchange, distance between capillaries and alveoli, the structural and functional properties of the alveolar-capillary membrane, and lung volume.[7] It is clear that pathophysiological alterations of alveolar-capillary permeability influence the clearance rate of Tc-99m DTPA of the lungs. For example, degeneration of the alveolar-capillary membrane may retard clearance of alveolar DTPA by increasing the diffusion distance for the solute.[12] Conversely, intercellular junctional loosening and cellular denudations may increase the surface area for transfer of the solute, thereby accelerating DTPA clearance.[21] The large alveolar cells in the alveolar epithelial lining synthesize the surfactant, which contains fatty acids and phospholipids, and it is essential to maintain alveolar-capillary stability.[22] Increased surfactant over the alveolar epithelium could cause an increase in the surface area of the Tc-99m DTPA aerosol droplet with more rapid absorption and thus, an increase in clearance rate,[23] or excessive increases of surfactant may limit the alveolar transfer of Tc-99m DTPA due to increased diffusion distance. On the other hand, it has been shown that when lung oxygen consumption is increased, there is an increase in the production of reactive oxygen radicals.[24] As might be expected, reactive oxygen radicals could induce lung injury that is characterized by damage to cells in the alveolar epithelium, which could be causing increased alveolar-capillary permeability.[25]

Regarding hyperthyroidism, it has been shown that phospholipid synthesis and reactive oxygen radicals are increased due to the increased rate of oxygen consumption in lung tissue in hyperthyroid rats.[8,26] As expected, we considered in this study that hyperthyroidism could cause impaired permeability of the alveolar-capillary membrane by several mechanisms. However, from our results, we did not detect any dysfunction of alveolar-capillary membrane by using Tc-99m DTPA in hyperthyroidism. Kumar et al.[8] also reported that despite the increased phospholipids biosynthesis in lung tissue, surfactant levels of hyperthyroid rats are not altered. It has been speculated in this experimental study that the increase observed in the phospholipid content of the lung tissue in the hyperthyroid rat is likely to be due to an accelerated synthesis of lipids. On the other hand, the mechanism underlying the increase in clearance of Tc-99m DTPA at high lung volume is not known, but could be due to increased surface area for diffusion.[27] In this study, there were no differences in lung volumes between the groups. For this reason, we think that lung volumes did not affect the results of the clearance of Tc-99m DTPA. To our knowledge, this is the first report to evaluate alveolar-capillary membrane permeability in patients with hyperthyroidism by using a radioaerosol scintigraphy method. So, we speculate that elevated thyroid hormone levels are not associated with increased surfactant levels and reactive oxygen radicals in lung. There is clearly need for further studies of interventions with the functions of surfactant and oxygen radicals to corroborate this contention.

Concurrently, we observed that the values of DLCO and DLCO/VA, which determine the permeability of alveolar-capillary membrane, were similar in hyperthyroid patients and the healthy controls. Pino-Garcia et al.[28] showed similar DLCO values in patients with hyperthyroidism before and after treatment when compared with a control group. Mahajan et al.[29] found that hyperthyroid patients had similar DLCO values compared with control subjects although significant improvement was present in DLCO values after therapy. On the other hand, our results clearly demonstrated a statistically significant linear relationship between DLCO/VA and the clearance of Tc-99m DTPA in patients with hyperthyroidism.

Our results showed that alveolar-capillary integrity was not damaged in hyperthyroid patients when compared to age- and sex-matched control subjects. We conclude that different mechanisms concerning the respiratory system may cause respiratory failure in hyperthyroidism.

Study Limitations

This study has several limitations. First, we could evaluate only 19 hyperthyroid patients. Second, our analyses are based on a single base-line determination that may not reflect the patient's status in the long term. Third, the research may have included hyperthyroid patients with clinical evidence of lung disease.

REFERENCES

1. Ladenson PW. Diseases of the thyroid gland. *J Clin*

Endocrinol Metab 1985; 14: 145–173.
2. Martin WH 3rd, Spina RJ, Korte E, Yarasheski KE, Angelopoulos TJ, Nemeth PM, et al. Mechanisms of impaired exercise capacity in short duration experimental hyperthyroidism. *J Clin Invest* 1991; 88: 2047–2053.
3. McElvaney GN, Wilcox PG, Fairbarn MS, Hilliam C, Wilkins GE, Pare PD, et al. Respiratory muscle weakness and dyspnea in thyrotoxic patients. *Am Rev Respir Dis* 1990; 141: 1221–1227.
4. Kendrick AH, O'Reilly JF, Laszlo G. Lung function and exercise performance in hyperthyroidism before and after treatment. *Q J Med* 1988; 68: 615–627.
5. Ayres J, Rees J, Clark TJ, Maisey MN. Thyrotoxicosis and dyspnoea. *Clin Endocrinol* 1982; 16: 65–71.
6. Iskandrian AS, Rose L, Hakki AH, Segal BL, Kane SA. Cardiac performance in thyrotoxicosis: analysis of 10 untreated patients. *Am J Cardiol* 1983; 51: 349–352.
7. Weibel ER, Taylor CR. Functional Design of Human Lung for Gas Exchange. In: *Fishman's Pulmonary Diseases and Disorders*, Fishman AP, Fishman LA, Grippi MA (eds), New York; Mc Graw Hill Co., 1998: 21–62.
8. Kumar R, Hedge KS. Influence of thyroid hormone on phospholipid composition of lung tissue and surfactant of rats. *Ind J Pharmac* 1983; 27: 203–208.
9. Redding RA, Douglas WH, Stein M. Thyroid hormone influence upon lung surfactant metabolism. *Science* 1972; 175: 994–996.
10. Groeneveld AB. Radionuclide assessment of pulmonary microvascular permeability. *Eur J Nucl Med* 1997; 24: 449–461.
11. Coates G, O'Brodovich H. Measurement of pulmonary epithelial permeability with ^{99m}Tc-DTPA aerosol. *Semin Nucl Med* 1986; 16: 275–284.
12. O'Doherty MJ, Peters AM. Pulmonary technetium-99m diethylene triamine penta-acetic acid aerosol clearance as an index of lung injury. *Eur J Nucl Med* 1997; 24: 81–87.
13. Durmuş-Altun G, Altun A, Salihoglu YS, Altaner Ş, Berkarda Ş. Value of technetium-99m diethyltriaminepentaaceticacid radioaerosol inhalation lung scintigraphy for the stage of amiodarone induced pulmonary toxicity. *Int J Cardiol* 2004; 95: 193–197.
14. Uh S, Lee SM, Kim HT, Chung Y, Kim YH, Park CS. The clearance rate of alveolar epithelium using ^{99m}Tc-DTPA in patients with diffuse infiltrative lung diseases. *Chest* 1994; 106: 161–165.
15. Jones JG, Minty BD, Lawler P, Hulands G, Crawley JCW, Veall N. Increased alveolar epithelial permeability in cigarette smoker. *Lancet* 1980; 12: 66–68.
16. Tabakoglu E, Kaya M, Kutucu Y, Özdemir L. Alveolar epithelial permeability in patients with primary spontaneous pneumothorax as determined by Tc-99m DTPA aerosol scintigraphy. *Ann Nucl Med* 2004; 18: 303–307.
17. Effros RM, Mason GR. Measurement of pulmonary epithelial permeability *in vivo*. *Am Rev Respir Dis* 1983; 127: S59–S65.
18. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 16: S5–S40.
19. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique—1995 update. *Am J Respir Crit Care Med* 1995; 152: 2185–2198.
20. Okudan B, Han S, Baldemir M, Yildiz M. Detection of alveolar epithelial injury by ^{99m}Tc-DTPA radioaerosol inhalation lung scan following blunt chest trauma. *Ann Nucl Med* 2004; 18: 573–577.
21. O'Brodovich H, Coates G. Pulmonary clearance of ^{99m}Tc-DTPA: a noninvasive assessment of epithelial integrity. *Lung* 1987; 165: 1–16.
22. Said SI, Klein RMS, Norrell LW, Maddox YT. Metabolism of alveolar cells: Histochemical evidence and relation to pulmonary surfactant. *Science* 1966; 152: 657–659.
23. Suga K, Mitra A, Domingues C, Alderson PO. Effect of inhaled surfactant on pulmonary deposition and clearance of technetium-99m-DTPA radioaerosol. *J Nucl Med* 1998; 39: 543–547.
24. Freeman BA, Crapo JD. Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *J Biol Chem* 1981; 256: 10986–10992.
25. Johnson KJ, Fantone JC 3rd, Kaplan J, Ward PA. *In vivo* damage of rat lungs by oxygen metabolites. *J Clin Invest* 1981; 67: 983–993.
26. Huffman LJ, Judy DJ, Rao KM, Frazer DG, Goldsmith WT. Lung responses to hypothyroidism, hyperthyroidism, and lipopolysaccharide challenge in rats. *J Toxicol Environ Health* 2000; 61: 623–639.
27. Rizk NW, Luce JM, Hoeffel JM, Price DC, Murray JF. Site of deposition and factors affecting clearance of aerosolized solute from canine lungs. *J Appl Physiol* 1984; 56: 723–729.
28. Pino-Garcia JM, Garcia-Rio F, Diez JJ, Gomez-Mendieta MA, Racionero MA, Diaz-Lobato S, et al. Regulation of breathing in hyperthyroidism: relationship to hormonal and metabolic changes. *Eur Respir J* 1998; 12: 400–407.
29. Mahajan KK, Gupta D, Malhotra KC, Mishra N. Lung transfer components in hyperthyroidism. *JAPI* 1991; 39: 618–620.