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Evaluation of alveolo-capillary permeability in thyrotoxicosis using Tc-99m DTPA aerosol scintigraphy

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Surfactant secreted from type II pneumocytes plays an important role in alveolo-capillary permeability. In thyrotoxicosis, high levels of T3 receptors detected at these cells might affect the alveolo-capillary permeability due to increased serum thyroid hormone levels. The results by CO-diffusion capacity measurement in thyrotoxicosis are conflicting. Changes in alveolo-capillary membrane permeability resulting from thyrotoxicosis are not well established yet. This prompted us to investigate the alveolo-capillary permeability in thyrotoxic patients in comparison with CO-diffusing capacity. For this aim twenty-two non-smoking thyrotoxic patients (before treatment) and fifteen healthy voluntary controls underwent ^{99m}Tc-DTPA aerosol scintigraphy. CO-diffusing and pulmonary function tests were performed in all subjects. After ventilation of radiotracer through a nebulizer for 15 minutes, 30 dynamic images (1 frame/minute) were taken from both lungs. ROI's were drawn over both lung areas, and the time-activity curves were generated. Then clearance half time ($CT_{1/2}$) for radioaerosol was obtained. $CT_{1/2}$ of thyrotoxic patients did not differ from that of the controls: 77.9 ± 25.9 min vs. 79.4 ± 22.3 min; $p > 0.05$. Similar result was found for CO-diffusion parameters. Also there was no significant correlation between $CT_{1/2}$ and CO-diffusion parameters. We concluded that in patients with thyrotoxicosis, the alveolo-capillary permeability is unaffected. Further experimental research is needed to establish the possible effects of thyroid hormones on alveolo-capillary membrane.

Key words: thyrotoxicosis, alveolo-capillary permeability, Tc-99m DTPA, aerosol scintigraphy

INTRODUCTION

IN THYROTOXICOSIS MANY ORGANS, such as heart, lung, are affected as a result of increased metabolism due to elevated levels of thyroid hormones.[1] High-affinity nuclear receptors for T3 were detected at type II pneumocytes in thyrotoxicosis.[2] Surfactant secreted from type II pneumocytes plays an important role in alveolo-capillary permeability. So thyrotoxicosis might affect the alveolo-capillary permeability via a possible effect on surfactant. The results by CO-diffusion capacity measurement in thyrotoxicosis are conflicting.

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Changes in alveolo-capillary membrane permeability due to thyrotoxicosis using radioaerosol scintigraphy are not established yet. ^{99m}Tc-DTPA-aerosol scintigraphy is accepted as a simple, non-invasive and easily applicable method to evaluate the alveolo-capillary permeability.[3–5] Our aim was to investigate the alveolo-capillary permeability in thyrotoxic patients using ^{99m}Tc-DTPA-aerosol scintigraphy in comparison with CO-diffusing capacity.

MATERIAL AND METHODS

Twenty-two (mean age 40.7 ± 12.5 yrs; 19 F, 3 M) non-smoking thyrotoxic patients, before treatment, and 15 (mean age 50.2 ± 7 yrs; 6 F, 9 M) healthy volunteer non-smoking subjects underwent ^{99m}Tc-DTPA aerosol scintigraphy. After ventilation of radiotracer through a nebulizer for 15 minutes, 30 dynamic images (1 frame/minute) were taken from both lungs. ROI's were drawn over both lung areas, and time-activity curves were generated from which clearance half time ($CT_{1/2}$) of the activity from lungs was

Table 1 FT3, FT4, TSH, anti-TPO, anti-Tg values, thyroid ultrasonographic and scintigraphic results of patients

Pt. No.	Age (yr)	Gender	FT3 (pg/d*l*)	FT4 (ng/m*l*)	TSH (μIU/m*l*)	anti-TPO (IU/m*l*)	anti-Tg (IU/m*l*)	USG	Scintigraphy
1	33	F	6.29	2.22	0.002	1000	3000	BDG	hoUpt.
2	49	F	10.7	5.77	0.12	195	145	BDG	hoUpt.
3	21	F	10	4.60	0.013	—	—	N	hoUpt.
4	37	F	5.35	2.13	0.041	214	20	NG	hypoactive
5	24	F	7.67	3.24	0.002	113	27	N, het.	hoUpt.
6	34	M	20	6	0.01	—	—	BDG	hoUpt.
7	57	F	7.28	3.25	0.002	—	—	NG	—
8	27	F	13.9	6	0.002	1000	60.6	DBG	hoUpt.
9	30	F	7.01	4.35	0.022	—	—	NG	normoactive
10	41	M	40	6	0.02	—	—	BDG	hoUpt.
11	24	F	10.9	4.14	0.002	1000	163	BDG	hoUpt.
12	47	M	14.2	6	0.034	—	—	N, het.	—
13	25	F	11.5	4.62	0.01	118	332	N	hoUpt.
14	50	M	14.2	4.84	0.002	14	131	N, het.	hoUpt.
15	52	F	8.44	2.97	0.02	10	20	N, het.	hoUpt.
16	17	F	7.99	3.44	0.002	105	821	BDG	hoUpt.
17	56	F	25.6	6	0.002	—	—	MNG	hypoactive
18	44	F	6.49	2.6	0.037	—	—	N	—
19	55	F	5.45	2.37	0.04	—	—	N	hoUpt.
20	43	F	6.46	2.29	0.017	—	—	MNHG	hypoactive
21	65	F	6.58	3.85	0.01	20	98.9	NG	hetUpt.
22	40	F	5.84	1.91	0.004	10	923	NG	hyperactive
23	36	F	15	6	0.046	10.8	20	N, het.	hoUpt.
24	49	F	6.54	3.5	0.002	—	—	N	hoUpt.

FT3 (1.8–5.0 pg/d*l*), FT4 (0.8–1.9 ng/m*l*), TSH (0.4–4.4 μIU/m*l*), anti-TPO (0–35 IU/m*l*), anti-Tg (0–40 IU/m*l*)
USG; N: normal sized thyroid, BDG: bilateral diffuse goiter, NG: nodular goiter, MNG: multinodular goiter, het.: heterogeneous
Scintigraphy; hoUpt.: homogeneous tracer uptake, hetUpt.: heterogeneous tracer uptake

calculated. CO-diffusing capacity was measured in all patients. Lung function test was performed in all subjects.

^{99m}Tc-DTPA Aerosol Scintigraphy: The radioaerosols were generated from a commercial lung aerosol delivery unit (Venti-Scan III BIODEX®), containing 35–40 mCi (1.295–1.480 GBq) ^{99m}Tc-DTPA in 2–4 m*l* saline. Aerosols with a mass median diameter of 0.5 μ were produced with an oxygen inflow 9 *l*/min. Subjects inhaled the radioaerosol for 15 minutes and then they were placed supine over a gamma camera, equipped with a low-energy high resolution parallel hole collimator set on 140 keV photopeak of ^{99m}Tc. Lungs were imaged in posterior projection with a low-energy, all-purpose collimator. Clearance from the lungs was measured for 30 min (1 min/frame). Areas of interest (ROI) were placed over both lung areas, and time-activity curves were obtained, and half time ($CT_{1/2}$) of ^{99m}Tc-DTPA was measured from the curves.

CO-DC: Carbon monoxide diffusing capacity (CO-CD) was measured using Single Breath method. By this method, a gas mixture of 0.3% CO and 10% He was inhaled by the patient who holds his breath for approximately 10 s. Then he exhaled maximally, and the first 750 m*l* of the exhaled gas volume was expired. From the rest, 1 *l* was analyzed in order to assay the Pco, diffusing

Table 2 FVC, FEV_1, VC, DL_{CO}/VA, $CT_{1/2}$ values of the patients and the controls

Pt. No.	DL_{CO}/VA (% pred.)	$CT_{1/2}$ (min)	Control No.	DL_{CO}/VA (% pred.)	$CT_{1/2}$ (min)
1	63	97.1	1	68	60.2
2	71	63.0	2	73	112.8
3	77	48.3	3	93	52.0
4	72	48.1	4	69	59.9
5	61	79.7	5	81	71.5
6	86	64.5	6	67	75.7
7	97	79.7	7	87	66.3
8	69	55.3	8	75	104.1
9	87	63.1	9	75	72.2
10	80	72.0	10	87	76.2
11	65	60.0	11	77	126.6
12	87	112.2	12	76	63.7
13	63	72.7	13	92	71.1
14	72	97.0	14	103	91.7
15	76	64.5	15	86	87
16	—	38.0			
17	60	71.3			
18	98	111.1			
19	69	66.4			
20	56	108.0			
21	61	137.5			
22	69	112.2			
23	—	101.0			
24	82	62.0			

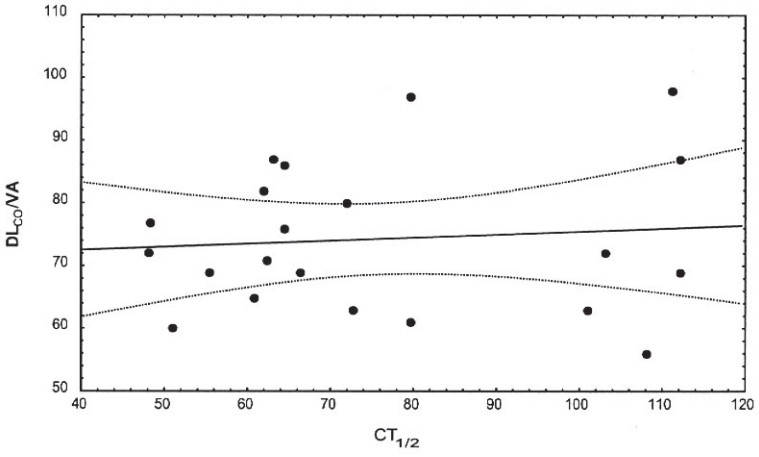

Fig. 1 Correlation graph between $CT_{1/2}$ and DL_{CO}/VA of thyrotoxic patients.

capacity (DL_{CO}), alveolar volume (VA) and transfer factor (DL_{CO}/VA) values. The effect of hemoglobin (Hb) concentration on DL_{CO} was corrected by the formula:

$$DL_{CO} = DL_{CO}/0.06965\ (Hb)$$

Statistical Analysis: $CT_{1/2}$ values of the patient and the control groups were compared with Mann-Whitney U-test, $CT_{1/2}$, and the relationship between $CT_{1/2}$ value and CO-Transfer Factor was done using Pearson correlation test. Any value of $p < 0.05$ was considered statistically significant.

RESULTS

Thyroid hormone, anti-TPO and anti-Tg values, and thyroid ultrasonographic and scintigraphic results of the patients were presented in Table 1. As shown in Table 1, almost all patients (20/22) in our study group had Grave's disease. Therefore, we were not able to compare the results according to the cause of the thyrotoxicosis. No patients had taken any medication, including antithyroid or β-blocker drug, for thyrotoxicosis before the study.

$CT_{1/2}$ and DL_{CO}/VA values of the patient and the control group were presented in Table 2. $CT_{1/2}$ of thyrotoxic patients were statistically not different from the controls; 77.9 ± 25.9 min vs. 79.4 ± 22.3 min; $p > 0.05$. There was no significant correlation either between $CT_{1/2}$ and CO-diffusion parameters (Fig. 1). Similarly, mean DL_{CO}/VA value of thyrotoxic patients was statistically not different from those of the controls: 74.3 ± 11.8% vs. 80.6 ± 10.5%; $p > 0.05$, respectively. DL_{CO}/VA decreased in 12 of 22 (54.5%) patients.

Pulmonary function test results of the patients were as follows; FVC: 84.3 ± 18.0%, FEV_1: 88.2 ± 17.5%, and VC: 73.7 ± 11.8%. VC was lower in 3 of 14 patients, and in one patient it was higher than the normal values.

DISCUSSION

In thyrotoxicosis the effects of elevated thyroid hormones on lung are tachypnea, respiratory muscle weakness, high-output congestive left ventricular failure, pulmonary artery dilatation and hypertension, increase in O_2 consumption, CO production, minute ventilation, ventilatory response to hyper- and hypocapnia, decrease in vital capacity, CO diffusing capacity, and lung compliance.[1] Although some information about the effects of elevated thyroid hormones on the alveolo-capillary membrane was obtained in animal studies, no information is available about the possible effects on adults lung. In thyrotoxicosis O_2 consumption is increased due to increased basal metabolism. Consequently, radical oxygen species production increases in other organs as well as in lungs. This might result in cellular damage in lung.

Almost all reported histo-pathological lung alterations in thyrotoxicosis were noted in experimental animal studies.[2,6,7] Increased number of the high-affinity binding sites for T3 hormone in type II pneumocytes was found in thyrotoxic rats.[8] Thus it could be postulated that the surfactant amount might increase in thyrotoxicosis.[9] In rats after the administration of a dose of 1 mg/kg/d L-Thyroxin for 6–7 days, an increase in phospholipids in lung tissue were detected.[2] But the surfactant showed no significant change, except for the phosphatidyl ethanolamine in the sediment fraction. In another experimental study, rats were administered 0.1 mg/100 mg/d L-Thyroxin for 16 days, and at the end of the administration one group was inhaled with air and the other with lipopolysaccharide (LPS).[10] In both groups alveolo-capillary permeability, phagocytes in broncho-alveolar lavage (BAL) fluid were significantly higher than in the controls. More marked changes were observed in the LPS inhaled group. Additionally, significantly elevated LDH, an indicator of cellular damage, was measured in BAL of the L-Thyroxin administered groups. Again, the increase was more marked

in LPS group.

Smith et al.[11] found that exogenous T3 decreases glycosaminoglicans in human skin fibroblast cultures, and suggested that thyroid hormones could change the extracellulary matrix structure in lungs. In thyrotoxic rats, an increase was found in dimensions and surfactant secretion amount in type II pneumocytes, but no change in the content of surfactant.[2] After removing surfactant by repeated lung lavage with isosaline in rabbits, the ^{99m}Tc-DTPA clearance decreased significantly.[12] After the inhalation of surfactant, it increased significantly. ^{99m}Tc-DTPA clearance decreased significantly in irradiated (20 Gy) dogs after 12 days, and was elevated on the 14th day.[13] A significant increase in the ^{99m}Tc-DTPA clearance was also found in non-irradiated dogs after surfactant inhalation. These findings indicate that the possible changes in alveolo-capillary membrane due to increased thyroid hormones could affect the solute particle permeability. However, in interstitial disorders or surfactant insufficiency of lung such as ARDS, asbestozis, pneumoconiosis, infections, hyaline membrane disease, idiopathic and pulmonary fibrosis, the alveolo-capillary permeability was found to be altered.[3–5]

In our study, there was no statistically significant difference between the thyrotoxic patients and the controls in ^{99m}Tc-DTPA clearances. We could not evaluate the possible alterations in surfactant since either BAL or microscopic examination of lung parenchyma is needed. We found a decrease in vital capacity in only 21% of our patients.

With respect to the DL_{CO}/VA value we found no significant difference in the thyrotoxic patients compared with the controls. Also there was no correlation between $CT_{1/2}$ and DL_{CO}/VA in our patients. The results of CO-diffusing capacity tests in the thyrotoxic patients were conflicting. CO-diffusing capacity is affected by membrane thickness and surface, diffusion constant of the gas, pressure gradient between two sides of the membrane, pulmonary blood flow, and hemoglobin level. Gas diffusion occurs in approximately 95% of the alveolo-capillary surface, and solid permeability in about 5% of this surface. Since in our patients, we could not investigate the surfactant amount in BAL, we are unable to determine whether the lack of change in surfactant content, contrary to expectation, could be the possible reason in our patients. This was the limitation of our study.

In the light of the previous studies and ours', we suggested that in thyrotoxicosis, either there was no change in alveolo-capillary membrane or we could not detect the possible alterations with the method we used. Possible alterations due to elevated thyroid hormones could be evaluated with histo-pathologic techniques more properly, but this is not an ethically used/approved method in humans. In conclusion, we report in this study that in patients with thyrotoxicosis, the alveolo-capillary permeability is unaffected. Further experimental research is needed to establish the possible effects of thyroid hormones on alveolo-capillary membrane.

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