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The influence of volatile anesthetics on alveolar epithelial permeability measured by noninvasive radionuclide lung scan

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Many volatile anesthetics have long been thought to affect pulmonary functions including lung ventilation (LV) and alveolar epithelial permeability (AEP). The purpose of this study is to examine the influence of volatile anesthetics on LV and AEP by noninvasive radionuclide lung imaging of technetium-99m labeled diethylene triamine pentaacetic acid radioaerosol inhalation lung scan (DTPA lung scan).

Twenty patients undergoing surgery and receiving volatile anesthesia with 1% halothane were enrolled as the study group 1. The other 20 patients undergoing surgery and receiving volatile anesthesia with 1.5% isoflurane were enrolled as the study group 2. At the same time, 20 patients undergoing surgery with intravenous anesthesia drugs were included as a control group. Before surgery, 1 hour after surgery, and 1 week after surgery, we investigated the 3 groups of patients with DTPA lung scan to evaluate LV and AEP by ^{99m}Tc DTPA clearance halftime (T1/2).

No significant change or abnormality of LV before surgery, 1 hour after surgery, or 1 week after surgery was found among the 3 groups of patients. In the control group, the ^{99m}Tc DTPA clearance T1/2 was 63.5 ± 16.4, 63.1 ± 18.4, and 62.8 ± 17.0 minutes, before surgery, 1 hour after surgery, and 1 week after surgery, respectively. In group 1, it was 65.9 ± 9.3, 62.5 ± 9.1, and 65.8 ± 10.3 minutes, respectively. No significant change in AEP before surgery, 1 hour after surgery, or 1 week after surgery was found. However, in group 2, the ^{99m}Tc DTPA clearance T1/2 was 65.5 ± 13.2, 44.9 ± 10.5, and 66.1 ± 14.0 minutes, respectively. A significant transient change in AEP was found 1 hour after surgery, but it recovered 1 week after surgery.

We conclude that volatile anesthesia is safe for LV and AEP, and only isoflurane can induce transient change of AEP.

Key words: volatile anesthetics, lung ventilation, alveolar epithelial permeability

INTRODUCTION

INTEREST IN LUNG FUNCTION during general anesthesia has increased because of the high incidence of pulmonary complications in clinical practice.[1–5] In recent years, noninvasive techniques have been developed to assess the integrity of the alveolo-capillary barrier. One such technique entails measuring the pulmonary clearance of technetium-99m labeled diethylene triamine pentaacetic acid (^{99m}Tc DTPA) radioaerosols. The permeability of ^{99m}Tc DTPA to the alveolo-capillary barrier is known to increase after exposure to various inhaled substances and in various diseases.[6–13] In addition, the ^{99m}Tc DTPA radioaerosol lung scan (DTPA lung scan) can be applied for the visualization of lung ventilation (LV).[7,8,13] The lung itself is the site of uptake and elimination of volatile or gaseous anesthetics, and many volatile anesthetics

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Table 1 Detailed data of the study group 1 patients

Patient No.	Age (years)	Sex	Operative procedure	Operation duration (hours)	^{99m}Tc DTPA clearance T1/2 (minutes)		
					before surgery	1 hour after surgery	1 week after surgery
1	37	F	Mastectomy	4.0	71.2	67.8	69.0
2	38	F	Mastectomy	4.0	54.3	50.9	51.2
3	40	F	Hysterectomy	5.0	55.6	49.0	53.1
4	41	F	Hysterectomy	4.0	59.0	56.7	60.9
5	43	F	Hysterectomy	5.0	65.1	67.1	69.8
6	44	F	Mastectomy	4.0	58.9	54.3	55.0
7	46	F	Hysterectomy	4.5	67.8	65.1	70.1
8	47	F	Mastectomy	4.5	78.9	73.1	80.1
9	49	F	Mastectomy	3.5	46.7	44.5	45.6
10	50	F	Hysterectomy	4.5	70.7	67.8	71.2
11	51	F	Hysterectomy	4.5	66.7	69.8	65.7
12	53	F	Mastectomy	4.5	60.6	55.8	68.0
13	55	M	Gastrectomy	4.0	78.9	71.2	76.9
14	55	M	Gastrectomy	4.5	65.7	60.7	66.7
15	56	F	Mastectomy	4.5	75.6	74.3	74.5
16	60	F	Mastectomy	4.5	65.7	60.9	61.3
17	60	M	Gastrectomy	5.5	61.6	56.7	58.9
18	62	F	Mastectomy	4.0	64.3	65.7	64.9
19	62	F	Mastectomy	4.5	65.7	60.1	65.1
20	66	M	Gastrectomy	5.0	85.7	79.0	88.7
Mean	50.8			4.4	65.9	62.5	65.8
SD	8.7			0.5	9.3	9.1	10.3
Maximum	66			5.5	85.7	79.0	88.7
Minimum	37			3.5	46.7	44.5	45.6

*SD; standard deviation, F; female, M; male

have long been thought to affect LV or AEP.[1–3,5,6,12] Therefore, the purpose of this study is to examine the effects of two common volatile anesthetics with halothane and isoflurane on LV and AEP based on the findings of DTPA lung scan.

MATERIALS AND METHODS

Group 1: 20 patients (16 women, 4 men; mean age: 50.8 ± 8.7 years) undergoing surgery (operation duration: 4.4 ± 0.5 hours) were included and a volatile anesthetic, 1% halothane, was administered for maintenance of anesthesia. Group 2: 20 patients (16 women, 4 men; mean age: 51.8 ± 7.1 years) undergoing surgery (operation duration: 4.4 ± 0.7 hours) were included and a volatile anesthetic, 1.5% isoflurane, was administered for maintenance of anesthesia. Control group: 20 patients (16 women, 4 men; mean age: 49.0 ± 11.0 years) undergoing surgery (operation duration: 4.4 ± 0.8 hours) were included and their anesthesia was maintained with the administration of intravenous anesthesia drugs (fentanyl and propofol) without volatile anesthetics. None of the 60 patients had a history of smoking or cardiopulmonary disease. All of the 60 patients showed normal chest X-ray findings, pulmonary function test results and laboratory data (including renal and liver function tests) before surgery, 1 hour after surgery and 1 week after surgery. All of the 60 patients underwent endotracheal intubation, and the oxygen concentration was adjusted to 50% by mixing with medical air. Informed consent was obtained from all the participating patients.

DTPA lung scans were performed on all 60 patients 1 day before surgery, 1 hour after surgery, and 1 week later. ^{99m}Tc was chelated with DTPA (Daiichi Radioisotope, Tokyo, Japan) by introducing 1.85 GBq (50 mCi) of $^{99m}TcO_4^-$ into a vial containing 20 mg of DTPA and 2.2 mg of tin chloride. ^{99m}Tc DTPA radioaerosol was generated by a commercial lung aerosol delivery unit (AERO/VENT, model AV-400 MEDI-NUCLEAR, California, USA) which contained 740 MBq (20 mCi) of ^{99m}Tc DTPA in 2 m*l* of saline. The radioaerosol droplet size was measured by an inertial impactor (Model PC-2, California Measurement Inc., California, USA). The mass median aerodynamic diameter (MMAD) of the ^{99m}Tc DTPA radioaerosol was smaller than 1 μm, with an oxygen air flow rate of 7 liters/minute. All of the subjects were studied in the supine position and inhaled for 2 minutes from the aerosol delivery unit until the total radioactivity was over 200,000 counts by normal tidal breathing. Data were collected over another 30 minutes by means of a large field computerized gamma camera (Dual Genesys, ADAC Laboratories, CA, USA) over the posterior view

Table 2 Detailed data of the study group 2 patients

Patient No.	Age (years)	Sex	Operative procedure	Operation duration (hours)	^{99m}Tc DTPA clearance T1/2 (minutes)		
					before surgery	1 hour after surgery	1 week after surgery
1	41	F	Hysterectomy	4.0	60.9	33.2	62.1
2	43	F	Hysterectomy	5.0	63.3	27.5	59.8
3	43	F	Hysterectomy	5.0	53.4	40.9	50.4
4	44	F	Mastectomy	3.5	57.2	48.2	56.3
5	45	F	Hysterectomy	4.5	69.4	35.5	72.3
6	47	F	Mastectomy	4.5	85.2	61.3	88.9
7	49	F	Mastectomy	3.5	47.1	43.1	46.2
8	49	F	Mastectomy	3.5	42.8	33.1	45.5
9	50	F	Hysterectomy	4.5	75.8	51.0	74.2
10	51	F	Hysterectomy	5.0	60.0	27.5	58.9
11	52	F	Mastectomy	4.0	68.9	48.3	65.3
12	52	M	Gastrectomy	4.5	57.9	41.2	59.0
13	53	F	Mastectomy	4.5	63.3	52.1	69.8
14	55	M	Gastrectomy	5.0	89.1	55.7	88.9
15	56	F	Mastectomy	4.5	82.0	61.7	88.7
16	56	F	Mastectomy	4.5	61.0	40.1	59.6
17	60	M	Gastrectomy	6.0	58.1	37.9	61.5
18	62	F	Mastectomy	3.0	67.6	57.5	60.3
19	62	F	Mastectomy	4.0	58.9	48.3	62.1
20	66	M	Gastrectomy	5.0	90.6	53.4	91.3
Mean	51.8			4.4	65.6	44.9	66.1
SD	7.1			0.7	13.2	10.5	14.0
Maximum	66			6.0	90.6	61.7	91.3
Minimum	41			3.0	42.8	27.5	45.5

Table 3 Detailed data of the control group patients

Patient No.	Age (years)	Sex	Operative procedure	Operation duration (hours)	^{99m}Tc DTPA clearance T1/2 (minutes)		
					before surgery	1 hour after surgery	1 week after surgery
1	29	F	Mastectomy	5.5	85.2	90.9	86.3
2	32	F	Hysterectomy	4.0	60.2	57.8	62.3
3	35	F	Hysterectomy	4.5	58.4	56.7	60.3
4	39	F	Hysterectomy	4.0	40.2	36.2	35.2
5	42	F	Hysterectomy	3.0	49.6	58.1	55.2
6	42	F	Hysterectomy	4.5	64.1	55.0	60.5
7	42	F	Hysterectomy	4.5	50.2	45.6	47.6
8	45	F	Hysterectomy	2.5	70.4	74.6	68.7
9	45	F	Mastectomy	5.0	63.3	55.9	59.8
10	48	F	Hysterectomy	5.0	98.3	105.6	92.3
11	49	F	Hysterectomy	4.0	65.6	61.2	62.3
12	52	M	Gastrectomy	4.5	63.3	70.2	69.8
13	53	F	Mastectomy	6.0	48.3	52.3	52.3
14	56	F	Hysterectomy	3.5	43.5	46.9	45.3
15	56	F	Gastrectomy	4.0	50.1	47.2	44.3
16	60	M	Colectomy	5.0	85.7	84.0	86.7
17	62	F	Hysterectomy	4.0	52.9	47.5	49.2
18	62	M	Gastrectomy	4.5	82.0	85.3	83.7
19	64	M	Colectomy	5.0	86.3	83.0	88.2
20	67	F	Gastrectomy	4.5	52.1	48.2	45.3
Mean	49.0			4.4	63.5	63.1	62.8
SD	11.0			0.8	16.4	18.4	17.0
Maximum	67			6.0	98.3	105.6	92.3
Minimum	29			2.5	40.2	36.2	35.2

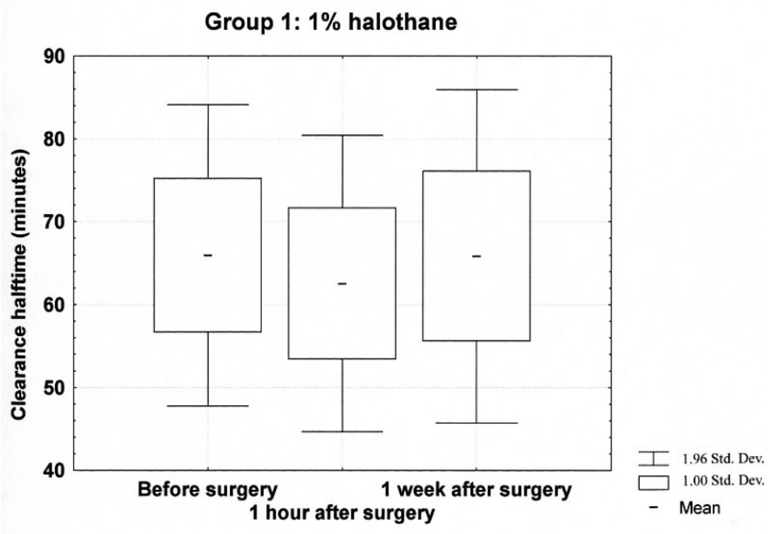

Fig. 1 The change in alveolar epithelial permeability which is represented as ^{99m}Tc DTPA T1/2 of the lungs, before surgery, 1 hour after surgery, and 1 week after surgery in the study group 1 patients.

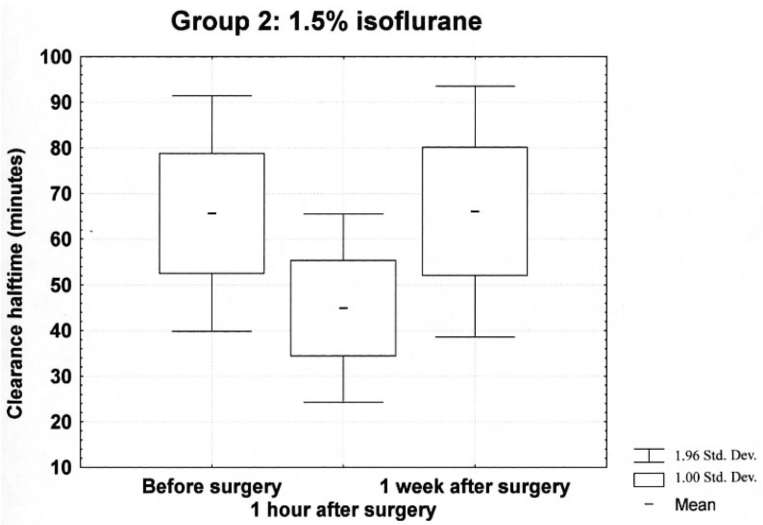

Fig. 2 The change in alveolar epithelial permeability which is represented as ^{99m}Tc DTPA T1/2 of the lungs, before surgery, 1 hour after surgery, and 1 week after surgery in the study group 2 patients.

including the entire chest. The data were acquired as a series of 30 consecutive frames of 1-minute duration each in a 64 × 64 matrix with a word mode. Interpretations of the DTPA lung scans were performed by two nuclear medicine specialists, and the procedures were as follows: (1) LV: The first image in the series was selected as the equilibrium lung ventilation image. Two independent observers judged the LV images according to the established criteria.[7,8,13] (2) AEP: The summation of the series of 30 images was displayed. A region of interest (ROI) was manually created over the total of both lungs. A power exponential fitting routine was then used to calculate the halftime (T1/2, minutes) of ^{99m}Tc DTPA radioaerosol lung clearance to represent AEP.[6–13]

RESULTS

The detailed data of the 2 study groups and control group patients are shown in Tables 1–3. Among the 3 groups, there were no significant differences in age or operative duration, or DTPA lung scan findings (including LA and AEP) before the operation (p values < 0.01 by dependent Student's tests).

In the study and control groups, no significant LV change or abnormality such as inhomogeneous distribution, inverted base to apex gradient, or segmental defects were found 1 hour and 1 week after surgery when compared with before surgery.

The ^{99m}Tc DTPA clearance T1/2 in group 1 was 65.9 ± 9.3, 62.5 ± 9.1, and 65.8 ± 10.3 minutes, before surgery, 1 hour after surgery, and 1 week after surgery, respectively. The difference in ^{99m}Tc DTPA clearance T1/2 before and after anesthesia was not significant (p values > 0.05, by dependent Student's tests) (Fig. 1). The ^{99m}Tc DTPA clearance T1/2 in group 2 was 65.5 ± 13.2, 44.9 ± 10.5, and 66.1 ± 14.0 minutes, before surgery, 1 hour after surgery, and 1 week after surgery, respectively. The difference was significant between the clearance T1/2 before surgery and 1 hour after surgery as well as between that 1 hour postoperatively and 1 week postoperatively (p

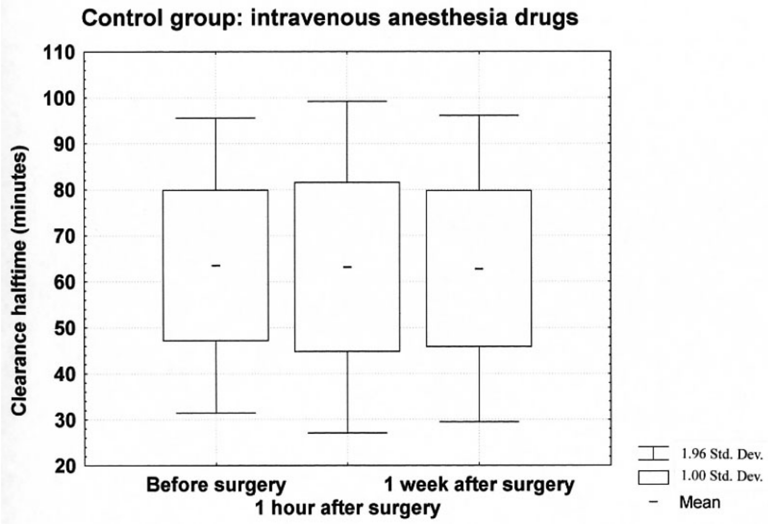

Fig. 3 The change in alveolar epithelial permeability which is represented as ^{99m}Tc DTPA T1/2 of the lungs, before surgery, 1 hour after surgery, and 1 week after surgery in the control group patients.

values < 0.01) (Fig. 2). In the control group, the ^{99m}Tc DTPA clearance T1/2 was 63.5 ± 16.4, 63.1 ± 18.4, and 62.8 ± 17.0 minutes, before surgery, 1 hour after surgery, and 1 week after surgery, respectively. The difference in ^{99m}Tc DTPA clearance T1/2 before and after anesthesia was not significant (p values > 0.05) (Fig. 3).

DISCUSSION

The integrity of the three compartments consisting of the alveolar space, capillary space, and interstitium is necessary to maintain normal gas exchange. Small aerosols can move across the three compartments via transcellular and intercellular routes.[14,15] ^{99m}Tc DTPA radioaerosols can deposit in the lining layer of the pulmonary epithelial surface and then pass through the barrier,[16] an activity which can be used to measure AEP change. The National Heart, Lung, and Blood Institute (NHLBI) Workshop on techniques to evaluate lung alveolar—microvascular injury (AEP change) concluded that the ^{99m}Tc DTPA radioaerosol lung clearance T1/2 can express an index of AEP change, and it is a highly sensitive tool with a wide spectrum for detecting lung injuries, even those of a mild degree.[6–13] In addition, DTPA lung scans can provide information about LV.[7,8,13]

In this study, the change in AEP resulting from pulmonary alveolo-capillary barrier damage following the administration of volatile anesthetics is considered to be an early event in the development of severe lung injury. Early detection and correction of such damage may sometimes be beneficial. However, detecting such an injury is often complicated and invasive because of the lack of an easily available and noninvasive tool. Therefore, this reinforces the finding that the technique, although with a non-specific weakness, is noninvasive, rapid, easy to perform, and extremely sensitive in detecting acute and mild alveolo-capillary barrier injuries resulting from the effects of the two common volatile anesthetic—halothane and isoflurane on the lung ventilation and permeability of the alveolo-capillary barrier (represented as AEP change) in this study.

We know that smoking can significantly increase lung clearance of ^{99m}Tc DTPA radioaerosols and shorten the T1/2.[17–19] Therefore, in this study, patients with a history of smoking were excluded. Wollmer and Royston et al. found significantly shortened pulmonary clearance of ^{99m}Tc DTPA in rabbits under general anesthesia for over 48 hours with high oxygen concentrations (≥99%).[4,5] However, in the present study, oxygen concentration was adjusted to only 50%, and the duration of anesthesia was shorter than 6 hours. Therefore, the more rapid pulmonary clearance of ^{99m}Tc DTPA in group 2 patients who received isoflurane should be indicative of the effects of volatile anesthetics rather than oxygen. It is well known that increased lung volume due to artificial ventilation may cause increased ^{99m}Tc DTPA radioaerosol lung clearance (shortened T1/2).[20] However, in our study, we did not consider the fact that subjects were ventilated could influence T1/2 of ^{99m}Tc DTPA radioaerosol lung clearance, because all study and control patients were ventilated by endotracheal intubation, in addition to which no significant abnormalities on pulmonary function test results were found in the 3 groups before or after surgery.

The shortened T1/2 of ^{99m}Tc DTPA lung clearance following the use of the volatile anesthetic—isoflurane in study group 2 patients suggests that the volatile anesthetic—isoflurane increased AEP. The findings of the literature about the influences of volatile anesthetics—isoflurane and halothane on lung clearance of ^{99m}Tc DTPA were controversial.[6,12,21] Our results are compatible with the recent reports[6,12] that only isoflurane, but not halothane, can transiently shorten T1/2 of lung clearance of ^{99m}Tc DTPA. However, the mechanism of AEP injury following exposure to the volatile anesthetic—isoflurane in study group 2 is still unclear. Surfactant has been shown to be of therapeutic value to improve AEP and prolong lung clearance T1/2 of ^{99m}Tc DTPA.[22–24] After reviewing the literature, volatile anesthetics—both isoflurane and halothane were found to inhibit surfactant synthesis. However, the influence of isoflurane seemed more significant than that of halothane.[25,26] Therefore, we propose that the shortened T1/2 of lung clearance of ^{99m}Tc DTPA may have been due to the effects of isoflurane on the pulmonary surfactant system, although we could not directly measure surfactant level changes in the study patients.

Although the mechanism of AEP injury following exposure to the volatile anesthetic—isoflurane in study group 2 is still unclear, we believe that DTPA lung scan is useful as an additional and sensitive method to detect early and minor lung injury due to volatile anesthetic—isoflurane based on the findings of this study. This may provide evidence that volatile anesthesia can induce only mild and transient changes in AEP. In accordance with our results, we think that the clinical use of volatile anesthesia should be safe and not induce permanent lung damage.

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