

Pulmonary function assessment in the early phase of patients with smoke inhalation injury from fire

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Objectives: Fire smoke contains toxic gases and numerous chemical compounds produced by incomplete combustion, and may cause injury to the airways. Increased airway reactivity, as well as a decrease in lung function, has been reported as a sequela of smoke inhalation injury. This study was undertaken to assess lung functions in the early phase of patients with smoke inhalation damage from fires.

Methods: A total of 15 patients with fire smoke inhalation (fire smoke group) and 15 subjects with chronic cough but no previous history of lung disease (chronic cough group) were enrolled. For diagnosis of inhalation injury, we performed bronchoscopy, high-resolution computed tomography (HRCT), as well as arterial carboxyhemoglobin (COHb) at admission. Clinical characteristics, pulmonary function tests (PFTs) and mannitol bronchial provocation tests (BPTs) were analyzed and compared between the two groups.

Results: In fire smoke group, initial COHb levels and the PaO₂/FiO₂ ratio were (14.8±18.49)% and 425.7±123.68, respectively. Of seven patients performing HRCT, 4 (57.1%) showed the CT findings compatible with lung involvement of inhalation injury. Post bronchodilator value of the percent of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) were (76.0±24.27)% and (79.8±27.82)%, respectively. Pre-and post- bronchodilator forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅) and the percent predicted FEF₂₅₋₇₅ were 2.41±1.47 *vs.* 2.65±1.45 L (P=0.045), and (68.7±37.29)% *vs.* (76.4±36.70)% (P=0.031), respectively. Two patients (13.3%) had positive bronchodilator response (BDR). In fire smoke and chronic cough group, all the subjects showed mannitol BPTs within normal limits.

Conclusions: Fire smoke inhalation leads to mild obstructive small airway disease pattern of pulmonary function in the early phase of patients with fire smoke damage. Further studies, however, need to be followed to identify the relationship between airway narrowing to inhaled mannitol and smoke inhalation injury.

Keywords: Bronchial provocation tests (BPTs); fires; mannitol; smoke inhalation injury

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Introduction

Fire smoke contains superheated gases, steam, and numerous noxious chemical compounds produced by incomplete combustion. It is generally accepted that the most striking features in the airways of the lungs after smoke inhalation are airway obstruction and bronchoconstriction due to intense inflammatory reaction and inspissated secretions caused by inhalation of particulate debris, irritant

materials, fumes, or various toxic vapors (1). The survivors from fire accidents may inhale toxic combustion products generated by fires and present with symptoms that resemble asthma, such as severe cough, sputum, choking sensation, and wheezing (2-4).

Bronchial provocation tests (BPTs) are widely used to identify individuals with bronchial hyperresponsiveness (BHR), which is an important pathophysiological feature of

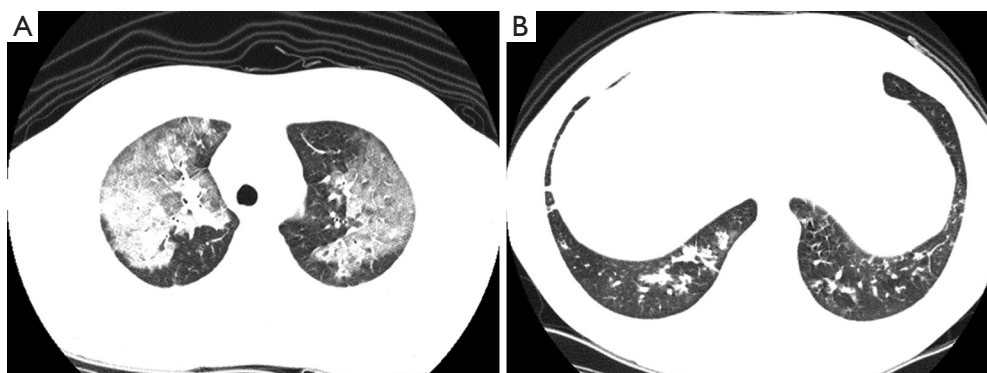


Figure 1 Bronchoscopy showing edema, inflammation, and soot in the carina and both main bronchi in a 22-year-old man with smoke inhalation injury at the first day after admission.

asthma (5). The airways of asthmatic patients are narrowed in response to the inhalation of aerosols of sodium chloride (6). The mechanism causing airway narrowing by hypertonic saline is thought to involve an increase in osmolarity and release of mediators from the mast cells and sensory nerves (6,7). Mannitol with high osmolarity is known to be more potent than sodium chloride in producing mast-cell histamines. An increased airway reactivity in previous healthy individuals may be expected after acute exposure to fire smoke, although the studies have shown that pulmonary function abnormalities in burn patients depend on the type of injury (8,9).

The present study was aimed to assess pulmonary functions by using pulmonary function test (PFT) and mannitol BPT in the early phase of patients who had smoke inhalation injury from fires.

Patients and methods

Study design and subjects

The study was approved by the local institutional review board, and the patients permitted their medical records for research from the hospital database. Between January 2010 and January 2012, we conducted an observational study in consecutive patients hospitalized at the burn center of Hallym University Hangang Sacred Heart Hospital in Seoul, South Korea.

The inclusion criteria were as follows: adult age, minor burns involving a total body surface area of less than 15%, initial arterial carboxyhemoglobin (COHb) levels of more than 5%, or a history of exposure to smoke in closed space and presence of singed nasal hairs, sooty sputum, or

auscultatory findings such as wheezing or rhonchi. Diagnosis of inhalation injury was made by fiberoptic bronchoscopy, which was normally performed within 48 h after admission. We characterized bronchoscopic findings for inhalation injury as follows: edema, blistering, carbonaceous material, soot, hemorrhage, inflammation, ulceration, and necrosis of the bronchial mucosa (*Figure 1*). The severity of inhalation injury was graded according to the number of presenting features: near normal, no features present; mild, 1-3 features present; moderate, 4-6 features present; severe, 7-8 features present (10). Patients who had underlying structural lung diseases and past history of tuberculosis, asthma, and atopy were excluded. After admission, patients with smoke inhalation were treated according to the lung care standards of our burn unit, including fluid and nutritional support, maneuvers to prevent pneumonia, endotracheal intubation for airway maintenance, and mechanical ventilation if indicated. We also performed high-resolution computed tomography (HRCT) to identify lung parenchymal involvement of inhalation injury.

During the study periods, the subjects complaining of cough were recruited after matching for age, sex, height and body mass index from our outpatient department after obtaining written informed consent. All participants who had suffered from cough for more than three weeks but had no previous history of respiratory disease or atopy.

High-resolution computed tomography (HRCT)

Computed tomography (CT) scans were acquired using a GE HiSpeed CT/i scanner (GE Medical System, Milwaukee, WI, USA) with no use of contrast media. All CT data were reconstructed by using a high-spatial-frequency (bone)

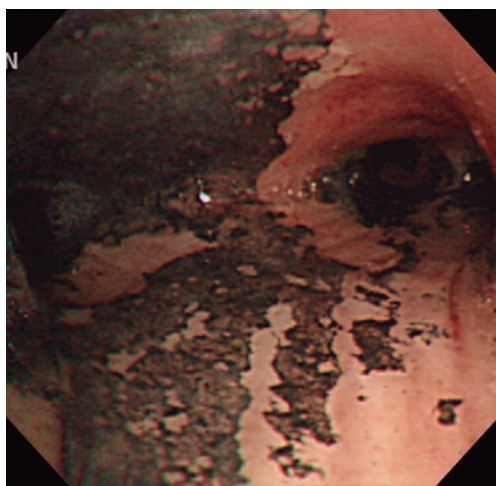


Figure 2 High-resolution computed tomography of a 27-year-old man with 3% of flame burn and inhalation injury at the first day after admission. (A) Extensive ground glass opacities with consolidations were seen in both upper lungs; (B) Peribronchovascular ground glass attenuations were seen in both lower lungs.

algorithm with a section thickness of 1 mm. Window width and window levels were 400 HU and 20 HU for the mediastinum, and 1,500 HU and -700 HU for the lungs, respectively.

If HRCT findings showed peribronchovascular ground glass opacity with/without consolidation, bronchial wall thickenings, branching linear attenuations, atelectasis, or interlobular septal thickening in patients with fire smoke inhalation, we considered inhalation injury to have resulted in lung parenchymal involvement (*Figure 2*).

Each CT finding was interpreted by a radiologist, and defined as; ground glass opacity, a hazy area of air space of increased lung attenuation with preservation of bronchial and vascular markings; consolidation, alveolar space that contains liquid instead of gas; atelectasis, a condition where the alveoli deflated; branching linear attenuations referred to as poorly defined, small centrilobular nodules and branching linear opacity of small airways (2-4 mm diameter) originate from a single stalk; bronchial wall thickening, greater than 0.3 mm or half the width of the accompanying pulmonary artery branch; interlobular septal thickening, greater than 2.0 cm in length and 0.1 mm in thickness (11,12).

PFT and mannitol bronchoprovocation test

Before the PFT and the mannitol BPT, all subjects were asked to refrain from taking short-acting bronchodilators for

6 hours and long-acting bronchodilator for 12 h prior to the study. And the two tests were performed on separate days.

For pulmonary functions test, we used a spirometer (Vmax22; SensorMedics; Yorba Linda, CA, USA), which was calibrated with a 3 L syringe on the morning of each day. In accordance with the American Thoracic Society, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}), peak expiratory flow (PEF) and diffusing capacity of the lung to transfer carbon monoxide (DLco) were measured. Subsequently, post-bronchodilator values were measured 15-20 min after the administration of an inhaled bronchodilator (e.g., 400 μ g of salbutamol) (13). Bronchodilator response (BDR) was assessed by comparing pre- and post- bronchodilator FEV_1 . An increase in FEV_1 greater than 200 mL and 12% of the baseline value was accepted as a positive BDR (14).

For mannitol BPT, dry powder mannitol (ARIDOL™) was prepared in kit form (Pharmaxis Ltd., NSW Australia) containing several capsules with different doses of mannitol. A single capsule contained 0, 5, 10, 20, or 40 mg. The dry powder device used for inhalation was the Osmohaler™ (RS-01, Pastiape™, Italy). Baseline FEV_1 was measured on presentation at our PFT laboratory. The dose protocol consisted of 0 (empty capsule as a placebo), 5, 10, 20, 40, 80, 160, 160 and 160 mg (15). Doses of more than 80 mg were given in multiples of 40 mg capsules. The FEV_1 was measured twice 60 s after each dose, and the highest FEV_1 value was recorded. The FEV_1 value measured after the 0-mg capsule was taken as the pre-challenge FEV_1 and was used to calculate the percentage decrease in FEV_1 in response to the mannitol challenge. If the FEV_1 fell by more than 10% in response to a single dose, the same dose was repeated. The mannitol challenge was completed when a 15% fall in FEV_1 was documented or a cumulative dose of 635 mg had been administered. After the completion of the test, an inhaled bronchodilator (e.g., 200 μ g of salbutamol) was administered.

Statistical analysis

Data were analyzed using dBSTAT for Windows Version 4.0 (DBSTAT Co, Chuncheon, South Korea). Categorical variables were described as frequencies (%) and continuous variables as mean $\pm$ standard deviation. We conducted independent two-sample and paired *t*-tests for the comparison of continuous variables and the χ^2 test or Fisher's exact test (if the expected values were below 5)

Table 1 Clinical characteristics of fire smoke group (N=15)

	Value
Burn mode	
Only smoke inhalation	13 (86.7)
Combined flame burn	2 (13.3)
Underlying illness	
Previously healthy	13 (86.7)
Others*	2 (13.3)
ICU care, yes	2 (13.3)
Intubation, yes	2 (13.3)
Initial COHb, %	14.81±18.49
Initial PaO ₂ /FiO ₂ , mmHg	425.68±123.68
Initial serum procalcitonin level, ng/mL	0.34±0.50
Bronchoscopy, yes	15 [100]
Date after admission, median days (range)	2 [0-2]
Bronchoscopic grades for inhalation injury	
Near normal	3 [20]
Mild	9 [60]
Moderate	3 [20]
HRCT, yes	7 (46.7)
Date after admission, median days (range)	1 [0-6]
Compatible with inhalation injury	4 (57.1)
PFT date after admission, median days (range)	2 [0-5]
Mannitol BPT date after admission, median days (range)	4 [2-18]
Data are presented as mean ± SD or n (%). *, neurofibromatosis [1], diabetes mellitus with hypertension [1]. Abbreviations: ICU, intensive care unit; COHb, carboxyhemoglobin; HRCT, high-resolution computed tomography; PFT, pulmonary function test; BPT, bronchial provocation test.	

for categorical variables. A P value of less than 0.05 was considered statistically significant.

Results

Subjects characteristics

In all, 30 adult participants were enrolled in this study: 15 in fire smoke group (5 men and 10 women) and chronic cough group in 15 (5 men and 10 women).

In fire smoke group, the majority of the patients (86.7%) suffered only from smoke inhalation; only 2 of 15 patients required E-tube insertion for airway maintenance and were admitted to the intensive care units. Initial arterial COHb

Table 2 Patient's characteristics and clinical symptoms between fire smoke and chronic cough group

Parameters	Fire smoke group (N=15)	Chronic cough group (N=15)	P
Age, years	33.93±13.89	33.93±14.51	1.000
Sex, male	5 (33.3)	5 (33.3)	1.000
BMI, kg/m ²	21.19±2.83	20.34±2.18	0.365
Clinical symptoms			
Cough	7 (46.7)	11 (73.3)	0.264
Nocturnal awakening	2 (13.3)	6 (40.0)	0.215
Chest discomfort	0	4 (26.7)	0.100
Chest pain	0	1 (6.7)	1.000
Wheezing	2 (13.3)	0	0.483
Dyspnea	1 (6.7)	0	1.000
Data are presented as mean ± SD or n (%). Abbreviation: BMI, body mass index.			

levels and the PaO₂/FiO₂ ratio were 14.81%±18.40% and 425.68±123.69 mmHg, respectively. Bronchoscopy was performed in all patients, and the grades for inhalation injury were as follows bronchoscopically: near normal, 3 (20%); mild, 9 (60%); moderate, 3 (20%); severe, 0. HRCT was performed in seven patients, and four of those (57.1%) showed the findings compatible with lung parenchymal involvement of inhalation injury (Table 1).

There were no significant differences in demographics and clinical symptoms between the two groups. The most common symptom was cough, 46.7% and 73.3% in fire smoke and chronic cough group, respectively (Table 2).

HRCT findings

Of the seven patients in whom HRCT was performed, 4 (57.1%) were found to have lung parenchymal abnormalities on HRCT scans resulted from fire smoke inhalation injury. Peribronchial ground glass opacities were the most common, and followed by segmental or subsegmental consolidations, atelectasis, branching linear attenuations, bronchial wall thickening, and interlobular septal thickening (Table 3).

PFT and mannitol bronchoprovocation test

In fire smoke group, FVC and FEF₂₅₋₇₅ were slightly less than 80% predicted, and other values including FEV₁, PEF,

Table 3 HRCT findings in fire smoke group (N=4)

Findings	Number
Peribronchial ground glass opacities	4 [100]
Segmental or subsegmental consolidations	2 [50]
Segmental or subsegmental atelectasis	2 [50]
Branching linear attenuations	2 [50]
Bronchial wall thickening	1 [25]
Interlobular septal thickening	1 [25]
Data are presented as n [%]. Abbreviation: HRCT, high-resolution computed tomography.	

Table 4 Pulmonary function tests in fire smoke group (N=15)

	Before BDR	After BDR	P
FVC, L	2.85±1.15	2.89±1.10	0.448
% predicted	74.3±23.90	76.0±24.27	0.614
FEV ₁ , L	2.30±1.04	2.41±1.02	0.060
% predicted	76.5±28.49	79.8±27.82	0.078
FEV ₁ /FVC, %	78.4±11.68	80.9±10.13	0.058
FEF ₂₅₋₇₅ , L	2.41±1.47	2.65±1.45	0.045
% predicted	68.7±37.29	76.4±36.70	0.031
PEF, L	5.23±2.76	5.31±2.60	0.641
% predicted	75.4±34.27	76.9±32.57	0.536
DLco, mL/min/mmHg	18.48±7.52		
% predicted	92.44±22.64		
Positive bronchodilator response	2 (13.3)		

Data are presented as mean ± SD or n (%). Abbreviations: BDR, bronchodilator response; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of the FVC; PEF, peak expiratory flow; DLco, diffusing capacity for carbon monoxide.

FEV₁/FVC and DLco were equal to or a little more than 80% predicted. Then, the values of FEF₂₅₋₇₅ and the percent of FEF₂₅₋₇₅ before and BDR were 2.4±1.47 L *vs.* 2.65±1.45 L (P=0.045), and 68.7±37.29% *vs.* 76.4±36.70% (P=0.031), respectively. The positive BDR was observed in two patients (13.3%) (Table 4).

We compared the results of mannitol BPTs in the two groups, but found no significant differences in baseline FEV₁, maximum decrease in FEV₁, and the total cumulative mannitol dose at the time of the maximum decrease in FEV₁. Moreover, all the subjects showed mannitol BPTs within normal limits (Table 5). All study participants were reported to tolerate the tests well without any side effects except complaining of mild cough.

Discussion

The fire victims suffering from smoke inhalation may have a number of complications caused by various pulmonary sequelae. Wheezing and chronic cough may reflect underlying hyperreactive airways. Chronic bronchitis, bronchiolitis obliterans, bronchial stenosis, lung fibrosis, bronchiectasis and atelectasis have been reported to be resulted from exposure to fire smoke and subsequent inflammatory consequences (16).

The understanding of precise pathophysiology in patients who had smoke inhalation damage from fires is of great important for effective airway management. The present study aimed to assess the lung functions in the early phase of patients with smoke inhalation injury. Initially, we taken into account that fire smoke inhalation is a strong stimulus that triggers bronchoconstriction. Unfortunately, we could not detect any significant BHR in mannitol BPTs to explain airway narrowing that commonly occurs after fire smoke inhalation (2,3). Although FEV₁, PEF, FEV₁/FVC and

Table 5 Comparison of mannitol bronchial provocation tests

	Fire smoke group	Chronic cough group	P
A total dose of mannitol used (635 mg)	15 [100]	15 [100]	–
Baseline FEV ₁ , L	3.05±0.77	2.73±0.82	0.282
Maximum decrease in FEV ₁ , %	6.53±4.27	6.60±2.95	0.961
FEV ₁ at maximum decrease in FEV ₁ , L	2.9±0.88	2.60±0.82	0.329
Cumulative mannitol dose*, mg	379.67±236.85	355.67±253.22	0.791
Positive results	0	0	

Data are presented as mean ± SD or n (%). *, at maximum decrease in FEV₁. Abbreviations: FEV₁, forced expiratory volume in one second; PD15, the provoking dose of mannitol to cause a 15% reduction in FEV₁.

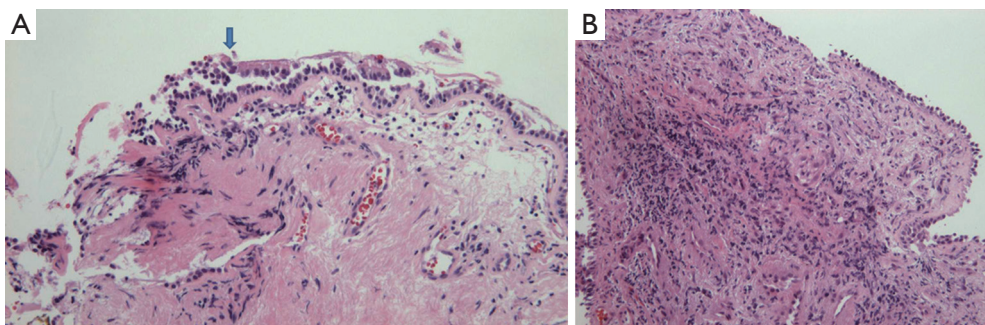


Figure 3 Bronchoscopic biopsy of a 67-year-old woman with smoke inhalation injury. (A) Epithelial exfoliation (arrow), vascular congestion and bronchial dilation (hematoxylin-eosin, $\times 200$); (B) Diffuse aggregates of neutrophils admixed with small numbers of histiocytes, lymphocytes and fibrin subepithelial stroma (hematoxylin-eosin, $\times 100$).

DLco were equal to or a little more than 80% predicted, post-bronchodilator FVC and FEF_{25-75} were less than 80% predicted. Moreover, the percent of FEF_{25-75} was significantly increased after BDR compared to the value before BDR, 68.7% to 76.4% ($P=0.031$). This finding gives us a relevance to initiate bronchodilators for airway management in patients who had smoke inhalation injury from fires.

Currently, there are two categories of BPTs defined by the mechanisms whereby they stimulate the airways to narrow. The direct stimuli include pharmacologic agents such as histamine or methacholine, which act directly on specific receptors on the bronchial smooth muscle to cause airway contraction. The indirect stimuli refer to physical stimuli such as exercise; hyperventilation; osmotic aerosols including hypertonic saline or mannitol; and adenosine monophosphate, which trigger airway narrowing indirectly by causing the release of various contractile mediators (e.g., leukotrienes, prostaglandins, and histamine) from inflammatory cells within the airways (15). The ultimate goal of precise evaluation of airway narrowing due to an inhalation injury is to provide optimal early management (17-20).

After fire smoke inhalation, a variety of consequences in the respiratory system may be followed by an intense cellular response with neutrophil infiltration, airways edema, bronchoconstriction from aerosolized irritants, small airway occlusion from sloughed endobronchial debris or cast, and alveolar flooding from epithelial disruption (21). These injuries evolve over time and parenchymal lung dysfunction is often minimal for 24-72 h after fire smoke inhalation (22). The airways obstruction and bronchoconstriction, which mimic asthma, and usually manifest themselves in the first 24 h (23). In the previous studies, the airways reactivity was assessed by mainly methacholine test, which showed often

positive results (2,3). Then, we applied mannitol BPTs on the median four days after admission to a narrow spectrum of patients who mostly had smoke inhalation. Kinsella *et al.* reported that BHR to methacholine usually manifested itself within three days of injury (2). In our study, it remains unclear why BHR to inhaled mannitol was not produced. A delay of the BPT may be a factor not to provoke BHR in fire smoke group. In addition to, one possible explanation is that the airway epithelium after smoke inhalation may be severely injured or even denuded to a degree so that the changes in the airway osmolarity in response to inhaled mannitol could not have occurred. Another reason is that the pathological findings in smoke inhalation injury are quite different from those in asthma, that is, chronic bronchitis with eosinophil infiltration. We have experienced airway inflammatory cells composed mainly of neutrophils, not eosinophils, in the acute stage of inhalation injury (Figure 3) (24). Likewise, this is why the study participants did not have BHR in mannitol BPTs, even if they had asthma-like symptoms. Moreover, the increased airway reactivity and prolonged obstructive airway disease have been reported to persist from 3 to 6 months as long-term sequelae of smoke inhalation injury (2,3,25). These findings are the cases when fire victims accompanying inhalation injury suffered from major burn, which probably might have resulted into prolonged BHR, due to intense systemic inflammatory reaction. In our study, the majority of patients had smoke inhalation injury and not fire-related injury. This fact would have contributed to their lack of BHR.

Chest CT scans have been reported to show the superior sensitivity in comparison to chest radiographs for the detection of pulmonary lesion in the early hours of inhalation injury (26). Yamamura *et al.* reported bronchial wall thickening, greater than 2 mm at initial CT scan, was

a predictive marker of prolonged intensive care unit (ICU) stays and the development of pneumonia in patients with inhalation injury (27). In our study, although CT findings such as ground glass opacity with/or without consolidation, atelectasis, branching linear attenuation and interlobular septal thickening, were obtained in patients with smoke inhalation, however, it remains as to which findings affect the pulmonary consequences and how much respiratory function restores since the injury.

The limitations of our study include a small sample size as well as the fact that the participants with chronic cough did not represent individuals with no exposure to fire smoke in whom PFTs were not routinely performed. In addition, we did not have long-term data on late sequelae of inhalation injury because some of the patients refused to undergo BPTs several months after discharge because they did not complain of further symptoms. Despite these limitations, this study demonstrates that FEF_{25-75} , reflecting obstructive small airway disease pattern, was mild decreased before BDR, and significant increased after BDR in fire smoke group, and a small number of patients had positive BDR. These findings may indicate a potential benefit from the use of bronchodilator drugs (28).

In conclusion, the present preliminary study shows that fire smoke inhalation has something with mild obstructive small airway disease pattern of pulmonary function in the early phase in patients with inhalation injury. However, more evidence is necessary to know as to the relationship between airway narrowing to inhaled mannitol and smoke inhalation injury through a large-scaled prospective study.

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