Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Increased expression of TRPV1 in patients with acute or chronic cough after lung cancer surgery

Yong-fu Zhu[1,2†], Sheng-bing Wu[3†], Mei-qi Zhou[3,4], Ming-ran Xie[5], Ran Xiong[5], Shi-bin Xu[5] & Guang-wen Xu[5]

1 Graduate School of Anhui University of Chinese Medicine, Hefei, China
2 Department of Oncology, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China
3 Research Institute of Acupuncture and Meridian, Anhui Academy of Chinese Medicine, Hefei, China
4 Bozhou Research Institute of Chinese Medicine, Anhui Academy of Chinese Medicine, Bozhou, China
5 Department of Thoracic Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Keywords
Acute cough; chronic cough; lobectomy; lung cancer; TRPV1.

Correspondence
Mei-qi Zhou, Research Institute of Acupuncture and Meridian, Anhui Academy of Chinese Medicine, No.1 Qianjian Road, Hefei City, Anhui Province 230012, China.
Tel: +86 551 6516 9793
Fax: +86 551 6516 9793
Email: meiqizhou77@sina.com

Ming-ran Xie, Department of Thoracic Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, No.7, Lujiang Rd, Hefei City, Anhui Province, 230000, China.
Tel: +86 551 6228 3326
Fax: +86 551 6228 3326
Email: xiemingran@hotmail.com

†Co-first authors with equal contribution.

Received: 7 February 2019;
Accepted: 22 February 2019.

doi: 10.1111/1759-7714.13042

Thoracic Cancer **10** (2019) 988–991

Abstract

Background: We investigated preoperative and postoperative TRPV1, bradykinin (BK), and prostaglandin e-2 (PGE2) levels in patients who underwent lung cancer surgery and evaluated the correlations between these levels and the development of acute or chronic cough after surgery.

Methods: We evaluated 60 patients with non-small cell lung cancer who underwent lobectomy at our center between August and October 2018. TRPV1, BK, and PGE2 levels were determined by enzyme-linked immunosorbent assay and postoperative cough was assessed using the visual analog scale (VAS).

Results: The postoperative serum TRPV1, BK, and PEG2 levels of the 60 patients were significantly higher than the preoperative levels ($P < 0.001$). Thirty-five patients (58.3%) were diagnosed with acute cough (VAS ≥ 60 mm), and 25 were diagnosed with non-acute cough (41.7%). Three days after surgery, the serum TRPV1, BK, and PGE2 levels were significantly higher in the acute cough group than in the non-acute cough group ($P < 0.001$). Twenty-two patients (36.7%) were diagnosed with chronic cough (VAS ≥ 60 mm), and 25 (62.3%) were diagnosed with non-chronic cough. Eight weeks after surgery, the serum TRPV1, BK, and PGE2 levels were significantly higher in the chronic cough group than in the non-chronic cough group ($P < 0.05$).

Conclusions: The postoperative TRPV1, BK and PGE2 levels were significantly higher than the preoperative levels. The TRPV1 level was also higher in patients with an acute or chronic cough than in patients without. Postoperative acute or chronic cough symptoms can be improved and alleviated by blocking the TRPV1 pathway.

Introduction

In recent years, the incidence and mortality rates of lung cancer have been higher than those of any other malignant tumor worldwide.[1,2] Surgery is the main treatment for resectable non-small cell lung cancer (NSCLC). Postoperative cough is one of the most common complications of lung cancer surgery, with an incidence as high as 30–50%, which seriously affects postoperative quality of life.[3–6] According to the literature, a postoperative cough is hypothesized to be related to pulmonary C-fiber activation, extraction of the vagus nerve, acid regurgitation, endobronchial sutures, and mediastinal lymph node resection, as well as other anatomical factors.[7,8] However, the

underlying mechanism and characteristics of cough development after lung cancer surgery remain controversial.

A cough is a common symptom of respiratory disease and the most important respiratory defense reflex. Signals are transmitted along the vagus nerve to the brainstem cough center after the sensory nerve is stimulated. After the signal is integrated, it is transmitted to the effectors (diaphragm, throat, chest, abdominal muscles, etc.), resulting in cough symptoms. Afferent nerves associated with cough reflexes in the airway mainly include myelinated Aδ fibers sensitive to various mechanical stimuli and unmyelinated C fibers sensitive to various types of chemical stimuli. C-fiber nerve endings contain TRPV1, and a variety of physical and chemical stimuli can activate TRPV1 to induce coughing in different pathways.[9,10] However, whether a postoperative cough is related to this mechanism is not yet known. This study used enzyme-linked immunosorbent assay (ELISA) to determine the preoperative and postoperative TRPV1, bradykinin (BK), and prostaglandin e-2 (PGE2) expression levels in patients who underwent lung cancer surgery and to evaluate the correlations between these levels and acute or chronic cough after lung cancer surgery.

Methods

Patient selection

The Anhui University of Chinese Medicine ethics committee approved this study. Written informed consent was obtained from all patients. Sixty patients with lung cancer who underwent lobectomy in our hospital from August to October 2018 were selected. The inclusion criteria were: (i) histopathologically diagnosed NSCLC, (ii) lobectomy and systemic lymph node dissection, (iii) R0 resection, (iv) no neoadjuvant therapy, and (v) signed informed consent. The exclusion criteria were: (i) patients diagnosed with acute respiratory disease within one month; (ii) patients diagnosed with pneumonia via a positive chest X-ray; (iii) a history of allergies, asthma, or tuberculosis; (iii) patients taking ace inhibitors; and (iv) patients who had used hormonal drugs in the past three months.

Surgical technique

Double-lumen endotracheal intubation and single-lung ventilation were performed with the patient in a lateral position on the unaffected side. All patients underwent minimally invasive or thoracotomy lobectomy combined with mediastinal lymph node dissection. For right lung cancer, the 2R, 3A, 3P, 4R, 7, 8, 9, and 10 groups and intrapulmonary lymph nodes were routinely probed and resected. For left lung cancer, the 4L, 5, 6, 7, 8, 9, and 10 groups and intrapulmonary lymph nodes were routinely probed and resected.

Diagnostic criteria for cough

Postoperative cough was assessed using the visual analog scale (VAS). Patients were diagnosed with a cough when the scale was ≥ 60 mm (range: 0–100 mm; diagnostic criteria were used for acute and chronic coughs).[11] According to the American College of Chest Physicians (ACCP) criteria for the diagnosis and treatment of a cough, cough symptoms lasting eight weeks indicate a chronic cough.[12] All patients in this study were subjected to VAS assessment one day before surgery and three days and eight weeks after surgery.

Prostaglandin e-2, bradykinin, and TRPV1 enzyme-linked immunosorbent assay

Whole blood samples were allowed to stand at room temperature for two hours or at 4°C overnight and were then centrifuged at 1000 rpm for 20 minutes. Tests were conducted as recommended by the supplier (USCN Business Co., Ltd., Wuhan, China).

Statistical analyses

Statistical analyses were performed using SPSS version 19.0. Normally distributed data are shown as the mean ± standard deviation, and independent sample *t*-tests were used to compare groups. Pearson's χ^2 test was used to conduct single-factor correlation analyses, and differences were statistically significant when $P < 0.05$.

Results

The study group consisted of 37 (56.7%) men and 23 (43.3%) women with NSCLC, and their ages ranged from 45 to 72 years (mean: 63 years). All of the patients had a Karnofsky score ≥ 80. Tumor node metastasis (TNM) staging was based on the eighth edition International Association for Lung Cancer Research (IASLC) classification. This study included 38 patients with stage I disease, 14 patients with stage II disease, and 8 patients with stage III disease.

Compared to the preoperative baseline level, the postoperative serum TRPV1, BK, and PEG2 levels in the 60 patients were significantly upregulated (Table 1).

A total of 35 patients (58.3%) were diagnosed with acute cough (VAS ≥ 60 mm), and 25 with non-acute cough (41.7%). The groups were similar in terms of age; gender; smoking history; TNM staging, incidence of comorbidities; and the levels of serum TRPV1, BK, and PGE2 before surgery ($P > 0.05$). At three days after surgery, the levels of serum TRPV1, BK, and PGE2 were significantly higher in the acute than in the non-acute cough group (Table 2).

Table 1 Serum TRPV1, BK, and PEG2 levels of 60 lung cancer patients before and after surgery

Variables	Before surgery (ng/ml)	After surgery (ng/ml)	*t*	*P*
TRPV1	6.40 ± 0.53	15.44 ± 1.60	41.73	< 0.001
BK	4.29 ± 0.27	6.40 ± 0.79	19.71	< 0.001
PGE2	10.38 ± 0.59	16.29 ± 1.15	35.88	< 0.001

BK, bradykinin; PGE2, prostaglandin e-2.

Table 2 Serum TRPV1, BK, and PEG2 levels of patients with or without acute cough after surgery

Variables	Acute cough (ng/ml, *n* = 37)	Non-acute cough (ng/ml, *n* = 23)	*t*	*P*
TRPV1	16.61 ± 0.88	13.81 ± 0.62	14.43	< 0.001
BK	6.81 ± 0.72	5.81 ± 0.42	6.79	< 0.001
PGE2	16.97 ± 0.92	15.33 ± 0.63	7.77	< 0.001

BK, bradykinin; PGE2, prostaglandin e-2.

A total of 22 patients (36.7%) were diagnosed with chronic cough (VAS ≥ 60 mm), and 25 patients (62.3%) with non-chronic cough. The groups were similar in terms of age; gender; smoking history; TNM staging; incidence of comorbidities and the serum levels of TRPV1, BK, and PGE2 before surgery ($P > 0.05$). At eight weeks after surgery, the TRPV1, BK, and PGE2 serum levels were significantly higher in the chronic than in the non-chronic cough group (Table 3).

Discussion

TRPV1 is widely distributed in mammalian respiratory sensory nerves, especially in C fibers. The C fiber is distributed throughout almost the entire respiratory system from the upper airway (nose, pharynx, and larynx) to the lower airway and the lung parenchyma (alveolar wall). The C-fiber terminal is located in the airway epithelial cell space or under the airway mucosal basement membrane and forms a direct network.[13] In addition, smooth muscle, epithelial, vascular endothelial, submucosal gland, and inflammatory cells also express TRPV1.[14–16] TRPV1 receptors can be activated by a variety of physical and chemical factors and neuroinflammatory mediators. Pulmonary surgery introduces multiple physical and chemical stimuli in the patient's respiratory system, including:

Table 3 Serum TRPV1, BK, and PEG2 levels of patients with or without chronic cough after surgery

Variables	Chronic cough (ng/mL, *n* = 25)	Non-chronic cough (ng/mL, *n* = 35)	*t*	*P*
TRPV1	12.35 ± 1.43	11.67 ± 0.61	2.242	0.032
BK	5.47 ± 0.54	5.05 ± 0.35	3.40	0.002
PGE2	13.46 ± 1.39	12.65 ± 0.78	2.63	0.013

BK, bradykinin; PGE2, prostaglandin e-2.

(i) local inflammation of lung tissues and peripheral nerves caused by surgery; (ii) physical changes to small airways after surgery, such as local torsion caused by poor ventilation; (iii) surgical scars and chronic stimulation from foreign bodies, such as sutures in the trachea; and (iv) local pleurisy and pleural effusion. This study found that the TRPV1 levels measured three days after surgery were significantly lower than the preoperative baseline levels. The TRPV1 levels after surgery were also higher in patients diagnosed with acute or chronic cough than in patients without. These findings suggest that the TRPV1 pathway may also induce acute and chronic cough caused by lung surgery.

Few studies on the mechanism underlying postoperative cough in lung cancer have been conducted. Among the factors involved in these mechanisms, TRPV1 is expressed in the respiratory tract and plays a role in inflammation regulation, airway smooth muscle tone, the activation of sensory afferents, and a definite role in cough.[17] Our results showed that patients who underwent surgery for lung cancer, especially those diagnosed with an acute or chronic cough, had significantly upregulated serum levels of PGE2 and BK, which are the upstream proteins of TRPV1. Therefore, we believe that the development of a postoperative cough and upregulated TRPV1 levels are the result of the body's response to tissue damage and inflammation. The body releases endogenous inflammatory mediators, such as PGE2 and BK, which activate G-protein coupled receptors, which in turn activate the TRPV1 pathway, increasing airway inflammation and triggering an increase in coughing. This result also shows that the mechanism of the development of acute or chronic cough after lung cancer surgery is directly related to chronic inflammatory stimuli.

This study also found that patients with a chronic cough eight weeks after surgery had significantly higher TRPV1 levels than those with a non-chronic cough. Regarding postoperative TRPV1 levels in patients with chronic cough, we hypothesized that postoperative chronic cough was activated by airway difficulties and local vascular and neurological destruction during surgery, which activates the TRPV1 pathway. The sustained inflammatory response caused by damage from the operation results in the maintenance of a high serum TRPV1 level and a highly reactive airway, which shows symptoms of chronic cough under sustained endogenous stimulation. This response may be one of the mechanisms underlying postoperative chronic cough. In previous studies, PGE2 and BK caused coughing in conscious animals and humans when inhaled as an aerosol, whereas patients taking an angiotensin-converting enzyme inhibitor also developed an excessive cough as a result of the reduced breakdown of bradykininase.[18–20] Therefore, we believe that intervening in the TRPV1 pathway and reducing airway inflammation can prevent and reduce chronic cough in lung cancer patients after surgery.

There are some limitations to this study. First, because of the retrospective nature of the study, some selection bias is unavoidable. Second, the sample size is relatively small. Third, to avoid potential bias, the clinicians that performed sampling and assessment not aware of the treatment allocation before and after treatment and during the follow-up protocol, which needs to be addressed in future research.

In summary, our results revealed that the postoperative TRPV1 level in lung cancer patients was significantly upregulated compared to the preoperative baseline level. The TRPV1 level in patients diagnosed with acute or chronic cough was also upregulated compared to patients without acute or chronic cough. Therefore, we believe that trauma from lung cancer surgery can lead to the release of inflammatory factors, especially PGE2 and BK, through various pathways and can activate the TRPV1 pathway, leading to the development of acute or chronic cough after surgery. Postoperative acute or chronic cough symptoms after surgery can be improved and alleviated through drug or non-drug interventions to block the TRPV1 pathway.

Acknowledgments

This work was supported by the National Basic Research Program of China (973 Program) (2018YFC1704600), the Natural Science Foundation of Anhui Province (1708085MH179), Fundamental Research Funds for the Central Universities (WK9110000021), and the Department of Thoracic Surgery, the First Affiliated Hospital of University of Science and Technology of China (USTC), Division of Life Sciences and Medicine, USTC, Hefei City, Anhui Province, China.

Disclosure

No authors report any conflict of interest.

References

1 Bao F, Yuan X, Abuduwufuer A, Yuan P, Yang Y. Does single-incision achieve more nodes than multiple-incision for thoracoscopic pulmonary anatomical resections. *Ann Surg* 2017; **265**: E75–6.
2 Raz DJ, Sun V, Kim JY *et al.* Long-term effect of an interdisciplinary supportive care intervention for lung cancer survivors after surgical procedures. *Ann Thorac Surg* 2016; **101**: 495–502.
3 Sarna L, Evangelista L, Tashkin D *et al.* Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest* 2004; **125**: 439–45.
4 Lin R, Che G. Risk factors of cough in non-small cell lung cancer patients after video-assisted thoracoscopic surgery. *J Thorac Dis* 2018; **10**: 5368–75.
5 Yang P, Cheville AL, Wampfler JA *et al.* Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol* 2012; **7**: 64–70.
6 Lin R, Che G. Validation of the Mandarin Chinese version of the Leicester cough questionnaire in non-small cell lung cancer patients after surgery. *Thorac Cancer* 2018; **9**: 486–90.
7 Canning BJ, Chang AB, Bolser DC *et al.* Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest* 2014; **6**: 1633–48.
8 Mazzone SB, Undem BJ. Vagal afferent innervation of the airways in health and disease. *Physiol Rev* 2016; **3**: 975–1024.
9 Miyamoto H, Sakao Y, Sakuraba M *et al.* Usefulness of suplatast tosilate for chronic cough following lung cancer surgery. *Gen Thorac Cardiovasc Surg* 2009; **9**: 463–6.
10 Birring SS, Brew J, Kilbourn A *et al.* Rococo study: A real-world evaluation of an over-the-counter medicine in acute cough (a multicentre, randomised, controlled study). *BMJ Open* 2017; **7**: e14112.
11 Morice AH, Jakes AD, Faruqi S *et al.* A worldwide survey of chronic cough: A manifestation of enhanced somatosensory response. *Eur Respir J* 2014; **44**: 1149–55.
12 Bonvini SJ, Belvisi MG. Cough and airway disease: The role of ion channels. *Pulm Pharmacol Ther* 2017; **47**: 21–8.
13 Song WJ, Morice AH. Cough hypersensitivity syndrome: A few more steps forward. *Allergy Asthma Immunol Res* 2017; **5**: 394–402.
14 Birrell MA, Bonvini SJ, Dubuis E *et al.* Tiotropium modulates transient receptor potential V1 (TRPV1) in airway sensory nerves: A beneficial off-target effect? *J Allergy Clin Immunol* 2014; **3**: 679–87.
15 Mcalexander MA, Taylor-Clark T. The role of transient receptor potential channels in respiratory symptoms and pathophysiology. *Adv Exp Med Biol* 2011; **704**: 969–86.
16 Chung KF. Chronic "cough hypersensitivity syndrome:" A more precise label for chronic cough. *Pulm Pharmacol Ther* 2011; **3**: 267–71.
17 Ebihara S, Kohzuki M, Sumi Y *et al.* Sensory stimulation to improve swallowing reflex and prevent aspiration pneumonia in elderly dysphagic people. *J Pharmacol Sci* 2011; **2**: 99–104.
18 Chou YL, Mori N, Canning BJ. Opposing effects of bronchopulmonary C-fiber subtypes on cough in guinea pigs. *Am J Physiol Regul Integr Comp Physiol* 2018; **314**: R489–98.
19 Gokhale M, Girman C, Chen Y, Pate V, Funk MJ, Stürmer T. Comparison of diagnostic evaluations for cough among initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf* 2016; **25**: 512–20.
20 Okazaki A, Hara J, Ohkura N *et al.* Role of prostaglandin E_2 in bronchoconstriction-triggered cough response in guinea pigs. *Pulm Pharmacol Ther* 2018; **48**: 62–70.

