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Decreased capsaicin cough reflex sensitivity predicts hospitalisation due to COPD

Yoshihiro Kanemitsu ,[1] Ryota Kurokawa,[1] Taisuke Akamatsu,[2] Kensuke Fukumitsu,[1] Satoshi Fukuda,[1] Yutaka Ito,[1] Norihisa Takeda,[1] Hirono Nishiyama,[1] Keima Ito,[1] Tomoko Tajiri,[1] Yuta Mori,[1] Takehiro Uemura,[1] Hirotsugu Ohkubo,[1] Masaya Takemura,[1] Ken Maeno,[1] Tetsuya Oguri,[1] Toshihiro Shirai,[2] Akio Niimi[1]

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YK and RK contributed equally.

YK and RK are joint first authors.

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[1]Department of Respiratory Medicine, Allergy, and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences and Medical School, Nagoya, Japan
[2]Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan

Correspondence to
Dr Yoshihiro Kanemitsu; kaney32@med.nagoya-cu.ac.jp

ABSTRACT

Introduction Patients with chronic obstructive pulmonary disease (COPD) are often hospitalised due to severe acute exacerbation (AE) or community-acquired pneumonia (CAP). Previous studies revealed the association of cough reflex sensitivity with the pathophysiology of COPD and pneumonia. We hypothesised that cough reflex sensitivity may be associated with severe AE or CAP requiring hospitalisation in patients with COPD.

Methods We prospectively recruited 68 patients with COPD between June 2018 and January 2020. Patient characteristics, lung and cardiac functions, and biomarkers, including capsaicin cough reflex sensitivity and blood eosinophil count, were evaluated at enrolment. All participants were monitored for AE or CAP requiring hospitalisation for 12 months. We determined the risk factors and ORs for hospitalisation in patients with COPD using a multivariate analysis.

Results Eight patients experienced AE (n=3) or CAP (n=5) and required hospitalisation during follow-up. Patients in the hospitalisation+ group had higher modified Medical Research Council scores and blood eosinophil counts (≥300 µL) than those in the hospitalisation− group. Capsaicin cough reflex sensitivity tended to decrease in the hospitalisation+ group compared with that in the hospitalisation− group. Multivariate analysis revealed that a decreased capsaicin cough reflex and high eosinophil count (≥300 µL) were predictive risk factors for future hospitalisation due to AE-COPD or CAP.

Conclusion In addition to eosinophils, decreased capsaicin cough reflex sensitivity was associated with hospitalisation due to AE-COPD or CAP. Capsaicin cough reflex sensitivity in patients with COPD may play a role in the prevention of severe AE or pneumonia requiring hospitalisation.

Trial registration number UMIN000032497.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Acute exacerbations (AE) and pneumonia are major causes of hospitalisation in chronic obstructive pulmonary disease (COPD). Increased capsaicin cough reflex sensitivity is associated with AE. Meanwhile, it rather decreases in patients who experience frequent pneumonia.

WHAT THIS STUDY ADDS?

⇒ Decreased capsaicin cough reflex sensitivity is an important risk factor for severe AE or community-acquired pneumonia (CAP) requiring hospitalisation in patients with COPD in addition to higher blood eosinophil counts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ Decreased capsaicin cough reflex sensitivity was associated with hospitalisation due to AE-COPD or CAP. Cough reflex sensitivity in COPD may play a role in the prevention of severe AE or pneumonia requiring hospitalisation.

INTRODUCTION

The incidence of chronic obstructive pulmonary disease (COPD) mainly caused by cigarette smoke exposure is increasing[1] and is the third leading cause of death worldwide (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). Mortality due to COPD in all age groups increased by 11.6% between 1990 and 2015.[2] The number of deaths due to COPD was eight times higher than that due to asthma. Acute exacerbation (AE) of COPD (AE-COPD), defined by worsening of respiratory symptoms such as dyspnoea, cough and/or sputum beyond ordinary day-to-day variations and requiring changes in medication,[3] is one of the major causes of death from COPD, along with pneumonia, cardiovascular disorders and cancer.[4 5] Community-acquired pneumonia (CAP) often coexists with AE-COPD, resulting in hospitalisation.[5–9] CAP is associated with severe clinical manifestations during hospitalisation such as higher rates of ICU admission,[6] assisted ventilation[6 7] and mortality[7–10] in patients with COPD. Thus,

preventing hospitalisation due to AE-COPD or CAP is important in the management of COPD.

Cough, sputum and dyspnoea are some of the most prevalent symptoms of COPD.[11] Both cough and sputum are associated with bronchial colonisation by pathogenic bacteria and frequent exacerbations and hospitalisation,[11–13] leading to the deterioration of COPD and death.[13] Altered cough reflex sensitivity is associated with COPD pathophysiology.[14] The capsaicin cough reflex sensitivity was more heightened in patients with COPD than in healthy subjects. In addition, it is associated with cough frequency in the daytime[15] and frequent exacerbations.[16 17] Meanwhile, cough plays a role in protecting the lower airways from particles in the external field and aspiration of the oral and gastro-oesophageal contents. Indeed, capsaicin cough reflex sensitivity declines in patients who experience recurrent pneumonia compared with healthy subjects.[18] We hypothesised that capsaicin cough reflex sensitivity may not increase but decrease in patients with COPD with severe AE or CAP requiring hospitalisation.

In the present study, we prospectively investigated the association between capsaicin cough reflex sensitivity and hospitalisation in patients with COPD. We thought that decreased capsaicin cough reflex sensitivity was associated with future hospitalisation due to severe AE-COPD or CAP.

METHODS

Subjects and the definition of COPD and comorbid asthma

We prospectively recruited patients with COPD who visited the Nagoya City University Hospital and Shizuoka General Hospital between June 2018 and January 2020. We enrolled patients in this study if their condition was stable at the time of their outpatient department visit. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 as follows: (1) a postbronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of less than 0.70 (fixed airflow limitation); (2) persistent respiratory symptoms such as dyspnoea, cough, sputum production or wheezing and (3) significant exposure to noxious stimuli such as tobacco smoke or other environmental particles. We permitted to include patients with comorbid asthma, called 'asthma-COPD overlap' in the present study. Patients were diagnosed with comorbid asthma if they had some clinical features of asthma, such as (1) variable or paroxysmal clinical symptoms, (2) a diagnosis of asthma before the age of 40 years, (3) elevated levels of fractional nitric oxide (FeNO) of 35 ppb or higher and (4) a history of perennial allergic rhinitis, airway hyperresponsiveness, elevated peripheral blood eosinophils and total or allergen-specific immunoglobulin E levels, in addition to fixed airflow limitation.[19] Conversely, patients were not recruited to the present study when they denied participation in the study, had chronic respiratory diseases other than asthma or had a postbronchodilator FEV_1/FVC ratio of 0.7 or higher. Patients were not eligible for this study if they were in a nursing care home, were bedridden at home, had a history of aspiration pneumonia or underwent tubal feeding. Patients who had a respiratory infection within 4 weeks of enrolment or hospitalisation due to AE-COPD or CAP within 12 weeks before enrolment were also excluded because they could influence the results of the capsaicin cough challenge test. This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry. Written informed consent was obtained from all the participants.

Patient and public involvement statement

Patients were not involved in the development of study design or recruitment of participants.

Measurements

All patients underwent blood biomarker analyses (blood neutrophil and eosinophil counts, serum total IgE, albumin, lactate dehydrogenase, C reactive protein (CRP), haemoglobin A1c and plasma brain natriuretic peptide), echocardiography (ejection fraction), FeNO measurement, lung function test, CT of the chest and capsaicin cough challenge test at enrolment. They also completed the Leicester Cough Questionnaire, COPD Assessment Test and modified Medical Research Council (mMRC) dyspnoea scale at that time. Clinical information (pneumococcal vaccinations, smoking history (current or ex-smoking and pack-years), the use of inhaled corticosteroids or home oxygen therapy, a history of asthma, perennial allergic rhinitis, AE-COPD or CAP and hospitalisations due to AE-COPD or CAP) was also assessed. The number of AE-COPD, CAP and hospitalisations due to AE-COPD or CAP was prospectively counted for 1 year after enrolment in the study. Detailed information on the measurements, except for the capsaicin cough challenge test, is provided in online supplemental manuscript.

The capsaicin cough challenge test

The capsaicin cough challenge test was performed using an Astograph (Chest, Tokyo, Japan) after blood collection, echocardiography, FeNO measurement and spirometry. Detailed information on this method has been previously reported.[20] Briefly, 10 doubling concentrations of capsaicin (0.61 to 312.5 µM) were inhaled for 15 s per concentration at 1 min intervals in increasing order, following inhalation of physiological saline for 1 min. Saline was inhaled for 45 s until the initiation of the next inhalation of capsaicin to increase patient blindness. When patients coughed five or more times, the challenge ended at the end of the following saline inhalation for 45 s. The test ended when patients finished inhaling short-acting β_2 agonists for 2 min after the capsaicin cough challenge. The concentrations required to induce

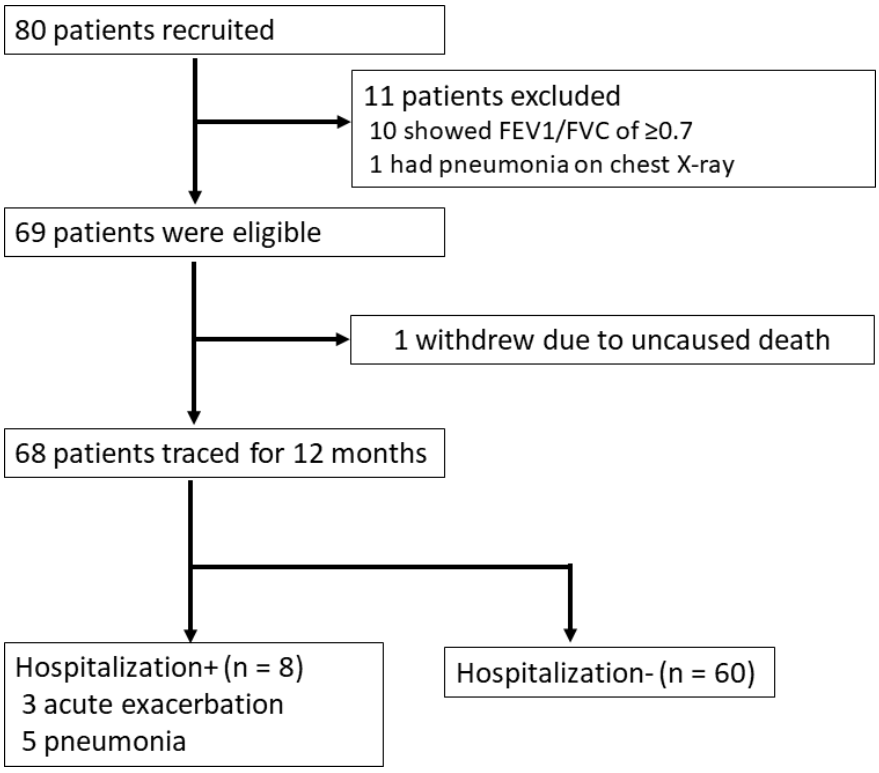

Figure 1 FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

at least two (C2) and five (C5) coughs were recorded. Lower C2 and C5 values indicate heightened capsaicin cough reflex sensitivity.[20 21] We planned to perform a capsaicin cough challenge test 1 year after enrolment in the study, but we evaluated capsaicin cough reflex sensitivity 1 year after enrolment in only 22 patients because of the restriction of measurements due to the coronavirus disease 2019 pandemic.

Definition of AE-COPD and pneumonia

AE-COPD was defined as an acute worsening of respiratory symptoms that resulted in additional treatments such as bronchodilators, antibiotics and systemic corticosteroids. CAP was diagnosed when new infiltration was observed on chest radiography and/or CT with two or more of the following findings: (1) fever (body temperature >37.5°C or <36.0°C), (2) leukocytosis or leucopenia (white blood cells >10 000/mm^3 or <4000/mm^3) and (3) purulent tracheal aspirate and/or sputum.[22]

Statistical analysis

Statistical analysis was performed using the JMP V.14.3 software (SAS Institute Japan, Tokyo, Japan). Values are expressed as mean (SD) for continuous variables and n (%) for categorical variables. We categorised patients into the hospitalisation+ group (AE-COPD or patients with CAP requiring hospitalisation during 1 years after enrolment) and the hospitalisation− group. Two group comparisons were performed using unpaired t-test or Fisher's exact test, as appropriate. The values of C2 and C5 were expressed as the number of doubling concentrations. The number of doubling concentrations ranges from 1 to 10, with a high number indicating a decreased cough sensitivity of inhaled capsaicin. Corresponding inhalation concentration of capsaicin to the number of doubling concentration is noted in online supplemental manuscript. They reflect base2 logarithmic values of C5. Multivariate analysis was performed to determine the OR for hospitalisation. A sensitivity analysis confined to patients who were hospitalised before enrolment was also performed to clarify the association between capsaicin cough reflex sensitivity and hospitalisation in patients with COPD. Longitudinal data on capsaicin cough reflex sensitivity were compared using paired t tests. A variable was considered significant if the p value was ≤0.05. Some data were missing (n=64 for total IgE, and n=66 for CRP and ejection fraction). We handled missing data as a blank because these did not affect main results of this study.

RESULTS

Patient characteristics

A diagram of patient recruitment flow is shown in figure 1. We recruited 80 patients, and 11 were not eligible for this study (11 showed a post-bronchodilator FEV_1/FVC ratio≥0.7, and one had pneumonia on chest radiography at enrolment). We traced 68 of 69 patients with COPD for 12 months after enrolment (one patient died of an unknown cause during the follow-up period). Table 1 shows the characteristics of the 68 patients with

Table 1 Patient's characteristics at enrolment (n = 68)

Age	74 (7.3)	mMRC scale, grade	1.6 (1.2)
Body mass index, kg/m^2	21.6 (3.3)	CAT, point	13 (8)
Sex, male	58 (85.3)	LCQ, point	18.4 (2.6)
Smoking, ex/current	54 (79.4)/14 (20.6)	Neutrophils, /μL	3978 (1557)
Pack-years	56.5 (31.1)	Eosinophils, /μL	249 (207)
GOLD classification, A/B/C/D	19 (27.9)/ 23 (33.8)/ 6 (8.8)/ 20 (29.4)	Eosinophils ≥300/ μL†	12 (17.6)
COPD stage 1/2/3/4	14 (20.6)/38 (55.9)/ 12 (17.6)/4 (5.9)	Albumin, g/dL	4.0 (0.3)
Long acting muscarinic antagonists use, +	48 (70.6)	Lactate dehydrogenase, IU/L	195 (35)
Long acting β_2 agonists use, +	57 (83.8)	Haemoglobin A1c, %	6.0 (0.8)
Inhaled corticosteroids use, +	21 (30.9)	Brain natriuretic peptide, pg/mL	64.5 (95.2)
Home oxygen use, +	9 (13.2)	C reactive protein, mg/L*	0.31 (0.50)
Pneumococcal vaccination, +	34 (50)	IgE, IU/L†	361 (610)
Asthma, +	10 (14.7)	FeNO, ppb	25.9 (16.4)
Cerebrovascular disease, +	7 (10.3)	C2, the number of doubling concentration	4.7 (2.6)
Pneumonia <2 year, +	20 (29.4)	C5, the number of doubling concentration	5.8 (2.5)
Frequent pneumonia (≥2), +	5 (7.4)	C5≤2.44 μM	5 (7.4)
Acute exacerbation <2 year, +	19 (27.9)	Ejection fraction, %*	64.2 (22.3)
Frequent acute exacerbation (≥2), +	8 (11.8)	Postbronchodilator FEV$_1$, mL	1618 (668)
Hospitalisation, +	34 (50)	Postbronchodilator FEV$_1$ predicted, %	64.2 (22.4)
Hospitalisation<2 year, +	27 (39.7)	Postbronchodilator FEV$_1$/FVC, %	50.0 (12.6)
Frequent hospitalisation (≥2), +	10 (14.7)	Reversibility, %	4.6 (8.1)

Global initiative for chronic obstructive lung disease.
The number of doubling concentration was shown as follows; eg, 0.61 μM, 1.22 μM, 2.44 μM, 4.88 μM, 9.76 μM, 19.52 μM, 39.04 μM, 78.1 μM, 156.2 μM and 312.5 μM correspond to 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 doubling concentrations, respectively. *n =66, †n = 64.
C2 and C5, concentrations of inhaled capsaicin required to induce at least two (C2) and five coughs (C5); CAT, COPD assessment test; FeNO, fractional nitric oxide; FEV$_1$, forced expiratory volume in 1s; FVC, forced vital capacity; Ig, immunoglobulin; LCQ, Leicester Cough Questionnaire; mMRC, modified Medical Research Council.

COPD at enrolment in this study. Fifty-eight patients were men, and the median age was 75 years. All patients had a history of smoking, and 14 were current smokers. Thirty-four patients (50%) were hospitalised due to AE-COPD or CAP, and 27 (39.7%) were hospitalised within 2 years prior to enrolment. Ten patients (14.7%) had a history of frequent hospitalisation (≥2) and nine of whom experienced hospitalisation within 2 years prior to enrolment. Twenty and 19 patients had a history of CAP and AE within 2 years prior to enrolment, respectively. Seven patients had a history of cerebrovascular disease (including one with silent cerebral infarction), and none had neuromuscular diseases. During the 12-month follow-up period, no patients with cerebrovascular diseases were hospitalised due to AE-COPD or CAP. Only 19 patients (27.9%) were categorised into group A according to the GOLD guidelines, indicating that this cohort included many patients with severe COPD. Ten patients met criteria of 'asthma–COPD overlap'. The biomarkers that were used are listed in table 1. The median doubling concentration of C5 was 5.8 (SD 2.5). Capsaicin cough reflex sensitivity was unaffected by current smoking or cerebrovascular diseases (data not shown).

Predictive factors of hospitalisation in patients with COPD

Fifteen patients (22.1%) experienced an acute worsening of respiratory symptoms during the 12-month follow-up period. Of these, eight (11.8%) experienced AE-COPD (n=3) or CAP (n=5) requiring hospitalisation. When patients were stratified according to the presence or absence of hospitalisation during the 12-month follow-up (table 2), all eight patients had a history of AE-COPD or CAP requiring hospitalisation within 2 years prior to enrolment. Half of the patients (n=4) had a history of hospitalisation two times or more owing to AE-COPD or CAP. Furthermore, patients in the hospitalisation+ group frequently experienced AE-COPD and hospitalisation within 2 years prior to enrolment more as those in the hospitalisation– group (table 2). Meanwhile,

Table 2 Comparison of characteristics, functional markers and biomarkers between patients in the hospitalisation+ and in the hospitalisation− groups

	Hospitalisation− (n=60)	Hospitalisation+ (n=8)	P value
Age	74 (7.6)	71 (3.6)	0.096
Body mass index, kg/m^2	21.9 (3.0)	19.9 (4.7)	0.29
Sex, male	51 (85)	7 (87.5)	>0.99
Smoking, ex/current	46 (76.7)/14 (23.3)	8 (100)/0 (0)	0.19
Pack-years	55 (31.8)	65 (24.9)	0.32
GOLD classification, A/B/C/D	19 (31.7)/22 (37.7)/ 5 (8.3)/14 (23.3)	0 (0)/1 (12.5)/ 1 (12.5)/6 (75.0)	0.01
COPD stage 1/2/3/4	14 (23.3)/34 (56.7)/ 11 (18.3)/1 (1.7)	0 (0)/4 (50)/ 1 (12.5)/3 (37.5)	0.0006
Asthma, +	8 (13.3)	2 (25.0)	0.33
Cerebrovascular disease, +	7 (11.7)	0 (0)	0.59
Pneumonia <2 year, +	17 (28.3)	3 (37.5)	0.68
Acute exacerbation<2 year, +	14 (23.3)	5 (62.5)	0.03
Hospitalisation, +	26 (43.3)	8 (100)	0.005
Hospitalisation<2 year, +	19 (31.7)	8 (100)	0.0003
mMRC scale, grade	1.5 (1.1)	2.8 (1.4)	0.036
CAT, point	12.6 (8.2)	18.3 (8.0)	0.091
LCQ, point	18.4 (2.7)	18.3 (2.2)	0.93
Neutrophils, /µL	4035 (1498)	3552 (2014)	0.53
Eosinophils, /µL	232 (186)	373 (318)	0.26
Eosinophils≥300/µL, +	8 (13.3)	4 (50)	0.028
Albumin, g/dL	4.0 (0.3)	3.8 (0.5)	0.16
Lactate dehydrogenase, IU/L	195 (33)	198 (52)	0.87
Haemoglobin A1c, %	6.1 (0.8)	5.8 (0.6)	0.32
Brain natriuretic peptide, pg/mL	55 (84)	136 (143)	0.16
C-reactive protein, mg/L*	0.29 (0.42)	0.49 (0.89)	0.54
IgE, IU/L†	362 (630)	360 (475)	0.99
FeNO, ppb	24.9 (15.5)	33.7 (22.0)	0.31
C2, the number of doubling concentration	4.5 (2.5)	6.6 (2.7)	0.061
C5, the number of doubling concentration	5.5 (2.4)	7.5 (2.3)	0.051
Ejection fraction, %*	64 (8)	62 (15)	0.71
Postbronchodilator FEV_1, mL	1700 (643)	1001 (550)	0.008
Postbronchodilator FEV_1 predicted, %	67.2 (21.0)	41.5 (19.7)	0.007
Postbronchodilator FEV_1/FVC, %	51.4 (11.5)	39.3 (16.2)	0.076
Reversibility, %	4.7 (8.4)	3.9 (5.9)	0.76

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The number of doubling concentration was shown as follows; for example, 0.61 µM, 1.22 µM, 2.44 µM, 4.88 µM, 9.76 µM, 19.52 µM, 39.04 µM, 78.1 µM, 156.2 µM and, 312.5 µM correspond to 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 doubling concentrations, respectively. *n=66, †n=64.
C2 and C5, concentrations of inhaled capsaicin required to induce at least two (C2) and five coughs (C5); CAT, COPD assessment test; FeNO, fractional nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Ig, immunoglobulin; LCQ, Leicester Cough Questionnaire; mMRC, modified Medical Research Council.

the proportion of patients who experienced CAP within 2 years prior to enrolment was similar between the two groups. The mMRC scores were higher, but lung function was lower in the hospitalisation+ group than in the hospitalisation− group. Accordingly, GOLD classification was more severe in the hospitalisation+ group than in the hospitalisation− group. Patients in the hospitalisation+ group tended to have decreased capsaicin cough reflex sensitivity compared with those in the hospitalisation− group (table 2). Although blood eosinophil

Table 3 Risk factors contributed to severe acute exacerbation or community-acquired pneumonia requiring hospitalisation in patients with COPD

	OR	95% CI	P value
Age	0.93	0.77 to 1.12	0.47
C5, the number of doubling concentration	2.19	1.08 to 4.44	0.029
mMRC scores, grade	4.29	0.91 to 20.1	0.065
FEV_1, %predicted	0.88	0.77 to 1.01	0.078
Eosinophils ≥300/µL, +	45.9	1.09 to 1934	0.045

The number of doubling concentration was shown as follows; for example, 0.61 µM, 1.22 µM, 2.44 µM, 4.88 µM, 9.76 µM, 19.52 µM, 39.04 µM, 78.1 µM, 156.2 µM and 312.5 µM correspond to 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 doubling concentrations, respectively.
C5, concentration of inhaled capsaicin required to induce at least five coughs; FEV_1, forced expiratory volume in 1 s; mMRC, modified Medical Research Council.

counts were similar between the two group, the proportion of patients with higher blood eosinophil counts of ≥300/µL was significantly higher in the hospitalisation+ group than in the hospitalisation− group (50% vs 13.3%, p=0.028). A similar result was obtained when comparing patients with CAP requiring hospitalisation (n=5) and those not requiring hospitalisation (blood eosinophil counts ≥300/µL: 60% vs 13.3%, p=0.03). Meanwhile, comorbid asthma and levels of FeNO and serum IgE were not related to hospitalisation. Cough-specific quality of life (QoL) assessed using the Leicester Cough Questionnaire, cardiac function assessed using echocardiography and other biomarkers were also comparable between the two groups.

Multivariate logistic regression analysis was performed to determine OR for hospitalisation in patients with COPD (table 3). Decreased capsaicin cough reflex sensitivity and higher absolute eosinophil counts (≥300/µL) were associated with future hospitalisations due to AE-COPD or CAP. If the number of doubling concentrations of C5 rose to the next number (eg, from 7 to 8), OR for hospitalisation increased by 2.19 times.

Association of decreased cough reflex sensitivity with repeated hospitalisation in patients with COPD

To further clarify the association between capsaicin cough reflex sensitivity and hospitalisation in patients with COPD, a sensitivity analysis confined to patients who experienced hospitalisation before enrolment was performed (table 4). Although the mMRC scores and lung function were similar between patients who were hospitalised during the follow-up period (n=8) and those who did not (n=26), there were significant differences in capsaicin cough reflex sensitivity and the proportion of patients with blood eosinophil counts ≥300/µL between the two groups (table 4). This suggests that decreased capsaicin cough reflex sensitivity may be a risk factor for repeated hospitalisation due to severe AE and CAP in patients with COPD, along with a higher blood eosinophil count.

Longitudinal changes of capsaicin cough reflex sensitivity in patients with COPD

We assessed the changes in capsaicin cough reflex sensitivity in 22 patients with COPD. The capsaicin cough reflex sensitivity did not change during the 12-month follow-up period (data not shown).

DISCUSSION

Several reports have described an association between altered cough reflex sensitivity and COPD pathophysiology. However, the clinical implications of altered cough reflex sensitivity on its pathophysiology are poorly understood. We showed for the first time that decreased capsaicin cough reflex sensitivity is an important risk factor for severe AE or CAP requiring hospitalisation in patients with COPD, particularly when they had a history of recent hospitalisation (≤2 years) due to AE-COPD or CAP.

The role of cough reflex sensitivity in the pathophysiology of respiratory diseases has been previously reported. In asthma, cough reflex sensitivity is a component of the pathophysiology of severe asthma.[23] We showed that heightened capsaicin cough reflex sensitivity was associated with worse clinical outcomes of asthma, such as poor asthma control and frequent exacerbations,[20] and that some treatments, such as tiotropium and bronchial thermoplasty, can reduce the capsaicin cough reflex sensitivity of asthma.[24 25] Furthermore, tiotropium alleviates acute cough due to upper respiratory infections by improving heightened capsaicin cough reflex sensitivity,[26] indicating that upper airway respiratory infections may increase capsaicin cough reflex sensitivity. In contrast, decreased capsaicin cough reflex sensitivity is a risk factor for recurrent pneumonia.[18] Based on this evidence, we suggest that increased capsaicin cough sensitivity caused by infection prevents severe pneumonia that requires hospitalisation.

Previous studies have shown an association between increased capsaicin cough reflex sensitivity and AE-COPD,[16 17] which were converse outcome to this study. The discrepancy between previous work and ours could be explained by the reason for hospitalisation. In our study, five of eight patients with COPD were admitted to the hospital with CAP. Additionally, wheezes and dyspnoea, rather than a cough, were the main symptoms of AE in the three patients who required hospitalisation. Therefore, differences in the causes of AE (eg, the worsening of cough) may result in contradictory outcomes between previous studies and ours. Furthermore, previous studies did not investigate whether increased capsaicin cough reflex sensitivity was associated with future hospitalisation for AE-COPD or CAP.[16 17] The role of capsaicin cough reflex sensitivity may differ between severe and non-severe AE or CAP in patients with COPD. We speculate that cough reflex sensitivity is a biological defence response

Table 4 Comparison of characteristics, functional markers and biomarkers between patients in the hospitalisation+ and in the hospitalisation− groups when confined to the history of hospitalisation

	Hospitalisation− (n=26)	Hospitalisation+ (n=8)	P value
Age	75 (8.2)	71 (3.6)	0.046
Body mass index, kg/m^2	21.2 (3.1)	19.9 (4.7)	0.5
Sex, male	22 (85)	7 (87.5)	>0.99
Smoking, ex/current	22 (85)/4 (15)	8 (100)/0 (0)	0.55
Pack-years	63 (31.3)	65 (24.9)	0.79
GOLD classification, A/B/C/D	3 (11.5)/4 (15.4)/ 5 (19.2)/14 (53.9)	0 (0)/1 (12.5)/ 1 (12.5)/6 (75.0)	0.52
COPD stage 1/2/3/4	2 (7.7)/15 (57.7)/ 8 (30.8)/1 (3.9)	0 (0)/4 (50)/ 1 (12.5)/3 (37.5)	0.08
Asthma, +	6 (20.7)	2 (25.0)	0.37
Cerebrovascular disease, +	3 (11.5)	0 (0)	>0.99
Pneumonia <2 year, +	15 (57.7)	3 (37.5)	0.43
Acute exacerbation <2 year, +	11 (42.3)	5 (62.5)	0.43
Hospitalisation <2 year, +	19 (73.1)	8 (100)	0.16
mMRC scale, grade	2.0 (1.0)	2.8 (1.4)	0.17
CAT, point	14.0 (9.2)	18.3 (8.0)	0.22
LCQ, point	17.9 (2.8)	18.3 (2.2)	0.64
Neutrophils, /μL	3908 (1443)	3552 (2014)	0.65
Eosinophils, /μL	197 (113)	373 (318)	0.17
Eosinophils ≥300/μL, +	3 (11.5)	4 (50)	0.037
Albumin, g/dL	4.0 (0.3)	3.8 (0.5)	0.22
Lactate dehydrogenase, IU/L	202 (33)	198 (52)	0.84
Haemoglobin A1c, %	6.0 (0.6)	5.8 (0.6)	0.45
Brain natriuretic peptide, pg/mL	78 (120)	136 (143)	0.32
C reactive protein, mg/L*	0.31 (0.47)	0.49 (0.89)	0.59
IgE, IU/L†	346 (634)	360 (475)	0.95
FeNO, ppb	23.0 (13.5)	33.7 (22.0)	0.23
C2, the number of doubling concentration	3.8 (2.3)	6.6 (2.7)	0.023
C5, the number of doubling concentration	4.6 (2.2)	7.5 (2.3)	0.009
Ejection fraction, %*	62 (9)	62 (15)	0.9
Postbronchodilator FEV_1, mL	1432 (481)	1001 (550)	0.073
Postbronchodilator FEV_1 predicted, %	58.3 (16.5)	41.5 (19.7)	0.054
Postbronchodilator FEV_1/FVC, %	48.1 (10.6)	39.3 (16.2)	0.19
Reversibility, %	5.7 (7.8)	3.9 (5.9)	0.51

Global initiative for chronic obstructive lung disease.
The number of doubling concentration was shown as follows; for example, 0.61 μM, 1.22 μM, 2.44 μM, 4.88 μM, 9.76 μM, 19.52 μM, 39.04 μM, 78.1 μM, 156.2 μM and 312.5 μM correspond to 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, in order. *n=66, †n=64.
C2 and C5, concentrations of inhaled capsaicin required to induce at least two (C2) and five coughs (C5); CAT, COPD assessment test; FeNO, fractional nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Ig, immunoglobulin; LCQ, Leicester Cough Questionnaire; mMRC, modified Medical Research Council.

designed to prevent the development of severe AE and pneumonia requiring hospitalisation.

We found that blood eosinophil count (≥300/μL) was a potential biomarker for future hospitalisation in patients with COPD. Recently, eosinophils are important therapeutic target against COPD.[27] The GOLD guidelines strongly recommend that the use of inhaled corticosteroids is beneficial in patients with eosinophil count of 300/μL or higher for the prevention of severe exacerbations requiring hospitalisation. In addition, the incidence of pneumonia requiring hospitalisation was 2.17-fold higher in patients with COPD with a high blood eosinophil count (≥0.34×10^9 cells/L) than

in those with a normoeosinophil count.[28] Thus, the presence of blood eosinophilia when analysed under stable conditions indicates a high risk of hospitalisation in patients with COPD. In contrast, in a retrospective study on the impact of blood eosinophilia on CAP in patients with COPD, those with blood eosinophilia determined by >2% at the time of the emergency department had higher lung function, less severe COPD, lower leucocyte counts and lower risk of prolonged length of respiratory intensive care unit stay (≥14 days) than those without (≤2%).[29] However, the lower eosinophil counts observed in that study may be an epiphenomenon of more severe infections. Indeed, a subsequent study showed that lower blood eosinopenia (<50/μL) at the time of admission was associated with increased 18-month mortality and more severe infection in patients with AE-COPD and CAP requiring hospitalisation.[30]

The association between hospitalisation, lower lung function and severe dyspnoea has been well documented in previous studies. Worse lung function is associated with an increased risk of hospitalisation owing to severe exacerbation and subsequent mortality.[31 32] It is also an independent risk factor for CAP that requires hospitalisation in patients with COPD together with older age.[33 34] CAP is prone to develop in patients with severe COPD assigned to stage III or IV according to the GOLD classification.[35] The mMRC scores are widely used to assess dyspnoea in clinical practice. A primary care population survey conducted in the United Kingdom revealed that higher mMRC scores are risk factors for frequent exacerbations (≥2) that require hospitalisation, along with severely impaired lung function, older age and osteoporosis.[36] In addition, higher mMRC scores (≥2) and acute respiratory acidosis at admission were predictors of prolonged hospitalisation (>7days) in AE-COPD.[37] These results are consistent with those of the previous studies.

The present study had some limitations. Although patients were recruited from two hospitals, the present cohort consisted of a small number of patients (n=68) with a 12-month follow-up period. Therefore, only eight patients experienced severe AE or pneumonia requiring hospitalisation. However, the capsaicin cough challenge test was only performed for research purposes. Because we focused on the association between capsaicin cough reflex sensitivity and hospitalisation in patients with COPD, we could not enrol a larger number of patients. It is extremely difficult to perform capsaicin cough challenge tests in many hospitals. Second, the concentration of inhaled capsaicin for C2 and C5 was marginally but not significantly higher in the hospitalisation group than in the non-hospitalisation group (table 2). Therefore, decreased capsaicin cough reflex sensitivity may have a minor impact on hospitalisation in patients with COPD when compared with other factors such as higher blood eosinophil counts and a history of AE-COPD or pneumonia. Last, we could not perform the capsaicin cough challenge test 12 months after enrolment due to the COVID-19 pandemic. We refrained from performing all the aerosol-generated measurements at that time. It remains unclear how changes in capsaicin cough reflex sensitivity affect future severe AE or pneumonia requiring hospitalisation. Further studies are needed to evaluate the association between longitudinal changes in capsaicin cough reflex sensitivity and hospitalisation due to COPD. Despite these limitations, we showed for the first time an association between capsaicin cough reflex sensitivity and hospitalisation due to COPD in the present study.

Although an association between heightened capsaicin cough reflex sensitivity and AE-COPD has been reported in previous studies, we speculate that increased capsaicin cough reflex sensitivity in patients with COPD may protect against the development of severe AE or pneumonia requiring hospitalisation. Meanwhile, other well-known risk factors for AE or CAP in patients with COPD include higher blood eosinophil counts and a history of AE-COPD or CAP. Therefore, targeting therapy for capsaicin cough reflex sensitivity may not necessarily reduce severe AE-COPD and pneumonia requiring hospitalisation. Larger studies are required to confirm these findings.

Contributors YK: established the conception of the study and contributed to the performance of diagnostic tests, the collection of data, the recruitment of patients, disease diagnosis and management, the acquisition and interpretation of data, and drafting the manuscript. RK contributed to the performance of the diagnostic tests, and data acquisition, analysis, and interpretation. TA, KF, SF and YI contributed to the patient recruitment, diagnostic tests, and data collection and interpretation. NT, TT, HN and KI contributed to the performance of diagnostic tests, data collection, and data acquisition and interpretation. YM, TU, HO, MT, KM and TO contributed to the diagnostic tests, data collection, and interpretation. TS and AN contributed to the patient recruitment, disease diagnosis and management, data interpretation, and manuscript revision. YK is responsible for the overall content as guarantor.

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Competing interests YK received research grants from Novartis Pharma, MSD, Sanofi, and Kyowa-Kirin Corporation and personal fees from GSK, Novartis Pharma, AstraZeneca, Sanofi, and Kyorin. KF received research grants from Novartis Pharma and GSK. SF received personal fees from AstraZeneca and Eli Lilly. HO received a research grant from Boehringer Ingelheim. KM received personal fees from Pfizer and Chugai Pharmaceutical. TO reports personal fees from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Pfizer, Chugai Pharmaceutical, MSD, Daiichi Sankyo, and Asahi Kasei Pharma, as well as research grants and personal fees from Kyowa Hakko Kirin, Boehringer Ingelheim, Ono Pharmaceutical, and Novartis. MT has received a research grant from Pfizer. AN reports personal fees from Astellas, AstraZeneca, Kyorin, GSK, MSD, Shionogi, Bayer, Sanofi, Taiho, and Boehringer Ingelheim, and research grants from Astellas, Kyorin, Boehringer Ingelheim, Novartis, MSD, Daiichi Sankyo, Taiho, Teijin, Ono, Takeda, and Sanofi Pharmaceutical. The other authors did not receive any grants or personal fees.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000032497). Written informed consent was obtained from all the participants.

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ORCID iD

Yoshihiro Kanemitsu http://orcid.org/0000-0002-1529-9477

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Online supplemental manuscript:

Decreased capsaicin cough reflex sensitivity predicts hospitalization due to COPD

Yoshihiro Kanemitsu, MD, PhD[1]*, Ryota Kurokawa, MD, PhD[1]*, Taisuke Akamatsu, MD, PhD[2], Kensuke Fukumitsu, MD, PhD[1], Satoshi Fukuda, MD, PhD[1], Yutaka Ito, MD, PhD[1], Norihisa Takeda, MD, PhD[1], Hirono Nishiyama, MD, PhD[1], Keima Ito, MD[1], Tomoko Tajiri, MD, PhD[1], Yuta Mori, MD, PhD[1], Takehiro Uemura, MD, PhD[1], Hirotsugu Ohkubo, MD, PhD[1], Masaya Takemura, MD, PhD[1], Ken Maeno, MD, PhD[1], Tetsuya Oguri, MD, PhD[1], and Toshihiro Shirai, MD, PhD[2], Akio Niimi, MD, PhD[1]

Affiliation:

[1]Department of Respiratory Medicine, Allergy, and Clinical Immunology. Nagoya City University, Graduate school of Medical Sciences, Nagoya, Aichi, Japan

[2]Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan

Corresponding author: Yoshihiro Kanemitsu, MD, PhD

Contact address: 1, Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, Japan

Tell: +81-52-853-8216, **Fax:** +81-52-852-0849

Email: kaney32@med.nagoya-cu.ac.jp

Methods:

Subjects and the definition of COPD and comorbid asthma

We prospectively recruited patients with COPD who visited the Nagoya City University Hospital and Shizuoka General Hospital between June 2018 and January 2020. We enrolled patients in this study if their condition was stable at the time of their outpatient department visit. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 as follows: (1) a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of less than 0.70 (fixed airflow limitation); (2) persistent respiratory symptoms such as dyspnea, cough, sputum production, or wheezing; and (3) significant exposure to noxious stimuli such as tobacco smoke or other environmental particles. We permitted to include patients with comorbid asthma, called "asthma-COPD overlap" in the present study. Patients were diagnosed with comorbid asthma if they had some clinical features of asthma, such as (1) variable or paroxysmal clinical symptoms, (2) a diagnosis of asthma before the age of 40 years, (3) elevated levels of fractional nitric oxide (FeNO) of 35 ppb or higher, and (4) a history of perennial allergic rhinitis, airway hyperresponsiveness, elevated peripheral blood eosinophils, and total or allergen-specific immunoglobulin E (IgE) levels, in addition to fixed airflow limitation[1]. Conversely, patients were not recruited to the present

study when they denied participation in the study, had chronic respiratory diseases other than asthma, or had a post-bronchodilator FEV_1/FVC ratio of 0.7 or higher. Patients were not eligible for this study if they were in a nursing care home, were bedridden at home, had a history of aspiration pneumonia, or underwent tubal feeding. Patients who experienced respiratory infection within four weeks or hospitalization due to AE-COPD or CAP within 12 weeks prior to enrollment were also excluded because they may have affected the results of the capsaicin cough challenge test. This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000032497). Written informed consent was obtained from all the participants.

Measurements

All patients underwent blood biomarker analyses (blood neutrophil and eosinophil counts, serum total IgE, albumin, lactate dehydrogenase, C-reactive protein, hemoglobin A1c, and plasma brain natriuretic peptide), echocardiography (ejection fraction), FeNO measurement, lung function test, computed tomography of the chest, and capsaicin cough challenge test at enrollment. Pre- and post-bronchodilator spirometry were performed according to the ATS/ERS recommendation using a Chestac-8900 (Chest Corp, Tokyo, Japan) [2]. The patients inhaled 400 μg of salbutamol using a spacer after

completing the first spirometry test. They underwent post-bronchodilator spirometry 15 min after inhalation of 400 μg salbutamol. Post-bronchodilator FEV_1 values were used. FeNO levels were determined at an expiratory flow rate of 50 ml/s using a Sievers NOA 280i chemiluminescence analyzer (GE Analytical Instruments, Boulder, CO, USA) [3].

They also completed the Leicester Cough Questionnaire, COPD Assessment Test, and modified Medical Research Council (mMRC) dyspnea scale at that time. The Leicester Cough Questionnaire contains 19 items with three subdomains: physical, social, and psychological, ranging from 3 to 21[4]. Higher scores indicate a better cough-specific QoL. This questionnaire was translated from English into Japanese using the international protocol of the International Quality of Life Assessment translation protocol[5]. The validity and reliability of the Japanese version of the LCQ[4] has been confirmed in a previous study[5]. If patients expectorated sputum, they were cultured to assess the bacterial colonization of the airways. The COPD assessment test is a self-report questionnaire regarding the health status of patients with COPD, which includes eight items related to cough, phlegm, chest tightness, dyspnea, activities, confidence, sleep, and energy. It ranges from 0 to 40. Higher scores indicate worse health status[6]. The mMRC dyspnea scale is a five-point Likert scale that assesses dyspnea. It ranges from 0 (only breathlessness after heavy exercise) to 4 (too breathless to leave the house)[7].

Capsaicin cough challenge test

The capsaicin cough challenge test was performed using an Astograph® (Chest, Tokyo, Japan) after blood collection, echocardiography, FeNO measurement, and spirometry. Detailed information on this method has been previously reported [8]. Briefly, 10 doubling concentrations of capsaicin (0.61 to 312.5 μM) were inhaled for 15 s per concentration at 1-minute intervals in increasing order, following inhalation of physiological saline for 1 min. Saline was inhaled for 45 s until the initiation of the next inhalation of capsaicin to increase patient blindness. When patients coughed five or more times, the challenge ended at the end of the following saline inhalation for 45 s. The test ended when patients finished inhaling short-acting β_2 agonists (SABAs) for two min after the capsaicin cough challenge. The concentrations required to induce at least two (C2) and five (C5) coughs were recorded. Lower C2 and C5 values indicate heightened capsaicin cough reflex sensitivity[8 9]. We planned to perform a capsaicin cough challenge test 1 year after enrollment in the study, but we could not evaluate capsaicin cough reflex sensitivity 1 year after enrollment because of the restriction of measurements due to the coronavirus disease 2019 pandemic.

Definition of AE-COPD and pneumonia

AE-COPD was defined as an acute worsening of respiratory symptoms that

resulted in additional treatments such as bronchodilators, antibiotics, and systemic corticosteroids. CAP was diagnosed when new infiltration was observed on chest radiography and/or computed tomography with two or more of the following findings: (1) fever (body temperature >37.5°C or <36.0°C), (2) leukocytosis or leukopenia (white blood cells >10,000/mm^3 or <4,000/mm^3), and (3) purulent tracheal aspirate and/or sputum[10].

Statistical analysis

Statistical analysis was performed using the JMP 14.3 software (SAS Institute Japan, Tokyo, Japan). Values are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables. We categorized patients into the hospitalization+ group (AE-COPD or CAP patients requiring hospitalization during 1 years after enrollment) and the hospitalization- group. Two-group comparisons were performed using unpaired t-test or Fisher's exact test, as appropriate. The values of C2 and C5 are expressed as the number of doubling concentrations. The number of doubling concentrations ranges from 1 to 10, with a high number indicating a decreased cough sensitivity of inhaled capsaicin. Corresponding inhalation concentration of capsaicin to the number of doubling concentration was shown as follows; e.g. 0.61 μM, 1.22 μM, 2.44 μM, 4.88 μM, 9.76 μM, 19.52 μM, 39.04 μM, 78.1 μM, 156.2 μM and, 312.5 μM

correspond to 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 doubling concentrations, respectively. They reflect base2 logarithmic values of C5. Multivariate analysis was performed to determine the odds ratio for hospitalization. We adapted the number of doubling concentration of C5 when conducting the multivariate analysis because readers can easily understand the odds ratio for hospitalization if the concentration of C5 rises to the next concentration. A sensitivity analysis confined to patients who were hospitalized before enrollment was also performed to clarify the association between capsaicin cough reflex sensitivity and hospitalization in patients with COPD. Longitudinal data on capsaicin cough reflex sensitivity were compared using paired t-tests. A variable was considered significant if the p-value was ≤ 0.05. Some data were missing (n = 64 for total IgE, and n = 66 for CRP and ejection fraction). We handled missing data as a blank because these did not affect main results of this study.

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