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Short report

Long-term clinical follow-up of irritant-induced occupational asthma

Jussi Lantto ,[1,2] Hille Suojalehto,[1] Hanna Jantunen,[1] Irmeli Lindström [1]

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[1]Occupational Medicine, Finnish Institute of Occupational Health, Helsinki, Finland
[2]Doctoral Programme in Clinical Research, University of Helsinki Faculty of Medicine, Helsinki, Finland

Correspondence to
Jussi Lantto;
jussi.lantto@helsinki.fi

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ABSTRACT

Background Occupational exposure to irritants is associated with poor asthma control, but the long-term clinical characteristics of irritant-induced occupational asthma (IIA) are poorly known.

Objective To evaluate whether any distinguishable features contribute to IIA patients' poor outcomes and whether clinical characteristics change over time.

Methods We re-evaluated 28 IIA patients with a median of 6.8 years (IQR 4.6–11.1) after their diagnosis at the Finnish Institute of Occupational Health in 2004–2018. We measured their lung function, non-specific bronchial hyper-responsiveness, inflammation profile and exercise capacity using an ergometric bicycle test. The participants also underwent an Asthma Control Test (ACT) and responded to questionnaires assessing their laryngeal hypersensitivity (LHQ) and dysfunctional breathing (Nijmegen Questionnaires, NQ).

Results At follow-up, 22 (79%) participants used inhaled corticosteroids, 4 (14%) had asthma exacerbation within 1 year, 11 (39%) had ACT<20 (ie, poor asthma symptom control), 7 (26%) had abnormal spirometry and 8 (36%) had a positive methacholine challenge test result. 17 (61%) participants showed at least one elevated eosinophilic inflammation marker. Six (23%) had an abnormal LHQ score and 7 (26%) had an abnormal NQ score. 15 (58%) participants showed reduced physical capacity that was related to extensive asthma medication, poor asthma symptom control and acute IIA phenotype. A higher ACT score was the only significant change between diagnosis and follow-up (p=0.014).

Conclusion Most of the IIA patients had normal lung function at follow-up, which had only changed a little over time. Reduced physical capacity was a common finding and appears to be related to poor asthma symptom control.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Occupational exposure to irritants can cause irritant-induced asthma (IIA). IIA patients frequently have poor asthma symptom control, but the long-term clinical characteristics of IIA are poorly known.

WHAT THIS STUDY ADDS

⇒ In this study, spirometry showed that only a minority of IIA patients had airway obstruction when they used regular asthma medication. However, many of them showed poor exercise capacity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should consider other treatments besides regular asthma medication for IIA patients. These patients might benefit from physical rehabilitation.

INTRODUCTION

Irritant-induced occupational asthma (IIA) refers to asthma that is considered to develop via irritant mechanism.[1 2] The European Academy of Allergy and Clinical Immunology's position paper proposes that acute and subacute IIA cases can show sufficient evidence of a causal relationship between occupational exposure and asthma.[1] According to surveillance data, acute IIA represents 4%–15% of new occupational asthma cases.[3–5] However, IIA has remained poorly understood; only one study has clinically evaluated the long-term outcome of acute IIA.[6]

Previously, we have observed that IIA patients show poorer asthma outcomes at diagnosis than those whose occupational asthma has developed via immunological mechanisms.[7] A follow-up questionnaire revealed that four-fifths of the IIA patients whose asthma was uncontrolled 6 months after diagnosis still had poor asthma control.[8] Therefore, the current study aimed to assess whether any distinguishable features contribute to IIA patients' poor asthma symptom control and whether their clinical characteristics had changed after the diagnosis.

METHODS

We identified 69 patients who were diagnosed with acute or subacute IIA at the Finnish Institute of Occupational Health (FIOH) in 2004–2018.[7] The diagnostic criteria were (1) no evidence of active asthma in adulthood before the exposure; (2) exposure to a high concentration of an airborne irritant; (3) occurrence of asthma symptoms in a close temporal relationship with the exposure; (4) asthma verification by reversible obstruction or non-specific bronchial hyper-responsiveness; (5) persistence of symptoms for ≥3 months and (6) no other pulmonary disorder that explained the symptoms. We classified 30 patients with only one high-level exposure event within 24 hours as acute IIA and 39 patients with repeated exposure to high levels of irritants during a period of more than 24 hours as subacute IIA.[7]

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28 (41%) of the 69 identified IIA patients were willing to participate and gave their written, informed consent to a follow-up evaluation at FIOH between May 2021 and August 2022. The participants had shorter duration of asthma symptoms before baseline and time since the first exposure to follow-up than the non-participants (online supplemental table 1). The latter group also had a tendency for higher doses of asthma medication and IgE level than the former. Otherwise, the groups seemed comparable.

Spirometry, non-specific bronchial hyper-reactivity (NSBH), fractional exhaled nitric oxide (FeNO), blood eosinophilia (B-Eos) were measured and the Asthma Control Test (ACT) was performed at both the time of diagnosis (baseline) and follow-up. At follow-up, the participants also underwent a high-sensitivity C reactive protein test (S-hs-CRP) and induced sputum and completed the Newcastle Laryngeal Hypersensitivity Questionnaire (LHQ) and the Nijmegen questionnaires (NQ), which screen for laryngeal hypersensitivity and dysfunctional breathing, respectively.

At follow-up, 26 (93%) participants underwent a bicycle ergometric test. We measured the predicted mean workload attained during the last 4 min of the test ($W_{max4\%}$), and a $W_{max4\%}$ of ≥80% is generally considered normal exercise capacity.[9 10] The detailed methodology is presented in online supplemental material.

RESULTS

The participants' median interval from baseline was 6.8 years (IQR 4.6–11.1). 18 participants had been working at baseline, and we could not rule out continued exposure to the causal agent for 6 of them. These figures were 17 and 1 at follow-up, respectively. The causative agents were mixtures (seven cases), acid aerosols or fumes (six cases), base aerosols or fumes (four cases), dusts (three cases), endotoxins (three cases), a mixture of acid and base aerosols or fumes (two cases), inorganic gases (one case), oxidising agents (one case) and other chemicals (one case).

Table 1 displays the participants' clinical characteristics at baseline and follow-up. The majority (93%) were male, and 11 (39%) had acute IIA. At follow-up, 13 (46%) had ≥2 comorbidities, and 12 (43%) had a body mass index (BMI) of ≥30 kg/m^2. 11 (39%) had a smoking history of ≥10 pack-years—1 more than at baseline. 12 (43%) participants used high-dose inhaled corticosteroids, 18 (64%) were on GINA 4–5 step asthma medication, 4 (15%) had 1 exacerbation and none had a hospital stay during the previous year. Seven (25%) needed a daily short-acting beta-agonist, and 11 (39%) obtained an ACT score of ≤19. Six (22%) participants had a forced expiratory volume in 1 s (FEV1%) of <80% and three (11%) an FEV1/forced vital capacity (FVC) of <0.70, whereas eight (36%) showed hyper-reactivity in the methacholine challenge test.

Seven (25%) participants had a FeNO of ≥25 ppb and 10 (36%) a B-Eos of ≥300 µg/L. 19 had analysable induced sputum sample, and 8 (42%) had ≥2% eosinophils. Overall, 17 (61%) participants had at least one elevated eosinophilic inflammation marker. Six (32%) had ≥61% sputum neutrophils, and seven (25%) had S-hs-CRP of ≥3 mg/L indicating systemic inflammation. Six (23%) obtained an abnormal score in the LHQ and seven (26%) in the NQ. Both questionnaires were abnormal for five (20%) participants.

15 (58%) participants had reduced exercise capacity in the bicycle ergometric test. These had acute IIA (60% vs 9%, p=0.014), were on GINA 4–5 step asthma medication (80% vs 36%, p=0.043) and their LHQ and NQ scores were abnormal (43% vs 0, p=0.024; and 43% vs 0, p=0.020, respectively) more often than those with

Table 1 Characteristics of participants at time of diagnosis (baseline) and at follow-up

	Participants (n=28)	
Characteristics	**Baseline**	**Follow-up**
Time since first exposure, years median (IQR)	1.9 (1.0–5.8)	11.0 (6.6–15.6)
Possible continued exposure to causal agent at work	6 (21)	1 (4)
Time since IIA diagnosis to follow-up, years, median (IQR)	X	6.8 (4.6–11.1)
Age, years, mean (SD)	46 (10.7)	54 (9.5)
Male	26 (93)	X
Smoking history		
► Less than 10 pack years	18 (64)	17 (61)
► Current smoker and ≥10 pack-years	5 (18)	3 (11)
► Ex-smoker and ≥10 pack-years	5 (18)	8 (29)
Body mass index (kg/m^2), mean (SD)	28.7 (5.2)	30.4 (6.6)
Comorbid diseases ≥2	X	13 (46)
IIA phenotype		
► Acute	11 (39)	X
► Subacute	17 (61)	
Asthma outcome		
Daily dose of inhaled corticosteroid		
► No inhaled corticosteroids	9 (32)	6 (21)
► Low dose	3 (11)	1 (4)
► Medium dose	8 (29)	9 (32)
► High dose	8 (29)	12 (43)
Global Initiative for Asthma 4–5 step medication	12 (43)	18 (64)
Exacerbation without exposure to causal agent for ≤1 year	4 (14)	4 (14)
Short-acting beta-agonist daily	11/25 (44)	7 (25)
Asthma control test score of≤19	13/17 (76)	11 (39)
Spirometry		
► Prebronchodilator FEV1% of <80%	8 (29)	6/27 (22)
► Postbronchodilator FEV1/FVC of <0.70	6 (21)	3/27 (11)
Non-specific bronchial hyper-reactivity	13/25 (52)	8/22 (36)
Inflammation profile		
Fractional exhaled nitric oxide of ≥25 ppb	8 (29)	7 (25)
Blood eosinophilia of ≥300 ug/L	5/27 (18)	10 (36)
Serum high-sensitivity C reactive protein of ≥3.0 mg/L	X	7 (25)
Induced sputum		
► Eosinophils of ≥2%	X	8/19 (42)
► Neutrophils of ≥61%	X	6/19 (32)
Questionnaire		
Score of <17.1 on Newcastle Laryngeal Hypersensitivity Questionnaire	X	6/26 (23)
Score of ≥23 in Nijmegen Questionnaire	X	7/27 (26)
Exercise capacity		
W4max%, mean (SD)	X	72% (28)
► Reduced exercise capacity*	X	15/26 (58)

Categorical data are presented as n (%) if not otherwise stated. Normally distributed quantitative data are expressed as mean (SD); abnormally distributed quantitative data are expressed as median (IQR). Unless otherwise specified, the number of participants was 28. *W*max4%, Percentages of mean predicted workload attained during last 4 min of bicycle ergometric test.[9 10]
*A $W_{max4\%}$ of <80% represented reduced exercise capacity.
FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity; IIA, irritant-induced asthma.

a normal outcome (online supplemental table 2). $W_{max4\%}$ correlated positively with ACT (Spearman correlation (r_s)=0.476, p=0.014) and negatively with B-Eos and S-hs-CRP (r_s=−0.422, p=0.032; r_s=−0.412, p=0.036, respectively). ACT correlated negatively with BMI and S-hs-CRP (r_s=−0.444, p=0.018; r_s=−0.717, p<0.001, respectively) and positively with LHQ (r_s=0.512, p=0.007).

A higher ACT score at follow-up was the only significant difference from baseline (p=0.014); however, only 17 (61%) participants had completed this questionnaire at baseline.

DISCUSSION

We examined 28 IIA patients with a median of 11 years after their exposure to respiratory irritants. We observed that most of them had good lung function when they used regular asthma medication. On the other hand, poor exercise capacity was a common finding and was related to a poor ACT score and frequent use of GINA 4–5 step asthma medication. Our findings also suggested that comorbid conditions, such as laryngeal hypersensitivity, might have contributed to some of the participants' poor outcomes. Acute IIA patients showed poorer exercise capacity than those with subacute IIA. Otherwise, their results were similar.

Our participants' lung functions had remained stable over time: Only a minority had an obstruction in spirometry at baseline or at follow-up. In their study, Malo *et al*[6] evaluated 35 patients with acute IIA a mean of 13.6 years after exposure and reported that 54% had an FEV1 of <80%, 34% had an FEV1/FVC of <0.70 and 74% showed hyper-reactivity in NSBH. In our study, these proportions were 18%, 18% and 38% for the acute IIA patients, respectively. Fewer of Malo's participants used inhaled corticosteroids at follow-up (34% vs 82%), and they were more frequently smokers than our participants which might explain some of the differences.[6] We are not aware of any other studies that have evaluated the long-term outcome of subacute IIA.

Our findings suggest that IIA patients' inflammation profile contributes to their outcome: 17 (61%) of our participants had at least one elevated eosinophilic inflammation marker, and those with reduced physical capacity frequently had a high blood or sputum eosinophil count. Similarly, both poor physical capacity and poor asthma symptom control were connected to the level of S-hs-CRP. However, other factors likely play a greater part, and we lacked data on induced sputum and CRP levels at baseline; therefore, these results need to be interpreted with caution.

Regarding laryngeal hypersensitivity and dysfunctional breathing, one-fifth of this study's participants obtained an abnormal LHQ and NQ score, and all of them had reduced physical capacity. ACT scores showed a positive correlation with LHQ, and at least two of our participants expressed strong laryngeal symptoms during the exercise test. These results imply that laryngeal hypersensitivity probably contribute to IIA patients' poor outcomes. However, the diagnostic accuracy of these questionnaires is uncertain among asthmatics.[11 12]

Our study had several limitations. We had no reference group, and our sample size was modest, meaning that we were unable to perform a multivariate analysis. We cannot rule out our selection bias because there were also some differences in baseline characteristics between the participants and the non-participants. Laryngeal hypersensitivity and dysfunctional breathing were assessed using questionnaires instead of a clinical approach. We were unable to evaluate breathing patterns or gas exchange during the bicycle ergometry, and other factors, such as obesity and smoking, might have contributed to the outcome. Finally, for safety reasons, those who had the poorest outcomes did not undergo the NSBH or sputum induction, which might have led to underestimated hyper-reactivity and affected sputum cell counts. Nevertheless, we consider our findings noteworthy as very little available literature on the prognosis of IIA is available.

In conclusion, our results suggest that, despite poor asthma symptom control, many acute and subacute IIA patients tend to have good lung function but poor exercise capacity several years after exposure to irritants. These findings imply that IIA patients could benefit from other treatments besides regular asthma medication. Pulmonary rehabilitation, for instance, might increase their physical activity and capacity. Clinicians should also consider laryngeal hypersensitivity and dysfunctional breathing in this patient group.

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Contributors JL had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. JL, HS, HJ and IL contributed substantially to the study design, data collection, analysis and interpretation, and the writing of the manuscript.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and the Ethics committee of the Helsinki University Central Hospital approved this study (approval number HUS of 611/2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data are archived in the repository of Finnish Institute of Occupational Health, however, the data are publicly unavailable due to ethical reasons.

ORCID iDs
Jussi Lantto http://orcid.org/0000-0003-4710-7967
Irmeli Lindström http://orcid.org/0000-0002-6399-8846

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Title: The long-term clinical follow-up of irritant-induced occupational asthma

Authors: Jussi Lantto, MD[1,2], Hille Suojalehto MD, PhD[2], Hanna Jantunen MD, PHD[2], Irmeli Lindström MD, PHD[2]

1. Doctoral Programme in Clinical Research, University of Helsinki, Finland

2. Finnish Institute of Occupational Health, Helsinki, Finland

Supplement

Methods

Study design

We conducted a systemic search in the patient register of the Finnish Institute of Occupational Health (FIOH) to identify all patients diagnosed with irritant-induced asthma (IIA) at FIOH in 2004-2018. The initial diagnosis had been given by a multidisciplinary panel of pulmonologists, occupational health physicians, and occupational toxicologists. Our group, consisting of an occupational health physician, an occupational toxicologist, and two pulmonary physicians (JL, IL), confirmed that each participant met our IIA criteria.

All the patients' initial evaluations were performed at FIOH when the OA diagnosis was confirmed. The results of these evaluations represent the baseline values in this study. We sent notification of a follow-up study to the previously identified individuals. Those who gave their written informed consent to a clinical examination were re-evaluated at FIOH between May 2021 and August 2022.

Definitions

Smoking history was divided into nonsmokers, current smokers and ex-smokers. The last two had smoked ≥10 pack-years and the ex-smokers had quit smoking ≥6 months previously.

Asthma medication was graded in accordance with the 2020 Global Initiative for Asthma (GINA) guidelines. *Exacerbation* meant ≥3 days intake of corticosteroids equivalent to ≥30 mg prednisolone due to breathing difficulties. The patients' *symptom control* was assessed using the Asthma Control Test (ACT), the scores of which range from 5 to 20. A score of ≤19 represented poor symptom control.

Characteristics were measured using the following methods: *forced vital capacity* (*FVC*) and *forced expiratory volume in the first second* (*FEV1*) using a standard flow-volume spirometer (Spirostar USB

Medikro, Finland) based on Viljanen's *predicted values*; *NSBH* using the histamine or methacholine challenge test; *fractional exhaled nitric oxide* (*FeNO*) using an on-line chemiluminescence analyser (NIOX, Aerocrine AB, Solna, Sweden); *inducted sputum* using nebulization of 3% hypertonic saline (DeVILBISS UnltraNEB, Germany) and analysing the whole sputum sample; *serum high-sensitivity C-reactive protein* (*S-hs-CRP*) using turbidimetry (ARCHITECT c8000 System, Abbott Diagnostics, USA) in which values of ≥3 mg/l indicated systemic inflammation; *serum total IgE (S-IgE*) using the Phadia UniCAP system (Phadia, Uppsala, Sweden). *Atopy* was a ≥1 positive reaction (wheal diameter of ≥3 mm) in a skin prick test to common allergens (ALK-Abello, Horsholm, Denmark).

Laryngeal hypersensitivity was assessed using the Newcastle laryngeal hypersensitivity questionnaire (LHQ) in which a score of <17.1 is abnormal; and *dysfunctional breathing* using the Nijmegen questionnaire in which a score of ≥23 is abnormal.

Exercise capacity was assessed using bicycle ergometry (Cycle ergometer Corival cpet, Lode, Netherlands; Cardiac Testing System Cardiosoft, GE Healthcare, USA; Pulse CO-Oximeter Masimo Radical 7, USA; spirometry Spirostar USB Medikro Pro, Finland) in which the participants maintained a cycling speed of 60 revolutions per minute and the load was increased by 15 watts every one minute. We used Arstila's ergometric reference values. We measured the predicted mean workload attained during the last four minutes of the test ($W_{max4\%}$). A $W_{max4\%}$ of ≥80% is generally considered normal.

Statistics

We used SPSS version 28.0.0.0 for the statistical analyses. We presented the categorical valued as counts and percentages and expressed the quantitative data as a mean and standard deviation (SD), if the data followed normal distribution. If this assumption was violated, we presented the data as a median and interquartile range. With related samples, we used McNemar's test, the paired-samples T-test, and the

Wilcoxon matched-pair signed-rank test; and with independent samples, we applied Fisher's exact test, the independent-samples T-test, and the Mann-Whitney U test, respectively. We also calculated the Spearman correlation (r_s) between the continuous variables. A P -value of <0.05 was considered significant.

Ethics

The Ethics committee of the Helsinki University Central Hospital approved this study (approval number HUS of 611/2020).

Table 1. Participants vs non-participants: Demographic and clinical characteristics of patients at time of diagnosis (baseline) at the Finnish Institute of Occupational Health

Characteristics	Participants N=28	Non-participants N=41	P-value
Duration of asthma symptoms before baseline Median (IQR) y	1.3 (0.9-2.7)	2.1 (1.5-3.9)	**.014**
Time from last exposure event to baseline Median (IQR) y	0.7 (0.1-1.2)	1.1 (0.1-2.0)	.128
Time from first exposure to follow-up, Median (IQR) y	11.0 (6.6-15.6)	15.9 (11.7-22.0)	**.012**
Time since baseline to follow-up, Median (IQR) y	6.8 (4.6-11.1)	9.9 (5.4-14.2)	.217
Age Mean (SD)	46 (10.7)	46 (9.8)	.861
Male (%)	26 (93)	32 (78)	.179
Smoking history			
• Less than 10 pack years	18 (64)	24 (59)	.941
• Current smoker and ≥10 pack-years	5 (18)	8 (20)	
• Ex-smoker and ≥10 pack-years	5 (18)	9 (22)	
Body mass index, kg/m^2 Median (IQR)	27.9 (25.6-31.7)	28.4 (25.8-31.7)	.760
IIA phenotype			
• Acute	11 (39)	19 (46)	.626
• Subacute	17 (61)	22 (54)	
Asthma outcome			

Daily dose of inhaled corticosteroid • No inhaled corticosteroids • Low dose • Medium dose • High dose	 9 (32) 3 (11) 8 (29) 8 (29)	 5 (12) 5 (12) 20 (49) 11 (27)	 .184
Global Initiative for Asthma step 4-5 medication	12 (43)	24 (59)	.228
Exacerbation without exposure to causal agent for ≤1 year	4 (14)	9 (22)	.538
Short-acting beta agonist daily	11/25 (46)	13/36 (36)	.600
Asthma Control Test score of ≤19	13/17 (76)	16/22 (73)	1.000
Spirometry • FEV1 of <80% • FEV1/FVC of <0.70	 8 (29) 6 (21)	 14/40 (35) 6/40 (15)	 .610 .532
Non-specific bronchial hyperreactivity	13/25 (52)	19/29 (66)	.407
Inflammation profile			
Fractional exhaled nitric oxide of ≥25 ppb	8 (29)	6/40 (15)	.227
Blood eosinophilia of ≥300 ug/l	5/27 (19)	6/37 (16)	1.000
Atopy^	8 (29)	16 (39)	.445
Serum immunoglobulin E of >110 kU/L	4/25 (16)	16/38 (42)	.051

Categorical data presented as n (%) if not otherwise stated. Normally distributed quantitative data expressed as mean (SD) and independent-samples T-test used; abnormally distributed quantitative data expressed as median (IQR) and Mann-Whitney U test used. Unless otherwise specified, the number of patients was 28 and 41, respectively

^≥1 positive skin prick test reaction to common environmental allergens

IIA, irritant-induced asthma

IQR, interquartile range

7

77 *SD*, standard deviation

78 **Table II. Comparison of participants with reduced and normal exercise capacity in bicycle ergometric**

79 **test^**

Characteristics	Reduced exercise capacity (N=15)	Normal exercise capacity (N=11)	P-value
Age, mean (SD)	56 (8.8)	51 (10.5)	.175
Male	13 (87)	11 (100)	.492
Smoking history of ≥10 pack years	7 (47)	3 (27)	.428
Body mass index (kg/m^2), mean (SD)	30.2 (6.6)	29.5 (6.1)	.785
Comorbid diseases ≥2	8 (53)	4 (36)	.453
IIA phenotype			**.014**
• Acute	9(60)	1 (9)	
• Subacute	6 (40)	10 (91)	
Asthma outcome			
Medium or high daily dose of inhaled corticosteroid	13 (87)	6 (55)	.095
Global Initiative for Asthma 4-5 step medication	12 (80)	4 (36)	**.043**
Exacerbation ≤1 year	3 (23)	1 (9)	.596
Short-acting beta agonist daily	4 (27)	1 (9)	.356
Asthma Control Test score of ≤19	7 (47)	2 (18)	.217
Spirometry			
• FEV1% of <80%	5/14(36)	1 (9)	.180
• FEV1/FVC of <0.70	2/14 (14)	1 (9)	1.000
Non-specific bronchial hyperreactivity	4/10 (40)	4 (36)	1.000
Inflammation profile			

Fractional exhaled nitric oxide of ≥25 ppb	4 (27)	3 (27)	1.000
Blood eosinophilia of ≥300 ug/l	7 (47)	2 (18)	.217
Serum high-sensitivity C-reactive protein of ≥3.0 mg/l	5 (33)	1 (9)	.197
Induced sputum • Eosinophilia of ≥2% • Neutrophilia of ≥61%	 6/9 (67) 3/9 (33)	 2/8 (25) 2/8 (25)	 .153 1.000
Questionnaire			
Score of <17.1 in Newcastle Laryngeal Hypersensitivity questionnaire	6/14 (43)	0/10	**.024**
Score of ≥23 in Nijmegen questionnaire	6/14 (43)	0	**.020**

Categorical data presented as n (%) if not otherwise stated. Normally distributed data expressed as mean (SD) and independent-samples T-test used. Unless otherwise specified, the number of participants was 15 and 11, respectively.

^Percentages of predicted mean workload attained during last 4 min of bicycle ergometric test. (6, 7)

IIA, irritant-induced asthma

SD, standard deviation