

# Impact of non-invasive ventilation on exacerbation frequency in COPD patients

Maximilian Zimmermann<sup>1,2\*</sup>, Sarah B. Stanzel<sup>1,2\*</sup>, Doreen Kroppen<sup>1,2</sup>, Georgi Margalitadze<sup>1,2</sup>, Daniel S. Majorski<sup>1,2</sup>, Melanie Berger<sup>1,2</sup>, Wolfram Windisch<sup>1,2</sup>, Maximilian Wollsching-Strobel<sup>1,2</sup>

## ABSTRACT

**INTRODUCTION** Acute exacerbations of COPD are key events in the natural course of the patient's illness, as they significantly impair the health condition, accelerate the deterioration of lung function, worsen the prognosis for the patient and account for the majority of the COPD-related healthcare costs. Particularly in patients with a pre-existing non-invasive ventilation (NIV) therapy, a reduction of exacerbation frequency is crucial, as they are at high risk for a lasting morbidity and increased mortality.

**METHODS** A prospective cohort study was conducted. Data from adult patients with COPD diagnosis and existing High-Intensity NIV (HINIV) therapy from August 2021 to September 2023, were used. Exacerbation history of moderate and severe exacerbations of the past 12 months and blood gases at initiation and during HINIV therapy, were analyzed.

**RESULTS** A total of 20 patients were included in the study (mean age 69.2 ± 9.0 years; 70% female). After initiation of HINIV therapy the frequency of exacerbation showed a significant reduction from 1.5 ± 0.9 to 0.5 ± 0.5 per year ( $p < 0.001$ ). In addition, improvements in  $p\text{CO}_2$  (73.0 ± 22.0 mmHg vs 44.0 ± 4.8 mmHg,  $p < 0.001$ ), the pH (7.33 ± 0.1 vs 7.42 ± 0.0,  $p < 0.001$ ) and  $\text{HCO}_3^-$  (33.0 ± 4.9 mmol/L vs 27.9 ± 3.2 mmol/L,  $p < 0.001$ ), were successfully demonstrated.

**CONCLUSIONS** The present study demonstrates the positive effects of high-intensity NIV on COPD exacerbation rate, measured by the number of moderate and severe exacerbations in one year. Most significant effects were observed when patients had a high number of exacerbations before the initiation of NIV therapy.

**ABBREVIATIONS** CHRF: chronic hypercapnic respiratory failure, EPAP: expiratory positive airway pressure, HINIV: high-intensity NIV therapy, IPAP: inspiratory positive airway pressure, NIV: non-invasive ventilation

## INTRODUCTION

COPD is currently the fourth leading cause of death with approximately 3.2 million deaths in 2019<sup>1,2</sup>. In the course of the disease, chronic hypercapnic respiratory failure (CHRF) can occur due to the failure of the respiratory pump<sup>3</sup>. COPD patients with CHRF have higher rates of unplanned hospital admissions and rapid clinical deterioration after hospitalization due to a severe exacerbation. Additionally, chronic hypercapnia is a decisive factor contributing to mortality<sup>4,5</sup>. Therefore, reducing factors, influencing mortality, such as exacerbation rate, is an essential therapeutic goal. Non-invasive ventilation (NIV) with a facemask is the preferred choice of treatment to reduce mortality and hospitalization rate after acute exacerbation with persistent hypercapnia<sup>6,7</sup>. However, these positive effects are evident only when NIV is used with the target of maximal possible  $p\text{CO}_2$  reduction<sup>8,9</sup>. This ventilatory strategy, based on maximal

relief of the respiratory pump is referred to as high-intensity NIV therapy (HINIV). The required inspiratory positive airway pressures (IPAP) vary individually, as they depend on side effects of the NIV therapy, patient tolerance and adherence to therapy.

Despite the central therapeutic goal of reducing the exacerbation rate in the treatment of COPD patients, given its significant impact on the health condition, acceleration of lung function deterioration, worsening prognosis of the patient and responsibility for the majority of COPD-associated healthcare costs, scientific data on the effects of a HINIV therapy on the exacerbation rate are insufficient. A large German study by Koehnlein et al.<sup>7</sup> was the first to observe reduction in mortality with the use of HINIV in COPD patients, but no conclusion could be drawn regarding the influence of HINIV on exacerbation frequency, as it was not part of the study. In a large British study investigating

## AFFILIATION

**1** Department of Pneumology, Cologne Merheim Hospital, Kliniken der Stadt Köln gGmbH, Cologne, Germany

**2** Witten/Herdecke University, Witten, Germany

\* Contributed equally

## CORRESPONDENCE TO

Sarah B. Stanzel. Department of Pneumology, Cologne Merheim Hospital, Kliniken der Stadt Köln gGmbH, Ostmerheimer Strasse 200 D-51109, Cologne, Germany.

Email: [sarah.stanzel@uni-wh.de](mailto:sarah.stanzel@uni-wh.de)

ORCID iD: <https://orcid.org/0000-0001-8989-0211>

## KEYWORDS

Non-invasive ventilation, exacerbation, COPD, respiratory insufficiency, hospitalization

**Received:** 11 November 2023

**Revised:** 10 January 2024

**Accepted:** 23 January 2024

the effect of HINIV on hospitalization-free survival after acute exacerbation of COPD and acute respiratory failure, only severe exacerbations leading to hospitalization were recorded<sup>6</sup>. The impact of HINIV on moderate exacerbation, however, is scientifically insufficiently documented<sup>10</sup>.

The present analysis has addressed the lack of scientific evidence by initiating a study, evaluating the course of exacerbation retrospectively as well as prospectively, which compares the exacerbation frequency before initiation of HINIV and the exacerbation frequency after at least 12 months of HINIV therapy.

## METHODS

The study protocol was approved by the Ethics Committee of Witten/Herdecke University and was conducted in accordance to the ethical guidelines of the declaration of Helsinki (last revised in October 2013). Written informed consent was obtained from all patients.

### Patients

The data presented in this study are a preliminary analysis, which was registered at the German register for studies (DRKS00029273) and investigates supplementary telemonitoring of COPD patients after experiencing a severe exacerbation. Adult patients with the diagnosis of COPD receiving HINIV due to hypercapnic respiratory failure (PrismaVent Type 30 (n=16) and type 40 (n=4), Löwenstein medical SE & Co. KG Bad Ems, Germany) between August 2021 and September 2023, were enrolled in the study. Patients with mental retardation or those receiving invasive mechanical ventilation were not included in the study. The existing dataset of the main study was analyzed to determine availability of datasets regarding history of exacerbation as well as blood gases at the time of initiation or under existing HINIV therapy. The history of exacerbations is based on data from the clinical information system as well as from the anamnestic information provided by the patient, thus including exacerbations without hospitalization. Exacerbations that could be classified as moderate or severe according to the recommendations of the recent GOLD report were assessed<sup>10</sup>. Therefore, exacerbations requiring treatment with a fast-acting bronchodilator and oral corticosteroid (with/without antibiotics) or requiring hospitalization, were included. The anamnestic exacerbations were recorded using a predefined checklist as well as existing patient data records. The exacerbations were evaluated over the past 12 months in relation to the date of the consultation.

### Ventilation setting

NIV was applied using either assisted pressure-controlled ventilation (aPCV) or pressure-supported ventilation (PSV). NIV was delivered via nasal or full-face masks. The treatment indication was based on the German guideline for treatment of chronic respiratory insufficiency, which recommends the initiation of NIV therapy in chronic hypercapnia or persistent

hypercapnia after acute respiratory insufficiency<sup>3</sup>. In this case, ventilation should be performed as HINIV. HINIV refers to a specific ventilation setting in which NIV settings are aimed at achieving the lowest PaCO<sub>2</sub> values. In HINIV, the ventilator settings are gradually increased, either up to an individually tolerated maximum value or up to the values required to achieve normocapnia<sup>8,9</sup>. If feasible, these targets should already be aimed during initiation of NIV.

### Study design and measurements

Demographic data (age, sex, exacerbation history) were evaluated for all patients. Additionally, laboratory parameters (pH, pCO<sub>2</sub>, pO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>) were documented pre-therapeutically and after a minimum of 12 months after initiation of NIV therapy. If the data were collected during acute respiratory insufficiency, the ABG values were documented immediately after admission. There was no analysis of possible consultations between these two times, as the control intervals were different for all patients and this would not allow the interim results to be compared.

### Statistical analysis

The data analysis was descriptive. Group comparison was conducted using Student's t-test for normally distributed data and the Mann-Whitney-U test for data with non-normally distributed data. Due to the small number of participants, the results are primarily intended to provide a descriptive analysis. Values of p<0.05 were therefore considered significant, although they do not provide statistical significance.

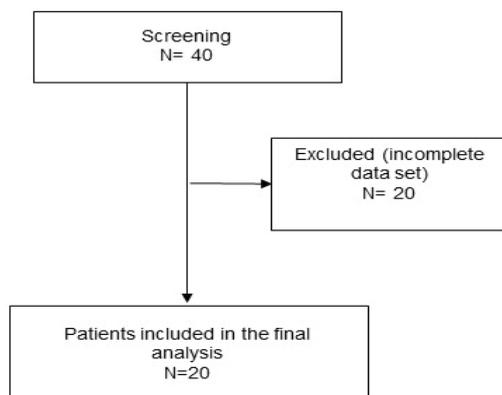
## RESULTS

A total of 20 patients were included in the study (Figure 1). From those, 14 patients were female (70%). Average age of the patients was 69.2 ± 9.0 years. In the cohort analyzed, 15 patients had cardiac comorbidities, 7 of them suffering from coronary heart disease. Two patients had a sleep-related breathing disorder, one patient had chronic kidney failure, and 4 patients suffered from diabetes mellitus type II. The included patients had been treated with NIV therapy for 4.9 ± 3.5 years. Long-term NIV therapy was initiated for 9 patients, as a result of acute NIV therapy with respiratory acidosis. Patients were using the HINIV therapy 8.9 ± 4.5 h/day. The demographic data and the ventilation parameters from the time of blood gas analysis during therapy are listed in Table 1. Significant improvements in blood gas analysis were observed during therapy, compared to the results before HINIV initiation. Results of the blood gas analyses are detailed in Table 2.

A separate analysis was conducted for patients who were initiated on NIV therapy under stable conditions without acute respiratory insufficiency. The results of this subgroup of 11 patients are presented in Table 3.

Prior to the start of HINIV therapy, patients reported an exacerbation frequency of 1.5 ± 0.9 exacerbations per

**Figure 1. Diagram for patient inclusion**



year. With HINIV therapy, this frequency was successfully reduced to  $0.5 \pm 0.5$  per year ( $p < 0.001$ ). In patients who had  $\geq 2$  exacerbations prior to initiation of HINIV, there was a greater mean difference in the number of exacerbations before and after therapy. Patients who had less than 2 exacerbations per year before initiation of HINIV therapy showed a mean difference in the number of exacerbations before compared to the time after initiation of therapy of 0.5 exacerbations/year versus 2 exacerbations/year in patients with  $\geq 2$  exacerbations prior HINIV. Individual differences were observed, as shown in Figure 2.

**Table 1. Demographic data and ventilation settings during HINIV of all patients (N=20)**

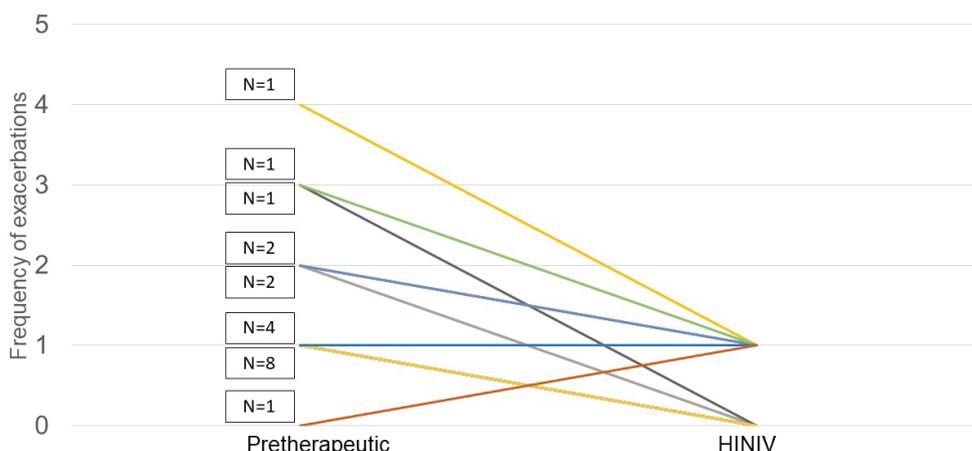
Characteristics	Mean $\pm$ SD
Female, n (%)	14 (70)
Age (years)	69.2 $\pm$ 9.0
Body mass index (kg/m <sup>2</sup> )	27.1 $\pm$ 6.1
Smoking status, n (active : prior)	6 : 14
Smoking index (pack-years)	45.9 $\pm$ 16.4
Time under NIV (years)	4.9 $\pm$ 3.5
<b>NIV initiation</b>	
Following acute NIV, n (%)	9 (45)
Chronic elective NIV, n (%)	11 (55)
<b>Ventilator settings</b>	
IPAP (mbar)	24.4 $\pm$ 3.1
EPAP (mbar)	6.7 $\pm$ 1.4
Rise time - inspiratory (s)	1.6 $\pm$ 0.8
Rise time - expiratory (s)	2.9 $\pm$ 0.7
Adherence (h/day)	8.9 $\pm$ 4.5

NIV: non-invasive ventilation. IPAP: inspiratory positive airway pressure. EPAP: expiratory positive airway pressure.

**Table 2. Comparison of blood gas values before and after initiation of HINIV therapy of the total population (N=20)**

	Pre-therapeutic Mean $\pm$ SD	HINIV Mean $\pm$ SD	p
pH	7.33 $\pm$ 0.1	7.42 $\pm$ 0.0	<0.001
pCO <sub>2</sub> (mmHg)	73.0 $\pm$ 22.0	44.0 $\pm$ 4.8	<0.001
pO <sub>2</sub> (mmHg)	79.0 $\pm$ 27.0	69.8 $\pm$ 17.3	0.2
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	33.0 $\pm$ 4.9	27.9 $\pm$ 3.2	<0.001

**Figure 2. Illustration of individual differences in exacerbation frequency before and after established HINIV therapy (N=20)**



**Table 3. Comparison of blood gas values before and after initiation of HINIV therapy in patients who had no acute respiratory insufficiency at the time of initiation (N=11)**

	Pre-therapeutic Mean $\pm$ SD	HINIV Mean $\pm$ SD	p
pH	7.4 $\pm$ 0	7.4 $\pm$ 0	0.03
pCO <sub>2</sub> (mmHg)	61.4 $\pm$ 10.6	45.7 $\pm$ 5.3	<0.001
pO <sub>2</sub> (mmHg)	84.6 $\pm$ 23.1	66.3 $\pm$ 15.4	0.08
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	32.9 $\pm$ 3.6	28.5 $\pm$ 3.9	0.01

## DISCUSSION

This study provides further information on reducing the frequency of moderate and severe exacerbations with established HINIV therapy. The following are the main findings, which will be discussed further.

Firstly, a significant reduction in the number of exacerbations was demonstrated with HINIV. Secondly, it has been shown that a significant reduction of hypercapnia is observed during HINIV therapy, both in the setting of acute respiratory failure and chronic respiratory failure. Thirdly, further blood gas analysis parameters showed a significant improvement under the established HINIV therapy. Fourthly, there was a strong reduction in the frequency of exacerbations, especially in patients with a high frequency of exacerbations before the HINIV therapy was initiated.

The significant reduction in exacerbation frequency under HINIV therapy differs meaningfully from previous studies that examined exacerbation frequency in hypercapnic COPD patients on NIV, but used significantly lower pressures and therefore could not reduce pCO<sub>2</sub> (low intensity NIV)<sup>11,12</sup>. This suggests that the impact of the NIV therapy on the exacerbation frequency can only be achieved with a sufficient augmentation of ventilation and thereby a significant reduction of hypercapnia. In patients with persistent hypercapnic respiratory insufficiency, a reduction in re-admissions or mortality, following acute respiratory insufficiency, could be demonstrated after initiation of HINIV<sup>6</sup>.

Furthermore, a recently published study by Hedsund et al.<sup>13</sup> demonstrated that the time to re-admission with an acute respiratory insufficiency, due to an exacerbation within 12 months, could be reduced by HINIV, although, a statistical significance could not be shown due to insufficient recruitment<sup>13</sup>. Nevertheless, a significant reduction in the number of exacerbations was observed, particularly in patients with frequent acute respiratory insufficiency. The lesser effects in comparison to the present study could be attributed to the fact that normocapnic patients were included as well and no re-evaluation according to current recommendations was performed<sup>14</sup>. All these studies only recorded the number of severe exacerbations that were hospitalized and did not include exacerbations that were treated in the outpatient setting.

The underlying pathophysiological mechanism of these reduced exacerbation rates resulting from HINIV therapy remains unknown. Besides the decrease in pCO<sub>2</sub> levels, mechanical bronchial dilatation itself may alter the microbiological milieu. This has already been demonstrated with pharmacological bronchodilation<sup>15-17</sup>. It has been shown that cytokines of the airways, which are elevated in patients with COPD, can be influenced by an effective treatment with bronchodilators<sup>18</sup>. Whether these biomarkers can also be influenced by HINIV therapy is the subject of ongoing research.

## Limitations

The present study has several limitations that should be taken into account. The data on exacerbations were mainly based on anamnestic information from the patient. Therefore, a higher incidence of exacerbations cannot be excluded. In addition, mild exacerbations were not recorded, so it is not possible to make any statements about the effect of HINIV on these exacerbations. The data were supplemented with information from the clinical information system. In addition, the number of participants is limited, resulting in a descriptive nature of data analysis, requiring larger subsequent studies to validate the findings presented here.

## CONCLUSIONS

This study shows significant positive effects of HINIV on COPD exacerbation rate, measured by frequency of moderate and severe exacerbations in patients with severe COPD. Greatest effects are observed when patients present with a high number of exacerbations prior to initiation of NIV therapy. To verify these effects in a larger cohort, further studies are needed.

## ACKNOWLEDGMENTS

This work has already been published as a pre-print under [medrxiv.org](https://www.medrxiv.org/content/10.1101/2023.11.13.23298441v1) (<https://www.medrxiv.org/content/10.1101/2023.11.13.23298441v1>).

## CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE

form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. M. Zimmerman, M. Wollsching, D. Kroppen, D.S. Majorski and S.B. Stanzel received travel grants from companies dealing with mechanical ventilation products. D.S. Majorski reports open research grant from Philips Respiration/USA. M. Zimmerman and W. Windisch received lecturing fees from companies dealing with mechanical ventilation products. The study group received open research grants from Löwenstein Medical/Germany since the initial planning of the work, and in the past from Löwenstein Medical/Germany, Weinmann/Germany, Vivisol/Germany, VitalAire/Germany, and Philips Respiration/USA.

## FUNDING

The main study was financially supported by Löwenstein medical SE & Co. KG (Bad Ems, Germany) with an open research grant, without influence on the study design. This additional detailed analysis was performed without separate financial support.

## ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Ethics Committee of Witten/Herdecke University (Approval number: 255/2021; Date: 29 November 2021). Patients provided informed consent.

## DATA AVAILABILITY

The authors intend to share individual deidentified participant data with any other unfunded or funded research-related purpose under appropriate circumstances. Please contact the corresponding author for more information.

## AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

## REFERENCES

1. World Health Organization. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. World Health Organization; 2019. Accessed January 10, 2024. <https://iris.who.int/bitstream/handle/10665/324835/9789241565707-eng.pdf?sequence=9>
2. 2023 GOLD REPORT: GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2023 Report. Global Initiative for Chronic Obstructive Lung Disease – GOLD. Accessed November 8, 2023. <https://goldcopd.org/2023-gold-report-2/>
3. Windisch W, Geiseler J, Simon K, Waltersbacher S, Dreher M; on behalf of the Guideline Commission. German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation: Revised Edition 2017 - Part 1. Respiration. 2018;96(1):66-97. doi:[10.1159/000488001](https://doi.org/10.1159/000488001)
4. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, Midgren B, Ekström MP. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res. 2014;15(1):30. doi:[10.1186/1465-9921-15-30](https://doi.org/10.1186/1465-9921-15-30)
5. Saraiva C, Abreu T, Neves D, Rodrigues F. Mortality Predictive Factors in Subjects With COPD After a Pulmonary Rehabilitation Program: A 3-Year Study. Respir Care. 2016;61(9):1179-1185. doi:[10.4187/respcare.04477](https://doi.org/10.4187/respcare.04477)
6. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317(21):2177-2186. doi:[10.1001/jama.2017.4451](https://doi.org/10.1001/jama.2017.4451)
7. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698-705. doi:[10.1016/S2213-2600\(14\)70153-5](https://doi.org/10.1016/S2213-2600(14)70153-5)
8. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303-308. doi:[10.1136/thx.2009.124263](https://doi.org/10.1136/thx.2009.124263)
9. Schwarz SB, Magnet FS, Windisch W. Why High-Intensity NPPV is Favourable to Low-Intensity NPPV: Clinical and Physiological Reasons. COPD. 2017;14(4):389-395. doi:[10.1080/15412555.2017.1318843](https://doi.org/10.1080/15412555.2017.1318843)
10. Agustí A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023;61(4):2300239. doi:[10.1183/13993003.00239-2023](https://doi.org/10.1183/13993003.00239-2023)
11. Raveling T, Vonk J, Struik FM, et al. Chronic non-invasive ventilation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2021;8(8):CD002878. doi:[10.1002/14651858.CD002878.pub3](https://doi.org/10.1002/14651858.CD002878.pub3)
12. Cline E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(3):529-538. doi:[10.1183/09031936.02.02162001](https://doi.org/10.1183/09031936.02.02162001)
13. Hedsund C, Linde Ankjærgaard K, Peick Sonne T, et al. Long-term non-invasive ventilation for COPD patients following an exacerbation with acute hypercapnic respiratory failure: a randomized controlled trial. Eur Clin Respir J. 2023;10(1):2257993. doi:[10.1080/20018525.2023.2257993](https://doi.org/10.1080/20018525.2023.2257993)

14. Ergan B, Oczkowski S, Rochweg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J.* 2019;54(3):1901003. doi:[10.1183/13993003.01003-2019](https://doi.org/10.1183/13993003.01003-2019)
15. Noble PB, Pascoe CD, Lan B, et al. Airway smooth muscle in asthma: linking contraction and mechanotransduction to disease pathogenesis and remodelling. *Pulm Pharmacol Ther.* 2014;29(2):96-107. doi:[10.1016/j.pupt.2014.07.005](https://doi.org/10.1016/j.pupt.2014.07.005)
16. Gosens R, Grainge C. Bronchoconstriction and airway biology: potential impact and therapeutic opportunities. *Chest.* 2015;147(3):798-803. doi:[10.1378/chest.14-1142](https://doi.org/10.1378/chest.14-1142)
17. Grainge CL, Lau LCK, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med.* 2011;364(21):2006-2015. doi:[10.1056/NEJMoa1014350](https://doi.org/10.1056/NEJMoa1014350)
18. Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J.* 2001;18(suppl 34):50s-59s. doi:[10.1183/09031936.01.00229701](https://doi.org/10.1183/09031936.01.00229701)