

# Effectiveness of glycopyrronium bromide in the treatment of small airway dysfunction: A retrospective study

SAGE Open Medicine

Volume 10: 1–6

© The Author(s) 2022

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/20503121221145605

journals.sagepub.com/home/smo



Albino Petrone<sup>1</sup>, Corrado Pelaia<sup>2</sup> , Michela Quartieri<sup>1</sup>,  
Ludovico Petrone<sup>2</sup>, Giuseppe Francesco Rago<sup>1</sup>,  
Clementina Columbro<sup>1</sup> and Girolamo Pelaia<sup>2</sup>

## Abstract

**Objective:** Glycopyrronium bromide has a quaternary ammonium structure and a low oral bioavailability, which reduces its systemic effects; it acts through a bronchodilating blockade of muscarinic receptors. The aim of this retrospective study was to analyze a possible relationship between the changes in the small airways and the efficacy of a bronchodilation with glycopyrronium bromide; exercise tolerance was also assessed, by performing the six-minute walking test.

**Methods:** Forty-one patients were identified (23 females/18 males; mean age  $66.82 \pm 9.75$  years), with a normal forced expiratory volume in 1 s ( $FEV_1$ )/forced vital capacity ratio of  $77.45\% \pm 4.86\%$ , a reduced forced mid-expiratory flow between 25% and 75% of forced vital capacity ( $FEF_{25-75}$ ) of  $42.9\% \pm 10.5\%$ , with an increased residual volume/total lung capacity ratio of  $132.68\% \pm 6.41\%$ ,  $FEV_1$   $1.85 \pm 0.54$  L, forced vital capacity  $2.39 \pm 0.71$  L, airway resistance (sR tot)  $168.18\% \pm 42.5\%$ , total lung capacity  $98.28\% \pm 8.9\%$ , six-minute walking test distance  $318.3 \pm 36.6$  m, modified British Medical Research Council dyspnea scale  $1.48 \pm 0.77$ . All patients were initiated with glycopyrronium bromide 50  $\mu$ g/die and reassessed after 4 months.

**Results:** After the treatment with glycopyrronium bromide, a significant improvement was noted regarding forced vital capacity ( $p = 0.04$ ),  $FEF_{25-75}$  ( $p < 0.001$ ), sR tot ( $p < 0.001$ ), residual volume/total lung capacity ratio ( $p < 0.001$ ) with reduction of dynamic hyperinflation, the significant increase of the distance covered during the six-minute walking test ( $p < 0.001$ ), and modified British Medical Research Council ( $p < 0.001$ ) showed enhanced exercise tolerance.  $FEV_1$  improved, but the difference was not statistically significant.

**Conclusions:** Small airway dysfunction is associated with bronchodilator responsiveness. Glycopyrronium bromide has proven to be capable of inducing favorable effects on lung hyperinflation and its functional and clinical consequences, with a decrease in dyspnea and an increase in exercise capacity. The use of anticholinergic drugs is useful in the management of small airway disease.

## Keywords

Anticholinergic drugs, bronchodilator, small airway, glycopyrronium bromide, COPD

Date received: 06 July 2022; accepted: 28 November 2022

## Introduction

Glycopyrronium bromide (GB) is an inhaled, long-acting muscarinic receptor antagonist (LAMA) with a quaternary ammonium structure and a low oral bioavailability, which reduces its systemic effects. It acts as a bronchodilator by blocking the muscarinic receptors M1 and M3. It does not cross the blood–brain barrier and therefore has few or no central effects. In clinical trials, patients who received GB as a symptom controller for moderate or severe chronic obstructive pulmonary disease (COPD)<sup>1,2</sup> experienced a relevant

amelioration in lung function, associated with an increased control of COPD symptoms, as well as with a lower need for rescue medication inhalers. An improvement in the quality

<sup>1</sup>Department of Respiratory Diseases, Annunziata Hospital, Cosenza, Italy

<sup>2</sup>Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

### Corresponding author:

Corrado Pelaia, Department of Health Sciences, University Magna Graecia of Catanzaro, Viale Europa, Catanzaro 88100, Italy.

Email: [pelaia.corrado@gmail.com](mailto:pelaia.corrado@gmail.com)



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

of life was also reported. Quality of life represents an important aspect of COPD management.<sup>3,4</sup> Published studies have shown that the damage caused by the inhalation of toxic particles, such as cigarette smoke and environmental pollutants, affects the “small airways.” Small airways—the quiet zone between the conducting and the respiratory lung zones—consist of respiratory bronchioles, which have a partially alveolated wall, and terminal bronchioles, that are devoid of cartilage and mucous-secreting glands.<sup>5</sup> The disease of the small airways is characterized by an inflammation of smallest bronchi and bronchioles, with inflammatory cellular infiltration, metaplasia of goblet cells and fibrosis, which leads to an increased thickness and tortuosity of the walls, as well as to an enhanced airway resistance, due to bronchial obstruction. This produces airflow limitation during expiration, resulting in lung hyperinflation and air trapping.<sup>6,7</sup> We have studied a particular phenotype of patients, in whom the rate of bronchial caliber as forced expiratory volume in 1 s ( $FEV_1$ )/forced vital capacity (FVC) ratio was in the normal range, but the forced expiratory flow in the middle half of the patient’s exhaled volume, forced mid-expiratory flow between 25% and 75% of FVC ( $FEF_{25-75}$ ) was reduced.  $FEF_{25-75}$  may be a more sensitive index for identifying obstruction at level of small airways. We recorded an increased value of residual volume (RV)/total lung capacity (TLC) ratio, as a marker of lung hyperinflation, and assessed the exercise tolerance by performing the six-minute walking test (6MWT) distance. The aim of this study was to determine whether there is a relationship between the changes in the small airways and the efficacy of the bronchodilation with GB.

## Methods

This study included consecutive patients without acute manifestations of any disease and in a stable clinical state, whose dyspnea and exercise intolerance induced a referral to the Department of Respiratory Pathophysiology of “Mariano Santo” Hospital in Cosenza, Italy. Participants were evaluated by respiratory physicians from January 2018 to December 2018. All data were collected retrospectively. A detailed clinical history was taken, and a physical examination was performed. Lung function was measured through spirometry, carried out according to the American Thoracic Society/European Respiratory Society guidelines<sup>8</sup>; exercise tolerance was assessed by performing the 6MWT.<sup>9</sup> Symptoms were also evaluated using the modified British Medical Research Council (mMRC) scale.<sup>10</sup> Patients were excluded if they had reported exacerbations in the previous 4 weeks, or in case of other lung diseases and uncontrolled comorbidities, such as severe cardiovascular diseases and malignant disorders.

Small airway obstruction is characterized by premature airway closure and air trapping, regional heterogeneity, and exaggerated volume dependence of airflow limitation.

Therefore, tests that focus on these functional aspects can be useful surrogates in order to detect and quantify small airway disease. High levels of RV can be detected in the presence of premature airway closure and air trapping, TLC is commonly increased in obstructive disease, and the RV/TLC ratio is the best measure of RV increase, being also considered the first indicator of hyperinflation.  $FEF_{25-75}$  is the most cited functional measure of small airway obstruction. By excluding the initial peak of expiratory flow and averaging the flow rate over the mid-quartile range of FVC,  $FEF_{25-75}$  is very sensitive to the same small airway characteristics that result in the concavity of the expiratory flow-volume curve.

As a measure of airflow limitation,  $FEF_{25-75}$  is highly correlated with  $FEV_1$ /FVC ratio, but non-linearly, so that  $FEF_{25-75}$  decreases more steeply than  $FEV_1$ /FVC at mild obstruction levels. We considered a  $FEV_1$ /FVC ratio <70% as a marker of obstruction,<sup>11</sup> a  $FEF_{25-75}$  <60% of predicted value as an expression of small airway dysfunction,<sup>12</sup> and an increase in RV/TLC ratio >20% as an indicator of lung hyperinflation. All subjects who exhibited a  $FEF_{25-75}$  reduction, a normal  $FEV_1$ /FVC ratio, and an increased RV/TLC ratio with symptoms of dyspnea upon exertion, were treated with a bronchodilator therapy consisting of GB at the dosage of 50  $\mu$ g once a day for 4 months. Patients did not receive other inhaled therapies during the study period. Clinical and functional parameters were collected at baseline and after 4 months of GB treatment. Because of the mild impairment of lung function detected in these patients, we decided to treat them only with an effective and safe LAMA, and our choice thus pointed to GB. Therefore, this therapeutic approach was part of an institutional protocol, aimed to avoid the use of albuterol or salbutamol on demand. Indeed, we think that the use of short-acting  $\beta_2$  agonists as rescue medications is not able to improve lung hyperinflation in such patients as those recruited in our retrospective study. All subjects released a written informed consent to the study, in accordance with the Helsinki Declaration.

## Statistical analysis

The statistical analysis was performed using the SPSS program for Windows, version 9.0.0 (SPSS, Inc., Chicago, IL, USA). Data are shown as mean  $\pm$  standard deviation (SD). Comparisons between data before and after treatment, within each group of patients, were done by paired Student’s *t*-test. The level of significance was set at  $p < 0.05$ .

## Results

Overall, 115 patients were screened. Among these, 41 subjects met the inclusion criteria (23 females/18 males; mean age  $66.82 \pm 9.75$  years), who had a normal  $FEV_1$ /FVC ratio of  $77.45\% \pm 4.86\%$ , a reduced  $FEF_{25-75}$  of  $42.9\% \pm 10.5\%$ , with increased RV/TLC ratio of  $132.68\% \pm 6.41\%$ ,  $FEV_1$   $1.85 \pm 0.54$  L, FVC  $2.39 \pm 0.71$  L. Their main demographic

and clinical features are shown in Table 1. All patients had a diurnal respiratory function characterized by an obstruction of the small airways, associated with air trapping. Twenty-eight patients were smokers, while 13 subjects never smoked. A decreased exercise tolerance was shown by both baseline 6MWT ( $318.3 \pm 36.6$  m), and the information provided in the mMRC questionnaire ( $1.48 \pm 0.77$ ).

After treatment with GB, a significant improvement in lung function was noted as FVC ( $2.39 \pm 0.71$  L versus  $2.70 \pm 0.68$  L,  $p=0.04$ ),  $FEF_{25-75}$  ( $42.9\% \pm 10.5\%$  versus  $52.9\% \pm 9.5\%$ ,  $p<0.001$ ), sR tot ( $168.18\% \pm 42.5\%$  versus  $132.01\% \pm 33.8\%$ ,  $p<0.001$ ), RV/TLC ratio ( $132.68\% \pm 6.41\%$  versus  $105.98\% \pm 6.73\%$ ,  $p<0.001$ ), with a reduction in dynamic hyperinflation (Table 2).

Patients showed an enhanced exercise tolerance, quantified as a significant increase in the distance covered during the 6MWT ( $318.3 \pm 36.6$  m versus  $339.1 \pm 31.8$  m,  $p<0.001$ ) and a subjective reduction in the dyspneic symptoms reported in the mMRC questionnaire ( $1.48 \pm 0.77$  versus  $0.53 \pm 0.64$ ,  $p<0.001$ ) (Table 2).  $FEV_1$  improved numerically but the difference was not statistically significant ( $1.85 \pm 0.5$  L versus  $2.02 \pm 0.5$  L,  $p=0.12$ ) (Table 2).

Smokers showed a greater obstruction at the level of the small airways ( $31.1\% \pm 6.9\%$  versus  $55.2\% \pm 4.1\%$ ,  $p<0.001$ ) (Table 3).

No side effects were recorded after the administration of GB.

**Table 1.** Demographics and clinical characteristics of patients.

|  |                   |
|--|-------------------|
| Female gender, N (%)                     | 23 (56.1)         |
| Male gender, N (%)                       | 18 (43.9)         |
| Age, mean ( $\pm$ SD), years             | 66.82 $\pm$ 9.75  |
| Height, mean ( $\pm$ SD), cm             | 159.43 $\pm$ 8.71 |
| Weight, mean ( $\pm$ SD), kg             | 73.94 $\pm$ 15.06 |
| BMI, mean ( $\pm$ SD), kg/m <sup>2</sup> | 28.78 $\pm$ 5.76  |
| Smokers, N (%)                           | 28 (68.3)         |

SD, standard deviation; BMI, body mass index.

**Table 2.** Functional and clinical features of patients at baseline and after treatment with GB.

|   | Pre-treatment     | Post-treatment    | p      |
|---|-------------------|-------------------|--------|
| FVC, mean ( $\pm$ SD), L                | 2.39 $\pm$ 0.71   | 2.70 $\pm$ 0.68   | 0.04   |
| $FEV_1$ , mean ( $\pm$ SD), L           | 1.85 $\pm$ 0.54   | 2.02 $\pm$ 0.5    | 0.12   |
| $FEV_1$ /FVC ratio, mean ( $\pm$ SD), % | 77.45 $\pm$ 4.86  | 75.1 $\pm$ 2.9    | 0.01   |
| $FEF_{25-75}$ , mean ( $\pm$ SD), %     | 42.9 $\pm$ 10.5   | 52.9 $\pm$ 9.5    | <0.001 |
| PEF, mean ( $\pm$ SD), %                | 72.8 $\pm$ 25.1   | 74.2 $\pm$ 10.9   | 0.63   |
| sR tot, mean ( $\pm$ SD), %             | 168.18 $\pm$ 42.5 | 132.01 $\pm$ 33.8 | <0.001 |
| TLC, mean ( $\pm$ SD), %                | 98.28 $\pm$ 8.9   | 97.78 $\pm$ 4.7   | 0.76   |
| RV/TLC ratio, mean ( $\pm$ SD), %       | 132.68 $\pm$ 6.41 | 105.98 $\pm$ 6.73 | <0.001 |
| 6MWT distance, mean ( $\pm$ SD), meters | 318.3 $\pm$ 36.6  | 339.1 $\pm$ 31.8  | <0.001 |
| mMRC, mean ( $\pm$ SD)                  | 1.48 $\pm$ 0.77   | 0.53 $\pm$ 0.64   | <0.001 |

SD, standard deviation; FVC, forced vital capacity;  $FEV_1$ , forced expiratory volume in 1 s;  $FEF_{25-75}$ , forced mid-expiratory flow between 25% and 75% of FVC; PEF, peak of expiratory flow; sR tot, airway resistance; TLC, total lung capacity; RV, residual volume; 6MWT, six-minute walking test; mMRC, modified British Medical Research Council.

## Discussion

COPD is currently recognized as a complex clinical syndrome, rather than a specific disease entity, thus being considered as a broad term comprising a heterogeneous group of phenotypes that may have different treatment responses. In light of this understanding, the approach based on “one treatment to fit all” may not be appropriate, and there is a trend toward the individualization of the COPD therapy based on distinct phenotypes. More specifically, a key contributing factor to poor disease control might be the fact that such patients express a “small airway phenotype,” in the presence of an ongoing and unopposed small airway inflammation which is not being targeted nor controlled.<sup>13,14</sup> Many patients who come to our observation with symptoms such as shortness of breath and recurrent cough display small airway parameter changes (decreased  $FEF_{25-75}$ ) and significant hyperinflation (increased RV/TLC ratio), with a  $FEV_1$ /FVC ratio within the normal range as observed with spirometry testing. It can be useful to treat patients with this phenotype. This is the first study that highlights the efficacy of LAMA treatment in patients with  $FEV_1$ /FVC ratio within the normal range, but with a significant obstruction of small airways. Generally, small airway dysfunctions are associated with bronchodilator responsiveness. Bronchodilation effectiveness can be demonstrated as a significant improvement in both  $FEV_1$  and FVC, when compared to the values measured before bronchodilator use.<sup>15,16</sup> In our study, after LAMA treatment, we recorded an improvement in FVC. Lung hyperinflation is more closely associated with symptoms and exercise performance than spirometric assessments of reduced maximal expiratory flow rates. The progressive increase in resting hyperinflation as the disease advances has major implications for dyspnea and exercise limitation in COPD.<sup>17,18</sup> It is well established that the widespread inflammatory damage to the peripheral airways, lung parenchyma and pulmonary vasculature can occur with only minor air-flow obstruction.<sup>19</sup> Gas trapping, as assessed by expiratory

**Table 3.** Smokers/non-smokers and obstruction in the small airways.

| Patients                             | Smokers (28) | Non-smokers (13) | <i>p</i> |
|--------------------------------------|--------------|------------------|----------|
| FEF <sub>25-75</sub> , mean (±SD), % | 31.1 ± 6.9   | 55.2 ± 4.1       | <0.001   |

SD, standard deviation; FEF<sub>25-75</sub>, forced mid-expiratory flow between 25% and 75% of FVC.

CT scans, can exist in the absence of structural emphysema, and it is believed to indirectly reflect small airway dysfunction in mild COPD.<sup>20,21</sup> Corbin et al.,<sup>22</sup> in a 4-year longitudinal study on smokers with chronic bronchitis, reported a progressive increase in lung compliance leading to gas trapping, manifested by an increase in RV without significant changes in FEV<sub>1</sub>.<sup>22</sup> The net effect is that resting lung hyperinflation contributes to an increased elastic load on the inspiratory muscles, while simultaneously impairing their force-generating capacity.<sup>22,23</sup> Small airway closure can lead to expiratory flow limitation through the increase in airways resistance, a consequence of the bronchial-bronchiolar caliber reduction due to structural remodeling and augmented vagal tone, together with the destruction of elastic pulmonary tissue. In these conditions, the RV increases, because the volume at which the balance between the elastic pressures of the lung and chest wall occurs is increased, leading to static lung hyperinflation.<sup>24,25</sup> Thus, lung hyperinflation and the consequent changes in respiratory mechanics cause an increased respiratory work, that in turn leads to respiratory muscles fatigue, increased load, and respiration inefficiency. Dyspnea usually arises when the gas exchange is inefficient, as in ventilation/perfusion mismatching, exercise-induced hypoxemia, and impaired respiratory mechanics, where an uncoupling occurs between the increased ventilatory stimulus and the decreased mechanical performance.<sup>26,27</sup> Bronchodilators, the cornerstone of COPD therapy, reduce the airway obstruction, leading to a decrease in the RV, and allow patients to exercise longer, thus positively impacting their quality of life.<sup>28</sup> The majority of the published studies aim to estimate the effectiveness of the drug through the improvement in FEV<sub>1</sub>, which correlates with little change in symptoms and exercise tolerance, being more linked to the reduction in lung inflation. In this study, we showed that GB can induce favorable effects on lung hyperinflation and its functional and clinical consequences, leading to a decrease in dyspnea and an increase in exercise capacity. In these patients, the most important effect was the increase in FVC, which sustained symptom improvement, even in the absence of FEV<sub>1</sub>/FVC ratio changes.<sup>29,30</sup> FEV<sub>1</sub> increase after bronchodilation is generally small, if any.

The most significant change after bronchodilation is the decrease in RV/TLC ratio, with a subsequent RV reduction, underlying a lowered lung hyperinflation, regardless of the basal FEV<sub>1</sub> value.<sup>27</sup> Interestingly, the therapeutic efficacy of

anticholinergic bronchodilation was primarily shown in our patients by the decrease in peripheral airway resistance. This appears to be a class effect due to LAMA utilization. In particular, we decided to use GB rather than the more referenced tiotropium bromide, because GB is characterized by a faster onset of action which provides a more rapid relief of dyspnea. Antimuscarinic bronchodilators, such as GB, have proven to be very useful in terms of lung deflation and exercise tolerance.<sup>30,31</sup> Indeed, after treatment our patients experienced a better 6MWT performance. Evidence is growing in support of the concept that the airways dysfunction and inflammation in the small airway region of the lung may be contributing to distinct patient phenotypes. Besides the well-known concept that non-neuronal acetylcholine plays a relevant inflammatory role, the muscarinic receptor antagonism of non-neuronal acetylcholine released from airway epithelium is also important,<sup>32,33</sup> thus potentially contributing to GB effects at level of small airways.<sup>34-36</sup> Taken together, the results of the present study suggest that GB is capable of positively and significantly affecting lung hyperinflation, respiratory symptoms, and the psycho-physical status of patients with mild lung function impairment, likely allowing them to better use tidal volume and improve their ventilatory performance.<sup>37,38</sup> Bronchodilation induced by GB is maintained throughout 24h, after the administration of a single daily dose. This certainly represents a considerable advantage with regard to therapy adherence, because it is well known that the efficacy of a treatment also depends on patient's compliance.<sup>29,31</sup> An increased awareness of the importance of small airway dysfunction is an obvious first step, but the therapeutic challenge is to reverse the damage or at least to prevent disease progression. Earlier diagnosis could allow a more effective understanding of the role of small airways in triggering COPD pathogenesis, thereby driving a more rational approach to treatment, which may ultimately affect the prognosis of this disabling respiratory disorder. However, the small size of patient population, the lack of an appropriate calculation regarding sample size/power analysis, the absence of both a control arm and a randomization procedure, as well as the single-center nature of this study represent some relevant limitations.

## Conclusions

In summary, based on the above-mentioned results, this study shows that GB can provide a beneficial effect on lung hyperinflation and its clinical and functional consequences. Anticholinergic bronchodilators such as GB can play an important role in the management of small airway dysfunction. There is currently a great interest in identifying clinical phenotypes of COPD that will ultimately guide toward a more personalized approach to disease management. This is a retrospective study which suggests, without definitely establishing, that LAMA may be potentially effective in patients with small airway impairment. Within this context,



our limited clinical experience implies that further studies are needed to determine whether the patient with lung hyperinflation due to diseases of small airways will qualify as a distinct phenotype, possibly susceptible to specific therapeutic approaches.

### Acknowledgements

The Authors thank Carmen Innes, an independent medical writer, who provided English language editing and journal styling on behalf of Springer Healthcare Communications. This editorial assistance was funded by Novartis Farma, Italy.

### Author contributions

AP, CP, GP, MQ analyzed, interpreted the patient data regarding the respiratory physiopathology, and were a major contributor in writing the manuscript. LP, CC, LM were involved in data collection and statistical procedures. All authors read and approved the final manuscript.

### Availability of data and material

All data generated or analyzed during this study are included in this published article.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethics approval

The study was approved by the local Ethical Committee of Calabria Region (N. 12/2018). All patients provided a written informed consent.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: No specific funding was received for this research. The editorial assistance was funded by Novartis Farma, Italy.

### Informed consent

Written informed consent was obtained from all subjects before the study.

### ORCID iD

Corrado Pelaia  <https://orcid.org/0000-0002-4236-7367>

### References

- Pelaia G, Maselli R and Gallelli L. Pharmacologic rationale, efficacy and safety of fixed-dose co-formulation of indacaterol and glycopyrronium. *Multidiscip Respir Med* 2014; 9: 64.
- Chapman KR, Beeh K-M, Bejer J, et al. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. *BMC Pulm Med* 2014; 14: 4.
- Agusti A, Hedner J, Marin JM, et al. Night-time symptoms: a forgotten dimension of COPD. *Eur Respir Rev* 2011; 20(121): 183–194.
- Roche N, Chavannes NH and Miravitlles M. COPD symptoms in the morning: impact, evaluation and management. *Respir Res* 2013; 14: 112.
- Vogelmeier C, Verkindre C, Cheung D, et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Pulm Pharmacol Ther* 2010; 23: 438–444.
- D'Urzo A, Ferguson GT, van Noord JA, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir Res* 2011; 12: 156.
- Macklem PT. The physiology of small airway. *Am J Respir Crit Care Med* 1998; 157: S181–S183.
- Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019; 200: e70–e88.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166(1): 111–117.
- Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). *BMJ* 1960; 2: 1665.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2022 report) 2022, <https://goldcopd.org> (2022, accessed 23 February 2022).
- Knox-Brown B, Mulhern O, Feary J, et al. Spirometry parameters used to define small airways obstruction in population-based studies: systematic review. *Respir Res* 2022; 23(1): 67.
- Schivo M, Albertson TE, Haczku A, et al. Paradigms in chronic obstructive pulmonary disease: phenotypes, immunobiology, and therapy with a focus on vascular disease. *J Investig Med* 2017; 65(6): 953–963.
- Golpe R, Sanjuán López P, Cano Jiménez E, et al. Distribution of clinical phenotypes in patients with chronic obstructive pulmonary disease caused by biomass and tobacco smoke. *Arch Bronconeumol* 2014; 50(8): 318–324.
- Loring SH, Garcia-Jacques M and Malhotra A. Pulmonary characteristics in COPD and mechanisms of increased work of breathing. *J Appl Physiol* 2009; 107(1): 309–314.
- McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011; 365(17): 1567–1575.
- Cannon D, Buys N, Sriram KB, et al. The effects of chronic obstructive pulmonary disease self-management interventions on improvement of quality of life in COPD patients: a meta-analysis. *Respir Med* 2016; 121: 81–90.
- Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med* 2016; 193(3): 299–309.
- Bhatia RS. Diseases of small airways of lung. *J Indian Acad Clin Med* 2001; 2(3): 222–224.
- Langer D, Ciavaglia CE, Neder JA, et al. Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. *Exp Rev Respir Med* 2014; 8(6): 1–19.

21. Pisi R, Aiello M, Zanini A, et al. Small airway dysfunction and flow and volume bronchodilator responsiveness in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 1191–1197.
22. Corbin RP, Loveland M, Martin RR, et al. A four-year follow-up study of lung mechanics in smokers. *Am Rev Respir Dis* 1979; 120(2): 293–304.
23. Allen TC. Pathology of small airways disease. *Arch Pathol Lab Med* 2010; 134(5): 702–718.
24. Haruna A, Oga T, Muro S, et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med* 2010; 10: 10.
25. Deesomchok A, Webb KA, Forkert L, et al. Lung hyperinflation and its reversibility in patients with airway obstruction of varying severity. *COPD* 2010; 7: 428–437.
26. O'Donnell DE, Revill SM and Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
27. O'Donnell DE, Forkert L and Webb KA. Evaluation of bronchodilator responses in patients with “irreversible” emphysema. *Eur Respir J* 2001; 18: 914–920.
28. Johnson BD, Reddan WG, Pegelow DF, et al. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis* 1991; 143: 960–967.
29. Sanguinetti MC. The lungs need to be deflated: effects of glycopyrronium on lung hyperinflation in COPD patients. *Multidiscip Respir Med* 2014; 9: 19.
30. Riario-Sforza GG, Ridolo E, Riario-Sforza E and Incorvaia C. Glycopyrronium bromide for the treatment of chronic obstructive pulmonary disease. *Expert Rev Respir Med* 2015; 9(1): 23–33.
31. Beeh KM, Singh D, Di Scala L, et al. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 503–513.
32. Barnes PJ. Distribution of receptor targets in the lung. *Proc Am Thorac Soc* 2004; 1(4): 345–351.
33. Kummer W and Krasteva-Christ G. Non-neuronal cholinergic airway epithelium biology. *Curr Opin Pharmacol* 2014; 16: 43–49.
34. Arieievich H, Overend T, Renard D, et al. A novel model-based approach for dose determination of glycopyrronium bromide in COPD. *BMC Pulm Med* 2012; 12: 74.
35. Buhl R and Banerji D. Profile of glycopyrronium for once-daily treatment of moderate-to-severe COPD. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 729–741.
36. Kerwin E, Hébert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur Respir J* 2012; 40: 1106–1114.
37. Ulrik CS. Once-daily glycopyrronium bromide (Seebri Breezhaler®) for the treatment of chronic obstructive pulmonary disease (COPD). *Expert Opin Pharmacother* 2015; 16(17): 2653–2659.
38. Carter NJ. Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. *Drugs* 2013; 73(7): 741–753.