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Investigating Fractional Exhaled Nitric Oxide (FeNO) in Chronic Obstructive Pulmonary Disease (COPD) and Asthma-COPD Overlap (ACO): A Scoping Review Protocol

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Title:

Investigating Fractional Exhaled Nitric Oxide (FeNO) in Chronic Obstructive Pulmonary Disease (COPD) and Asthma-COPD Overlap (ACO): A Scoping Review Protocol

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ABSTRACT

Introduction

During the last decade, many articles have been published, including reviews on fractional exhaled nitric oxide (FeNO) usefulness in clinical practice and for monitoring and identifying eosinophilic airway inflammation, especially in asthma, and evaluating corticosteroid responsiveness. However, the exact role of FeNO in patients with chronic obstructive pulmonary disease (COPD) and its ability to distinguish COPD patients and those having concomitant asthma, i.e., asthma-COPD overlap (ACO) is still unclear and needs to be defined. Due to the broad topics of FeNO in chronic airway disease, we undertook a scoping review. The present article describes the protocol of a scoping review of peer-reviewed published literature specific to FeNO in COPD/ACO over the last decade.

Methods and analysis

We utilized Joanna Briggs Institute Reviewers'Manual scoping review methodology as well as Levac et al's and Arksey et al's framework as guides. We searched variety of databases, including Medline, EMBASE, CINAHL, Cochrane library, Web of Science, BIOSIS. Additional studies will be recognized by exploring the reference list of identified eligible studies. Screening of eligible studies will be independently performed by two reviewers and any disagreement will be solved by the third reviewer. We will analyze the gathered data from article bibliographies and abstracts.

Ethics and Dissemination

To investigate the body of published studies regarding the role of FeNO in COPD patients and its usefulness in the clinical setting, a scoping review can be utilized as a modern and pioneer model, which does not need ethics approval. By this review, research gaps in the current published literature will be recognized. Moreover, new insights for conducting new research specific to FeNO in COPD/ACO population will emerge. The results of this study

will be reported in the scientific meetings and conferences, which aim to provide information to the clinicians, primary care providers, and basic science researchers.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

- To the best of our knowledge, this will be the first scoping review undertaken to describe the FeNO role in identifying ACO patients and differentiating them from patients with COPD as well as guiding the treatment decision and management approach in COPD and ACO; thus, result of this review will be crucial in establishing the way to identify gaps in the current literature for conducting future research in this field and within this topic.
- This scoping review will include all languages but it will be limited to the year 2005 onwards, as this is the year that the first ATS/ERS guideline regarding FeNO measurement was published.
- Due to the nature of this review, i.e., a scoping review, it will not involve an assessment of the quality of the primary studies.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a respiratory disease and an inflammatory condition characterized by a persistent, progressive and incomplete reversible airflow limitation due to chronic exposure to harmful gases or substances such as tobacco smoke (1, 2). This airflow limitation is defined by a post bronchodilator ratio of the forced expiratory volume in 1 second over the forced vital capacity (FEV1/FVC) below 0.7, (1, 2). Asthma is another chronic obstructive airway disease with airway hyperresponsiveness as well as airway inflammation. Compared to COPD, the airflow limitation in asthma is mainly reversible (3, 4) and is often associated with a history of allergy and/or atopy typically early in life (3-6). Regarding pathogenesis, airway inflammation in COPD is usually driven by, CD8+ T-lymphocytes, macrophages and neutrophils while in asthma CD4+ T-lymphocytes and eosinophils are the predominant cells (7, 8).

Interestingly, there is a remarkable proportion of patients that share clinical features of both asthma and COPD (9). This condition has been called asthma-COPD overlap syndrome by the Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease (GINA/GOLD) (2, 10, 11). Recently this term has changed to asthma-COPD overlap (ACO) (12). The prevalence of ACO varies from 15 to 60% according to the age group, the population sample and the definitions of asthma and COPD (2, 13). To date, there is not a universally accepted definition of ACO. However, despite a variety of definitions, compared to asthma or COPD alone ACO is associated with more frequent exacerbations(14, 15), increased hospitalizations (15, 16), worse health-status (14, 17), and a higher level of health care utilization and health cost.(18) Furthermore, compared to COPD or asthma alone, there are discrepancies in disease presentation and response to therapy in patients with ACO (19).

Therefore, it would be important to be able to identify ACO in COPD patients beyond using questionnaires and/or doctor's personal opinion (9, 19). Although ACO is clinically important, there are insufficient scientific data describing and allowing a proper identification of ACO patients as well as guiding their treatment (2, 19-22).

Based on the provided above data, it would be necessary to have a biomarker that can differentiate ACO patients from those with COPD alone. For the sake of this purpose, FeNO has been proposed. FeNO is an inflammatory biomarker that is produced in the catalysis of nitric oxide synthase in different kinds of respiratory epithelial cells. It is utilized as a known marker of the total number of inflammatory cells in the airways, eosinophilic airway inflammation, T-helper cell 2 (Th2)-mediated airway inflammation and airway hyperresponsiveness (23-25). FeNO can be measured noninvasively, fast, reproducibly, and in an easy way in close to real time. Devices are used for measuring FeNO consist of electrochemical detection, chemiluminescence, or laser spectroscopy devices (23, 26, 27). FeNO is clinically used for the diagnosis of asthma and also for monitoring airway inflammation, identifying eosinophilic airway inflammation and evaluating corticosteroid responsiveness during asthma follow-up (28, 29). However, the exact role of FeNO in COPD, and more specifically for monitoring ACO and patients undergoing inhaled corticosteroid therapy is still unclear and needs to be defined (4, 5). Moreover, literature defining the role of FeNO and the practical cutoff value in patients with ACO and established COPD is minimal (30).

Our preliminary search showed no comprehensive review, neither a scoping or a systematic review with a view of the role of FeNO measurement in patients with COPD and/or ACO.

As this topic covers a wide range of research questions and due to the exploratory nature of these questions, a scoping review will be conducted to evaluate the breadth and depth of knowledge around this topic. The goal of this scoping review will be i) to evaluate the FeNO measurement role and useful cutoff value in phenotyping COPD patients such as COPD patients or COPD patients who share asthma symptoms (ACO); ii) to determine its association with inflammatory markers (Immunoglobulin E (IgE), blood/sputum eosinophils), outcome/prognosis, and concomitant asthma; and iii) to assess its use in COPD patients to the response of inhaled bronchodilators and/or inhaled corticosteroid (ICS). The composition of research on this topic can help researchers to find out the current state of the evidence and determine areas for future research.

METHODS

Different types of systematic approaches available for reviewing published literature have been taken into account and eventually, a scoping review of peer-reviewed published articles was selected as the most appropriate method. Scoping reviews provide readers and researchers with an overview of a topic, knowledge gaps, determining key concepts, and types of evidence within a developing field of research (31). Compared to a systematic review, the research questions defined for a scoping review are considered quite wide (31). A scoping review is appropriate for the topic of FeNO in COPD because the purpose of this study is to have a comprehensive review in an area that is relatively complex. Therefore, required further studies within the field can be understood by researchers (31). This study will be conducted as per the methodology outlined in the Joanna Briggs Institute Reviewers'Manual (32) and reported as per the Preferred Reporting Items for Systematic

Review and Meta-Analysis Protocols (PRISMA-P) statement (33). It is also according to the Levac et al's (34) and Arksey et al's (31) framework for scoping a review. We have listed in table 1 the research questions categorized into six themes.

Table 1. List of Research Questions that will be included in the Scoping Review

Research Questions
1. **FeNO and modifying factors:** Which factors have been demonstrated to modify the level of FeNO?
2. **FeNO level alterations/optimal cutoff value in COPD:** Does the FeNO level increase in patients with COPD and is there an optimal cutoff value which may be useful in phenotyping COPD patients or in anticipating treatment response?
3. **FeNO and inflammatory biomarkers:** Are FeNO values associated with changes in the level of inflammatory biomarkers such as blood/sputum eosinophils and/or IgE in patients with COPD?
4. **FeNO and Asthma-COPD Overlap (ACO):** Are there any differences in FeNO levels between COPD patients with asthma-like symptoms (ACO) or patients with COPD-only?
5. **FeNO and disease severity (exacerbation)/progression:** Are FeNO values associated with disease severity or disease progression (FEV1: GOLD 1, 2, 3 and 4 and FEV1 annual decline) and/or risk of exacerbations (symptoms based or event based, i.e., requiring antibiotic or prednisone, emergency room or hospital admission) in patients with COPD?
6. **FeNO and treatment response:** Whether increased or decreased FeNO level has an influence on treatment response, especially inhaled bronchodilator therapy

and/or ICS therapy (in exacerbations) in patients with COPD

FeNO: Fractional exhaled nitric oxide; COPD: chronic obstructive pulmonary disease; IgE: Immunoglobulin E; ICS: Inhaled corticosteroid; FEV1: Forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease

Eligibility criteria

To be eligible, studies of all languages, from 2005 onwards and including n>10 will be considered. Any intervention will be taken into consideration, except the ones that have no focus on FeNO measurement. Table 2 shows inclusion and exclusion criteria for selecting eligible studies, i.e. types of study, participants and outcomes.

Table 2. Inclusion and exclusion criteria for selecting eligible studies of the Scoping Review

Inclusion criteria	**Exclusion criteria**
Type of study	
Randomized clinical trials (RCT), cohorts, longitudinal studies	Reviews, letters, reports, comments, opinions, editorials, case studies and case series conferences, and meeting abstracts as well as other non-peer-reviewed abstracts/articles
Participants	
COPD and/or asthma-COPD overlap	Other pulmonary diseases such as asthma
Outcomes	
Clinical usefulness and reproducibility of FeNO alone or combined with other	Without any focus on FeNO

inflammatory biomarkers	

FeNO: Fractional exhaled nitric oxide; COPD: chronic obstructive pulmonary disease

Information Source (Databases), Literature Search and Search Strategy

A structured comprehensive literature search will be conducted in major databases including Medline (via OvidSP), EMBASE (via OvidSP), CINAHL (via EBSCO host), Cochrane library (via Wiley Online), Web of Science, BIOSIS Previews, BIOSIS Previews Archives. The inception of database searches is from the year 2005 onwards as this was the year when the ATS/ERS (American Thoracic Society/European Respiratory Society) guideline concerning FeNO and its measurement was published. There is no limitation regarding language in this search strategy. We will use a variety of keywords/text words and database subject heading such as COPD/Chronic Obstructive Lung Disease, Emphysema, Chronic Bronchitis, ACOS/ Asthma-COPD Overlap Syndrome/Concomitant asthma and COPD AND FeNO/Fractional Exhaled Nitric Oxide.

Study Selection

Two reviewers (SMY Mostafavi-Pour-Manshadi and Nafiseh Naderi) will independently review the title and abstract of retrieved articles from the database searches for the purpose of screening. Then, the full text of potential articles, which will be retrieved from first screening, will be investigated as the second screening. Discrepancies will be solved by reaching the consensus between two reviewers according to the criteria eligibility. If the two reviewers could not reach the consensus concerning the specific article(s) or both were suspicious about including/excluding the articles, these papers will be reviewed by the third reviewer (Jean Bourbeau) and the issue will be solved.

Data extraction

Data collection/extraction will be done by using a designated data extraction form and gathered electronically. We will use PICOS (33, 35) approach for designing the form and extracting data as well which will be developed from our research questions. The form will be reviewed and revised again by the reviewers after completing to reach the consensus among reviewers. Data extraction will be independently done by two reviewers (SMY Mostafavi-Pour-Manshadi and Nafiseh Naderi). The data will include study title, first author's name, publication year, the name of the journal, sample size, sample description, setting description, and outcomes. Concerning outcomes, the data will be as follows but not limited to FeNO values, eosinophil level/IgE in sputum and/or in blood, pulmonary function tests, computed tomography (CT) scan findings, and exacerbations with the view to symptoms based or evidence based, i.e. requiring antibiotics or prednisolone, emergency or hospital admission. The evidence base will be summarized by producing descriptive summary tables. Table 3 shows the data extraction framework.

Table 3. Data extraction framework of the Scoping Review

Bibliometrics	**Comments**
• Author(s)	• First author, et al.
• Title	• Full title
• Year	• Year of Publication
• Country	• Country of conducted study
Data extraction	
• Aim of study	• Full aim, regardless of our research questions
• Design of study, if applicable	• Type of Study
• Intervention, if applicable	
• Methods	• Not applicable
• Setting/Sample of study	• For FeNO measurement • Outpatient or inpatient or as described by the author (s)/ population number (N) in analysis (including N in total/COPD if it is different from N in analysis)
• COPD population characteristic, if applicable	• Number of COPD patients, mean /median age or range of age, gender, BMI, smoke pack-year, exacerbation
• Results	• Overall results and specific ones in regard to our study
• Conclusions/Key findings	

• Research gaps • Future recommended studies/research	• Overall and specific to our study • As identified by author(s) • As suggested by the author(s)

FeNO: fractional exhaled nitric oxide; COPD: chronic obstructive pulmonary disease; BMI: Body mass index.

Then the findings will be given in an explanatory and a narrative review and briefed in a table to make the comparisons of different studies easy. The replication of studies' results and their differences will be considered and reported. The results classification will be performed according to the studies' findings and other relevant indicators of interest.

Quality Assessment of Included Studies

In accordance with scoping review guidance (32), we did not appraise methodological quality or risk of bias of the included articles. This approach is consistent with scoping reviews of clinical topics (36, 37).

CONCLUSIONS

This scoping review will provide a comprehensive overview of FeNO utility and validity in describing patients with COPD and/or ACO. This scoping review provides a new practical model to combine a variety of research articles specific to FeNO in COPD/ACO. We expect to report the results by the end of 2017. Reviewing and analyzing this large amount of peer-reviewed published literature as a scoping review may expose new needs and directions for FeNO research in COPD/ACO.

ETHICS AND DISSEMINATION

As this study is a scoping review, there will be no need for formal ethical review. The scoping review will be presented at a relevant conference and be published in a peer-reviewed journal.

REFERENCES

1. Aggarwal AN, Gupta D, Agarwal R, Jindal SK. Comparison of the lower confidence limit to the fixed-percentage method for assessing airway obstruction in routine clinical practice. Respiratory care. 2011;56(11):1778-84.
2. Cataldo D, Corhay JL, Derom E, Louis R, Marchand E, Michils A, et al. A Belgian survey on the diagnosis of asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2017;12:601-13.
3. Burgel PR, Paillasseur JL, Roche N. Identification of clinical phenotypes using cluster analyses in COPD patients with multiple comorbidities. BioMed research international. 2014;2014:420134.
4. Feng JX, Lin Y, Lin J, He SS, Chen MF, Wu XM, et al. Relationship between Fractional Exhaled Nitric Oxide Level and Efficacy of Inhaled Corticosteroid in Asthma-COPD Overlap Syndrome Patients with Different Disease Severity. Journal of Korean medical science. 2017;32(3):439-47.
5. Chen FJ, Huang XY, Liu YL, Lin GP, Xie CM. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. International journal of chronic obstructive pulmonary disease. 2016;11:2385-90.
6. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). The European respiratory journal. 2008;31(4):869-73.
7. Rufino R, Lapa e Silva JR. Cellular and biochemical bases of chronic obstructive pulmonary disease. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2006;32(3):241-8.
8. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Therapeutic advances in chronic disease. 2016;7(1):34-51.
9. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2095-128.
10. Soler-Cataluna JJ, Cosio B, Izquierdo JL, Lopez-Campos JL, Marin JM, Aguero R, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Archivos de bronconeumologia. 2012;48(9):331-7.
11. Deng DD, Zhou AY, Shuang QC, Chen P. [The value of fractionated exhaled nitric oxide in the diagnosis of asthma-chronic obstructive pulmonary disease overlap syndrome]. Chung Hua Chieh Ho Ho Hu Hsi Tsa Chih. 2017;40(2):98-101.
12. Barnes PJ. Asthma-COPD Overlap. Chest. 2016;149(1):7-8.
13. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? The Lancet Respiratory medicine. 2015;3(9):719-28.
14. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, et al. The clinical features of the overlap between COPD and asthma. Respiratory research. 2011;12:127.
15. Menezes AM, Montes de Oca M, Perez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest. 2014;145(2):297-304.

16. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. The clinical respiratory journal. 2013;7(4):342-6.
17. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpelainen M, Kinnula VL, et al. Overlap syndrome of asthma and COPD predicts low quality of life. The Journal of asthma : official journal of the Association for the Care of Asthma. 2011;48(3):279-85.
18. Rhee CK, Yoon HK, Yoo KH, Kim YS, Lee SW, Park YB, et al. Medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease and asthma. Copd. 2014;11(2):163-70.
19. Kiljander T, Helin T, Venho K, Jaakkola A, Lehtimaki L. Prevalence of asthma-COPD overlap syndrome among primary care asthmatics with a smoking history: a cross-sectional study. NPJ primary care respiratory medicine. 2015;25:15047.
20. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64(8):728-35.
21. Miravitlles M, Calle M, Soler-Cataluna JJ. Clinical phenotypes of COPD: identification, definition and implications for guidelines. Archivos de bronconeumologia. 2012;48(3):86-98.
22. Sin DD, Miravitlles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. The European respiratory journal. 2016;48(3):664-73.
23. Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, et al. Current evidence and future research needs for FeNO measurement in respiratory diseases. Respiratory medicine. 2014;108(6):830-41.
24. Hart CM. Nitric oxide in adult lung disease. Chest. 1999;115(5):1407-17.
25. Korhonen R, Lahti A, Kankaanranta H, Moilanen E. Nitric oxide production and signaling in inflammation. Current drug targets Inflammation and allergy. 2005;4(4):471-9.
26. Alcazar-Navarrete B, Romero-Palacios PJ, Ruiz-Sancho A, Ruiz-Rodriguez O. Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes. Nitric oxide : biology and chemistry. 2016;54:67-72.
27. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American journal of respiratory and critical care medicine. 2013;187(4):347-65.
28. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. American journal of respiratory and critical care medicine. 2011;184(5):602-15.
29. Tamada T, Sugiura H, Takahashi T, Matsunaga K, Kimura K, Katsumata U, et al. Biomarker-based detection of asthma-COPD overlap syndrome in COPD populations. International journal of chronic obstructive pulmonary disease. 2015;10:2169-76.
30. Donohue JF, Herje N, Crater G, Rickard K. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. International journal of chronic obstructive pulmonary disease. 2014;9:745-51.
31. Arksey H OML. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8:19-32.
32. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. International journal of evidence-based healthcare. 2015;13(3):141-6.

33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.
34. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation science : IS. 2010;5:69.
35. Stone PW. Popping the (PICO) question in research and evidence-based practice. Applied nursing research : ANR. 2002;15(3):197-8.
36. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, et al. A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology. 2016;16:15.
37. Pham MT, Rajic A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Research synthesis methods. 2014;5(4):371-85.

Authors' Contribution

All authors have made substantive intellectual contributions to the development of this protocol. All authors were involved in developing the review questions and the review design. SMYMPM and NN were involved in writing this protocol. JB, MB and AD commented critically on several drafts of the manuscript. SMYMPM, NN and JB were involved in conceptualizing this review. All authors approve the final version of the protocol manuscript.

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Competing interests

None

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ABSTRACT

Introduction

During the last decade, many articles have been published, including reviews on fractional exhaled nitric oxide (FeNO) utility in clinical practice and for monitoring and identifying eosinophilic airway inflammation, especially in asthma, and evaluating corticosteroid responsiveness. However, the exact role of FeNO in patients with chronic obstructive pulmonary disease (COPD) and its ability to distinguish COPD patients and those having concomitant asthma, i.e., asthma-COPD overlap (ACO) is still unclear and needs to be defined. Due to the broad topics of FeNO in chronic airway disease, we undertook a scoping review. The present article describes the protocol of a scoping review of peer-reviewed published literature specific to FeNO in COPD/ACO over the last decade.

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We utilized Joanna Briggs Institute Reviewers'Manual scoping review methodology as well as Levac et al's and Arksey et al's framework as guides. We searched a variety of databases, including Medline, EMBASE, CINAHL, Cochrane Library, Web of Science, BIOSIS on June 29, 2016. Additional studies will be recognized by exploring the reference list of identified eligible studies. Screening of eligible studies will be independently performed by two reviewers and any disagreement will be solved by the third reviewer. We will analyze the gathered data from article bibliographies and abstracts.

Ethics and Dissemination

To investigate the body of published studies regarding the role of FeNO in COPD patients and its usefulness in the clinical setting, a scoping review can be utilized as a modern and pioneer model, which does not need ethics approval. By this review, new insights for conducting new research specific to FeNO in COPD/ACO population will emerge. The

results of this study will be reported in the scientific meetings and conferences, which aim to provide information to the clinicians, primary care providers, and basic science researchers.

Strengths and Limitations of This Review

- To the best of our knowledge, this will be the first scoping review undertaken on FeNO and COPD patients; the intent of our scoping review will be to present an overview of the existing literature in a field of interest, i.e., FeNO in COPD, and as well synthesize and aggregate findings from different studies.
- The strength of this review is the use of an established scoping review methodology, a systematic approach, and a multidisciplinary search strategy developed strongly in consultation with a professional medical librarian.
- This scoping review will include all languages, but it will be limited to the year 2005 onwards, as this was the year that the first ATS/ERS guideline regarding FeNO measurement was published.
- The possibility of missing potentially relevant articles as well as excluding gray literature, conference and meeting (non-peer-reviewed) abstracts can be considered as limitations of this review. However, the reference lists of eligible articles will be exploring to identify articles missed by the search strategy.
- Due to the nature of this review, i.e., a scoping review, it will not involve a formal assessment of the quality of the primary studies.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common obstructive pulmonary disease, which is characterized by airflow limitation (1, 2). Asthma-COPD overlap (ACO) (3) syndrome (ACOS) (4) is a distinct clinical phenotype that represents a subset of COPD patients who share features of asthma (5). Initiation of pharmacotherapy for the treatment of these two diseases is different (6), patients with COPD alone should usually be started on bronchodilators mono or combined therapy and those recognized with ACO should have combined bronchodilators and inhaled corticosteroids (3, 7). Therefore, differentiating patients with COPD alone from those who show asthma-like symptoms is clinically relevant, especially for the need of ensuring close monitoring of ACO patients who have worse outcomes and also in guiding treatment decision.

There is a lack of gold standard for the diagnosis of ACO (2, 8), and diagnostic criteria have often been established primarily based on consensus opinion. Fractional exhaled nitric oxide (FeNO) is one of the inflammatory biomarkers that have recently attracted the attention of clinicians as well as researchers. FeNO can be measured noninvasively, fast, reproducibly, and in an easy way in close to real time (9, 10). It is suggested using FeNO for the management of asthma and also for monitoring airway inflammation, identifying eosinophilic and T-helper cell 2 (Th2)-mediated airway inflammation and evaluating corticosteroid responsiveness during asthma follow-up (11, 12). The exact role of FeNO in COPD, and more specifically for monitoring ACO and patients undergoing inhaled corticosteroid therapy is still unclear and needs to be defined (13, 14). Moreover, literature defining the role of FeNO and the practical cut-off value in patients with ACO and established COPD is minimal (15).

Our preliminary search showed no comprehensive review, neither a scoping nor a systematic review with a view of the role of FeNO measurement in patients with COPD and/or ACO.

As this topic of FeNO and COPD covers a wide range of potential questions and because of its exploratory nature, a scoping review will be conducted. The intent of our scoping review is to present an overview of the existing literature in a field of interest, i.e., FeNO in COPD, and as well synthesize and aggregate findings from different studies. We are considering specific questions/objectives to guide our review but through our search of the literature, we may have opportunities to refine some of these questions. The objectives of this scoping review will be i) to investigate COPD patients' factors that can modify FeNO measurements including but not limited to age, cigarette smoking, sex, glucocorticoids (ICS/GCS), bronchodilators, and exacerbations; ii) to evaluate the FeNO role and if a useful cut-off value can be used in differentiating COPD patients from healthy individuals; iii) to determine the relationship of FeNO with disease severity and/or progression (lung function, health status, and exacerbations); iv) to assess the role of FeNO and if a useful cut-off value can be used to differentiate patients with COPD-only from those with concomitant asthma (ACO); v) to determine the relationship of FeNO with inflammatory markers (Immunoglobulin E (IgE), blood/sputum eosinophils) and; vi) to assess the utility of FeNO measurement in treatment response of COPD/ACO patients, especially inhaled corticosteroid (ICS)/glucocorticoids (GCS) therapy with or without inhaled bronchodilators.

Methods

Different types of systematic approaches available for reviewing published literature have been taken into account and eventually, a scoping review of peer-reviewed published articles was selected as the most appropriate method. This scoping review will provide the readers and researchers with an overview of the topic, determining key concepts, and exploring gaps within a developing field of research (16). Compared to a systematic review, the research questions defined for a scoping review are broader than for a systematic review (16). A

scoping review is appropriate for the topic of FeNO in COPD because the purpose of this study is to have a comprehensive review in an area that is relatively complex. However, there are limitations regarding scoping reviews. These limitations include missing some relevant studies (17) which is related to the database search, exclusion of gray literature (17), lack of critical quality appraisal of included studies, and therefore difficulty in addressing the gaps in the evidence base (17, 18), and limitation of depth of analysis (19, 20). It would be a huge challenge to assess quality among the wide range of study designs and a large volume of literature that will be included in the scoping review. The balance between breadth and depth of analysis is also a challenge (17). To minimize this, we are planning to aggregate findings from different studies under themes and synthesize the data under each of these themes.

This study will be conducted as per the methodology outlined in the Joanna Briggs Institute Reviewers'Manual (21) and reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (22). It is also according to the Levac et al's (23) and Arksey et al's (16) framework for a scoping review.

Eligibility Criteria

To be eligible, studies of all languages, from 2005 onwards and including n>10 will be considered. Diagnosed COPD/ACO patients according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (24) and GOLD-Global Initiative for Asthma (GINA) (7), respectively will be included. Any intervention will be taken into consideration, except the ones that have no focus on FeNO measurement. Table 1 shows inclusion and exclusion criteria for selecting eligible studies, i.e. types of study, participants and outcomes.

Table 1. Inclusion and exclusion criteria for selecting eligible studies of the scoping review

Inclusion criteria	**Exclusion criteria**

Type of study	
Randomized clinical trials (RCT), cohorts, longitudinal studies, cross-sectional studies	Reviews, letters, reports, comments, opinions, editorials, case studies and case series, conference and meeting abstracts as well as other non-peer-reviewed abstracts/articles, gray literature
Participants	
COPD and/or asthma-COPD overlap	Other pulmonary diseases such as asthma
Outcomes	
Clinical usefulness and reproducibility of FeNO alone or combined with other inflammatory biomarkers	Without any focus on FeNO

COPD: Chronic obstructive pulmonary disease; FeNO: Fractional exhaled nitric oxide

Information Source (Databases), Literature Search and Search Strategy

A structured comprehensive literature search was conducted in major databases including Medline (via OvidSP), EMBASE (via OvidSP), CINAHL (via EBSCO host), Cochrane Library (via Wiley Online), Web of Science, BIOSIS Previews, BIOSIS Previews Archives on June 26, 2016 and an updated search was performed on June 29, 2017. Additional studies will be recognized by exploring the reference list of identified eligible studies. The first inception of database searches was conducted without date limitation but it will be limited to the year 2005 onwards as this was the year when the ATS/ERS (American Thoracic Society/European Respiratory Society) guideline (25) concerning FeNO and its measurement was published. There is no limitation regarding language in this search strategy. We used a variety of keywords/text words and database subject heading such as [COPD OR Chronic

Obstructive Lung Disease OR Emphysema OR Chronic Bronchitis OR ACOS OR Asthma-COPD Overlap Syndrome OR Concomitant asthma] AND [FeNO OR Fractional Exhaled Nitric Oxide]. Table 2 shows search strategy on Medline. The updated search strategy on this database can be found in the supplementary file.

Table 2. Search strategy on Medline via OvidSP

#	Searches	Results
1	("10712994" or "10907593" or "11296168" or "11413349" or "15817806" or "15939243" or "16289590" or "16646959" or "17426212" or "18460522" or "18547853" or "19124359" or "19401794" or "19820080" or "19881162" or "20210889" or "21143751" or "21530214" or "23445725" or "23509896" or "23681903" or "23989961" or "24013942" or "24719850" or "24929061" or "25053884" or "26252571" or "26372312" or "26491283" or "26496331" or "26497109" or "26814886" or "26916083" or "26952317" or "27142135" or "27209003").ui.	36
2	exp Pulmonary Disease, Chronic Obstructive/	43308
3	Lung Diseases, Obstructive/	18072
4	exp Pulmonary Emphysema/	14866
5	(obstructive adj2 (pulmonary or lung$ or respirat$ or air$)).tw,kf.	44058
6	(chronic air$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	1428
7	(chronic bronch$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	95
8	(chronic$ adj2 bronch$).tw,kf.	12908
9	COPD.tw,kf.	32628
10	COAD.tw,kf.	222
11	emphysema$.tw,kf.	24011
12	(acos and asthm*).tw,kf.	86
13	or/2-12	99543
14	Nitric Oxide/	78284
15	(feno and (fraction* or exhal* or nitric)).tw,kf.	1099
16	(fe no and (fraction* or exhal* or nitric)).tw,kf.	401
17	nitric oxid*.tw,kf.	126245
18	or/14-17	140975
19	13 and 18	750
20	1 and 19	32
21	1 not 20	4

Study Selection

Two reviewers (SMY Mostafavi-Pour-Manshadi and Nafiseh Naderi) will independently review the title and abstract of retrieved articles from the database searches for the purpose of screening. Then, the full text of potential articles, which will be retrieved from first screening, will be investigated as the second screening. Discrepancies will be solved by reaching the consensus between two reviewers according to the criteria eligibility. If the two reviewers could not reach the consensus concerning the specific article(s) or both were suspicious about including/excluding the articles, these papers will be reviewed by the third reviewer (Jean Bourbeau) and the issue will be solved.

Data Extraction

Data collection/extraction will be done by using a designated data extraction form and gathered electronically. We will use PICOS (22, 26) approach for designing the form and extracting data as well, which will be developed from our research questions. The form will be reviewed and revised again by the reviewers after completing to reach the consensus among reviewers. Data extraction will be independently done by two reviewers (SMY Mostafavi-Pour-Manshadi and Nafiseh Naderi). The data will include study title, first author's name, publication year, the name of the journal, sample size, sample description, setting description, and outcomes. Concerning outcomes, the data will be as follows but not limited to FeNO values, eosinophil level/IgE in sputum and/or in blood, pulmonary function tests, computed tomography (CT) scan findings, and exacerbations (symptoms-based or evidence-based, i.e. requiring antibiotics or non-inhaled/systemic corticosteroids, emergency or hospital admission). The information from the studies will be summarized by producing descriptive summary tables. Table 3 shows the data extraction framework.

Table 3. Data extraction framework of the scoping review

Bibliometrics	**Comments**
• Author(s)	• First author, et al.
• Title	• Full title
• Year	• Year of Publication
• Country	• Country of conducted study
Data extraction	
• Aim of study	• Full aim, regardless of our research questions
• Design of study, if applicable	• Type of study
• Intervention, if applicable	
• Methods	
• Setting/Sample of study	• Outpatient or inpatient or as described by the author(s)/ population number (N) in analysis (including N in total/COPD if it is different from N in analysis)
• COPD population characteristic, if applicable	• Number of COPD patients, mean /median age or range of age, gender, BMI, smoke pack-year, exacerbation
• Results	• Overall results and specific ones in regard to our study
• Conclusions/Key findings	• Overall and specific to our study

• Research gaps • Future recommended studies/research	• As identified by author(s) • As suggested by the author(s)

FeNO: Fractional exhaled nitric oxide; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index

Then the findings will be given in an explanatory and a narrative review and briefed in a table to make the comparisons of different studies easy. The replication of studies' results and their differences will be considered and reported. The results classification will be performed according to the studies' findings and other relevant indicators of interest. This scoping review will provide a comprehensive overview of FeNO utility and validity in describing patients with COPD and/or ACO. In addition, it will provide a new practical model to combine a variety of research articles specific to FeNO in COPD/ACO. We expect to report the results in early 2018. Reviewing and analyzing this large amount of peer-reviewed published literature as a scoping review may expose new needs and directions for FeNO research in COPD/ACO.

Quality Assessment of Included Studies

In accordance with scoping review guidance (32), we did not appraise methodological quality or risk of bias of the included articles. This approach is consistent with scoping reviews of clinical topics (27, 28).

Ethics and Dissemination

As this study is a scoping review, there will be no need for formal ethical review. The scoping review will be presented at a relevant conference and be published in a peer-reviewed journal.

References

1. Aggarwal AN, Gupta D, Agarwal R, Jindal SK. Comparison of the lower confidence limit to the fixed-percentage method for assessing airway obstruction in routine clinical practice. Respiratory care. 2011;56(11):1778-84.
2. Cataldo D, Corhay JL, Derom E, Louis R, Marchand E, Michils A, et al. A Belgian survey on the diagnosis of asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2017;12:601-13.
3. Barnes PJ. Asthma-COPD Overlap. Chest. 2016;149(1):7-8.
4. Global Initiative for Asthma. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). A joint project of GINA and GOLD. 2014.
5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2095-128.
6. Kiljander T, Helin T, Venho K, Jaakkola A, Lehtimaki L. Prevalence of asthma-COPD overlap syndrome among primary care asthmatics with a smoking history: a cross-sectional study. NPJ primary care respiratory medicine. 2015;25:15047.
7. Global Initiative for Asthma. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). A joint project of GINA and GOLD. 2015.
8. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64(8):728-35.
9. Alcazar-Navarrete B, Romero-Palacios PJ, Ruiz-Sancho A, Ruiz-Rodriguez O. Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes. Nitric oxide : biology and chemistry. 2016;54:67-72.
10. Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, et al. Current evidence and future research needs for FeNO measurement in respiratory diseases. Respiratory medicine. 2014;108(6):830-41.
11. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. American journal of respiratory and critical care medicine. 2011;184(5):602-15.
12. Tamada T, Sugiura H, Takahashi T, Matsunaga K, Kimura K, Katsumata U, et al. Biomarker-based detection of asthma-COPD overlap syndrome in COPD populations. International journal of chronic obstructive pulmonary disease. 2015;10:2169-76.
13. Feng JX, Lin Y, Lin J, He SS, Chen MF, Wu XM, et al. Relationship between Fractional Exhaled Nitric Oxide Level and Efficacy of Inhaled Corticosteroid in Asthma-COPD Overlap Syndrome Patients with Different Disease Severity. Journal of Korean medical science. 2017;32(3):439-47.
14. Chen FJ, Huang XY, Liu YL, Lin GP, Xie CM. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. International journal of chronic obstructive pulmonary disease. 2016;11:2385-90.
15. Donohue JF, Herje N, Crater G, Rickard K. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. International journal of chronic obstructive pulmonary disease. 2014;9:745-51.
16. Arksey H OML. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8:19-32.

17. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Research synthesis methods. 2014;5(4):371-85.
18. Brien SE, Lorenzetti DL, Lewis S, Kennedy J, Ghali WA. Overview of a formal scoping review on health system report cards. Implementation science : IS. 2010;5:2.
19. Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, et al. A review and critical appraisal of measures of therapist-patient interactions in mental health settings. Health technology assessment (Winchester, England). 2008;12(24):iii, ix-47.
20. Bostock L, Brodie I, Clapton J, Fish S, Morris M, Kearney P, et al. Increasing the Number of Care Leavers in 'settled, Safe accommodation': Scoping Review 3. London: Centre for Excellence and Outcomes in Children and Young People's Services; 2009.
21. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. International journal of evidence-based healthcare. 2015;13(3):141-6.
22. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.
23. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation science : IS. 2010;5:69.
24. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2017.
25. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. American journal of respiratory and critical care medicine. 2005;171(8):912-30.
26. Stone PW. Popping the (PICO) question in research and evidence-based practice. Applied nursing research : ANR. 2002;15(3):197-8.
27. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, et al. A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology. 2016;16:15.
28. Pham MT, Rajic A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Research synthesis methods. 2014;5(4):371-85.

Authors' Contribution

All authors have made substantive intellectual contributions to the development of this protocol. All authors were involved in developing the review questions and the review design. SMYMPM and JB were involved in writing this manuscript. NN, MB and AD commented critically on several drafts of the manuscript. SMYMPM, NN and JB were involved in conceptualizing this scoping review protocol. All authors approve the final version of the protocol manuscript.

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Competing interests

None

Search Strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present> (Updated from June 2016-June 2017)

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/	47131
2	Lung Diseases, Obstructive/	18301
3	exp Pulmonary Emphysema/	15328
4	(obstructive adj2 (pulmonary or lung$ or respirat$ or air$)).tw,kf.	48677
5	(chronic air$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	1482
6	(chronic bronch$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	100
7	(chronic$ adj2 bronch$).tw,kf.	13305
8	COPD.tw,kf.	37206
9	COAD.tw,kf.	251
10	emphysema$.tw,kf.	25309
11	(acos and asthm*).tw,kf.	161
12	or/1-11	107273
13	Nitric Oxide/	81932
14	(feno and (fraction* or exhal* or nitric)).tw,kf.	1310
15	(fe no and (fraction* or exhal* or nitric)).tw,kf.	413
16	nitric oxid*.tw,kf.	133212
17	or/13-16	148646
18	12 and 17	818
19	(2016-06* or 2016-07* or 2016-08* or 2016-09* or 2016-1* or 2017*).ez,dt.	1334389
20	18 and 19	53

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Not applicable
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5,6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7,8

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8,9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Not applicable
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Not applicable
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Not applicable
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Not applicable
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Not applicable
Confidence in cumulative	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

evidence			

*Adopted and modified from: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647.