eAppendix 1: Detailed method.

Study registration and methodology

The protocol of this systematic review and meta-analysis was prospectively registered at PROSPERO (www.crd.york.ac.uk/prospero ; CRD: 42018103358). It has been designed according to the *Cochrane Handbook for Systematic Reviews of Interventions* [1] and reported according to the PRISMA statement.

Criteria for considering studies for this review

Types of studies

Parallel and cross-over randomized trials, included those in the format of an abstract, assessing one or more of the considered outcomes.

Type of participants

Adult patients with stable COPD (no acute exacerbation in the previous 3 weeks), of any age, diagnosed based on the individual study's criteria. Studies with a mixed population of COPD and other respiratory disease(s) could be included if the data for the participants with COPD could be extracted separately.

Type of intervention

NHF with air, or supplemental oxygen if indicated by the patient's clinical status, compared with the same gas delivered without NHF.

Type of outcome measures:

Primary outcomes:

1. Arterial carbon dioxide partial pressure measured transcutaneously ($PtcCO_2$) or by arterial blood gases ($PaCO_2$);
2. Arterial oxygen partial pressure measured transcutaneously (TcO2) or by arterial blood gases (PaO_2);
3. pH measured by arterial blood bases;
4. Quality of life (assessed either with a general or a disease-specific questionnaire);
5. Deaths;
6. Number of acute exacerbations per year;
7. Number of hospitalizations per year;

Secondary outcomes:

1. Oxygen saturation measured by pulse or transcutaneous oximetry (SpO_2 and StO_2 respectively) or by arterial blood gases (SaO_2);
2. Cardiorespiratory function (heart rate (HR); forced expired volume in 1s (FEV_1); forced vital capacity (FVC);
3. Breathing pattern (volume tidal (Vt); respiratory rate (RR); minute ventilation (MV); rapid shallow breathing index (RSBI));
4. Respiratory mechanics (gastric pressure (Pga); oesophageal pressure (Poes); transdiaphragmatic pressure (Ptdia); end-expiratory lung impedance);
5. Dyspnea assessed either during or after an exercise or at rest;
6. Exercise capacity measured either by a maximal cardiopulmonary exercise testing or field tests;
7. Objective or self-reported physical activity;
8. Comfort and patient preference;
9. Adverse events.

Search methods for identification of studies

Electronic searches

MEDLINE, CENTRAL, Science Direct, Scopus, PEDro, OpenGrey and Greylit were searched from inception up to January 2019 for relevant studies in English or French. Reference list of the included studies were also checked for eligible studies.

The following key words were used and combined using Boolean operators and a sensitivity-maximizing method: “COPD”; “pulmonary disease, chronic obstructive”; “chronic respiratory failure”; “high-flow”; “high-flow cannula”; “high-flow nasal cannula”; “nasal cannula”; “humidified high-flow”; “high-flow oxygen”; “humidification therapy”; “HFNC”; “high-flow heated and humidified oxygen”.

The search strategy for PubMed using a sensitity-maximizing searching method was adapted for the other databases:

#1 “COPD”[tiab] OR “pulmonary disease, chronic obstructive”[mh] OR “chronic obstructive pulmonary disease”[tiab] OR “chronic respiratory failure”[tiab]
#2 “high-flow”[tiab] OR “high-flow cannula”[tiab] OR “high-flow nasal cannula”[tiab] OR “nasal cannula”[tiab] OR “humidified high-flow”[tiab] OR “high-flow oxygen”[tiab] OR “humidification therapy”[tiab] OR “HFNC”[tiab] OR “high-flow heated and humidified oxygen”[tiab]
#3 “randomized controlled trial”[pt] OR “randomized controlled trial”[tiab] OR “controlled clinical trial”[pt] OR “controlled clinical trial”[tiab] OR “randomized”[pt] OR “randomized”[tiab] OR “random”[pt] OR “random”[tiab]
#4 #1 AND #2 AND #3

[tiab] denotes a word in the title or abstract.

[mh] denotes a Medical Subject Heading term.

[pt] denotes a Publication Type term.

Data collection and analysis

Details about the data collection and analysis strategy are shown in eAppendix 1.

Selection of studies

Two authors (TB, CP) independently assessed relevant studies for inclusion. Any disagreement was resolved by discussion and the intervention of a third author (GP). The level of agreement was assessed using a kappa statistic.

Data extraction and management

Two authors (TB, CP) independently extracted data on the outcome of interest using a common data extraction form. For continuous outcomes, mean (SD) change from baseline and/or mean (SD) post-treatment values for each group were recorded. When they were not available in another format, data were graphically extracted using Get Data Graph Digitizer 2.24. Skewed data were converted into mean (SD).[2,3] The number of events was recorded for count outcomes. Study characteristics (methods, participants, intervention and outcomes) were also extracted.

Data from cross-over studies were managed according to the *Cochrane Handbook for Systematic Reviews of Interventions.*[1] Studies were grouped into the following categories with each category of studies analyzed separately: short-term studies (less than 7 days, including single treatment studies); studies of NHF during exercise; and long-term studies. In the case of studies with multiple intervention arms, the higher flow was considered for analysis. In the case of studies that measured outcomes at multiple time points, the latest period or the closest matched time point was considered for analysis.

Assessment of risk of bias in the included studies

Two authors (TB, GP) independently assessed the methodological quality of the included studies using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions.*[1] The methodological criteria included random sequence generation, allocation

concealment, blinding, incomplete outcome data, selective reporting and other potential bias. Any disagreement was resolved by discussion or the intervention of a third author (CP).

Measures of treatment effect

The effect of the treatment was estimated by mean differences (MD) or standardized mean difference (SMD) for continuous outcomes and risk ratio (RR) for counts, with their corresponding confidence intervals (CIs).

Unit of analysis issue

The unit of analysis was at the participant level. There were no cluster-randomized studies included in this systematic review.

Dealing with missing data

The impact of missing data was assessed in the "risk of bias" assessment. Original authors were contacted to obtain complementary data when necessary and analysis was performed based on available data.

Assessment of heterogeneity

Heterogeneity was assessed using the I^2 and Chi^2 statistic, considering values $I^2 \geq 50\%$ as a sign of moderate to high heterogeneity.

Assessment of reporting bias

The protocol for the systematic review stated that this would be assessed by funnel plot of 10 or more studies were available for a given meta-analysis.

Data synthesis

Meta-analysis was performed with a fixed-effect model when heterogeneity was low (< 50%), using the inverse-variance method. In the case of moderate to high heterogeneity, a random-effect model was used. RevMan 5.3.5 was used for every analysis. The quality of evidence was rated using the GRADE system. When meta-analysis was not possible, a narrative synthesis of original study data was performed.

Subgroup analysis

The protocol for the systematic review stated that subgroup analyses would be done to assess the effect low flow (10 to 20L/min) and high flow (30 or more L/min) NHF compared with control, if there were sufficient studies.

Sensitivity analysis

The protocol for the systematic review stated that sensitivity analyses would be done to assess the consistency of the results after removing high-bias studies.

References

1. Higgins JPT, Green A. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* www.cochrane-handbook.org: The Cochrane Collaboration; 2011.
2. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology.* 2005;5(13).
3. Greco T, Biondi-Zoccai G, Gemma M, Guérin C, Zangrillo A, Landoni G. How to impute study-specific standard deviations in meta-analyses of skewed continuous endpoints? *World J Meta-Anal.* 2015;3(5):215-224.