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Airflow relieves chronic breathlessness in people with advanced disease: An exploratory systematic review and meta-analyses

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Abstract

Background: Chronic breathlessness is a neglected symptom of advanced diseases.

Aim: To examine the effect of airflow for chronic breathlessness relief.

Design: Exploratory systematic review and meta-analysis.

Data sources: Medline, CINAHL, AMED and Cochrane databases were searched (1985–2018) for observational studies or randomised controlled trials of airflow as intervention or comparator. Selection against predefined inclusion criteria, quality appraisal and data extraction was conducted by two independent reviewers with access to a third for unresolved differences. 'Before and after' breathlessness measures from airflow arms were analysed. Meta-analysis was carried out where possible.

Results: In all, 16 of 78 studies (n = 929) were included: 11 randomised controlled trials of oxygen versus medical air, 4 randomised controlled trials and 1 fan cohort study. Three meta-analyses were possible: (1) Fan at rest in three studies (n = 111) offered significant benefit for breathlessness intensity (0–100 mm visual analogue scale and 0–10 numerical rating scale), mean difference −11.17 (95% confidence intervals (CI) −16.60 to −5.74), p = 0.06 I^2 64%. (2) Medical air via nasal cannulae at rest in two studies (n = 89) improved breathlessness intensity (visual analogue scale), mean difference −12.0 mm, 95% CI −7.4 to −16.6, $p < 0.0001$ $I^2 = 0\%$. (3) Medical airflow during a constant load exercise test before and after rehabilitation (n = 29) in two studies improved breathlessness intensity (modified Borg scale, 0–10), mean difference −2.9, 95% CI −3.2 to −2.7, $p < 0.0001$ $I^2 = 0\%$.

Conclusion: Airflow appears to offer meaningful relief of chronic breathlessness and should be considered as an adjunct treatment in the management of breathlessness.

Keywords

Dyspnoea, self-management, review, airflow (relevant term as the intervention subject heading)

What is already known?

- Randomised controlled trials and cohort data have demonstrated that airflow delivered from the fan at rest offers significant relief of breathlessness.
- Systematic review and randomised controlled trials of oxygen versus medical air have failed to demonstrate additional benefit from oxygen therapy and suggest that medical air delivery, airflow, is likely to be an active intervention.
- All current evidence available for the effect of airflow for chronic breathlessness relief has not been explored using systematic review methods.

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What this paper adds?

This exploratory systematic review and meta-analyses provide promising data to suggest that

- airflow from the fan at rest improves breathlessness in people with breathlessness due to a variety of causes
- airflow delivered as cylinder medical air at rest improves breathlessness in advanced cancer
- airflow delivered as cylinder medical air during a constant load exercise test improves breathlessness in people with chronic obstructive pulmonary disease and who have completed pulmonary rehabilitation

Implications for practice and theory

- Clinicians should consider the fan as an adjunct to treatment for breathlessness at rest in patients who do not require oxygen-enriched air.
- Airflow may benefit exertion-induced breathlessness, but further work is required to investigate the role of the fan with everyday general activity and in relation to exercise.
- Recovery time from exertion-induced breathlessness, self-efficacy and daily activity are key outcomes to explore in future studies of airflow.

Introduction

Breathlessness is a common and often poorly managed symptom in people with advanced diseases. It is associated with reduced quality of life,[1] decreased activities of daily living,[2] unplanned emergency hospital attendance and admission.[3–5] Breathlessness inflicts devastating and disabling physical, psychological and social burden on normal daily life for the patient, carers and close family members.[6–8] Chronic breathlessness, that is, breathlessness that persists despite optimal treatment for the underlying pathophysiology and causing such disability,[9] all too often is left for patients to manage themselves despite a developing evidence base for interventions targeted at the breathlessness itself.

Growing evidence supports complex non-pharmacological interventions to reduce the impact of the symptom and improve quality of life.[10–12] Components target peripheral and central afferent sources of breathlessness sensation, such as facial airflow delivered by the battery-operated handheld fan (fan).[13–17] Cooling of the facial skin innervated by the second and third branches of the trigeminal nerve, nasal mucosae or the upper airway flow receptors could modulate the central perception of breathlessness leading to decreased neural respiratory drive, thereby reducing the sensation of breathlessness.[18–22] A recent multimethods of secondary analysis of qualitative interview data from three studies found that 80/111 (72%) participants experienced benefit when the fan was used in conjunction with other components of a complex intervention.[23] Airflow delivered from the fan may offer a valuable contribution to the self-management of chronic breathlessness[13,15,23] and has been identified as a potentially useful strategy in a variety of situations, for example, breathlessness crisis,[24] a component of pulmonary rehabilitation to assist recovery from exercise, or with general everyday activities.[15]

Systematic reviews of oxygen in a variety of non-hypoxic patient groups (cancer, chronic heart failure, kyphoscoliosis, chronic obstructive pulmonary disease and interstitial lung disease) have not demonstrated additional benefit from oxygen therapy over medical air delivery.[25–30] An updated Cochrane review of chronic obstructive pulmonary disease found low-quality evidence for modest relief of breathlessness.[31] The results from a large, adequately powered trial that randomised 239 participants (chronic obstructive pulmonary disease 63%, cancer 16%) to receive at least 15 hours a day of oxygen or medical air delivered via home concentrator for 7 days reaffirm earlier suggestions that medical air used in the placebo arm may not be an inert comparator as previously thought and point to the likelihood of an active intervention.[29,32] Therefore, the placebo arm of oxygen studies may provide useful preliminary data regarding the role of airflow for the relief of chronic breathlessness. This systematic review aims to identify and evaluate data from studies of airflow, both from studies of the handheld fan and the comparator arm data for breathlessness intensity from oxygen studies, analysed as 'before and after' airflow exposure cohort data.

Aim

To examine the current evidence for the effectiveness of airflow for the relief of chronic breathlessness.

Methods

The systematic review methods employed an exploratory approach in that only the airflow arm of studies were used and the data analysed as cohort 'before and after' treatment.

Study design

The search methods employed are adapted from the Cochrane Handbook of Systematic Reviews[33] and reported

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[34] A review protocol is not preregistered but available from the University of Hull Library (Flavia Swan PhD Thesis).

Inclusion and exclusion criteria

Types of studies

Randomised controlled trials, controlled clinical trials (quasi-randomised experimental trials with or without blinding) and observational cohort studies were included.

Types of participants

Adults with chronic breathlessness from any advanced disease aetiology are as shown below:

- Malignancy: advanced primary and metastatic cancer patients, who have undergone disease treatments such as chemotherapy, radiotherapy or surgical interventions.
- Chronic obstructive pulmonary disease with forced expiratory volume in 1 second of less than 50% predicted value.
- Interstitial lung disease or pulmonary fibrosis where breathlessness is present.
- Chronic heart failure: New York Heart Association stage III–IV.
- Motor neurone disease and other neurological disease where breathlessness is present or forced vital capacity less than 80% predicted value.
- Kyphoscoliosis: a moderate-to-severe sideways and forwards curvature of the spine Cobb angle $>$50° and forced expiratory volume of less than 50% predicted value.

Studies were included, if at least 50% of the study population was classified as advanced, palliative or in the later stages of disease as defined above. These criteria were adapted from the Cochrane review of non-pharmacological interventions for breathlessness.[35]

Studies of participants with mild hypo- or normoxaemia, who do not fulfil the criteria for long-term oxygen therapy,[36] were included. Studies of hypoxic participants or patients with any condition not assessed as progressive, refractory to treatment and advanced such as asthma were excluded.

Types of exposure

Airflow: (1) delivered from either a fan (handheld or table) or non–oxygen-enriched compressed air or from a non-invasive ventilatory method (nasal cannula, mask or mouthpiece), but not nasal intermittent positive pressure ventilation and (2) directed at the cheek of the face, nasal mucosae or mouth.

Administration: as (1) a single dose *during ambulation* or *at rest* taken as needed (*pro re nata*),[37] (2) placebo short burst oxygen therapy intermittent use *before* exercise or *after* exercise for recovery[36] or (3) continuously over 15 hr a day as placebo long-term oxygen therapy studies or during the night as placebo nocturnal oxygen therapy.[38]

Studies where airflow was directly administered to the trachea or at sub-zero temperatures were excluded.

Types of outcome measure

Unidimensional breathlessness outcomes. American Thoracic Society (ATS) domains of dyspnoea measurement[20] including breathlessness severity or intensity rated on unidimensional scales are as shown below:

- Modified Borg score, a categorical scale with ratio properties
- Visual analogue scale, 0–100 mm anchored 0 = no shortness of breath and 100 mm = shortness of breath as bad as can be
- Numerical rating scales, 0–10 numbered scale anchored 0 = not breathless at all and 10 = the worst imaginable breathlessness
- Likert-type scales with verbal responses such as ‘a bit better’, ‘much better’ or ‘no difference’ or any other validated unidimensional scale for measuring breathlessness.

Studies were only included if they reported the breathlessness outcome at baseline and post-treatment measured as either primary or secondary outcomes. If severity or intensity was measured as part of a multidimensional or composite scale, for example, the Chronic Respiratory Questionnaire, that unidimensional measure of breathlessness was *not* extracted and analysed separately. Breathlessness-related function/quality of life measures were *not* used as primary breathlessness outcomes in the absence of unidimensional scales.

Other outcomes. Other outcomes as shown below are measured as either primary or secondary outcomes.

- Participant preference and satisfaction with the treatment
- Participant withdrawal and drop out from the studies
- Adverse effects recorded

Data sources and searches

Medline, CINAHL, AMED and Cochrane databases were searched (1985–2015; updated January 2018) for observational or randomised controlled trials of airflow as intervention versus control or as comparator versus oxygen. Reference lists were scanned. A full search strategy can be seen in Online Supplementary Table 1.

Study selection

Titles and abstracts (and, where unclear, full papers) were screened against the eligibility criteria by two independent reviewers F.S. and A.N., with recourse to M.J. as a third reviewer in case of disagreement.

Data extraction and synthesis

Baseline and post-intervention measures of breathlessness intensity were extracted from the fan studies and from the comparator arm of oxygen studies. Data were analysed as 'before and after' airflow exposure cohort observational data.

Risk of bias

F.S. and A.N. judged the reporting quality and internal validity for each of the included studies. The cohort study was evaluated according to the Cochrane guidelines for assessing bias in a non-randomised study.[39] As there is no tool that is applicable directly to the data extracted from the randomised controlled trials control arms, we assessed instead the quality of the parent randomised controlled trials as a proxy marker for quality data. The randomised controlled trials were assessed with the Cochrane Risk of Bias Tool.[33] See Online Supplementary Table 2.

Statistical analysis

Results from the meta-analyses were reported for the primary outcome, breathlessness intensity or severity where heterogeneity allowed or where not possible these were described narratively. Numerical rating scales and visual analogue scales were combined by equating one point on a numerical rating scales scale to 10 mm on a visual analogue scales.[40,41]

Data calculations for mean difference and standard deviation used STATA Version 12.1 (Stata Corp LLC Texas 77845-4512, USA). Breathlessness measurements were analysed as continuous outcomes. Data from the placebo arm of crossover randomised controlled trials were treated as single-arm before-after studies. For studies that recorded median values, the mean values were calculated from the extracted study data.[42] The I^2 statistic was used to assess heterogeneity.[43] Where the result indicated significant heterogeneity, a random effects model was chosen, otherwise a fixed effects model was applied. All analyses were undertaken on Review Manager 5.5. A sensitivity analysis was attempted for any study identified as including a subgroup not fitting the review criteria of mild hypo or normoxaemia to assess for any significant difference in the breathlessness outcome between the hypoxic and non-hypoxic participants.

Results

A total of 403 records were identified for screening. After removal of duplicates, 78 records were reviewed, of which 14 abstracts were rejected for not meeting inclusion criteria and the remaining 64 full text articles were assessed for eligibility. Of these, 16 studies met the review inclusion criteria and the other 48 studies were excluded (see Figure 1; flow chart[34] and Online Supplementary Table 3).

Overall studies represented 929 participants (age median 61.5, range 33–90 years; 47% men).

Airflow was delivered by fan[13,14,16,17,44] or as medical air.[29,32,45–53] See Table 1 for study characteristics.

Description of fan studies

Design

Five studies (n = 230) used the fan. Two feasibility randomised controlled trials: (n = 49)[13] and (n = 30),[44] a feasibility cohort study (n = 31),[14] a feasibility longitudinal randomised controlled trial (n = 70)[16] and a phase III crossover randomised controlled trial (n = 50).[17]

Patient characteristics

Four studies recruited a mixed population of people with breathlessness due to a variety of advanced conditions including chronic obstructive pulmonary disease (n = 101), cancer (n = 55), heart failure (n = 23) and other causes (n = 21),[13,14,16,17] and one study recruited advanced cancer only (n = 30).[44]

Intervention and comparator characteristics

Three studies used the fan to face at rest,[14,17,44] two with comparator groups, fan to leg[17] or no fan use and carer support,[44] and the other was a cohort design.[14] One study assessed acceptability of the fan when used with general activity over 6 months compared with an acupressure wristband,[16] and the remaining study assessed the fan when used with exercise advice over 4 weeks.[13]

Breathlessness outcome

Three studies focused on the sensory-perceptual domain of dyspnoea measurement and used breathlessness intensity as the primary outcome[17] or main outcome.[14,44]

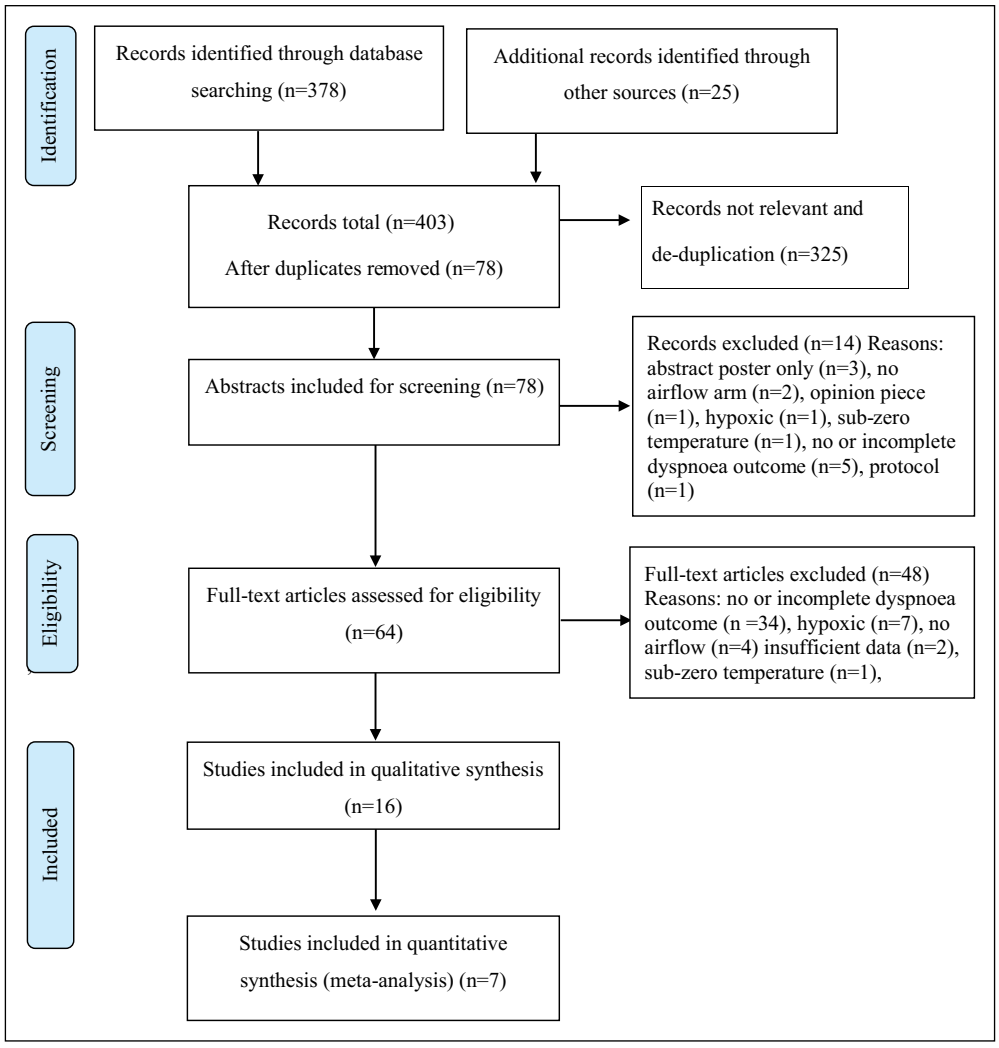

Figure 1. Flow diagram of study selection and retrieval.[34]

These studies selected the visual analogue scale,[17] the numerical rating scale[44] or both visual analogue scale and numerical rating scale.[14] The other two studies assessed symptom impact and the sensory-perceptual domain. These studies selected the numerical rating scale breathlessness intensity[13] and the modified Borg scale of breathlessness severity.[16]

Other outcomes

All of the fan studies reported participant withdrawals.[13,14,16,17,44] These ranged from 0 to 6 participants.[13,14,44] One study reported that there were no adverse events[13] and the other fan studies did not include any adverse event details.[14,16,17,44] Airflow preferences were described in four fan studies[13,16,17,44] and not in one study.[14] In addition, one study quantified the experience of fan use at 2 months.[16]

Description of medical air studies

Design

Eleven randomised controlled trials (n = 699) used oxygen, helium hyperoxia or both gases for the intervention compared with medical air.[29,32,45–53] Study size ranged from 16 to 239 participants.[29,48] Four were crossover[32,48,49,51] and seven used a parallel group design.[29,45–47,50,52,53] Nine studies were double blind,[29,45–52] and two were single blind.[32,53]

Patient characteristics

The 11 studies represent chronic obstructive pulmonary disease (n = 537), cancer (n = 109), other lung diseases (n = 21), cardiac disease (n = 14) and other causes (n = 18). Inclusion criteria required moderate-to-severe chronic obstructive pulmonary disease,[45–50,52,53] advanced cancer,[51]

Table 1. Characteristics of included studies.

Study author	Study design	Population (mean; standard deviation)	Intervention	Comparator	Mode of gas delivery	Dyspnoea Outcome measure(s)	Other outcomes: withdrawals, adverse events (AEs), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment) (mean; standard deviation)	Improvement with airflow Yes/No
Fan										
Booth et al.[14]	Feasibility observational cohort	n = 31 males: 20 Age mean: 74.8; 11.49 Mixed population, non-malignant, cardiorespiratory disease: 8 (26%) Baseline dyspnoea score: mean visual analogue scale 48 mm; 27.4	Handheld fan to face	No comparator group	Airflow from handheld fan to face for 5 min	Visual analogue scale (mm), numerical rating scale	Withdrawals = 6 AE and airflow preferences not reported	After 5 min at rest	Visual analogue scale = mean 35 mm; 25.7 after 5 min air Mean change = 12 mm; 21.2	Yes
Bausewein et al.[16]	Feasibility longitudinal phase II randomised controlled trial	n = 70 males: 36 Age mean: 65.6 yrs SD 8.80 chronic obstructive pulmonary disease = 45, cancer = 25 Baseline dyspnoea score: 3.7; 1.83	Handheld fan to face	Wristband	Airflow from handheld fan	Modified Borg score	Withdrawals at 2 months = 16/33 (48%) AE not reported Airflow preferences: Positive = 13/38 Negative = 7/38	Monthly over 6 months	Mean Borg score change over 2 months = 0.6; 2.1, p = 0.90	No, phase II not powered to test
Galbraith et al.[17]	Crossover randomised controlled trial	n = 50 Males: 23 Age mean: 71.3, range 33–90 yrs Mixed population; chronic obstructive pulmonary disease = 26, lung cancer = 11, heart disease = 15 Baseline dyspnoea score: visual analogue scale fan/face first group = 31 mm; 12–61 mm	Handheld fan to face	Handheld fan to leg	Airflow from handheld fan to face for 5 min	Visual analogue scale (mm)	Withdrawals = 1 AE not reported Airflow preferences: positive patient comments, numbers not reported	After 5 min at rest and after 10 min washout	Visual analogue scale = –7.0 mm median change after 5 min fan/face first group (interquartile range 1.5–14.5) Visual analogue scale = –10.0 mm median change including 10 min washout fan/face first group (interquartile range 3.5–17), p = 0.003	Yes
Johnson et al.[13]	Feasibility phase II randomised controlled trial	n = 49 males: 26 Age mean: 68 (range 46–88) Mixed population; chronic obstructive pulmonary disease = 28, cancer = 9, heart disease = 5, others = 7 Baseline dyspnoea score: mean numerical rating scale = 5.7; 1.5	Handheld fan to face at high or low flow rate	Usual care: verbal and written exercise and breathlessness management advice	Airflow from handheld fan	Numerical rating scale	Withdrawals = 6 No AE Airflow preference: positive patient comments, numbers not reported	After 4 weeks	Numerical rating scale = 6.0; 2.0 at 4 weeks Mean change 0.0; 3.0	No, phase II not powered to test
Wong et al.[44]	Feasibility phase II randomised controlled trial	n = 30 males: 14 Age: not reported Lung cancer = 13, other cancers = 17 Baseline dyspnoea score Control group: numerical rating scale mean 5.6;1.55 Intervention group: numerical rating scale mean 6.13; 2.48	Table fan with low flow rate	Placebo accompanied by carer	Airflow from table fan to face for 5 min	Numerical rating scale	No withdrawals AE not reported Airflow preference: mixed patient comments, numbers not reported	After 5 min at rest	Numerical rating scale = 4.60 after 5 min fan to face Mean change −1.53 (1.06) $p < 0.001$	Yes

Table 1. (Continued)

Study author	Study design	Population (mean; standard deviation)	Intervention	Comparator	Mode of gas delivery	Dyspnoea Outcome measure(s)	Other outcomes: withdrawals, adverse events (AEs), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment) (mean; standard deviation)	Improvement with airflow Yes/No
Medical air										
Abernethy et al.[29]	Double-blind randomised controlled trial	n = 239 males: 63% Age mean: Air = 74 yrs; 10 Mixed: chronic obstructive pulmonary disease = 152, primary lung cancer = 33 Baseline dyspnoea score: Am air = 4.6; 2.4 Pm air = 4.7; 2.3	Oxygen	Room air via concentrator	2 L/min via nasal cannula for at least 15 hr a day (long-term oxygen therapy)	Numerical rating scale 1–10	Withdrawals = 15 Few AE, number not reported Side effects reported Airflow preferences not reported, oxygen only	Am and pm each day, within 30 min of waking and bedtime for 7 days	Am = −0.7 numerical rating scale point change Pm = −0.5 numerical rating scale point change (p = 0.5)	Yes
Booth et al.[32]	Single-blind crossover randomised controlled trial	n = 38 males: 22 Age median: 71 range: 54–90 yrs Lung cancer 20, chronic obstructive pulmonary disease 13, cardiac 4 Baseline dyspnoea score: visual analogue scale 59 mm	Oxygen	Cylinder air	4 L/min for 15 min via nasal cannula	Visual analogue scale (mm) Modified Borg scale	No withdrawals AE and airflow preferences not reported	After 15 min of breathing oxygen or air at rest.	Visual analogue scale = −11 mm change after air 48 mm, $p < 0.001$	Yes
Eaton et al.[45]	Double-blind parallel randomised controlled trial	n = 78 males: 36 Age mean: 77.3 yrs; 7.06 moderate/severe chronic obstructive pulmonary disease Baseline Chronic Respiratory Questionnaire score: air = 17.5; 4.2	Oxygen	Cylinder air	2 L/min via nasal cannula over 6 months (SBOT)	Chronic Respiratory Questionnaire	Withdrawals = 21 AE and airflow preferences not reported	Monthly over 6 months	Chronic Respiratory Questionnaire = average change over 6 months: air group = −3.6	No
Eves et al.[46]	Double-blind randomised controlled trial	n = 38 males: 23 Age mean: 65.5 yrs (SD 8) Stable chronic obstructive pulmonary disease Baseline dyspnoea score: constant load exercise Borg mean: air = 6.0; 2.2 Incremental load exercise Borg mean: air = 5.6; 2.0	Helium-hyperoxia (60% HE: 40% O^2)	Cylinder air	Face mask (non-rebreathing)	Modified Borg score	No withdrawals No AE Airflow preferences not reported	During exercise test before and after 6 weeks pulmonary rehabilitation programme, 3 times a week for 30 min on cycle ergometer	Constant load exercise Borg mean: air = 4.2; 2.1 mean change = −1.8 (95% CI −3.1 to −0.2), $p < 0.05$ incremental load exercise Borg mean: air = 5.6; 2.1 No change (95% CI −0.7 to 0.7)	Yes
Jolly et al.[47]	Double-blind randomised controlled trial	n = 20 males: 19 Age mean: 68.5 yrs (SEM 2.5) Stable chronic obstructive pulmonary disease Baseline dyspnoea score: Borg mean score Desat group: baseline 6-min walking test (6MWT) = 5.82 (SEM 0.46) Non-desat group: baseline 6MWT = 4.22 (SEM 0.46)	Oxygen	Cylinder air	3 L/min via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after 3 x 6MWTs with at least 45 min washout between walks	Borg mean score: Desat group Air 6MWT = 5.82 (SEM 0.42) No change Non-desat group Air 6MWT = 4.44 (SEM 0.73) No change	No

(Continued)

Table 1. (Continued)

Study author	Study design	Population (mean; standard deviation)	Intervention	Comparator	Mode of gas delivery	Dyspnoea Outcome measure(s)	Other outcomes: withdrawals, adverse events (AEs), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment) (mean; standard deviation)	Improvement with airflow Yes/No
Marciniuk et al.[48]	Double-blind crossover randomised controlled trial	n = 16 males: 7 Age mean: 67 (SD 8) Moderate-to-severe chronic obstructive pulmonary disease Baseline dyspnoea score: Borg mean score Baseline 6MWT = 5; 2	100% Oxygen or helium-hyperoxia (70% HE: 30% O^2)	Cylinder air	15 L/min via face mask 8 L/min via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after each 6MWTs on visit 1,2 and 3 with 60 min washout between walks	Borg mean score After 6MWT air = 3.5 mean Borg score change = −1.5 decrease	Yes
McDonald et al.[49]	Double-blind crossover randomised controlled trial	n = 26 males: 24 Age mean: 73; 6 Stable severe chronic obstructive pulmonary disease Baseline dyspnoea score 6MWT: air group = 3.8; 1.4 Chronic Respiratory Questionnaire = 14; 5	Oxygen	Cylinder air	4 L/min via nasal cannula	Modified Borg score Chronic Respiratory Questionnaire	Withdrawals = 7 AE and airflow preferences not reported	After 6 and 12 weeks of home cylinder air using 6MWT exercise test with 20 min washout between walks	Borg mean score home air: 6MWT with cylinder air = 3.8 (SD 1.5) no change Chronic Respiratory Questionnaire score home air = 17; 6 3 point change	No with 6MWT Yes with Chronic Respiratory Questionnaire
Moore et al.[50]	Double-blind randomised controlled trial	n = 143 males: 99 Age mean: 71.8 yrs; 9.8 range: 43–78 Stable chronic obstructive pulmonary disease Baseline dyspnoea score: air = 17.5; 4.9	Oxygen	Cylinder air	6 L/min via nasal cannula at home for 12 weeks with activity (SBOT)	Chronic Respiratory Questionnaire	Withdrawals = 4 AE not reported Airflow preferences: 45% prefer no cylinder	At 4 weeks and 12 weeks	Air: 4 weeks = 18.4; 5.8 12 weeks = 18.4; 5.8 Air: Chronic Respiratory Questionnaire = mean change at 4 and 12 weeks = 0.9	Yes
Philip et al.[51]	Double-blind crossover randomised controlled trial	n = 51 males: 31 Age median: 65 range: 33–82 yrs Non-small cell lung cancer = 22, small cell lung cancer = 6, breast = 8, colorectal = 4, others = 11 Baseline dyspnoea score: visual analogue scale median Air first = 52 mm (range 23–92) Visual analogue scale median Air second = 42 mm (range 10–70)	Oxygen	Medical Air	4 L/min for 15 min via nasal cannula	Visual analogue scale (mm)	No withdrawals AE not reported Airflow preferences: Positive: n = 15 (29%)	Before and after 15 min of gas	Visual analogue scale median after air first = –3 mm change (range −19 to 7) Visual analogue scale median after air second = −11.5 mm change (range −20 to 45) Visual analogue scale mean change = −13.4 mm	Yes

Table 1. (Continued)

Study author	Study design	Population (mean; standard deviation)	Intervention	Comparator	Mode of gas delivery	Dyspnoea Outcome measure(s)	Other outcomes: withdrawals, adverse events (AEs), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment) (mean; standard deviation)	Improvement with airflow Yes/No
Scorsone et al.[52]	Double-blind randomised controlled trial	n = 30 males: 23 Age mean: 67.3 yrs (SD 8.3) Moderate-to-severe chronic obstructive pulmonary disease Baseline dyspnoea score: Before training incremental load exercise Borg: air = 7; 3 Before training constant load exercise Borg: Air = 8; 3	40% Oxygen or helium-hyperoxia (60% HE: 40% O^2)	Humidified room air	Mouthpiece from a Douglas bag	Modified Borg score	No withdrawals AE and airflow preferences not reported	During exercise before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 20 min on cycle ergometer	After training incremental load exercise Borg: air = 4; 2 After training constant load exercise Borg = 5; 3 Borg change = −3 point decrease both exercise tests	Yes
Wadell et al.[53]	Single-blind crossover randomised controlled trial	n = 20 males: 10 Age mean: 67 yrs Range: 52–73 Stable chronic obstructive pulmonary disease Baseline dyspnoea median score: Test A (air) at rest; pretraining Borg: air group = 1.5 (0–3) Test A (air) after 6MWT, pretraining Borg: air group = 6.5 (4–9)	Oxygen	Air	5 L/min via nasal cannula	Modified Borg score	Withdrawals = 2 AE and patient preferences not reported	During exercise using 2 x 6MWT (air/O^2 or O^2/air) with 1 hour washout before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 30 min on a treadmill	Test A (air) at rest; post-training Borg: air group = 1 (0–3) Test A (air) after 6MWT, post-training Borg: air group = 6 (1–7) Borg change = −0.5 point at rest and after exercise test	Yes

or were a mixed population with no specific stipulation of severity.[29,32]

Intervention characteristics

The source of airflow was an oxygen cylinder,[32,45–50] a sham concentrator[29] and a Douglas bag.[52] Two studies did not state the airflow source.[51,53] Medical air or compressed air was delivered through nasal cannulae,[29,32,45,47,49–51,53] face mask and nasal cannula,[48] a non-rebreathing face mask[46] and a mouthpiece.[52] The flow rates varied widely in the studies: 2 L/min,[29,45] 3 L/min,[47] 4 L/min,[32,49,51] 5 L/min,[53] 6 L/min[50] and 8 L/min via nasal cannula or 15 L/min with face mask.[48] Two studies did not report flow rate details.[46,52] The timing of airflow delivery was 15 min at rest,[32,51] with daily activity over 3[50] or 6 months,[45] 15 hours a day over 1 week,[29] or in conjunction with exertion-induced breathlessness during pulmonary rehabilitation[46,52,53] or a walking test.[47–49] The pulmonary rehabilitation programme parameters for airflow delivery were with treadmill exercise 3 times a week for 30 min over 2 months,[53] a cycle ergometer used 3 times a week for 30 min over 6 weeks[46] or 3 times a week for 20 min over 2 months.[52] The 6-min walk test parameters for airflow delivery were (1) three same day 6-min walk tests with 45 min washout, using room air for the basal walk and compressed air for the subsequent walks,[47] (2) five 6-min walk tests performed over three visits (timing not stated) using room air for the practice walk on visit one and cylinder air for the two 6-min walk tests with 60 min washout on visits two and three[48] and (3) three same day 6-min walk tests using cylinder air with 20 min washout between tests at baseline, 6 and 12 weeks, as well as short burst use at home with daily activity during the study period.[49]

Breathlessness outcome

Two studies focused on the sensory-perceptual domain of dyspnoea measurement and recorded breathlessness intensity as a primary outcome with the visual analogue scale and Borg scale[32] or the visual analogue scale only.[51] All of the other studies focused on symptom impact and the sensory-perceptual domain.[29,45–50,52,53] Of these, three studies measured breathlessness intensity as a primary outcome with the numerical rating scale[29] or the Chronic Respiratory Questionnaire dyspnoea domain.[45,50] The remaining six studies identified the modified Borg scale as one of the main outcomes[47–49,52,53] or a secondary measure.[46] One study in addition selected the Chronic Respiratory Questionnaire.[49]

Other outcomes

Participant withdrawals were reported in all of the studies,[29,32,45–51,53] apart from one.[52] Five studies reported no withdrawals,[32,46–48,51] and in the other five studies withdrawals ranged from 2 to 21 participants.[45,53] Adverse events were poorly reported with only two studies including details, 'few' or 'no adverse events'.[29,46] All of the other studies omitted reporting adverse events.[32,45,47–53] Airflow preferences were only reported in one study.[51] The remaining studies did not report airflow preferences,[29,32,45–48,50,52,53] although one study did quantify side effects[29] and a second study examined preference for cylinder delivery of airflow.[50]

Risk of bias

The quality appraisal is summarised in Online Supplementary Table 2 and described below.

Allocation

All of the studies, apart from one, a cohort design,[14] were described as randomised controlled trials. It was possible to verify the randomisation process in eight studies.[13,16,17,29,32,45,46,50] There was insufficient information to determine the risk of allocation bias in the other randomised controlled trials.[44,47–49,51–53]

Blinding

Two of the fan studies attempted to blind the participants;[16,17] a placebo wristband was used as a comparator[16] and participants were not told if the fan to face or fan to leg was the active intervention.[17] There was no blinding in two studies, a cohort and phase II randomised controlled trial,[13,14] and the fifth study stated single blinding that could not be verified from the methods described.[44] All five were judged high risk of bias due to incomplete blinding or limited description. Nine medical air randomised controlled trials were described as double blind.[29,45–52] All were judged low risk of bias,[29,45,46,48–50,52] apart from one study that was unclear due to the lack of detail reported.[51] Two randomised controlled trials were single blind;[32,53] one was judged low risk of bias[32] and the other was regarded as unclear risk due to the inadequate description.[53]

Incomplete outcome data

Thirteen studies adequately addressed withdrawals and incomplete outcome data; these were considered low risk of bias.[13,14,17,29,32,46–53] Three studies were uncertain risk:[16,45] one due to the proportion of attrition[16] and the other two lacked description of how any missing data were statistically managed.[44,45]

Selective outcome reporting

All of the studies reported the prespecified outcomes and were judged as low risk of bias.[13,14,16,17,29,32,44–53] Study protocols were available for eight studies.[13,14,16,17,29,46,50,51]

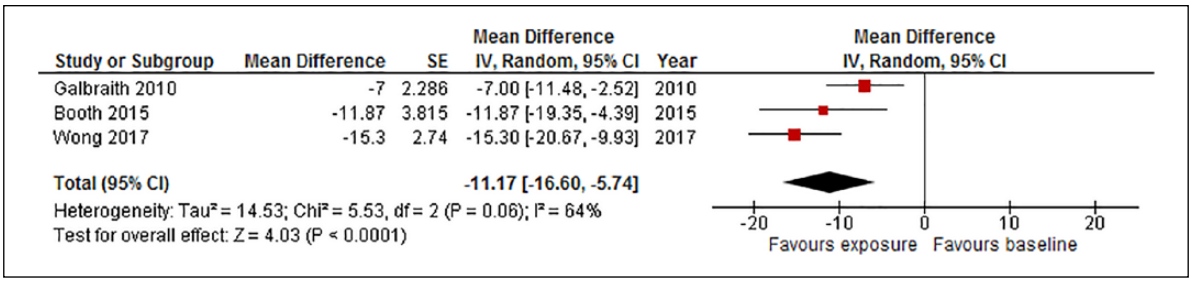

Figure 2. Meta-analysis of fan at rest.

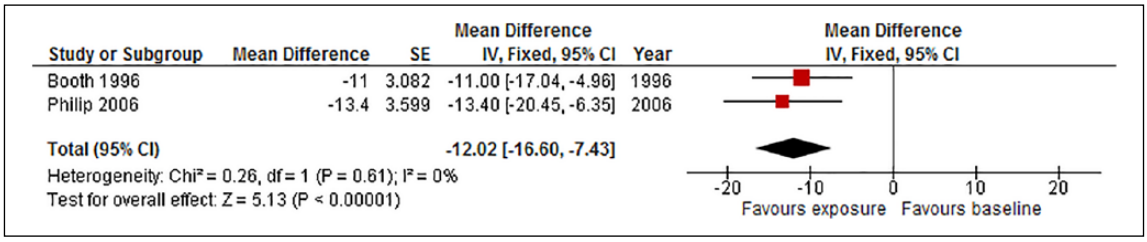

Figure 3. Meta-analysis of cylinder air at rest.

Other issues of bias

Twelve studies appeared free from other bias and were judged low risk.[13,16,17,29,44–46,48,50–53] Three studies reported insufficient information to adequately assess risk,[32,47,49] and one study, a cohort design, was judged high risk.[14]

Effect of interventions

The airflow was delivered (1) at rest,[14,17,32,44,51] (2) over days or weeks (either intermittently or as periods of continuous flow) while the participant continued with usual general activities[13,16,29,45,50] or (3) during specific episodes of exertion-induced breathlessness.[46–49,52,53]

At rest

Five studies demonstrated improvement with airflow delivery at rest.

Results from 5 min fan use to the face in three studies were visual analogue scale breathlessness intensity difference from baseline mean −7 mm (confidence interval (CI) −11.5 to −2.5)[17] and mean −12 mm (CI −19.3 to −4.4)[14] and for the numerical rating scale mean change −1.53 (−9.6 to −6.5).[44]

Cylinder medical air delivery for 15 min demonstrated improvement visual analogue scale breathlessness intensity mean −11 mm (CI −17.0 to −5.0)[32] and mean −13 mm (CI −20.5 to −6.3).[51] Four studies were subdivided into two groups and included in meta-analyses.

Fan. Airflow from the fan at rest improved breathlessness in a mixed population (n = 111; 58% cancer): visual analogue scale (mm) mean difference −11.17 (CI −16.60 to −5.74), p = 0.06. Significant heterogeneity was observed, χ^2 p-value = 0.2 (I^2 = 64%) (see Figure 2).

Medical air. Airflow delivered as cylinder medical air at rest improved breathlessness in advanced cancer (n = 89) visual analogue scale (mm) mean difference −12.0, CI −16.6 to −7.4, $p < 0.0001$. No evidence of heterogeneity was observed, χ^2 p-value = 0.6 (I^2 = 0%) (see Figure 3).

General activity

Six studies used airflow at home with everyday general activity. A narrative description was used for these due to study diversity. Breathlessness point changes from four cylinder air studies were mixed,[29,45,49,50] with Chronic Respiratory Questionnaire −3.6 after 6 months,[45] 3.0 after 12 weeks[49] or 0.9 at 12 weeks,[50] or numerical rating scale −0.7 (am) and −0.5 numerical rating scale (pm) after 7 days.[29] In the two fan studies, a modified Borg score of −0.6 (SD 2.1) was found after 2 months,[16] but there was no numerical rating scale score change after 4 weeks of fan use with exercise advice.[13]

Exertion-induced breathlessness

Six studies examined airflow delivery with exertion-induced breathlessness. Results for mean Borg breathlessness score during a walking test for three studies varied; no change during a 6-min walk test repeated on the same day,[47] or at 12 weeks,[49] and an improvement of −1.5 for a 6-min walk test repeated on three separate

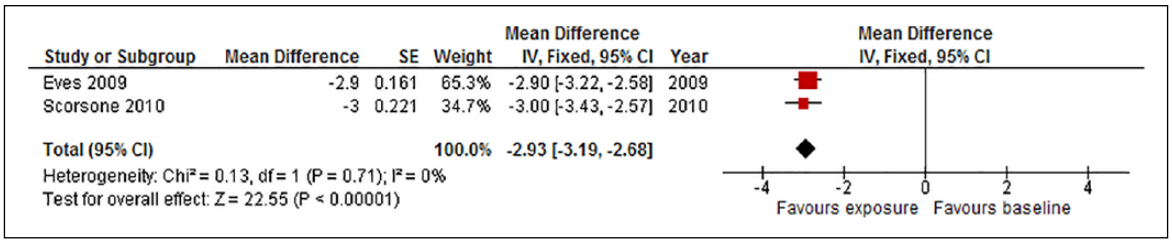

Figure 4. Meta-analysis of cylinder medical air for exertion-induced breathlessness.

visits.[48] Airflow delivered during a constant load exercise test after pulmonary rehabilitation in three studies also demonstrated variable improvement in mean Borg breathlessness scores: −1.8 points[46] and −3 points[52] using a cycle ergometer and −0.5 point from a treadmill test.[53] Two studies were suitable to include in a meta-analysis (see Figure 4).[46,52]

Medical air. Airflow delivered as cylinder medical air during a constant load exercise test after PR in chronic obstructive pulmonary disease (n = 29) significantly improved breathlessness Borg score mean difference −2.9 (CI −3.2 to −2.7), $p < 0.0001$. No evidence of heterogeneity was observed, χ^2 p-value = 0.7 ($I^2 = 0\%$) (Figure 4).

Discussion

These exploratory data support that facial and nasal airflow delivery at rest offers relief of breathlessness intensity consistent with a moderate clinically important difference[54,55] and during exertion.[46,52] All participants in the cylinder medical air delivery at rest studies had advanced cancer, but nearly half of those in the fan 'at rest' studies had other conditions indicating that airflow for breathlessness at rest is of benefit irrespective of cause.

In a recent pooled qualitative data study of facial airflow use from the fan in 133 people with chronic breathlessness,[9] over 80% patients reported some or substantial benefit.[23] However, the data presented here varied with regard to relief of breathlessness intensity when facial or nasal airflow delivery was used with everyday general activity or with exertion-induced breathlessness. This may reflect the use of outcome measures that do not reliably capture change in breathlessness intensity in the context of exertion. Studies that used a 6-min walk test [47–49] highlight the problem of a self-paced test that allows patients to control their walking speed and thus limit the maximal level of exertion-induced breathlessness experienced. In contrast, studies that used an externally paced test, such as the cycle ergometer, identified relief of breathlessness intensity.[46,52] The relationship between exercise and breathlessness intensity is complex, and measuring one without taking the other into account may miss relevant improvement. Scores are likely to remain static after the introduction of an intervention as patients are able to exert themselves to the same level of breathlessness without noticing an increase in their exercise tolerance,[56] or indeed the outcome may be of little value to the patient.[23]

A previous study of recovery time after an incremental shuttle walk test in people with thoracic cancer (n = 57) reported a rapid reduction in breathlessness intensity with a return to baseline time of median 4 min (interquartile range 2–5 min).[57] The analysis of 133 patient interviews found that a faster recovery time was a key patient-reported benefit of airflow delivered from the fan, irrespective of breathlessness intensity.[23] Even though recovery time may only be a matter of minutes, interventions which shorten this further are clearly welcomed and give the patient a sense of self-control that may help prevent a breathlessness-anxiety spiral. The ability to recover quickly and predictably from bouts of exertion is likely to encourage further activity and prevent the deconditioning cycle.

The fan therefore seems suitable as a patient-delivered intervention to target the recovery time from exertion-induced breathlessness. Preliminary magnetoencephalography imaging data suggest airflow delivery during recovery from exercise may modulate central perception of breathlessness by modifying sensory attention.[58] Cooling of the facial skin innervated by the second and third branches of the trigeminal nerve and/or stimulation of nasal mucosa and upper airway 'flow' receptors is reported to improve breathlessness intensity and exercise tolerance[18,19,59,60] and could 'fool' the brain into thinking that the respiratory status is adequate.[22]

Unpleasant respiratory sensations associated with exercise are known to adversely influence adherence to an exercise regime.[61] Therefore, use of airflow as part of pulmonary rehabilitation may help the problems of low patient attendance and poor maintenance of long-term outcomes.[62–65] Facial airflow from fan use during a cycle ergometer test in chronic obstructive pulmonary disease patients resulted in significant breathlessness reduction and a longer total exercise time.[66] Likewise, the meta-analysis result from this systematic review suggests significant relief of breathlessness when airflow is delivered during

exercise. These data highlight the potential value of using airflow delivery with pulmonary rehabilitation or home-based exercise programmes. In addition, intervention preference and adverse event data support the role of the fan in this context as a portable device that is unlikely to harm and therefore appropriate for the majority of patients to try.

Finally, it is likely that any positive benefits of airflow delivery from fan use with everyday general activity and at rest were not captured in the review data. The lack of signal from the results may in part reflect the complexity and the nuances of when, where and how this intervention is used by patients.[23] Current breathlessness management is modelled on a complex intervention, of which the fan is identified as a valuable therapeutic component alongside other interventions and strategies that are tailored to the patient's breathlessness needs.[11,67]

Limitation of methods

Data were analysed as cohort 'before and after' design, and no adjustments were made to control for confounding bias. The pre–post comparison increases the potential risk of bias, and it is possible that results may be influenced by the timing of 'before and after' measures. For example, studies of longer duration (up to 6 months) may not be representative of the immediate benefits of airflow, but rather reflect more complex use and mechanism of any observed benefit may be related to reconditioning, facilitated by airflow, over time. Risk of bias was assessed using a tool designed for randomised controlled trials; therefore, it is possible that this assessment may not capture potential sources of bias associated with the observational methods used in this systematic review.

Overall, the qualitative synthesis represents findings from 929 participants, the largest to date; however, the meta-analyses pertain to a small number of participants and only provide a preliminary indication of the pooled effect estimate of airflow. The meta-analyses involve few studies; therefore, heterogeneity is difficult to estimate and the accuracy of the I^2 value is less certain.[68] The number of studies that fulfilled the review criteria was restricted by the need for baseline breathlessness measures. Some of the included studies[32,51] did not report repeated measurements in a format suitable for meta-analysis necessitating statistical assumptions.[42]

Implications for practice and further research

Airflow is safe and should be used as an adjunct to treatment for breathlessness at rest in those who do not require oxygen-enriched air. Clinicians should consider airflow an important intervention to use as part of a breathlessness management programme in breathlessness at rest irrespective of cause. The relief of breathlessness during exertion in those with chronic obstructive pulmonary disease may provide a useful intervention during pulmonary rehabilitation where breathlessness is a reason for poor adherence.

The fan, when taught by an appropriately trained clinician, offers patients an inexpensive and portable source of airflow likely to benefit exertion-induced breathlessness. Recovery time from exertion-induced breathlessness is an important patient-reported outcome, and further work is needed to explore the role of airflow in recovery, self-efficacy and increased daily activity as part of complex breathlessness intervention programmes including rehabilitation.

Conclusion

These data support facial or nasal airflow for clinically meaningful relief of breathlessness at rest. This systematic review pulls together the growing evidence to support airflow as an effective self-management option for people with chronic breathlessness and identifies airflow as an intervention for future study.

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Data management and sharing

The full search strategy has been described in the Online Supplementary Materials and included and excluded papers are presented.

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Supplemental material

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